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JONUŠIS

Cyclization of Functionally Substituted 1,3-Diarylalkynones to Isoxazoles, Chromones and 2,3,5-Trisubstitutedthiophenes

DOCTORAL DISSERTATION

Life Sciences,
Chemistry (N 003)

VILNIUS 2020

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VILNIAUS UNIVERSITETAS
FIZINIŲ IR TECHNOLOGIJOS MOKSLŲ CENTRAS

Mantas
JONUŠIS

1,3-Diarilalkinonų ciklizacijos reakcijos susidarant izoksazolams, chromonams ir 2,3,5-tripakeistiems tiofenams

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ABOUT THE AUTHOR

Mantas Jonušis was born in Vilnius, Lithuania in 1990. In 2009 he finished Vilnius "Minties" Gymnasium and started studies in Vilnius University where he acquired Bachelor (2013) and Master of Science (Magna cum laude, 2015) degrees in the field of chemistry. In the same year he started Ph. D. studies in a group of prof. dr. Inga Čikotienė. Mantas Jonušis is also a laureate of Dr. Bronislovas Lubys scholarship (2015) and has also been in ERASMUS internship in Eberhard Karls Universität Tübingen (2012) and international workshops in Latvian Institute of Organic Synthesis, Riga, Latvia (2016), AM Technology, Runcorn, United Kingdom (2017), DTU Energy, Roskilde, Denmark (2018), GenoSynth GmbH, Berlin, Germany (2018). Mantas Jonušis has clear research interests in the synthesis of heterocyclic compounds, triple bond chemistry and natural compounds.

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- "Tyrėjų naktis 2016/2017", ES "Horizontas 2020" MCSA program, 722959, BPTI, 2016-06-01:2017-11-30.
- VP1-3.1-ŠMM-07-K-01-002, "Kompleksinė naujų priešvėžinių junginių paieška: nuo fundamentaliųjų tyrimų iki kryptingų modeliavimo ir sintezės", Europos socialinis fondas (ESF), 2011-03-01:2015-03-31.
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LIST OF ABBREVIATIONS

1,10-Phen	–	1,10-Phenanthroline
9-AJ	–	9-Azajulolidine
Ac	–	Acetyl
AIE	–	Aggregation induced emission
AIEE	–	Aggregation induced emission enhancement
BIPY	–	Bipyridyl
BZI	–	Benzimidazoyl
DCC	–	*N*,*N'*-Dicyclohexylcarbodiimide
DCE	–	Dichloroethane
DCM	–	Dichloromethane
DIB	–	(Diacetoxyiodo)benzene
DIPEA	–	*N*,*N*-Diisopropylethylamine
DMA	–	Dimethylacetamide
DMAc	–	*N*,*N*-Dimethylacetamide
DMAP	–	4-Dimethylaminopyridine
DMF	–	*N*,*N*-Dimethylformamide
DMSO	–	Dimethyl sulfoxide
DMT	–	4,6-Dimethoxy-1,3,5-triazin-2-yl
DTBP	–	Di-*tert*-butyl peroxide
EA	–	Ethyl acetate
EDG	–	Electron donating group
ESI	–	Electrospray ionization
EWG	–	Electron withdrawing group
HRMS	–	High resolution mass spectrometry
IMD	–	Imidazolyl
IPr	–	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
LAH	–	Lithium aluminum hydride
LDA	–	Lithium diisopropylamide
MOF	–	Metal oxide framework
MS	–	Mass spectrometry
MW	–	Microwave
NBS	–	*N*-Bromosuccinimide
NCS	–	*N*-Chlorosuccinimide
NHC	–	*N*-Heterocyclic carbene
NMM	–	*N*-Methylmorpholine
NMR	–	Nuclear magnetic resonance
PCC	–	Pyridinium chlorochromate
PE	–	Petroleum ether

PEDOT – Poly(3,4-ethylenedioxythiophene)
PEG – Polyethylene glycol
Ph – Phenyl
Pic – 2-Picolinato
PLQY – Photoluminescence quantum yield
PSS – Polystyrene sulfonate
Py – Pyridyl
TADF – Thermally activated delayed fluorescence
TBAI – Tetrabutylammonium iodide
TBDMS – *tert*-Butyldimethylsilyl
TBN – *t*-Butyl nitrite
TCE – Trichlorethylene
TEMPO – (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf – Trifluoromethanesulfonyl
THF – Tetrahydrofuran
TICT – Twisted intramolecular charge transfer
TIPS – Triisopropylsilyl
TLC – Thin layer chromatography
TMEDA – Tetramethylethylenediamine
TMS – Trimethylsilyl group
$TMSN_3$ – Trimethylsilyl azide
TMSOTf – Trimethylsilyl trifluoromethanesulfonate
Ts – Tosyl
TSQ – Triple-Stage Quadrupole

INTRODUCTION

1,3-Diarylalkynones were first mentioned in literature in 1892 [1]. Since then alkynones became very valuable starting materials in organic synthesis and many synthetical strategies leading towards 1,3-diarylalkynones have been developed [2]. These substrates are versatile intermediates for five or six membered heterocycles such as, isoxazoles, chromones, thiophenes, pyrroles and others. Many of these heterocycles are known for their beneficial physicochemical or bioactive properties [3].

During the past ten years our team has focused on the chemistry of C≡C triple bond. For example, nucleophilic addition of primary aliphatic amines to 2-(1-alkynyl)-2-alken-1-ones [4] or formation of condensed 1*H*-pyrrol-2-ylphosphonates and 1,2-dihydropyridin-2-ylphosphonates via Kabachnik−Fields reaction of acetylenic aldehydes and subsequent 5-exo-dig or 6-endo-dig cyclization [5] were studied. We have also noted that oxocarbenium ions generated from corresponding acetals and Lewis acid mediated yne-carbonyl or yne-thioxo transformations of a range of *O*- and *N*-propargylic compounds [6]. It led to the development of a new method for the synthesis of functionalized 4*H*-1,3-oxazines, 4*H*-1,3-thiazines, 4,5-dihydrothiazoles, and α-substituted enones. Hence, we decided to explore chemical reactivity between oxocarbenium ions and 1,3-diarylalkynones which are structurally similar to previously studied propargylic compounds. These studies led to the development of new synthetic method of potentially bioactive alkoxymethyl groups containing isoxazoles and chromones [7]. Furthermore, we have used 1,3-diarylalkynones for the synthesis of series of 2,3,5-trisubstituded thiophenes which exhibited photoluminescence [8].

The main aim of this work is investigation of new synthetic pathways from 1,3-diarylalkynones towards functionalized heterocycles (Fig. 1)

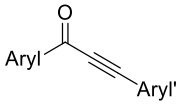


Figure 1. General structure of 1,3-diarylalkynones.

Main tasks for the achievement of the aim:

- ***Task 1*** To analyze scientific literature of current synthesis methods of isoxazoles, thiophenes and flavones from 1,3-diarylalkynones.
- ***Task 2*** To develop new synthetic method for isoxazoles and flavones from 1,3-diarylalkynones.
- ***Task 3*** To synthesize series of 2,3,5-trisubstituted thiophene derivatives from 1,3-diarylalkynones and explore photophysical properties.

In terms of significance of the work it is stated that:

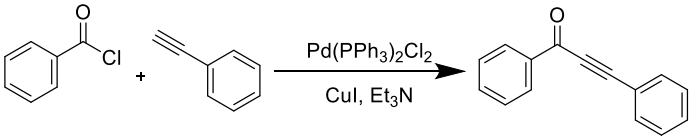
1. Alkoxyarylmethyl groups containing isoxazoles and alkoxyarylmethyl groups containing chromones can be synthesized by our newly developed method from (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyl oximes by treatment with 1 equivalent of BF_3*Et_2O and corresponding acetal in acetonitrile at room temperature.
2. (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyl oximes without electron-donating alkoxy groups does not participate in electrophilic cyclization with oxocarbenium ions. But cyclization of 3-aryl-1-(2-methoxyphenyl)-prop-2-yn-1-ones toward chromones is general to electronic effects of aryl substituent (EWGs and EDGs are both tolerated).
3. Carbamimidothioates can be effectively used as a sulfur containing building blocks for the synthesis of 2,3,5-trisubstituted thiophenes via Fiesselmann type cyclization. Series of 2,3,5-trisubstituted thiophenes have been synthesized by this newly developed method.
4. Group of our synthesized 2,3,5-trisubstituted thiophenes exhibits photoluminescence. Introduction of 5,6-dichloro-2-benzimidazolyl substituent in position 2 and EWG-substituted arenes in 3rd and EDG-substituted arenes in 5th position of thiophene core results in the highest PLQY of our studied 2,3,5-trisubstituted thiophenes.

The structure of this thesis consists of 3 sections. ***Section 1*** covers synthesis of starting materials - 1,3-diarylakynones. ***Section 2*** focuses on application of 1,3-diarylakynones towards alkoxymethyl substituted isoxazoles and chromones. And finally, s***ection 3*** describes experiments of 1,3-diarylalkynones towards substituted thiophenes. S***ection 3*** also covers results of and photophysical measurements and summarizes the research findings.

SYNTHESIS OF 1,3-DISUBSTITUTED ALKYNONES (LITERATURE REVIEW)

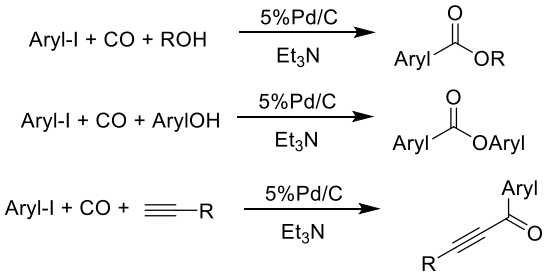
Many methods were developed for the synthesis of alkynyl ketones during the past century [1][2]. This chapter is dedicated for the most recent discoveries of the synthesis of alkynyl ketones.

The most common synthetical pathway towards 1,3-diarylalkynones in the current literature is the Sonogashira type reaction between alkynes and chloroanhydrides in the presence of $Pd(PPh_3)_2Cl_2$ and CuI [9][10][11][12][13] (Scheme 1).



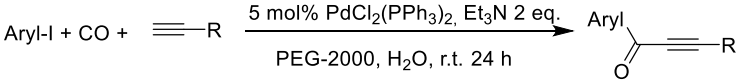
Scheme 1. General reaction between alkynes and chloroanhydrides.

Literature examples of carbonylative Sonogashira type reaction are also very common. For example Xia group reported alkoxycarbonylation of aryl iodides by using palladium on carbon catalyst and triethylamine as a base without any phosphine ligands [14]. They have also demonstrated recyclability of palladium catalyst and versatility of developed reaction conditions (Scheme 2). Esters or alkynones can be synthesized by this method from commercially available materials.



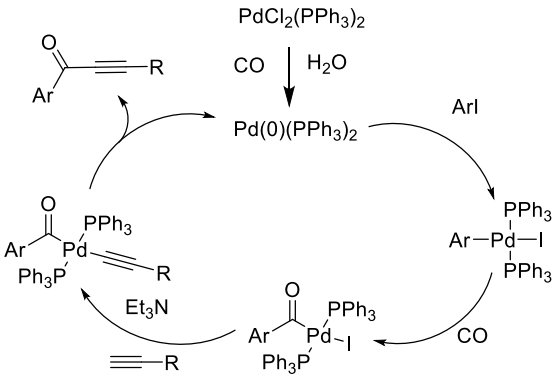
Scheme 2. Synthesis of esters and alkynones from aryl iodides.

Cai group demonstrated that PEG-2000 and $Pd(PPh_3)_2Cl_2$ mixture in the water is extraordinarily good catalytic system to perform carbonylative Sonogashira reaction of terminal alkynes with aryl iodides [15] (Scheme 3).



Scheme 3. Carbonylative Sonogashira reaction between terminal alkynes and aryl iodides.

Authors also provided possible mechanistic explanation of the reaction (Scheme 4). First Pd(2+) is reduced to Pd(0) species by CO and water. Then arylpalladium(2+) complex is provided by the oxidative addition of an aryl iodide to Pd(0)$(PPh_3)_2$ and subsequent insertion of carbon monoxide gives acylpalladium(2+) complex. Following transmetallation between acylpalladium(2+) complex and terminal alkyne in the presence of Et_3N and reductive elimination of alkynyl ketone regenerates palladium(0) and triphenylphosphine complex for the next catalytical cycle.



Scheme 4. Proposed explanation for the carbonylative coupling of aryl iodide and terminal alkyne.

Moreover Li group reported very high yielding MOF based catalyst (Pd(II)@ZrMOF-BIPY) for carbonylative Sonogashira coupling of aryl iodides with terminal alkynes that produces 1,3-diarylalkynones in high yields from broad scope of starting materials with electron donating and withdrawing groups [16].

Ali group [17] also developed Pd based catalyst for carbonylative Sonogashira reaction of alkyl alkynes and aryl iodides. They have invented the catalyst (Fig. 2) that is very impressive because of extraordinary low molar equivalents needed to perform the reaction – just 0.1 mol%.

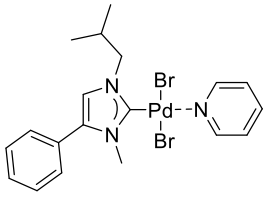


Figure 2. Pd–NHC–Py Complex catalyst for carbonylative Sonogashira coupling.

Moreover, literature examples exist where noxious carbon monoxide gas is replaced by formic acid as a source of CO in mild conditions to perform carbonylative Sonogashira cross-coupling reactions. Quite good yields (~80%) were reported for a very broad scope of substrates. Starting materials are usually aryl iodides and terminal alkynes. I_2 [18] or DCC [19] are used as formic acid decomposition promoters.

Several more exotic examples of carbonylative Sonogashira type synthesis of 1,3-diarylalkynones exist in scientific literature. For example Wu has published an article where diazonium salts instead of aryl iodides and 1,3-butadiene instead of PPh_3 were used to produce alkynones [20].

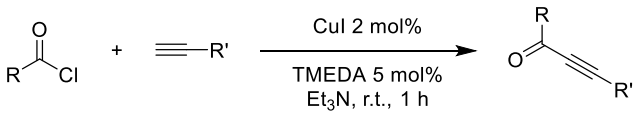
In 2015 Natour and Abu-Reziq have reported Mesoporous Silica Nanoparticle-Supported Palladium catalyst for carbonylative Sonogashira cross-coupling of aryl iodides and terminal alkynes [21]. The catalyst is very interesting because it can be separated from the reaction mixture by magnetic field.

Group of scientists from China developed palladium catalyst that can be easily separated from reaction mixtures by simple filtration and reused many times [22].

Chen and Li from Department of Chemistry, Tulane University, Canada developed an interesting method to synthesize alkynones in water media from terminal alkynes and acid chlorides that are known to be water sensitive. Surfactant – lauryl sulfate and base potassium carbonate were used to facilitate the reaction [23].

Ley group has developed method for the preparation of alkynones in flow reactor. $Pd(OAc)_2$ and diisopropylamine were used as a catalyst and a base accordingly [24]. Alkynones were further modified in the same reactor to furnish versatile heterocycles such as flavones, pyrimidines and pyrazoles.

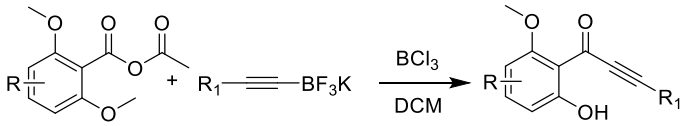
The more reactive nature of aroyl chlorides in comparison to aryl halides enable coupling reaction to proceed even without using any form of palladium. For example, H. He group developed coupling reaction of acid chlorides with terminal alkynes where CuI/TMEDA system acts as a catalyst. A wide substrate scope has been screened and very high yields (84 – 96 %) were achieved in most of the cases (Scheme 5) (R = Ph, *t*Bu, CO_2Et, 4-ClPh, 2-MePh, etc. R' = Ph, 4-BrPh, 2-ClPh, 4-MeOPh, etc.) [25].



Scheme 5. Coupling reaction of acid chlorides with terminal alkynes.

F. Zhang group developed phenol-formaldehyde resin-supported copper nanoparticles catalyst and showed its superior catalytic performance in the synthesis of alkynones via Sonogashira type reaction. Catalyst can also be recycled and used for more than ten times without significant loss of catalytic activity [26].

C. Taylor and Y. Bolshan studied preparation of sterically hindered alkynoylphenols [27]. Authors managed to synthesize desired alkynones by demethylative synthesis from mixed anhydrides and alkynyl trifluoroborates using 1.5 equivalents of BCl_3 in DCM (Scheme 6).

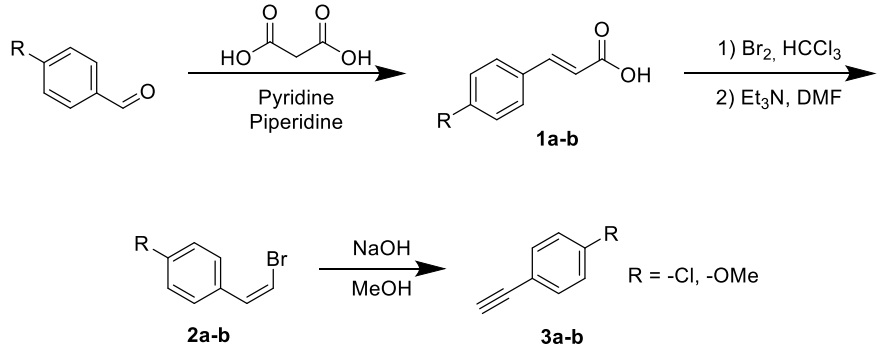


Scheme 6. Synthesis of *o*-demethylated ynones from mixed anhydrides.

SYNTHESIS OF 1,3-DISUBSTITUTED ALKYNONES

The 1,3-diarylakynones **7** that were necessary for the further work as starting materials were prepared by Sonogashira type coupling reaction from commercially available or prepared in laboratory substituted phenylacetylenes and aroyl chlorides. Sonogashira type reaction was chosen because it gives high and stable yields with broad substrate scope and workup is easy.

Arylacetylenes **3** were prepared from corresponding aldehydes by condensation with malonic acid [28] to afford cinnamic acids **1a-b** which were brominated and turned to cis β-bromostyrenes **2a-b** by decarboxylative elimination [29]. Cis β-bromostyrenes yielded acetylenes **3a-b** in good to moderate yields by treatment with sodium hydroxide in methanol at reflux temperature. It is worth to mention that only cis β-bromostyrenes participated in elimination reaction towards acetylenes (Table 1, Scheme 7).



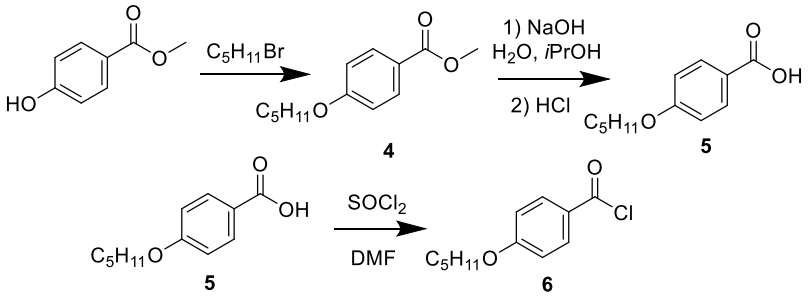
Scheme 7. General synthesis of substituted phenylacetylenes from corresponding aldehydes.

Table 1. Yields of synthesized phenylacetylenes and intermediates.

Entry	R	Yield, %
1	OMe	**1a** (79)
2	OMe	**2a** (85)
3	OMe	**3a** (60)
4	Cl	**1b** (92)
5	Cl	**2b** (73)
6	Cl	**3b** (80)

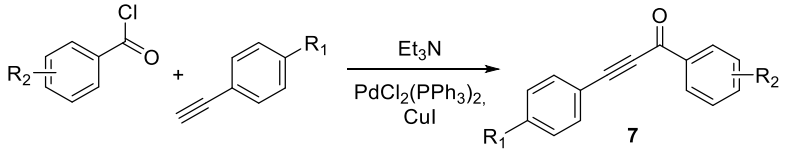
Aroyl chlorides were prepared from carboxylic acids by treatment with the excess of thionyl chloride and catalytic amount of dimethylformamide. In case

of 4-(pentyloxy)benzoyl chloride **6** (Scheme 8) synthesis was started from methyl 4-hydroxybenzoate. Phenolic OH has been alkylated with *n*PeBr in acetone with potassium carbonate as a base using modified literature procedure [30], followed by ester hydrolysis with sodium hydroxide in boiling water and isopropanol mixture. Free acid has been liberated by acidification of reaction mixture with conc. $HCl_{(aq)}$. After air drying chloroanhydride was formed by treatment with thionyl chloride and catalytical amount of DMF at room temperature [31].



Scheme 8. Synthesis of 4-(pentyloxy)benzoyl chloride from 4-hydroxybenzoate.

We have tested multiple methodologies for the synthesis of 1,3-disubstituted alkynones. For example, carbonylative Sonogashira type reaction between aryl iodides and aryl acetylenes [32] (carbon monoxide was generated in a separate vessel by dehydration of formic acid with concentrated sulfuric acid [33]) or reaction between aroyl chlorides and aryl acetylenes catalyzed by copper iodide [10]. But the best results were obtained by previously mentioned Sonogashira type coupling between aroyl chlorides and aryl acetylenes (Scheme 9) [34].



Scheme 9. The synthesis of 1,3-disubstituted alkynones.

Coupling reaction proceeded in decent or medium yields with all substrates (containing electron donating or electron withdrawing groups) (Table 2).

Table 2. The synthesis of 1,3-disubstituted alkynones.

Entry	R^1	R^2	Yield, %
1	OMe	H	**7a** (85)
2	OBu	H	**7b** (88)
3	OPe	H	**7c (**94)
4	OHex	H	**7d** (80)
5	H	H	**7e** (98)
6	Cl	H	**7f** (76)
7	OMe	*o*-OMe	**7g** (60)
8	OBu	*o*-OMe	**7h** (80)
9	OHex	*o*-OMe	**7i** (62)
10	F	*o*-OMe	**7j** (65)
11	OMe	*p*-OMe	**7k** (78)
12	OMe	*p*-CF_3	**7l** (80)
13	CF_3	*p*-OMe	**7m** (62)
14	CF_3	*p*-CF_3	**7n** (60)
15	OPe	*p*-OPe	**7o** (71)
16	Cl	*p*-OMe	**7p** (57)
17	OMe	*p*-Cl	**7r** (61)
18	OMe	*p*-CN	**7s** (86)
19	OMe	*p*-NO_2	**7t** (83)

CYCLIZATION OF 1,3-DISUBSTITUTED ALKYNONES TO ISOXAZOLES AND CHROMONES (LITERATURE REVIEW)

Isoxazoles are versatile heterocycles in pharmaceutical and material chemistry. Isoxazole ring is present in several bioactive natural products (muscimol [35] , ibotenic acid [36], cycloserine [37]) and in a large variety of unnatural pharmaceuticals, such as isocarboxazide [38], parecoxib [39], leflunomide [40], risperidone [41] and β-lactamase-resistant antibiotics cloxacillin, oxacillin, flucloxacillin and dicloxacillin [42][43] (Fig. 3).

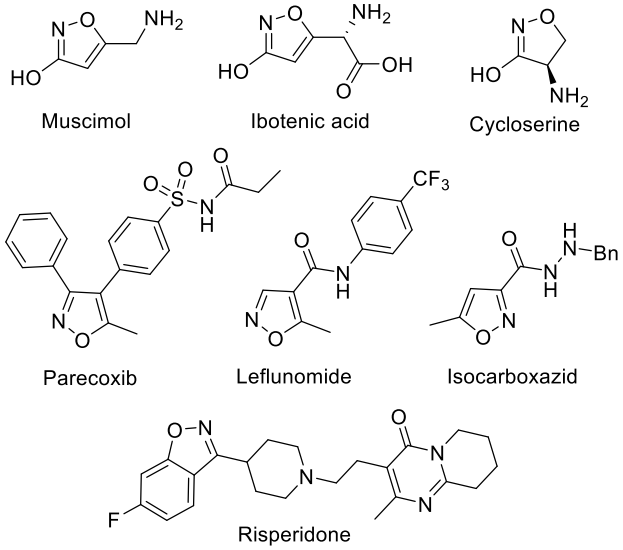
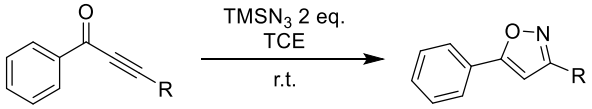


Figure 3. Isoxazole abundance in natural and artificial molecules.

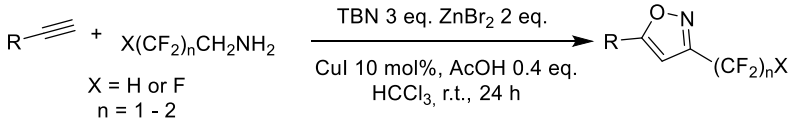
Isoxazoles are also very useful in material sciences [44] also as a coordinating ligands in transition metal complexes because of their flat structure and presence of two heteroatoms with external electron pairs [45]. Moreover, isoxazoles are considered as useful synthetic intermediates in total organic synthesis because of ability to participate in reactions as isosteres of 1,3-dicarbonyl compounds [46].

Recently Reddy group published new method for the synthesis of isoxazoles from ynones using trimethylsilyl azide as a source of nitrogen [47]. Authors claimed that reaction proceeds via hydroazidation of the alkyne and denitrogenative cyclization. Best results were obtained by using 2 equivalents of $TMSN_3$ in industrially very common solvent – trichloroethylene (Scheme 10).



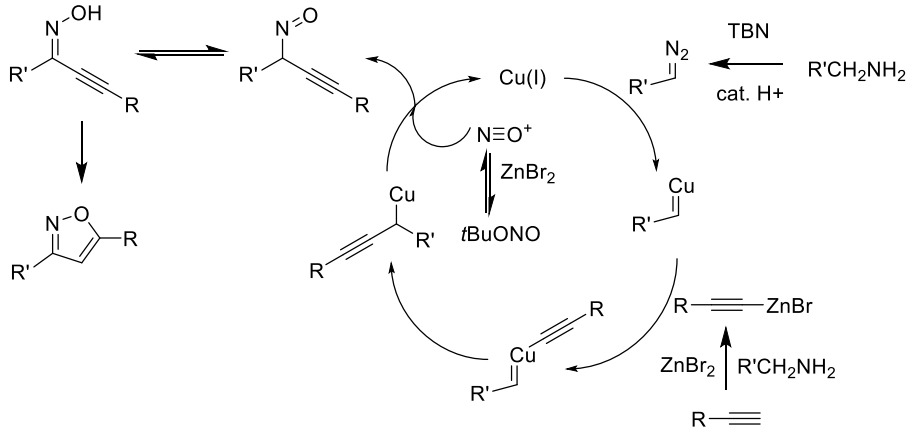
Scheme 10. Reaction of $TMSN_3$ with ynones to form isoxazoles.

Hu and coworkers developed one-pot reaction for the preparation of fluoroalkylated isoxazoles. Protocol utilizes commercially available amines and alkynes [48] (Scheme 11).



Scheme 11. Synthesis of fluoroalkylated isoxazoles.

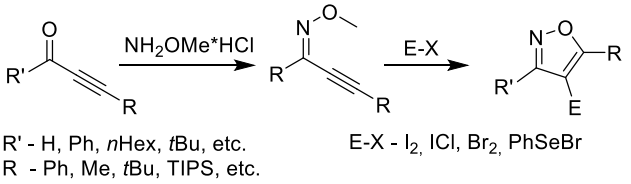
Authors also proposed reaction mechanism where they show an importance of all added reactants (Scheme 12). Reaction of amine with *t*Bu nitrite generates diazo compound which forms Cu-carbene. Zinc acetylide transmetalates with Cu-carbene and migratory insertion yields Cu-carbenoid. Further, nitrosonium ion (from *t*BuONO and $ZnBr_2$) captures Cu-carbenoid and after tautomerization yields oxime. Finally, 5-endo-dig cyclization of oxime takes place and generates isoxazole.



Scheme 12. Proposed reaction mechanism.

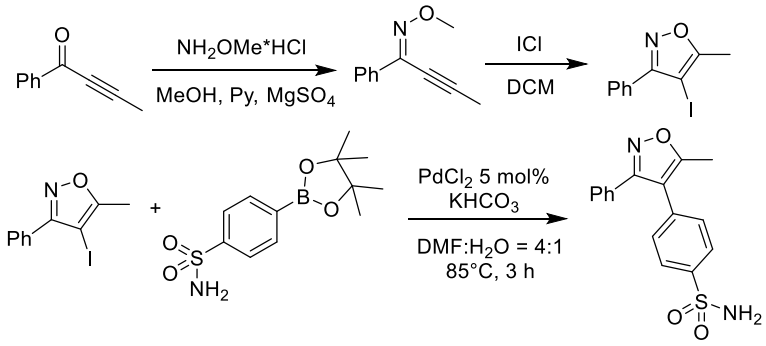
In 2005 R. Larock group reported synthesis of 3,5-disubstituted 4-halo(seleno)isoxazoles from 2-alkyn-1-one *O*-methyl oximes with ICl, I_2, Br_2 and PhSeBr [49]. *O*-methyl oximes were prepared by stirring the alkynone in

the presence of methoxylamine hydrochloride with pyridine and dehydrating agent Na_2SO_4 at room temperature using methanol as the solvent (Scheme 13).



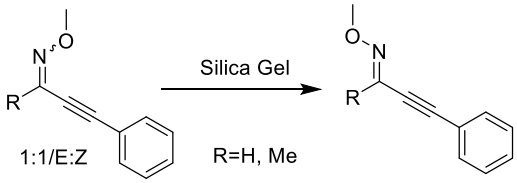
Scheme 13. Synthesis of 3,5-disubstituted 4-halo(seleno)isoxazoles.

J. P. Waldo and R. Larock reported the synthesis of 4-iodoisoxazoles by reaction of 2-alkyn-1-one *O*-methyl oximes with iodine monochloride [50]. They have also demonstrated versatility of 4-iodoisoxazoles by accomplishing synthesis of selective cyclooxygenase-2 inhibitor – valdecoxib [51] (Scheme 14).



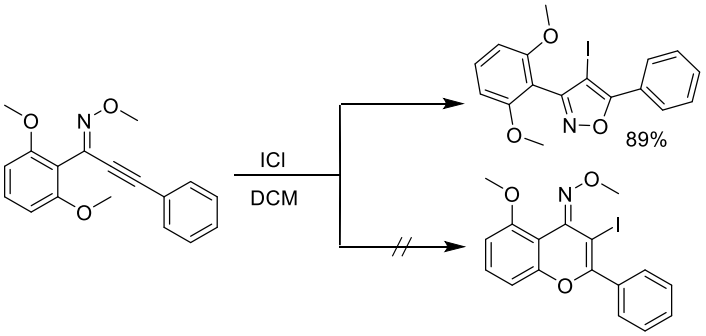
Scheme 14. Synthesis of 4-iodoisoxazoles and Valdecoxib.

Authors also noted that it is very important to have *Z*-isomer of *O*-methyl oxime because *E* isomer does not react under reported conditions. Interestingly *E* isomer formation was observed on silica gel when R is H or Me group (Scheme 15).



Scheme 15. Isomerization of *O*-methyl oximes on silicagel.

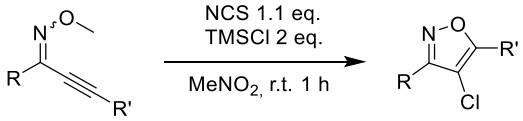
Even more, authors determined that steric bulk in ortho positions did not hinder the reaction. Also, 6-endo dig chromone oximes were not observed in this case because OMe group from methoxime part is more reactive and 5-endo dig isoxazole forms exclusively in a short reaction time (Scheme 16).



Scheme 16. 5-endo dig isoxazole formation.

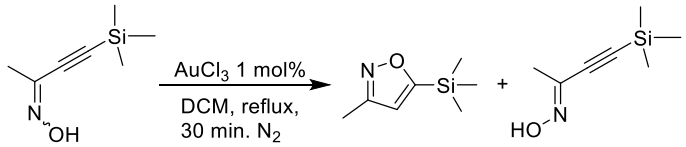
This method has its benefits and scope in organic synthesis because it does not require transition-metal catalysis and the final products contain functional groups which are suitable for further functionalization.

Ruchirawat and coworkers developed new methodology for the synthesis of 4-haloisoxazoles from (*E*/*Z*)-alkynyl-*O*-methyl oximes in the nitromethane solvent. Interestingly both isomers react under developed conditions [52] (Scheme 17). Authors propose that the reaction proceeds via Cl_2 (generated from NCS and TMSCl) induced cyclization.



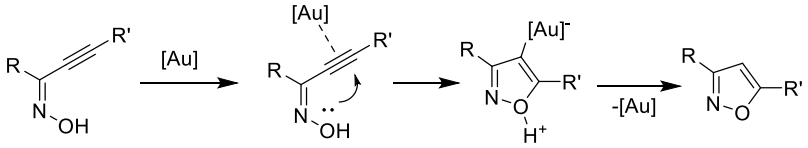
Scheme 17. Cyclization of (*E*/*Z*)-alkynyl-*O*-methyl oximes.

P. T. Perumal group developed gold (III) chloride catalyzed synthesis of isoxazoles from *α,β*-acetylenic oximes [53]. Oximes were prepared from alkynones with hydroxylammonium chloride and $NaHCO_3$ solution in methanol. Interestingly spontaneous cyclization did not occur. Importance of oxime isomerism for the reaction to proceed was also noted (Scheme 18).



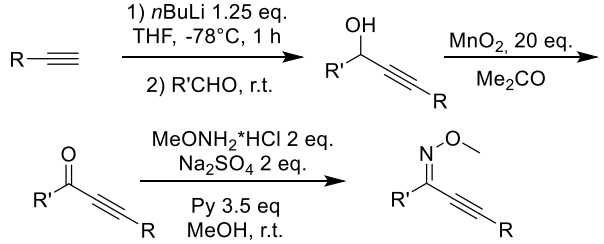
Scheme 18. Isoxazole formation.

Authors also proposed reaction mechanism. They claimed that reaction proceeded via pi activation of triple bond by carbophilic gold (III) chloride. It leads to pi complex which undergoes 5-endo-dig cyclization and protodeauration to afford the substituted isoxazole (Scheme 19).



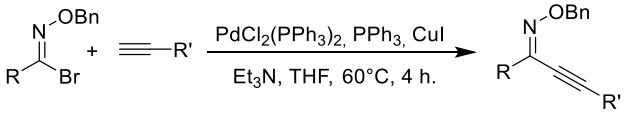
Scheme 19. Mechanism of isoxazole formation.

J. Ryu group developed direct room temperature synthesis of 4-fluoroisoxazoles from 2-alkynone *O*-methyl oximes [54]. Substrates for the reaction were synthesized from terminal alkynes by treatment with *n*BuLi and aldehyde. Oxidation of secondary alcohols gave alkynones which after treatment with hydroxylamine hydrochloride, pyridine and Na_2SO_4 gave desired 2-alkynone *O*-methyl oximes (Scheme 20).



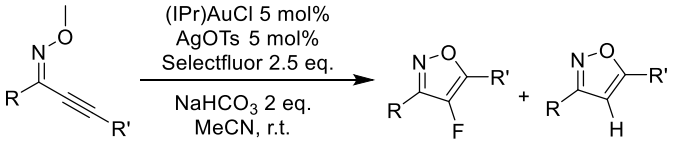
Scheme 20. Synthesis of substrates for the reaction.

Alternatively, 2-alkynone *O*-methyl oximes or 2-alkynone *O*-benzyl oximes can be prepared from *N*-alkoxyimidoyl bromides and terminal alkynes in one step palladium catalyzed cross coupling (R = Ph, 2-Furyl, 4-CF_3Ph, 4-MeOPh, etc., R' = TMS, Ph, *n*Bu, CH_2OTBS, etc.) (Scheme 21) [55].



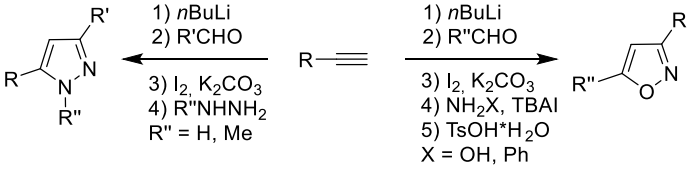
Scheme 21. Palladium catalyzed cross coupling of *N*-Alkoxyimidoyl bromides and terminal alkynes.

After screening of reaction conditions authors found the most efficient way to prepare 4-fluoroisoxazoles (Scheme 22). Selectfluor has been used as a source of fluorine, $NaHCO_3$ as a base and acetonitrile as a solvent. Reaction was driven by Ag and Au catalytical system.



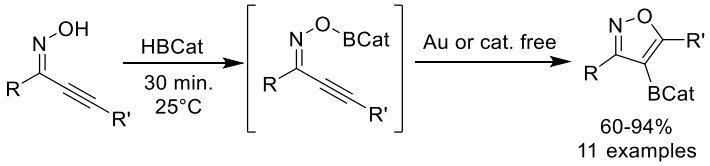
Scheme 22. Synthesis of 4-fluoroisoxazoles.

H. Togo group published one pot approach toward the synthesis of 3,5-disubstituted pyrazoles and isoxazoles from terminal alkynes and aldehydes [56]. After treatment of terminal alkyne with *n*BuLi aromatic aldehyde was added followed by subsequent addition of iodine and K_2CO_3 (in some cases other oxidants such as DIB or $Fe(NO_3)_3$ in the presence of TEMPO) after this step hydrazine or hydroxylamine was added to yield substituted pyrazoles or isoxazoles (Scheme 23).



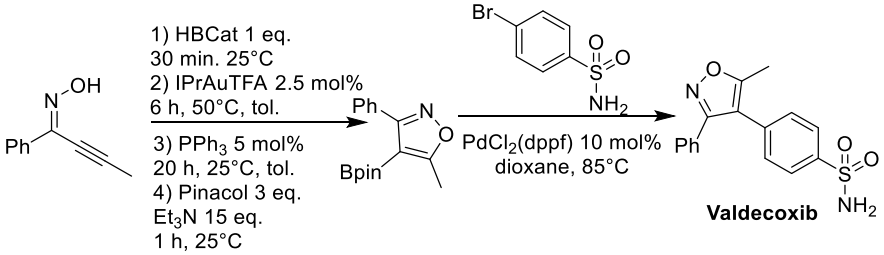
Scheme 23. Synthesis of 3,5-disubstituted pyrazoles and isoxazoles.

Blum group developed a new oxyboration strategy to convert oximes to borylated isoxazoles [57] (Scheme 24).



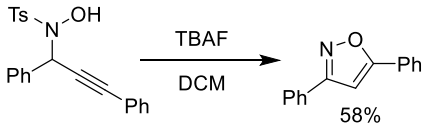
Scheme 24. Synthesis of borylated isoxazoles.

This reaction can procced at a room temperature with gold catalysis or just by simple heating. It is the first example of uncatalyzed oxyboration of C−C π bonds by B−O σ bonds and the second example of catalyzed oxyboration in scientific literature. Furthermore, authors performed gram scale experiment and showed applicability of this new methodology by synthesizing anti-inflammatory drug valdecoxib (Scheme 25).



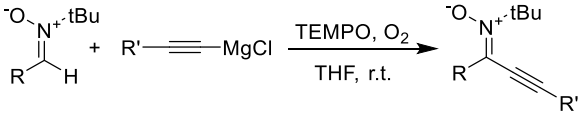
Scheme 25. Synthesis of Valdecoxib.

Reddy and coworkers developed methodology of synthesis of 3,5-disubstituted isoxazoles from propargylic alcohols [58]. Propargylic alcohols were synthesized from terminal acetylenes and aromatic aldehydes by using *n*BuLi in THF. Propargylic alcohols were transformed to propargylic *N*-hydroxylamines. These were easily cycloisomerized to the corresponding isoxazoles by treatment with TBAF in DCM (Scheme 26). Transformation was also achieved by using K_2CO_3 in MeCN or CsF in DCM. But yields were significantly lower (58% and 36% respectively).



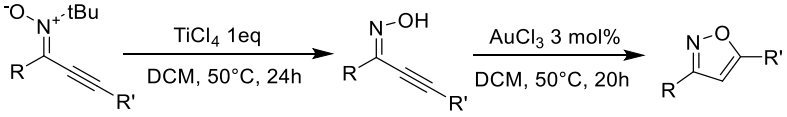
Scheme 26. Synthesis of 3,5-disubstituted isoxazoles.

S. Murarka and A. Studer reported one-pot synthesis of the alkynylated nitrones by the cross-coupling of nitrones and alkynyl-magnesium compounds using TEMPO as a catalyst and oxygen as oxidant [59] (Scheme 27).



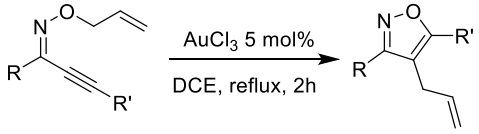
Scheme 27. Synthesis of alkynylated nitrones.

Alkynylated nitrones are easily transformed to regioisomerically pure 3,5-disubstituted isoxazoles by treatment with BCl_3 or $TiCl_4$ and $AuCl_3$. Or catalytically with $Zn(OTf)_2$ [60]. After *t*Bu cleavage alkynylated nitrones can be cyclized to isoxazole derivatives (Scheme 28).



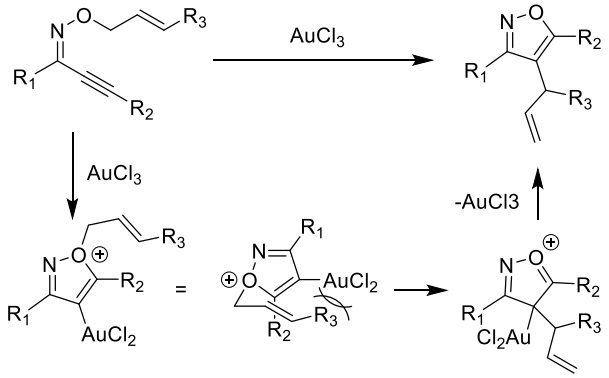
Scheme 28. Synthesis of 3,5-disubstituted isoxazoles.

O. Miyata group developed gold-catalyzed cyclization and subsequent Claisen-type rearrangement to afford 3,4,5-trisubstituted isoxazoles in a direct manner [61] (Scheme 29).



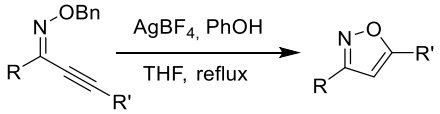
Scheme 29. Synthesis of 3,4,5-trisubstituted isoxazoles.

Possible reaction pathway was also provided by the authors (Scheme 30).



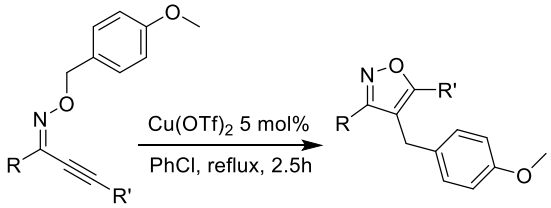
Scheme 30. Possible pathway of gold-catalyzed reaction.

Okiko Miyata group developed silver catalyzed cyclization of alkynyl oxime ethers to yield 3,5-disubstituted isoxazoles (R = Ph, H, CO_2Me, 4-MeOPh, etc. R' = *n*Bu, Ph, CH_2OAc, CH_2OH, etc.) (Scheme 31). This new method was applied to the synthesis of a biologically active isoxazolecarboxylic acid [62].



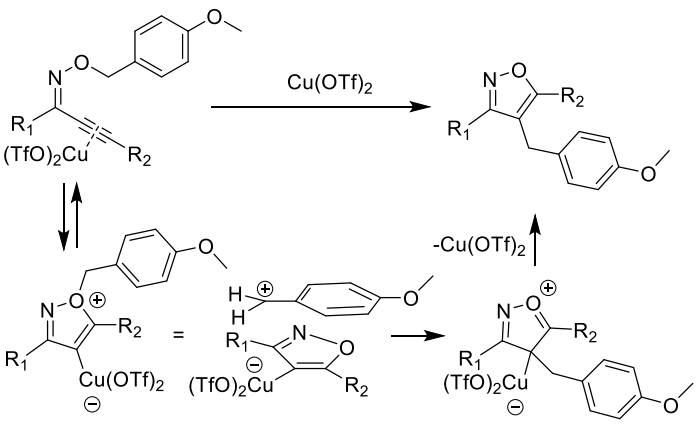
Scheme 31. Silver catalyzed cyclization and scope.

Moreover, O. Miyata group developed catalytic synthesis of 3,4,5-trisubstituted isoxazoles from *O*-arylmethyl alkynyl oxime ethers by treatment with 5 mol% of $Cu(OTf)_2$ in chlorobenzene. They have also tested different catalysts like gold or silver salts but copper triflate seems to be the most active in this particular case [63] (Scheme 32).



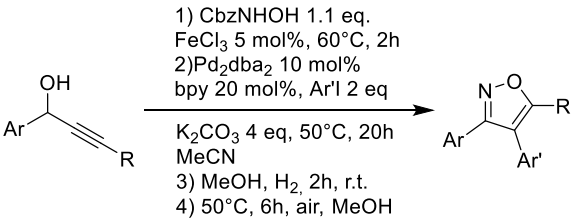
Scheme 32. Synthesis of 4-arylmethylisoxazoles.

Authors Explain that 1,3-migration of the arylmethyl group proceeds in a similar manner as in the previous example with $AuCl_3$ catalysis (Scheme 33).



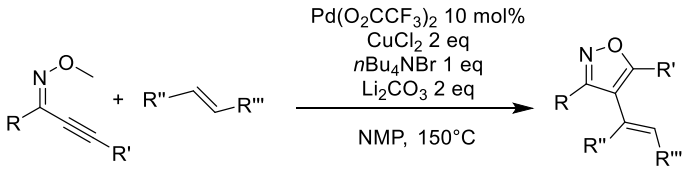
Scheme 33. Possible reaction pathway.

E. Vrancken and J. Campagne group developed one pot four step synthesis of 3,4,5-trisubstituted isoxazoles form propargylic alcohols [64]. Reaction conditions were noted (Scheme 34) authors claim that it is important to maintain provided sequence of adding reactants. Otherwise only starting materials were recovered and product formation was not observed.



Scheme 34. Synthesis of 3,4,5-trisubstituted isoxazoles.

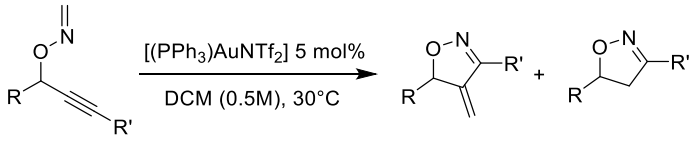
Y. Chen group developed palladium-catalyzed, cascade 5-endo-dig cyclization−alkenylation of 2-Alkyn-1-one *O*-methyl oximes to substituted isoxazoles [65] (Scheme 35) (R = *t*Bu, Ph, *p*-CN-Ph, etc. R' = Ph, *p*MePh, etc. R''= CHO, Ph, H, CO_2Et, etc. R''' = H, OAc, Me).



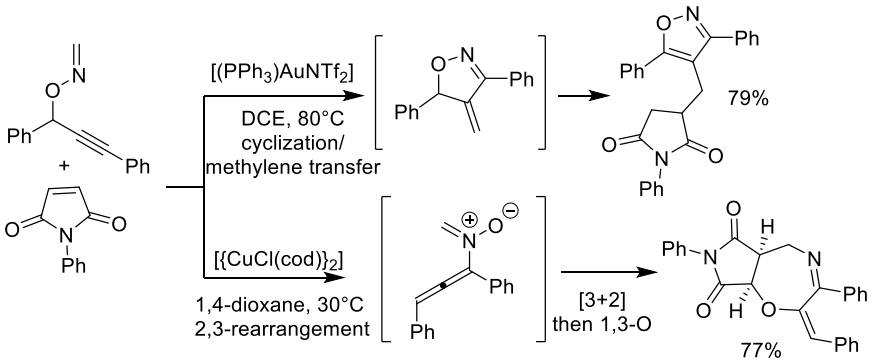
Scheme 35. Preparation of 3,4,5-Trisubstituted Isoxazoles.

Authors noted that the addition of 1 eq. of *n*Bu_4NBr significantly increased the yield of the desired 4-alkenyl-3,4,5-trisubstituted isoxazoles.

Prof. dr. Itaru Nakamura and coworkers developed gold catalyzed rearrangement of *O*-propargylic formaldoximes to 4-methylene-2-isoxazolines (Scheme 36). Scientists also studied differences between Au and Cu catalysis and have found that the cascade reaction in the presence of gold proceeds by cyclization/methylene transfer and a subsequent ene reaction. And with Cu catalyst it proceeds via 2,3-rearrangement [66] (Scheme 37) (R = Ph, Cy, H, *n*Pr, etc. R' = Ph, Cy, H, pMeOPh, etc.).

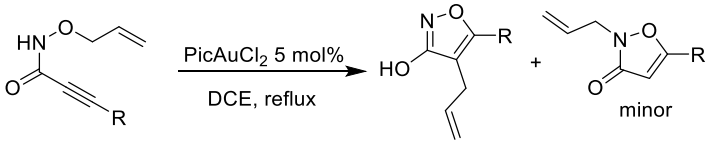


Scheme 36. Gold catalyzed rearrangement of *O*-propargylic formaldoximes.



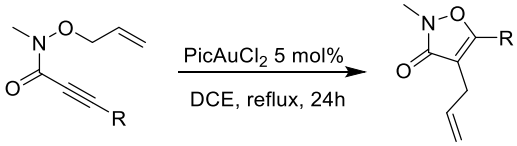
Scheme 37. Differences between Au and Cu catalysis.

O. Miyata and colleagues developed gold-catalyzed sequential reaction for the preparation of isoxazole-3-ones and 3-hydroxyisoxazoles from *O*-allyl hydroxamates bearing an alkyne moiety [67] (Scheme 38) (R = *n*Bu, Cy, Me, *p*FPh, *p*MeOPh, etc.).



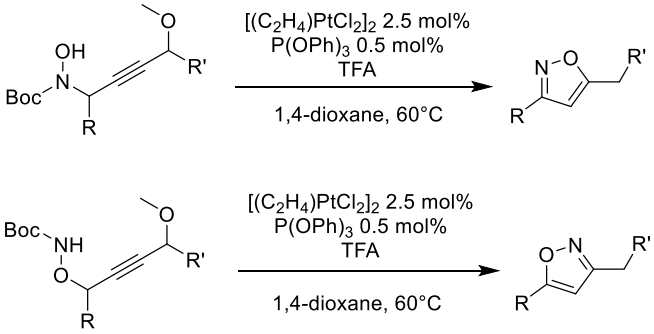
Scheme 38. Gold-catalyzed cyclization–rearrangement reaction of hydroxamate.

Cyclization of *N*-methylhydroxamates yielded isoxazolones only (Scheme 39) (R = Ph, Cy, 4-F-Ph, etc.).



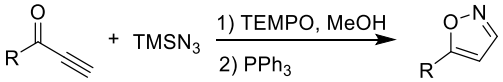
Scheme 39. Cyclization and rearrangement reaction of *N*-methylhydroxamates.

Paul A. Allegretti and Eric M. Ferreira developed a novel synthesis of regioisomeric isoxazoles via Pt-carbene intermediate formed from substrates with oxygen or nitrogen-based nucleophiles (Scheme 40) (R = Et, Cy, *i*Bu, $BnCH_2$. R' = $Ph(CH_2)_3$, $TBSO(CH_2)_3$, etc.) [68].



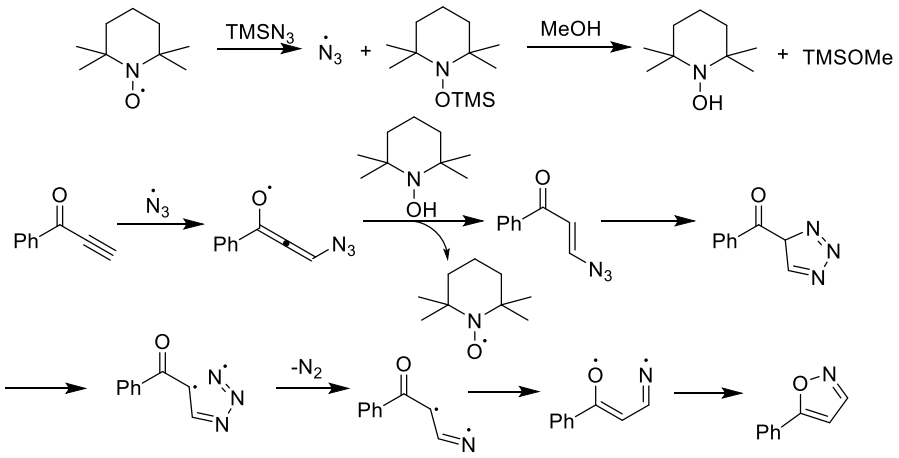
Scheme 40. Synthesis of isoxazoles from propargylic *N*-hydroxycarbamates and propargylic *N*-Boc amino ethers.

H. Wang and Y. Pan developed TEMPO-catalyzed synthesis of 5-substituted isoxazoles from $TMSN_3$ and terminal propargylic ketones [69] (Scheme 41).



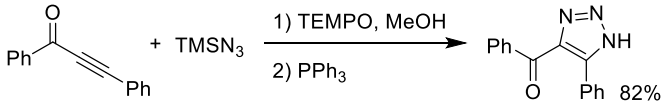
Scheme 41. Reaction of $TMSN_3$ with propargylic ketones.

Authors claimed that reaction proceeds via radical pathway (Scheme 42).



Scheme 42. Proposed radical reaction mechanism.

Unfortunately, authors have found that non-terminal propargylic ketones could not yield desired product under reported reaction conditions. 4,5-Disubstituted 1,2,3-triazoles were synthesized instead of isoxazoles (Scheme 43).



Scheme 43. 4,5-Disubstituted 1,2,3-triazole formation.

According to literature examples 1,3-disubstituted alkynones are good starting materials not for isoxazoles only but for many more heterocycles including chromones and flavones (Fig. 4).

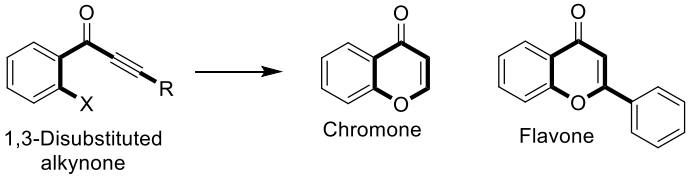
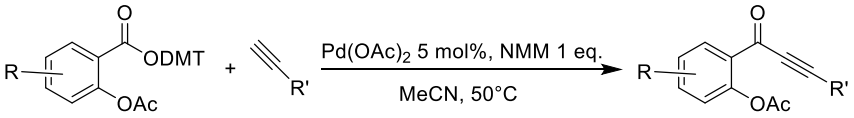


Figure 4. 1,3-Disubstituted alkynones as starting materials towards chromones and flavones.

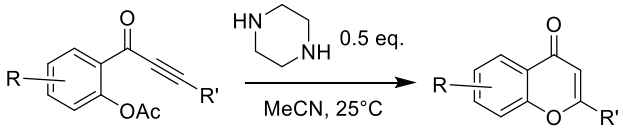
Structures of flavones and chromones are mainly found in natural compounds derived from plant material [70]. These substances exhibit strong biological activity such as antimicrobial, anticancer, antiinflamatory, antioxidant properties [71]. Many modern and classical synthetic methods of flavones and chromones are published in the scientific literature.

