VILNIUS UNIVERSITY

Rita Bukšnaitienė

STUDY ON CYCLIZATION REACTIONS OF HETEROCYCLIC COMPOUNDS BEARING ETHYNYL AND FORMYL GROUPS IN CLOSE PROXIMITY TO EACH OTHER

Summary of Doctoral Dissertation
Physical Sciences, Chemistry (03P)

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Scientific Supervisor:

dr. Inga Čikotienė (Vilnius University, Physical Sciences, Chemistry – 03P)

The dissertation defense session is to be held at the Scientific board (Chemistry Branch):

Chairman:

Prof. habil. dr. Eugenijus Butkus (Vilnius University, Physical sciences, chemistry – 03P)

Members:

Prof. dr. Vytautas Getautis (Kaunas University of Technology, Physical sciences, chemistry – 03P)

Prof. habil. dr. Albertas Malinauskas (Center for Physical Sciences and Technology, Institute of Chemistry, Physical sciences, chemistry – 03P)

Prof. habil. dr. Vytautas Mickevičius (Kaunas University of Technology, Physical sciences, chemistry – 03P)

Doc. dr. Albinas Žilinskas (Vilnius University, Physical sciences, chemistry – 03P)

Official opponents:

Prof. dr. Vytas Martynaitis (Kaunas University of Technology, Physical sciences, chemistry – 03P)

Prof. habil. dr. Povilas Vainilavičius (Vilnius University, Physical sciences, chemistry – 03P)

The official discussion will be held on 1 p.m. November 16, 2012 at the meeting of the Scientific board at the Inorganic chemistry lecture hall of the Faculty of Chemistry of Vilnius University.

Address: Naugarduko 24, LT – 03225, Vilnius, Lithuania

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The dissertation is available at the Libraries of Vilnius University and Center for Physical Sciences and Technology, Institute of Chemistry.

VILNIAUS UNIVERSITETAS

Rita Bukšnaitienė

HETEROCIKLINIŲ JUNGINIŲ, GRETIMOSE PADĖTYSE TURINČIŲ ETINIL– IR FORMILFRAGMENTUS, CIKLIZACIJOS REAKCIJŲ TYRIMAS

Daktaro disertacija

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dr. Inga Čikotienė (Vilniaus universitetas, fiziniai mokslai, chemija – 03P)

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Pirmininkas:

Prof. habil. dr. Eugenijus Butkus (Vilniaus universitetas, fiziniai mokslai, chemija – 03P)

Nariai:

Prof. dr. Vytautas Getautis (Kauno technologijos universitetas, fiziniai mokslai, chemija – 03P)

Prof. habil. dr. Albertas Malinauskas (Fizinių ir technologijos mokslų centras, Chemijos institutas, fiziniai mokslai, chemija – 03P)

Prof. habil. dr. Vytautas Mickevičius (Kauno technologijos universitetas, fiziniai mokslai, chemija – 03P)

Doc. dr. Albinas Žilinskas (Vilniaus universitetas, fiziniai mokslai, chemija – 03P)

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Disertacija bus ginama viešame chemijos mokslo krypties tarybos posėdyje 2012 m. lapkričio mėn. 16 d. 13 val. Vilniaus Universiteto Chemijos fakulteto Neorganinės chemijos auditorijoje.

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1. Introduction

Functionally substituted alkynes are versatile building blocks in organic synthesis for the preparation of various carbo– and heterocyclic compounds. A literature survey revealed that cyclization *o*–alkynylbenzencarbaldehydes could undergo transition metal–catalyzed or electrophile–induced formation of a wide variety of heterocycles. However in the scientific literature there were not a lot of papers describing intramolecular cyclizations of heterocyclic substrates bearing an alkynyl moiety and a carbonyl group in close proximity to each other. Recently our group has showed that some alkynylazines bearing formyl, imino or nitro functional groups can undergo various cycloizomerization reactions or cyclization reactions with various nucleophiles (amines, alcohols, thioles and *C*–pronucleophiles). In the most cases these reactions underwent smoothly without transition metal catalysts or electrophilic initiators, and it can be explained by electron – withdrawing properties of azine rings. Moreover in some cases we observed a number of novel mechanistically interesting and synthetically useful reactions of alkynylazines. And finally, a lot of products were found to be promising pharmacophores exhibiting notable antitumor activity in several cell lines.