W. Zhang and Z. Gao group suggested an interesting approach towards alkynones and synthesis of flavones and γ-benzopyranones by Pd catalyzed couplings of "superactive esters" and terminal alkynes [72] (Scheme 44).



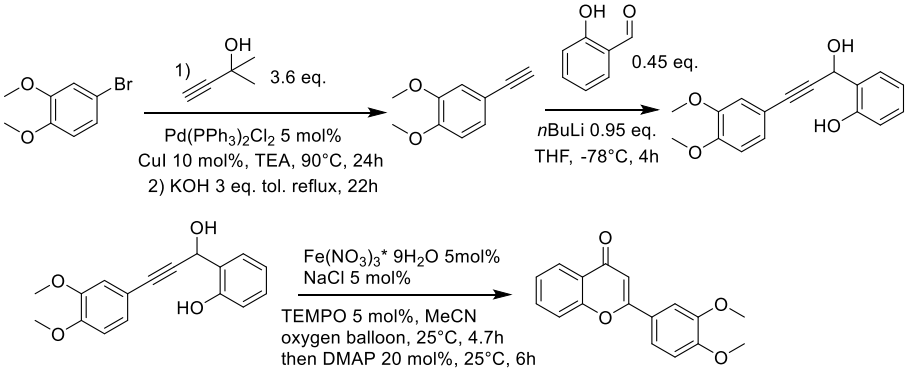
Scheme 44. Synthesis of alkynones.

Reaction mechanism has been studied by analysis of reaction mixture by ESI–MS. Results unveiled two palladium triazine species - the adduct of palladium acetate and triazine ester and oxidative addition intermediate. Scientists performed screening of bases for cyclization of obtained alkynones to flavones or γ-benzopyranones and have found that piperazine in acetonitrile gives superior results (Scheme 45).



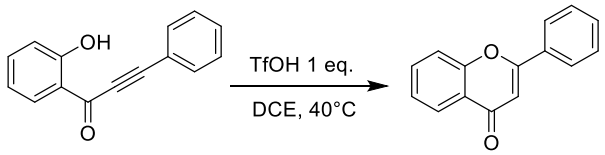
Scheme 45. Synthesis of flavones or γ-benzopyranones.

M. Jia with coworkers developed synthesis of γ-benzopyranones by iron-catalyzed aerobic oxidation of propargylic alcohols and base catalyzed subsequent cyclization [73]. Authors tested various bases and have found that DMAP gives superior selectivity and yield of γ-benzopyranones. Authors have also demonstrated the application of newly developed method for the synthesis of naturally occurring 3',4'-dimethoxyflavone (Scheme 46).



Scheme 46. Synthesis of naturally occurring 3',4'-dimethoxyflavone.

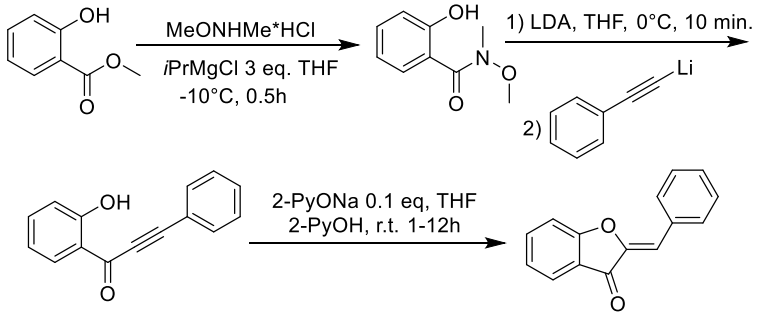
T. Doi with coworkers published triflic acid catalyzed synthesis of γ-benzopyranones from *o*-alkynoylphenols [74]. Interestingly only 6-endo cyclization product was observed without formation of any 5-exo benzofuranone derivatives (Scheme 47).



Scheme 47. 6-Endo cyclization product formation.

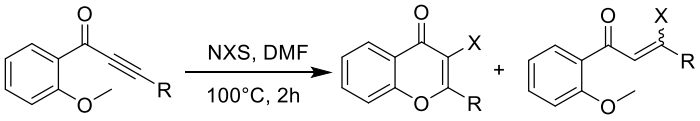
Authors explained that reaction possibly proceeds via TfOH addition and formation of vinyl triflate which is good Michael acceptor and it opens the door for 1,4 intramolecular addition of phenolic OH group followed by the elimination of trifluoromethanesulfonic acid.

J. Lee invented and published conditions to synthesize 5-exo cyclized product selectively [75]. Alkynones were synthesized through Weinreb amide and cyclization to aurones was performed in THF solvent using sodium 2-pyridyloxide as a base (Scheme 48).



Scheme 48. Synthesis route of aurones.

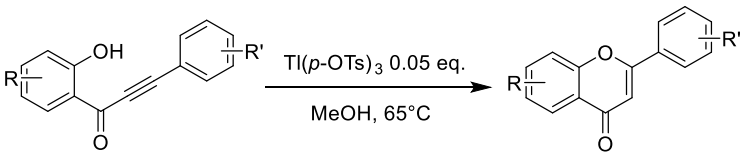
M. Wu group have found that treatment of 2-(1-aryl-3-propynoyl)anisoles NCS or NBS gives 3-halogenated flavones in moderate yields. Authors claim that optimal conditions for 3-halogenated flavones is treatment of *o*-methoxy alkynones with NCS or NBS in DMF solvent at 100°C for 2 hours [76] (Scheme 49) (R = $(CH_2)_4CH_3$, *p*-CNPh, 2-Pyridinyl, *p*-MePh, etc. X = Cl, Br).



Scheme 49. Synthesis of 3-halogenated flavones and aurone intermediates.

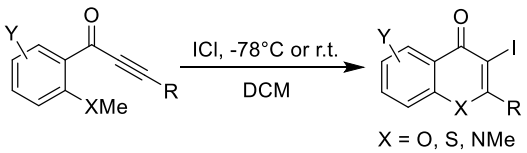
Authors noted that when *O*-Benzyl or *O*-TBDMS analogs of starting materials are used. Dominant formation of aurones instead of 3-halogenated flavones is observed.

J. Lee and H. Kim developed thallium catalyzed method for the synthesis of flavones in high yields. Scientists state that starting materials - *o*-(alkynon-1-yl)phenols are cyclized at 65°C via 6-endo cyclization to flavone derivatives in methanol solvent with 0.05 equivalent of Tl(*p*-OTs)$_3$ as a catalyst only [77] (Scheme 50).



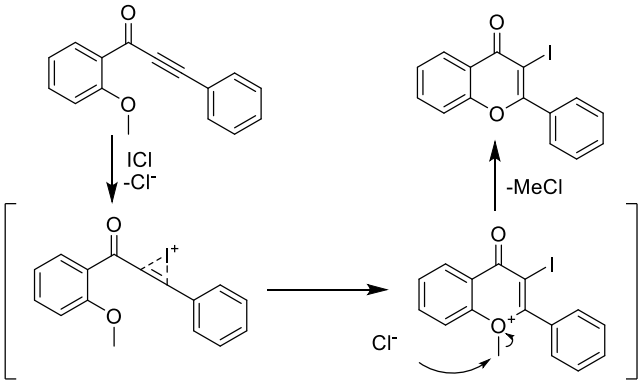
Scheme 50. 6-Endo cyclization of *o*-(alkynon-1-yl)phenols.

C. Zhou, A. V. Dubrovsky and R. C. Larock discovered that 2-methoxyaryl-containing alkynones can be cyclized to 3-iodochromones by treatment with ICl at -78°C using DCM as a solvent. Even more authors discovered that 2-methylthioaryl-containing alkynones and 2-methylaminoaryl-containing alkynones also gives 6-endo cyclization products – Iodothiochromenones and iodoquinolinones correspondingly by similar ICl-induced cyclizations [78] (Scheme 51).



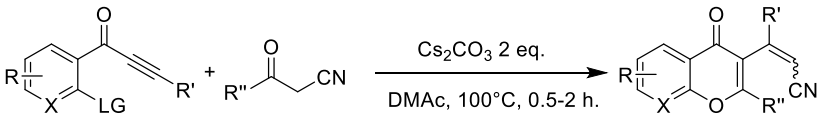
Scheme 51. Synthesis of 3-iodochromones and analogs.

Authors also provided proposed mechanism. First of all, iodonium intermediate is formed. Secondly nucleophilic attack of the oxygen on the activated iodonium intermediate proceeds to produce a chromonium salt which reacts further with Cl^- anion (S_N2 displacement) to produce 3-iodochromone and one molecule of MeCl as a side product (Scheme 52).



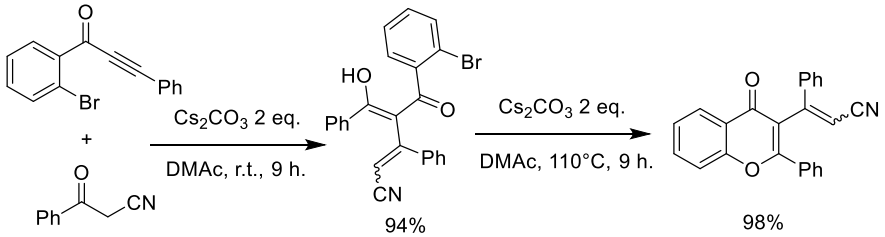
Scheme 52. Proposed reaction mechanism.

Y. Li and coworkers developed base-promoted insertion of alkynes into C-C σ-bonds of alpha cyano ketones to furnish highly functionalized conjugated olefins or chromone derivatives [79] (Scheme 53) (X = CH, N, R = H, 6-F, 7-F, 6,7-diMeO, etc. R' = Ph, Alkyl, subst. Ph, R'' = Ph, *t*Bu).



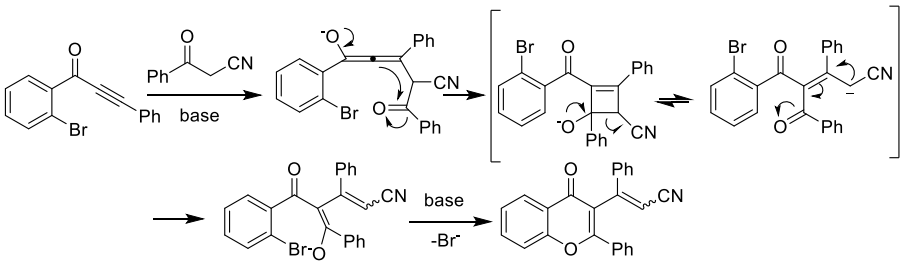
Scheme 53. Synthesis of chromone derivatives.

To clarify reaction mechanism authors performed experiment at room temperature and isolated insertion product which cyclize to chromone derivative after heating with cesium carbonate in DMAc (Scheme 54).



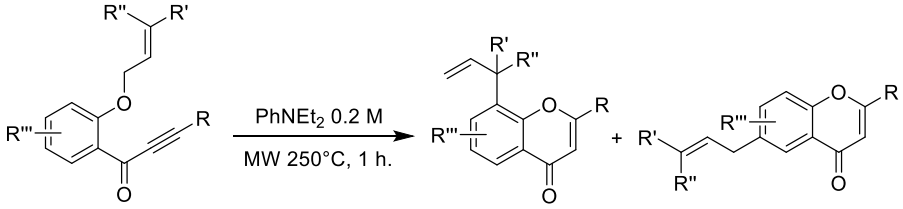
Scheme 54. Temperature control experiment.

Finally, authors proposed mechanism of the reaction (Scheme 55).



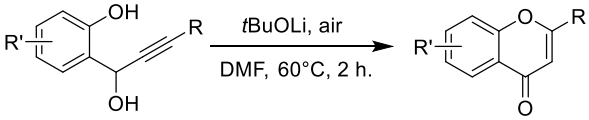
Scheme 55. Plausible reaction mechanism.

Schmidt and others developed microwave-promoted Claisen/Cope rearrangement/6-endo-dig cyclization of allyl, dimethylallyl and prenyl ethers derived from o-acylphenols [80]. Interestingly authors have found that allyl and dimethylallyl ethers gave 8-substituted chromones and prenyl ethers gave 6-prenylated chromones (Scheme 56).



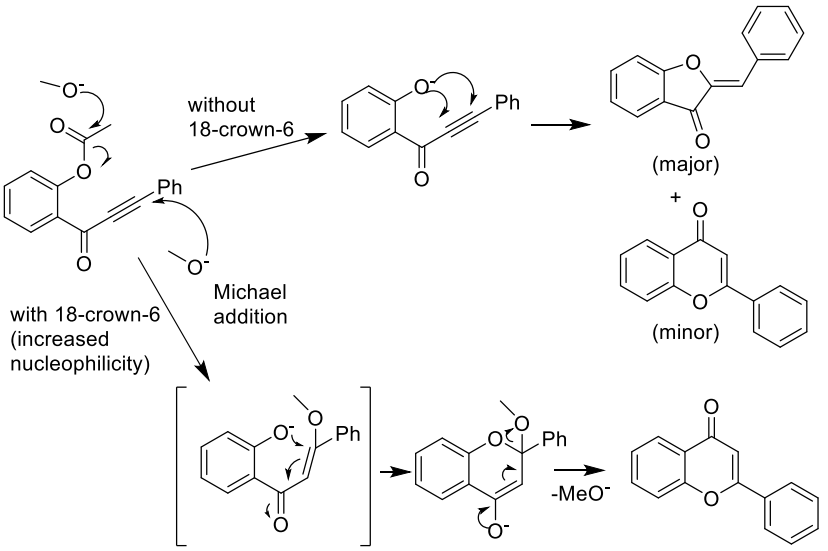
Scheme 56. Microwave-promoted Claisen/Cope rearrangement/6-endo-dig cyclization.

Z. Wang group developed a cascade oxidative synthesis of the chromone derivatives by cyclization of *o*-alkynoylphenols with *t*BuOLi as a mediator and oxygen from ambient air as an oxidant [81] (Scheme 57).



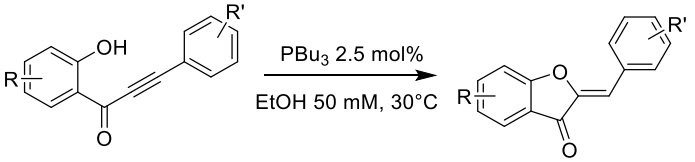
Scheme 57. Oxidative synthesis of chromones.

Y. Chang developed an efficient method for the synthesis of γ-benzopyranones and flavones [13]. Authors studied cyclization reaction with various bases and measured amounts of obtained 5-exo-dig and 6-endo-dig cyclization products. They found that addition of 18-crown-6 ether to the reaction mixture facilitates 6-endo dig product formation. Authors also observed that changing the base to MeOK gives pure flavones without any 5-exo-dig cyclization products (Scheme 58).



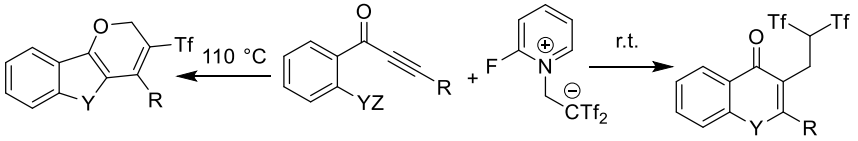
Scheme 58. Possible cyclization reaction mechanism.

T. Doi group have found that *o*-alkynoylphenols participates in 5-exo cyclization reaction to form aurones in superior yields and selectivity in DMF as a solvent and tributylphosphine as a catalyst [82] (Scheme 59).



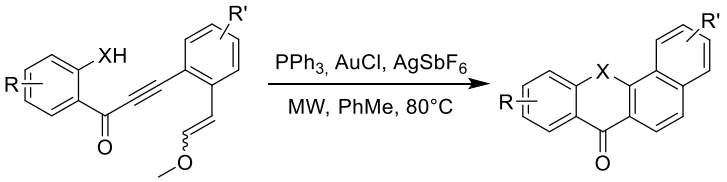
Scheme 59. 5-exo cyclization of *o*-alkynoylphenols.

Dr. Patricia Delgado-Martínez with coworkers have found that functionalized alkynones can be activated by $Tf_2C{=}CH_2$. By tweaking reaction conditions authors managed to synthesize series of bis(triflyl)flavones, bis(triflyl)thioflavones, bis(triflyl)selenoflavones, (triflyl)benzothienopyrans, (triflyl)benzoselenophenopyrans, (triflyl)vinyl aurones, and (triflyl)pyranoindoles [83] (Scheme 60) (YZ = OH, OMe, NHG, SMe, SeMe).



Scheme 60. Synthesis of "triflones".

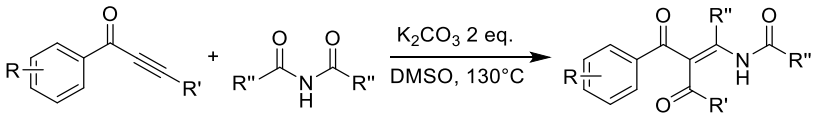
M. Cheng group developed gold catalyzed synthesis of of 12*H*-benzo[a]xanthen-12-ones and benzo[a]acridin-12(7*H*)-ones which core motifs xanthone and acridone are structurally similar to flavones [84] (Scheme 61) (X = O, NH).



Scheme 61. Synthesis of 12*H*-benzo[a]xanthen-12-ones and benzo[a]acridin-12(7*H*)-ones.

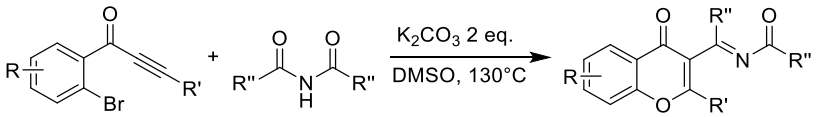
Starting substrate was synthesized in five steps from commercially available *o*-bromobenzaldehyde by establishing Sonogashira coupling then Wittig reaction followed by deprotection of alkyne with methanolic potassium carbonate and attachment of salicylic aldehyde using *n*BuLi as a base and finally oxidation with activated MnO_2 in DCM.

Yanzhong Li and coworkers developed the synthesis of substituted enamides and chromones by transition-metal-free reaction of alkynones bearing an ortho-bromo-substituted aryl ring and C–N σ-bonds of imides [85]. Several base and solvent combinations were screened but K_2CO_3 and DMSO gave superior results. Scope of tetrasubstituted enamides were synthesized (Scheme 62).



Scheme 62. Synthesis of tetrasubstituted enamides.

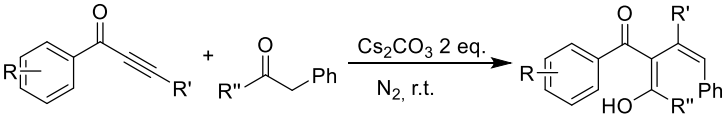
When *o*-bromo-substituted alkynones were used reaction gave chromones in superior yields (Scheme 63).



Scheme 63. Synthesis of substituted chromones.

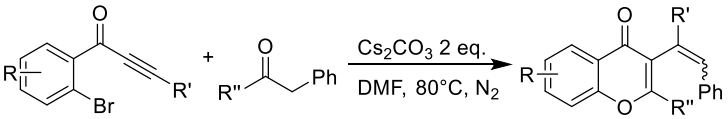
Yanzhong Li developed method to synthesize multi-substituted chromones and hydroxydienones by transition-metal free insertions of alkynes into carbon–carbon σ-bonds of ethanones [86]. Authors claim that it is the first example in scientific literature where insertion reaction of isolated carbon–

carbon triple bond into carbon–carbon σ-bond with active methylene compounds bearing only one electron-withdrawing group occurs. When alkynones without an ortho-bromo-substituted aryl ring are used hydroxydienone compounds are formed (Scheme 64) (R = H, *p*Me, *p*Br, R' = Ph, *p*-substituted-Ph, R'' = Ph, *p*-substituted-Ph).



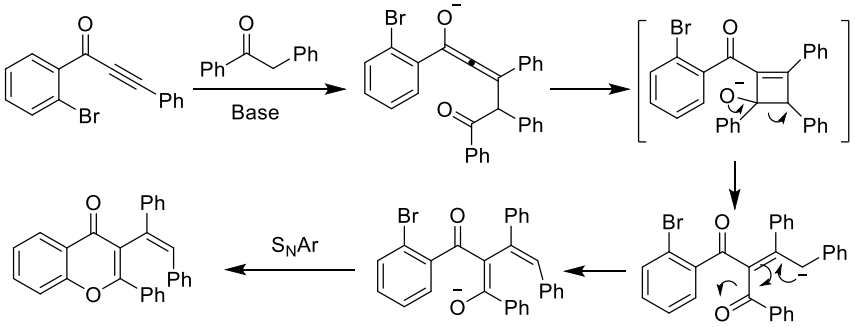
Scheme 64. Synthesis of hydroxydienones.

When *o*-bromo-substituted alkynones were used reaction gave chromone derivatives in excellent yields (Scheme 65).



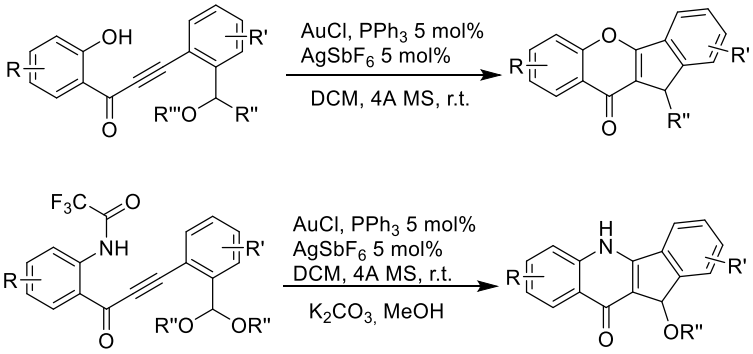
Scheme 65. Synthesis of chromones.

Plausible reaction mechanism was also discussed in paper. Authors contemplated that starting alkynone is attacked by ethanone in the presence of a base to give intermediate which undergoes an intramolecular nucleophilic addition/fragmentation reaction cascade which results in an alkyne insertion into the C–C *σ*-bond of the ethanone that gives intermediate which after enolization and nucleophilic aromatic substitution (S_NAr) yields desired chromone (Scheme 66).



Scheme 66. Plausible reaction mechanism.

M. Cheng group developed new tandem cyclization strategy for the synthesis of indeno-chromen-4-ones and indeno-quinolin-4-ones. Reaction is gold-catalyzed and authors claim that hydrogen bond existing between the hydroxyl group (or the amide group) and the carbonyl group plays essential role in controlling the selectivity of product formation [87] (Scheme 67).

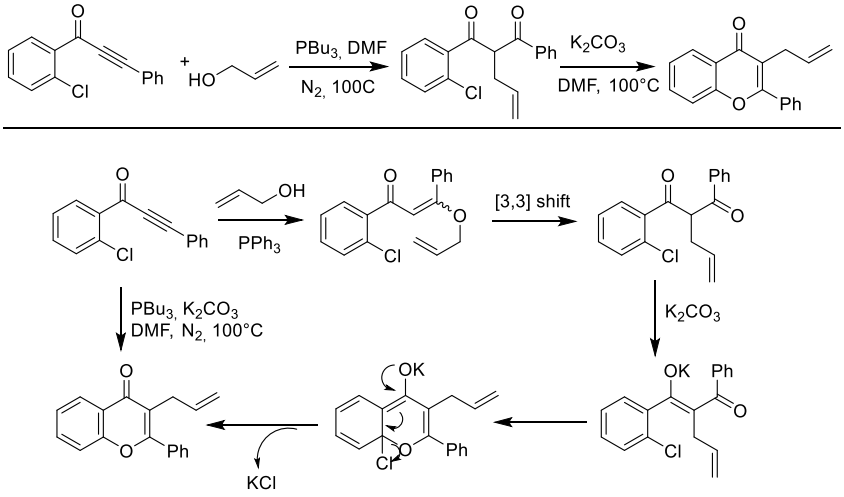


Scheme 67. Synthesis of indeno-chromen-4-ones and indeno-quinolin-4-ones.

Xuesong Wang, Guolin Cheng and Xiuling Cui developed metal free approach to 3-allyl-chromones from allylic alcohols and alkynones [88]. Optimal reaction conditions are: PBu_3 (only 10 mol%) and K_2CO_3 as a base in DMF solvent at 100°C and nitrogen atmosphere (Scheme 68).

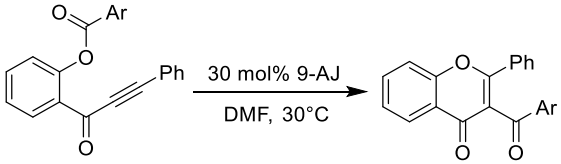
Scheme 68. Synthesis of 3-allyl-chromones.

Authors also provided plausible reaction mechanism. It seems that reaction proceeds via a tandem Michael addition Claisen rearrangement and *O*-arylation (Scheme 69).



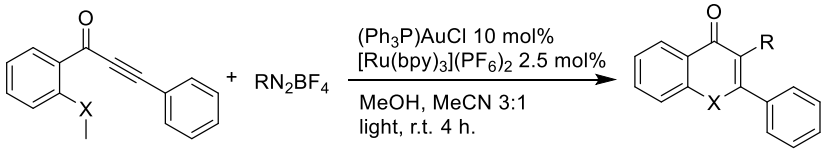
Scheme 69. Proposed reaction mechanism.

T. Doi and coworkers developed the synthesis of 3-aroylflavones from acylated *o*-alkynoylphenols [89]. Authors have found that DMAP in DMF catalyzes such reaction and after screening different bases developed optimal conditions. 30 mol% of 9-AJ (9-Azajulolidine) as a base in DMF at 30°C gave the best yields and selectivity towards 3-aroylflavones (Scheme 70).



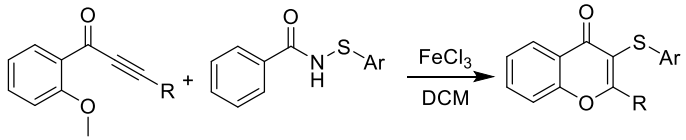
Scheme 70. Synthesis of 3-aroylflavones.

Lunaa group have studied gold and ruthenium photoredox catalyzed and visible light-promoted reactions of alkynes having heteroatom in the structure and arenediazonium salts. Many substituted heterocycles were synthesized including isocoumarins, benzosultams and flavones [90] (Scheme 71) (X = O, S, R = Ph, 4-BrPh, 4-(CO_2Et)Ph, 4-ClPh, 4-CF_3Ph).



Scheme 71. Synthesis of 3-aryl-thioflavones and 3-aryl-flavones.

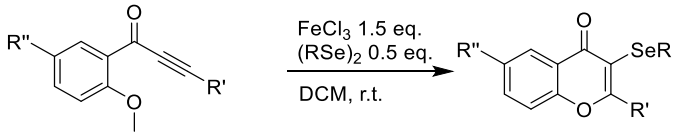
X. Zhang group developed regioselective cyclization of alkynyl aryl ketones with *N*-arylthiobenzamides to 3-sulfenylflavone derivatives. The reaction is promoted by ferric chloride [91] (Scheme 72).



Scheme 72. Synthesis of 3-sulfenylflavones.

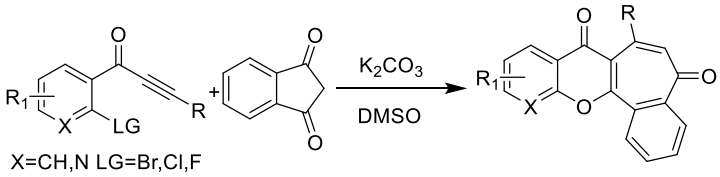
Authors noted that only 6-endo-dig cyclization product was observed without formation of any 5-exo-dig substituted aurones.

G. Zeni group developed the synthesis of 3-organoselenylchromenones from alkynones and diselenides via $FeCl_3$ promoted intramolecular 6-endo-dig cyclization [92]. Authors claim that methodology is very regioselective and gives only six-membered regioisomers (Scheme 73). Another advantage is that reaction proceeds at room temperature.



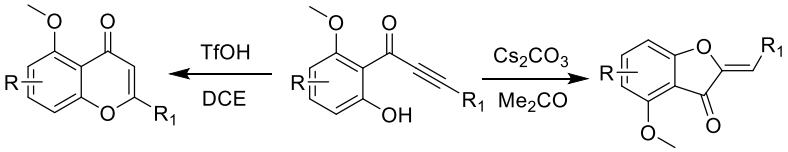
Scheme 73. Cyclization reaction with diselenides.

Y. Li with coworkers developed ring expansion reaction of indene-1,3-dione with alkynyl ketones under transition-metal-free conditions [93]. Authors have found that optimal conditions for the synthesis of chromone derivatives from alkynones are K_2CO_3 (3 equivalents) in DMSO at 110°C (Scheme 74).



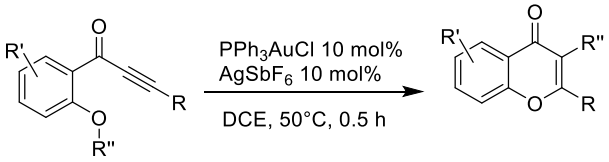
Scheme 74. Synthesis of chromone derivatives.

o-Alkynoylphenol derivatives were cyclized to flavone derivatives under acidic conditions in DCE at 80°C. Aurones were synthesized from the same *o*-alkynoylphenols using Cs_2CO_3 in acetone (Scheme 75) [27].



Scheme 75. Synthesis of flavone and aurone derivatives.

N. Gouault group from France have investigated the gold-catalyzed intramolecular addition of ethers to alkynes. Various substituted chromones were synthesized using newly developed method [94] (Scheme 76, Table 3).

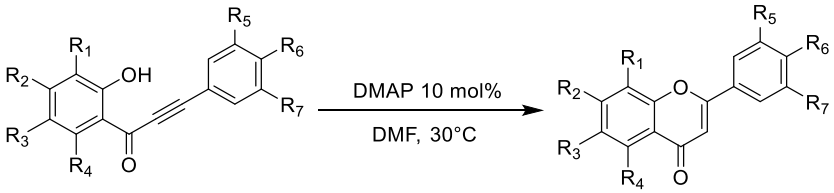


Scheme 76. Synthesis of flavones.

Table 3. Scope of flavones synthesized by N. Gouault group.

Entry	R''	R'	R	Yield, %
1	$PhCH_2$-	3-MeO-	*n*Pr-	45
2	$PhCH_2$-	H-	*n*Pr-	31
3	$PhCH_2$-	3,5-Br-	*n*Pr-	40
4	$PhCH_2$-	3-Allyl-	*n*Pr-	38
5	$PhCH_2$-	H-	4-MeOPh-	25
6	4-ClBn-	H-	*n*Pr-	40
7	4-MeOBn-	H-	*n*Pr-	0
8	Allyl-	H-	Ph-	38
9	Allyl-	H-	H-	35
10	Et-	H-	*n*Pr-	0
11	Et-	H-	Ph-	0

Takayuki Doi and colleagues developed method to synthesize flavone derivatives in very high yields from *o*-alkynoylphenols without synthesizing 5-exo cyclized aurones [95]. After performing lots of experiments authors have found that the most optimal conditions for the synthesis of flavone derivatives are using 10 mol% of DMAP in DMF solvent at room temperature R_1-R_5 = H or OMe (Scheme 77).

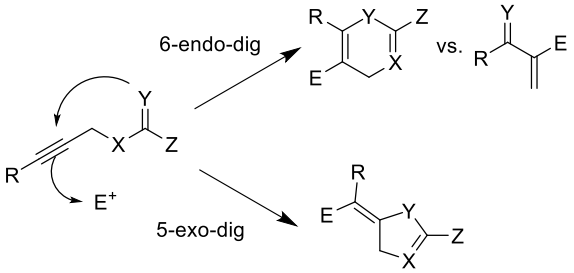


Scheme 77. Synthesis of flavone derivatives.

REACTIONS OF 1,3-DIARYLALKYNONES TOWARDS ALKOXYMETHYL SUBSTITUTED ISOXAZOLES AND CHROMONES

It is known that alkynones can be cyclized to isoxazole or chromone derivatives by using transition metal salts and complexes or electrophilic reagents such as ICl by activating alkyne functionality [96][97].

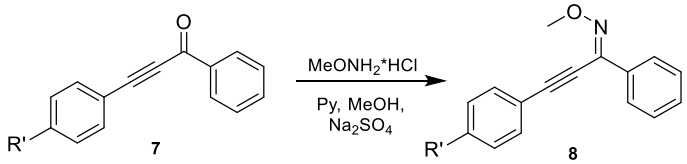
Several years ago, our group reported about the generation of electrophilic oxocarbenium ions and its use in transformations of functionally substituted alkynes (Scheme 78) [98][6].



Scheme 78. Use of oxocarbenium ions in transformations of functionally substituted alkynes.

We have decided to investigate electrophilic oxocarbenium ions as potential cyclization promoters of 1,3-diarylalkynones **7** and *O*-methyl oxime derivatives **8**.

First of all, starting materials were synthesized from corresponding alkynones **7**. (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyl oximes **8** were prepared by reacting alkynones and methoxyamine hydrochloride with pyridine in MeOH with Na_2SO_4 (Scheme 79, Table 4). Yields of the reaction were moderate to good. Interestingly, when pyridine was substituted by triethylamine no desired product **8** formed. Instead Michael addition to triple bond product was obtained. It is also known from the literature that when 1,3-diarylakynones react with methoxyamine without pyridine - l,4-addition product is formed [99].



Scheme 79. Synthesis of (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyl oximes.

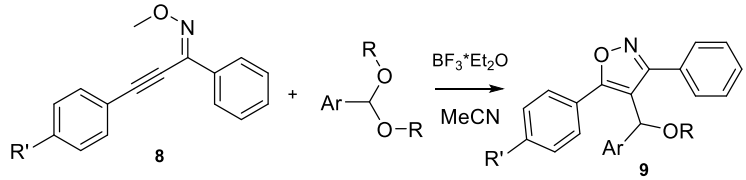
Table 4. Scope of synthesized methoximes **8**.

Entry	Starting material	R'	Yield, %
1	**7a**	OMe	**8a** (81)
2	**7b**	OBu	**8b** (78)
3	**7c**	OPn	**8c** (70)
4	**7d**	OHex	**8d** (66)
5	**7e**	H	**8e** (78)
6	**7f**	Cl	**8f** (73)

It is known from the literature that oxocarbenium ions can be generated from acetals by activating them with different Lewis acids [100][101]. We have chosen compound **8a** for screening of optimal reaction conditions because **8a** has alkyne-methoxime functionality and MeO group in *p* position of phenyl ring near the triple C≡C bond which makes it favorable substrate for cyclization with electrophiles.

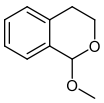
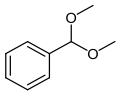
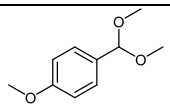
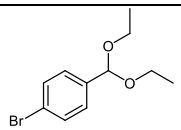
Several Lewis acids were screened: BF_3*Et_2O, $FeCl_3$, $AgSbF_6$, SbF_5, BBr_3, TMSOTf in different solvents (MeCN, DCM, DCE, THF, CH_3NO_2) at different reaction temperatures. It was found that **8a** with 1 equivalent of BF_3*Et_2O in MeCN at room temperature gave the best yield of desired isoxazoles **9**.

Various (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyl oximes reacted with aromatic acetals under optimized conditions. Full conversion of starting materials **8** was reached in ~15 min. Oxocarbenium ion triggered cyclization reaction proceeded very smoothly without formation of many impurities or tars. After workup with sodium bicarbonate solution, extraction and chromatography purification, final isoxazoles were isolated in good yields (Scheme 80, Table 5).



Scheme 80. Synthesis of alkoxymethyl groups containing isoxazoles.

Table 5. Scope of synthesized isoxazoles **9**.

Entry	Starting material	Acetal	R’	Yield, %
1	**8a**		OMe	**9a** (57)
2	**8b**		OBu	**9b** (43)
3	**8c**		OPn	**9c** (84)
4	**8d**		OHex	**9d** (58)
5	**8e**		H	N.R.
6	**8f**		Cl	N.R.
7	**8a**		OMe	**9e** (55)
8	**8b**		OBu	**9f** (59)
9	**8d**		OHex	**9g** (58)
10	**8a**		OMe	**9h** (79)
11	**8b**		OBu	**9i** (48)
12	**8c**		OPn	**9j** (66)
13	**8d**		OHex	**9k** (47)
14	**8a**		OMe	**9l** (58)
15	**8d**		OHex	**9m** (59)
16	**8a**		OMe	**9n** (77)
17	**8c**		OPn	**9o** (30)
18	**8d**		OHex	**9p** (56)

It is worth to mention that cyclization reaction towards isoxazoles proceeded smoothly with alkynones where triple bond is activated by electron-donating alkoxy groups only. Alkynones without such substituents for example chlorosubstituted phenyl or unsubstituted phenyl ring containing alkynones did not participate in cyclization and remained unreactive at all. It can be explained by resonance stabilization of the vinylic carbocation forming after the addition of oxocarbenium ion to the triple bond (Fig. 5).

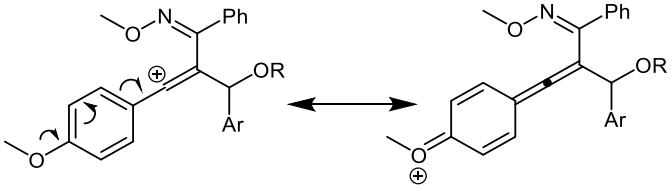
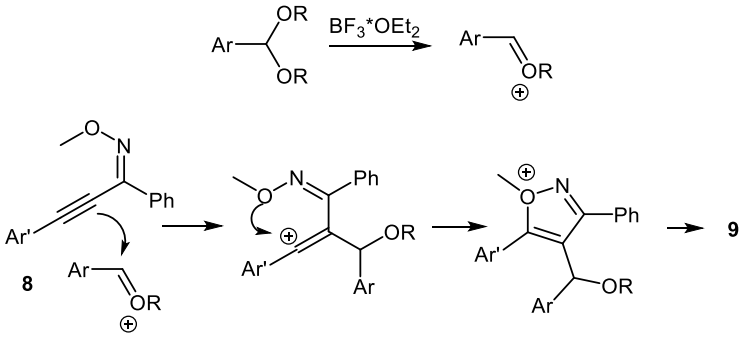


Figure 5. Resonance stabilization of the vinylic carbocation.

From the mechanistic point of view, it seems that at the beginning of the reaction generation of oxocarbenium ion by cleavage of C-O bond of starting acetal by BF_3*Et_2O takes place. Secondly formation of vinylic carbocations occur when electrophiles are trapped by electron rich alkynes. The subsequent 5-*endo*-dig cyclization leads to isoxazolium salt. Finally, isoxazoles are generated by removal of methyl group (Scheme 81).



Scheme 81. Plausible mechanism of oxocarbenium ion mediated cyclization.

Moreover, we have tested our newly developed reaction conditions on 3-aryl-1-(2-methoxyphenyl)prop-2-yn-1-ones that have methoxy group in close proximity to the triple bond similarly like (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyl oximes (Fig. 6).

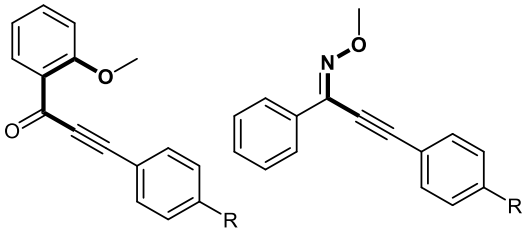
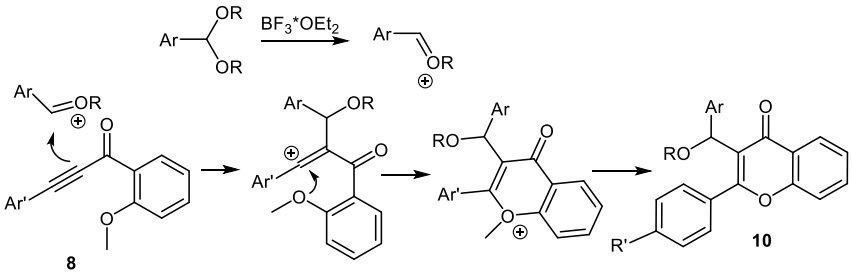


Figure 6. Isosteric 3-aryl-1-(2-methoxyphenyl)prop-2-yn-1-ones and (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyl oximes.

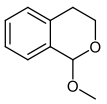
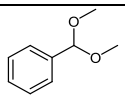
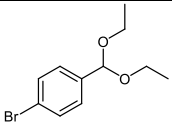
When 3-aryl-1-(2-methoxyphenyl)prop-2-yn-1-ones were mixed with BF_3*Et_2O in MeCN at room temperature 6-e*ndo*-dig cyclization took place and chromonium salts were formed (Scheme 82).



Scheme 82. Formation of chromonium salts and 6-e*ndo*-dig cyclization towards 3-alkoxyarylmethyl-2-aryl-*4H*-chromen-4-ones **10**.

Finally, smooth removal of the methyl group generated 2-aryl-*4H*-chromen-4-ones **10** with alkoxyarylmethyl groups in the 3rd position (Scheme 82). Interestingly, yields were good and the outcome of reactions did not depend on the presence of electron donating or acceptor groups on the substituted phenyl ring next to the C≡C triple bond (Table 6).

Table 6. Scope of synthesized 3-alkoxyarylmethyl-2-aryl-*4H*-chromen-4-ones - **10**.

Entry	Starting material	Acetal	R'	Yield, %
1	**7g**		OMe	**10a** (99)
2	**7h**		OBu	**10b** (88)
3	**7i**		OHex	**10c** (70)
4	**7j**		F	**10d** (97)
5	**7g**		OMe	**10e** (83)
6	**7h**		OBu	**10f** (79)
7	**7i**		OHex	**10g** (80)
8	**7g**		OMe	**10h** (76)
9	**7g**		OMe	**10i** (82)

To sum up, we have found that (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyl oximes **8a-f** and 3-aryl-1-(2-methoxyphenyl)prop-2-yn-1-ones **7g-j** are cyclized to substituted isoxazoles **9a-p** and 2-aryl-*4H*-chromen-4-ones **10a-i** correspondingly by treatment with oxocarbenium ions generated from acetals and BF_3*Et_2O in MeCN.

BUILDING OF THIOPHENE RING CONTAINING MOLECULES FROM 1,3-DISUBSTITUTED-ALKYNONES AND ALKYNOATES (LITERATURE REVIEW)

Thiophene is often observed as a part of the structure in pharmaceuticals [102] [103] [104] [105]. For example, methaphenilene is known antihistamine and anticholinergic agent tiagabine is used for treatment of epilepsy. Anti-inflammatory, anti-HIV and anticancer agents based on thiophene are also known. Thiophene ring is also abundant in antipsychotic and anxiolytic drugs such as well-known in psychiatry olanzapine and thienodiazepines with thienotriazolodiazepines (Fig. 7).

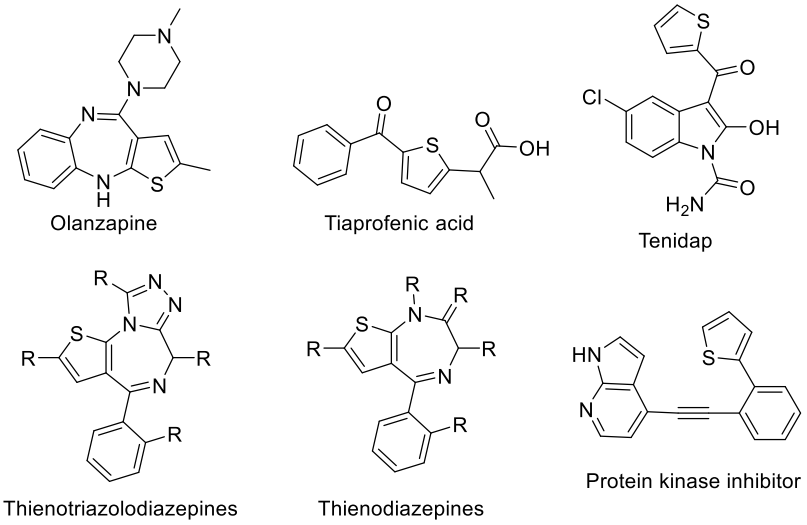


Figure 7. Notable examples of thiophene containing drugs.

Furthermore, thiophene containing structures are frequently applied in electronic and optical materials [106][107][108][109]. Polythiophene itself or modified polythiophenes such as PEDOT:PSS (Fig. 8) are very attractive and versatile materials for electronics because they form transparent, flexible and conductive layers [110][111][112].

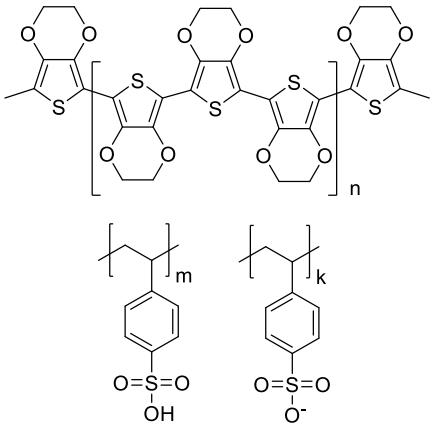


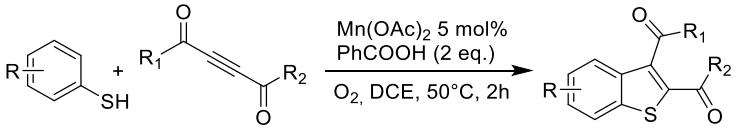
Figure 8. PEDOT:PSS electroconductive polymer.

Moreover, several reports on the emissive properties of monomeric thiophenes exist [113][114]. These studies led to the application of thiophenes in three-dimensional optical storage [115] and AIE [116][117].

Many synthetical methods of thiophene heterocycle are reported in scientific literature. Thiophenes are usually built from acyclic precursors in majority of the reported literature [118].

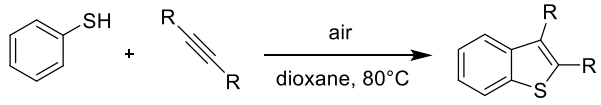
Following in this chapter the most recent developments of the syntheses of thiophenes by cyclization of alkynes or alkynones with sulfur containing molecules or sulfur itself are reviewed.

in 2013 Z. Li group developed an efficient direct intermolecular oxidative cyclization between thiophenols and alkynes towards benzothiophenes [119] (Scheme 83). $Mn(OAc)_2$ was used as a catalyst and O_2 as an oxidant. It is believed that reaction proceeds via radical pathway.



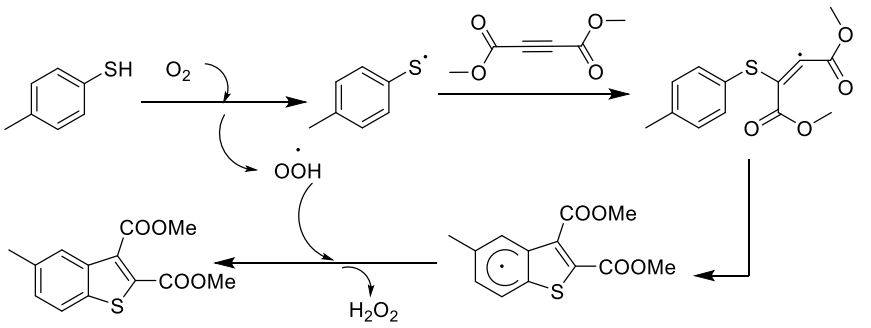
Scheme 83. Cyclization of thiophenols to benzothiophenes.

C. Huo and his coworkers developed air promoted intermolecular annulation of alkynes with thiophenols to form benzothiophenes [120]. No catalyst or additive is needed for reaction to proceed. Dioxane has been screened as the best performing solvent and air oxygen as sufficient oxidant (Scheme 84).



Scheme 84. Annulation of alkynes with thiophenols.

Authors also provided reaction mechanism which claim that reaction proceeded radically. Interestingly, that hydrogen peroxide was produced as byproduct (Scheme 85).

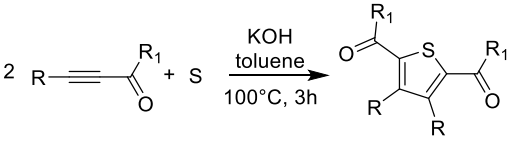


Scheme 85. Proposed reaction mechanism.

B. Konig reported the photocatalytic reaction of *o*-methylthio-arenediazonium salts with alkynes which yields substituted benzothiophenes. Large substrate scope was tested. Regioselectivity and yields were high. Green light irradiation activates eosin Y dye and it initiated the radical photoredox reaction [121] (Scheme 86).

Scheme 86. Photocatalytic cyclization *o*-methylthio-arenediazonium salts with alkynes.

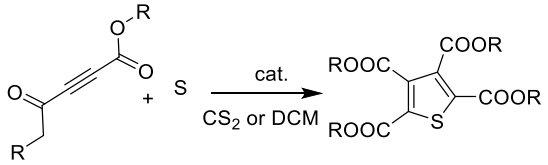
In 2015 H. Liu [122] developed base-Induced [2+2+1] cycloaddition reaction between alkynes and elemental sulfur. Interestingly reaction proceeds without reducing, oxidizing agents or metal catalysts (Scheme 87).



Scheme 87. Reactions of various alkynones or alkynoates to thiophenes.

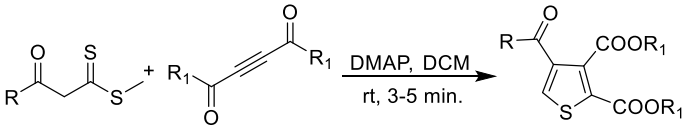
R. Hosseinpour and A. Alizadeh developed method for the synthesis of tetraalkyl 2,3,4,5-thiophenetetracarboxylate derivatives [123]. Dialkyl acetylenedicarboxylates react with elemental sulfur in the presence of

pyridine, triethyl phosphite, isoquinoline or 1-methyl-1*H*-imidazole. DCM or CS_2 is used as a solvent (Scheme 88).



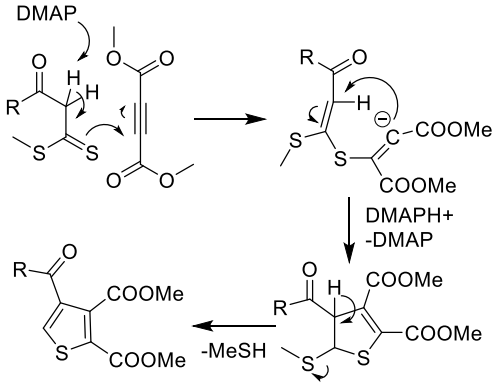
Scheme 88. Synthesis of tetraalkyl 2,3,4,5-thiophenetetracarboxylate derivatives.

M. Shankar Singh group developed one-pot two-component [3 + 2] cycloaddition/annulation reaction for synthesis of thiophenes which are highly substituted [124]. After screening they found that optimal base and solvent for the reaction to proceed are DMAP and DCM (Scheme 89). Thiophenes forms at room temperature in a very short manner of time which makes these conditions very favorable for scale up.



Scheme 89. Mild reaction conditions for substituted thiophene synthesis.

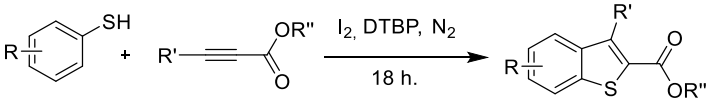
Plausible reaction mechanism has been also suggested. It showed that only catalytical amount of DMAP was needed to accomplish full conversion (Scheme 90). Reaction intermediate lost methyl mercaptan in the last stage to yield substituted thiophene ring.



Scheme 90. Plausible mechanism of the reaction.

H. Wang group [125] developed novel iodine-catalyzed method for the synthesis of benzothiophenes. Starting materials are substituted thiophenols

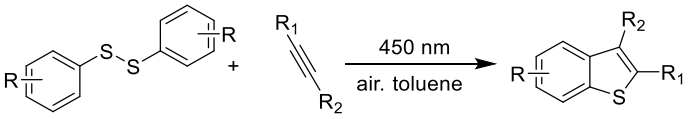
and alkynes. Reaction proceeds under solvent- and metal-free conditions (Scheme 91).



Scheme 91. Reaction of alkynes with subst. thiophenols.

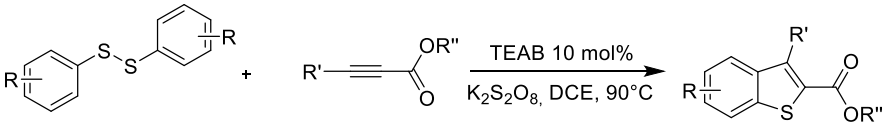
Researchers have found that thiophenols are oxidized and forms electrophilic species – PhSI which react further.

Ming Yan group developed very similar reaction conditions but their reaction is promoted by light. Oxygen from air is also necessary as an oxidant [126]. No heating is required (Scheme 92).



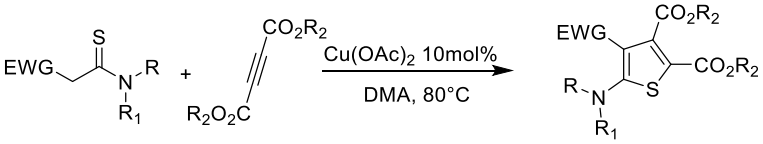
Scheme 92. Light promoted annulation of alkynes with thiophenols.

H. Wang group developed green and efficient Et_4NBr-catalyzed method for the synthesis of benzothiophenes via cascade reactions of alkynes with substituted disulfides [127] (Scheme 93). High functional group tolerance has been experimentally proved. Authors claim that reaction proceeds through S–S bond cleavage and alkenyl radical cyclization.



Scheme 93. Et_4NBr-catalyzed synthesis of benzothiophenes.

Wei-Ping Deng with colleagues reported Cu(II)-catalyzed synthesis of 2-aminothiophenes from thioamides with alkynoates under an air atmosphere (Scheme 94) [128].

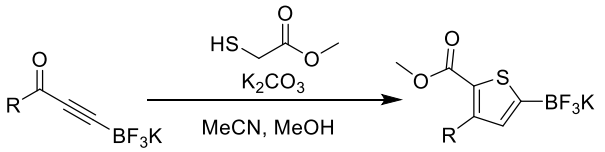


Scheme 94. Synthesis of 2-aminothiophenes.

After screening they found that optimal solvent for the reaction is DMA and best catalyst is copper (II) acetate. Reaction proceeds smoothly with slight

heating. Authors also reported possible reaction mechanism. Importance of oxygen and copper catalysis is discussed in paper.

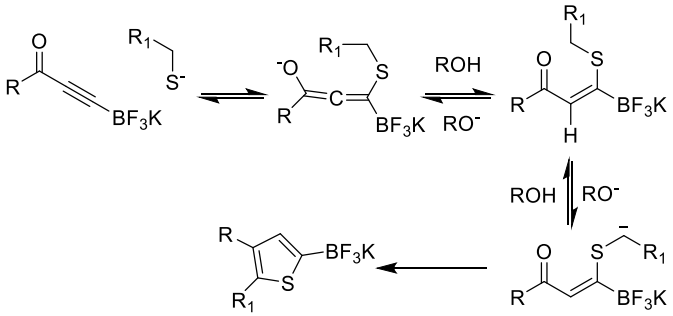
Recently J. P. A. Harrity group published synthesis of thiophene boronates from ynone trifluoroborate salts and alkylthiols [129]. With optimal conditions reaction proceeds at room temperature with K_2CO_3 as a base and MeCN, MeOH solvent mixture (Scheme 95).



Scheme 95. Synthesis of thiophene boronates.

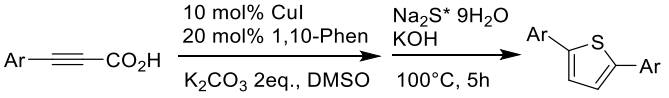
Authors have found that when *t*BuOK/*t*BuOH are used instead of K_2CO_3/MeOH other thiols also react with ynone trifluoroborate salts to form thiophenes. Unfortunately, only alkylthiols bearing electron deficient substituents can be used.

Mechanistic studies were also accomplished. Authors speculate that thiol adds to the ynone reversibly (Scheme 96).



Scheme 96. Proposed reaction mechanism.

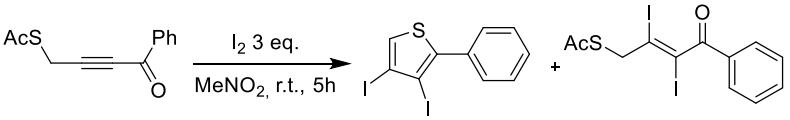
S. Lee developed method for direct synthesis of furans and thiophenes via decarboxylative coupling of alkynyl carboxylic acids (Scheme 97). Interestingly H_2O or Na_2S are used as a source of oxygen for furans and sulfur for thiophenes [130].



Scheme 97. Synthesis of 2,5-diaryl furans and thiophenes.

Y. Yamamoto group reported synthesis of dihaloheterocycles via electrophilic iodocyclization of substituted but-2-yn-1-ones bearing -OH, -NTs, and -SAc

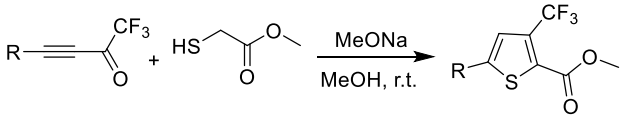
functional groups [131]. Diiodothiophenes were synthesized in perfect yields using nitromethane as a solvent (Scheme 98).



Scheme 98. Formation of diiodothiophenes.

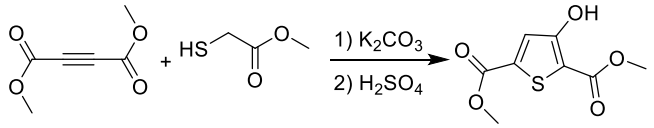
Authors also report applicability of synthesized diiodocompounds. For example, the synthesis of rubrene.

In 2018 V. G. Nenajdenko reported synthesis of 3-CF_3-thiophene derivatives form the reaction of CF_3-ynones with methyl thioglycolate [132] (Scheme 99) (R = Ph, 4-ClPh, 4-MePh, *n*Hex, 4-MeOPh, 4-MeSPh 4-*t*BuPh).



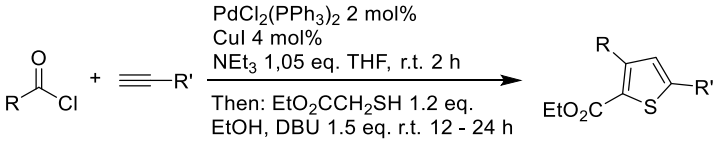
Scheme 99. Synthesis of 3-CF_3-thiophene derivatives.

Pierre Frere group reported synthesis of 3-substituted thieno[3,2-*b*]furans [133] via series of reactions all starting from methyl thioglycolate and dimethyl acetylenedicarboxylate (Scheme 100).



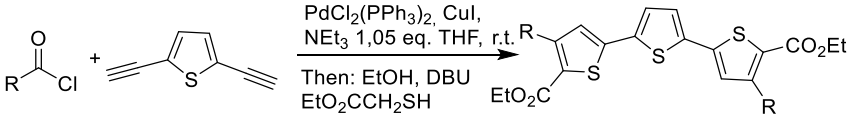
Scheme 100. Reaction of methyl thioglycolate with dimethyl acetylenedicarboxylate.

M. Teiber and T. J. J. Müller developed three-component synthesis of 2,4-disubstituted thiophene 5-carboxylates via consecutive Sonogashira–Fiesselmann sequence starting from ethyl 2-mercapto acetate, terminal alkynes and aroyl or heteroaroyl chlorides (Scheme 101). Reported yields of the products are good to excellent [134] (R = 2-thienyl, 4-MeOPh, 4-MePh. R' = Ph, $SiMe_3$, ferrocenyl, 2-thienyl).

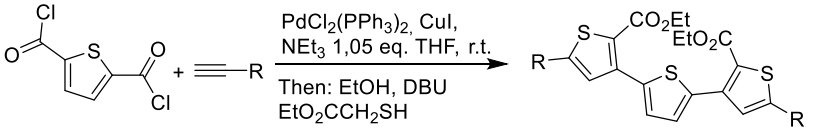


Scheme 101. Consecutive three-component Sonogashira alkynylation–Fiesselmann condensation.

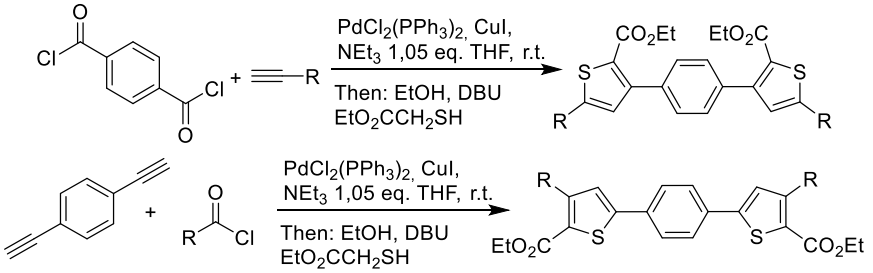
T. J. J. Müller group established earlier developed methodology towards the synthesis of highly luminescent symmetrical terthiophenes and quinquethiophenes (Scheme 102). These highly luminescent symmetrical molecules were synthesized from ethyl 2-mercapto acetate and heteroaryl bisacidchlorides (Scheme 103) or aryl bisacidchlorides and terminal alkynes or acidchlorides and terminal dialkynes (Scheme 104). Authors have also demonstrated that these systems can be further modified to valuable halogenated substrates for metal-catalyzed reactions like Sonogashira coupling [135].



Scheme 102. Consecutive pseudo-five-component Sonogashira alkynylation- Fiesselmann cyclocondensation synthesis of symmetrically substituted ter- and quinquethiophenes.



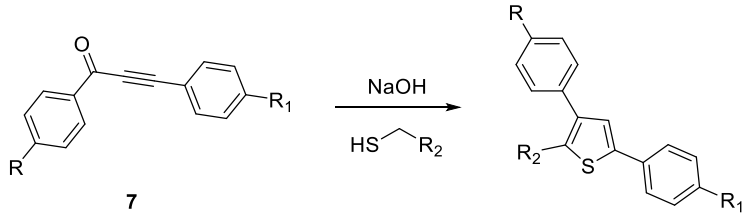
Scheme 103. Consecutive pseudo-five-component Sonogashira alkynylation- Fiesselmann cyclocondensation synthesis of centrally α,α'-disubstituted ter- and quinquethiophenes.



Scheme 104. Consecutive pseudo-five-component Sonogashira alkynylation-Fiesselmann cyclocondensation synthesis of the dithienyl dumbbells.

SYNTHESIS AND STUDY OF PHOTOPHYSICAL PROPERTIES OF 2,3,5-TRISUBSTITUTEDTHIOPHENES DERIVED FROM 1,3-DIARYLALKYNONES

We have decided to investigate applicability of 1,3-diaryl alkynones as starting compounds for potentially fluorescent substituted thiophenes. From variety of methods for the synthesis of 2,3,5-trisubstituted thiophenes we chose the Fiesselmann reaction. Which is especially suitable because 2,3,5-trisubstituted thiophenes can be synthesized from 1,3-diaryl alkynones **7** and mercaptoacetate or substituted methylene thiols in one step [136] [137] (Scheme 105).



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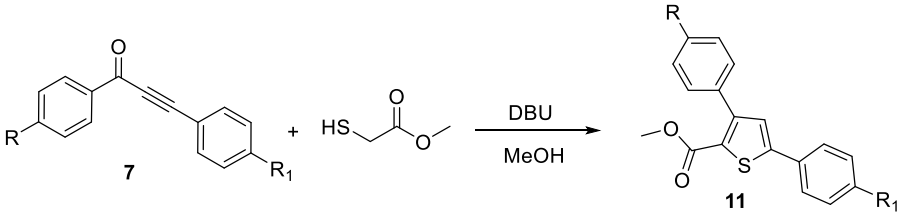
Scheme 105. Fiesselmann approach towards 2,3,5-trisubstituted thiophenes.

We have noticed that several of our newly synthesized thiophene derivatives **14** glow under UV light. We have also found that very little information about optoelectronic properties of monomeric thiophenes exist. According to literature the relationship between emissive properties and the structure of monomeric thiophenes has never been systematically studied. And there is only one example in the scientific literature where benefits of phenanthroimidazole or benzimidazole introduction in the position 2 of thiophene ring to photophysical properties are described [114]. Additionally, scientists have demonstrated that emissive properties of oligomeric thiophenes are almost unaffected when non conjugating aromatic substituents are introduced [107]. The lack of scientific literature on the topic of emissive properties of monomeric thiophenes and our hope to find really applicable new substituted thiophene fluorophores inspired us to synthesize and explore physicochemical properties (quantum yield, absorption and emission maximum) of 2,3,5-trisubstituted thiophenes with different substituents (electron donating or withdrawing groups) on aryl moieties.

First of all, we have synthesized several methyl thiophene-2-carboxylates **11** by utilizing alkynones **7** and methyl mercaptoacetate with catalytical amount of DBU in MeOH (Scheme 106, Table 7).

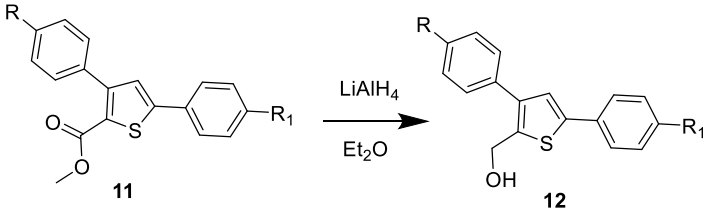


Scheme 106. Synthesis of methyl thiophene-2-carboxylates **11**.

Table 7. Scope of synthesized methyl 3,5-disubstitutedphenylthiophene-2-carboxylates **11**.

Entry	Starting material	R	R^1	Yield, %
1	**7k**	OMe	OMe	**11a** (84)
2	**7p**	OMe	Cl	**11b** (77)
3	**7e**	H	H	**11c** (78)
4	**7a**	H	OMe	**11d** (84)
5	**7s**	CN	OMe	**11e** (81)

Substituted methyl thiophene-2-carboxylates were reduced by LAH in absolute Et_2O to afford 3,5-disubstituted thiophen-2-ylmethanols [138] (Scheme 107, Table 8).

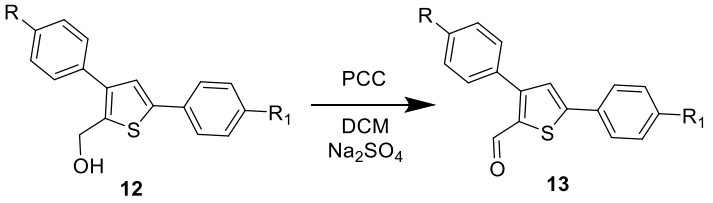


Scheme 107. Reduction of ester group with LAH.

Table 8. Scope of synthesized 3,5-disubstituted thiophen-2-ylmethanols **12**.

Entry	Starting material	R	R^1	Yield, %
1	**11a**	OMe	OMe	**12a** (99)
2	**11b**	OMe	Cl	**12b** (68)
3	**11c**	H	H	**12c** (93)

3,5-Disubstituted thiophen-2-ylmethanols **12** were oxidized with mild oxidizing reagent PCC in DCM as a solvent to afford aldehydes (Scheme 108, Table 9). Addition of sodium sulfate to the reaction mixture helped to ease filtration during workup.

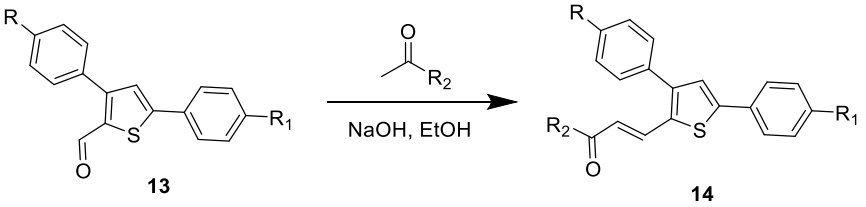


Scheme 108. Mild oxidation with PCC.

Table 9. Scope of synthesized 3,5-disubstituted thiophene-2-carbaldehydes **13**.

Entry	Starting material	R	R^1	Yield, %
1	**12a**	OMe	OMe	**13a** (65)
2	**12b**	OMe	Cl	**13b** (70)
3	**12c**	H	H	**13c** (62)

Various chalcone derivatives were obtained from previously synthesized 3,5-disubstituted diphenylthiophene-2-carbaldehydes and acetophenones in ethanol as a solvent with catalytical amount of sodium hydroxide [139] (Scheme 109, Table 10).



Scheme 109. Synthesis of chalcone derivatives.

Table 10. Scope of synthesized (*E*)-3-(3,5-disubstitutedphenylthiophen-2-yl)-1-substitutedprop-2-en-1-ones **14**.

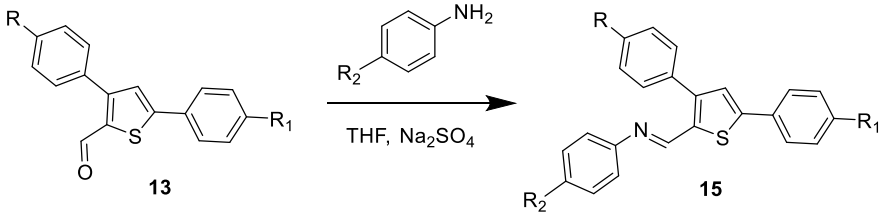
Entry	Starting material	R	R^1	R^2	Yield, %
1	**13a**	OMe	OMe	4-Cl-Ph	**14a** (84)
2	**13a**	OMe	OMe	3-Py	**14b** (98)
3	**13c**	H	H	4-CN-Ph	**14c** (87)
4	**13a**	OMe	OMe	4-MeO-Ph	**14d** (77)
5	**13a**	OMe	OMe	4-Br-Ph	**14e** (90)
6	**13a**	OMe	OMe	4-CN-Ph	**14f** (90)
7	**13b**	OMe	Cl	4-OMe-Ph	**14g** (78)
8	**13b**	OMe	Cl	3-Py	**14h** (58)
9	**13b**	OMe	Cl	4-Pe-Ph	**14i** (43)
10	**13b**	OMe	Cl	4-CN-Ph	**14j** (71)

We have measured photophysical properties of our newly synthesized chalcone type derivatives **14** (Table 11). Emission maxima was observed in green range from 516 nm to 562 nm. Measured quantum yields were quite low in solid state and in MeCN solution from 0.2% to 14.9%.

Table 11. Results of photophysical measurements of chalcone derivatives **14.**

Comp.	R	R^1	R^2	Abs., nm	Em., nm	QY, % (solution)	QY, % (solid)
14a	OMe	OMe	4-ClPh	240, 262, 282, 360	537	0.5	14.9
14b	OMe	OMe	3-Py	254, 422	538	0.4	8.9
14c	H	H	4-CNPh	264, 408	516	0.2	6.9
14d	OMe	OMe	4-MeOPh	240, 296, 410	523	0.4	2.9
14e	OMe	OMe	4-BrPh	240, 262, 282, 420	536	0.7	10.1
14f	OMe	OMe	4-CNPh	264, 430	562	1.8	4.6
14g	OMe	Cl	4-OMePh	235, 272, 334	458	0.4	4.0
14h	OMe	Cl	3-Py	235, 267, 408	510	0.2	2.8
14i	OMe	Cl	4-PePh	240, 273, 334	460	0.7	0.7
14j	OMe	Cl	4-CNPh	263, 414	529	0.5	2.5

Inspired by promising results of photophysical measurements of previously studied chalcone type derivatives **14** we have synthesized scope of (*E*)-1-(3,5-disubstitutedphenylthiophen-2-yl)-*N*-substitutedphenylmethanimines **15** (Scheme 110, Table 12). Sadly, none of these imines **15** exhibited fluorescence under UV light. It might be that non-radiative energy transfer is responsible for the absence of fluorescence in compounds **15**.

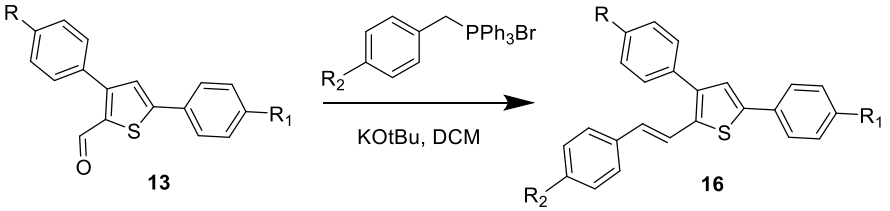


Scheme 110. Synthesis of (*E*)-1-(3,5-disubstitutedphenylthiophen-2-yl)-*N*-substitutedphenylmethanimines **15**.

Table 12. Scope of synthesized imines **15**.

Entry	Starting material	R	R^1	R^2	Yield, %
1	**13b**	OMe	Cl	Ph	**15a** (73)
2	**13b**	OMe	Cl	4-MeO-Ph	**15b** (75)
3	**13b**	OMe	Cl	4-F-Ph	**15c** (76)
4	**13b**	OMe	Cl	PhNH-	**15d** (75)
5	**13b**	OMe	Cl	4-Br-Ph	**15e** (17)

After failed attempts to synthesize fluorescent molecules. We have synthesized series of (*E*)-3,5-disubstitutedphenyl-2-styrylthiophenes **16** from aldehydes **13** by Wittig reaction (Scheme 111, Table 13) these molecules are structurally similar to chalcone type derivatives **14** but lacks C=O fragment.



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Scheme 111. Synthesis of styrylthiophenes **16**.

Table 13. Scope of synthesized (*E*)-3,5-disubstitutedphenyl-2-styrylthiophenes **16**.

Entry	Starting material	R	R^1	R^2	Yield, %
1	**13b**	OMe	Cl	H	**16a** (65)
2	**13b**	OMe	Cl	4-MeO-Ph	**16b** (69)
3	**13b**	OMe	Cl	4,5-diMeO-Ph	**16c** (59)
4	**13b**	OMe	Cl	Cl	**16d** (72)

When measured photophysical properties of newly synthesized (*E*)-3,5-disubstitutedphenyl-2-styrylthiophenes **16** (Fig. 9) we have observed significant improvement of PLQY in comparison to chalcone type derivatives **14** – up to 20.5%. Emission maxima of **16** is in blue range. Between 428 – 467 nm (Table 14).

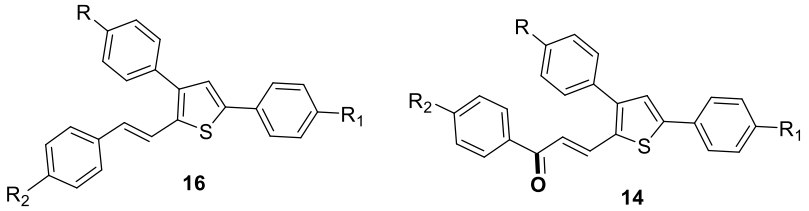
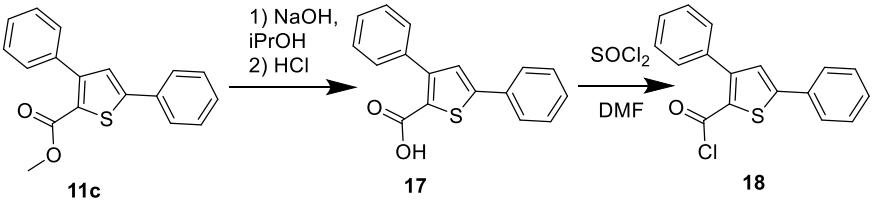


Figure 9. (*E*)-3,5-disubstitutedphenyl-2-styrylthiophene type derivatives **16**.

Table 14. Photophysical measurements of (*E*)-3,5-disubstitutedphenyl-2-styrylthiophenes **16.**

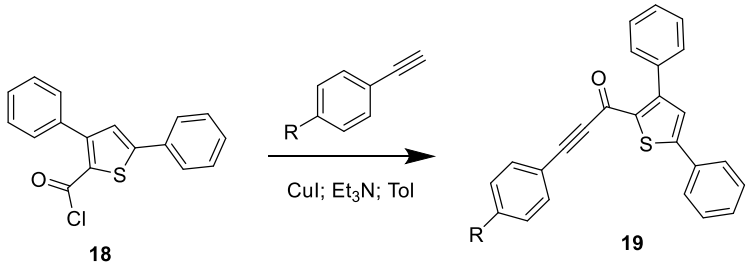
Comp.	R	R^1	R^2	Abs., nm	Em., nm	QY, % (solution)	QY, % (solid)
16a	OMe	Cl	H	240, 281, 366	428, 449	2.7	7.4
16b	OMe	Cl	4-MeOPh	241, 287, 381	459	12.7	20.5
16c	OMe	Cl	4,5-diMeOPh	238, 284, 382	467	12.7	4.7
16d	OMe	Cl	Cl	239, 281, 367	453	2.1	19.6

Quantum yields and other properties of chalcone **14**, imine **15** and styrylthiophene **16** derivatives were insufficient for the application in optoelectronics. But these compounds were good leads for the further research and optimization towards the better fluorophores. Thus, we have decided to synthesize 1-(3,5-diphenylthiophen-2-yl)-3-substitutedphenylprop-2-yn-1-ones **19** and build various heterocycles from alkynone moiety in order to extend conjugated pi double bond system. We have synthesized several more substituted 1,3-diarylakynones from 1,3-diarylakynones themselves. Starting from previously synthesized methyl 3,5-diphenylthiophene-2-carboxylate **11c** corresponding carboxylic acid **17** has been synthesized by hydrolysis with sodium hydroxide in boiling *i*PrOH and precipitation by adding water and adjusting pH to below 2 with conc. HCl. Obtained carboxylic acid was air dried and reacted with thionyl chloride and catalytic amount of DMF to afford 3,5-diphenylthiophene-2-carbonyl chloride **18** (Scheme 112).



Scheme 112. Synthesis of 3,5-disubstituted thiophene-2-carbonyl chloride **18**.

Obtained 3,5-disubstituted thiophene-2-carbonyl chloride **18** reacted with phenylacetylenes under Sonogashira reaction conditions to afford 1-(3,5-disubstituted phenylthiophen-2-yl)-3-substituted phenylprop-2-yn-1-ones **19** (Scheme 113, Table 15).

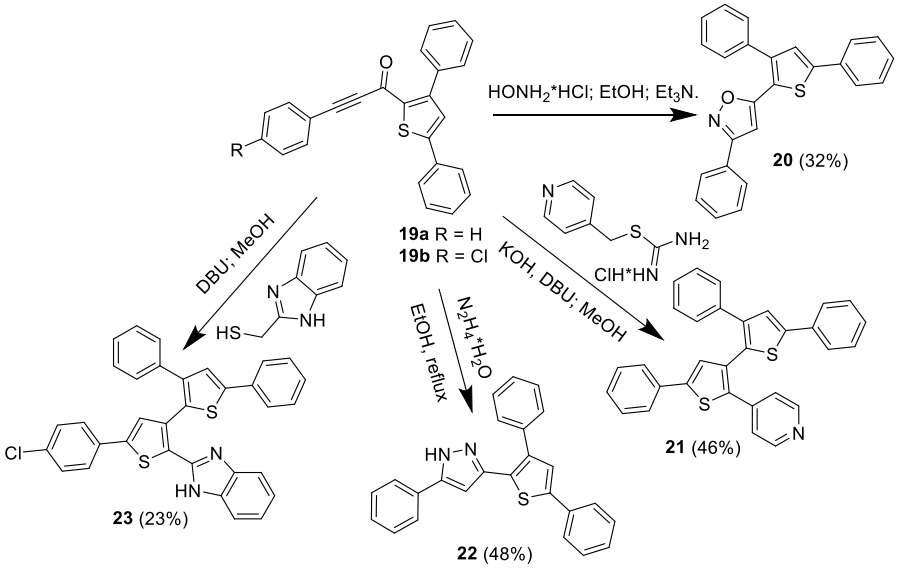


Scheme 113. Synthesis of 1-(3,5-diphenylthiophen-2-yl)-3-substitutedphenylprop-2-yn-1-ones **19**.

Table 15. Synthesized 1-(3,5-diphenylthiophen-2-yl)-3-substitutedphenylprop-2-yn-1-ones **19**.

Entry	R	Yield, %
1	H	**19a** (80)
2	Cl	**19b** (32)

Next, 1-(3,5-diphenylthiophen-2-yl)-3-substitutedphenylprop-2-yn-1-ones **19** were cyclized by utilizing reactions with hydroxylamine, pyridin-4-ylmethanethiol, hydrazine, (1*H*-benzo[*d*]imidazol-2-yl)methanethiol and various substituted heterocycles - isoxazole, thiophene, pyrazine and subst. 2-(thiophen-2-yl)-1*H*-benzo[*d*]imidazole were obtained accordingly (Scheme 114).



Scheme 114. Synthesis of substituted heterocycles from **19**.

Photophysical properties of our newly synthesized isoxazole, thiophene, pyrazine and subst. 2-(thiophen-2-yl)-1*H*-benzo[*d*]imidazole derivatives were also measured (Table 16).

Table 16. Photophysical measurements of isoxazole **20**, thiophene **21**, pyrazine **22** and substituted 2-(thiophen-2-yl)-1*H*-benzo[*d*]imidazole **23.**

Compound	Abs., nm	Em., nm	QY, % (solution)	QY, % (solid)
20	262, 336	419	2.3	26.2
21	240, 264, 312	474	2.1	1.6
22	258, 322	394	2.7	1.7
23	240, 266, 322, 364	466	4.3	1.69

Quantum yields were low in comparison to smaller substituted thiophenes **14**, **15**, **16**. We have decided to reduce complexity of the molecule in order to obtain more planar geometry of conjugated bond system which is important factor for fluorescent materials to achieve higher quantum yields (Fig. 10).

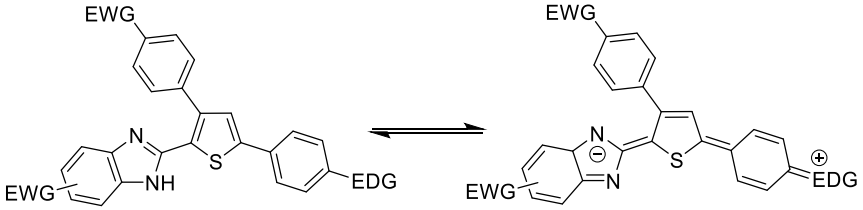
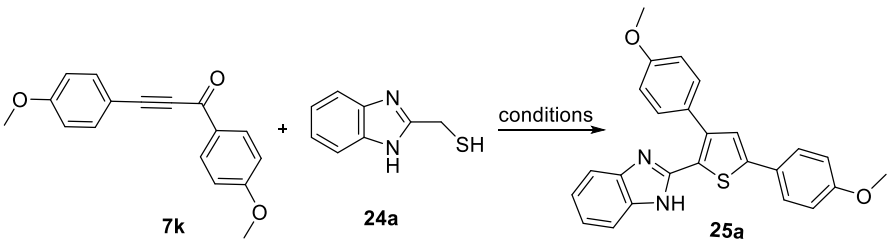


Figure 10. Resonance forms of substituted 2-(thiophen-2-yl)-1*H*-benzo[*d*]imidazoles.

We have attempted to construct 2-(thiophen-2-yl)-1*H*-benzo[*d*]imidazoles by the adapted literature method [134] via Fiesselmann cyclization reaction between 1,3-diarylalkynones and 1*H*-benzimidazole-2-methanethiol **24a**. According to the literature DBU is used as a base in the Fiesselmann cyclization in most of the cases. But when we attempted cyclization of 1 eq. 1,3-bis(4-methoxyphenyl)prop-2-yn-1-one **7k** with 1 eq. of 1*H*-benzimidazole-2-methanethiol **24a** in ethanol at reflux temperature with 1 eq. of DBU as a base desired thiophene derivative **25a** was obtained in 19% yield only. Increase of the yield up to 51% was observed when large excess of thiol **24a** (6 eq.) was used but isolation of desired compound from reaction mixture was complicated. Solvent change to DMF or THF did not improve yield of the product. After testing various reaction conditions, we were pleased to find that KOH or NaOH in ethanol gives nearly quantitative yield of desired thiophene **25a** (Scheme 115, Table 17).



Scheme 115. Screening of optimal reaction conditions.

Table 17. Optimization of the Fiesselmann reaction conditions.

Entry	Eq. of **7k**	Eq. of **24a**	Base, eq	Solvent	Temp.	Yield, %
1	1	1.5	DBU, 1	EtOH	reflux	19
2	1	3	DBU, 1	EtOH	reflux	37
3	1	6	DBU, 1	EtOH	reflux	51
4	1	1.5	DBU, 1	THF	reflux	63
5	1	1.5	DBU, 1	DMF	80°C	54
6	1	1.5	NaOH, 1	EtOH	reflux	92

Most of the literature examples use easy-to-oxidize, relatively toxic and smelly mercaptans. It is one of the most essential drawbacks of the Fiesselmann cyclization. Thiols tend to get easily oxidized by oxygen in the air to disulfides which do not participate in cyclization reaction under our developed conditions. Thiols also have unpleasant odor and are relatively toxic. We were pleased to find that carbamimidothioates **24c-e** (Fig. 11) can be used in place of thiols. These substances are easy to synthesize from thiourea and are easy to handle and very stable at storage conditions.

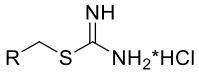
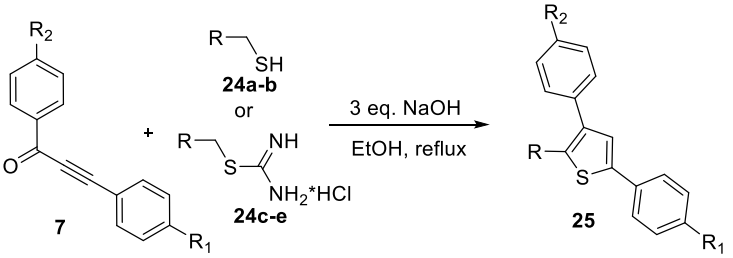


Figure 11. General structure of carbamimidothioates **24c-e.**

Several substituted thiophenes **25** were synthesized by using optimized reaction conditions. We have found that our optimized conditions are general to wide scope of alkynones **7**. Although electron rich substrates with electron donating groups such as methoxy gave better yields in comparison with electron poor substrates bearing electron withdrawing trifluoromethyl substituents. Similar relationship between electronic effects and yields was observed for thiols and carbamimidothioates. More electron rich thiols and carbamimidothioates provided better yields (Scheme 116, Table 18).

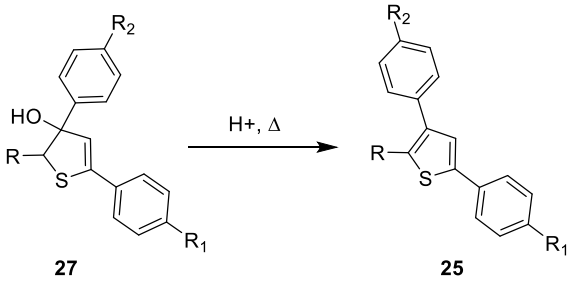


Scheme 116. Synthesis of 2,3,5-trisubstituted thiophenes **25**.

Table 18. The Fiesselmann type reaction between alkynones **7** and thiols **24a-b** or carbamimidothioates **24c-e**.

Entry	Starting material	R^2	R^1	RCH_2SX	Yield, %
1	**7e**	H	H	BZI-2-CH_2SH **24a**	**25a** (62)
2	**7k**	OMe	OMe		**25b** (92)
3	**7l**	CF_3	OMe		**25c** (42); **27a** (10)
4	**7m**	OMe	CF_3		**25d** (64)
5	**7n**	CF_3	CF_3		**25e** (44); **27f** (50)
6	**7o**	OPe	OPe		**25f** (72)
7	**7e**	H	H	2-(5-Cl-BZI)-CH_2SH **24b**	**25g** (55)
8	**7k**	OMe	OMe		**25h** (58)
9	**7l**	CF3	OMe		**25i** (64)
10	**7e**	H	H	2-(5,6-diCl-BZI)-$CH_2SC(NH_2)_2Cl$ **24c**	**25j** (60)
11	**7k**	OMe	OMe		**25k** (74)
12	**7l**	CF3	OMe		**25l** (62)
13	**7e**	H	H	4-Py-$CH_2SC(NH_2)_2Cl$ **24d**	**25m** (67)
14	**7k**	OMe	OMe		**25n** (89)
15	**7l**	CF_3	OMe		**25o** (51)
16	**7m**	OMe	CF_3		**25p** (67)
17	**7n**	CF_3	CF_3		**25r** (50)
18	**7k**	OMe	OMe	2-(1-Me-IMD)-$CH_2SC(NH_2)_2Cl$ **24e**	**25s** (30)

Interestingly in some cases we have succeeded to isolate intermediates of cyclization reaction **27**. In cases 1-3 (Table 19) even after prolonged heating of reaction mixtures dihydrothiophen-3-ols **27a** – **27c** were observed as the major products. Dihydrothiophen-3-ols can be easily aromatized to corresponding thiophenes **25** by heating in acidified solution (Scheme 117). We have also observed slow dehydration of **27** to thiophenes **25** in NMR samples dissolved in DMSO.



27 **25**

Scheme 117. Dehydration of dihydrothiophen-3-ols **27** to thiophenes **25**.

Table 19. Scope of isolated dihydrothiophen-3-ols.

Entry	Starting material	R^2	R^1	RCH_2SX	Product (Yield, %)
1	**7l**	CF_3	OMe	2-(1-Me-IMD)-$CH_2SC(NH_2)_2Cl$ **24e**	**27a** (38)
2	**7m**	OMe	CF_3		**27b** (44)
3	**7n**	CF_3	CF_3		**27c** (41)
4	**7e**	H	H		**27d** (10)
5	**7l**	CF_3	OMe	BZI-2-CH_2SH **24a**	**27e** (50)
6	**7n**	CF_3	CF_3		**27f** (50)

Moreover, after synthesizing series of 2-substituted-3,5-diphenylthiophenes **25** where R = 2-BZI, 2-(5-Cl-BZI), 2-(5-Cl-BZI) we have investigated photophysical properties of these compounds (Table 20).

Table 20. Photophysical properties of 2,3,5-trisubstitutedthiophenes **25**.

Comp.	R^2	R^1	R	Abs., nm	Em. nm. Solution	Em. nm. Solid	QY, % solution	QY % solid
25a	H	H	2-BZI	237, 266, 347	433	456	38.9	8.5
25b	OMe	OMe	2-BZI	235, 278, 356	445	467	28.0	17.0
25c	CF_3	OMe	2-BZI	234, 274, 358	454	459	77.5	22.0
25d	OMe	CF_3	2-BZI	238, 280, 354	444	457	28.6	4.5

Table 20 continuation. Photophysical properties of 2,3,5-trisubstitutedthiophenes **25**.

Comp.	R^2	R^1	R	Abs., nm	Em. nm. Solution	Em. nm. Solid	QY, % solution	QY % solid
25e	CF_3	CF_3	2-BZI	238, 272, 352	442	512	53.5	2.1
25f	OPe	OPe	2-BZI	234, 280, 356	441	464	33.8	1.8
25g	H	H	2-(5-Cl-BZI)	235, 266, 350	435	459	45.0	17.5
25h	OMe	OMe	2-(5-Cl-BZI)	234, 280, 360	445	463	42.5	11.6
25i	CF_3	OMe	2-(5-Cl-BZI)	235, 274, 360	460	467	77.4	30.6
25j	H	H	2-(5,6-diCl-BZI)	232, 268, 355	434	475	63.1	52.2
25k	OMe	OMe	2-(5,6-diCl-BZI)	234, 280, 368	467	465	34.6	15.1
25l	CF_3	OMe	2-(5,6-diCl-BZI)	236, 275, 365	462	478	82.6	30.9
25m	H	H	4-Py	265, 329	416	414	2.1	2.0
25n	OMe	OMe	4-Py	252, 280, 340	440	538	4.0	0.9
25o	CF_3	OMe	4-Py	236, 270, 340	460	550	33.9	11.9
25p	OMe	CF_3	4-Py	242, 284, 332	436	436, 525	1.9	8.4
25r	CF_3	CF_3	4-Py	240, 268, 326	406	446	2.0	6.1
25t	OMe	OMe	2-(1-Me-IMD)	236, 272, 318	420	NA	1.4	NA

We have studied that when R1 and R2 are electron donating groups (OMe) thiophene ring resulted in increase of the solid state PLQY and decrease of PLQY in solution in comparison to **25a** where R1=R2=H.
Interestingly when R1=R2=OPe **25f** observed PLQY was similar to thiophene without alkyloxy groups **25a**. When R1 and R2 are EWGs observed PLQY was lower in solid state but increase of PLQY was observed in the solution.
Increase of PLQY in both solution and in solid state was observed when R2 is electron withdrawing group (CF_3) and R1 was electron donating (OMe) group **25c**.
Exchange of substituents R1 and R2 resulted in decrease of PLQY in both solution and in solid state **25d** (Table 20).
We have also studied the effect of electronic properties of the benzimidazole core to the PLQY of derivatives **25**. Introduction of Cl substituents to benzimidazole resulted in increased PLQY **25g** (5-Cl-BZI) and **25j** (5,6-diCl-BZI) compared to **25a** (Table 20).
The highest PLQY in both solution and solid state of studied compounds was observed for **25l** with the most electron deficient benzimidazole core and R1=CF_3, R2=OMe (Table 20).
We have also studied importance of benzimidazole substituent at position 2 and found that when pyridine **25m-25r** or *N*-methylimidazole **25t** are introduced in the place of benzimidazole significant decrease of PLQY is observed.
It can be concluded that the introduction of 5,6-dichloro-2-benzimidazolyl substituent in 2nd and EWG-substituted arenes in 3rd and EDG-substituted arenes in 5th position of thiophene core results in the highest PLQY.
Thiophenes where R = 2-benzimidazolyl (unsubstituted, 5-Cl, and 5,6-di-Cl) showed three characteristic absorption bands in solid state at 232 – 238 (band 1); 266 – 280 (band 2) and 347 – 368 (band 3) nm respectively (Table 20). Only one broad emission band with maxima at 433 – 467 nm was observed in acetonitrile solutions for these thiophenes.
By comparing **25j** and **25k** it becomes clear that the presence of EDG in 5th position of thiophene ring gives bathochromic shift of emission peak maxima (from 434 to 467 nm), absorption band 2 (from 268 to 280 nm), band 3 (from 355 to 368 nm).
Bathochromic shifts were also observed for thiophenes substituted with 4-pyridinyl group in 2nd position and EDG (4-methoxyphenyl) in 3rd or 5th or both positions of thiophene core.
All of our studied thiophenes in acetonitrile solution gave broad emission peaks without any distinctive bands (Table 20). According to literature TICT phenomenon is characteristic to compounds with broad emission peaks [140].

Moreover, solvatochromism and viscosity studies were conducted to prove whether TICT is responsible or not for the observed emission because it is known that TICT is sensitive to viscosity and solvent effects [140] [141][142]. Thiophene **25o** was used in the viscosity and solvatochromism study due to high solubility and relatively high intensity of the emission (33.9% PLQY). The shift of emission maxima from 440 nm in dioxane to 468 nm in DMSO (Fig. 12) provides evidence for TICT.

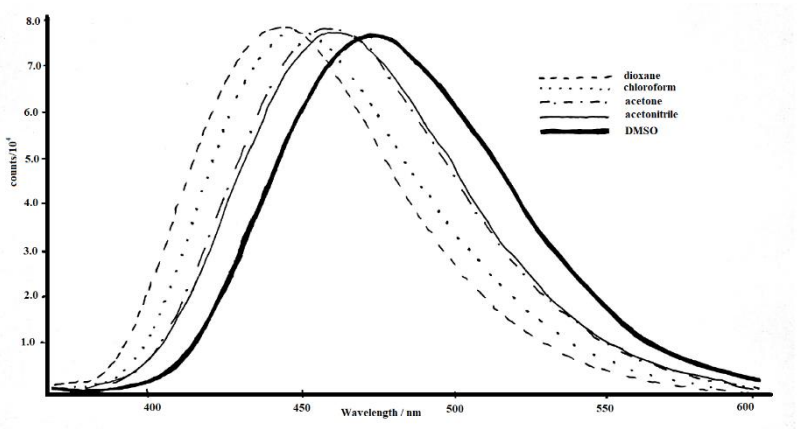


Figure 12. Dependence of emission intensity on solvent polarity.

We have also measured emission intensity of **25o** in various EtOH/glycerol mixtures (Fig. 13).

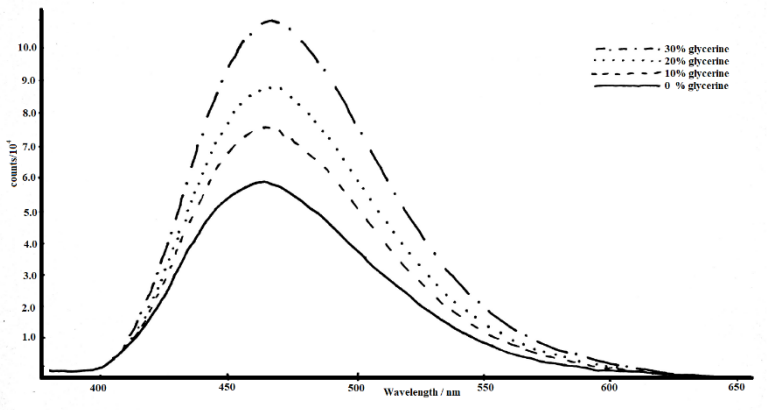


Figure 13. Dependence of emission intensity on solvent viscosity.

Observed correlation between viscosity of the solvent and the emission intensity provided further support of TICT. We have measured the emission intensity of **25o** in degassed with nitrogen and aerated solutions and observed

no difference – intensity of emission was similar in both solutions (Fig. 14). It means that triplet states do not participate in the emission because triplet states would be quenched by air oxygen and it would cause differences in the emission intensities in aerated and nitrogen purged solutions [143].

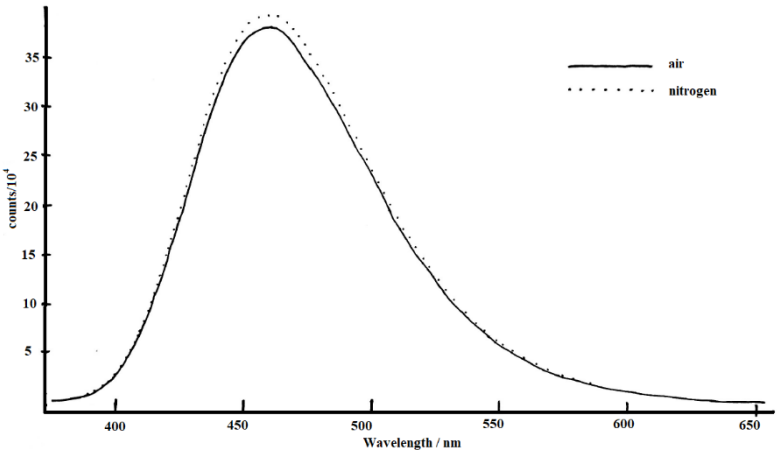


Figure 14. Dependence of emission intensity on presence/absence of oxygen.

We have also measured the emission intensity of **25o** at lowered temperature (from 293K to 233K) (Fig. 15) and registered increase of emission intensity.

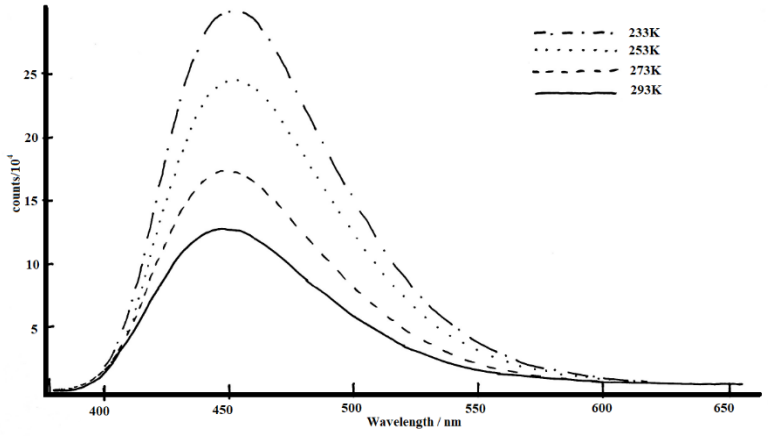


Figure 15. Emission intensity of **25o** at lowered temperature.

Both experiments prove that our studied materials do not possess TADF character and that singlet states are responsible for the emission of light.

General information: C^{13}, H^1 NMR spectra were recorded at 100 MHz and 400 MHz accordingly with Bruker AscendTM spectrometer. Chemical shifts are reported in ppm using the residual protic solvent as the internal standard. Data is reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). Mass spectra were recorded with a TSQ EnduraTM spectrometer (ESI) in positive mode. Melting points of synthesized compounds were monitored in open capillary with "Stuart SMP 10" apparatus. Reaction process was monitored by TLC using Silicagel 60 F254 Merc plates. For purification Silicagel 60 (40-63 μm), hexane or petroleum ether (PE), ethyl acetate (EA), toluene (Tol), chloroform ($CHCl_3$), acetonitrile (MeCN) and their mixtures were used as eluents.
Absorption and emission in the solution (MeCN 10^{-6} M), as well as solid state emission spectra were measured on the FS5-Edinburgh instruments spectrofluorometer in ambient atmosphere and room temperature. The PLQY were determined by the absolute method at ambient temperature using an integrating sphere. Compounds were excited in the wavelength they absorbed in. The temperature measurements were conducted in a cryostat using EtOH/liquid nitrogen as coolant.

Synthesis of cinnamic acids (1a-b) (general procedure):
Aldehyde (1 eq. 0.2 mol) is added to round bottom flask with malonic acid (1.5 eq. 0.3 mol) and piperidine (6 mol%, 1 g, 1.2 ml) together with (2.4 eq. 38 g, 34 ml) pyridine. Reaction mixture is stirred for 3 hours in oil bath set to 120°C. After cooling reaction mixture to room temperature HCl 2M is added until pH = 1. Precipitate is filtered and recrystallized from *i*PrOH.

(*E*)-3-(4-methoxyphenyl)acrylic acid (1a)
White crystals, m.p. 174 °C (lit. 171 - 173°C [144]) (Rf = 0.7, DCM:MeOH = 9:1), Yield: 79%.

(*E*)-3-(4-chlorophenyl)acrylic acid (1b)
White crystals, m.p. 240 °C (lit. 241 - 243°C [145]) (Rf = 0.5, $HCCl_3$:MeOH = 9:1), Yield: 92%.

Synthesis of (*Z*)-1-(2-bromovinyl)-4-substitutedbenzenes (2a-b) (general procedure):

Cinnamic acid **1** is dissolved in $HCCl_3$ (25 ml for 5g) and bromine 1.05 eq. is added dropwise. Precipitate formed in 10 min. is filtered and washed with petroleum ether and dried in vacuum. Crystalline material is transferred into round bottom flask and DMF (90 ml for 40 g) is added. After addition of triethylamine 1.02 eq. reaction mixture is heated at 80°C for 0.5 h. Water is added and mixture is extracted with MTBE. Organic layer is washed with sat. NaCl solution and dried with Na_2SO_4. Solvent is removed under vacuum and obtained oily residue is used for the next step without further purification.

(*Z*)-1-(2-bromovinyl)-4-methoxybenzene (2a)

Yellow oil, Yield: 85%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (2H, d, J = 8.8 Hz), 7.01 (1H, d, J = 8.4 Hz), 6.91 (2H, d, J = 8.8 Hz), 6.30 (1H, d, J = 8.4 Hz), 3.85 (3H, s) ppm.

(*Z*)-1-(2-bromovinyl)-4-chlorobenzene (2b)

Yellow oil, Yield: 73%.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.72 (2H, d, J = 8.5 Hz), 7.49 (2H, d, J = 8.6 Hz), 7.27 (1H, d, J = 8.0 Hz), 6.78 (1H, d, J = 8.0 Hz) ppm.

Synthesis of 4-substitutedphenylacetylenes (3a-b) (general procedure):

(*Z*)-1-(2-bromovinyl)-4-substitutedbenzene **2** (1 eq. 0.2 mol) is dissolved in MeOH (5 ml for 2 g) and NaOH (2 eq. 0.4 mol, 16 g) is added. Reaction mixture is refluxed for 5 h. Solvent removed under vacuum and water is added. Mixture is extracted twice with PE. Organic layer dried with Na_2SO_4 and solvent removed under vacuum. In case of **3a** product distilled under vacuum. In case of **3b** product crystallized spontaneously after removal of the solvent.

1-Ethynyl-4-methoxybenzene (3a)

Transparent colorless liquid, b.p. 95-97°C @ 25torr (Rf = 0.5, PE:EA = 20:1), Yield: 60%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (2H, d, *J* = 8.9 Hz), 6.87 (2H, d, *J* = 8.9 Hz), 3.84 (3H, s), 3.03 (1H, s) ppm.

1-Chloro-4-ethynylbenzene (3b)

White crystals, m.p. 44-46 °C (Rf = 0.2, PE:EA = 4:1), Yield: 80%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (2H, d, *J* = 8.5 Hz), 7.32 (2H, d, *J* = 8.6 Hz), 3.13 (1H, s) ppm.

Synthesis of methyl 4-(pentyloxy)benzoate (4):
Into 500 ml round bottomed flask 200 ml acetone and 44g K_2CO_3 together with 40g of methyl 4-hydroxybenzoate were loaded. Mixture was degassed with argon and 40 ml of freshly distilled ylbromide was added. Mixture was refluxed for 12 h. Reaction mixture was poured into 1000 ml water and extracted with MTBE. Organic layer washed with sat. NaCl solution and dried with anhydrous Na_2SO_4. After removal of the solvent yellowish oil was obtained which was sufficiently pure for the further chemical transformations. Yellowish oil. Yield: 93%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (2H, d, J = 8.8 Hz), 6.92 (2H, d, J = 8.8 Hz), 4.02 (2H, t, J = 6.6 Hz), 3.91 (3H, s), 1.93 – 1.76 (2H, m), 1.52 – 1.31(4H, m), 0.96 (3H, t, J = 7.6 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.03, 163.01, 131.58, 114.09, 68.21, 51.84, 28.80, 28.13, 22.41, 13.97, 13.88 ppm.

Synthesis of 4-(pentyloxy)benzoic acid (5):
54g of ester **4** is transferred into 500 ml round bottomed flask and 230 ml of *i*PrOH with 20 ml H_2O and 20g NaOH are added. Mixture is refluxed for 1 h. and 200 ml H_2O is added together with HCl until pH = 1. Formed white material is filtered and washed with H_2O and air dried.
White powder, m.p. 119 - 122 °C. (lit. 122 - 124°C [146]) Yield: 67%.

Synthesis of 4-(pentyloxy)benzoyl chloride 6:
Carboxylic acid **5** (1 eq. 100 mmol) is added to round bottomed flask with magnetic stirrer and 10 eq. $SOCl_2$. While stirring DMF is added 0.1 mol %. After stirring 30 min. complete dissolution of **5** is observed. Unreacted $SOCl_2$ is removed under vacuum. Remaining oil is purified by distillation under vacuum.
Yellowish oil, b.p. 195 – 196 ºC @ 25 torr. (lit. 198 – 200 @ 30 torr [147]) Yield: 83%.

Synthesis of 1,3-diarylpropynones 7a-t (general procedure):
Into round bottomed flask are added: substituted benzoyl chloride 1.3 eq., 30 eq. TEA. Mixture is degassed with argon and $PdCl_2(PPh_3)_2$ is added 0.4 mol%. Finally substituted alkyne **3** 1 eq. and CuI 2 mol% are added. Reaction mixture is stirred at room temperature until completion of the reaction (monitored by TLC). Saturated aqueous NH_4Cl solution is added and mixture is extracted with MTBE. Organic phase is dried with anhydrous Na_2SO_4. After removal of the solvent under vacuum residue is crystallized from *i*PrOH or purified by chromatography.

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (7a)
Brownish crystals, m.p. 78-80 °C. (lit. 77 - 79°C [147]) Yield: 85%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (2H, d, *J* = 7.4 Hz), 7.63 (3H, m), 7.51 (2H, m), 6.94 (2H, d, *J* = 8.7 Hz), 3.86 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 161.8, 137.1, 135.2, 133.9, 129.5, 128.6, 114.5, 111.9, 94.3, 86.9, 55.5 ppm.

3-(4-Butoxyphenyl)-1-phenylprop-2-yn-1-one (7b)
White solid, m.p. 52-58 °C. Yield: 88%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 – 8.22 (2H, m), 7.69 – 7.62 (3H, m), 7.57 – 7.50 (2H, m), 6.98 – 6.92 (2H, m), 4.03 (2H, t, *J* = 6.5 Hz), 1.86 – 1.76 (2H, m), 1.59 – 1.47 (2H, m), 1.01 (3H, t, *J* = 7.4 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 161.4, 137.1, 135.2, 133.9, 129.5, 128.6, 114.9, 111.6, 94.5, 86.9, 68.0, 31.1, 19.2, 13.8 ppm.

3-(4-(Pentyloxy)phenyl)-1-phenylprop-2-yn-1-one (7c)
White solid, m.p. 51-52 °C (Rf = 0.5 PE:EA = 19:1). Yield: 94%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 – 8.21 (2H, m), 7.71 – 7.61 (3H, m), 7.54 (2H, t, *J* = 7.6 Hz), 6.94 (2H, d, *J* = 8.8 Hz), 4.02 (2H, t, *J* = 6.6 Hz), 1.89 – 1.78 (2H, m), 1.52 – 1.36 (4H, m), 0.97 (3H, t, *J* = 7.1 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1, 161.4, 137.1, 135.2, 133.9, 129.5, 128.6, 114.9, 111.6, 94.6, 86.9, 68.3, 28.8, 28.1, 22.4, 14.0 ppm.

3-(4-(Hexyloxy)phenyl)-1-phenylprop-2-yn-1-one (7d)
Orange crystals, m.p. 60-62°C (*i*PrOH). Yield: 80%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (2H, d, *J* = 7.2 Hz), 7.71 – 7.61 (3H, m), 7.54 (2H, t, *J* = 7.6 Hz), 6.95 (2H, d, *J* = 8.8 Hz), 4.08 – 3.98 (2H, m), 1.88 – 1.76 (2H, m), 1.48 (2H, m), 1.41 – 1.31 (4H, m), 0.94 (3H, t, *J* = 6.9 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1, 161.4, 137.1, 135.2, 133.9, 129.5, 128.6, 114.9, 111.6, 94.6, 86.9, 68.3, 31.5, 29.1, 25.7, 22.6, 14.0 ppm.