So, encouraged by our previous and literature results, we decided to perform a more detailed and extensive study on the intramolecular and multicomponent cyclization reactions of heterocyclic compounds bearing a triple bond and formyl group in close proximity to each other.

The main aims of present investigation were to investigate cyclization reactions of electron–deficient 6–alkynylpyrimidine–5–carbaldehydes and 2–alkynylquinoline–3–carbaldehydes, and electron–rich 2–alkynylindole–3–carbaldehydes and 2–alkynylthiophene–3–carbaldehydes with *N*–, *S*–. *O*–, *C*– and *P*–nucleophiles. Plausible mechanistic pathways of these transformations were also discussed.

The main results obtained in this work are as follows:

It was found, that 6–arylethynylpyrimidine–5–carbaldehydes under the treatment with *tert*–butylamine underwent thermal or microwave–induced cyclization reaction to form pyrido[4,3–*d*]pyrimidines.

A novel and fast synthetic method for preparation of 2,3–disubstituted 1,2–dihydro–1–(trichloromethyl/tribromomethyl)benzo[*b*][1,6]naphthyridines by means of a three–component reaction between 2–alkynylquinoline–3–carbaldehydes, primary amines and chloroform or bromoform was developed. Moreover 2–alkynylquinoline–3–carbaldehydes reacted with dimethylphosphite and aromatic amines in the presence of copper (I) iodide and dimethyl 2,3–disubstituted 1,2–dihydrobenzo[*b*][1,6]naphthyridin–1–ylphosphonates formed.

It was showed, that methyl mercaptoacetate was able to trigger a novel benzannulation reaction of the starting materials. The reaction did not require metal–catalysts and moreover – it is really unique method of the synthesis of benzoannelated

heterocycles, since the key step is formation of benzene ring instead of usual heterocyclic ring formation.

Novel, concise and regioselective synthetic methods of 5,7–dihydrofuro[3,4–*d*]pyrimidine, 5*H*–pyrano[4,3–*d*]pyrimidine, 1,3–dihydrofuro[3,4–*b*]quinolines and 1*H*–pyrano[4,3–*b*]quinolines frameworks *via* regioselective acetalisation/cyclization reactions of 2,4–disubstituted 6–phenylethynylpyrimidine–5–carbaldehydes and 2–alkynylquinoline–3–carbaldehydes were developed. Silver nitrate or silver trifluoroacetate were found to be the most effective catalysts for the cyclization processes and it was shown that regioselectivity can be controlled by using base, various types of catalysts and heating method.

A relatively short and efficient synthesis of 2–(2–oxoethyl)–1*H*–indole–3–carbaldehydes *via* tandem 6–*endo*–dig cyclization process followed by smooth hydrolysis from 2–alkynylindole–3–carbaldehydes was developed.

It was found that 2–alkynylquinoline–3–carbaldehydes react with dimethylphosphite in basic medium to produce classical products of the Pudovik reaction. The latter compounds underwent subsequent phosphonate – phosphate rearrangement in basic media. On the other hand when the triple bond of the starting materials is more activated by electron–withdrawing heterocycles (in the case of 2–(pyridin–2–ylethynyl)quinoline–3–carbaldehyde and 2,4–disubstituted 6–arylethynylpyrimidine–5–carbaldehydes), a smooth and regioselective tandem 5–*exo*–dig cyclization reactions become possible.

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2. Results and Discussion

2.1 Synthesis of starting compounds

For the synthesis of starting compounds, bearing a formyl group and ethynyl moiety in close proximity to each other, we utilized a classical well known palladium – catalyzed Sonogashira coupling between halogen derivatives and terminal acetylenes. 4–Substituted 6–chloro–2–methylthiopyrimidine–5–carbaldehydes **1a–t** reacted with 1–arylacetylenes to give the corresponding 4–substituted 6–arylethynyl–2–methylthiopyrimidine–5–carbaldehydes **2a–t.** The reactions were carried out in dimethylformamide and triethylamine mixture under argon atmosphere in the presence of catalytic amount of $PdCl_2(PPh_3)_2$ and CuI. It should be noted, that reaction of 4–substituted 6–chloro–2–methylthiopyrimidine–5–carbaldehydes **1a–t** with alkynylacetylenes were complicated in most cases, the formation of several side products was observed.