1,3-Diphenylprop-2-yn-1-one (7e)
Yellow crystals, m.p. 40-45 °C. (lit. 47–48°C [148]) Yield: 98%.
IR: 2198,96 cm^{-1} (C≡C), 1636,94 cm^{-1} (C=O).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27-8.24 (2H, m), 7.72-7.70 (2H, m), 7.69-7.64 (1H, m); 7.57-7.50 (3H, m), 7.47-7.43 (2H, m) ppm.

3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-one (7f)
Yellow crystals, m.p. 104-108°C. Yield: 76%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (2H, d, J = 8.5 Hz), 7.69-7.59 (3H, m), 7.55-7.50 (2H, m), 7.41 (2H, d, J = 8.7 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 137.3, 136.9, 134.5, 134.5, 129.7, 129.3, 128.9, 118.6, 91.7, 87.6 ppm.

3-(4-Methoxyphenyl)-1-(2-methoxyphenyl)prop-2-yn-1-one (7g)
White crystals, m.p. 58-60 °C (Rf = 0.3, Toluene). Yield: 60%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (1H, dd, *J* = 7.7, 1.5 Hz), 7.61 (2H, d, *J* = 8.7 Hz), 7.58 – 7.52 (1H, m), 7.10 – 7.01 (2H, m), 6.93 (2H, d, *J* = 8.7 Hz), 3.99 (3H, s), 3.87 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.8, 161.5, 159.7, 135.0, 134.8, 132.5, 127.0, 120.3, 114.3, 112.5, 112.2, 92.8, 89.2, 55.9, 55.4 ppm.

3-(4-Butoxyphenyl)-1-(2-methoxyphenyl)prop-2-yn-1-one (7h)
Brownish crystals, m.p. 67-70 °C (Et_2O/PE). Yield: 80%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 – 8.05 (1H, m), 7.64 – 7.44 (3H, m), 7.15 – 7.00 (2H, m), 6.91 (2H, d, *J* = 8.7 Hz), 4.09 – 3.84 (5H, m), 1.88 – 1.71 (2H, m), 1.51 (2H, m), 1.00 (3H, t, *J* = 7.4 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.9, 161.1, 159.7, 135.0, 134.7, 132.5, 127.0, 121.3, 120.3, 114.8, 112.2, 93.0, 89.2, 67.9, 55.9, 31.1, 19.2, 13.8 ppm.

3-(4-(Hexyloxy)phenyl)-1-(2-methoxyphenyl)prop-2-yn-1-one (7i)
Yellowish crystals, m.p. 73-75 °C. Yield: 62%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (1H, dd, *J* = 7.7, 1.6 Hz), 7.59 (2H, d, *J* = 8.8 Hz), 7.58 – 7.52 (1H, m), 7.11 – 7.01 (2H, m), 6.92 (2H, d, *J* = 8.8 Hz), 4.04 – 3.97 (5H, m), 1.87 – 1.75 (2H, m), 1.55 – 1.43 (2H, m), 1.41 – 1.31 (4H, m), 0.93 (3H, t, *J* = 6.8 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.8, 161.1, 159.7, 135.0, 134.7, 134.0, 132.5, 127.2, 120.3, 114.8, 114.6, 112.2, 93.0, 89.2, 68.2, 55.9, 31.5, 29.0, 25.7, 22.6, 14.0 ppm.

3-(4-Fluorophenyl)-1-(2-methoxyphenyl)prop-2-yn-1-one (7j)
White crystals, m.p. 52-55 °C (*i*PrOH) (Rf = 0.5, EA:PE = 4:1). Yield: 65%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 – 8.06 (1H, m), 7.65 (2H, dd, *J* = 8.4, 5.5 Hz), 7.60 – 7.53 (1H, m), 7.09 (4H, dt, *J* = 24.6, 8.7 Hz), 3.99 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.6, 163.8 (d, *J* = 253 Hz), 159.8, 135.2 (d, *J* = 8.8 Hz), 135.0, 132.5, 126.7, 120.4, 116.9 (d, *J* = 3.4 Hz), 116.1 (d, *J* = 22.3 Hz), 112.2, 90.5, 89.1, 56.0 ppm.

1,3-Bis(4-methoxyphenyl)prop-2-yn-1-one (7k)
White crystals, m.p. 78-79 °C. Yield: 78%.
IR: 2197.38 cm^{-1} (C≡C), 1635.41 cm^{-1} (C=O).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (2H, d, J = 8.8 Hz), 7.65 (2H, d, J = 8.8 Hz), 7.01 (2H, d, J = 8.8 Hz), 6.95 (2H, d, J = 8.7 Hz), 3.92 (3H, s), 3.88 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.8, 164.3, 161.6, 135.0, 131.9, 130.5, 114.4, 113.8, 112.2, 93.4, 86.8, 55.6, 55.4 ppm.

3-(4-Methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (7l)
Light yellow crystals, m.p. 98-100 °C. Yield: 80%.
IR: 2190.50 cm^{-1} (C≡C), 1635.13 cm^{-1} (C=O).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (2H, d, *J* = 8.8 Hz), 7.80 (2H, d, *J* = 8.8 Hz), 7.68 (2H, d, *J* = 8.8 Hz), 6.97 (2H, d *J* = 8.8 Hz), 3.89 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.7, 162.1, 139.6, 135.4, 135.0 (q, *J* = 32.7 Hz), 129.7, 125.6 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.9 Hz), 114.6, 111.4, 95.9, 86.8, 55.5 ppm.

1-(4-Methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (7m)
Light yellow crystals, m.p. 105-110 °C. Yield: 62%.
IR: 2206.38 cm^{-1} (C≡C), 1633.54 cm^{-1} (C=O).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (2H, d, *J* = 8.8 Hz), 7.75 (2H, d, *J* = 8.1 Hz), 7.65 (2H, d, *J* = 8.2), 6.97 (2H, d, *J* = 8.8 Hz), 3.88 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.2, 164.8, 133.1, 132.0 (q, *J* = 32.7 Hz), 132.1, 130.0, 125.6 (q, *J* = 3.7 Hz), 124.2, 123.6 (q, *J* =270.9 Hz), 114.0, 89.7, 88.2, 55.6 ppm.

1,3-Bis(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (7n)
Yellow crystals, m.p. 85-90 °C. Yield: 60%.
IR: 2206.53 cm^{-1} (C≡C), 1648.63 cm^{-1} (C=O).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (2H, d, J = 8 Hz), 7.81-7.80 (4H, m), 7.71 (2H, d, J = 8 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 139.0; 135.5 (q, *J* =32.6 Hz); 133.3, 132.6 (q, *J* = 32.9 Hz), 129.9, 125.8 (q, *J* = 3.7 Hz), 125.7 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 270.9 Hz), 123.5; 123.4 (q, *J* = 271.3 Hz) ppm.

1,3-Bis(4-(pentyloxy)phenyl)prop-2-yn-1-one (7o)

White crystals, m.p. 62-64ºC. (*i*PrOH) (Rf = 0.5 PE:EA = 10:1) Yield: 71%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (2H, d, *J* = 8.8 Hz), 7.64 (2H, d, *J* = 8.7 Hz), 6.99 (2H, d, *J* = 8.8 Hz), 6.93 (2H, d, *J* = 8.8 Hz), 4.07 (2H, t, *J* = 6.5 Hz), 4.02 (2H, t, *J* = 6.6 Hz), 1.90 – 1.77 (4H, m), 1.53 – 1.36 (8H, m), 0.97 (6H, t, *J* = 7.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.8, 163.9, 161.2, 135.0, 132.8, 131.9, 130.3, 114.9, 114.3, 93.5, 86.8, 68.4, 68.2, 28.8, 28.8, 28.1, 28.1, 22.4, 14.0 ppm.

3-(4-Chlorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (7p)

Yellowish crystals, m.p. 101-102 °C. (*i*PrOH) Yield: 57%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 – 8.16 (2H, m), 7.62 (2H, d, *J* = 8.6 Hz), 7.42 (2H, d, *J* = 8.6 Hz), 7.01 (2H, d, *J* = 8.9 Hz), 3.93 (3H, s) ppm.

1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one (7r)

Yellowish crystals, m.p. 120-121 °C. (*i*PrOH), (Rf = 0.5, PE:EA =10:1) Yield: 61%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (2H, d, *J* = 8.5 Hz), 7.66 (2H, d, *J* = 8.7 Hz), 7.51 (2H, d, *J* = 8.5 Hz), 6.96 (2H, d, *J* = 8.7 Hz), 3.89 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.7, 161.9, 140.5, 135.5, 135.2, 130.8, 128.9, 114.5, 111.6, 94.9, 86.6, 55.5 ppm.

4-(3-(4-Methoxyphenyl)propioloyl)benzonitrile (7s)

Yellowish crystals, m.p. 125-130°C. (*i*PrOH), Yield: 86%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (2H, d, *J* = 8.3 Hz), 7.83 (2H, d, *J* = 8.2 Hz), 7.67 (2H, d, *J* = 8.7 Hz), 6.97 (2H, d, *J* = 8.7 Hz), 3.89 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.1, 162.2, 139.9, 135.4, 132.4, 129.7, 118.0, 116.9, 114.6, 111.2, 96.6, 86.7, 55.5 ppm.

3-(4-Methoxyphenyl)-1-(4-nitrophenyl)prop-2-yn-1-one (7t)

Yellow crystals, m.p. 175-180°C. (Et_2O), Yield: 83%.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.41 (4H, s), 7.84 (2H, d, *J* = 8.3 Hz), 7.12 (2H, d, *J* = 8.4 Hz), 3.86 (3H, s) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ: 175.9, 162.67, 151.1, 141.1, 136.3, 130.9, 124.6, 115.5, 110.5, 96.9, 87.1, 56.1 ppm.

Synthesis of (*Z*)-1,3-di-substituted-prop-2-yn-1-one *O*-methyl oximes 8a-f (general procedure):

Alkynone **7** (1eq. 0.4 mmol) methoxyamine hydrochloride (2 eq. 0.8 mmol, 67 mg) Na_2SO_4 (2eq. 0.8 mmol, 114 mg) and methanol with pyridine (10 eq. 40 mmol, 3.1g, 3 ml) were added into round bottom flask and stirred overnight at room temperature. Water was added into reaction mixture and extraction with EtOAc performed. Organic layer was separated and dried with Na_2SO_4. Solution was passed through plug of silicagel and solvent was removed under vacuum.

(*Z*)-3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (8a)

White solid, m.p. 30-33°C. Yield: 81%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 – 7.91 (2H, m), 7.59 (2H, d, *J* = 8.9 Hz), 7.47 – 7.39 (3H, m), 6.93 (2H, d, *J* = 8.8 Hz), 4.17 (3H, s), 3.87 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7, 140.1, 133.9, 133.8, 129.6, 128.4, 126.5, 114.1, 113.8, 101.7, 78.6, 63.1, 55.4 ppm.

(*Z*)-3-(4-butoxyphenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (8b)

White solid, m.p. 35-42°C. Yield: 78%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 – 7.92 (2H, m), 7.60 – 7.55 (2H, m), 7.45 – 7.40 (3H, m), 6.94 – 6.87 (2H, m), 4.16 (3H, s), 4.02 (2H, t, *J* = 6.5 Hz), 1.85 – 1.76 (2H, m), 1.58 – 1.47 (2H, m), 1.01 (3H, t, *J* = 7.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 140.2, 133.8, 133.8, 129.6, 128.4, 126.5, 114.6, 113.5, 101.8, 78.6, 67.8, 63.0, 31.2, 19.2, 13.8 ppm.

(*Z*)-3-(4-(pentyloxy)phenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (8c)

Yellow oil. Yield: 70%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 – 7.86 (2H, m), 7.58 (2H, d, *J* = 8.8 Hz), 7.45 – 7.40 (3H, m), 6.91 (2H, d, *J* = 8.8 Hz), 4.16 (3H, s), 4.01 (2H, t, *J* = 6.6 Hz), 1.87 – 1.78 (2H, m), 1.53 – 1.37 (4H, m), 0.97 (3H, t, *J* = 7.1 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 140.2, 133.8, 133.8, 129.6, 128.4, 126.6, 114.6, 113.5, 101.8, 78.7, 68.1, 63.1, 28.8, 28.2, 22.4, 14.0 ppm.

(*Z*)-3-(4-(hexyloxy)phenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (8d)

Yellow oil. Yield: 66%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 – 7.91 (2H, m), 7.60 – 7.55 (2H, m), 7.44 – 7.39 (3H, m), 6.94 – 6.89 (2H, m), 4.16 (3H, s), 4.01 (2H, t, *J* = 6.6 Hz),

1.87 – 1.77 (2H, m), 1.48 (2H, m), 1.41 – 1.33 (4H, m,), 0.94 (3H, t, J = 6.9 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 140.2, 133.8, 129.6, 128.4, 126.5, 114.9, 114.6, 113.5, 101.8, 78.5, 68.2, 63.0, 31.6, 29.1, 25.7, 22.6, 14.0 ppm.

(Z)-1,3-diphenylprop-2-yn-1-one *O*-methyl oxime (8e)
White solid, m.p. 41-44°C. Yield: 78%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93-7.91 (2H, m), 7.65-7.59 (2H, m), 7.44-7.36 (6H, m), 4.15 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.8, 134.0, 132.4, 130.1, 129.8, 128.7, 128.6, 126.8, 122.1, 101.5, 79.9, 63.4 ppm.

(*Z*)-3-(4-chlorophenyl)-1-phenylprop-2-yn-1-one *O*-methyl oxime (8f)
White solid, m.p. 53°C. Yield: 73%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (2H, d, J = 8.8 Hz), 7.62 (2H, m), 7.42-7.35 (3H, m), 7.39 (2H, d, J = 8.8 Hz), 4.14 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.0, 135.5, 132.2, 132.2, 129.8, 128.5, 128.5, 127.8, 121.6, 101.5, 78.8, 63.3 ppm.

Synthesis of isoxazoles (9a-p) and 4*H*-Chromen-4-ones (10a-i) (general procedure):
To the solution of (*Z*)-1-phenyl-3-arylprop-2-yn-1-one *O*-methyloxime **8a-f** (0.4 mmol) or 3-(2-methoxyphenyl)-1-arylprop-2-yn-1-one **7g-j** (0.4 mmol) and acetal (0.44 mmol) in anhydrous MeCN (2 mL), $BF_3{\cdot}Et_2O$ (56.8 mg, 49.4 μL, 0.4 mmol) was added with stirring at room temperature after TLC monitoring indicated the full conversion of the starting material (approx. 10 min), the mixture was quenched by the addition of aq. $NaHCO_3$. The mixture was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried (anhyd. Na_2SO_4), and the solvent was evaporated to give a yellowish solid or oil. The product was purified by column chromatography (PE/EtOAc gradient from 20:1 to 4:1).

4-(Isochroman-1-yl)-5-(4-methoxyphenyl)-3-phenylisoxazole (9a)
Yellow plates, m.p. 144 – 146 °C. Yield: 57%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77–7.68 (2H, m), 7.63–7.54 (2H, m), 7.36–7.26 (3H, m), 7.03–6.96 (2H, m), 6.95–6.92 (2H, m), 6.91–6.82 (1H, m), 6.68 (1H, m), 5.94 (1H, s), 4.40–4.36 (1H, m), 3.98–3.92 (1H, td, ^{3}J = 11.7 Hz, ^{2}J = 3.2 Hz), 3.82 (3H, s), 3.17–3.11 (1H, m), 2.69–2.65 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.5, 164.2, 161.1, 135.8, 133.7, 129.6, 129.4, 129.2, 128.9, 128.5, 128.0, 126.8, 126.1, 125.4, 120.3, 114.1, 113.2, 71.2, 65.8, 55.4, 28.6 ppm.
HRMS (ESI) calcd. for $C_{25}H_{22}NO_3$ (MH^+): 384.1600; found 384.1597.

5-(4-Butoxyphenyl)-4-(isochroman-1-yl)-3-phenylisoxazole (9b)
Colorless oil. Yield: 43%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (2H, d, J = 8.9 Hz), 7.58 (2H, dd, J = 7.5, 2.0 Hz), 7.35–7.27 (3H, m), 7.02–6.96 (2H, m), 6.93 (2H, d, J = 8.9 Hz), 6.90–6.85 (1H, m), 6.69 (1H, d , J =7.7 Hz), 5.94 (1H, s), 4.38 (1H, ddd, J = 10.4, 6.1, 1.0 Hz), 3.99 (2H, t, J = 6.5 Hz), 3.95 (1H, td, J = 11.6, 3.0 Hz), 3.19–3.11 (1H, m), 2.68 (1H, d, ^3J = 15.1 Hz), 1.82–1.75 (2H, m), 1.57–1.46 (2H, m), 0.99 (3H, t, J = 7.4 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 164.1, 160.7, 135.9, 133.7, 129.6, 129.4, 129.1, 128.9, 128.4, 128.0, 126.8, 126.1, 125.4, 120.0, 114.6, 113.1, 71.2, 67.8, 65.7, 31.2, 28.6, 19.2, 13.9 ppm.
HRMS (ESI) calcd. for $C_{28}H_{28}NO_3$ (MH^+): 426.2069; found 426.2072.

4-(Isochroman-1-yl)-5-[4-(pentyloxy)phenyl]-3-phenylisoxazole (9c)
Colorless oil. Yield: 84%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (2H, d, ^3J = 8.4 Hz), 7.57–7.55 (2H, m), 7.30–7.28 (3H, m), 7.01–6.95 (2H, m), 6.92 (2H, d, ^3J = 8.8 Hz), 6.89–6.85 (1H, m), 6.68 (1H, d, ^3J = 7.6 Hz), 5.92 (1H, s), 4.37 (1H, dd, ^3J = 11.4 Hz, ^2J = 6.0 Hz), 3.98 (2H, t, ^3J = 6.8 Hz), 3.94 (1H, td, ^3J = 11.6 Hz, ^2J = 3.2 Hz), 3.18–3.10 (1H, m), 2.66 (1H, d, ^3J = 14.8 Hz), 1.80 (2H, quint, ^3J = 6.8 Hz), 1.48–1.35 (4H, m), 0.94 (3H, t, ^3J = 6.8 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7, 164.2, 160.8, 136.0, 133.8, 129.7, 129.5, 129.2, 129.0, 128.5, 128.1, 126.9, 126.2, 125.5, 120.1, 114.6, 113.2, 71.3, 68.2, 65.8, 29.0, 28.6, 28.3, 22.5, 14.1 ppm.
HRMS (ESI) calcd. for $C_{29}H_{30}NO_3$ (MH^+): 440.2226; found 440.2236.

5-[4-(Hexyloxy)phenyl]-4-(isochroman-1-yl)-3-phenylisoxazole (9d)
Light yellow solid, m.p. 108–110 °C. Yield: 58%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76–7.69 (2H, d, ^3J = 8.8 Hz), 7.61–7.56 (2H, dd, ^3J = 7.4 Hz, ^4J = 1.8 Hz), 7.37–7.29 (3H, m), 7.04–6.97 (2H, m), 6.87–6.97 (3H, m), 6.74–6.68 (1H, d, ^3J = 7.7 Hz), 5.95 (1H, s), 4.46–4.35 (1H, dd, ^3J = 11.2 Hz, ^3J = 5.7 Hz), 4.03–3.99 (2H, t, ^3J = 6.6 Hz), 3.99–3.93 (1H, td, ^3J = 11.7 Hz, ^4J = 3.1 Hz), 3.23–3.09 (1H, m), 2.74–2.64 (1H, d, ^3J = 15.4 Hz), 1.88–1.76 (2H, quint, ^3J = 7.0 Hz), 1.55–1.43 (2H, m), 1.43–1.32 (4H, m), 1.00–0.89 (3H, t, ^3J = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 164.1, 160.7, 135.9, 133.7, 129.6, 129.4, 129.1, 128.9, 128.4, 128.0, 126.7, 126.1, 125.4, 120.0, 114.5, 113.0, 71.2, 68.1, 65.7, 31.6, 29.1, 28.5, 25.7, 22.6, 14.0 ppm.
HRMS (ESI) calcd. for $C_{30}H_{32}NO_3$ (MH^+): 454.2382; found 454.2390.

4-(1,3-Dihydroisobenzofuran-1-yl)-5-(4-methoxyphenyl)-3-phenylisoxazole (9e)
Yellow plates, m.p. 89–95 °C. Yield: 55%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.62 (2H, m), 7.44–7.36 (2H, m), 7.35–7.22 (3H, m), 7.20–7.09 (2H, m), 7.08–7.01 (1H, m), 6.99–6.92 (2H, m), 6.90–9.84 (1H, m), 6.37 (1H, s), 5.12 (1H, dd, ^2J = 12.1 Hz, ^4J = 2.3 Hz), 5.00 (1H, dd, ^2J = 12.1 Hz, ^4J = 2.3 Hz), 3.86 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4, 164.1, 161.2, 139.6, 139.5, 129.7, 129.3, 129.0, 128.8, 128.0, 127.8, 127.4, 121.8, 120.7, 120.1, 114.1, 112.7, 77.2, 72.7, 55.4 ppm.
HRMS (ESI) calcd. for $C_{24}H_{20}NO_3$ (MH^+): 370.1443; found 370.1444.

5-(4-Butoxyphenyl)-4-(1,3-dihydroisobenzofuran-1-yl)-3-phenylisoxazole (9f)
Light yellow solid, m.p. 105–108 °C. Yield: 59%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (2H, d, J = 8.9 Hz), 7.40–7.36 (2H, m), 7.32–7.23 (3H, m), 7.19–7.10 (2H, m), 7.06 (1H, t, J = 7.3 Hz), 6.95 (2H, d, J = 8.9 Hz), 6.87 (1H, d, J = 7.5 Hz), 6.38 (1H, s), 5.12 (1H, dd, ^2J = 12.1 Hz, ^4J = 2.5 Hz), 4.99 (1H, dd, ^2J = 12.1 Hz, ^4J = 2.5 Hz), 4.02 (2H, t, J = 6.5 Hz), 1.89–1.74 (2H, m), 1.60–1.48 (2H, m), 1.02 (3H, t, J = 7.4 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.5, 164.1, 160.8, 139.6, 139.5, 129.6, 129.3, 129.0, 128.8, 128.0, 127.8, 127.4, 121.8, 120.7, 119.8, 114.6, 112.6, 77.2, 72.7, 67.8, 31.2, 19.2, 13.8 ppm.
HRMS (ESI) calcd. for $C_{27}H_{26}NO_3$ (MH^+): 412.1913; found 412.1910.

4-(1,3-Dihydroisobenzofuran-1-yl)-5-[4-(hexyloxy)phenyl]-3-phenylisoxazole (9g)
Light yellow solid, m.p. 105–108 °C. Yield: 58%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69–7.60 (2H, d, ^3J = 8.8 Hz), 7.41–7.35 (2H, m), 7.35–7.22 (3H, m), 7.21–7.09 (2H, m), 7.09–7.01 (1H, t, ^3J = 7.3 Hz), 6.98–6.91 (2H, d, ^3J = 8.8 Hz), 6.90–6.84 (1H, d, ^3J = 7.5 Hz), 6.37 (1H, s), 5.16–5.07 (1H, dd, ^2J = 12.1 Hz, ^4J = 2.3 Hz), 5.04–4.95 (1H, dd, ^2J = 12.1 Hz, ^4J = 2.2 Hz), 4.06–3.97 (2H, t, ^3J = 6.6 Hz), 1.87–1.77 (2H, quint, ^3J = 7.0 Hz), 1.54–1.44 (2H, m), 1.43–1.33 (4H, m), 0.98–0.90 (3H, t, ^3J = 6.9 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.5, 164.1, 160.8, 139.6, 139.5, 129.6, 129.3, 129.0, 128.8, 128.0, 127.7, 127.4, 121.8, 120.7, 119.8, 114.6, 112.6, 77.2, 72.7, 68.2, 31.6, 29.1, 25.7, 22.6, 14.0 ppm.
HRMS (ESI) calcd. for $C_{29}H_{30}NO_3$ (MH^+): 440.2226; found 440.2240.

5-(4-Methoxyphenyl)-4-[methoxy(phenyl)methyl]-3-phenylisoxazole (9h)
White crystals, m.p. 82–83 °C. Yield: 79%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (2H, d, ^3J = 8.6 Hz), 7.54 (2H, d, J = 7.7 Hz), 7.46–7.35 (3H, m), 7.35–7.19 (5H, m), 6.95 (2H, d, ^3J = 8.6 Hz), 5.59 (1H, s), 3.86 (3H, s), 3.33 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7, 164.3, 161.0, 139.9, 129.8, 129.4, 129.2, 129.0, 128.4, 128.3, 127.6, 126.7, 120.2, 114.0, 111.9, 76.0, 56.8, 55.3 ppm.
HRMS (ESI) calcd. for $C_{24}H_{21}NO_3Na$ (MNa^+): 394.1419; found 394.1403.

5-(4-Butoxyphenyl)-4-[methoxy(phenyl)methyl]-3-phenylisoxazole (9i)
Yellowish oil. Yield: 48%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (2H, d, J = 8.9 Hz), 7.56–7.51 (2H, m), 7.45–7.35 (3H, m), 7.34–7.21 (5H, m), 6.94 (2H, d, J = 8.9 Hz), 5.59 (1H, s), 4.01 (2H, t, J = 6.5 Hz), 3.33 (3H, s), 1.84–1.77 (2H, m), 1.59–1.45 (2H, m), 1.01 (3H, t, J = 7.4 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7, 164.2, 160.7, 139.9, 129.8, 129.4, 129.3, 129.1, 128.3, 128.3, 127.6, 126.7, 120.0, 114.6, 111.8, 76.0, 67.8, 56.8, 31.2, 19.2, 13.8 ppm.
HRMS (ESI) calcd. for $C_{27}H_{28}NO_3$ (MH^+): 414.2069; found 414.2068.

4-[Methoxy(phenyl)methyl]-5-[4-(pentyloxy)phenyl]-3-phenylisoxazole (9j)
Yellowish oil. Yield: 66%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (2H, d, ^3J = 9.2 Hz), 7.52–7.50 (2H, m), 7.41–7.33 (3H, m), 7.30–7.20 (5H, m), 6.91 (2H, d, ^3J = 8.8 Hz), 5.56 (1H, s), 3.98 (2H, t, ^3J = 6.4 Hz), 3.30 (3H, s), 1.80 (2H, quint, ^3J = 6.8 Hz), 1.47–1.36 (4H, m), 0.94 (3H, t, ^3J = 6.8 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 164.4, 160.8, 140.1, 129.9, 129.5, 129.4, 129.2, 128.5, 128.4, 127.7, 126.8, 120.1, 114.7, 111.9, 76.1, 68.2, 56.9, 29.0, 28.3, 22.6, 14.1 ppm.
HRMS (ESI) calcd. for $C_{28}H_{30}NO_3$ (MH^+): 428.2226; found 428.2226.

5-[4-(Hexyloxy)phenyl]-4-[methoxy(phenyl)methyl]-3-phenylisoxazole (9k)

Yellowish oil. Yield: 47%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78–7.71 (2H, d, ^3J = 8.8 Hz), 7.57–7.50 (2H, m), 7.44–7.35 (3H, m), 7.34–7.29 (2H, m), 7.28–7.20 (3H, m), 6.98–6.90 (2H, d, ^3J = 8.8 Hz), 5.59 (1H, s), 4.05–3.96 (2H, t, ^3J = 6.5 Hz), 3.33 (3H, s), 1.87–1.77 (2H, quint, 3J = 7.0 Hz), 1.54–1.44 (2H, m), 1.43–1.33 (4H, m), 0.98–0.90 (3H, t, ^3J = 6.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 164.3, 160.7, 140.0, 129.8, 129.4, 129.3, 129.1, 128.3, 128.3, 127.5, 126.7, 120.0, 114.6, 111.8, 76.0, 68.1, 56.8, 31.6, 29.1, 25.7, 22.6, 14.0 ppm.

HRMS (ESI) calcd. for $C_{29}H_{32}NO_3$ (MH^+): 442.2382; found 442.2387.

5-(4-Methoxyphenyl)-4-[methoxy(4-methoxyphenyl)methyl]-3-phenylisoxazole (9l)

White plates, m.p. 118–120 °C. Yield: 58%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (2H, d, ^3J = 8.9 Hz), 7.60–7.51 (2H, m), 7.47–7.34 (3H, m), 7.31–7.22 (2H, m), 6.95 (2H, d, ^3J = 8.9 Hz), 6.83 (2H, d, ^3J = 8.7 Hz), 5.53 (1H, s), 3.85 (3H, s), 3.79 (3H, s), 3.28 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 164.3, 161.0, 159.1, 132.1, 129.8, 129.4, 129.3, 129.0, 128.4, 128.1, 120.3, 114.0, 113.7, 111.8, 75.9, 56.7, 55.3, 55.2 ppm.

HRMS (ESI) calcd. for $C_{25}H_{24}NO_4$ (MH^+): 402.1705; found 402.1703.

5-[4-(Hexyloxy)phenyl]-4-[methoxy(4-methoxyphenyl)methyl]-3-phenylisoxazole (9m)

Yellowish solid, m.p. 84–86 °C. Yield: 59%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80–7.71 (2H, d, ^3J = 8.8 Hz), 7.58–7.50 (2H, d, ^3J = 8.1 Hz), 7.47–7.35 (3H, m), 7.27–7.21 (2H, d, ^3J = 8.6 Hz), 6.98–6.90 (2H, d, ^3J = 8.8 Hz), 7.86–7.78 (2H, d, ^3J = 8.7 Hz), 5.52 (1H, s), 4.04–3.96 (2H, t, ^3J = 6.5 Hz), 3.80 (3H, s), 3.27 (3H, s), 1.86–1.76 (2H, quint, ^3J = 7.0 Hz), 1.53–1.43 (2H, m), 1.42–1.33 (4H, m), 0.97–0.90 (3H, t, ^3J = 6.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.5, 164.2, 160.6, 159.0, 132.1, 129.8, 129.4, 129.3, 129.0, 128.4, 128.1, 120.0, 114.5, 113.7, 111.6, 75.9, 68.1, 56.7, 55.2, 31.6, 29.1, 25.7, 22.6, 14.0 ppm.

HRMS (ESI) calcd. for $C_{30}H_{34}NO_4$ (MH^+): 472.2488; found 472.2508.

4-[(4-Bromophenyl)(ethoxy)methyl]-5-(4-methoxyphenyl)-3-phenylisoxazole (9n)

White crystals, m.p. 119–120 °C. Yield: 77%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (2H, d, ^3J = 8.9 Hz), 7.58–7.52 (2H, m), 7.47–7.33 (5H, m), 7.21 (2H, d, ^3J = 8.4 Hz), 6.96 (2H, d, ^3J = 8.8 Hz), 5.62 (1H, s), 3.85 (3H, s), 3.57–3.37 (2H, m), 1.14 (3H, t, ^3J = 7.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 164.1, 161.1, 139.4, 131.3, 129.8, 129.5, 129.2, 129.1, 128.5, 128.4, 121.5, 120.1, 114.1, 112.1, 73.5, 64.6, 55.4, 15.1 ppm.

HRMS (ESI) calcd. for $C_{25}H_{23}BrNO_3$ (MH^+): 464.0861; found 464.0864.

4-[(4-Bromophenyl)(ethoxy)methyl]-5-[4-(pentyloxy)phenyl]-3-phenylisoxazole (9o)

Colorless oil. Yield: 30%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (2H, d, ^3J = 8.8 Hz), 7.51–7.49 (2H, m), 7.42–7.33 (5H, m), 7.15 (2H, d, ^3J = 8.4 Hz), 6.91 (2H, d, ^3J = 8.8 Hz), 5.57 (1H, s), 3.98 (2H, t, ^3J = 6.4 Hz), 3.51–3.44 (1H, m), 3.41–3.34 (1H, m), 1.80 (2H, quint, ^3J = 6.8 Hz), 1.48–1.34 (4H, m), 1.10 (3H, t, ^3J = 6.8 Hz), 0.94 (3H, t, ^3J = 6.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 164.2, 160.9, 139.5, 131.4, 129.9, 129.6, 129.32, 129.17, 128.57, 128.49, 121.56, 119.9, 114.7, 112.1, 73.6, 68.3, 64.7, 29.0, 28.3, 22.6, 15.2, 14.1 ppm.

HRMS (ESI) calcd. for $C_{29}H_{31}BrNO_3$ (MH^+): 520.1487; found 520.1503.

4-[(4-Bromophenyl)(ethoxy)methyl]-5-[4-(hexyloxy)phenyl]-3-phenylisoxazole (9p)

Yellow oil. Yield: 56%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75–7.68 (2H, d, ^3J = 8.9 Hz), 7.56–7.50 (2H, m), 7.46–7.33 (5H, m), 7.22–7.14 (2H, d, ^3J = 8.3 Hz), 6.99–6.90 (2H, d, ^3J = 8.9 Hz), 5.59 (1H, s), 4.03–3.98 (2H, t, ^3J = 6.6 Hz), 3.56–3.35 (2H, m), 1.88–1.76 (2H, quint, ^3J = 7.0 Hz), 1.55–1.44 (2H, m), 1.41–1.32 (4H, m), 1.16–1.10 (3H, t, ^3J = 7.0 Hz), 0.98–0.89 (3H, t, ^3J = 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7, 164.1, 160.7, 139.7, 131.3, 129.7, 129.5, 129.2, 129.0, 128.4, 128.4, 121.4, 119.8, 114.6, 111.9, 73.5, 68.2, 64.6, 31.6, 29.1, 25.7, 22.6, 15.0, 14.0 ppm.

HRMS (ESI) calcd. for $C_{30}H_{33}BrNO_3$ (MH^+): 534.1644; found 534.1668.

3-(Isochroman-1-yl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (10a)

Yellow oil. Yield: 99%.

IR (KBr): 1647 cm^{-1} (C=O).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (1H, d, ^{3}J = 7.9 Hz), 7.76–7.61 (3H, m), 7.49 (1H, d, ^{3}J = 8.4 Hz), 7.39 (1H, t, ^{3}J = 7.5 Hz), 7.13–7.06 (2H, m), 7.05–6.99 (1H, m), 6.97 (2H, d, ^{3}J = 8.4 Hz), 6.84 (1H, d, ^{3}J = 7.6 Hz), 6.05 (1H, s), 4.41–4.32 (1H, m), 3.96–3.88 (1H, m), 3.87 (3H, s), 3.32–3.16 (1H, m), 2.73–2.62 (1H, m) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.0, 166.0, 161.4, 156.0, 137.4, 133.9, 133.6, 130.7, 128.5, 126.2, 126.1, 126.0, 125.4, 125.0, 124.0, 123.9, 121.4, 117.9, 113.6, 72.9, 65.3, 55.5, 28.9 ppm.
HRMS (ESI) calcd. for $C_{25}H_{21}O_4$ (MH^+): 385.1440; found 385.1438.

2-(4-Butoxyphenyl)-3-(isochroman-1-yl)-4*H*-chromen-4-one (10b)
Yellow wax. Yield: 88%.
IR (KBr): 1649 cm^{-1} (C=O).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25–8.18 (1H, m), 7.73–7.63 (3H, m), 7.49 (1H, d, ^{3}J = 8.4 Hz), 7.39 (1H, t, ^{3}J = 7.5 Hz), 7.12–7.06 (2H, m), 7.05–6.99 (1H, m), 6.96 (2H, d, ^{3}J = 8.6 Hz), 6.84 (1H, d, ^{3}J = 7.6 Hz), 6.03 (1H, br. s), 4.40–4.32 (1H, m), 4.04 (2H, t, ^{3}J = 6.5 Hz), 3.96–3.87 (1H, m), 3.30–3.16 (1H, m), 2.71–2.62 (1H, m), 1.87–1.75 (2H, m), 1.61–1.48 (2H, m), 1.03 (3H, t, ^{3}J = 7.4 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.0, 166.0, 161.0, 156.0, 137.4, 133.9, 133.5, 130.7, 129.0, 128.5, 126.2, 126.0, 126.0, 125.1, 124.9, 124.0, 121.3, 117.8, 114.2, 73.0, 67.9, 65.3, 31.2, 28.9, 19.2, 13.8 ppm.
HRMS (ESI) calcd. for $C_{28}H_{27}O_4$ (MH^+): 427.1909; found 427.1906.

2-[4-(Hexyloxy)phenyl]-3-(isochroman-1-yl)-4*H*-chromen-4-one (10c)
Yellow oil. Yield: 70%.
IR (KBr): 1649 cm^{-1} (C=O).
^{1}H NMR (400 MHz, CD_3CN) δ: 8.11–8.01 (1H, dd, ^{3}J = 7.9 Hz, ^{4}J = 1.3 Hz), 7.80–7.73 (1H, ddd, ^{3}J = 8.6 Hz, ^{3}J = 7.2 Hz, ^{4}J = 1.7 Hz), 7.73–7.68 (2H, d, ^{3}J = 8.7 Hz), 7.60–7.54 (1H, d, ^{3}J = 8.1 Hz), 7.47–7.40 (1H, m), 7.10–7.02 (2H, m), 7.02–6.93 (3H, m), 6.87–6.77 (1H, d, ^{3}J = 7.6 Hz), 5.91 (1H, s), 4.32–4.23 (1H, ddd, ^{3}J = 11.6 Hz, ^{3}J = 5.5 Hz, ^{4}J = 2.0 Hz), 4.08–4.00 (2H, t, ^{3}J = 6.6 Hz), 3.88–3.79 (1H, td, ^{3}J = 11.2 Hz, ^{4}J = 3.1 Hz), 3.16–3.05 (1H, m), 2.69–2.60 (1H, d, ^{2}J = 16.1 Hz), 1.84–1.72 (2H, quint, ^{3}J = 7.0 Hz), 1.53–1.42 (2H, m), 1.42–1.32 (4H, m), 0.98–0.88 (3H, t, ^{3}J = 7.0 Hz) ppm.
^{13}C NMR (100 MHz, CD_3CN) δ: 176.42, 166.0, 161.0, 156.1, 137.6, 134.2, 133.9, 130.8, 128.3, 125.8, 125.7, 125.3, 125.2, 125.0, 124.0, 123.7, 120.8, 118.2, 114.1, 72.8, 68.1, 64.9, 31.3, 28.8, 28.5, 25.4, 22.3, 13.3 ppm.
HRMS (ESI) calcd. for $C_{30}H_{31}O_4$ (MH^+): 455.2222; found 455.2222.

2-(4-Fluorophenyl)-3-(isochroman-1-yl)-4*H*-chromen-4-one (10d)

White crystals, m.p. 130–135 °C. Yield: 97%.

IR (KBr): 1634 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$) δ: 8.27–8.21 (1H, m), 7.73–7.66 (1H, m), 7.65–7.58 (2H, m), 7.50–7.45 (1H, m), 7.48 (1H, d, ^3J = 8.3 Hz), 7.12–6.97 (5H, m), 6.81 (1H, d, ^3J = 7.6 Hz), 6.11 (1H, s), 4.34–4.24 (1H, m), 3.89 (1H, td, ^3J = 11.3 Hz, ^2J = 3.1 Hz), 3.11–2.98 (1H, m), 2.62 (1H, d, ^3J = 16.1 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.0, 163.8 (d, ^1J = 251.6 Hz), 156.0, 137.2, 133.8, 133.7, 131.2 (d, ^2J = 8.6 Hz), 129.3, 129.2, 128.5, 126.3, 126.1 (d, ^3J = 11.5 Hz), 125.2, 124.2, 123.7, 122.4, 117.9, 115.2, 115.0, 72.1, 65.3, 28.7 ppm.

HRMS (ESI) calcd. for $C_{24}H_{17}FO_3Na$ (MNa^+): 395.1059; found 395.1054.

3-(1,3-Dihydroisobenzofuran-1-yl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (10e)

Yellow wax. Yield: 83%.

IR (KBr): 1646 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$) δ: 8.15 (1H, dd, ^3J = 8.0 Hz; ^4J = 1.4 Hz), 7.70–7.61 (3H, m), 7.50–7.43 (1H, m), 7.40–7.33 (1H, m), 7.31–7.23 (2H, m), 7.23–7.17 (1H, m), 7.10–7.05 (1H, m), 7.04–6.98 (2H, m), 6.39 (1H, s), 5.37–5.28 (1H, m), 5.21–5.15 (1H, m), 3.89 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 166.0, 161.4, 156.0, 140.6, 140.1, 133.6, 130.8, 127.4, 127.1, 126.0, 124.9, 124.9, 124.1, 120.6, 120.5, 120.1, 117.8, 113.9, 80.7, 74.1, 55.5 ppm.

HRMS (ESI) calcd. for $C_{24}H_{19}O_4$ (MH^+): 371.1283; found 371.1284.

2-(4-Butoxyphenyl)-3-(1,3-dihydroisobenzofuran-1-yl)-4*H*-chromen-4-one (10f)

Yellow wax. Yield: 79%.

IR (KBr): 1648 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$) δ: 8.15 (1H, dd, ^3J = 7.9 Hz, ^4J = 1.2 Hz), 7.70–7.61 (3H, m), 7.47 (1H, d, ^3J = 8.4 Hz), 7.36 (1H, t, ^3J = 7.5 Hz), 7.32–7.17 (3H, m), 7.08 (1H, d, ^3J = 7.5 Hz), 7.02 (2H, d, ^3J = 8.7 Hz), 6.40 (1H, s), 5.39–5.30 (1H, m), 5.23–5.15 (1H, m), 4.06 (2H, t, ^3J = 6.5 Hz), 1.89–1.77 (2H, m), 1.61–1.48 (2H, m), 1.03 (3H, t, ^3J = 7.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 165.3, 161.1, 156.0, 140.6, 140.1, 133.5, 130.8, 127.4, 127.1, 125.9, 124.9, 124.6, 124.1, 120.6, 120.5, 120.1, 117.8, 114.4, 80.8, 74.1, 67.9, 31.2, 19.2, 13.8 ppm.

HRMS (ESI) calcd. for $C_{27}H_{25}O_4$ (MH^+): 413.1753; found 413.1761.

3-(1,3-Dihydroisobenzofuran-1-yl)-2-[4-(hexyloxy)phenyl]-4*H*-chromen-4-one (10g)

Yellow oil. Yield: 80%.

IR (KBr): 1648 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$) δ: 8.18–8.10 (1H, dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz), 7.71–7.61 (3H, m), 7.51–7.44 (1H, d, ^3J = 8.3 Hz), 7.41–7.33 (1H, t, ^3J = 7.5 Hz), 7.32–7.24 (2H, m), 7.24–7.17 (1H, td, ^3J = 6.3 Hz, ^4J = 1.7 Hz), 7.10–7.05 (1H, d, ^3J = 7.4 Hz), 7.04–6.97 (2H, d, ^3J = 8.7 Hz), 6.38 (1H, s), 5.38–5.30 (1H, dd, ^2J = 11.6 Hz, ^4J = 2.4 Hz), 5.22–5.15 (1H, d, ^2J = 11.5 Hz), 4.09–3.99 (2H, t, ^3J = 6.5 Hz), 1.89–1.79 (2H, quint, ^3J = 7.0 Hz), 1.56–1.46 (2H, m), 1.44–1.32 (4H, m), 0.99–0.89 (3H, t, ^3J = 6.9 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 165.3, 161.0, 156.0, 140.6, 140.1, 133.5, 130.8, 127.4, 127.1, 126.0, 124.9, 124.6, 124.1, 120.6, 120.4, 120.0, 117.8, 114.4, 80.8, 74.1, 68.3, 31.6, 29.1, 25.7, 22.6, 14.1 ppm.

HRMS (ESI) calcd. for $C_{29}H_{29}O_4$ (MH^+): 441.2066; found 441.2069.

2-(4-Methoxyphenyl)-3-[methoxy(phenyl)methyl]-4*H*-chromen-4-one (10h)

Yellow wax. Yield: 76%.

IR (KBr): 1650 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, dd, ^3J = 7.9 Hz; ^4J = 1.3 Hz), 7.71–7.65 (1H, m), 7.51–7.38 (4H, m), 7.30–7.24 (2H, m), 7.23–7.17 (2H, m), 7.17–7.11 (1H, m), 6.95–6.87 (2H, m), 5.90 (1H, s), 3.87 (3H, s), 3.44 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 165.5, 161.2, 156.1, 141.0, 133.6, 130.7, 127.7, 126.5, 126.3, 125.9, 125.4, 125.0, 123.4, 121.2, 117.9, 113.4, 77.1, 57.2, 55.4 ppm.

HRMS (ESI) calcd. for $C_{24}H_{21}O_4$ (MH^+): 373.1440; found 373.1438.

3-[(4-Bromophenyl)(ethoxy)methyl]-2-(4-methoxyphenyl)-4*H*-chromen-4-one (10i)

Yellow wax. Yield: 82%.

IR (KBr): 1634 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (1H, d, ^3J = 7.8 Hz), 7.68 (1H, t, ^3J = 7.7 Hz), 7.48–7.38 (4H, m), 7.29 (2H, d, ^3J = 8.4 Hz), 7.11 (2H, d, ^3J = 8.3 Hz), 6.90 (2H, d, ^3J = 8.7 Hz), 5.99 (1H, s), 3.87 (3H, s), 3.63–3.49 (2H, m), 1.20 (2H, t, ^3J = 7.1 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 165.6, 161.3, 156.1, 140.7, 133.7, 130.8, 130.6, 127.7, 126.2, 125.3, 125.1, 123.3, 121.6, 120.2, 117.9, 113.3, 74.3, 64.8, 55.4, 15.3 ppm.

HRMS (ESI) calcd. for $C_{25}H_{22}BrO_4$ (MH^+): 465.0701; found 465.0709.

Synthesis of methyl 3,5-bis(4-substitutedphenyl)thiophene-2-carboxylates (11a-e) (general procedure):

Alkynone **7** (1 eq, 29 mmol), methyl thioglycolate (1.5 eq. 44 mmol, 4.7 g), DBU (5 mol%, 0.25 ml) and 100 ml MeOH were added to 100 ml round bottomed flask. Reaction mixture was refluxed until completion (monitored by TLC). After cooling reaction mixture down to +4°C formed crystals were filtered and washed with cold methanol to yield pure **11**.

Methyl 3,5-bis(4-methoxyphenyl)thiophene-2-carboxylate (11a)

White crystals, m.p. 122-125 °C. Yield: 84%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (2H, d, *J* = 8.7 Hz), 7.49 (2H, d, *J* = 8.7 Hz), 7.20 (1H, s), 6.97 (4H, m), 3.88 (3H, s), 3.87 (3H, s), 3.82 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6, 160.3, 159.5, 149.6, 148.4, 130.5, 128.2, 127.5, 126.5, 126.0, 123.6, 114.5, 113.3, 55.4, 55.3, 51.8 ppm.

Methyl 5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophene-2-carboxylate (11b)

White solid, m.p. 131-133 °C. Yield: 77%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (2H, d, J = 8.6 Hz), 7.47 (2H, d, J = 8.8 Hz), 7.41 (2H, d, J = 8.6 Hz), 7.27 (1H, s), 6.98 (2H, d, J = 8.8 Hz), 3.88 (3H, s), 3.82 (3H ,s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4, 159.6, 149.5, 146.8, 134.8, 131.8, 130.5, 129.3, 127.8, 127.7, 127.3, 125.0, 113.4, 55.3, 52.0 ppm.

Methyl 3,5-diphenylthiophene-2-carboxylate (11c)

White solid, m.p. 68-72°C. Yield: 78%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.60 (2H, m), 7.50-7.31 (8H, m), 7.29 (1H, s), 3.75 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4, 149.6, 148.5, 135.7, 133.0, 130.0, 129.1, 128.8, 128.0, 127.9, 127.4, 126.1, 125.4, 51.9 ppm.

Methyl 5-(4-methoxyphenyl)-3-phenylthiophene-2-carboxylate (11d)

White solid, m.p. 76-80 °C. Yield: 84%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (2H, d, *J* = 8.8 Hz), 7.55 – 7.50 (2H, m), 7.49 – 7.38 (3H, m), 7.22 (1H, s), 6.97 (2H, d, *J* = 8.8 Hz), 3.88 (3H, s), 3.81 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5, 160.3, 149.7, 148.6, 135.9, 129.2, 128.0, 127.8, 127.5, 126.5, 126.0, 124.4, 114.5, 55.4, 51.8 ppm.

Methyl 3-(4-cyanophenyl)-5-(4-methoxyphenyl)thiophene-2-carboxylate (11e)

White solid, m.p. 186-190 °C. Yield: 81%

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.87 (2H, d, *J* = 8.0 Hz), 7.76 – 7.69 (4H, m), 7.55 (1H, s), 7.03 (2H, d, *J* = 8.6 Hz), 3.82 (3H, s), 3.72 (3H, s) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.8, 160.8, 148.9, 147.4, 140.5, 132.1, 130.7, 128.0, 126.9, 125.1, 122.4, 119.2, 115.3, 110.9, 55.9, 52.5 ppm.

Synthesis of (3,5-bis(4-substitutedphenyl)thiophen-2-yl)methanols 12a-c (general procedure):

Methyl 3,5-bis(4-substitutedphenyl)thiophene-2-carboxylate **11** (1eq, 22 mmol) and 150 ml of Et_2O were added into 250 ml round bottomed flask. Solution was cooled in the ice bath and $LiAlH_4$ (2eq. 44 mmol, 1.7 g) was added to the reaction mixture. After the addition of reducing agent reaction mixture was stirred for 6 h at room temperature. LAH was quenched by the addition of 1 ml H_2O, 1 ml 10% NaOH and 3 ml of H_2O subsequentially. Obtained slurry was filtered and solids were washed with ethyl acetate. Organic solution was washed 3*50 ml H_2O, with brine and dried with Na_2SO_4. Solvent was evaporated under reduced pressure to yield **12a-c**.

(3,5-Bis(4-methoxyphenyl)thiophen-2-yl)methanol (12a)

White solid, m.p. 94-99 °C. Yield: 99%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 – 7.53 (2H, m), 7.47 – 7.42 (2H, m), 7.19 (1H, s), 7.03 – 6.97 (2H, m), 6.97 – 6.92 (2H, m), 4.82 (2H, d, *J* = 7.4 Hz), 3.87 (3H, s), 3.86 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 159.0, 142.7, 141.0, 135.7, 129.8, 128.5, 127.0, 127.0, 124.1, 114.4, 114.0, 58.4, 55.4, 55.3 ppm.

(5-(4-Chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)methanol (12b)

White solid, m.p. 115-117 °C. Yield: 68%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (2H, d, *J* = 8.5 Hz), 7.42 (2H, d, *J* = 8.7 Hz), 7.36 (2H, d, *J* = 8.5 Hz), 7.27 (1H, s), 6.99 (2H, d, *J* = 8.7 Hz), 4.82 (2H, s), 3.87 (3H, s), 2.09 (1H, br. s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 141.3, 141.1, 137.2, 133.4, 132.7, 129.7, 129.1, 128.2, 126.9, 125.5, 114.1, 58.4, 55.4 ppm.

(3,5-Diphenylthiophen-2-yl)methanol (12c)
White solid, m.p. 82-90 °C. Yield: 93%
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (2H, d, *J* = 7.5 Hz), 7.55 – 7.30 (9H, m), 4.86 (2H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.0, 141.3, 137.6, 135.9, 134.1, 129.0, 128.8, 128.7, 127.8, 127.5, 125.8, 125.1, 58.4 ppm.

Synthesis of 3,5-bis(4-substitutedphenyl)thiophene-2-carbaldehydes (13a-b) (general procedure):
Into 250 ml round bottomed flask was added **12** (20 mmol) and 120 ml of dry DCM and 5 g of Na_2SO_4. Flask was immersed into ice bath and PCC (40 mmol, 8.6 g) was added. Reaction mixture was stirred for 12h at room temperature. Reaction mixture was filtered through plug of silicagel and remaining solids were washed with DCM. Filtrate was evaporated under reduced pressure to yield **13** as yellowish solids.

3,5-Bis(4-methoxyphenyl)thiophene-2-carbaldehyde (13a)
White solid, m.p. 142-149 °C. Yield: 65%
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.83 (1H, s), 7.64 (2H, d, *J* = 7.6 Hz), 7.46 (2H, d, *J* = 7.5 Hz), 7.29 (1H, s), 7.02 (2H, d, *J* = 7.5 Hz), 6.96 (2H, d, *J* = 7.6 Hz), 3.89 (3H, s), 3.86 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 183.8, 160.8, 160.3, 152.8, 152.4, 135.6, 130.7, 129.5, 127.8, 126.6, 125.7, 125.2, 114.6, 114.3, 55.4 ppm.

5-(4-Chlorophenyl)-3-(4-methoxyphenyl)thiophene-2-carbaldehyde (13b)
White solid, m.p. 139-141 °C. Yield: 70%
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (1H, s), 7.64 (2H, d, *J* = 8.4 Hz), 7.47 (2H, d, *J* = 8.5 Hz), 7.43 (2H, d, *J* = 8.4 Hz), 7.39 (1H, s), 7.04 (2H, d, *J* = 8.5 Hz), 3.90 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 184.0, 160.4, 152.2, 151.0, 136.8, 135.4, 131.6, 130.7, 129.4, 127.6, 126.6, 126.3, 114.4, 55.5 ppm.

3,5-Diphenylthiophene-2-carbaldehyde (13c)
White solid, m.p. 93-96 °C (lit. 98-99 °C [149]). Yield: 62%
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (1H, s), 7.70 (2H, d, *J* = 5.5 Hz), 7.54-7.48 (5H, m), 7.47-7.38 (4H, m) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 184.0, 152.7, 152.3, 137.1, 134.1, 133.1, 129.5, 129.5, 129.1, 129.0, 128.9, 126.4, 126.4 ppm.

Synthesis of (*E*)-3-(3,5-bis(4-substitutedphenyl)thiophen-2-yl)-1-substitutedphenyl prop-2-en-1-ones (14a-j) (general procedure):

Into 50 ml round bottomed flask with magnetic stirrer were added **13** (0.7 mmol), NaOH (0.07 mmol, 3 mg), 4-substituted acetophenone 1.05 mmol and 15 ml of EtOH. Reaction mixture was refluxed until completion (monitored by TLC). After cooling down to room temperature formed crystals were filtered and washed with cold EtOH. Crystalline mass was recrystallized from EtOH to obtain pure **14**.

(*E*)-3-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)-1-(4-chlorophenyl)prop-2-en-1-one (14a)

Yellow solid, m.p. 142-150°C. Yield: 84%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, d, *J* = 15.1 Hz), 7.97 (2H, d, *J* = 8.3 Hz), 7.62 (2H, d, *J* = 8.6 Hz), 7.47 (2H, d, *J* = 8.3 Hz), 7.39 (2H, d, *J* = 8.4 Hz), 7.29 (1H, d, *J* = 15.1 Hz), 7.26 (1H, s), 7.02 (2H, d, *J* = 8.4 Hz), 6.96 (2H d, *J* = 8.6 Hz), 3.89 (3H, s), 3.87 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.1, 160.2, 159.7, 148.7, 146.2, 138.9, 137.6, 136.8, 132.6, 130.5, 129.7, 128.9, 127.7, 127.4, 126.1, 125.4, 119.2, 114.5, 114.3, 55.4, 55.4 ppm.

(*E*)-3-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)-1-(pyridin-3-yl)prop-2-en-1-one (14b)

Orange solid, m.p. 131-135°C. Yield: 98%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.24 (1H, s), 8.80 (1H, s), 8.29 (1H, d, *J* = 7.5 Hz), 8.06 (1H, d, *J* = 15.0 Hz), 7.63 (2H, d, *J* = 8.3 Hz), 7.49 – 7.44 (1H, m), 7.40 (2H, d, *J* = 8.1 Hz), 7.30 (2H, d, *J* = 15.4 Hz), 7.03 (2H, d, *J* = 8.1 Hz), 6.98 (2H, d, *J* = 8.3 Hz), 3.89 (3H, s), 3.88 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.1, 160.3, 159.8, 152.9, 149.6, 149.3, 146.7, 138.2, 135.7, 133.8, 132.4, 130.5, 127.7, 127.5, 126.0, 125.5, 123.6, 118.9, 114.6, 114.3, 55.4, 55.4 ppm.

(*E*)-4-(3-(3,5-diphenylthiophen-2-yl)acryloyl)benzonitrile (14c)

Orange solid, m.p. 155-160 °C. Yield: 87%

^{1}H NMR (400 MHz, CDCl3) δ: 8.11 – 8.03 (3H, m), 7.81 (2H, d, J = 8.3 Hz), 7.70 (2H, d, J = 7.3 Hz), 7.54 – 7.39 (9H, m), 7.33 (1H, d, J = 15.1 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.0, 149.4, 146.8, 141.6, 138.3, 135.0, 133.9, 133.1, 132.5, 129.3, 129.2, 129.0, 128.9, 128.7, 128.5, 126.6, 126.1, 119.6, 118.1, 115.8 ppm.

(*E*)-3-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (14d)

Yellow powder, m.p. 100-105ºC. Yield: 77%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10-7.99 (3H, m), 7.62 (2H, d, J = 8.6 Hz), 7.45-7.35 (3H, m), 7.30-7.25 (1H, m), 7.06-6.94 (6H, m), 3.91 (3H, s), 3.89 (3H, s), 3.88 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.8, 163.3, 160.1, 159.6, 147.9, 145.4, 136.3, 133.0, 131.3, 130.6, 130.4, 127.9, 127.3, 126.3, 125.3, 119.9, 114.5, 114.2, 113.8, 55.5, 55.4, 55.4 ppm.

(*E*)-3-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)-1-(4-bromophenyl)prop-2-en-1-one (14e)

Yellow solid, m.p. 148-152ºC. Yield: 90%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, d, *J* = 15.0 Hz), 7.90 (2H, d, *J* = 8.4 Hz), 7.65 (4H, dd, *J* = 15.1, 7.1 Hz), 7.40 (2H, d, *J* = 8.5 Hz), 7.33 – 7.26 (2H, m), 7.03 (2H, d, *J* = 8.5 Hz), 6.98 (2H, d, *J* = 8.6 Hz), 3.90 (3H, s), 3.88 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.3, 160.2, 159.7, 148.7, 146.2, 137.6, 137.2, 132.6, 131.8, 130.4, 129.8, 127.8, 127.8, 127.4, 126.1, 125.4, 119.2, 114.5, 114.3, 55.4, 55.4 ppm.

(*E*)-4-(3-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)acryloyl)benzonitrile (14f)

Yellow solid, m.p. 165-167ºC. Yield: 90%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 – 8.02 (3H, m), 7.80 (2H, d, *J* = 8.0 Hz), 7.62 (2H, d, *J* = 8.4 Hz), 7.39 (2H, d, *J* = 8.3 Hz), 7.28 (2H, s), 7.03 (2H, d, *J* = 8.3 Hz), 6.97 (2H, d, *J* = 8.4 Hz), 3.90 (3H, s), 3.88 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.0, 160.4, 159.9, 149.5, 146.9, 141.8, 138.7, 132.4, 132.4, 130.4, 128.7, 127.6, 127.4, 126.0, 125.5, 118.7, 118.1, 115.7, 114.6, 114.3, 55.4, 55.4 ppm.

(*E*)-3-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (14g)

Yellow solid, m.p. 146-148 °C. Yield: 78%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (2H, d, *J* = 8.9 Hz), 7.99 (1H, d, *J* = 15.1 Hz), 7.59 (2H, d, *J* = 8.5 Hz), 7.43-7.35 (5H, m), 7.32 (1H, s), 7.00 (4H, t, *J* = 8.9 Hz), 3.90 (3H, s), 3.88 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.7, 163.4, 159.7, 147.7, 143.7, 135.9, 134.4, 134.3, 132.0, 131.2, 130.7, 130.4, 129.3, 127.6, 127.1, 126.7, 120.7, 114.3, 113.8, 55.5, 55.4 ppm.

(*E*)-3-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)-1-(pyridin-3-yl)prop-2-en-1-one (14h)

Orange solid, m.p. 133-135 °C. Yield: 58%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.21 (1H, d, *J* = 1.5 Hz), 8.77 (1H, dd, *J* = 4.7 Hz, *J* = 1.5 Hz), 8.25 (1H, dt, *J* = 7.9 Hz, *J* = 1.8 Hz), 8.01 (1H, d, *J* = 15.1 Hz), 7.58 (2H, d, *J* = 8.5 Hz), 7.43 (1H, dd, *J* = 7.7 Hz, *J* = 4.9 Hz), 7.39 – 7.34 (4H, m), 7.32 (1H, s), 7.29 (1H, d, *J* = 15.2 Hz), 7.00 (2H, d, *J* = 8.6 Hz), 3.86 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.0, 159.9, 153.0, 149.6, 148.9, 144.9, 137.8, 135.7, 134.7, 133.6, 133.6, 131.8, 130.4, 129.3, 127.3, 127.2, 126.8, 123.6, 119.7, 114.4, 55.4 ppm.

(*E*)-3-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)-1-(4-pentylphenyl)prop-2-en-1-one (14i)

Yellow solid, m.p. 141-143 °C. Yield: 43%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (1H, d, *J* = 15.1 Hz), 7.96 (2H, d, *J* = 6.7 Hz), 7.62 (2H, d, *J* = 6.8 Hz), 7.44-7.27 (8H, m), 7.03 (2H, d, *J* = 6.7 Hz), 3.89 (3H, s), 2.70 (2H, m), 1.67 (2H, m), 1.36 (4H, m), 0.92 (3H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.0, 159.7, 148.6, 147.9, 143.9, 136.3, 135.9, 134.4, 134.2, 132.0, 130.4, 129.3, 128.7, 128.5, 127.6, 127.2, 126.7, 120.9, 114.3, 55.4, 36.0, 31.5, 30.9, 22.5, 14.0 ppm.

(*E*)-4-(3-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)acryloyl)benzonitrile (14j)

Yellow solid, m.p. 211-213 °C. Yield: 71%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (2H, d, *J* = 7.5 Hz), 8.05 (1H, d, *J* = 15.2 Hz), 7.82 (2H, d, *J* = 7.3 Hz), 7.62 (2H, d, *J* = 7.5 Hz), 7.42 (2H, d, *J* = 8.1 Hz), 7.39 (2H, d, *J* = 8.5 Hz), 7.35 (1H, d, *J* = 16.9 Hz), 7.29 (1H, s), 7.04 (2H, d, *J* = 7.7 Hz), 3.90 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.0, 159.9, 149.2, 145.1, 141.6, 138.4, 134.8, 133.5, 132.5, 131.7, 130.5, 129.4, 128.7, 127.3, 127.2, 126.9, 119.4, 118.1, 115.8, 114.4, 55.4 ppm.

Synthesis of (*E*)-1-(3,5-bis(4-substitutedphenyl)thiophen-2-yl)-*N*-(4-substitutedphenyl)methanimines (15a-e) (general procedure):

Into 50 ml round bottom flask **13b** (1 eq, 0.7 mmol) was added together with 10 ml of THF. Na_2SO_4 1.5 eq. and corresponding aniline 1.5 eq. were added and reaction mixture was refluxed for 2 h. After cooling to room temperature reaction mixture was filtered and concentrated under reduced pressure. Remaining solids were washed with cold MeOH to obtain imines **15**.

(*E*)-1-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)-*N*-phenylmethanimine (15a)

Yellow solid, m.p. 179-181 °C. Yield: 73%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, s), 7.65 (2H, d, *J* = 8.3 Hz), 7.48 – 7.35 (7H, m), 7.27 – 7.19 (3H, m), 7.03 (2H, d, *J* = 8.4 Hz), 3.89 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 153.0, 151.4, 147.8, 136.1, 134.5, 132.2, 130.4, 129.3, 129.2, 127.6, 127.5, 127.2, 126.2, 126.1, 121.2, 114.3, 55.4 ppm.

(*E*)-1-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)-*N*-(4-methoxyphenyl)methanimine (15b)

Yellow solid, m.p. 141-142 °C. Yield: 75%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, s), 7.64 (2H, d, *J* = 8.3 Hz), 7.41 (4H, dd, *J* = 11.2, 8.6 Hz), 7.34 (1H, s), 7.22 (2H, d, *J* = 8.6 Hz), 7.03 (2H, d, *J* = 8.4 Hz), 6.92 (2H, d, *J* = 8.6 Hz), 3.89 (3H, s), 3.84 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 158.4, 150.9, 147.0, 145.8, 144.4, 136.5, 134.3, 132.3, 130.7, 130.4, 129.2, 127.6, 127.2, 126.2, 122.4, 114.4, 55.5, 55.4 ppm.

(*E*)-1-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)-*N*-(4-fluorophenyl)methanimine (15c)

Yellow solid, m.p. 179-181 °C. Yield: 76%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, s), 7.64 (2H, d, *J* = 8.2 Hz), 7.46 – 7.39 (4H, m), 7.35 (1H, s), 7.21 – 7.15 (2H, m), 7.10 – 7.00 (4H, m), 3.89 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5, 160.0, 159.8, 152.7, 135.9, 133.3 (d, *J* = 241.4 Hz), 130.7, 130.4, 129.4, 129.3, 127.4, 127.2, 126.2, 122.6 (d, *J* = 8.3 Hz), 115.9 (d, *J* = 22.5 Hz), 114.3, 114.3, 55.4 ppm.

(*E*)-1-((5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)methylene)-2-phenylhydrazine (15d)

Yellow crystals, m.p. 178-180 °C. Yield: 75%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (1H, s), 7.59 (2H, d, *J* = 8.1 Hz), 7.42 – 7.34 (4H, m), 7.34 – 7.27 (3H, m), 7.23 (1H, s), 7.10 (2H, d, *J* = 7.5 Hz), 7.01 (2H, d, *J* = 8.0 Hz), 6.96 – 6.87 (1H, m), 3.89 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 144.3, 141.8, 141.7, 134.3, 133.5, 132.6, 131.9, 130.2, 129.3, 129.1, 128.2, 126.8, 125.7, 120.3, 114.1, 112.7, 55.4 ppm.

(*E*)-*N*-(4-bromophenyl)-1-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)thiophen-2-yl)methanimine (15e)

Yellow crystals, m.p. 165-170 °C. Yield: 17%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, s), 7.64 (2H, d, *J* = 7.8 Hz), 7.48 (2H, d, *J* = 8.0 Hz), 7.45 – 7.39 (4H, m), 7.36 (1H, s), 7.09 (2H, d, *J* = 7.8 Hz), 7.03 (2H, d, *J* = 7.9 Hz), 3.89 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.9, 153.2, 150.3, 148.2, 146.9, 135.9, 134.6, 132.2, 132.1, 130.4, 129.3, 127.3, 127.2, 126.2, 122.8, 119.4, 114.3, 55.4 ppm.

Synthesis of (*E*)-3,5-bis(4-substitutedphenyl)-2-(4-substitutedstyryl)thiophenes 16a-d (general procedure):

Solution of aryltriphenylphosphonium bromide 1.2 eq in DCM 5 ml was made. KO*t*Bu (1.2 eq. 40 mg) and **13b** (1 eq, 0.3 mmol) were added. Reaction mixture was stirred at room temperature until completion (monitored by TLC). Reaction mixture was transferred to separatory funnel and washed with 2*10 ml NH_4Cl saturated solution and with 10 ml H_2O. Organic layer was separated and dried with Na_2SO_4. After evaporation of the solvent under reduced pressure remaining solid was purified using column chromatography (PhMe as eluent) to yield pure **16**.

(*E*)-5-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-styrylthiophene (16a)

Yellow crystals, m.p. 144-146 °C. Yield: 65%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66-7.19 (13H, m), 7.13-6.91 (3H, m), 3.91 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 141.6, 139.9, 137.1, 136.7, 133.4, 132.6, 130.3, 129.1, 129.0, 128.7, 128.5, 127.6, 126.8, 126.4, 126.2, 121.1, 114.1, 55.4 ppm.

(*E*)-5-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-(4-methoxystyryl)thiophene (16b)

Yellow crystals, m.p. 133-135 °C. Yield: 69%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (2H, d, *J* = 8.6 Hz), 7.39 (2H, d, *J* = 8.8 Hz), 7.36 (4H, d, *J* = 8.5 Hz), 7.25 (1H, s), 7.11 (1H, d, *J* = 16 Hz), 7.00 (2H, d, *J* = 8.8 Hz), 6.94 (1H, d, *J* = 16 Hz), 6.87 (2H, d, *J* = 8.8 Hz), 3.88 (3H, s), 3.82 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 159.0, 140.8, 139.3, 137.2, 133.3, 132.7, 130.3, 129.9, 129.1, 128.9, 128.7, 127.7, 126.7, 126.2, 119.1, 114.2, 114.0, 55.4, 55.4 ppm.

(*E*)-5-(4-chlorophenyl)-2-(3,4-dimethoxystyryl)-3-(4-methoxyphenyl)thiophene (16c)

Yellow crystals, m.p. 128-130 °C. Yield: 59%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (2H, d, *J* = 8.5 Hz), 7.40 (2H, d, *J* = 8.7 Hz), 7.35 (2H, d, *J* = 8.5 Hz), 7.25 (1H, s), 7.10 (1H, d, *J* = 16 Hz), 7.00 (2H, d, *J* = 8.7 Hz), 6.99 (1H, dd, *J* = 7.9 Hz, 2.0 Hz), 6.93 (1H, d, *J* = 16 Hz), 6.83 (2H, d, *J* = 8.3 Hz), 3.89 (6H, s), 3.88 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 149.1, 149.0, 140.9, 139.4, 137.0, 133.3, 132.6, 130.3, 129.1, 129.0, 129.0, 128.7, 126.7, 126.2, 119.6, 119.3, 114.0, 111.3, 109.1, 56.0, 55.9, 55.4 ppm.

(*E*)-5-(4-chlorophenyl)-2-(4-chlorostyryl)-3-(4-methoxyphenyl)thiophene (16d)

Yellow solid, m.p. 146-148°C. Yield: 72%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (2H, d, *J* = 8.6 Hz), 7.40 (1H, s), 7.38 (1H, s), 7.34 (2H, d, *J* = 2.4 Hz), 7.32 (2H, d, *J* = 2.2 Hz), 7.29 – 7.28 (1H, m), 7.25 – 7.24 (1H, m), 7.04 (2H, d, *J* = 8.7 Hz), 7.00 (2H, d, *J* = 8.7 Hz), 6.93 (1H, d, *J* = 16.0 Hz), 3.91 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 142.0, 136.3, 135.6, 133.4, 130.4, 130.3, 130.3, 129.1, 128.9, 128.7, 127.5, 126.9, 126.2, 124.7, 123.5, 121.7, 114.1, 55.4 ppm.

Synthesis of 3,5-diphenylthiophene-2-carboxylic acid 17:

Into 500 ml round bottomed flask **11c** (14 g) was added together with 250 ml H_2O and NaOH 1.5 eq. and 20 ml *i*PrOH. Reaction mixture was refluxed until fully transparent solution was obtained. Reaction mixture was filtered into 1000 ml beaker and diluted to 700 ml. pH was adjusted to <2 by addition of conc. HCl. Obtained white crystalline mass was filtered, washed with water and air dried to obtain 13g **17**.

White solid, m.p. 231-235°C (Lit. 235 °C [150]). Yield: 97%

Synthesis of 3,5-diphenylthiophene-2-carbonyl chloride 18:

3,5-diphenylthiophene-2-carboxylic acid **17** (13 g) was added into 250 ml round bottomed flask and $SOCl_2$ 150 ml added all at once. While stirring at room temperature with reflux condenser DMF (0.5 ml) was added. Reaction mixture was stirred until complete dissolution of **17**. Unreacted $SOCl_2$ was removed under reduced pressure and remaining solid recrystallized from hexane to yield 19g of **18**.

White solid, m.p. 215-216 °C (dec.). Yield: 96%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 – 7.70 (2H, m), 7.54 – 7.45 (8H, m), 7.40 (1H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 154.1, 152.7, 134.7, 132.3, 130.0, 129.5, 129.4, 128.9, 128.8, 128.4, 128.2, 126.3 ppm.

Synthesis of 3-(4-substitutedphenyl)-1-(3,5-diphenylthiophen-2-yl)prop-2-yn-1-ones 19a-b (general procedure):
Into 25 ml round bottomed flask (inert atmosphere) were added: **18** (1 eq, 2 mmol), CuI 0.06 eq, toluene 3ml and 4-substituted phenyl acetylene 1.4 eq. with TEA 5.2 eq. Flask was immersed into preheated oil bath (88 °C) and reaction mixture was magnetically stirred for 5 h. After cooling down to room temperature mixture was transferred into separatory funnel and washed with NH_4Cl saturated solution and with H_2O. Organic layer was separated and dried with Na_2SO_4 and filtered through plug of silicagel. After removal of the solvent under reduced pressure **19** was obtained as a solid.

1-(3,5-Diphenylthiophen-2-yl)-3-phenylprop-2-yn-1-one (19a)
White solid, m.p. 152-155°C. (Rf = 0.6; Tol.) Yield: 80%
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 6.9 Hz), 7.63 (2H, d, *J* = 6.6 Hz), 7.50 – 7.39 (7H, m), 7.36 (1H, s), 7.33 – 7.27 (2H, m), 7.18 (2H, d, *J* = 7.3 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 151.2, 149.6, 138.0, 135.7, 133.2, 132.9, 130.5, 129.8, 129.4, 129.2, 128.4, 128.3, 128.2, 128.2, 126.3, 120.0, 93.3, 87.8 ppm.

3-(4-Chlorophenyl)-1-(3,5-diphenylthiophen-2-yl)prop-2-yn-1-one (19b)
Yellowish solid, m.p. 157-159°C. (Rf = 0.5, PE:EA = 10:1) Yield: 32%
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.71 (2H, m), 7.64 – 7.60 (2H, m), 7.50 – 7.40 (6H, m), 7.36 (1H, s), 7.29 – 7.25 (2H, m), 7.09 – 7.03 (2H, m) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 151.5, 149.8, 138.0, 136.9, 135.7, 134.3, 132.9, 129.9, 129.5, 129.2, 128.7, 128.5, 128.3, 128.2, 126.3, 118.4, 91.9, 88.4 ppm.

Synthesis of 5-(3,5-diphenylthiophen-2-yl)-3-phenylisoxazole (20):
Into 25 ml round bottomed flask with magnetic stirrer were added **19a** (1 eq, 84 mg), hydroxylamine hydrochloride (1.1 eq, 24 mg), EtOH 5 ml and TEA (1.5 eq). Reaction mixture was refluxed for 4 h. after cooling to room temperature formed crystals were filtered and washed with small amount of cold EtOH and air dried to afford 26 mg of pure **20**.
White needles, m.p. 118-121°C. Yield: 32%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73-7.66 (4H, m), 7.53-7.40 (10H, m), 7.39-7.32 (2H, m), 6.18 (1H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1, 162.7, 146.1, 143.3, 135.8, 133.3, 130.0, 129.1, 128.9, 128.9, 128.9, 128.8, 128.5, 128.4, 126.8, 126.6, 125.9, 123.0, 98.4 ppm.

Synthesis of 4-(3,5,5'-triphenyl-[2,3'-bithiophen]-2'-yl)pyridine (21):
Into 25 ml round bottomed flask with **19a** (1 eq, 56 mg) were added **24d** 2 eq. and KOH 5 eq. with MeOH 5 ml. Reaction mixture was refluxed for 5 h. and after cooling to room temperature water was added and organic material was extracted with DCM. After washing of organic layer with H2O and drying with Na2SO4 silicagel was added and solvent was evaporated under reduced pressure. Remaining solid was transferred into silicagel column and chromatography performed with Tol:PE = 5:1 to obtain pure **21**.
Yellowish crystals, m.p. 110-115ºC. Yield: 46%
^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.37-8.33 (2H, m), 7.77-7.70 (5H, m), 7.66 (1H, s), 7.48-7.41 (4H, m), 7.40-7.31 (2H, m), 7.18-7.10 (5H, m), 7.03-6.99 (2H, m) ppm.
^{13}C NMR (100 MHz, DMSO-d_6) δ: 150.2, 144.3, 143.6, 141.6, 140.6, 136.8, 135.7, 133.5, 133.0, 132.9, 130.5, 129.7, 129.4, 129.0, 128.7, 128.6, 128.3, 128.2, 127.4, 126.1, 125.9, 125.7, 122.1 ppm.

Synthesis of 3-(3,5-diphenylthiophen-2-yl)-5-phenyl-1*H*-pyrazole (22):
Into 50 ml round bottomed flask with **19a** (1 eq, 136 mg) were added EtOH 4 ml and hydrazine hydrate 2 eq. Reaction mixture was refluxed for 2 h. and when cooled back to room temperature large amount of crystalline mass appeared. Crystals were filtered and washed with small amount of cold EtOH and air dried to afford **22**.
White needles, m.p. 196-198ºC. Yield: 48%
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 – 7.59 (4H, m), 7.52 – 7.26 (13H, m), 6.44 (1H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.1, 140.4, 136.3, 133.8, 130.9, 129.0, 128.9, 128.8, 128.8, 128.6, 128.4, 127.9, 127.9, 127.5, 126.3, 125.7, 125.6, 125.5, 101.9 ppm.

Synthesis of 2-(5'-(4-chlorophenyl)-3,5-diphenyl-[2,3'-bithiophen]-2'-yl)-1*H*-benzo[*d*]imidazole (23):
Into 25 ml pear shaped flask were added **19b** (1 eq, 155 mg) and **24a** (1.2 eq, 77mg) together with DBU (0.4 ml) and MeOH 4 ml. Reaction mixture was

refluxed for 4 h. Solvent vas removed under reduced pressure and remaining residue was purified by column chromatography PE:EA = 4:1 to afford **23**.
Yellowish powder, m.p. 140-144ºC. Yield: 23%
^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.05 (1H, br. s), 7.81 (1H, s), 7.75 (2H, d, *J* = 7.3 Hz), 7.68 (2H, d, *J* = 8.6 Hz), 7.50 (2H, d, *J* = 8.6 Hz), 7.47-7.41 (3H, m), 7.40 (1H, s), 7.39-7.31 (3H, m), 7.23-7.10 (6H, m) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.3, 143.5, 143.2, 142.0, 135.9, 133.7, 133.6, 133.5, 131.9, 130.3, 129.8, 129.8, 129.7, 129.7, 128.6, 128.6, 128.6, 128.5, 127.6, 127.6, 126.5, 126.5, 126.2, 125.7 ppm.

Synthesis of thiols 24a-b (general procedure):
Based on known procedure [151]. Benzene-1,2-diamine or 4-chlorobenzene-1,2-diamine 1 mol eq. is added to round bottomed flask and H_2O (5 ml for 1g diamine) is added. Conc. HCl (same volume as H_2O) is also added to the flask. Reaction mixture is stirred for 5 min. and thioglycolic acid 1 eq. is added. Reaction mixture was refluxed for 12 h. After cooling down to room temperature $NaHCO_3$ was cautiously added (lots of foam) until pH was > 8. Formed solid material was filtered, washed with water and air dried to afford **24a-b**.

(1*H*-benzo[*d*]imidazol-2-yl)methanethiol (24a)
Grey powder, m.p. 155-160 ºC (lit. 156-157 ºC [150]). Yield: 70%
^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.60 (1H, s), 7.60 – 7.48 (2H, m), 7.37 (1H, s), 7.18 (2H, dd, *J* = 5.9, 3.1 Hz), 4.21 (2H, s) ppm.
^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.1, 151.1, 143.4, 128.8, 122.3, 119.1, 111.8, 36.3 ppm.

(5-Chloro-1H-benzo[*d*]imidazol-2-yl)methanethiol (24b)
Brownish crystals, m.p. 118-125 ºC (lit. 125 ºC [152]). Yield: 52%

Synthesis of carbamimidothioates 24c-e (general procedure):
Based on literature method [113]. Into 50 ml round bottomed flask corresponding substituted methyl chloride 1 eq. is added together with thiourea 1.2 eq. and ethanol 20 ml is poured into the flask. Reaction mixture is refluxed for 4 h. and cooled back to room temperature. Formed crystals are filtered, washed with cold EtOH, acetone and air dried.

(5,6-Dichloro-1*H*-benzo[*d*]imidazol-2-yl)methyl carbamimidothioate hydrochloride (24c)
Brownish crystals, m.p. 225-235 ºC (lit. 231-233 ºC [153]). Yield: 82%

Pyridin-4-ylmethyl carbamimidothioate hydrochloride (24d)
White crystals, m.p. 209-217 ºC (lit. 214 ºC [154]). Yield: 71%

(1-Methyl-1*H*-imidazol-2-yl)methyl carbamimidothioate hydrochloride (24e)
White crystals, m.p. 190-195 ºC. Yield: 98%

Synthesis of 3,5-diaryl-2-heteroarylthiophenes (25a-s) and 2-heteroaryl-3,5-diaryl-2,3-dihydrothiophen-3-ols (27a-e).
To the 25 ml round bottomed flask the corresponding heteroarylmethanethiol **24a-b** or heteroarylmethyl carbamimidothioate **24c-e** (1.5 eq, 0.45 mmol) and NaOH 3 eq. were added with 5 ml EtOH. Reaction mixture was refluxed for 1 hour under inert atmosphere, then the corresponding 1,3-diarylpropynone **7** 1 eq. was added and refluxing was continued until full completion of the reaction (monitored by TLC). The solvent was evaporated under reduced pressure. Residue was portioned between DCM and water. The organic layer was separated and washed with water, dried with Na_2SO_4 and concentrated under reduced pressure. The resulting solid material was purified by crystallization or column chromatography.

2-(3,5-Diphenylthiophen-2-yl)-*1H*-benzo[*d*]imidazole (25a)
Yellowish powder, m.p. 210 – 215 ºC (*i*PrOH). Yield: 62%
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.89 (1H, s), 7.79 (1H, d, *J* = 7.8 Hz), 7.69 (2H, d, *J* = 7.3 Hz), 7.62 – 7.49 (5H, m), 7.43 (2H, t, *J* = 7.5 Hz), 7.39 – 7.31 (2H, m), 7.29 – 7.23 (1H, m), 7.20 (2H, m) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.0, 143.1, 141.8, 136.0, 133.4, 129.4, 129.1, 129.0, 128.8, 128.4, 126.6, 125.8, 123.3, 122.6, 119.5, 110.5 ppm.
HRMS (ESI) calcd. for $C_{23}H_{17}N_2S$ (MH^+): 353.1106; found 353.1109.

2-(3,5-Bis(4-methoxyphenyl)thiophen-2-yl)-*1H*-benzo[*d*]imidazole (25b)
Yellow crystals, m.p. 255 – 258 °C (EtOH). Yield: 92%.
^{1}H NMR (400 Hz, $CDCl_3$) δ: 9.18 (1H, br. s), 7.56 (2H, d, *J* = 8.0 Hz), 7.50 - 7.42 (4H, m), 7,20 - 7,13 (3H, m), 6.99 (2H, d, *J* = 8.0 Hz), 6.91 (2H, d, *J* = 4.8 Hz), 3.85 (3H, s), 3.83 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 146.8, 145.9, 141.8, 130.1, 128.1, 127.1, 126.2, 125.6, 122.8, 114.7, 114.4, 55.3 ppm.
HRMS (ESI) calcd. for $C_{25}H_{21}N_2O_2S$ (MH^+): 413.1318; found 413.1322.

2-(5-(4-Methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-*1H*-benzo[*d*]imidazole (25c)

Yellow crystals, m.p. 260 – 270 ºC (Rf = 0.4, PE:EA = 3:1). Yield: 42%.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.62 (1H, s), 7.82 – 7.67 (7H, m), 7.65 – 7.59 (1H, m), 7.44 - 7.36 (1H, m), 7.26 - 7.14 (2H, m), 7.05 (2H, d, *J* = 8.7 Hz), 3.81 (3H, s) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.1, 145.9, 145.4, 143.9, 140.6, 139.6, 135.3, 129.9, 128.5 (q, *J* = 31.3 Hz), 127.5, 126.9, 126.2, 126.0 (q, *J* = 3.7 Hz), 125.8, 124.8 (q, *J* = 270 Hz), 123.3, 122.3, 119.2, 115.2, 112.1, 55.8 ppm.

HRMS (ESI) calcd. for $C_{25}H_{18}F_3N_2OS$ (MH^+): 451.1086; found 451.1091.

2-(3-(4-Methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-*1H*-benzo[*d*]imidazole (25d)

Yellow crystals, m.p. 120 – 125 ºC (Rf = 0.4, PE:EA = 3:1). Yield: 64%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.49 (1H, br. s), 7.64 (2H, d, *J* = 8.0 Hz); 7.56 (2H, d, *J* = 8.0 Hz), 7.48 (2H, br. s), 7.36 (2H, d, *J* = 8.4 Hz), 7.27 (1H, s), 7.23-7.20 (2H, m), 6.91 (2H, d, *J* = 8.8 Hz), 3.79 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.2, 143.8, 142.0, 136.7, 130.0 (q, *J* = 32.6 Hz), 130.0, 127.8, 127.7, 127.5, 126.0 (q, *J* = 3.6 Hz), 125.8, 124.0 (q, *J* = 270.4 Hz), 123.1, 114.7, 55.3 ppm.

HRMS (ESI) calcd. for $C_{25}H_{18}F_3N_2OS$ (MH^+): 451.1086; found 451.1090.

2-(3,5-Bis(4-(trifluoromethyl)phenyl)thiophen-2-yl)-*1H*-benzo[*d*]imidazole (25e)

Yellow crystals, m.p. 130 – 135 ºC (Rf = 0.5, PE:EA = 4:1). Yield: 44%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.17 (1H, br. s), 7.53 - 7.49 (5H, m), 7.47 - 7.42 (5H, m), 7.26 - 7.21 (3H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.3, 144.4, 140.6, 138.6, 136.0, 130.2 (q, *J* = 33.0 Hz), 130.4 (q, *J* = 33.0 Hz), 128.9, 128.5, 128.3, 127.9, 127.1, 126.0 (q, *J* = 3.7 Hz), 125.9 (q, *J* = 3.7 Hz), 125.6, 123.8 (q, *J* = 270.0 Hz), 123.7 (q, *J* = 271.0 Hz), 123.5 ppm.

HRMS (ESI) calcd. for $C_{25}H_{15}F_6N_2S$ (MH^+): 489.0855; found 489.0859.

2-(3,5-Bis(4-(pentyloxy)phenyl)thiophen-2-yl)-*1H*-benzo[*d*]imidazole (25f)

White powder, m.p. 95 - 100 ºC (*i*PrOH). Yield: 72%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (1H, br. s), 7.58 (2H, d, *J* = 8.6 Hz), 7.45 (2H, d, *J* = 8.5 Hz), 7.29 (1H, s), 7.26 – 7.12 (3H, m), 7.15 (1H, s), 7.02 (2H, d, *J* = 8.6 Hz), 6.93 (2H, d, *J* = 8.7 Hz), 4.08 – 3.95 (4H, m), 1.90 – 1.78 (4H, m), 1.56 – 1.36 (8H, m), 1.04 – 0.91 (6H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.5, 159.4, 147.0, 145.9, 143.2, 141.8, 133.5, 130.1, 128.0, 127.1, 126.1, 125.6, 125.6, 123.0, 122.4, 119.3, 115.3, 115.0, 110.4, 68.2, 68.1, 29.0, 28.9, 28.2, 28.2, 22.5, 22.4, 14.0, 14.0 ppm.
HRMS (ESI) calcd. for $C_{33}H_{37}N_2O_2S$ (MH^+): 379.2268; found 379.2270.

5-Chloro-2-(3,5-diphenylthiophen-2-yl)-*1H*-benzo[*d*]imidazole (25g)
Yellowish powder, m.p. 205 – 209 ºC (*i*PrOH). Yield: 55%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.29 (1H, s), 7.82 (2H, d, *J* = 7.3 Hz), 7.78 (1H, s), 7.73 – 7.35 (10H, m), 7.22 (1H, d, *J* = 8.1 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.7, 145.3, 142.8, 135.2, 133.3, 130.1, 129.8, 129.2, 129.1, 129.0, 128.7, 128.5, 127.5, 126.9, 126.0, 123.1, 120.5, 118.4, 113.5 ppm.
HRMS (ESI) calcd. for $C_{23}H_{16}ClN_2S$ (MH^+): 387.0717; found 387.0719.

2-(3,5-Bis(4-methoxyphenyl)thiophen-2-yl)-5-chloro-*1H*-benzo[*d*]imidazole (25h)
Yellow powder, m.p. 235 – 237 ºC (EtOH). Yield: 58%.
^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.03 (1H, br. s), 7,72 (2H, d, *J* = 8.6 Hz), 7.60-7.53 (2H, m), 7.50 (1H, d, *J* = 8.3 Hz), 7.41 (2H, d, *J* = 8.6 Hz), 7.19 (1H, dd, *J* = 8.5, 1.6 Hz), 7.03 (2H, d, *J* = 8.7 Hz), 6.98 (2H, d, *J* = 8.6 Hz), 3.81 (3H, s), 3.79 (3H, s) ppm.
^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.0, 159.6, 148.1, 145.2, 142.5, 130.3, 127.7, 127.7, 127.4, 127.4, 126.8, 126.3, 126.0, 124.1, 124.1, 122.7, 122.7, 115.1, 114.6, 55.8, 55.6 ppm.
HRMS (ESI) calcd. for $C_{25}H_{20}ClN_2O_2S$ (MH^+): 447.0928; found 447.0934.

5-Chloro-2-(5-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-*1H*-benzo[*d*]imidazole (25i)
Yellow crystals, m.p. 200 – 205 °C (Rf = 0.2, $CHCl_3$:MeCN = 98:2), Yield: 64%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, br. s), 7.72 (2H, d, *J* = 8.0 Hz), 7.69 (1H, s), 7.61 (2H, d, *J* = 8.0 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 7.26-7.15 (2H, m), 7.16 (1H, s), 6.92 (2H, d, *J* = 8.0 Hz), 3.84 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1, 147.1, 140.6, 139.4, 139.4, 130.8, 130.6 (q, *J* = 32.6 Hz), 130.6, 129.3, 127.2, 126.3, 126.2 (q, *J* = 3.5 Hz), 125.9, 125.7, 125.3, 125.2, 125.1, 123.8 (q, *J* = 270.6 Hz), 114.6, 113.7, 55.4 ppm.
HRMS (ESI) calcd. for $C_{25}H_{17}ClF_3N_2OS$ (MH^+): 485.0697; found 485.0701.

5,6-Dichloro-2-(3,5-diphenylthiophen-2-yl)-*1H*-benzo[*d*]imidazole (25j)
Yellowish powder, m.p. 232 – 233 ºC (*i*PrOH). Yield: 60%.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.32 (1H, br. s), 7.89 - 7.68 (5H, m), 7.56-7.31 (8H, m) ppm.
^{13}C NMR (100 MHz, DMSO-d_6) δ: 148.9, 145.7, 143.2, 139.5, 135.1, 133.2, 129.8, 129.2, 129.1, 129.1, 128.6, 127.6, 126.1, 125.6, 125.1, 116.8 ppm.
HRMS (ESI) calcd. for $C_{23}H_{15}Cl_2N_2S$ (MH^+): 421.0328; found 421.0332.

2-(3,5-Bis(4-methoxyphenyl)thiophen-2-yl)-5,6-dichloro-*1H*-benzo[*d*]imidazole (25k)
Yellow crystals, m.p. 122 - 127 °C (Rf = 0.3, PE:EA = 4:1), Yield 74%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (1H, br. s), 7.79 (1H, s), 7.59 (2H, d, *J* = 8.4 Hz), 7.43 (2H, d, *J* = 8.8 Hz), 7.31 (1H, s), 7.14 (1H, s), 7.05 (2H, d, *J* = 8.4 Hz), 6.94 (2H, d, *J* = 8.8 Hz), 3.90 (3H, s), 3.85 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1, 160.0, 148.9, 146.8, 145.2, 142.7, 132.7, 130.1, 127.8, 127.2, 126.0, 125.7, 124.6, 120.2, 114.9, 114.5, 111.8, 55.4 ppm.
HRMS (ESI) calcd. for $C_{25}H_{19}Cl_2N_2O_2S$ (MH^+): 481.0539; found 481.0545.

5,6-Dichloro-2-(5-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-*1H*-benzo[*d*]imidazole (25l)
Yellow crystals, m.p. 227 – 231 °C (Rf = 0.3, $CHCl_3$:MeCN = 98:2), Yield 62%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.13 (1H, br. s), 7.76 (1H, s), 7.72 (2H, d, *J* = 8.0 Hz), 7.60 (2H, d, *J* = 8.0 Hz), 7.54 (2H, d, *J* = 8.8 Hz), 7.34 (1H, s), 7.16 (1H, s), 6.92 (2H, d, *J* = 8.8 Hz), 3.84 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 148.0, 147.6, 142.6, 141.0, 139.3, 130.9 ($^{2}J_{C\text{-}F}$ = 32.6 Hz), 130.7, 129.3, 127.2, 126.3 (q, *J* = 3.5 Hz), 125.5, 125.4, 125.2, 123.8 (q, *J* = 270.9 Hz), 114.6, 112.0, 55.4 ppm.
HRMS (ESI) calcd. for $C_{25}H_{16}Cl_2F_3N_2OS$ (MH^+): 519.0307; found 519.0315.

4-(3,5-Diphenylthiophen-2-yl)pyridine (25m)
Yellowish plates, m.p. 107 – 110 °C (EtOH). Yield: 67%.
^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.50 (2H, d, *J* = 5.0 Hz), 7.79 – 7.75 (2H, m), 7.70 (1H, s), 7.47 (2H, t, *J* = 7.6 Hz), 7.43 – 7.34 (6H, m), 7.22 (2H, dd, *J* = 4.6, 1.5 Hz) ppm.
^{13}C NMR (100 MHz, DMSO-d_6) δ: 150.5, 144.2, 141.7, 141.4, 135.8, 134.0, 133.3, 129.7, 129.3, 129.2, 128.8, 128.3, 128.0, 125.9, 123.2 ppm.
HRMS (ESI) calcd. for $C_{21}H_{16}NS$ (MH^+): 314.0998; found 314.0998.

4-(3,5-Bis(4-methoxyphenyl)thiophen-2-yl)pyridine (25n)
Yellow crystals, m.p. 120 – 125 °C (Rf = 0.5, Tol:EA = 1:1). Yield: 89%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (2H, br. s), 7.57 (2H, d, *J* = 8.0 Hz), 7.24-7.22 (2H, m), 7.20-7.17 (3H, m), 6.94 (2H, d, *J* = 8.0Hz), 6.89 (2H, d, *J* = 8.0 Hz), 3.84 (6H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 159.2, 149.9, 144.5, 142.3, 141.3, 137.9, 132.5, 132.5, 130.1, 128.5, 127.1, 126.4, 114.5, 114.2, 55.4, 55.3 ppm.
HRMS (ESI) calcd. for $C_{23}H_{19}NO_2S$ (MH^+): 374.1209; found 374.1212.

4-(5-(4-Methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)thiophen-2-yl)pyridine (25o)
Amber oil (Rf = 0.3, PE:EA = 2:1), yield: 51%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (2H, d, *J* = 6.0 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.8 Hz), 7.41 (2H, d, *J* = 8.0 Hz), 7.22 (1H, s), 7.14 (2H, d, *J* = 6.0 Hz), 6.93 (2H, d, *J* = 8.8 Hz), 3.82 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 149.9, 145.4, 141.7, 139.7, 139.7, 134.1, 129.7 ($^2J_{C\text{-}F}$ = 32.3 Hz), 129.3, 127.1, 125.9, 125.7 ($^3J_{C\text{-}F}$ = 3.7 Hz), 125.6, 124.1 ($^1J_{C\text{-}F}$ = 270.5 Hz), 123.0, 114.5, 55.4 ppm.
HRMS (ESI) calcd. for $C_{23}H_{17}F_3NOS$ (MH^+): 412.0977; found 412.0981.

4-(3-(4-Methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)thiophen-2-yl)pyridine (25p)
Yellow crystals, m.p. 120 - 125°C (Rf = 0.3, Tol:EA = 2:1). Yield: 67%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (2H, d, *J* = 6.0 Hz), 7.74 (2H, d, *J* = 8.4 Hz), 7.66 (2H, d, *J* = 8.4 Hz), 7.41 (1H, s), 7.24 (2H, d, *J* = 8.8 Hz), 7.22 (2H, d, *J* = 6.0 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 3.84 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 149.9, 142.4, 141.9, 141.5, 137.0, 134.9, 130.1, 129.7, 129.9 (q, *J* = 32.5 Hz), 128.4, 127.9, 126.1 (q, *J* = 3.7 Hz), 125.8, 124.0 (q, *J* = 270.1 Hz), 114.3, 55.3 ppm.
HRMS (ESI) calcd. for $C_{23}H_{17}F_3NOS$ (MH^+): 412.0977; found 412.0981.

4-(3,5-Bis(4-(trifluoromethyl)phenyl)thiophen-2-yl)pyridine (25r)
Yellow crystals, m.p. 115 – 130 °C (Rf = 0.4, Tol:EA = 2:1). Yield: 50%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (2H, d, *J* = 8.0 Hz), 7.75 (2H, d, *J* = 8.0 Hz), 7.68 (2H, d, *J* = 8.0 Hz), 7.63 (2H, d, *J* = 8.0 Hz), 7.44 (2H, d, *J* = 8.0 Hz), 7.44 (1H, s), 7.19 (2H, d, *J* = 8.0 Hz) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.1, 143.2, 141.1, 139.9, 139.1, 136.7, 136.6, 130.2 (q, *J* = 33.0 Hz), 130.0 (q, *J* = 32.0 Hz), 129.3, 127.8, 126.2 ($^3J_{C\text{-}F}$ = 3.7 Hz), 125.9, 125.8 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 271.0 Hz), 124.0 (q, *J* = 270.0 Hz), 123.1 ppm.
HRMS (ESI) calcd. for $C_{23}H_{14}F_6NS$ (MH^+): 450.0746; found 450.0751.

2-(3,5-Bis(4-methoxyphenyl)thiophen-2-yl)-1-methyl-*1H*-imidazole (25s)
Brown oil (Rf = 0.6, Tol:EA = 1:1). Yield: 30%.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (2H, d, *J* = 8.0 Hz), 7.38 (1H, s), 7.16 - 7.15 (2H, m), 7.14 (1H, s), 6.91 (2H, d, *J* = 8.0 Hz), 6.84 - 6.83 (2H, m), 6.81 (1H, s), 3.81 (3H, s), 3.77 (3H, s), 3.00 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.6, 159.0, 145.4, 142.2, 141.5, 129.0, 128.9, 128.6, 127.1, 126.6, 123.4, 123.1, 121.7, 114.4, 114.2, 55.4, 55.2, 33.3 ppm.
HRMS (ESI) calcd. for $C_{22}H_{21}N_2O_2S$ (MH^+): 377.1318; found 377.1312.

(2*R*,3*S*) or (2*S*,3*R*)-5-(4-methoxyphenyl)-2-(1-methyl-*1H*-imidazol-2-yl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol (27a)
Brown oil. Yield: 38%.
^{1}H NMR (400 Hz, $CDCl_3$) δ: 7.73 (2H, d, *J* = 8.4 Hz), 7.57 (2H, d, *J* = 8.0 Hz), 7.50 (2H, d, *J* = 8.8 Hz), 7.03 (1H, s), 6.89 (2H, d, *J* = 8.8 Hz), 6.82 (1H, s), 6.10 (1H, s), 5.08 (1H, s), 3.83 (3H, s), 3.42 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 142.7, 141.7 (q, *J* = 265.0 Hz), 137.8, 129.7 (q, *J* = 32.0 Hz), 128.8, 128.1, 127.2, 126.3, 125.1 (q, *J* = 4.0 Hz), 123.1, 122.0, 113.9, 88.7, 55.4, 55.3, 52.4, 32.5 ppm.

(2*R*,3*S*) or (2*S*,3*R*)-3-(4-methoxyphenyl)-2-(1-methyl-*1H*-imidazol-2-yl)-5-(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol (27b)
Brown oil. Yield: 44%.
^{1}H NMR (400 Hz, DMSO-d_6) δ: 7.82 (2H, d, *J* = 8.4 Hz), 7.79 (2H, d, *J* = 8.8 Hz), 7.44 (2H, d, *J* = 8.8 Hz), 7.16 (1H, s), 6.93 (1H, s), 6.90 (2H, d, *J* = 8.4 Hz), 6.53 (1H, s), 5.42 (1H, s), 3.75 (3H, s), 3.46 (3H, s) ppm.
^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.0, 142.7, 138.9 (q, *J* = 271.9 Hz), 137.3, 129.4 (q, *J* = 31.8 Hz), 128.3, 127.5, 127.3, 126.7, 126.1 (q, *J* = 3.6 Hz), 123.4, 123.1, 113.8, 88.4, 55.5, 55.5, 53.5, 33.0 ppm.

(2*R*,3*S*) or (2*S*,3*R*)-2-(1-methyl-*1H*-imidazol-2-yl)-3,5-bis(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol (27c)
Brown oil. Yield 41%.
^{1}H NMR (400 Hz, $CDCl_3$) δ: 7.76 (2H, d, *J* = 8.0 Hz), 7.72-7.65 (6H, m), 7.62 (2H, d, *J* = 8.0 Hz), 7.07 (1H, s), 6.86 (1H, s), 6.33 (1H, s), 5.15 (1H, s), 3.47 (3H, s) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.3, 139.9 (q, *J* = 266.0 Hz), 139.8 (q, *J* = 272.0 Hz), 137.9, 136.5, 131.0 (q, *J* = 32.0 Hz), 130.0 (q, *J* = 32.0 Hz), 129.6, 129.0, 127.4, 127.0, 126.2, 125.6 (q, *J* = 3.7 Hz), 125.2 (q, *J* = 3.7 Hz), 121.6, 88.6, 52.4, 32.5 ppm.

(2*R*,3*S*) or (2*S*,3*R*)-2-(1*H*-benzo[d]imidazol-2-yl)-5-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol (27d)

Brown oil. Yield: 10%.

^{1}H NMR (400 Hz, $CDCl_3$) δ: 7.62 - 7.60 (4H, m), 7.55 - 7.52 (2H, m), 7.49 - 7.44 (4H, m), 6.84 (2H, d, *J* = 8.0 Hz), 6.02 (1H, s), 5.46 (1H, s), 3.79 (3H, s) ppm.

(2*R*,3*S*) or (2*S*,3*R*)-2-(*1H*-benzo[*d*]imidazol-2-yl)-3,5-bis(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol (27e)

Brown oil. Yield: 50%.

^{1}H NMR (400 Hz, $CDCl_3$) δ: 7.64 - 7.58 (8H, m), 7.54 - 7.25 (4H, m), 6.23 (1H, s), 5.47 (1H, s) ppm.

CONCLUSIONS

1. 19 alkynones **7** were synthesized by Sonogashira-type reaction between terminal acetylenes and chloroanhydrides with the aim to use them as a starting material for investigation of cyclization reactions.

2. Simple one step procedure towards alkoxyarylmethyl group containing isoxazole and chromone rings from 1,3-diarylalkynones was developed. Optimal conditions for the synthesis of alkoxymethyl group containing isoxazoles are (*Z*)-3-aryl-1-phenylprop-2-yn-1-one-*O*-methyl oxime with 1 equivalent of BF_3*Et_2O in acetonitrile at room temperature. Same reaction conditions apply to the synthesis of chromones.

3. The importance of triple bond activation for successful cyclization reactions was investigated. Thus, Isoxazoles were obtained in high yields from the starting materials where triple bond is activated by electron-donating alkoxy groups only. Reactions did not proceed when triple bond of the starting material was not activated by electron-donating alkoxy groups. However, chromones are obtained in high yields from the starting 1,3-diarylalkynones having either EWG substituents or EDG substituents.

4. We have found that odorless, stable, and easily synthesized carbamimidothioates can be used as building blocks for 2,3,5-trisubstituted thiophenes via Fiesselmann type cyclization between alkynones and carbamimidothioates.

5. It was found, that the introduction of electron deficient arenes in 3rd position and electron rich arenes in 5th position of the thiophene ring not only allowed to achieve PLQY up to 83% for 2-(2-benzimidazoyl) thiophenes (**25l**) but also enhances PLQY of the less emissive pyridine-containing thiophenes.

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SUMMARY / SANTRAUKA

ĮVADAS

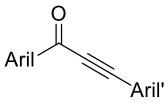
1,3-Diarilalkinonai pirmą kartą paminėti mokslinėje literatūroje 1982 m. Nuo tada sukurta daugybė metodų 1,3-diarilalkinonams sintetinti. Ši junginių klasė yra naudojama kaip prekursoriai penkianarių ir šešianarių heterociklinių junginių (izoksazolai, tiofenai, chromonai, pirolai ir k.t.) sintezei. Yra žinoma daugybė savo fotofizikinėmis savybėmis vertingų ar biologiškai aktyvių medžiagų savo struktūroje turinčių šių heterociklų fragmentus.

Per pastaruosius dešimt metų mūsų mokslinė grupė intensyviai vystė C≡C trigubojo ryšio chemiją. Pavyzdžiui, alifatinių aminų prijungimo prie 2-(1-alkinil)-2-alken-1-onų reakcijų tyrimai arba „Kabachnik−Fields" reakcijos būdu iš acetileninių aldehidų gautų 1*H*-pirol-2-il-fosfonatų ir 1,2-dihidropiridin-2-il-fosfonatų tyrimai. Mes taip pat pastebėjome, kad panaudojant acetalius ir Lewis'o rūgštis sugeneruoti oksokarbenio jonai dalyvauja reakcijose su *O* ir *N* propargilintais junginiais. Tai mums leido sukurti naują funkcionalizuotų 4*H*-1,3-oksazinų, 4*H*-1,3-tiazinų, 4,5-dihidroksitiazolų ir α-pakeistų enonų sintezės metodą.

Taigi mūsų mokslinė grupė nusprendė detaliau išstudijuoti oksokarbenio jonų pritaikomumą - išbandėme juos reakcijose su 1,3-diarilalkinonais, turinčiais struktūrinių panašumų į prieš tai studijuotus propargil grupę turinčius junginius. Taip buvo sukurtas naujas, alkoksimetil grupes turinčių, izoksazolų ir chromonų sintezės metodas.

Taip pat iš 1,3-diarilakinonų susintetinome seriją 2,3,5-tripakeistų tiofenų ir ištyrėme jų fotofizikines savybes.

Pagrindinis **disertacijos tikslas** – naujų sintezės kelių paieška funkcionalizuotiems heterocikliniams junginiams sintetinti panaudojant 1,3-diarilalkinonus (1 pav.).



1 Paveikslas. Bendra 1,3-diarilalkinonų struktūra.

Tikslui įgyvendinti iškelti šie **uždaviniai:**

1. Ištirti esamą mokslinę literatūrą apie 1,3-diarilalkinonų panaudojimą izoksazolų, tiofenų ir flavonų sintezei.
2. Sukurti naują sintezės metodą izoksazolams ir flavonams iš 1,3-diarilalkinonų sintetinti.
3. Panaudojant 1,3-diarilalkinonus susintetinti seriją 2,3,5-tripakeistų tiofenų ir ištirti gautų junginių fotofizikines savybes.

Santraukoje tyrimų rezultatai pateikiami trijuose skyriuose. Pirmajame skyriuje aptariama 1,3-diarilalkinonų sintezė. Antrajame skyriuje nagrinėjamas 1,3-diarilalkinonų pritaikymas alkoksimetil grupes turintiems izoksazolams ir chromonams sintetinti. Trečiajame skyriuje glaustai aptariamas 1,3-diarilalkinonų pritaikymas 2,3,5-tripakeistų tiofenų sintezėje bei šių tiofenų fotofizikinių savybių matavimai.

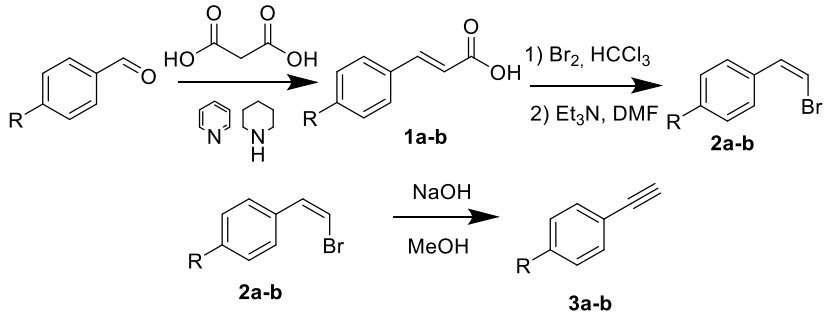
Iš gautų rezultatų buvo suformuluoti šie **ginamieji teiginiai:**

1. (*Z*)-3-aril-1-fenilprop-2-in-1-onų *O*-metil oksimai veikiami atitinkamais acetaliais ir BF_3*Et_2O acetonitrile virsta į alkoksimetil grupes turinčius izoksazolus.
2. 3-aril-1-(2-metoksifenil)-prop-2-in-1-onai veikiami atitinkamais acetaliais ir BF_3*Et_2O acetonitrile virsta į alkoksimetil grupes turinčius chromonus.
3. Nustatyta, kad (*Z*)-3-aril-1-fenilprop-2-in-1-onų *O*-metil oksimai neturintys elektronų donorinių grupių nedalyvauja elektrofilinėje ciklizacijoje su oksokarbenio jonais. Tačiau 3-aril-1-(2-metoksifenil)-prop-2-in-1-onai lengvai virsta alkoksimetil grupes turinčiais chromonais esant tiek elektronus ištraukiančioms, tiek donorinėms grupėms aromatiniame žiede greta trigubojo ryšio.
4. Karbamimidotioatai gali būti panaudojami Fiesselmann'o tipo reakcijoje 2,3,5-tripakeistiems tiofenams sintetinti. Tokiu būdu susintetinta serija 2,3,5-tripakeistų tiofenų.
5. Mes taip pat atradome, kad dalis mūsų sintetintų 2,3,5-tripakeistų tiofenų pasižymi fotoliuminescencija. Detaliau tyrinėjant nustatyta, kad tiofenai turintys 5,6-dichlor-2-benzimidazoil pakaitą 2-oje padetyje ir elektronakceptorinę grupę 3-ioje bei elektrondonorinę grupę 5-oje padėtyse pasižymi aukščiausiomis kvantinėmis išeigomis.