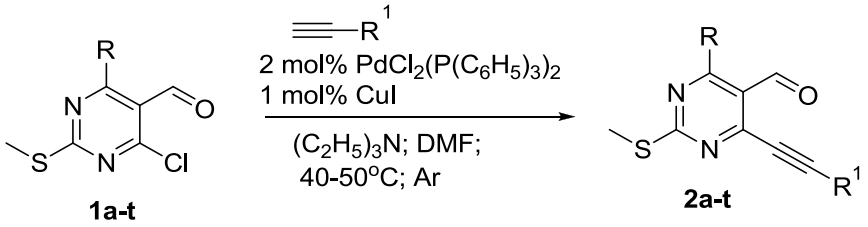


Table 1. Data of the synthesis of 4–substituted 6–arylethynyl–2–methylthiopyrimidine–5–carbaldehydes **2a–t.**

Starting compound	R	R^1	Product	Yield, %
1a	NH_2	C_6H_5	**2a**	42
1b	NH_2	$4–C_2H_5C_6H_4$	**2b**	45
1c	$NHCH_3$	C_6H_5	**2c**	85
1d	$N(CH_3)_2$	C_6H_5	**2d**	86
1e	$N(C_2H_5)_2$	C_6H_5	**2e**	62
1f	$N(C_2H_5)_2$	$4–CH_3C_6H_4$	**2f**	65
1g	$N(C_2H_5)_2$	$4–C_2H_5C_6H_4$	**2g**	70
1h	$N(CH_2)_4O$	C_6H_5	**2h**	80
1i	$N(CH_2)_4O$	$4–C_2H_5C_6H_4$	**2i**	88
1j	NHC_6H_5	C_6H_5	**2j**	75
1k	$3–CF_3C_6H_4NH$	C_6H_5	**2k**	85
1l	$3–BrC_6H_4NH$	C_6H_5	**2l**	89
1m	$4–CH_3OC_6H_4NH$	C_6H_5	**2m**	69
1n	$4–C_2H_5OC_6H_4NH$	C_6H_5	**2n**	69
1o	$3–CF_3C_6H_4NH$	*n*–Bu	**2o**	85
1p	$3–BrC_6H_4NH$	*n*–Bu	**2p**	87
1r	NHC_6H_5	*n*–Bu	**2r**	55
1s	$3–CF_3C_6H_4NH$	$Si(CH_3)_3$	**2s**	88
1t	$3–BrC_6H_4NH$	$Si(CH_3)_3$	**2t**	88

Analogously, 2–chloro–3–quinolinecarbaldehyde **3** reacted with terminal acetylenes in tetrahydrofurane to give the corresponding 2–alkynylquinoline–3–cabaldehydes **4a–g.**

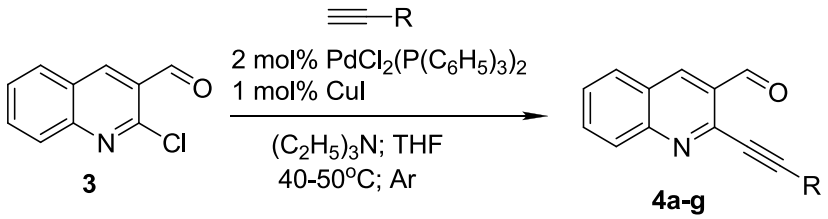


Table 2. Data of the synthesis of 2–alkynylquinoline–3–carbaldehydes **4a–g**.