TYRIMŲ REZULTATAI

1. 1,3-Dipakeistų alkinonų sintezė

Panaudojant Sonogashira tipo reakciją iš komerciškai prieinamų ir iš laboratorijoje pagamintų 4-pakeistų fenilacetilenų bei aroilchloridų susintetinti 1,3-diarilalkinonai. Sonogashira tipo reakcija buvo pasirinkta dėl jos operacinio paprastumo ir didelių išeigų esant plačiam pakaitų spektrui.
Reikalingi fenilacetilenai **3a-b** susintetinti iš atitinkamų aldehidų. Pirma, aldehidai kondensuoti su malono rūgštimi – gautos cinamono rūgštys **1a-b**. Šias rūgštis veikiant bromu ir vėliau eliminuojant, kartu vykstant dekarboksilinimui, gauti *β*-bromstirenai **2a-b**. Junginius **2a-b** veikiant natrio šarmu metanolyje gauti fenilacetilenai **3a-b** (1 schema, 1 lentelė).



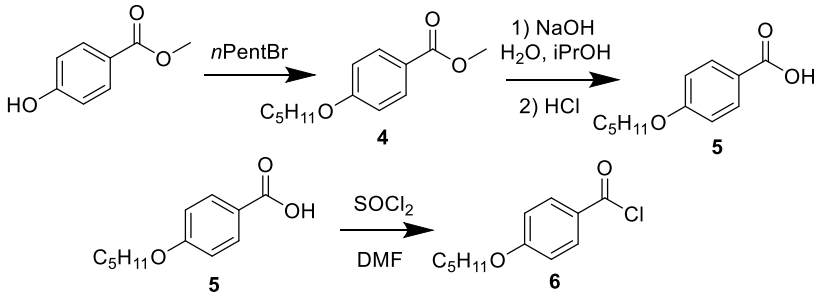
1 Schema. Pakeistų fenilacetilenų sintezės iš aldehidų kelias.

1 Lentelė. Susintetintų fenilacetilenų ir tarpinių junginių išeigos.

Numeris	R	Išeiga, %
1	OMe	**1a** (79)
2	OMe	**2a** (85)
3	OMe	**3a** (60)
4	Cl	**1b** (92)
5	Cl	**2b** (73)
6	Cl	**3b** (80)

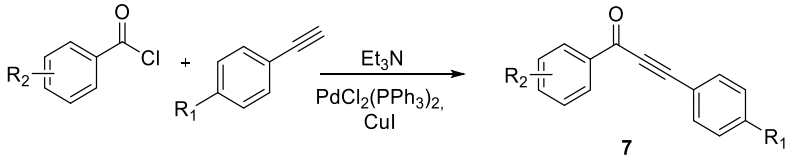
Aroil chloridai susintetinti atitinkamas karboksirūgštis veikiant tionilo chlorido pertekliumi bei katalitiniu *N*,*N*-dimetilformamido kiekiu. Junginio **6** (4-(pentiloksi)benzoil chlorido) atveju sintezė pradėta nuo metil 4-hidroksibenzoato. Šio junginio fenolinė OH grupė alkilinta pagal modifikuotą literatūroje aprašytą procedūrą su *n*PeBr acetone esant kalio bikarbonato. Vėliau atlikta junginio **4** esterinės grupės hidrolizė panaudojant natrio šarmą

izopropanolio ir vandens mišinyje. Laisva karboksi rūgštis **5** gauta į atvėsintą reakcijos mišinį pridėjus konc. druskos rūgšties. Nufiltravus ir išdžiovinus karboksi rūgštis **5** buvo veikiama tionilo chlorido pertekliumi su katalitiniu *N*,*N*-dimetilformamido kiekiu – tokiu būdu gautas junginys **6** (2 schema).



2 Schema. Junginio **6** sintezė iš metil 4-hidroksibenzoato.

Mes išbandėme įvairias 1,3-dipakeistų alkinonų sintezės metodikas: vario (I) jodidu katalizuojamą reakciją tarp aroilchloridų ir terminalinių acetilenų, Sonogashira tipo reakciją tarp aril jodidų ir terminalinių acetilenų kartu įterpiant anglies monoksidą (sugeneruotą reaguojant skruzdžių rūgščiai su sieros rūgštimi). Tačiau pastebėjome, kad taikant Sonogashira tipo reakciją tarp aroil chloridų ir terminalinių acetilenų, naudojant katalizatorius $PdCl_2(PPh_3)_2$ ir CuI trietilamine (3 schema, 2 lentelė), gaunamos geriausios produktų išeigos.



3 Schema. 1,3-Dipakeistųalkinonų sintezės schema.

2 Lentelė. 1,3-Dipakeistų alkinonų **7a-t** sintezė.

Numeris	R^1	R^2	Išeiga, %
1	OMe	H	**7a** (85)
2	OBu	H	**7b** (88)
3	OPe	H	**7c (**94)
4	OHeks	H	**7d** (80)
5	H	H	**7e** (98)
6	Cl	H	**7f** (76)
7	OMe	*o*-OMe	**7g** (60)

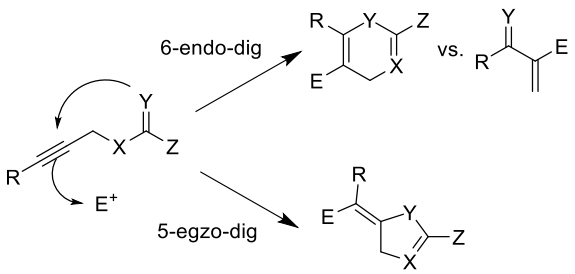
2 Lentelės tęsinys. 1,3-Dipakeistų alkinonų **7a-t** sintezė.

Numeris	R^1	R^2	Išeiga, %
8	OBu	*o*-OMe	**7h** (80)
9	OHeks	*o*-OMe	**7i** (62)
10	F	*o*-OMe	**7j** (65)
11	OMe	*p*-OMe	**7k** (78)
12	OMe	*p*-CF_3	**7l** (80)
13	CF_3	*p*-OMe	**7m** (62)
14	CF_3	*p*-CF_3	**7n** (60)
15	OPe	*p*-OPe	**7o** (71)
16	Cl	*p*-OMe	**7p** (57)
17	OMe	*p*-Cl	**7r** (61)
18	OMe	*p*-CN	**7s** (86)
19	OMe	*p*-NO_2	**7t** (83)

2. 1,3-Diarilalkinonų reakcijos susidarant alkoksimetil pakaitus turintiems izoksazolams ir chromonams

Žinoma, kad panaudojant įvairias pereinamųjų metalų druskas, kompleksinius junginius arba elektrofilinius reagentus, tokius kaip ICl, alkinonuose galima aktyvuoti C≡C trigubąjį ryšį ir taip susintetinti įvairius izoksazolus bei chromonus.

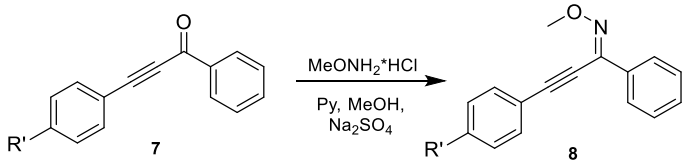
Prieš kelerius metus mūsų grupė pranešė apie elektrofilinių oksokarbenio jonų generavimą iš acetalių bei šių jonų panaudojimą pakeistų alkinų transformacijose (4 schema).



4 Schema. Oksokarbenio jonų panaudojimas funkciškai pakeistų alkinų transformacijose.

Taigi, mes nusprendėme ištirti oksokarbenio jonų dalyvavimą galimose ciklizacijos reakcijose su 1,3-diarilalkinonais bei 1,3-diarilalkinonų *O*-metil oksimais. Iš pradžių buvo susintetinti pradiniai junginiai alkinonams sintetinti

bei patys alkinonai ir jų *O*-metil oksimai (reaguojant alkinonams su metoksiamino hidrochloridu bei piridinu metanolyje, pridėjus Na_2SO_4 (5 Schema)). *O*-metil oksimų sintezės išeigos buvo geros (3 lentelė). Įdomu tai, kad piridiną pakeitus trietilaminu norimi produktai nesusidarė. Buvo stebimas tik Michaelio prisijungimo prie trigubojo ryšio produkto susidarymas. Mokslinėje literatūroje taip pat esama duomenų, kad 1,3-diarilalkinonai veikiami metoksiaminu be piridino dalyvauja 1,4-prijungimo reakcijoje.



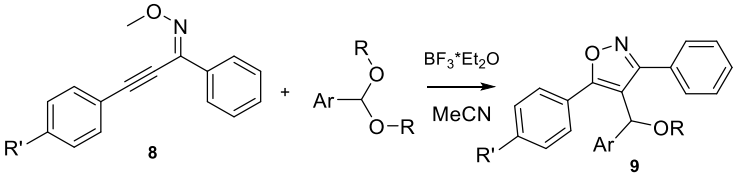
5 Schema. (*Z*)-3-aril-1-fenilprop-2-in-1-onų *O*-metil oksimų sintezė.

3 Lentelė. Sintetintų *O*-metil oksimų **8** išeigos.

Nr.	Pradinė medžiaga	R’	Išeiga, %
1	**7a**	OMe	**8a** (81)
2	**7b**	OBu	**8b** (78)
3	**7c**	OPe	**8c** (70)
4	**7d**	OHeks	**8d** (66)
5	**7e**	H	**8e** (78)
6	**7f**	Cl	**8f** (73)

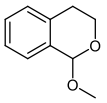
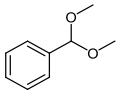
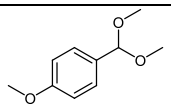
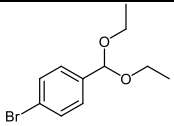
Iš mokslinės literatūros duomenų yra žinoma, kad oksokarbenio jonai gali būti generuojami acetalius veikiant įvairiomis pereinamųjų metalų druskomis arba Lewis‘o rūgštimis. Optimalių ciklizacijos reakcijos sąlygų paieškai mes pasirinkome junginį **8a**, kadangi šis junginys turi alkino ir metoksi imino funkcines grupes bei metoksi grupę vieno iš benzeno žiedų para padėtyje. Toks grupių išsidėstymas yra palankus ciklizacijos reakcijoms su elektrofilais vykti. Be to, junginys **8a** yra vienas iš struktūriškai paprasčiausių, tai palengvina produktų BMR spektrų analizę po ciklizacijos reakcijų. Mes išmėginome keletą Lewis‘o rūgščių (BF_3*Et_2O, $FeCl_3$, $AgSbF_6$, SbF_5, BBr_3, TMSOTf) skirtinguose tirpikliuose (MeCN, DCM, DCE, THF, $MeNO_2$) skirtingose temperatūrose ir radome, kad optimalios sąlygos izoksazolų **9** sintezei yra: 1 ekv. **8a** su 1 ekv. BF_3*Et_2O acetonitrile kambario temperatūroje.

Taikant optimizuotas sąlygas mes susintetinome įvairius alkoksimetil grupes turinčius izoksazolus iš *O*-metil oksimų su aromatiniais acetaliais. Reakcijos vidutinė trukmė ~15 min. Reakcijos mišinius apdirbus natrio bikarbonato tirpalu geromis išeigomis gauti izoksazolai (6 schema, 4 lentelė).

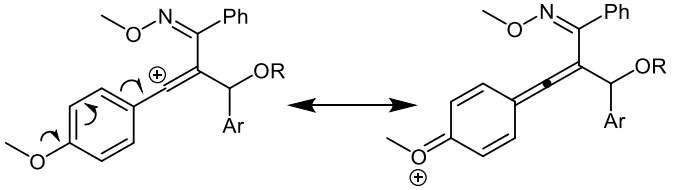


6 Schema. Alkoksimetil grupes turinčių izoksazolų sintezė.

4 Lentelė. Susintetinti izoksazolai **9**.

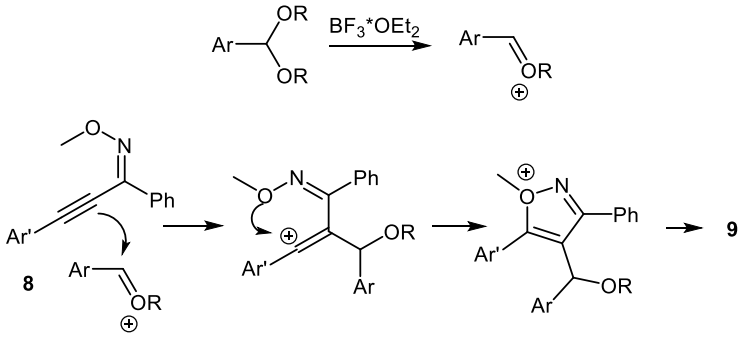
Nr.	Pradinis junginys	Acetalis	R’	Išeiga, %
1	**8a**		OMe	**9a** (57)
2	**8b**		O-*n*Bu	**9b** (43)
3	**8c**		O-*n*Pn	**9c** (84)
4	**8d**		O-*n*Heks	**9d** (58)
5	**8e**		H	N.R.
6	**8f**		Cl	N.R.
7	**8a**		OMe	**9e** (55)
8	**8b**		O-*n*Bu	**9f** (59)
9	**8d**		O-*n*Heks	**9g** (58)
10	**8a**		OMe	**9h** (79)
11	**8b**		O-*n*Bu	**9i** (48)
12	**8c**		O-*n*Pn	**9j** (66)
13	**8d**		O-*n*Heks	**9k** (47)
14	**8a**		OMe	**9l** (58)
15	**8d**		O-*n*Heks	**9m** (59)
16	**8a**		OMe	**9n** (77)
17	**8c**		O-*n*Pn	**9o** (30)
18	**8d**		O-*n*Heks	**9p** (56)

Verta paminėti, kad alkinonų *O*-metil oksimų ciklizacijos reakcijos į alkoksimetil grupes turinčius izoksazolus gerai vyko tik su pradiniais junginiais kurių trigubasis C≡C ryšys yra aktyvuotas elektronų donorine alkoksi grupe. Alkinonų *O*-metil oksimai neturintys alkoksi grupės para padėtyje ciklizacijos reakcijose su oksokarbenio jonais nedalyvavo. Tokį reaktingumą galima paaiškinti susidariusio vinil - karbokatijono rezonansiniu stabilizavimu (7 schema). Šis karbokatijonas susidaro oksokarbenio jonui prisijungus prie trigubojo ryšio.



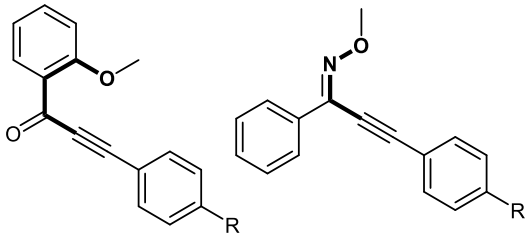
7 Schema. Vinilinio karbokatijono rezonansinis stabilizavimas.

Mes manome, kad izoksazolų susidarymas yra keturių stadijų procesas. Pirma iš acetalio, veikiamo BF_3*Et_2O, susidaro oksokarbenio jonas. Šis jonas reaguoja su elektronais praturtintu alkinu susidarant vinil - karbokatijonui. Vėliau šis karbokatijonas 5-endo-dig ciklizacijos metu virsta izoksazolio druska. Galiausiai pašalinant metil grupę susidaro izoksazolas **9** (8 schema).



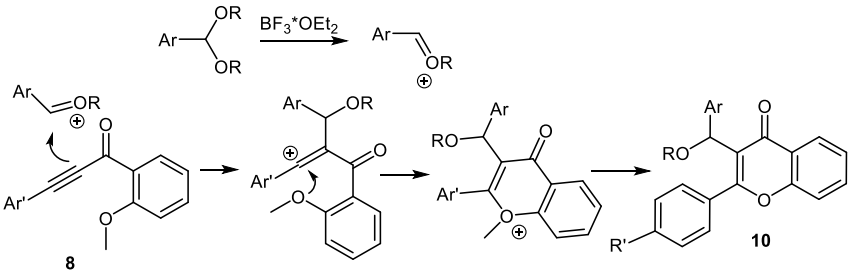
8 Schema. Galimas izoksazolų **9** susidarymo mechanizmas.

Mes taip pat išbandėme 3-aril-1-(2-metoksifenil)prop-2-in-1-onus, turinčius metoksi grupę greta alkinono fragmento (2 pav.), paveikti oksokarbenio jonais.



2 Paveikslas. Izosteriniai 3-aril-1-(2-metoksifenil)prop-2-in-1-onai ir (*Z*)-3-aril-1-fenilprop-2-in-1-onų *O*-metil oksimai.

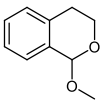
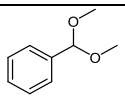
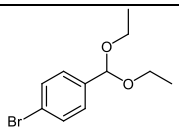
3-Aril-1(2-metoksifenil)prop-2-in-1-onams reaguojant kambario temperatūroje su BF_3*Et_2O acetonitrile, vyksta 6-e*ndo*-dig ciklizacija susidarant chromonio druskoms (9 schema).



9 Schema. Chromonio druskų susidarymas 3-Aril-1(2-metoksifenil)prop-2-in-1-onų 6-e*ndo*-dig ciklizacijos metu.

Galiausiai, pašalinus metilo grupę gaunami 2-aril-*4H*-chromen-4-onai **10**, turintys alkoksimetil grupę 3-ioje heterociklo pozicijoje (9 schema).
Įdomu pastebėti, kad reakcijų išeigos nepriklauso nuo to ar benzeno žiede šalia trigubojo C≡C ryšio yra elektronus ištraukiantys ar donuojantys pakaitai. Visais atvejais gaunamos geros 3-alkoksiarilalkil-2-aril-*4H*-chromen-4-onų išeigos (5 lentelė).

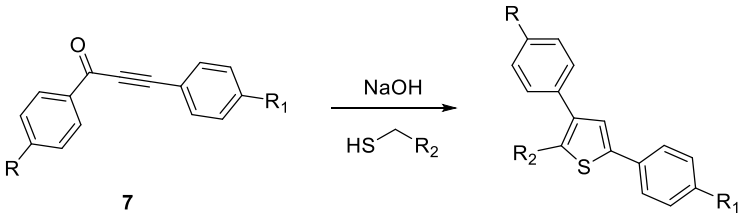
5 Lentelė. Susintetinti 3-alkoksiarilalkil-2-aril-*4H*-chromen-4-onai - **10**.

Nr.	Pradinis junginys	Acetalis	R’	Išeiga, %
1	**7g**		OMe	**10a** (99)
2	**7h**		OBu	**10b** (88)
3	**7i**		OHex	**10c** (70)
4	**7j**		F	**10d** (97)
5	**7g**		OMe	**10e** (83)
6	**7h**		OBu	**10f** (79)
7	**7i**		OHex	**10g** (80)
8	**7g**		OMe	**10h** (76)
9	**7g**		OMe	**10i** (82)

Apibendrinant, mes atradome, kad (*Z*)-3-aril-1-fenilprop-2-in-1-onų *O*-metil oksimai **8a-f** ir 3-aril-1-(2-metoksifenil)prop-2-in-1-onai **7g-j** veikiami oksokarbenio jonais (gautais iš atitinkamų acetalių ir BF_3*Et_2O acetonitrile) ciklizuojasi į pakeistus izoksazolus **9a-p** ir 3-alkoksiarilalkil-2-aril-*4H*-chromen-4-onus **10a-i**.

3. 1,3-diarilalkinonų panaudojimas 2,3,5-tripakeistų tiofenų sintezei bei susintetintų tiofenų fotofizikinių savybių tyrimas

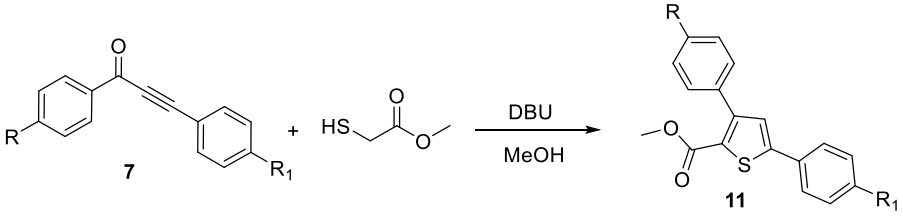
Mes nusprendėme ištirti 1,3-diarilalkinonų pritaikomumą potencialiai fluorescuojančių pakeistų tiofenų sintezei. Iš daugybės žinomų sintezės metodų 2,3,5-tripakeistiems tiofenams pasirinkome Fiesselmann'o reakciją. Kadangi šios reakcijos pagalba galima lengvai gauti norimus tiofenus iš 1,3-diarilalkinonų **7** veikiant juos metilmerkaptoacetatu arba pakeistais metilentioliais (10 schema).



10 Schema. Fiesselmann'o reakcija 2,3,5-tripakeistiems tiofenams sintetinti.

Atlikę eksperimentus pastebėjome, kad keletas mūsų sintetintų junginių **14**, juos apšvietus UV spinduliais, švyti regima šviesa. Mes taip pat pastebėjome, kad mokslinėje literatūroje yra labai mažai duomenų apie monomerinių tiofenų fotofizikines savybes ar monomerinių tiofenų struktūros bei fotofizikinių savybių sąryšį. Radome tik vieną šaltinį kuriame minima fenantroimidazolo ar benzimidazolo įvedimo į 2-ą tiofeno žiedo padėtį teigiama įtaka fotofizikinėms savybėms. Mokslinės literatūros apie monomerinių tiofenų fotofizikines savybes stygius bei viltis sukurti naujus, efektyvius šviestukus tiofeno pagrindu mus paskatino susintetinti bei detaliai ištirti (kvantinę išeigą, absorbcijos bei emisijos maksimumus) 2,3,5-tripakeistų tiofenų seriją.

Visų pirma mes susintetinome metil tiofen-2-karboksilatus **11** iš alkinonų **7** ir metilmerkaptoacetato metanolyje, panaudodami DBU kaip katalizatorių (11 schema, 6 lentelė).

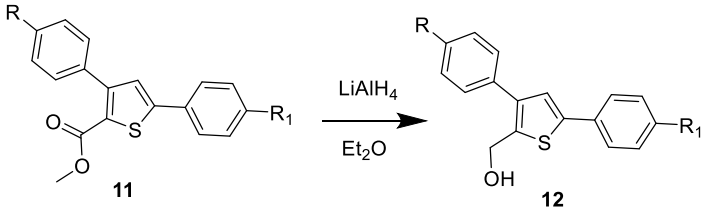


11 Schema. Metil tiofen-2-karboksilatų **11** sintezė.

6 Lentelė. Susintetinti metil tiofen-2-karboksilatai **11**.

Nr.	Pradinis junginys	R	R^1	Išeiga, %
1	**7k**	OMe	OMe	**11a** (84)
2	**7p**	OMe	Cl	**11b** (77)
3	**7e**	H	H	**11c** (78)
4	**7a**	H	OMe	**11d** (84)
5	**7s**	CN	OMe	**11e** (81)

Redukuojant metil tiofen-2-karboksilatus **11** su $LiAlH_4$ absoliučiame eteryje gauti junginiai **12** (12 schema, 7 lentelė).

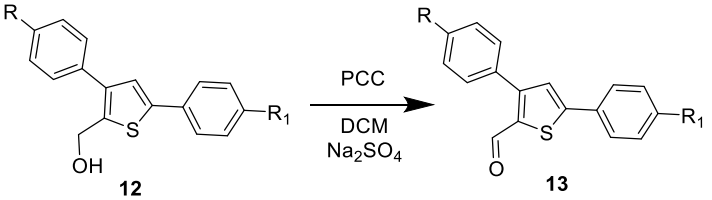


12 Schema. Esterinės grupės redukcija panaudojant $LiAlH_4$.

7 Lentelė. Susintetinti 3,5-dipakeisti tiofen-2-ilmetanoliai **12**.

Nr.	Pradinis junginys	R	R^1	Išeiga, %
1	**11a**	OMe	OMe	**12a** (99)
2	**11b**	OMe	Cl	**12b** (68)
3	**11c**	H	H	**12c** (93)

Oksidavus junginius **12** su PCC dichlormetane gauti aldehidai **13** (13 schema, 8 lentelė). Pastebėjome, kad natrio sulfato pridėjimas į reakcijos mišinius labai palengvino filtravimą produktų išskyrimo metu.

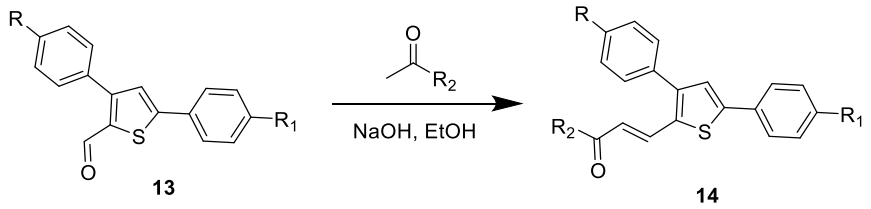


13 Schema. Junginio **12** oksidacija švelniomis sąlygomis

8 Lentelė. Susintetinti 3,5-dipakeisti tiofen-2-karbaldehidai **13**.

Nr.	Pradinis junginys	R	R^1	Išeiga, %
1	**12a**	OMe	OMe	**13a** (65)
2	**12b**	OMe	Cl	**13b** (70)
3	**12c**	H	H	**13c** (62)

Panaudodami junginius **13** susintetinome seriją chalkono tipo junginių **14**. Sintezės atliktos etanolyje panaudojant katalitinį kiekį NaOH ir atitinkamus acetofenonus (14 schema, 9 lentelė).



14 Schema. Junginių **14** sintezė.

9 Lentelė. Susintetinti (*E*)-3-(3,5-dipakeistitiofen-2-il)-1-pakeistiprop-2-en-1-onai **14**.

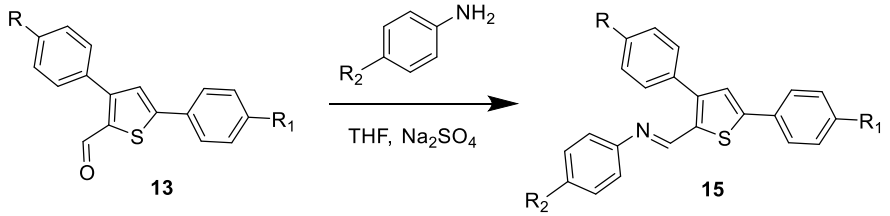
Nr.	Pradinė mežiaga	R	R^1	R^2	Išeiga, %
1	**13a**	OMe	OMe	4-Cl-Ph	**14a** (84)
2	**13a**	OMe	OMe	3-Py	**14b** (98)
3	**13c**	H	H	4-CN-Ph	**14c** (87)
4	**13a**	OMe	OMe	4-MeO-Ph	**14d** (77)
5	**13a**	OMe	OMe	4-Br-Ph	**14e** (90)
6	**13a**	OMe	OMe	4-CN-Ph	**14f** (90)
7	**13b**	OMe	Cl	4-OMe-Ph	**14g** (78)
8	**13b**	OMe	Cl	3-Py	**14h** (58)
9	**13b**	OMe	Cl	4-Pe-Ph	**14i** (43)
10	**13b**	OMe	Cl	4-CN-Ph	**14j** (71)

Išmatavę naujai susintetintų junginių **14** (14 Schema) fotofizikines savybes nustatėme, kad jų emisijos maksimumas yra 516 – 562 nm ruože. Išmatuotos kvantinės išeigos kietame būvyje ir tirpale (acetonitrile) ganėtinai mažos – 0,2 – 14,9 % (10 lentelė).

10 Lentelė. Junginių **14** fotofizikinių matavimų duomenys**.**

Junginys	R	R^1	R^2	Abs., nm	Em., nm	QY, % (tirpale)	QY, % (kietame būvyje)
14a	OMe	OMe	4-Cl-Ph	240, 262, 282, 360	537	0.5	14.9
14b	OMe	OMe	3-Py	254, 422	538	0.4	8.9
14c	H	H	4-CN-Ph	264, 408	516	0.2	6.9
14d	OMe	OMe	4-MeO-Ph	240, 296, 410	523	0.4	2.9
14e	OMe	OMe	4-Br-Ph	240, 262, 282, 420	536	0.7	10.1
14f	OMe	OMe	4-CN-Ph	264, 430	562	1.8	4.6
14g	OMe	Cl	4-OMe-Ph	235, 272, 334	458	0.4	4.0
14h	OMe	Cl	3-Py	235, 267, 408	510	0.2	2.8
14i	OMe	Cl	4-Pe-Ph	240, 273, 334	460	0.7	0.7
14j	OMe	Cl	4-CN-Ph	263, 414	529	0.5	2.5

Kadangi prieš tai sintetintų junginių **14** kvantinės išeigos buvo mažos, mes nusprendėme kiek pakeisti junginių struktūrą ir susintetinome seriją iminų **15** (15 schema, 11 lentelė). Deja junginiai **15** nepasižymėjo fluorescencinėmis savybėmis.

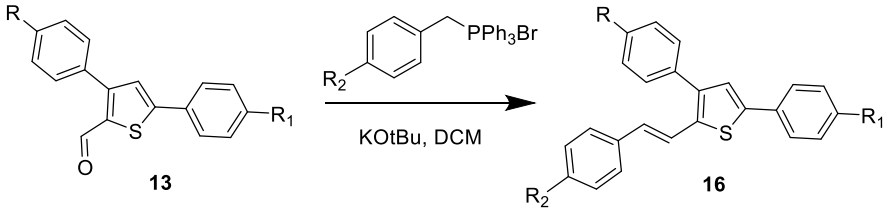


15 Schema. Junginių **15** sintezės schema.

11 Lentelė. Susintetinti iminai **15**.

Nr.	Pradinis junginys	R	R^1	R^2	Išeiga, %
1	**13b**	OMe	Cl	Ph	**15a** (73)
2	**13b**	OMe	Cl	4-MeO-Ph	**15b** (75)
3	**13b**	OMe	Cl	4-F-Ph	**15c** (76)
4	**13b**	OMe	Cl	PhNH-	**15d** (75)
5	**13b**	OMe	Cl	4-Br-Ph	**15e** (17)

Po nesėkmingų bandymų sukurti efektyviai fluorescuojančias molekules, panaudodami Wittig‘o reakciją, mes susintetinome seriją (*E*)-3,5-dipakeistų fenil-2-stiriltiofenų **16** (16 schema, 12 lentelė). Šios molekulės yra struktūriškai panašios į **14** tik neturi C=O fragmento.



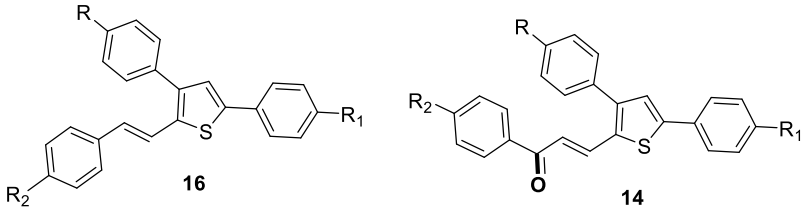
16 Schema. Stiriltiofenų **16** sintezė.

12 Lentelė. Susintetinti (*E*)-3,5-dipakeistifenil-2-stiriltiofenai **16**.

Nr.	Pradinis junginys	R	R^1	R^2	Išeiga, %
1	**13b**	OMe	Cl	H	**16a** (65)
2	**13b**	OMe	Cl	4-MeO-Ph	**16b** (69)
3	**13b**	OMe	Cl	4,5-diMeO-Ph	**16c** (59)
4	**13b**	OMe	Cl	Cl	**16d** (72)

Išmatavus junginių **16** fotofizikines savybes, pastebėjome, kad šių junginių emisijos maksimumas yra mėlyname bangų ruože, ties 428 – 467 nm, o

kvantinės išeigos (angl. PLQY) yra ženkliai didesnės lyginant su junginiais **14** (3 pav., 13 lentelė).

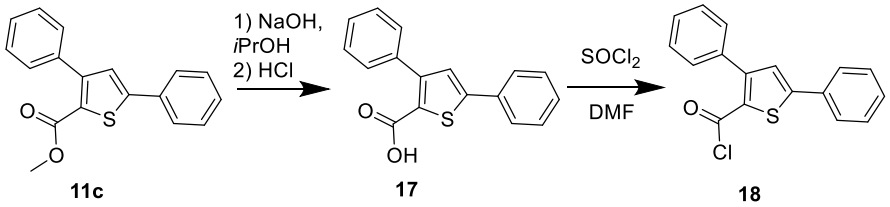


3 Paveikslas. Junginių **16** ir **14** struktūriniai ypatumai

13 Lentelė. Junginių **16** fotofizikinių tyrimų rezultatai.

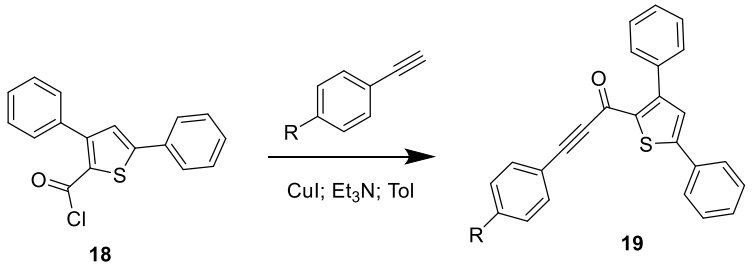
Junginys	R	R^1	R^2	Abs., nm	Em., nm	QY, % (tirpale)	QY, % (kietame būvyje)
16a	OMe	Cl	H	240, 281, 366	428. 449	2.7	7.4
16b	OMe	Cl	4-MeO-Ph	241, 287, 381	459	12.7	20.5
16c	OMe	Cl	4,5-diMeO-Ph	238, 284, 382	467	12.7	4.7
16d	OMe	Cl	Cl	239, 281, 367	453	2.1	19.6

Ištirtų chalkono tipo junginių **14**, iminų **15** bei stiriltiofenų **16** kvantinės išeigos nėra pakankamai didelės, kad juos būtų galima pritaikyti optoelektronikoje. Tačiau, remdamiesi gautais duomenimis mes nusprendėme optimizuoti tiofenų stuktūrą taip, kad sukurtume geresnius fluoroforus. Stengdamiesi prailginti konjuguotų pi dvigubų ryšių sistemą susintetinome pradinius junginius **19a-b** turinčius alkinono fragmentą kaip ir junginiai **7**. Junginiams **19a-b** sintetinti buvo panaudotas metil 3,5-difeniltiofen-2-karboksilatas **11c**. Junginys **11c** veikiamas natrio šarmu ir vėliau druskos rūgštimi iki pH < 2 virto karboksi rūgštimi **17**. Karboksirūgštis **17** veikiama tionilo chloridu ir katalitiniu kiekiu *N*,*N*-dimetilformamido tapo chloranhidridu **18** (17 schema).



17 Schema. 3,5-Dfeniltiofen-2-karbonil chlorido **18** sintezė.

Iš junginio **18** ir terminalinių fenilacetilenų, Sonogashira reakcijos būdu, gauti junginiai **19** (18 schema, 14 lentelė).

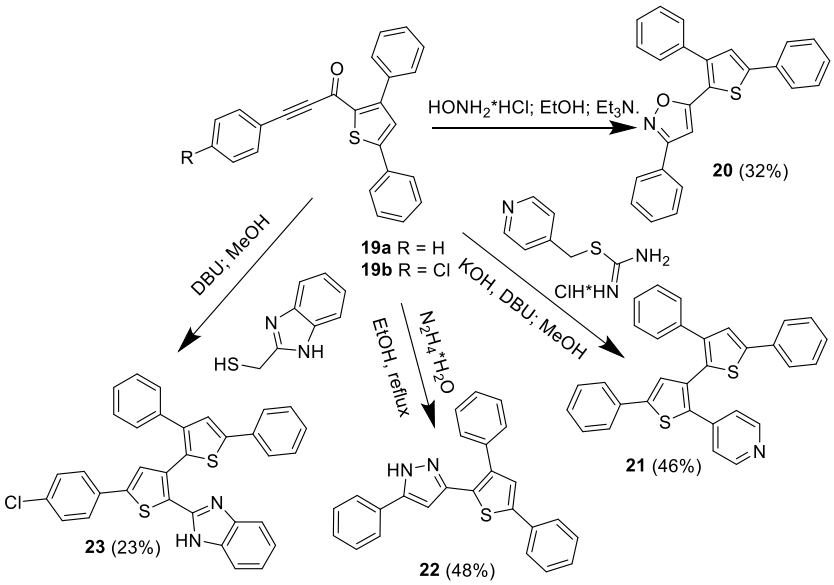


18 Schema. Junginių **19a-b** sintezė.

14 Lentelė. Susintetinti 1-(3,5-difeniltiofen-2-il)-3-pakeistifenilprop-2-in-1-onai **19**.

Nr.	R	Išeiga, %
1	H	**19a** (80)
2	Cl	**19b** (32)

Panaudojant junginius **19a-b** bei įvairius reagentus: hidroksilaminą, piridin-4-ilmetantiolį, hidraziną ir k.t. gauti pakeisti heterocikliniai junginiai (izoksazolai, tiofenai, pirazinai ir k.t.) **20**-**23** (19 schema).



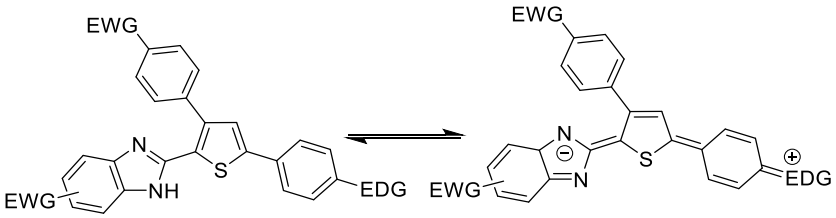
19 Schema. Pakeistų heterociklų sintezė iš junginių **19a-b**.

Išmatavę naujai susintetintų heterociklų **20-23** fotofizikines savybes nustatėmė, kad jie pasižymi mažesnėmis kvantinėmis išeigomis už prieš tai sintetintus mažamolekuinius junginius **14**, **16** (15 lentelė).

15 Lentelė. Junginių **20-23** fotofizikinių savybių matavimų duomenys.

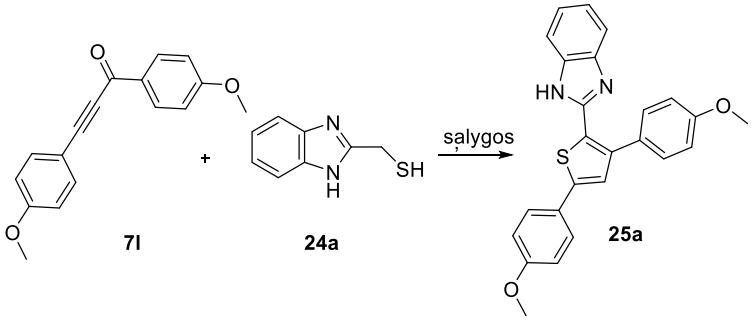
Junginys	Abs., nm	Em., nm	QY, % (tirpale)	QY, % (kietame būvyje)
20	262, 336	419	2.3	26.2
21	240, 264, 312	474	2.1	1.6
22	258, 322	394	2.7	1.7
23	240, 266, 322, 364	466	4.3	1.69

Mes nusprendėme susintetinti seriją mažiau sudėtingų molekulių, kurių konjuguotų dvigubųjų ryšių sistema būtu plokščia, taip tikėdamiesi pasiekti didesnes kvantines išeigas (4 pav.).



4 Paveikslas. 2-(tiofen-2-il)-1*H*-benzo[*d*]imidazolų rezonansinės formos.

1,3-Diarilalkinonus veikiant 1*H*-benzimidazo-2-metantioliu **24a** ir baze -DBU gaunami Fiesselmann'o ciklizacijos produktai – 2-(3,5-diariltiofen-2-il)-1*H*-benzo[*d*]imidazolai. Mes išbandėme ciklizuoti 1,3-bis(4-metoksifenil)prop-2-in-1-oną **7k** su 1 ekviv. **24a** virinant etanolyje su DBU ir taip gavome tikslinį junginį **25a**, tačiau išeiga siekė tik 19 %. Naudojant didelį pertekių tiolio **24a** (6 ekviv.) produkto išeigą pavyko padidinti iki 51%. Didelis perteklius tiolio apsunkino produkto **25a** išskyrimą iš reakcijos mišinio. Tirpiklio pakeitimas į DMF arba THF praktiškai neturėjo įtakos produkto išeigai. Mes likome maloniai nustebinti kai pakeitus DBU į NaOH ar KOH gavome praktiškai kiekybinę produkto **25a** išeigą (20 schema, 16 lentelė).



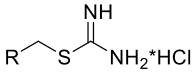
20 Schema. Optimalių sąlygų paieška junginiui **25a** sintetinti.

16 Lentelė. Fiesselmann'o reakcijos junginiui **25a** optimizavimas.

Nr.	Ekv. **7k**	Ekv. **24a**	Bazė, ekv.	tirpiklis	Temp.	Išeiga, %
1	1	1.5	DBU, 1	EtOH	vir.	19
2	1	3	DBU, 1	EtOH	vir.	37
3	1	6	DBU, 1	EtOH	vir.	51
4	1	1.5	DBU, 1	THF	vir.	63
5	1	1.5	DBU, 1	DMF	vir.	54
6	1	1.5	NaOH, 1	EtOH	vir.	92

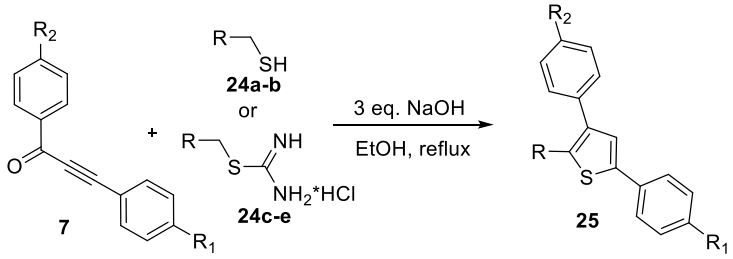
Dažniausiai Fiesselmann'o ciklizacijos reakcijoje naudojami tioliai. Šios medžiagos lengvai oksiduojasi susidarant disulfidams ir pasižymi labai stipriu

kvapu bei yra toksiškos. Mums pavyko tiolius pakeisti karbamimidotioatais **24c-e** (5 pav.).



5 Paveikslas. Bendra karbamimidotioatų struktūra.

Karbamimidotioatai yra stabilios, nelakios, praktiškai bekvapės, kristalinės medžiagos, lengvai sintetinamos iš tiourėjos. Susintetinę seriją junginių **25** (21 schema, 17 lentelė) pastebėjome, kad karbamimidotioatai su alkinonais **7** reaguoja panašiai kaip tioliai – gautos panašios išeigos. Geresnės išeigos gautos naudojant alkinonus su elektronų donorinėmis gupėmis nei su akceptorinėmis.



21 Schema. 2,3,5-tripakeistų tiofenų **25** sintezė.

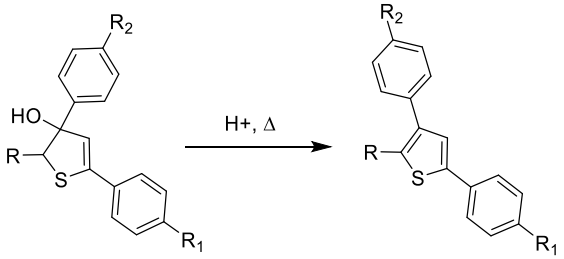
17 Lentelė. Fiesselmann'o tipo reakcija tarp alkinonų **7** ir tiolių **24a-b** ar karbamimidotioatų **24c-e**.

Nr.	Pradinis junginys	R^2	R^1	RCH_2SX	Išeiga, %
1	**7e**	H	H	BZI-2-CH_2SH **24a**	**25a** (62)
2	**7k**	OMe	OMe		**25b** (92)
3	**7l**	CF_3	OMe		**25c** (42); **27a** (10)
4	**7m**	OMe	CF_3		**25d** (64)
5	**7n**	CF_3	CF_3		**25e** (44); **27f** (50)
6	**7o**	OPe	OPe		**25f** (72)
7	**7e**	H	H	2-(5-Cl-BZI)-CH_2SH **24b**	**25g** (55)
8	**7k**	OMe	OMe		**25h** (58)
9	**7l**	CF_3	OMe		**25i** (64)

17 Lentelės tęsinys. Fiesselmann'o tipo reakcija tarp alkinonų **7** ir tiolių **24a-b** ar karbamimidotioatų **24c-e**.

Nr.	Pradinis junginys	R^2	R^1	RCH_2SX	Išeiga, %
10	**7e**	H	H	2-(5,6-diCl-BZI)-$CH_2SC(NH_2)_2Cl$ **24c**	**25j** (60)
11	**7k**	OMe	OMe		**25k** (74)
12	**7l**	CF_3	OMe		**25l** (62)
13	**7e**	H	H	4-Py-$CH_2SC(NH_2)_2Cl$ **24d**	**25m** (67)
14	**7k**	OMe	OMe		**25n** (89)
15	**7l**	CF_3	OMe		**25o** (51)
16	**7m**	OMe	CF_3		**25p** (67)
17	**7n**	CF_3	CF_3		**25r** (50)
18	**7k**	OMe	OMe	2-(1-Me-IMD)-$CH_2SC(NH_2)_2Cl$ **24e**	**25s** (30)

Tam tikrais atvejais mums pavyko išskirti tarpinius ciklizacijos reakcijos produktus **27a-f** dihidrotiofen-3-olius. Net ilgai kaitinant reakcijos mišinius **27a-c** stebimi kaip pagrindiniai produktai (18 lentelė). Junginius **27** galima lengvai aromatizuoti į atitinkamus **25** pašildant su rūgštimi arba ilgai laikant DMSO tirpale (22 schema).



27 **25**

22 Schema. Dihidrotiofen-3-olių **27** aromatizavimas iki tiofenų **25**.

18 Lentelė. Izoliuoti dihidrotiofen-3-oliai **27.**

Nr.	Pradinis junginys	R^2	R^1	RCH_2SX	Produktas (Išeiga, %)
1	**7l**	CF_3	OMe	2-(1-Me-IMD)-$CH_2SC(NH_2)_2Cl$ **24e**	**27a** (38)
2	**7m**	OMe	CF_3		**27b** (44)
3	**7n**	CF_3	CF_3		**27c** (41)
4	**7e**	H	H		**27d** (10)
5	**7l**	CF_3	OMe	BZI-2-CH_2SH **24a**	**27e** (50)
6	**7n**	CF_3	CF_3		**27f** (50)

Mes ištyrėme susintetintų junginių **25** fotofizikines savybes, kur R = 2-BZI, 2-(5-Cl-BZI), 2-(5-Cl-BZI) (19 lentelė).

19 Lentelė. 2,3,5-Tripakeistų tiofenų **25** fotofizikinių savybių tyrimai.

Nr.	R^2	R^1	R	Abs., nm	Em., nm. tirp.	Em., nm. kiet.	QY, % (tirp.)	QY, % (kiet.)
25a	H	H	2-BZI	237, 266, 347	433	456	38.9	8.5
25b	OMe	OMe	2-BZI	235, 278, 356	445	467	28.0	17.0
25c	CF3	OMe	2-BZI	234, 274, 358	454	459	77.5	22.0
25d	OMe	CF_3	2-BZI	238, 280, 354	444	457	28.6	4.5
25e	CF_3	CF_3	2-BZI	238, 272, 352	442	512	53.5	2.1
25f	OPe	OPe	2-BZI	234, 280, 356	441	464	33.8	1.8
25g	H	H	2-(5-Cl-BZI)	235, 266, 350	435	459	45.0	17.5

19 Lentelės tęsinys. 2,3,5-Tripakeistų tiofenų **25** fotofizikinių savybių tyrimai.

Nr.	R^2	R^1	R	Abs., nm	Em., nm. tirp.	Em., nm. kiet.	QY, % (tirp.)	QY, % (kiet.)
25h	OMe	OMe	2-(5-Cl-BZI)	234, 280, 360	445	463	42.5	11.6
25i	CF_3	OMe	2-(5-Cl-BZI)	235, 274, 360	460	467	77.4	30.6
25j	H	H	2-(5,6-diCl-BZI)	232, 268, 355	434	475	63.1	52.2
25k	OMe	OMe	2-(5,6-diCl-BZI)	234, 280, 368	467	465	34.6	15.1
25l	CF_3	OMe	2-(5,6-diCl-BZI)	236, 275, 365	462	478	82.6	30.9
25m	H	H	4-Py	265, 329	416	414	2.1	2.0
25n	OMe	OMe	4-Py	252, 280, 340	440	538	4.0	0.9
25o	CF_3	OMe	4-Py	236, 270, 340	460	550	33.9	11.9
25p	OMe	CF_3	4-Py	242, 284, 332	436	436, 525	1.9	8.4
25r	CF_3	CF_3	4-Py	240, 268, 326	406	446	2.0	6.1
25t	OMe	OMe	2-(1-Me-IMD)	236, 272, 318	420	NA	1.4	NA

Atlikę seriją matavimų mes nustatėme, kad kai R1 ir R2 yra elektronų donorinės grupės yra stebimas kvantinės išeigos padidėjimas kietame būvyje ir sumažėjimas acetonitrilo tirpale, lyginant su junginiu **25a** kur R1=R2= H. Kai R1=R2= OPe fotoliuminescencijos kvantinės išeigos, tiek tirpale, tiek kietame būvyje yra panašios į junginio neturinčio alkoksi grupių **25a**. Kai R1 ir R2 yra elektronus ištraukiančios grupės – stebimas kvantinių išeigų sumažėjimas kietame būvyje ir padidėjimas tirpale. Tačiau kai R1 – elektronų donorinė grupė, o R2 – elektronų akceptorinė grupė - yra stebimas kvantinės išeigos padidėjimas tirpale ir kietame būvyje **25c** (R1 = OMe, R2 = CF_3) lyginant su **25a** (R1=R2= H). R1 ir R2 grupių apkeitimas vietomis ženkliai sumažina kvanitnes išeigas tirpale ir kietame būvyje **25d** (19 lentelė).

Mes taip pat ištyrėme pakaitų, esančių prie benzimidazolo, svarbą. Nustatėme, kad Cl grupės įvedimas į 5-ą **25g** ar į 5-ą ir 6-ą **25j** benzimidazolo heterociklo padėtį padidino kvantinę išeigą lyginant su **25a** (19 lentelė). Aukščiausia kvantinė išeiga tirpale ir kietame būvyje stebima junginyje **25l**, turinčiame labiausiai elektronų deficitinį benzimidazolo pakaitą ir grupes R1=CF_3, R2=OMe (19 lentelė).

Mes taip pat nustatėme, kad pakeitus benzimidazolą esantį 2-oje tiofeno padėtyje į piridiną **25m-25r** arba į *N*-metilimidazolą **25t** – stebimas ženklus kvantinės išeigos sumažėjimas.

Galima daryti išvadą, kad į tiofeno žiedo 2-ą padėtį įvedus 5,6-dichloro-2-benzimidazoil pakaitą, o į 3-ią elektronų akceptorinį beį į 5-ą elektronų donorinį pakaitus, turinčius benzeno karbociklus, gaunami didžiausias kvantines išeigas turintys 2,3,5-tripakeisti tiofenai.

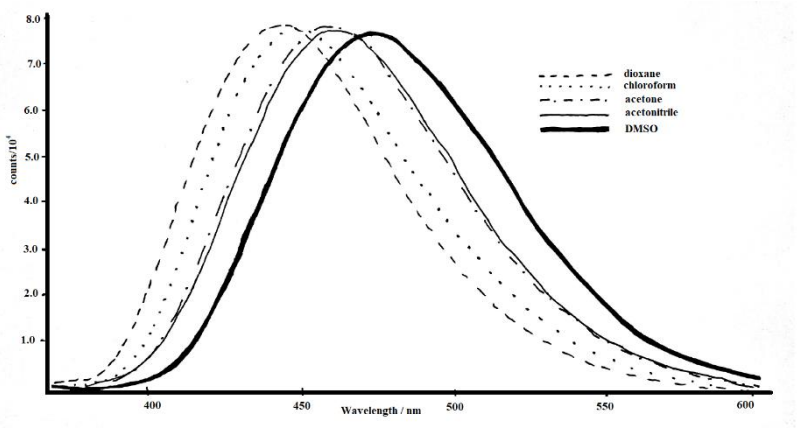
Tiofenai, 2-oje padėtyje turintys 2-benzimidazoil pakaitą (nepakeistą, 5-Cl, 5,6-diCl) kietame būvyje turi tris charakteringas absorbcijos linijas: 232-238, 266-280, 347-368 nm. Tirtų tiofenų emisijos acetonitrile buvo stebimos 433-467 nm ruože.

Lyginant tiofenus **25j** ir **25k** tampa akivaizdu, kad įvedus elektronų donorinę grupę į 5-ą tiofeno žiedo poziciją įvyksta batochrominis emisijos piko poslinkis (iš 434 į 467 nm). Taip pat matomi antros ir trečios absorbcijos linijų batochrominiai poslinkiai (iš 268 į 280 nm ir iš 355 į 368 nm).

Batochrominiai poslinkiai taip pat stebimi tiofenuose 2-oje padetyje turinčiuose 4-piridil pakaitą ir elektron donorinę grupę 3-ioje ar 5-oje arba 3-ioje ir 5-oje padėtyse.

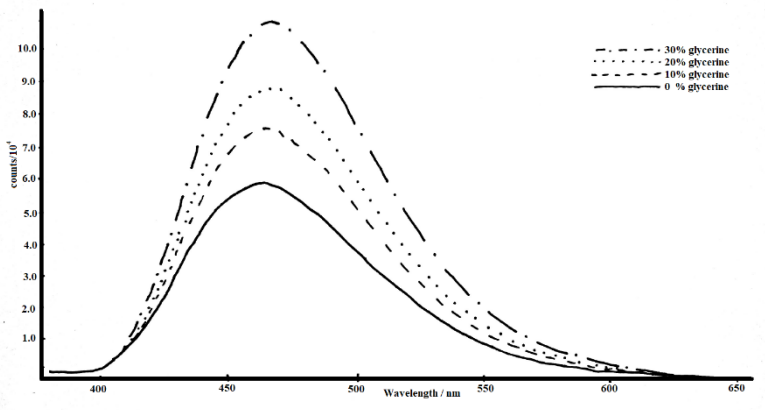
Visi mūsų tirti tiofenai **25** acetonitrilo tirpaluose pasižymėjo plačiu emisijos piku be jokių išskirtinių rėžių (19 lentelė). Remiantis literatūra yra žinoma, kad platūs emisijos pikai yra būdingi junginiams kuriuose pasireiškia „pasukto intramolekulinio krūvio perdavimo fenomenas“ (angl. TICT phenomenon). Tam, kad išsiaiškinti ar dėl šio fenomeno mūsų tirtos molekulės emituoja

šviesą, mes nusprendėme atlikti papildomus tyrimus. Tyrimams pasirinkome tiofeną **25o**, kadangi jis pasižymi geru tirpumu organiniuose tirpikliuose ir gan dideliu emituojamos šviesos intensyvumu (kvantinė išeiga - 33,9 %).
Mes nustatėme, kad emisijos maksimumas dioksane yra 440 nm, o DMSO 468 nm (6 pav.).



6 Paveikslas. Emisijos intensyvumo priklausomybė nuo tirpiklio poliškumo.

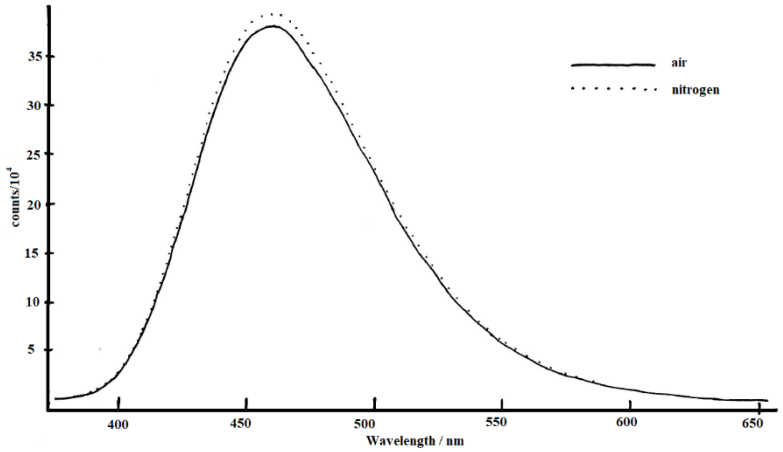
Taip pat išmatavome emisijos intensyvumą įvairiuose etanolio/glicerolio tirpaluose (7 pav.). Koreliacija tarp tirpiklio klampos ir emisijos intensyvumo bei batochrominis emisijos maksimumo poslinkis didėjant tirpiklio poliškumui patvirtina TICT fenomeno buvimą.



7 Paveikslas. Emisijos intensyvumo priklausomybė nuo tirpalo klampos.

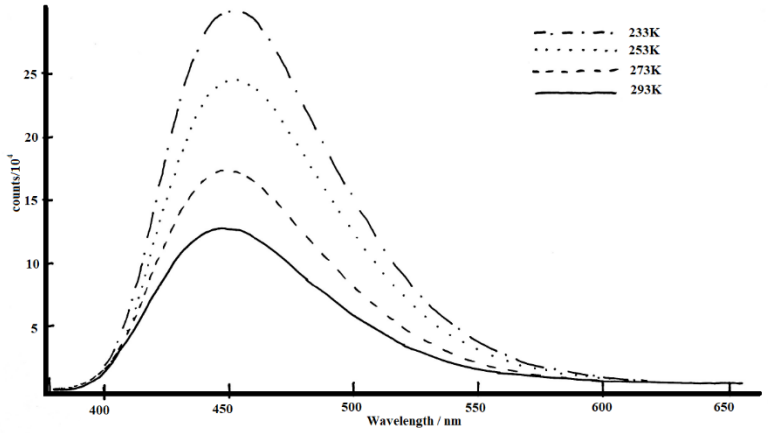
Mes išmatavome junginio **25o** emisijos intensyvumą tirpiklyje be deguonies (išstumtas leidžiant azotą) ir esant oro. Emisijos intensyvumas abiem atvejais buvo panašus (8 pav.). Iš šio eksperimento akivaizdu, kad tripletiniai būviai

emisijoje nedalyvauja, nes jie būtų slopinami ore esančio deguonies ir emisijos intensyvumas skirtųsi degazuotame ir nedegazuotame tirpaluose.



8 Paveikslas. Emisijos intensyvumas ore ir beorėje aplinkoje.

Mes taip pat išmatavome emisijos intensyvumą esant skirtingai temperatūrai (nuo 293K iki 233K) (9 pav.) ir pastebėjome emisijos intensyvumo didėjimą mažėjant temperatūrai.



9 Paveikslas. Emisijos intensyvumo priklausomybė nuo temperatūros.

Šie du eksperimentai įrodo termiškai aktyvuotos uždelstos fluorescencijos (angl. TADF) nebuvimą ir tai, jog mūsų tirti tiofenai emituoja šviesą dėl singletinių būvių.

IŠVADOS

1. Iš terminalinių acetilenų bei aroilchloridų, panaudojant Sonogashira tipo reakciją, susintetinta 19 alkinonų **7**. Šie alkinonai vėliau naudoti kaip pradinės medžiagos tiriant jų ciklizacijos reakcijas.
2. Sukūrėme paprastą, vieno žingsnio metodiką alkoksimetil grupes turinčių izoksazolų bei chromonų sintezei. Optimalios reakcijos sąlygos: (*Z*)-3-aril-1-fenilprop-2-in-1-ono-*O*-metil oksimas su 1 ekv. BF_3*Et_2O acetonitrile kambario temp. Tokios pat reakcijos sąlygos taikytos ir chromonams sintetinti.
3. Nustatyta, kad alkoksimetil grupes turintys izoksazolai gaunami tik iš oksimų, kuriuose trigubas C≡C ryšys aktyvuotas benzeno žiede esančios elektronų donorinės alkoksi grupės. Tačiau, chromonai lengvai sintetinami iš 1,3-diarilalkinonų turinčių tiek elektronų donorinius, tiek elektronų akceptorinius pakaitus.
4. Atradome, kad lengvai sintetinami karbamimidotioatai gali pilnai pakeisti tiolius Fiesselmann‘o reakcijoje sintetinant 2,3,5-tripakeistus tiofenus.
5. Nustatėme, kad elektron akceptorinius pakaitus turinčių arenų įvedimas į 3-ią tiofeno žiedo padėtį bei elektron donorinius pakaitus turinčių arenų įvedimas į tiofeno žiedo 5-ą padėtį ne tik leidžia pasiekti aukštas kvantines išeigas 2-(2-benzimidazoil) tiofenuose (**25l**) bet ir padidina 2-(4-piridil) tiofenų kvantines išeigas.

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2. I. Karpavičienė, M. Jonušis, K. Leduskrasts, I. Misiūnaitė, E. Suna, I. Čikotienė; Synthesis and photophysical properties of 3,5-diaryl-2-heteroarylthiophenes; Dyes and Pigments. **2019**, 170, 1076465.

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2. M. Jonušis, I. Misiūnaitė, G. Kisielius, I. Čikotienė; SYNTHESIS OF 3,5-DIARYL-2-SUBSTITUTED-THIOPHENES; "Latvijas Universitates 76. Starptautiska Konference", Ryga, Latvia, 2018.
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Paper 1

Synthesis of Alkoxymethyl Groups Containing Isoxazoles and Chromones

M. Jonušis, L. Šteinys, R. Bukšnaitienė, I. Čikotienė

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Synthesis of Alkoxymethyl Groups Containing Isoxazoles and Chromones

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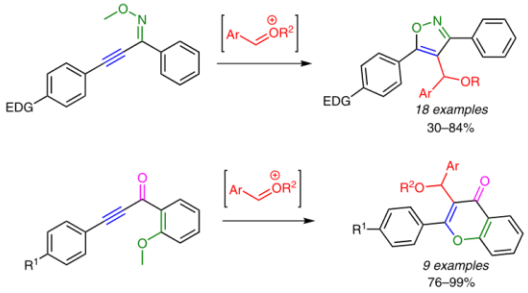

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Abstract An oxocarbenium ion mediated cyclization of (*Z*)-1,3-diarylprop-2-yn-1-one *O*-methyloximes and 3-arylprop-2-yn-1-(2-methoxyphenyl)-1-ones resulted in regioselective formation of functionalized isoxazoles and chromones, respectively. Alkoxy(aryl)methyl group containing compounds were obtained in good and high yields.

Key words isoxazoles, chromones, electrophile-mediated cyclization, oxocarbenium ion

Isoxazoles and chromones are valuable heterocycles in pharmaceutical and material chemistry. Thus, the isoxazole ring presenting in some bioactive natural products (cycloserine,[1] muscimol,[2] ibotenic acid[3]) and in a large variety of pharmaceuticals, such as parecoxib,[4] leflunomide,[5] isocarboxazide,[6] risperidone,[7] and β-lactamase-resistant antibiotics oxacillin, cloxacillin, flucloxacillin, and dicloxacillin.[8] Moreover, the flat structure of the ring as well as the presence of two heteroatoms with external electron pairs endow usefulness of isoxazoles in material sciences and as coordinating ligands in transition-metal complexes.[9] Additionally, isoxazole rings demonstrate the power of masked 1,3-dicarbonyl equivalents, so these compounds are considered as useful synthetic intermediates in organic chemistry and total synthesis.[10]

Chromone and flavone backbones are mainly found in natural products derived from cereals and herbs.[11] These compounds show rich antioxidant, anti-inflammatory, antimicrobial, and anticancer properties.[12]

A wide variation of classical and modern synthetic methods of isoxazoles and chromones are published in the scientific literature. The main preparative approaches to the isoxazole ring are [3+2] cycloadditions between nitrile oxides and alkynes or benzene equivalents, cycloisomerizations, and condensation reactions between β-dicarbonyls and hydroxylamine.[13] Traditionally, chromones can be synthesized using the Baker–Venkataraman reaction,[14] Claisen–Schmidt condensation,[15] Pd-carbonylative Sonogashira reaction,[16] and some others.

A decade ago, Larock et al. reported on the halogen- or chalcogen-mediated synthesis of isoxazoles and chromones by methods of electrophile-mediated cyclizations.[17] These types of reactions have their scope and benefits in organic synthesis, because the methods do not require transition-metal catalysis and the final products contain functional groups (usually halogen or chalcogen) suitable for further functionalizations.[18]

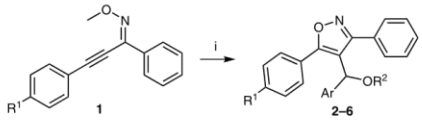
It is also known, that acetals can be used as sources of electrophilic oxocarbenium ions for the introduction of alkoxy(aryl)methyl groups into the structures of final compounds. Transition-metal salts usually are used as Lewis acids for the activation of acetals and alkyne functionalities.[19] Very recently, our group has reported about the metal-free generation of electrophilic oxocarbenium ions and its use in transformations of functionally substituted alkynes.[20] Herein we demonstrate the simple and powerful installation of alkoxy(aryl)methyl groups into isoxazole and chromone rings via one-step procedure.

The starting materials (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyloximes **1**[17a,b] and 3-aryl-1-(2-methoxyphenyl)prop-2-yn-1-ones **7**[17c,21] were prepared by known methods including as the key step a Pd-catalyzed coupling of arylacetylenes with the corresponding acyl chlorides.

For the synthesis of isoxazole derivatives we utilized the reaction between (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyloximes **1** and cyclic and acyclic aromatic acetals. As it is known from the literature, acetals can be activated by different Lewis acids for the reactions with carbon nucleophiles.[22] First of all, we tested several Lewis acids, such as $BF_3{\cdot}Et_2O$, $FeCl_3$, $AgSbF_6$, SbF_5, BBr_3, and TMSOTf, different

solvents (CH_2Cl_2, DCE, MeCN, THF, and $MeNO_2$), and different reaction temperatures. After this brief search for the most suitable reaction conditions, we came to the conclusion that 1 equivalent of $BF_3{\cdot}Et_2O$ in acetonitrile at room temperature gave the best results. The oxocarbenium ion triggered cyclization occurred very smoothly and full conversion of the starting materials was reached in 10–15 minutes. After the work-up of the reaction mixture, the final compounds **2–6** were isolated in moderate or good yields (Table 1). It is noteworthy that the reactions proceeded successfully only in the case of strong activation of the triple bond by electron-donating alkoxy groups (Table 1, entries 1–4, 7–18). This fact can be explained by resonance stabilization of the vinylic carbocation forming after addition of oxocarbenium ion to the triple bond. Unsubstituted phenyl or chloro-substituted phenyl ring containing starting materials **1e**,**f** remained unreactive towards the reaction conditions (Table 1, entries 5 and 6).

Table 1 Synthesis of 4-[Alkoxy(aryl)methyl]-5-aryl-3-phenylisoxazoles **2–6**[a]



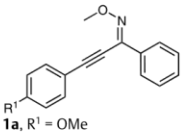
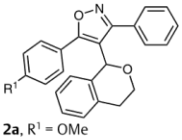
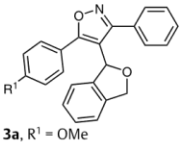
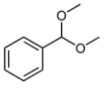
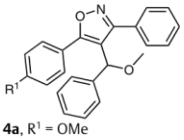
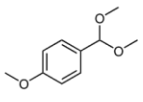
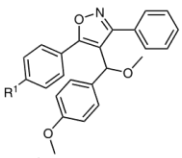
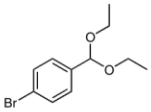
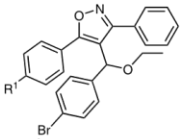
Entry	Starting material	Acetal R^2	Product	Yield (%)
				
1	**1a**, R^1 = OMe		**2a**, R^1 = OMe	57
2	**1b**, R^1 = OBu		**2b**, R^1 = OBu	43
3	**1c**, R^1 = $O(CH_2)_4Me$		**2c**, R^1 = $O(CH_2)_4Me$	84
4	**1d**, R^1 = $O(CH_2)_5Me$		**2d**, R^1 = $O(CH_2)_5Me$	58
5	**1e**, R^1 = H		no reaction	–
6	**1f**, R^1 = Cl		no reaction	–
				
7	**1a**		**3a**, R^1 = OMe	55
8	**1b**		**3b**, R^1 = OBu	59
9	**1d**		**3d**, R^1 = $O(CH_2)_5Me$	58
				
10	**1a**		**4a**, R^1 = OMe	79
11	**1b**		**4b**, R^1 = OBu	48
12	**1c**		**4c**, R^1 = $O(CH_2)_4Me$	66
13	**1d**		**4d**, R^1 = $O(CH_2)_5Me$	47

Table 1 (continued)

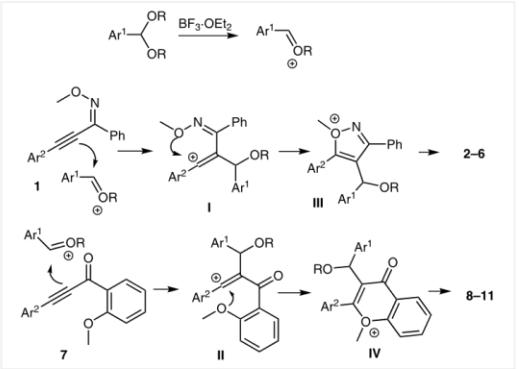
Entry	Starting material	Acetal R^2	Product	Yield (%)
				
14	**1a**		**5a**, R^1 = OMe	58
15	**1d**		**5d**, R^1 = $O(CH_2)_5Me$	59
				
16	**1a**		**6a**, R^1 = OMe	77
17	**1c**		**6c**, R^1 = $O(CH_2)_4Me$	30
18	**1d**		**6d**, R^1 = $O(CH_2)_5Me$	56

[a] Reaction conditions: (*i*) acetal (1.1 equiv), $BF_3{\cdot}OEt_2$ (1 equiv), MeCN, rt.

The corresponding 3-aryl-1-(2-methoxyphenyl)prop-2-yn-1-ones **7** having a methoxy group in close proximity to the triple bond are able to undergo a regioselective and smooth 6-*endo*-dig cyclization process. Thus, 2-aryl-4*H*-chromen-4-ones **8–11** with alkoxy(aryl)methyl groups in the 3-position can be synthesized (Table 2). All chromenones were isolated in high yields and the outcome of reactions did not depend on the presence or absence of strong electron-donating groups on the aryl ring next to the triple bond (Table 2).

We propose the following mechanism for the cyclization reactions. First, the formation of oxocarbenium ions via boron trifluoride mediated cleavage of the C–O bond of the starting acetals occurs. Next, the trapping of an electrophile by electron-rich alkynes takes place, resulting in the formation of vinylic carbocations **I** and **II**. The subsequent 5-*endo*-dig or 6-*endo*-dig cyclizations lead to isoxazolium and chromonium salts **III** and **IV**. Finally, smooth removal of the methyl group generates isoxazoles **2–6** and chromones **8–11** (Scheme 1).

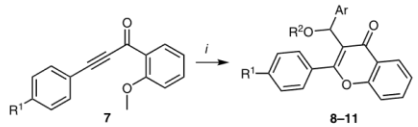
In conclusion, our method enables the synthesis of potentially bioactive 4-[alkoxy(aryl)methyl]-substituted isoxazoles and 3-[alkoxy(aryl)methyl]-substituted chromen-4-ones in good yields from easily obtainable starting materials. This reaction involves the in situ generation of an electrophilic oxocarbenium ion and cationic cyclization mechanism. Having in mind that isoxazoles and chromen-4-ones are important motifs in medicinal and synthetic organic chemistry and alkoxy(aryl)methyl groups can be further structurally modified, the developed method can find its synthetic application.

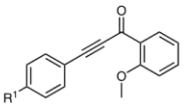
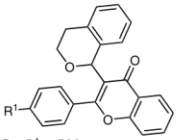
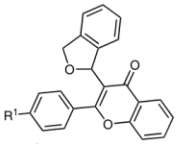
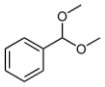
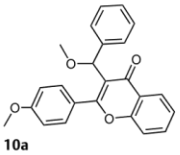
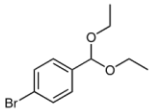
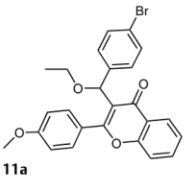


Scheme 1 Possible mechanism of oxocarbenium ion mediated cyclizations

IR spectra were run on samples prepared as KBr discs on a Perkin-Elmer FT spectrophotometer Spectrum BX II. ^1H and ^{13}C NMR spectra were recorded with a Bruker (400 MHz) in $CDCl_3$, using residual solvent signal as internal standard. HRMS spectra were obtained on a mass spectrometer Dual-ESI Q-TOF 6520 (Agilent Technologies). All reactions and the purity of the synthesized compounds monitored by

Table 2 Synthesis of 3-[Alkoxy(aryl)methyl]-2-aryl-4*H*-chromen-4-ones **8–11**[a]



Entry	Starting material	Acetal R^2	Product	Yield (%)
				
1	**7a**, R^1 = OMe		**8a**, R^1 = OMe	99
2	**7b**, R^1 = OBu		**8b**, R^1 = OBu	88
3	**7c**, R^1 = $O(CH_2)_5Me$		**8c**, R^1 = $O(CH_2)_5Me$	70
4	**7d**, R^1 = F		**8d**, R^1 = F	97
				
5	**7a**		**9a**, R^1 = OMe	83
6	**7b**		**9b**, R^1 = OBu	79
7	**7c**		**9c**, R^1 = $O(CH_2)_5Me$	80
8	**7a**		 **10a**	76
9	**7a**		 **11a**	82

[a] Reaction conditions: (*i*) acetal (1.1 equiv), $BF_3{\cdot}OEt_2$ (1 equiv), MeCN, rt.

TLC using Silica Gel 60 F254 aluminum plates (Merck). Visualization was accomplished by UV light and by treating the plates with vanillin stain followed by heating.

Starting (*Z*)-3-aryl-1-phenylprop-2-yn-1-one *O*-methyloximes **1**[17a,b] and 3-aryl-1-(2-methoxyphenyl)prop-2-yn-1-ones **7**[17c,21] were prepared by methods reported in the literature.

Isoxazoles 2–6 and 4*H*-Chromen-4-ones 8–11; General Procedure

To the solution of (*Z*)-1-phenyl-3-arylprop-2-yn-1-one *O*-methyloxime **1a–f** (0.4 mmol) or 3-(2-methoxyphenyl)-1-arylprop-2-yn-1-one **7a–d** (0.4 mmol) and acetal (0.44 mmol) in anhyd MeCN (2 mL), $BF_3{\cdot}Et_2O$ (56.8 mg, 49.4 µL, 0.4 mmol) was added with stirring at rt. After TLC monitoring indicated the full conversion of the starting material (approx. 10 min), the mixture was quenched by the addition of aq $NaHCO_3$. The mixture was extracted with EtOAc (3 × 10 mL), the

combined organic layers were dried (anhyd Na_2SO_4), and the solvent was evaporated to give a yellowish solid or oil. The product was purified by column chromatography (PE/EtOAc gradient from 20:1 to 4:1).

4-(Isochroman-1-yl)-5-(4-methoxyphenyl)-3-phenylisoxazole (2a)

Yellow plates; yield: 87 mg (57%); mp 144–146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.68 (m, 2 H, ArH), 7.63–7.54 (m, 2 H, ArH), 7.36–7.26 (m, 3 H, ArH), 7.03–6.96 (m, 2 H, ArH), 6.95–6.92 (m, 2 H, ArH), 6.91–6.82 (m, 1 H, ArH), 6.68 (m, 1 H, ArH), 5.94 (s, 1 H, OCH), 4.40–4.36 (m, 1 H, OCH_2), 3.98–3.92 (td, ^3J = 11.7 Hz, ^2J = 3.2 Hz, 1 H, OCH_2), 3.82 (s, 3 H, OCH_3), 3.17–3.11 (m, 1 H, $ArCH_2$), 2.69–2.65 (m, 1 H, $ArCH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5 (ArC), 164.2 (ArC), 161.1 (ArC), 135.8 (ArC), 133.7 (ArC), 129.6 (ArC), 129.4 (ArC), 129.2 (ArC), 128.9 (ArC), 128.5 (ArC), 128.0 (ArC), 126.8 (ArC), 126.1 (ArC), 125.4 (ArC), 120.3 (ArC), 114.1 (ArC), 113.2 (ArC), 71.2 (CH), 65.8 (OCH_2), 55.4 (OCH_3), 28.6 ($ArCH_2$).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{25}H_{22}NO_3$: 384.1600; found: 384.1597.

5-(4-Butoxyphenyl)-4-(isochroman-1-yl)-3-phenylisoxazole (2b)

Colorless oil; yield: 73 mg (43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.9 Hz, 2 H, ArH), 7.58 (dd, *J* = 7.5, 2.0 Hz, 2 H, ArH), 7.35–7.27 (m, 3 H, ArH), 7.02–6.96 (m, 2 H, ArH), 6.93 (d, *J* = 8.9 Hz, 2 H, ArH), 6.90–6.85 (m, 1 H, ArH), 6.69 (d , *J* = 7.7 Hz, 1 H, ArH), 5.94 (s, 1 H, OCH), 4.38 (ddd, *J* = 10.4, 6.1, 1.0 Hz, 1 H, OCH_2), 3.99 (t, *J* = 6.5 Hz, 2 H, $OCH_2C_3H_7$), 3.95 (td, *J* = 11.6, 3.0 Hz, 1 H, OCH_2), 3.19–3.11 (m, 1 H, $ArCH_2$), 2.68 (d, ^3J = 15.1 Hz, 1 H, $ArCH_2$), 1.82–1.75 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.57–1.46 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 0.99 (t, *J* = 7.4 Hz, 3 H, $OCH_2CH_2CH_2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6 (ArC), 164.2 (ArC), 160.7 (ArC), 135.9 (ArC), 133.7 (ArC), 129.6 (ArC), 129.4 (ArC), 129.1 (ArC), 128.9 (ArC), 128.4 (ArC), 126.8 (ArC), 126.1 (ArC), 125.4 (ArC), 120.0 (ArC), 114.6 (ArC), 113.0 (ArC), 71.2 (CH), 67.8 (OCH_2), 65.7 (OCH_2), 31.2 (CH_2), 28.6 (CH_2), 19.2 (CH_2), 13.8 (CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{28}H_{28}NO_3$: 426.2069; found: 426.2072.

4-(Isochroman-1-yl)-5-[4-(pentyloxy)phenyl]-3-phenylisoxazole (2c)

Colorless oil; yield: 147 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, ^3J = 8.4 Hz, 2 H, ArH), 7.57–7.55 (m, 2 H, ArH), 7.30–7.28 (m, 3 H, ArH), 7.01–6.95 (m, 2 H, ArH), 6.92 (d, ^3J = 8.8 Hz, 2 H, ArH), 6.89–6.85 (m, 1 H, ArH), 6.68 (d, ^3J = 7.6 Hz, 1 H, ArH), 5.92 (s, 1 H, OCH), 4.37 (dd, ^3J = 11.4 Hz, ^2J = 6.0 Hz, 1 H, OCH_2), 3.98 [t, ^3J = 6.8 Hz, 2 H, $OCH_2(CH_2)_3CH_3$], 3.94 (td, ^3J = 11.6 Hz, ^2J = 3.2 Hz, 1 H, OCH_2), 3.18–3.10 (m, 1 H, $ArCH_2$), 2.66 (d, ^3J = 14.8 Hz, 1 H, $ArCH_2$), 1.80 [quint, ^3J = 6.8 Hz, 2 H, $OCH_2CH_2(CH_2)_2CH_3$], 1.48–1.35 [m, 4 H, $OCH_2CH_2(CH_2)_2CH_3$], 0.94 [t, ^3J = 6.8 Hz, 3 H, $OCH_2(CH_2)_3CH_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (ArC), 164.2 (ArC), 160.8 (ArC), 136.0 (ArC), 133.8 (ArC), 129.7 (ArC), 129.5 (ArC), 129.2 (ArC), 129.0 (ArC), 128.5 (ArC), 128.1 (ArC), 126.9 (ArC), 126.2 (ArC), 125.5 (ArC), 120.1 (ArC), 114.6 (ArC), 113.2 (ArC), 71.3 (CH), 68.2 [$OCH_2(CH_2)_3CH$], 65.8 (OCH_2), 29.0 [$OCH_2CH_2(CH_2)_2CH_3$], 28.6 ($ArCH_2$), 28.3 [$OCH_2CH_2(CH_2)_2CH_3$], 22.5 [$OCH_2(CH_2)_2CH_2CH_3$], 14.1 [$OCH_2(CH_2)_2CH_2CH_3$].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{29}H_{30}NO_3$: 440.2226; found: 440.2236.

5-[4-(Hexyloxy)phenyl]-4-(isochroman-1-yl)-3-phenylisoxazole (2d)

Light yellow solid; yield: 105 mg (58%); mp 108–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.69 (d, ^3J = 8.8 Hz, 2 H, ArH), 7.61–7.56 (dd, ^3J = 7.4 Hz, ^4J = 1.8 Hz, 2 H, ArH), 7.37–7.29 (m, 3 H, ArH), 7.04–6.97 (m, 2 H, ArH), 6.87–6.97 (m, 3 H, ArH), 6.74–6.68 (d, ^3J = 7.7 Hz, 1 H, ArH), 5.95 (s, 1 H, OCH), 4.46–4.35 (dd, ^3J = 11.2 Hz, ^3J = 5.7 Hz, 1 H, OCH_2CH_2Ar), 4.03–3.99 (t, ^3J = 6.6 Hz, 2 H, OCH_2CH_2), 3.99–3.93 (td, ^3J = 11.7 Hz, ^4J = 3.1 Hz, 1 H, OCH_2CH_2Ar), 3.23–3.09 (m, 1 H, OCH_2CH_2Ar), 2.74–2.64 (d, ^3J = 15.4 Hz, 1 H, OCH_2CH_2Ar), 1.88–1.76 (quint, ^3J = 7.0 Hz, 2 H, OCH_2CH_2), 1.55–1.43 (m, 2 H, $OCH_2CH_2CH_2$), 1.43–1.32 [m, 4 H, $(CH_2)_2CH_3$], 1.00–0.89 (t, ^3J = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6 (ArC), 164.1 (ArC), 160.7 (ArC), 135.9 (ArC), 133.7 (ArC), 129.6 (ArC), 129.4 (ArC), 129.1 (ArC), 128.9 (ArC), 128.4 (ArC), 128.0 (ArC), 126.7 (ArC), 126.1 (ArC), 125.4 (ArC), 120.0 (ArC), 114.5 (ArC), 113.0 (ArC), 71.2 (OCH), 68.1 (OCH_2), 65.7 (OCH_2CH_2Ar), 31.6 ($CH_2CH_2CH_3$), 29.1 (OCH_2CH_2), 28.5 (OCH_2CH_2Ar), 25.7 ($OCH_2CH_2CH_2$), 22.6 (CH_2CH_3), 14.0 (CH_2CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{30}H_{32}NO_3$: 454.2382; found: 454.2390.

4-(1,3-Dihydroisobenzofuran-1-yl)-5-(4-methoxyphenyl)-3-phenylisoxazole (3a)

Yellow plates; yield: 81 mg (55%); mp 89–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.62 (m, 2 H, ArH), 7.44–7.36 (m, 2 H, ArH), 7.35–7.22 (m, 3 H, ArH), 7.20–7.09 (m, 2 H, ArH), 7.08–7.01 (m, 1 H, ArH), 6.99–6.92 (m, 2 H, ArH), 6.90–9.84 (m, 1 H, ArH), 6.37 (s, 1 H, CH), 5.12 (dd, ^2J = 12.1 Hz, ^4J = 2.3 Hz, 1 H, CH_2), 5.00 (dd, ^2J = 12.1 Hz, ^4J = 2.3 Hz, 1 H, CH_2), 3.86 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4 (ArC), 164.1 (ArC), 161.2 (ArC), 139.5 (ArC), 129.7 (ArC), 128.8 (ArC), 128.0 (ArC), 127.8 (ArC), 127.4 (ArC), 121.8 (ArC), 120.7 (ArC), 120.1 (ArC), 114.1 (ArC), 112.7 (ArC), 77.2 (CH), 72.7 ($ArCH_2$), 55.4 (OCH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{24}H_{20}NO_3$: 370.1443; found: 370.1444.

5-(4-Butoxyphenyl)-4-(1,3-dihydroisobenzofuran-1-yl)-3-phenylisoxazole (3b)

Light yellow solid; yield: 97 mg (59%); mp 105–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.9 Hz, 2 H, ArH), 7.40–7.36 (m, 2 H, ArH), 7.32–7.23 (m, 3 H, ArH), 7.19–7.10 (m, 2 H, ArH), 7.06 (t, *J* = 7.3 Hz, 1 H, ArH), 6.95 (d, *J* = 8.9 Hz, 2 H, ArH), 6.87 (d, *J* = 7.5 Hz, 1 H, ArH), 6.38 (s, 1 H, OCH), 5.12 (dd, ^2J = 12.1 Hz, ^4J = 2.5 Hz, 1 H, OCH_2), 4.99 (dd, ^2J = 12.1 Hz, ^4J = 2.5 Hz, 1 H, OCH_2), 4.02 (t, *J* = 6.5 Hz, 2 H, $OCH_2C_3H_7$), 1.89–1.74 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.60–1.48 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.02 (t, *J* = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5 (ArC), 164.1 (ArC), 160.8 (ArC), 139.6 (ArC), 139.5 (ArC), 129.6 (ArC), 129.3 (ArC), 129.0 (ArC), 128.8 (ArC), 128.0 (ArC), 127.8 (ArC), 127.4 (ArC), 121.8 (ArC), 120.7 (ArC), 119.8 (ArC), 114.6 (ArC), 112.6 (ArC), 77.2 (OCH), 72.7 (OCH_2Ar), 67.8 (OCH_2), 31.2 (CH_2), 19.2 (CH_2), 13.8 (CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{27}H_{26}NO_3$: 412.1913; found: 412.1910.

4-(1,3-Dihydroisobenzofuran-1-yl)-5-[4-(hexyloxy)phenyl]-3-phenylisoxazole (3d)

Light yellow solid; yield: 102 mg (58%); mp 105–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.60 (d, ^3J = 8.8 Hz, 2 H, ArH), 7.41–7.35 (m, 2 H, ArH), 7.35–7.22 (m, 3 H, ArH), 7.21–7.09 (m, 2 H, ArH), 7.09–7.01 (t, ^3J = 7.3 Hz, 1 H, ArH), 6.98–6.91 (d, ^3J = 8.8 Hz, 2 H, ArH), 6.90–6.84 (d, ^3J = 7.5 Hz, 1 H, ArH), 6.37 (s, 1 H, OCH), 5.16–5.07 (dd, ^2J = 12.1 Hz, ^4J = 2.3 Hz, 1 H, OCH_2Ar), 5.04–4.95 (dd, ^2J = 12.1 Hz, ^4J = 2.2 Hz, 1 H, OCH_2Ar), 4.06–3.97 (t, ^3J = 6.6 Hz, 2 H, OCH_2), 1.87–1.77 (quint, ^3J = 7.0 Hz, 2 H, OCH_2CH_2), 1.54–1.44 (m, 2 H, $OCH_2CH_2CH_2$), 1.43–1.33 [m, 4 H, $(CH_2)_2CH_3$], 0.98–0.90 (t, ^3J = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5 (ArC), 164.1 (ArC), 160.8 (ArC), 139.6 (ArC), 139.5 (ArC), 129.6 (ArC), 129.3 (ArC), 129.0 (ArC), 128.8 (ArC), 128.0 (ArC), 127.7 (ArC), 127.4 (ArC), 121.8 (ArC), 120.7 (ArC), 119.8 (ArC), 114.6 (ArC), 112.6 (ArC), 77.2 (OCH), 72.7 (OCH_2Ar), 68.2 (OCH_2), 31.6 ($CH_2CH_2CH_3$), 29.1 (OCH_2CH_2), 25.7 ($OCH_2CH_2CH_2$), 22.6 (CH_2CH_3), 14.0 (CH_2CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{29}H_{30}NO_3$: 440.2226; found: 440.2240.

5-(4-Methoxyphenyl)-4-[methoxy(phenyl)methyl]-3-phenylisoxazole (4a)

White crystals; yield: 117 mg (79%); mp 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, ^3J = 8.6 Hz, 2 H, ArH), 7.54 (d, J = 7.7 Hz, 2 H, ArH), 7.46–7.35 (m, 3 H, ArH), 7.35–7.19 (m, 5 H, ArH), 6.95 (d, ^3J = 8.6 Hz, 2 H, ArH), 5.59 (s, 1 H, CHO), 3.86 (s, 3 H, OCH_3), 3.33 (s, 3 H, $HCOCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7 (ArC), 164.3 (ArC), 161.0 (ArC), 139.9 (ArC), 129.8 (ArC), 129.4 (ArC), 129.2 (ArC), 129.0 (ArC), 128.4 (ArC), 128.3 (ArC), 127.6 (ArC), 126.7 (ArC), 120.2 (ArC), 114.0 (ArC), 111.9 (ArC), 76.0 ($HCOCH_3$), 56.8 ($HCOCH_3$), 55.3 (OCH_3).

HRMS (ESI) : *m*/*z* [M + Na] calcd for: $C_{24}H_{21}NO_3Na$: 394.1419; found: 394.1403.

5-(4-Butoxyphenyl)-4-[methoxy(phenyl)methyl]-3-phenylisoxazole (4b)

Yellowish oil; yield: 79 mg (48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.9 Hz, 2 H, ArH), 7.56–7.51 (m, 2 H, ArH), 7.45–7.35 (m, 3 H, ArH), 7.34–7.21 (m, 5 H, ArH), 6.94 (d, J = 8.9 Hz, 2 H, ArH), 5.59 (s, 1 H, CHO), 4.01 (t, J = 6.5 Hz, 2 H, OCH_2), 3.33 (s, 3 H, OCH_3), 1.84–1.77 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.59–1.45 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.01 (t, J = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7 (ArC), 164.2 (ArC), 160.7 (ArC), 139.9 (ArC), 129.8 (ArC), 129.4 (ArC), 129.3 (ArC), 129.1 (ArC), 128.3 (ArC), 128.3 (ArC), 127.6 (ArC), 126.7 (ArC), 120.0 (ArC), 114.6 (ArC), 111.8 (ArC), 76.0 ($HCOCH_3$), 67.8 (OCH_2), 56.8 (OCH_3), 31.2 (CH_2), 19.2 (CH_2), 13.8 (CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{27}H_{28}NO_3$: 414.2069; found: 414.2068.

4-[Methoxy(phenyl)methyl]-5-[4-(pentyloxy)phenyl]-3-phenylisoxazole (4c)

Yellowish oil; yield: 113 mg (66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, ^3J = 9.2 Hz, 2 H, ArH), 7.52–7.50 (m, 2 H, ArH), 7.41–7.33 (m, 3 H, ArH), 7.30–7.20 (m, 5 H, ArH), 6.91 (d, ^3J = 8.8 Hz, 2 H, ArH), 5.56 (s, 1 H, CH), 3.98 (t, ^3J = 6.4 Hz, 2 H, OCH_2), 3.30 (s, 3 H, OCH_3), 1.80 [quint, ^3J = 6.8 Hz, 2 H, $OCH_2CH_2(CH_2)_2CH_3$], 1.47–1.36 [m, 4 H, $OCH_2CH_2(CH_2)_2CH_3$], 0.94 [t, ^3J = 6.8 Hz, 3 H, $OCH_2(CH_2)_3CH_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (ArC), 164.4 (ArC), 160.8 (ArC), 140.1 (ArC), 129.9 (ArC), 129.5 (ArC), 129.4 (ArC), 129.2 (ArC), 128.5 (ArC), 128.4 (ArC), 127.7 (ArC), 126.8 (ArC), 120.1 (ArC), 114.7 (ArC), 111.9 (ArC), 76.1 ($HCOCH_3$), 68.2 (OCH_2), 56.9 (OCH_3), 29.0 [$OCH_2CH_2(CH_2)_2CH_3$], 28.3 [$OCH_2CH_2(CH_2)_2CH_3$], 22.6 [$OCH_2(CH_2)_2CH_2CH_3$], 14.1 [$OCH_2(CH_2)_2CH_2CH_3$].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{28}H_{30}NO_3$: 428.2226; found: 428.2226.

5-[4-(Hexyloxy)phenyl]-4-[methoxy(phenyl)methyl]-3-phenylisoxazole (4d)

Yellowish oil; yield: 83 mg (47%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.71 (d, ^3J = 8.8 Hz, 2 H, ArH), 7.57–7.50 (m, 2 H, ArH), 7.44–7.35 (m, 3 H, ArH), 7.34–7.29 (m, 2 H, ArH), 7.28–7.20 (m, 3 H, ArH), 6.98–6.90 (d, ^3J = 8.8 Hz, 2 H, ArH), 5.59 (s, 1 H, OCH), 4.05–3.96 (t, ^3J = 6.5 Hz, 2 H, OCH_2), 3.33 (s, 3 H, OCH_3), 1.87–1.77 (quint, ^3J = 7.0 Hz, 2 H, OCH_2CH_2), 1.54–1.44 (m, 2 H, $OCH_2CH_2CH_2$), 1.43–1.33 [m, 4 H, $(CH_2)_2CH_3$], 0.98–0.90 (t, ^3J = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8 (ArC), 164.3 (ArC), 160.7 (ArC), 140.0 (ArC), 129.8 (ArC), 129.4 (ArC), 129.3 (ArC), 129.1 (ArC), 128.3 (ArC), 128.3 (ArC), 127.5 (ArC), 126.7 (ArC), 120.0 (ArC), 114.6 (ArC), 111.8 (ArC), 76.0 (OCH), 68.1 (OCH_2), 56.8 (OCH_3), 31.6 ($CH_2CH_2CH_3$), 29.1 (OCH_2CH_2), 25.7 ($OCH_2CH_2CH_2$), 22.6 (CH_2CH_3), 14.0 (CH_2CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{29}H_{32}NO_3$: 442.2382; found: 442.2387.

5-(4-Methoxyphenyl)-4-[methoxy(4-methoxyphenyl)methyl]-3-phenylisoxazole (5a)

White plates; yield: 93 mg (58%); mp 118–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, ^3J = 8.9 Hz, 2 H, ArH), 7.60–7.51 (m, 2 H, ArH), 7.47–7.34 (m, 3 H, ArH), 7.31–7.22 (m, 2 H, ArH), 6.95 (d, ^3J = 8.9 Hz, 2 H, ArH), 6.83 (d, ^3J = 8.7 Hz, 2 H, ArH), 5.53 (s, 1 H, HC), 3.85 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.28 (s, 3 H, $HCOCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4 (ArC), 164.3 (ArC), 161.0 (ArC), 159.1 (ArC), 132.1 (ArC), 129.8 (ArC), 129.4 (ArC), 129.3 (ArC), 129.0 (ArC), 128.4 (ArC), 128.1 (ArC), 120.3 (ArC), 114.0 (ArC), 113.7 (ArC), 111.8 (ArC), 75.9 ($HCOCH_3$), 56.7 ($HCOCH_3$), 55.3 (OCH_3), 55.2 (OCH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{25}H_{24}NO_4$: 402.1705; found: 402.1703.

5-[4-(Hexyloxy)phenyl]-4-[methoxy(4-methoxyphenyl)methyl]-3-phenylisoxazole (5d)

Yellowish solid ; yield: 111 mg (59%); mp 84–86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.71 (d, ^3J = 8.8 Hz, 2 H, ArH), 7.58–7.50 (d, ^3J = 8.1 Hz, 2 H, ArH), 7.47–7.35 (m, 3 H, ArH), 7.27–7.21 (d, ^3J = 8.6 Hz, 2 H, ArH), 6.98–6.90 (d, ^3J = 8.8 Hz, 2 H, ArH), 7.86–7.78 (d, ^3J = 8.7 Hz, 2 H, ArH), 5.52 (s, 1 H, OCH), 4.04–3.96 (t, ^3J = 6.5 Hz, 2 H, OCH_2), 3.80 (s, 3 H, CH_3OAr), 3.27 (s, 3 H, OCH_3), 1.86–1.76 (quint, ^3J = 7.0 Hz, 2 H, OCH_2CH_2), 1.53–1.43 (m, 2 H, $OCH_2CH_2CH_2$), 1.42–1.33 [m, 4 H, $(CH_2)_2CH_3$], 0.97–0.90 (t, ^3J = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5 (ArC), 164.2 (ArC), 160.6 (ArC), 159.0 (ArC), 132.1 (ArC), 129.8 (ArC), 129.4 (ArC), 129.3 (ArC), 129.0 (ArC), 128.4 (ArC), 128.1 (ArC), 120.0 (ArC), 114.5 (ArC), 113.7 (ArC), 111.6 (ArC), 75.9 (OCH), 68.1 (OCH_2), 56.7 (OCH_3), 55.2 (CH_3OAr), 31.6 ($CH_2CH_2CH_3$), 29.1 (OCH_2CH_2), 25.7 ($OCH_2CH_2CH_2$), 22.6 (CH_2CH_3), 14.0 (CH_2CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{30}H_{34}NO_4$: 472.2488; found: 472.2508.

4-[(4-Bromophenyl)(ethoxy)methyl]-5-(4-methoxyphenyl)-3-phenylisoxazole (6a)

White crystals ; yield: 143 mg (77%); mp 119–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, ^3J = 8.9 Hz, 2 H, ArH), 7.58–7.52 (m, 2 H, ArH), 7.47–7.33 (m, 5 H, ArH), 7.21 (d, ^3J = 8.4 Hz, 2 H, ArH), 6.96 (d, ^3J = 8.8 Hz, 2 H, ArH), 5.62 (s, 1 H, CH), 3.85 (s, 3 H, OCH_3), 3.57–3.37 (m, 2 H, OCH_2), 1.14 (t, ^3J = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6 (ArC), 164.1 (ArC), 161.1 (ArC), 139.4 (ArC), 131.3 (ArC), 129.8 (ArC), 129.5 (ArC), 129.2 (ArC), 129.1 (ArC), 128.5 (ArC), 128.4 (ArC), 121.5 (ArC), 120.1 (ArC), 114.1 (ArC), 112.1 (ArC), 73.5 (HCOCH$_3$), 64.6 (OCH_2), 55.4 (OCH_3), 15.1 (CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{25}H_{23}BrNO_3$: 464.0861; found: 464.0864.

4-[(4-Bromophenyl)(ethoxy)methyl]-5-[4-(pentyloxy)phenyl]-3-phenylisoxazole (6c)

Colorless oil; yield: 62 mg (30%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, ^3J = 8.8 Hz, 2 H, ArH), 7.51–7.49 (m, 2 H, ArH), 7.42–7.33 (m, 5 H, ArH), 7.15 (d, ^3J = 8.4 Hz, 2 H, ArH), 6.91 (d, ^3J = 8.8 Hz, 2 H, ArH), 5.57 (s, 1 H, CH), 3.98 (t, ^3J = 6.4 Hz, 2 H, OCH_2), 3.51–3.44 (m, 1 H, OCH_2CH_3), 3.41–3.34 (m, 1 H, OCH_2CH_3), 1.80 [quint, ^3J = 6.8 Hz, 2 H, $OCH_2CH_2(CH_2)_2CH_3$], 1.48–1.34 [m, 4 H, $OCH_2CH_2(CH_2)_2CH_3$], 1.10 (t, ^3J = 6.8 Hz, 3 H, OCH_2CH_3), 0.94 [t, ^3J = 6.8 Hz, 3 H, $OCH_2(CH_2)_3CH_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8 (ArC), 164.2 (ArC), 160.9 (ArC), 139.5 (ArC), 131.4 (ArC), 129.9 (ArC), 129.6 (ArC), 129.32 (ArC), 129.17 (ArC), 128.57 (ArC), 128.49 (ArC), 121.56 (ArC), 119.9 (ArC), 114.7 (ArC), 112.1 (ArC), 73.6 (HC), 68.3 (OCH_2), 64.7 (OCH_2CH_3), 29.0 [$OCH_2CH_2(CH_2)_2CH_3$], 28.3 [$OCH_2CH_2(CH_2)_2CH_3$], 22.6 [$OCH_2(CH_2)_2CH_2CH_3$], 15.2 (OCH_2CH_3), 14.1 [$OCH_2(CH_2)_2CH_2CH_3$].

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{29}H_{31}BrNO_3$: 520.1487; found: 520.1503.

4-[(4-Bromophenyl)(ethoxy)methyl]-5-[4-(hexyloxy)phenyl]-3-phenylisoxazole (6d)

Yellow oil; yield: 119 mg (56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.68 (d, ^3J = 8.9 Hz, 2 H, ArH), 7.56–7.50 (m, 2 H, ArH), 7.46–7.33 (m, 5 H, ArH), 7.22–7.14 (d, ^3J = 8.3 Hz, 2 H, ArH), 6.99–6.90 (d, ^3J = 8.9 Hz, 2 H, ArH), 5.59 (s, 1 H, OCH), 4.03–3.98 (t, ^3J = 6.6 Hz, 2 H, OCH_2CH_2), 3.56–3.35 (m, 2 H, OCH_2CH_3), 1.88–1.76 (quint, ^3J = 7.0 Hz, 2 H, OCH_2CH_2), 1.55–1.44 (m, 2 H, $OCH_2CH_2CH_2$), 1.41–1.32 [m, 4 H, $(CH_2)_2CH_3$], 1.16–1.10 (t, ^3J = 7.0 Hz, 3 H, OCH_2CH_3), 0.98–0.89 (t, ^3J = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7 (ArC), 164.1 (ArC), 160.7 (ArC), 139.7 (ArC), 131.3 (ArC), 129.7 (ArC), 129.5 (ArC), 129.2 (ArC), 129.0 (ArC), 128.4 (ArC), 128.4 (ArC), 121.4 (ArC), 119.8 (ArC), 114.6 (ArC), 111.9 (ArC), 73.5 (OCH), 68.2 (OCH_2), 64.6 (OCH_2CH_3), 31.6 ($CH_2CH_2CH_3$), 29.1 (OCH_2CH_2), 25.7 ($OCH_2CH_2CH_2$), 22.6 (CH_2CH_3), 15.0 (OCH_2CH_3), 14.0 (CH_2CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{30}H_{33}BrNO_3$: 534.1644; found: 534.1668.

3-(Isochroman-1-yl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (8a)

Yellow oil; yield: 152 mg (99%).

IR (KBr): 1647 cm^{-1} (C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, ^3J = 7.9 Hz, 1 H, ArH), 7.76–7.61 (m, 3 H, ArH), 7.49 (d, ^3J = 8.4 Hz, 1 H, ArH), 7.39 (t, ^3J = 7.5 Hz, 1 H, ArH), 7.13–7.06 (m, 2 H, ArH), 7.05–6.99 (m, 1 H, ArH), 6.97 (d, ^3J = 8.4 Hz, 2 H, ArH), 6.84 (d, ^3J = 7.6 Hz, 1 H, ArH), 6.05 (s, 1 H, OCH), 4.41–4.32 (m, 1 H, OCH_2), 3.96–3.88 (m, 1 H, OCH_2), 3.87 (s, 3 H, OCH_3), 3.32–3.16 (m, 1 H, $ArCH_2$), 2.73–2.62 (m, 1 H, $ArCH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0 (C=O), 166.0 (ArC), 161.4 (ArC), 156.0 (OArC), 137.4 (ArC), 133.9 (ArC), 133.6 (ArC), 130.7 (ArC), 128.5 (ArC), 126.2 (ArC), 126.1 (ArC), 126.0 (ArC), 125.4 (ArC), 125.0 (ArC), 124.0 (ArC), 123.9 (ArC), 121.4 (ArC), 117.9 (ArC), 113.6 (ArC), 72.9 (OCH), 65.3 (OCH_2), 55.5 (OCH_3), 28.9 ($ArCH_2$).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{25}H_{21}O_4$: 385.1440; found: 385.1438.

2-(4-Butoxyphenyl)-3-(isochroman-1-yl)-4*H*-chromen-4-one (8b)

Yellow wax; yield: 150 mg (88%).

IR (KBr): 1649 cm^{-1} (C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25–8.18 (m, 1 H, ArH), 7.73–7.63 (m, 3 H, ArH), 7.49 (d, ^3J = 8.4 Hz, 1 H, ArH), 7.39 (t, ^3J = 7.5 Hz, 1 H, ArH), 7.12–7.06 (m, 2 H, ArH), 7.05–6.99 (m, 1 H, ArH), 6.96 (d, ^3J = 8.6 Hz, 2 H, ArH), 6.84 (d, ^3J = 7.6 Hz, 1 H, ArH), 6.03 (br s, 1 H, OCH), 4.40–4.32 (m, 1 H, OCH_2CH_2Ar), 4.04 (t, ^3J = 6.5 Hz, 2 H, OCH_2Pr), 3.96–3.87 (m, 1 H, OCH_2CH_2Ar), 3.30–3.16 (m, 1 H, OCH_2CH_2Ar), 2.71–2.62 (m, 1 H, OCH_2CH_2Ar), 1.87–1.75 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.61–1.48 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.03 (t, ^3J = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0 (C=O), 166.0 (ArC), 161.0 (ArC), 156.0 (OArC), 137.4 (ArC), 133.9 (ArC), 133.5 (ArC), 130.7 (ArC), 129.0 (ArC), 128.5 (ArC), 126.2 (ArC), 126.0 (ArC), 126.0 (ArC), 125.1 (ArC), 124.9 (ArC), 124.0 (ArC), 121.3 (ArC), 117.8 (ArC), 114.2 (ArC), 73.0 (HCO), 67.9 (OCH_2Pr), 65.3 (OCH_2CH_2Ar), 31.2 ($OCH_2CH_2CH_2CH_3$), 28.9 (OCH_2CH_2Ar), 19.2 ($OCH_2CH_2CH_2CH_3$), 13.8 (CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{28}H_{27}O_4$: 427.1909; found: 427.1906.

2-[4-(Hexyloxy)phenyl]-3-(isochroman-1-yl)-4*H*-chromen-4-one (8c)

Yellow oil; yield: 127 mg (70%).

IR (KBr): 1649 cm^{-1} (C=O).

^{1}H NMR (400 MHz, CD_3CN): δ = 8.11–8.01 (dd, ^3J = 7.9 Hz, ^4J = 1.3 Hz, 1 H, ArH), 7.80–7.73 (ddd, ^3J = 8.6 Hz, ^3J = 7.2 Hz, ^4J = 1.7 Hz, 1 H, ArH), 7.73–7.68 (d, ^3J = 8.7 Hz, 2 H, ArH), 7.60–7.54 (d, ^3J = 8.1 Hz, 1 H, ArH), 7.47–7.40 (m, 1 H, ArH), 7.10–7.02 (m, 2 H, ArH), 7.02–6.93 (m, 3 H, ArH), 6.87–6.77 (d, ^3J = 7.6 Hz, 1 H, ArH), 5.91 (s, 1 H, OCH), 4.32–4.23 (ddd, ^3J = 11.6 Hz, ^3J = 5.5 Hz, ^4J = 2.0 Hz, 1 H, OCH_2CH_2Ar), 4.08–4.00 (t, ^3J = 6.6 Hz, 2 H, OCH_2), 3.88–3.79 (td, ^3J = 11.2 Hz, ^4J = 3.1 Hz, 1 H, OCH_2CH_2Ar), 3.16–3.05 (m, 1 H, OCH_2CH_2Ar), 2.69–2.60 (d, ^2J = 16.1 Hz, 1 H, OCH_2CH_2Ar), 1.84–1.72 (quint, ^3J = 7.0 Hz, 2 H, OCH_2CH_2), 1.53–1.42 (m, 2 H, $OCH_2CH_2CH_2$), 1.42–1.32 [m, 4 H, $(CH_2)_2CH_3$], 0.98–0.88 (t, ^3J = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, CD_3CN): δ = 176.42 (C=O), 166.0 (OArC), 161.0 (ArC), 156.1 (ArC), 137.6 (ArC), 134.2 (ArC), 133.9 (ArC), 130.8 (ArC), 128.3 (ArC), 125.8 (ArC), 125.7 (ArC), 125.3 (ArC), 125.2 (ArC), 125.0 (ArC), 124.0 (ArC), 123.7 (ArC), 120.8 (ArC), 118.2 (ArC), 114.1 (ArC), 72.8 (OCH), 68.1 (OCH_2), 64.9 (OCH_2CH_2Ar), 31.3 ($CH_2CH_2CH_3$), 28.8 (OCH_2CH_2), 28.5 (OCH_2CH_2Ar), 25.4 ($OCH_2CH_2CH_2$), 22.3 (CH_2CH_3), 13.3 (CH_2CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{30}H_{31}O_4$: 455.2222; found: 455.2222.

2-(4-Fluorophenyl)-3-(isochroman-1-yl)-4*H*-chromen-4-one (8d)

White crystals; yield: 144 mg (97%); mp 130–135 °C.

IR (KBr): 1634 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.27–8.21 (m, 1 H, ArH), 7.73–7.66 (m, 1 H, ArH), 7.65–7.58 (m, 2 H, ArH), 7.50–7.45 (m, 1 H, ArH), 7.48 (d, ^3J = 8.3 Hz, 1 H, ArH), 7.12–6.97 (m, 5 H, ArH), 6.81 (d, ^3J = 7.6 Hz, 1 H), 6.11 (s, 1 H, OCH), 4.34–4.24 (m, 1 H, OCH_2CH_2Ar), 3.89 (td, ^3J = 11.3 Hz, ^2J = 3.1 Hz, 1 H, OCH_2CH_2Ar), 3.11–2.98 (m, 1 H, OCH_2CH_2Ar), 2.62 (d, ^3J = 16.1 Hz, 1 H, OCH_2CH_2Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0 (C=O), 163.8 (d, ^1J = 251.6 Hz, ArC), 156.0 (OArC), 137.2 (ArC), 133.8 (ArC), 133.7 (ArC), 131.2 (d, ^2J = 8.6 Hz, ArC), 129.3 (ArC), 129.2 (ArC), 128.5 (ArC), 126.3 (ArC), 126.1 (d, ^3J = 11.5 Hz, ArC), 125.2 (ArC), 124.2 (ArC), 123.7 (ArC), 122.4 (ArC), 117.9 (ArC), 115.2 (ArC), 115.0 (ArC), 72.1 (HCO), 65.3 (OCH_2CH_2), 28.7 (OCH_2CH_2).

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{24}H_{17}FO_3Na$: 395.1059; found: 395.1054.

3-(1,3-Dihydroisobenzofuran-1-yl)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (9a)

Yellow wax; yield: 123 mg (83%).