Product	R	Yield, %
4a	C_6H_5	85
4b	2–pyridyl	46
4c	$CH(CH_2)_2$	82
4d	*n*–C_4H_9	85
4e	$C(CH_3)_3$	99
4f	$Si(CH_3)_3$	80
4g	CH_2OCOCH_3	50

For the synthesis of 2–alkynylindol–3–carbaldehydes **6a–h** we utilized the similar method. However the double amount of catalysts (4 mol% $PdCl_2((C_6H_5)_3)_2$ and 2 mol% CuI) gave better conversions of the starting material.

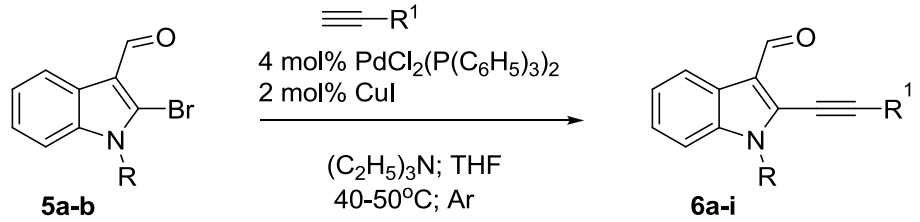


Table 3. Data of the synthesis of 2–alkynylindol–3–carbaldehydes **6a–h.**

Starting compound	R	R^1	Product	Yield, %
5a	H	C_6H_5	**6a**	60
5a	H	4–$CH_3C_6H_4$	**6b**	55
5a	H	4–$C_2H_5C_6H_4$	**6c**	59
5a	H	2–pyridyl	**6d**	79
5a	H	*n*–C_4H_9	**6e**	72
5a	H	$Si(CH_3)_3$	**6f**	66
5b	$CH_2C_6H_5$	2–pyridyl	**6g**	100
5b	$CH_2C_6H_5$	$CH(CH_2)_2$	**6h**	89
5b	$CH_2C_6H_5$	$C(CH_3)_3$	**6i**	100

Analogously, 2–alkynylthiophene–3–carbaldehydes **8a–e** were synthesized *via* the same reaction conditions.

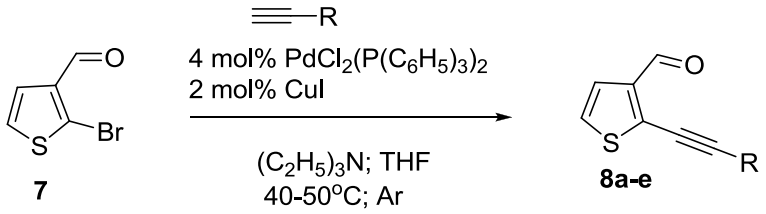
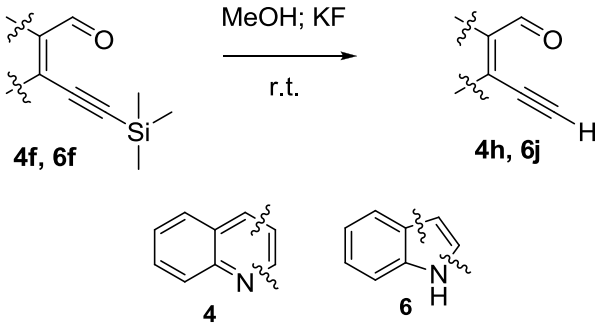


Table 4. Data of the synthesis of 2–alkynylthiophene–3–carbaldehydes **8a–e.**

Product	R	Yield, %
8a	C_6H_5	63
8b	4–$CH_3C_6H_4$	63
8c	4–$C_2H_5C_6H_4$	70
8d	*n*–C_4H_9	82
8e	$Si(CH_3)_3$	78