IR (KBr): 1646 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, ^3J = 8.0 Hz; ^4J = 1.4 Hz, 1 H, ArH), 7.70–7.61 (m, 3 H, ArH), 7.50–7.43 (m, 1 H, ArH), 7.40–7.33 (m, 1 H, ArH), 7.31–7.23 (m, 2 H, ArH), 7.23–7.17 (m, 1 H, ArH), 7.10–7.05 (m, 1 H, ArH), 7.04–6.98 (m, 2 H, ArH), 6.39 (s, 1 H, OCH), 5.37–5.28 (m, 1 H, CH_2), 5.21–5.15 (m, 1 H, CH_2), 3.89 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.23 (C=O), 166.0 (ArC), 161.4 (ArC), 156.0 (OArC), 140.6 (ArC), 140.1 (ArC), 133.6 (ArC), 130.8 (ArC), 127.4 (ArC), 127.1 (ArC), 126.0 (ArC), 124.9 (ArC), 124.9 (ArC), 124.1 (ArC), 120.6 (ArC), 120.5 (ArC), 120.1 (ArC), 117.8 (ArC), 113.9 (ArC), 80.7 (OCH), 74.1 (CH_2), 55.5 (OCH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{24}H_{19}O_4$: 371.1283; found: 371.1284.

2-(4-Butoxyphenyl)-3-(1,3-dihydroisobenzofuran-1-yl)-4*H*-chromen-4-one (9b)

Yellow wax; yield: 130 mg (79%).

IR (KBr): 1648 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, ^3J = 7.9 Hz, ^4J = 1.2 Hz, 1 H, ArH), 7.70–7.61 (m, 3 H, ArH), 7.47 (d, ^3J = 8.4 Hz, 1 H, ArH), 7.36 (t, ^3J = 7.5 Hz, 1 H, ArH), 7.32–7.17 (m, 3 H, ArH), 7.08 (d, ^3J = 7.5 Hz, 1 H, ArH), 7.02 (d, ^3J = 8.7 Hz, 2 H, ArH), 6.40 (s, 1 H, OCH), 5.39–5.30 (m, 1 H, $ArCH_2$), 5.23–5.15 (m, 1 H, $ArCH_2$), 4.06 (t, ^3J = 6.5 Hz, 2 H, OCH_2), 1.89–1.77 (m, 2 H, OCH_2CH_2), 1.61–1.48 (m, 2 H, CH_2CH_3), 1.03 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2 (C=O), 165.3 (ArC), 161.1 (ArC), 156.0 (OArC), 140.6 (ArC), 140.1 (ArC), 133.5 (ArC), 130.8 (ArC), 127.4 (ArC), 127.1 (ArC), 125.9 (ArC), 124.9 (ArC), 124.6 (ArC), 124.1 (ArC), 120.6 (ArC), 120.5 (ArC), 120.1 (ArC), 117.8 (ArC), 114.4 (ArC), 80.8 (OCH), 74.1 ($ArCH_2$), 67.9 (OCH_2CH_2), 31.2 (OCH_2CH_2), 19.2 (CH_2CH_3), 13.8 (CH_2CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{27}H_{25}O_4$: 413.1753; found: 413.1761.

3-(1,3-Dihydroisobenzofuran-1-yl)-2-[4-(hexyloxy)phenyl]-4*H*-chromen-4-one (9c)

Yellow oil; yield: 141 mg (80%).

IR (KBr): 1648 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.10 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 1 H, ArH), 7.71–7.61 (m, 3 H, ArH), 7.51–7.44 (d, ^3J = 8.3 Hz, 1 H, ArH), 7.41–7.33 (t, ^3J = 7.5 Hz, 1 H, ArH), 7.32–7.24 (m, 2 H, ArH), 7.24–7.17 (td, ^3J = 6.3 Hz, ^4J = 1.7 Hz, 1 H, ArH), 7.10–7.05 (d, ^3J = 7.4 Hz, 1 H, ArH), 7.04–6.97 (d, ^3J = 8.7 Hz, 2 H, ArH), 6.38 (s, 1 H, OCH), 5.38–5.30 (dd, ^2J = 11.6 Hz, ^4J = 2.4 Hz, 1 H, OCH_2Ar), 5.22–5.15 (d, ^2J = 11.5 Hz, 1 H, OCH_2Ar), 4.09–3.99 (t, ^3J = 6.5 Hz, 2 H, OCH_2), 1.89–1.79 (quint, ^3J = 7.0 Hz, 2 H, OCH_2CH_2), 1.56–1.46 (m, 2 H, $OCH_2CH_2CH_2$), 1.44–1.32 [m, 4 H, $(CH_2)_2CH_3$], 0.99–0.89 (t, ^3J = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2 (C=O), 165.3 (OArC), 161.0 (ArC), 156.0 (ArC), 140.6 (ArC), 140.1 (ArC), 133.5 (ArC), 130.8 (ArC), 127.4 (ArC), 127.1 (ArC), 126.0 (ArC), 124.9 (ArC), 124.6 (ArC), 124.1 (ArC), 120.6 (ArC), 120.4 (ArC), 120.0 (ArC), 117.8 (ArC), 114.4 (ArC), 80.8 (OCH), 74.1 (OCH_2Ar), 68.3 (OCH_2), 31.6 ($CH_2CH_2CH_3$), 29.1 (OCH_2CH_2), 25.7 ($OCH_2CH_2CH_2$), 22.6 (CH_2CH_3), 14.1 (CH_2CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{29}H_{29}O_4$: 441.2066; found: 441.2069.

2-(4-Methoxyphenyl)-3-[methoxy(phenyl)methyl]-4*H*-chromen-4-one (10a)

Yellow wax; yield: 113 mg (76%).

IR (KBr): 1650 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (dd, ^3J = 7.9 Hz; ^4J = 1.3 Hz, 1 H, ArH), 7.71–7.65 (m, 1 H, ArH), 7.51–7.38 (m, 4 H, ArH), 7.30–7.24 (m, 2 H, ArH), 7.23–7.17 (m, 2 H, ArH), 7.17–7.11 (m, 1 H, ArH), 6.95–6.87 (m, 2 H, ArH), 5.90 (s, 1 H, OCH), 3.87 (s, 3 H, OCH_3), 3.44 (s, 3 H, HCO-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6 (C=O), 165.5 (ArC), 161.2 (ArC), 156.1 (OArC), 141.0 (ArC), 133.6 (ArC), 130.7 (ArC), 127.7 (ArC), 126.5 (ArC), 126.3 (ArC), 125.9 (ArC), 125.4 (ArC), 125.0 (ArC), 123.4 (ArC), 121.2 (ArC), 117.9 (ArC), 113.4 (ArC), 77.1 (OCH), 57.2 (OCH_3), 55.4 ($ArOCH_3$).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{24}H_{21}O_4$: 373.1440; found: 373.1438.

3-[(4-Bromophenyl)(ethoxy)methyl]-2-(4-methoxyphenyl)-4*H*-chromen-4-one (11a)

Yellow wax; yield: 152 mg (82%).

IR (KBr): 1634 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, ^3J = 7.9 Hz, 1 H, ArH), 7.68 (t, ^3J = 7.7 Hz, 1 H), 7.48–7.38 (m, 4 H, ArH), 7.29 (d, ^3J = 8.4 Hz, 2 H, ArH), 7.11 (d, ^3J = 8.3 Hz, 2 H, ArH), 6.90 (d, ^3J = 8.7 Hz, 2 H, ArH), 5.99 (s, 1 H, OCH), 3.87 (s, 3 H, OCH_3), 3.63–3.49 (m, 2 H, OCH_2), 1.20 (t, ^3J = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.58 (C=O), 165.6 (ArC), 161.3 (ArC), 156.1 (OArC), 140.7 (ArC), 133.7 (ArC), 130.8 (ArC), 130.6 (ArC), 127.7 (ArC), 126.2 (ArC), 125.3 (ArC), 125.1 (ArC), 123.3 (ArC), 121.6 (ArC), 120.2 (ArC), 117.9 (ArC), 113.3 (ArC), 74.3 (OCH), 64.8 (OCH_2), 55.4 (OCH_3), 15.3 (CH_3).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{25}H_{22}BrO_4$: 465.0701; found: 465.0709,

Supporting Information

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Paper 2

Synthesis and photophysical properties of 3,5-diaryl-2-heteroarylthiophenes

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Synthesis and photophysical properties of 3,5-diaryl-2-heteroarylthiophenes

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ABSTRACT

A series of 3,5-diaryl-2-heteroarylthiophenes have been synthesized via Fiesselmann type reaction between alkynones and easily available heteroarylmethanethiols or heteroarylmethyl carbamimidothioates. A correlation between compounds structure and efficiency of luminescence has been established. These compounds exhibited photoluminescence with quantum yields up to 83%. An evidence of twisted intramolecular charge transfer and singlet emissive states have been demonstrated.

1. Introduction

Substituted thiophenes represent an important class of building blocks for the development of new pharmaceuticals [1,2] and optical materials [3–7]. There are numerous reports on the optoelectronic applications of thiophene-containing oligomeric or polymeric materials [8–13]. In contrast, the literature on the optoelectronic properties of monomeric thiophenes is relatively scarce. Although there are a few reports on the emissive properties of monomeric thiophenes [14], and these studies have led to the application of thiophenes in aggregation induced emission [15] and three-dimensional optical storage [16], the relationship between the structure and emissive behavior of monomeric thiophenes has not been systematically studied. It has been only shown that the introduction of benzimidazole (or structurally related phenanthroimidazole) [14] in the position 2 of the thiophene ring has helped to increase photoluminescence quantum yields (PLQY) to near unity in solution [14b]. In addition, Mueller has also demonstrated that aryl substituents that are not conjugated with the thiophene core have almost no effect on the emissive properties of oligomeric thiophenes [13]. Hence, we decided to utilize the beneficial effect of benzimidazole in position 2 and aryl substituents in positions 3 and 5 of thiophene scaffold in our study of emissive properties. The relationship between electronic and emissive properties of 2,3,5-trisubstituted thiophenes was systematically explored by the introduction of electron withdrawing groups (EWG) or electron donating groups (EDG) in aryl moieties (Fig. 1.). We were pleased to find that the proper choice of EWGs in the R_1 and R_2 positions and EDG in the R_3 position of 2,3,5-trisubstituted thiophenes allowed for PLQY of 83% to be achieved in solutions (Fig. 1).

Among a variety of methods for the synthesis of 2,3,5-trisubstituted thiophenes, Fiesselmann reaction is especially suitable. Early examples of Fiesselmann reaction involved a base-catalyzed condensation of acetylene dicarboxylates with mercaptoacetate to furnish 2,3,5-trisubstituted thiophenes (Scheme 1) [17]. The reaction experienced a renaissance in the late 90ties, when a tandem Michael addition/intramolecular Knoevenagel condensation between the appropriate 1,3-disubstituted propynones and mercaptoacetates was reported (Scheme 1) [18]. Later developments were mostly focused on various approaches for the *in situ* generation of ynones/ynoates under the Fiesselmann reaction conditions. Accordingly, Mueller elaborated the Fiesselmann reaction as a three-component or pseudo-five-component synthesis of 2,3,5-trisubstituted thiophenes and oligothiophenes [11–13] and Wu recently reported a four-component Fiesselmann reaction [19]. Importantly, easy-to-oxidize and relatively toxic mercaptans have been used as sulphur-containing building blocks in most of the above mentioned examples. Herein we report the use of heteroaryl substituted S-functionalized thioureas as a stable, non-toxic and easy-to-handle alternative to thiols [20] in the Fiesselmann reaction (Scheme 1).

2. Experimental section

2.1. General information

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100.6 MHz with Bruker Ascend™ spectrometer. Chemical shifts are reported in parts per million (ppm) using the residual protic solvent resonance as

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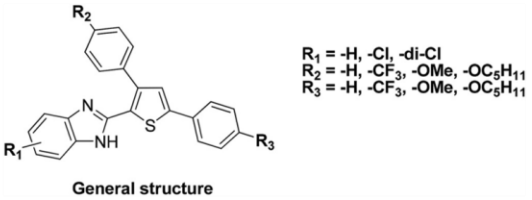


Fig. 1. General structure of luminescent 2,3,5-trisubstituted thiophenes.

the internal standard ($CHCl_3$: δ 7.28 (77.0), DMSO: δ 2.50 (39.5)) unless otherwise stated. Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration). Mass spectra were recorded with a TSQ Endura™ spectrometer (electrospray ionization) in positive mode. Melting points of synthesized compounds were monitored in open capillary with "Stuart SMP 10" apparatus. Reaction process was monitored by TLC using Silicagel 60 F_{254} Merc plates. For purification Silicagel 60 (40–63 μm), hexane or petroleum ether (PE), ethyl acetate (EA), toluene (Tol), chloroform ($CHCl_3$), acetonitrile (MeCN) and their mixtures were used as eluents. Hexane and petroleum ether were distilled before use.

The solution absorption and emission, as well as solid state emission spectra were measured on the FS5-*Edinburgh instruments* spectrofluorometer in ambient atmosphere and room temperature. The PLQYs were determined by the absolute method at ambient temperature using an integrating sphere. Compounds were excited in the wavelength they absorbed in. The temperature measurements were conducted in a cryostat using EtOH/liquid nitrogen as coolant.

2.2. Synthesis of compounds

2.2.1. Synthesis of starting materials

1,3-Diarylpropynones **1a-f** were synthesized according to known procedure [21] from corresponding alkynes and aroyl chlorides. (1*H*-benzo[*d*]imidazol-2-yl)methanethiols were prepared according to known procedure [22] in cyclization of aryl-1,2-diamine and mercaptoacetic acid and various substituted methyl carbamimidothioates were synthesized from corresponding alcohols in two step synthesis according the literature procedures [23] in good to excellent yield.

2.2.2. Synthesis of 3,5-diaryl-2-heteroarylthiophenes (3) and 2-heteroaryl-3,5-diaryl-2,3-dihydrothiophen-3-ols (4). General procedure

To the 25 ml round bottomed flask the corresponding heteroarylmethanethiol or heteroarylmethyl carbamimidothioate (0.45 mmol) and 36 mg NaOH (0.9 mmol) were added followed by 5 ml of ethanol. Reaction mixture was refluxed 1 h under argon atmosphere, then the corresponding 1,3-diarylpropynone **1** (0.3 mmol) was added and refluxing was continued until full completion (monitored by TLC). The solvent was evaporated under reduced pressure; the residue was portioned between DCM and water. The organic layer was separated, then washed with water, dried with sodium sulfate and concentrated under reduced pressure. The resulting solid material was purified by crystallization or column chromatography.

2.2.2.1. 2-(3,5-diphenylthiophen-2-yl)-1H-benzo[d]imidazole ***(3aa)***. Yellowish powder, m.p. 210–215 °C (*i*PrOH). Yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.89 (1H, s), 7.79 (1H, d, J = 7.8 Hz), 7.69 (2H, d, J = 7.3 Hz), 7.62–7.49 (5H, m), 7.43 (2H, t, J = 7.5 Hz), 7.39–7.31 (2H, m), 7.29–7.23 (1H, m), 7.20 (2H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.0, 143.1, 141.8, 136.0, 133.4, 129.4, 129.1, 129.0, 128.8, 128.4, 126.6, 125.8, 123.3, 122.6, 119.5, 110.5 ppm. HRMS (ESI) calcd. for $C_{23}H_{17}N_2S$ (MH^+): 353.1106; found 353.1109.

2.2.2.2. 5-Chloro-2-(3,5-diphenylthiophen-2-yl)-1H-benzo[d]imidazole ***(3ab)***. Yellowish powder, m.p. 205–209 °C (*i*PrOH). Yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.29 (1H, s), 7.82 (2H, d, J = 7.3 Hz), 7.78 (1H, s), 7.73–7.35 (10H, m), 7.22 (1H, d, J = 8.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.7, 145.3, 142.8, 135.2, 133.3, 129.8, 129.2, 129.1, 129.0, 128.7, 128.5, 127.5, 126.9, 126.0, 123.1, 120.5, 118.4, 113.5 ppm. HRMS (ESI) calcd. for $C_{23}H_{16}ClN_2S$ (MH^+): 387.0717; found 387.0719.

2.2.2.3. 5,6-Dichloro-2-(3,5-diphenylthiophen-2-yl)-1H-benzo[d] imidazole ***(3ac)***. Yellowish powder, m.p. 232–233 °C (*i*PrOH). Yield: 60%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.32 (1H, br. s), 7.89–7.68 (5H, m), 7.56–7.31 (8H, m) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 148.9, 145.7, 143.2, 139.5, 135.1, 133.2, 129.8, 129.2, 129.1, 129.1, 128.6, 127.6, 126.1, 125.6, 125.1, 116.8 ppm. HRMS (ESI) calcd. for $C_{23}H_{15}Cl_2N_2S$ (MH^+): 421.0328; found 421.0332.

2.2.2.4. 4-(3,5-diphenylthiophen-2-yl)pyridine ***(3ad)***. Yellowish plates, m.p. 107–110 °C (EtOH). Yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.50 (2H, d, J = 5.0 Hz), 7.79–7.75 (2H, m), 7.70 (1H, s), 7.47 (2H, t, J = 7.6 Hz), 7.43–7.34 (6H, m), 7.22 (2H, dd, J = 4.6, 1.5 Hz) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 150.5, 144.2, 141.7, 141.4, 135.8, 134.0, 133.3, 129.7, 129.3, 129.2, 128.8, 128.3, 128.0, 125.9, 123.2 ppm. HRMS (ESI) calcd. for $C_{21}H_{16}NS$ (MH^+): 314.0998; found 314.0998.

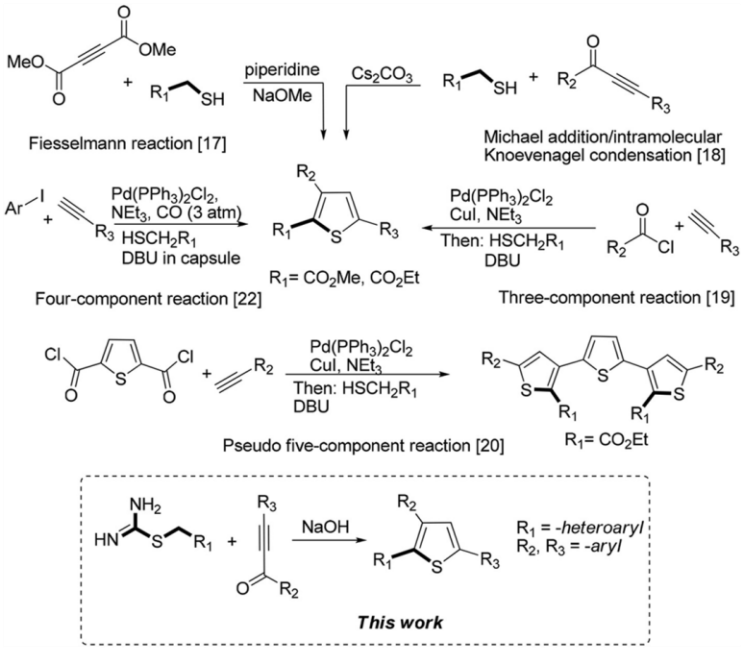
2.2.2.5. 2-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)-1H-benzo[d] imidazole ***(3ba)***. Yellow crystals, m.p. 255–258 °C (EtOH). Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.18 (1H, br. s), 7.56 (2H, d, J = 8.0 Hz), 7.50–7.42 (4H, m), 7.20–7.13 (3H, m), 6.99 (2H, d, J = 8.0 Hz), 6.91 (2H, d, J = 4.8 Hz), 3.85 (3H, s), 3.83 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 146.8, 145.9, 141.8, 130.1, 128.1, 127.1, 126.2, 125.6, 122.8, 114.7, 114.4, 55.3 ppm. HRMS (ESI) calcd. for $C_{25}H_{21}N_2O_2S$ (MH^+): 413.1318; found 413.1322.

2.2.2.6. 2-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)-5-chloro-1H-benzo[d] imidazole ***(3bb)***. Yellow powder, m.p. 235–237 °C (EtOH). Yield: 58%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.03 (1H, br. s), 7.72 (2H, d, J = 8.6 Hz), 7.60–7.53 (2H, m), 7.50 (1H, d, J = 8.3 Hz), 7.41 (2H, d, J = 8.6 Hz), 7.19 (1H, dd, J = 8.5, 1.6 Hz), 7.03 (2H, d, J = 8.7 Hz), 6.98 (2H, d, J = 8.6 Hz), 3.81 (3H, s), 3.79 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.0, 159.6, 148.1, 145.2, 142.5, 130.3, 127.7, 127.7, 127.4, 127.4, 126.8, 126.3, 126.0, 124.1, 124.1, 122.7, 122.7, 115.1, 114.6, 55.8, 55.6 ppm. HRMS (ESI) calcd. for $C_{25}H_{20}ClN_2O_2S$ (MH^+): 447.0928; found 447.0934.

2.2.2.7. 2-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)-5,6-dichloro-1H-benzo[d]imidazole ***(3bc)***. Yellow crystals, m.p. 122–127 °C (R_f = 0.3, PE:EA = 4:1). Yield 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (1H, br. s), 7.79 (1H, s), 7.59 (2H, d, J = 8.4 Hz), 7.43 (2H, d, J = 8.8 Hz), 7.31 (1H, s), 7.14 (1H, s), 7.05 (2H, d, J = 8.4 Hz), 6.94 (2H, d, J = 8.8 Hz), 3.90 (3H, s), 3.85 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1, 160.0, 148.9, 146.8, 142.7, 132.7, 130.1, 127.8, 127.2, 126.0, 125.7, 124.6, 120.2, 114.9, 114.5, 111.8, 55.4 ppm. HRMS (ESI) calcd. for $C_{25}H_{19}Cl_2N_2O_2S$ (MH^+): 481.0539; found 481.0545.

2.2.2.8. 4-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)pyridine ***(3bd)***. Yellow crystals, m.p. 120–125 °C (R_f = 0.5, Tol:EA = 1:1). Yield: 89% ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (2H, br. s), 7.57 (2H, d, J = 8.0 Hz), 7.24–7.22 (2H, m), 7.20–7.17 (3H, m), 6.94 (2H, d, J = 8.0 Hz), 6.89 (2H, d, J = 8.0 Hz), 3.84 (6H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 159.2, 149.9, 144.5, 142.3, 141.3, 137.9, 132.5, 132.5, 130.1, 128.5, 127.1, 126.4, 114.5, 114.2, 55.4, 55.3 ppm. HRMS (ESI) calcd. for $C_{23}H_{19}NO_2S$ (MH^+): 374.1209; found 374.1212.

2.2.2.9. 2-(3,5-bis(4-methoxyphenyl)thiophen-2-yl)-1-methyl-1H-imidazole ***(3be)***. Brown oil (R_f = 0.6, Tol:EA = 1:1). Yield: 30%. ^{1}H



Scheme 1. Fiesselmann reaction.

NMR (400 MHz, $CDCl_3$) δ: 7.55 (2H, d, J = 8.0 Hz), 7.38 (1H, s), 7.16–7.15 (2H, m), 7.14 (1H, s), 6.91 (2H, d, J = 8.0 Hz), 6.84–6.83 (2H, m), 6.81 (1H, s), 3.81 (3H, s), 3.77 (3H, s), 3.00 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.6, 159.0, 145.4, 142.2, 141.5, 129.0, 128.9, 128.6, 127.1, 126.6, 123.4, 123.1, 121.7, 114.4, 114.2, 55.4, 55.2, 33.3 ppm. HRMS (ESI) calcd. for $C_{22}H_{21}N_2O_2S$ (MH^+): 377.1318; found 377.1312.

2.2.2.10. 2-(5-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-1H-benzo[d]imidazole ***(3ca)***. Yellow crystals, m.p. 260–270 °C (R_f = 0.4, PE:EA = 3:1). Yield: 42%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.62 (1H, s), 7.82–7.67 (7H, m), 7.65–7.59 (1H, m), 7.44–7.36 (1H, m), 7.26–7.14 (2H, m), 7.05 (2H, d, J = 8.7 Hz), 3.81 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 160.1, 145.9, 145.4, 143.9, 140.6, 139.6, 135.3, 129.9, 128.5 ($^2J_{C\text{-}F}$ = 31.3 Hz), 127.5, 126.9, 126.2, 126.0 ($^3J_{C\text{-}F}$ = 3.7 Hz), 125.8, 124.8 ($^1J_{C\text{-}F}$ = 270.0 Hz), 123.3, 122.3, 119.2, 115.2, 112.1, 55.8 ppm. HRMS (ESI) calcd. for $C_{25}H_{18}F_3N_2OS$ (MH^+): 451.1086; found 451.1091.

2.2.2.11. 5-Chloro-2-(5-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl) thiophen-2-yl)-1H-benzo[d]imidazole ***(3 cb)***. Yellow crystals, m.p. 200–205 °C (R_f = 0.2, $CHCl_3$:MeCN = 98:2). Yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, br. s), 7.72 (2H, d, J = 8.0 Hz), 7.69 (1H, s), 7.61 (2H, d, J = 8.0 Hz), 7.55 (2H, d, J = 8.4 Hz), 7.26–7.15 (3H, m), 7.16 (1H, s), 6.92 (2H, d, J = 8.0 Hz), 3.84 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1, 147.1, 140.6, 139.4, 139.4, 130.6 ($^2J_{C\text{-}F}$ = 32.6 Hz), 130.6, 129.3, 127.2, 126.2 ($^3J_{C\text{-}F}$ = 3.5 Hz), 125.9, 125.7, 125.2, 125.1, 123.8 ($^1J_{C\text{-}F}$ = 270.6 Hz), 114.6, 113.7, 55.4 ppm. HRMS (ESI) calcd. for $C_{25}H_{17}ClF_3N_2OS$ (MH^+): 485.0697; found 485.0701.

2.2.2.12. 5,6-Dichloro-2-(5-(4-methoxyphenyl)-3-(4-(trifluoromethyl) phenyl)thiophen-2-yl)-1H-benzo[d]imidazole ***(3 cc)***. Yellow crystals, m.p. 227–231 °C (R_f = 0.3, $CHCl_3$:MeCN = 98:2). Yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.13 (1H, br. s), 7.76 (1H, s), 7.72 (2H, d, J = 8.0 Hz), 7.60 (2H, d, J = 8.0 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.34 (1H, s), 7.16 (1H, s), 6.92 (2H, d, J = 8.8 Hz), 3.84 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 148.0, 147.6, 142.6, 141.0, 139.3, 130.9 ($^2J_{C\text{-}F}$ = 32.6 Hz), 130.7, 129.3, 127.2, 126.3 ($^3J_{C\text{-}F}$ = 3.5 Hz), 125.5, 125.4, 125.2, 123.8 ($^1J_{C\text{-}F}$ = 270.9 Hz), 114.6, 112.0, 55.4 ppm. HRMS (ESI) calcd. for $C_{25}H_{16}Cl_2F_3N_2OS$ (MH^+): 519.0307; found 519.0315.

2.2.2.13. 4-(5-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)thiophen-2-yl)pyridine ***(3cd)***. Amber oil (R_f = 0.3, PE:EA = 2:1). Yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (2H, d, J = 6.0 Hz), 7.52 (2H, d, J = 8.4 Hz), 7.55 (2H, d, J = 8.8 Hz), 7.41 (2H, d, J = 8.0 Hz), 7.22 (1H, s), 7.14 (2H, d, J = 6.0 Hz), 6.93 (2H, d, J = 8.8 Hz), 3.82 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 149.9, 145.4, 141.7, 139.7, 139.7, 134.1, 129.7 ($^2J_{C\text{-}F}$ = 32.3 Hz), 129.3, 127.1, 125.9, 125.7 ($^3J_{C\text{-}F}$ = 3.7 Hz), 125.6, 124.1 ($^1J_{C\text{-}F}$ = 270.5 Hz), 123.0, 114.5, 55.4 ppm. HRMS (ESI) calcd. for $C_{23}H_{17}F_3NOS$ (MH^+): 412.0977; found 412.0981.

2.2.2.14. 2-(3-(4-methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-1H-benzo[d]imidazole ***(3da)***. Yellow crystals, m.p. 120–125 °C (R_f = 0.4, PE:EA = 3:1). Yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.49 (1H, br. s), 7.64 (2H, d, J = 8.0 Hz); 7.56 (2H, d, J = 8.0 Hz), 7.48 (2H, br. s), 7.36 (2H, d, J = 8.4 Hz), 7.27 (1H, s), 7.23–7.20 (2H, m), 6.91 (2H, d, J = 8.8 Hz), 3.79 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.2, 143.8, 142.0, 136.7, 130.0 ($^2J_{C\text{-}F}$ = 32.6 Hz), 130.0, 127.8, 127.7, 127.5, 126.0 ($^3J_{C\text{-}F}$ = 3.6 Hz), 125.8, 124.0 ($^1J_{C\text{-}F}$ = 270.4 Hz), 123.1, 114.7, 55.3 ppm. HRMS (ESI) calcd. for $C_{25}H_{18}F_3N_2OS$ (MH^+): 451.1086; found 451.1090.

2.2.2.15. 4-(3-(4-methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)thiophen-2-yl)pyridine ***(3dd)***. Yellow crystals, m.p. 120–125°C (R_f = 0.3, Tol:EA = 2:1). Yield: 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (2H, d,

J = 6.0 Hz), 7.74 (2H, d, J = 8.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.41 (1H, s), 7.24 (2H, d, J = 8.8 Hz), 7.22 (2H, d, J = 6.0 Hz), 6.90 (2H, d, J = 8.8 Hz), 3.84 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 149.9, 142.4, 141.9, 141.5, 137.0, 134.9, 130.1, 129.9 ($^2J_{C\text{-}F}$ = 32.5 Hz), 128.4, 127.9, 126.1 ($^3J_{C\text{-}F}$ = 3.7 Hz), 125.8, 124.0 ($^1J_{C\text{-}F}$ = 270.1 Hz), 114.3, 55.3 ppm. HRMS (ESI) calcd. for $C_{23}H_{17}F_3NOS$ (MH^+): 412.0977; found 412.0981.

2.2.2.16. 2-(3,5-bis(4-(trifluoromethyl)phenyl)thiophen-2-yl)-1H-benzo[d]imidazole ***(3ea)***. Yellow crystals, m.p. 130–135 °C (R_f = 0.5, PE:EA = 4:1). Yield: 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.17 (1H, br. s), 7.53–7.49 (5H, m), 7.47–7.42 (5H, m), 7.26–7.21 (3H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.3, 144.4, 140.6, 138.6, 136.0, 130.2 ($^2J_{C\text{-}F}$ = 33.0 Hz), 130.4 ($^2J_{C\text{-}F}$ = 33.0 Hz), 128.9, 128.5, 128.3, 127.9, 127.1, 126.0 ($^3J_{C\text{-}F}$ = 3.7 Hz), 125.9 ($^3J_{C\text{-}F}$ = 3.7 Hz), 125.6, 123.8 ($^1J_{C\text{-}F}$ = 270.0 Hz), 123.7 ($^1J_{C\text{-}F}$ = 271.0 Hz), 123.5 ppm. HRMS (ESI) calcd. for $C_{25}H_{15}F_6N_2S$ (MH^+): 489.0855; found 489.0859.

2.2.2.17. 4-(3,5-bis(4-(trifluoromethyl)phenyl)thiophen-2-yl)pyridine ***(3ed)***. Yellow crystals, m.p. 115–130 °C (R_f = 0.4, Tol:EA = 2:1). Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (2H, d, J = 8.0 Hz), 7.75 (2H, d, J = 8.0 Hz), 7.68 (2H, d, J = 8.0 Hz), 7.63 (2H, d, J = 8.0 Hz), 7.44 (2H, d, J = 8.0 Hz), 7.44 (1H, s), 7.19 (2H, d, J = 8.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.1, 143.2, 141.1, 139.9, 139.1, 136.7, 136.6, 130.2 ($^2J_{C\text{-}F}$ = 33.0 Hz), 130.0 ($^2J_{C\text{-}F}$ = 32.0 Hz), 129.3, 127.8, 126.2 ($^3J_{C\text{-}F}$ = 3.7 Hz), 125.9, 125.8 ($^3J_{C\text{-}F}$ = 3.7 Hz), 124.0 ($^1J_{C\text{-}F}$ = 271.0 Hz), 124.0 ($^1J_{C\text{-}F}$ = 270.0 Hz), 123.1 ppm. HRMS (ESI) calcd. for $C_{23}H_{14}F_6NS$ (MH^+): 450.0746; found 450.0751.

2.2.2.18. 2-(3,5-bis(4-(pentyloxy)phenyl)thiophen-2-yl)-1H-benzo[d]imidazole ***(3fa)***. White powder, m.p. 95–100 °C (*i*PrOH). Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (1H, br. s), 7.58 (2H, d, J = 8.6 Hz), 7.45 (2H, d, J = 8.5 Hz), 7.29 (1H, s), 7.26–7.12 (3H, m), 7.15 (1H, s), 7.02 (2H, d, J = 8.6 Hz), 6.93 (2H, d, J = 8.7 Hz), 4.08–3.95 (4H, m), 1.90–1.78 (4H, m), 1.56–1.36 (8H, m), 1.04–0.91 (6H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.5, 159.4, 147.0, 145.9, 143.2, 141.8, 133.5, 130.1, 128.0, 127.1, 126.1, 125.6, 125.6, 123.0, 122.4, 119.3, 115.3, 115.0, 110.4, 68.2, 68.1, 29.0, 28.9, 28.2, 28.2, 22.5, 22.4, 14.0, 14.0 ppm. HRMS (ESI) calcd. for $C_{33}H_{37}N_2O_2S$ (MH^+): 379.2268; found 379.2270.

2.2.2.19. (2R,3S) or (2S,3R)-2-(1H-benzo[d]imidazol-2-yl)-5-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol ***(4ca)***. Brown oil (R_f = 0.2, PE:EA = 4:1). Yield: 10%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62–7.60 (4H, m), 7.55–7.52 (2H, m), 7.49–7.44 (4H, m), 6.84 (2H, d, J = 8.0 Hz), 6.02 (1H, s), 5.46 (1H, s), 3.79 (3H, s) ppm.

2.2.2.20. (2R,3S) or (2S,3R)-2-(1H-benzo[d]imidazol-2-yl)-3,5-bis(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol ***(4ea)***. Brown oil (R_f = 0.3, PE:EA = 4:1). Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64–7.58 (8H, m), 7.54–7.25 (4H, m), 6.23 (1H, s), 5.47 (1H, s) ppm.

2.2.2.21. (2R,3S) or (2S,3R)-5-(4-methoxyphenyl)-2-(1-methyl-1H-imidazol-2-yl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol ***(4ce)***. Brown oil (R_f = 0.4, Tol:EA = 4:1). Yield: 38%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.0 Hz), 7.50 (2H, d, J = 8.8 Hz), 7.03 (1H, s), 6.89 (2H, d, J = 8.8 Hz), 6.82 (1H, s), 6.10 (1H, s), 5.08 (1H, s), 3.83 (3H, s), 3.42 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 142.7, 141.7 ($^1J_{C\text{-}F}$ = 265.0 Hz), 137.8, 129.7 ($^2J_{C\text{-}F}$ = 32.0 Hz), 128.8, 128.1, 127.2, 126.3, 125.1 ($^3J_{C\text{-}F}$ = 4.0 Hz), 123.1, 122.0, 113.9, 88.7, 55.4, 55.3, 52.4, 32.5 ppm.

2.2.2.22. (2R,3S) or (2S,3R)-3-(4-methoxyphenyl)-2-(1-methyl-1H-imidazol-2-yl)-5-(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol ***(4de)***. Brown oil (R_f = 0.45, Tol:EA = 2:1). Yield: 44%.^{1}H NMR (400 Hz, DMSO-d_6) δ: 7.82 (2H, d, J = 8.4 Hz), 7.79 (2H, d, J = 8.8 Hz), 7.44 (2H, d, J = 8.8 Hz), 7.16 (1H, s), 6.93 (1H, s), 6.90 (2H, d, J = 8.4 Hz), 6.53 (1H, s), 5.42 (1H, s), 3.75 (3H, s), 3.46 (3H, s) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.0, 142.7, 138.9 ($^1J_{C\text{-}F}$ = 271.9 Hz), 137.3, 129.4 ($^2J_{C\text{-}F}$ = 31.8 Hz), 128.3, 127.5, 127.3, 126.7, 126.1 ($^3J_{C\text{-}F}$ = 3.6 Hz), 123.4, 123.1, 113.8, 88.4, 55.5, 55.5, 53.5, 33.0 ppm.

2.2.2.23. (2R,3S) or (2S,3R)-2-(1-methyl-1H-imidazol-2-yl)-3,5-bis(4-(trifluoromethyl)phenyl)-2,3-dihydrothiophen-3-ol ***(4ee)***. Brown oil (R_f = 0.3, Tol:EA = 4:1). Yield 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (2H, d, J = 8.0 Hz), 7.72–7.65 (6H, m), 7.62 (2H, d, J = 8.0 Hz), 7.07 (1H, s), 6.86 (1H, s), 6.33 (1H, s), 5.15 (1H, s), 3.47 (3H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.3, 139.9 ($^1J_{C\text{-}F}$ = 266.0 Hz), 139.8 ($^1J_{C\text{-}F}$ = 272.0 Hz), 137.9, 136.5, 131.0 ($^2J_{C\text{-}F}$ = 32.0 Hz), 130.0 ($^2J_{C\text{-}F}$ = 32.0 Hz), 129.6, 129.0, 127.4, 127.0, 126.2, 125.6 ($^3J_{C\text{-}F}$ = 3.7 Hz), 125.2 ($^3J_{C\text{-}F}$ = 3.7 Hz), 121.6, 88.6, 52.4, 32.5 ppm.

2.2.3. Conversion of compound 4de to compound 3de

Compound **4de** (40 mg, 0.093 mmol) was refluxed in 5 ml of EtOH in the presence of 2 drops of concentrated H_2SO_4. Reaction was monitored by TLC. After the completion of reaction, solvent was evaporated under reduced pressure, the residue was treated with DCM and water. Organic layer was collected, dried with Na_2SO_4 giving 25 mg of crude oil 2-(3-(4-methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)thiophen-2-yl)-1-methyl-*1H*-imidazole **3de**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (2H, d, J = 8.0 Hz), 7.68 (2H, d, J = 8.0 Hz), 7.50 (1H, s), 7.37 (1H, d, J = 1.2 Hz), 7.17 (2H, d, J = 8.0 Hz), 6.99 (1H, d, J = 1.2 Hz), 6.89 (2H, d, J = 8.0 Hz), 3.83 (3H, s), 3.11 (3H, s) ppm.

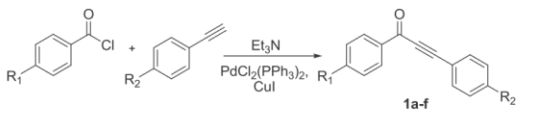
3. Results and discussion

3.1. Synthesis

The diarylalkynones **1a–f** were prepared by Sonogashira coupling reaction of commercially available aroyl chlorides with aryl alkynes [21]. The cross-coupling reaction proceeded in good to high yields with substrates containing both electron-donating and electron withdrawing substituents (Table 1). Next, the construction of thiophene ring *via* Fiesselmann-type reaction [11] between alkynones and easily available heteroarylmethanethiols was attempted.

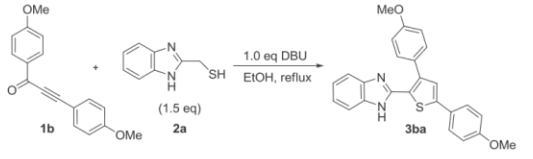
First, we performed a short screening of solvents and bases for the Fiesselmann cyclization. Although DBU is routinely used as a base in the cyclization, in our hands the reaction between alkynone **1b** and thiol **2a** in refluxing ethanol in the presence of 1 equiv. of DBU gave only 19% of the desired thiophene **3ba** (Table 2, entry 1). The yield of **3ba** was increased up to 37% and 51% when excess of thiol **2a** (3 and 6

Table 1
The synthesis of alkynones **1.**



Entry	R_1	R_2	Product (yield, %)
1	H	H	**1a** (98)
2	OMe	OMe	**1b** (78)
3	CF_3	OMe	**1c** (80)
4	OMe	CF_3	**1d** (62)
5	CF_3	CF_3	**1e** (60)
6	OC_5H_{11}	OC_5H_{11}	**1f** (71)

Table 2
Optimization of the Fiesselmann reaction conditions.



#	Deviation from initial conditions	Yield, %
1	None[a]	19
2	3 eq of **2a**	37
3	6 eq of **2a**	51
4	THF instead of EtOH	63
5	DMF instead of EtOH	54
6	NaOH instead of DBU	92

[a] Initial reaction conditions: 1.0 equiv. DBU, 1.0 equiv. **1b**, 1.5 equiv. **2a**, EtOH, reflux.

equiv, respectively) was used (Table 2, entries 2–3). However the isolation and purification of the product became challenging. Change of the solvent to THF or DMF did not improve the conversion (Table 2, entries 4–5). After extensive screening of various bases and solvents we were pleased to find that the yield of thiophene **3ba** can be increased to 92% by the use of sodium or potassium hydroxide in ethanol (Table 2, entry 6).

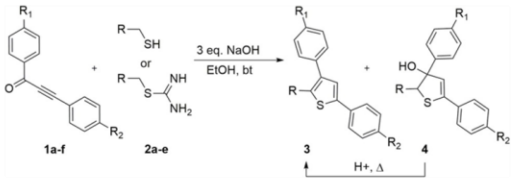
With optimized reaction conditions in hand, we elaborated on the scope of alkynones and thiols (Table 3, entries 1–9). Yields of thiophenes **3** depended on the electronic nature of both alkynones and thiols. The highest yield (92%) was observed for the most electron rich methoxy-substituted alkynone **1b** (Table 3, entry 2). In contrast, the lowest yields (42–44%) were observed for the electron deficient alkynones **1c,e** bearing trifluoromethyl substituents (Table 3, entries 3, 5). Similar relationship between electronic effects and yields of thiophenes was observed for thiols, with the more electron deficient thiol **2b** providing lower yields than **2a** (Table 3, entries 1–2 *vs* entries 7–8).

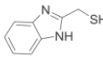
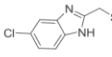
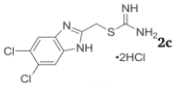
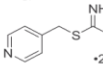
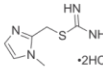
In the meantime, the use of thiols in the Fiesselmann thiophene synthesis is compromised by their inherent toxicity and propensity to oxidize to disulfide side-products that decreases yields of the desired thiophenes and complicates their purification. We were pleased to find that the more stable, easy-to-handle and readily available (see Experimental Section 2.2.1) carbamimidothioates **2c-e** can be used as an alternative to thiols in the Fiesselmann-type cyclization (Table 3, entries 10–19) affording the desired thiophenes in low to high yields. Interestingly, the reactions between alkynones **1c,e** and thiol **2a** (Table 3, entries 3 and 5) furnished intermediates **4ca** and **4ea** as major products. In addition, the methylimidazole (**2e**) ring–bearing starting material exclusively provided dihydrothiophen-3-ols **4ce–ee** instead of the desired thiophenes **3ce–ee** even after prolonged heating (Table 3, entries 20–22). Gratifyingly, all of the intermediates **4** can be dehydrated into the corresponding thiophenes **3** by the heating of acidified solutions (see example in Experimental Section 2.2.3). Slow dehydration process was also observed in DMSO solution after several weeks.

3.2. Photophysical properties

Photophysical properties of thiophenes **3** (Table 4) were studied in MeCN solution at *ca.* 10^{-6} M concentration. UV/Vis Absorption and emission spectra were measured under ambient atmosphere and at room temperature (for attenuation coefficients see SI page SI56). PLQY were measured using an integrating sphere. To evaluate the electronic effects on the emission in both solution and solid state, thiophene **3aa** (Table 4, entry 1) was chosen as a benchmark compound. The presence of EDG in both positions 3 and 5 resulted in a decrease in the solution

Table 3
The Fiesselmann type reaction between alkynones **1** and thiols or thioates **2**.



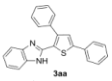
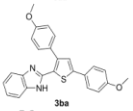
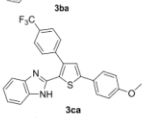
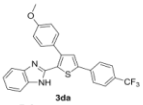
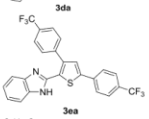
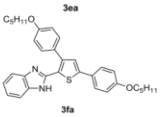
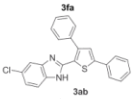
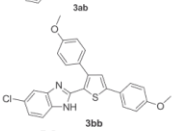
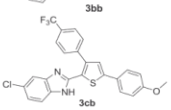
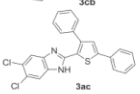
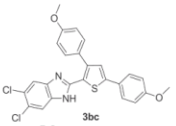
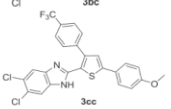
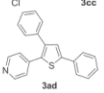
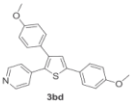
Entry	Starting material	RCH_2SX	Product (Yield, %)
1	**1a** ($R_1 = R_2 = H$)	 **2a**	**3aa** (62)
2	**1b** ($R_1 = R_2 = OCH_3$)		**3ba** (92)
3	**1c** ($R_1 = CF_3$, $R_2 = -OCH_3$)		**3ca** (42), **4ca** (10)
4	**1d** ($R_1 = OCH_3$, $R_2 = CF_3$)		**3da** (64)
5	**1e** ($R_1 = R_2 = CF_3$)		**3ea** (44), **4ea** (50)
6	**1f** ($R_1 = R_2 = OC_5H_{11}$)		**3fa** (72)
7	**1a**	 **2b**	**3 ab** (55)
8	**1b**		**3bb** (58)
9	**1c**		**3 cb** (64)
10	**1a**	 **2c** •2HCl	**3ac** (60)
11	**1b**		**3bc** (74)
12	**1c**		**3cc** (62)
13	**1a**	 **2d** •2HCl	**3ad** (67)
14	**1b**		**3bd** (89)
15	**1c**		**3cd** (51)
16	**1d**		**3dd** (67)
17	**1e**		**3ed** (50)
18	**1a**	 **2e** •2HCl	**3ae** (13), **4ae** (17)[a]
19	**1b**		**3be** (30)
20	**1c**		**4ce** (38)
21	**1d**		**4de** (44)
22	**1e**		**4ee** (41)

[a] Inseparable mixture, yields calculated *via* ^{1}H NMR integration.

PLQY, but a substantial increase in the solid state PLQY (Table 4, entry 2). However, the introduction of EWG in the position 3 and EDG in the position 5 resulted in a considerable increase of PLQY in the solution (Table 4, entry 3) and in the solid state PLQY. Mutual exchange of the EWG and EDG substituents resulted in a decrease in both the solution and the solid state PLQY (Table 4, entry 4). If both aryl moieties in positions 3 and 5 possess EWGs substituents, the solution PLQY is increased, but the solid state PLQY is lowered (Table 4, entry 5). Introduction of OC_5H_{11} groups in the positions 3 and 5 of aryl moieties (Table 4, entry 6) gave similar results as compared to the unsubstituted Ph groups. Thus, we can conclude that the introduction of EWG-substituted arenes in position 3 and EDG-substituted aromatic moieties in position 5 of the thiophene ring results in higher PLQY in thiophenes **3**.

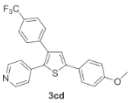
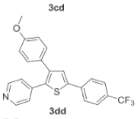
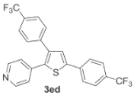
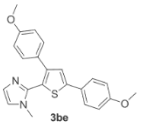
Next, the electronic properties of the benzimidazole core were altered by introducing chloro substituents (Table 4, entries 7–12). The PLQY increased when relatively electron deficient chloro-benzimidazoles **3 ab–cb** and **3ac–cc** were present in the molecule. The highest PLQY in solution (82.6%) and solid state (30.9%) was observed for **3 cc** with the most electron deficient benzimidazole core in a series. We also wanted to see whether the attachment of heterocycles other than benzimidazole to the position 2 of thiophene would affect the PLQY. Thus, the pyridine and *N*-methylimidazole was introduced in the position 2 (Table 4, entries 13–18). A sharp decrease of PLQY was observed for luminophores bearing pyridine and *N*-methylimidazole substituent, highlighting the importance of the benzimidazole subunit. However, **3cd** (Table 4, entry 15) still possessed relatively high (33.9%) PLQY in solution, possibly owing to the proper choice of EWG in the position 3

Table 4
Photophysical properties of thiophenes **3**.

Entry	Compound	λ max (abs), nm[a]	λ max (em), nm[b]	Stokes shifts (nm)	QY, % (solution)	QY, % (solid)
1	 **3aa**	237, 266, **347**	433 sn; 456 sd	86	38.9	8.5
2	 **3ba**	235, 278, **356**	445 sn; 467 sd	89	28.0	17.0
3	 **3ca**	234, 274, **358**	454 sn; 459 sd	96	77.5	22.0
4	 **3da**	238, 280, **354**	444 sn; 457 sd	90	28.6	4.5
5	 **3ea**	238, 272, **352**	442 sn; 512 sd	90	53.5	2.1
6	 **3fa**	234, 280, **356**	441 sn; 464 sd	85	33.8	1.8
7	 **3ab**	235, 266, **350**	435 sn; 459 sd	85	45.0	17.5
8	 **3bb**	234, 280, **360**	445 sn; 463 sd	85	42.5	11.6
9	 **3cb**	235, 274, **360**	460sn; 467 sd	100	77.4	30.6
10	 **3ac**	232, 268, **355**	434 sn; 475 sd	79	63.1	52.2
11	 **3bc**	234, 280, **368**	467 sn; 465 sd	99	34.6	15.1
12	 **3cc**	236, 275, **365**	462sn; 478 sd	97	82.6	30.9
13	 **3ad**	265, **329**	416 sn; 414 sd	87	2.1	2.0
14	 **3bd**	252, 280, **340**	440 sn; 538 sd	100	4.0	0.9

(*continued on next page*)

Table 4 (*continued*)

Entry	Compound	λ max (abs), nm[a]	λ max (em), nm[b]	Stokes shifts (nm)	QY, % (solution)	QY, % (solid)
15	 3cd	236, 270, **340**	460 sn; 550 sd	120	33.9	11.9
16	 3dd	242, 284, **332**	436 sn; 436, 525 sd	104	1.9	8.4
17	 3ed	240, 268, **326**	406 sn; 446 sd	80	2.0	6.1
18	 3be	236, 272, **318**	420	102	1.4	NA

[a] Absorption bands in bold correspond to the excitation wavelength.
[b] Emission spectra written in solution, otherwise indicated as Sn-in solution or Sd-in solid state.

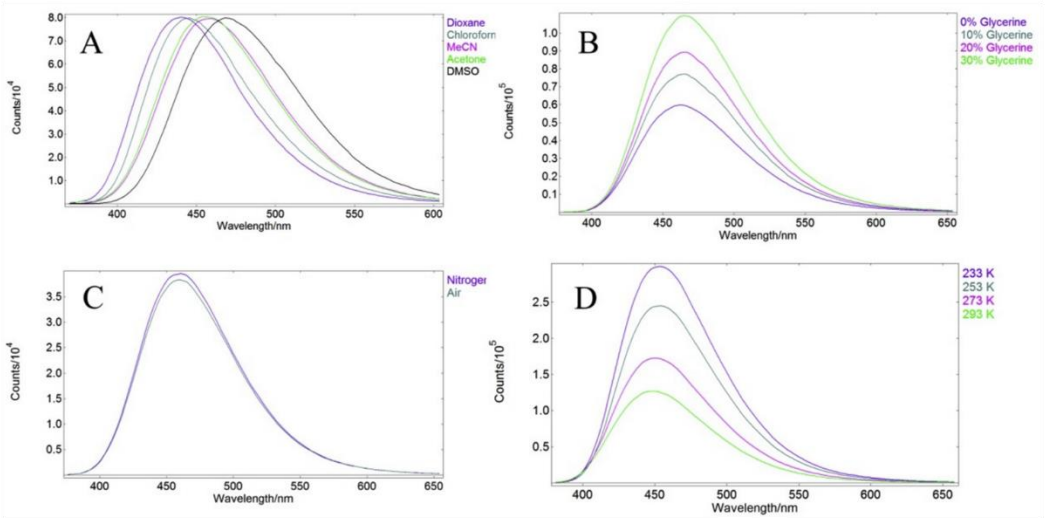


Fig. 2. Solvatochromism (A), viscosity (B), oxygen quenching (C) and variable temperature experiments (D) for **3cd**.

and EDG in the position 5 of the thiophene core. Additionally, aggregation induced emission enhancement (AIEE) was also observed for **3dd** and **3ed**.

The benzimidazole ring-containing compounds showed three characteristic absorption bands at 232–238 (band 1); 266–280 (band 2) and 347–368 (band 3) nm respectively (Table 4, entries 1–12). However, only one broad emission band with maxima at 433–467 nm was observed in MeCN solutions for these compounds. The presence of electron-donating substituent in the 5-aryl ring resulted in bathochromic shift of absorption bands 2 and 3 as well as of the emission peak maxima. This becomes clear by comparing **3ac** (Table 4, entry 10) and **3bc** (Table 4, entry 11), where introduction of electron-donating substituents results in the shift of absorption band 2 from 268 to 280 nm, and the shift of absorption band 3 from 355 to 368 nm. In addition, emission maxima were also shifted from 434 to 467 nm, when going from **3ac** to **3bc**. Similar bathochromic shifts were observed for 2-pyridinyl thiophenes bearing electron-rich 4-methoxyphenyl substituent in various positions of the thiophene subunit (Table 4, entries 14–16). Stokes shifts for all materials were in the range of 79–120 nm (see Table 4).

All thiophenes in MeCN solution feature broad emission peaks without any distinctive bands (Table 4). The broad nature of emission peaks is indicative of twisted intramolecular charge transfer (TICT) phenomenon [24]. To verify whether TICT is responsible for the observed emission, a solvatochromism study was conducted because sensitivity of TICT towards solvent effects is well-known [24,25]. Thiophene **3cd** was used in the solvatochromism study due to higher solubility and relatively high intensity of the emission (33.9% PLQY,

entry 15, Table 4). The emission maxima for **3cd** featured a shift from 440 nm in dioxane to 468 nm in DMSO (Fig. 2A), thus providing an evidence for the TICT. TICT states are also highly susceptible to viscosity of a solvent: enhanced emission is generally observed in solvents with higher viscosity [26]. Accordingly, the emission intensity of **3cd** was measured in various EtOH/glycerine mixtures (Fig. 2B). The observed correlation between the emission intensity and the viscosity of the solvent provided further support of TICT.

To verify the presence of triplet states in thiophene luminophores the intensity of **3cd** was measured in aerated and nitrogen-purged solutions. The observed similar emission intensity in both solutions (Fig. 2C) indicated that the triplet states, which would be quenched by oxygen, do not participate in the emission [27]. Furthermore, the emission intensity of **3cd** increased when temperature was lowered from 293 to 233 K (Fig. 2D). Both experiments provide evidence that singlet states are responsible for the emission and that these materials do not possess thermally activated delayed fluorescence character [28].

4. Conclusions

In summary, we have demonstrated that odorless, stable, easy-to-handle and readily available *S*-alkyl thioureas can be used as sulphur-containing building blocks for the assembly of 2,3,5-trisubstituted thiophene luminophores *via* the Fiesselmann type reaction. We have shown that the introduction of electron deficient arenes in position 3 and electron rich arenes in position 5 of the thiophene core not only results in enhancement of PLQYs to 83% for benzimidazole-containing luminophores, but also enhances PLQY of the less emissive, pyridine-containing thiophenes by more than an order of magnitude. Viscosity, solvatochromism and oxygen quenching experiments provided evidence that the observed emission of thiophenes **3** originates from TICT and singlet emissive states. Finally, we believe that the established correlation between the electronic properties of substituents and efficiency of luminescence will facilitate wider application of monomeric thiophenes in the design of luminophores.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dyepig.2019.107646.

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