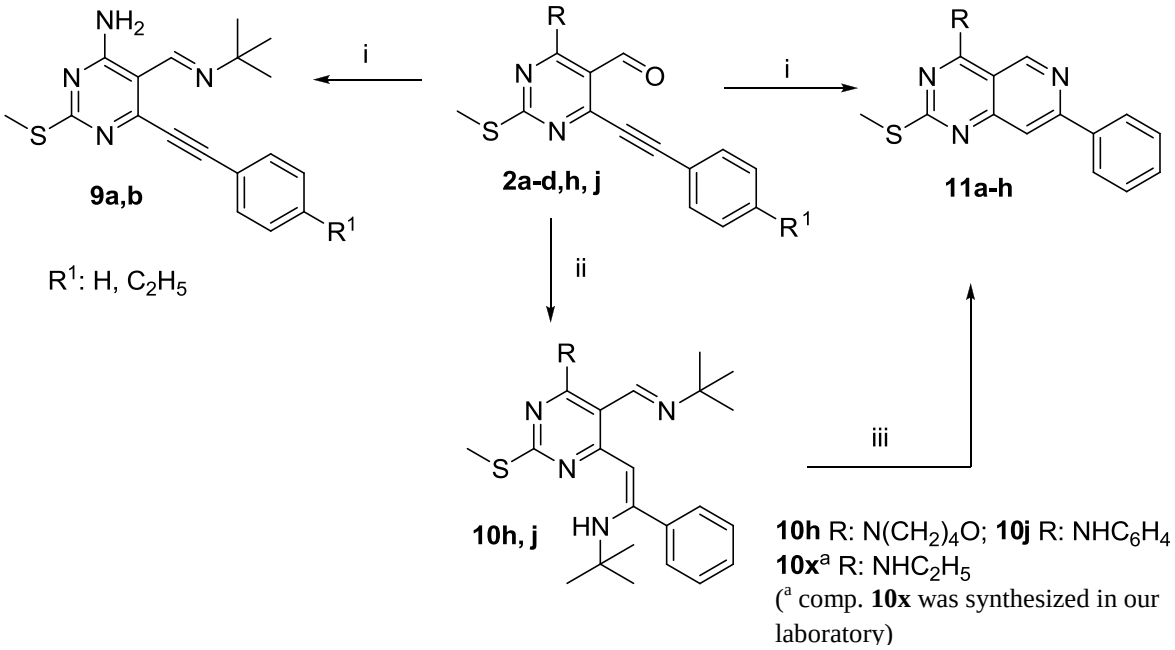
Terminal alkynes **4h** and **6j** were synthesized from compounds **4f** and **6f**. Compounds **4f** and **6f** were dissolved in methanol and treated with potassium fluoride dihydrate (3 equivalents) at room temperature. Compounds **4h** and **6j** were synthesized in 64% and 88% yields respectively.



2.2 Synthesis of pyrido[4,3–d]pyrimidines

In our research, which was aimed at the use of 6–arylethynylpyrimidines for the synthesis of fused pyrimidine derivatives, we have applied Larock's method for the synthesis of the pyrido[4,3–*d*]pyrimidine heterosystem by the intramolecular cyclization of 6–arylethynylpyrimidin–5–carbaldehydes **2a–d,h,j**. Compounds **2a,b** bearing primary amino group in position 4 of the pyrimidine ring, treated with *tert*–butylamine in sealed tube at 110–120 ^{o}C temperature, gave the corresponding 4–amino–6–arylethynyl–5–*N*–*tert*–butyliminomethyl–2–methylthiopyrimidines **9a,b**. However, surprisingly during performing a classical synthesis of *tert*–butylimines from some other 2,4–disubstituted 6–arylethynylpyrimidine–5–carbaldehydes (compounds **2c,d,h**, *tert*–butylamine, sealed tube, 110–120 °C) unexpected thermal catalyst–free formation of the 4–substituted 2–methylthio–7–phenylpyrido[4,3–*d*]pyrimidines **11c–e** took place. These results prompted us to investigate the thermal cyclization of the 6–arylethynylpyrimidine–5–carbaldehydes with *tert*–butylamine.

We assumed that thermal cyclization of the title compounds underwent *via* intermediate *tert*–butylimines as it was proposed in one literature source dealed with synthesis of γ–carbolines. However, when the reactions of compounds 4–substituted 6–arylethynyl–2–methylthiopyrimidine–5–carbaldehydes **2h,j** with *tert*–butylamine were carried out in sealed tubes at lower 80 – 90 °C temperature, we found that not only reaction of *tert*–butylamine with carbonyl group, but also 1,2–addition of second molecule of *tert*–butylamine to C≡C bond took place, so yellow colored products **10h,j** were produced**.**

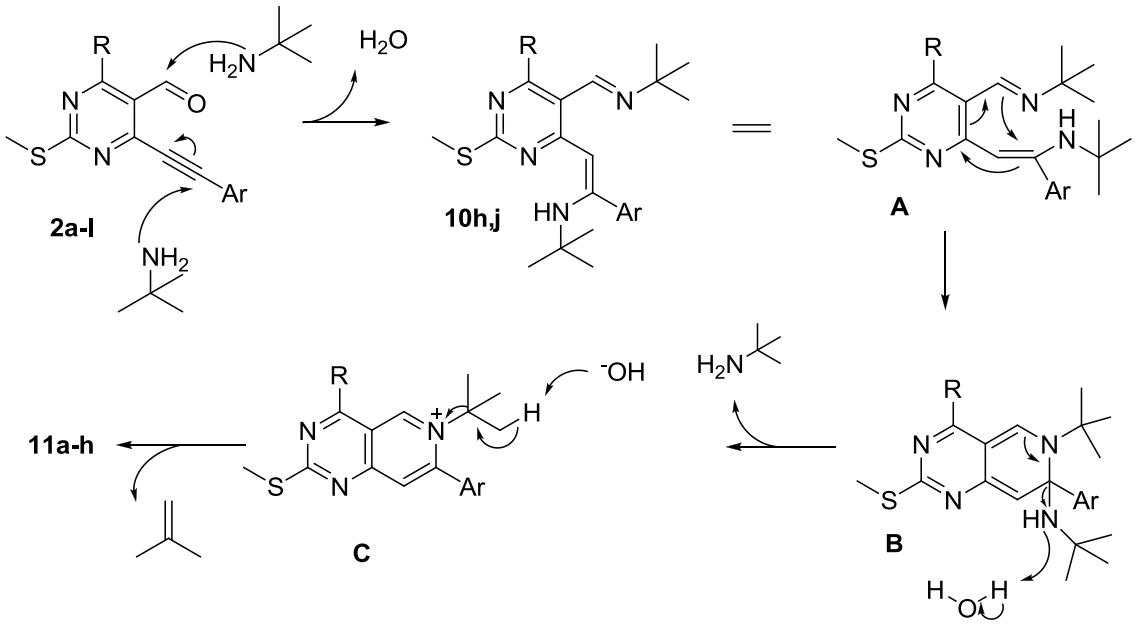


Scheme. *Reagents and conditions*: i) *t*–$BuNH_2$, sealed tube, 110–120 °C, 24 h; ii) *t*–$BuNH_2$, sealed tube, 80–90 °C, 20 h; iii) solvent (DMF), 120 °C.

Neither ^{13}C NMR nor IR spectra of **10h,j** showed the presence of C≡C or C=O groups in the molecules. In the ^{1}H NMR spectra two singlets at 1.19–1.21 and 1.22–1.30 ppm of *tert*–butylamine groups, and singlets at 5.21–6.17 ppm (CH) and 8.15–8.67 ppm (CH=N) were observed. These data indicated that addition reaction of amines to the triple bond took place. As it has been found earlier in our group, C≡C bond of some 6–arylethynylpyrimidines is electron–deficient due to activating effect of the pyrimidine ring, therefore is easily attacked by various nucleophiles in regio– and stereoselective manner. After the comparison with the ^{1}H NMR and ^{13}C NMR data of obtained compounds with our previous results, we supposed that addition reactions of *tert*–butylamine to C≡C bond of the starting compounds led to formation of *anti*–addition product or *Z*–isomer, stabilized by possible intramolecular *H*–bonding.

To our pleasant surprise, compound **10h** heated with *tert*–butylamine in sealed tube at higher (110–120 °C) temperature after 10 hours converted to the corresponding 2–methylthio–4–morpholino–7–phenylpyrido[4,3–*d*]pyrimidine **11e** in good yield. On the other hand, cyclization of compound **10h** to pyrido[4,3–*d*]pyrimidine

11e underwent smoothly in hot (110 °C) dimethylformamide. It is noteworthy that heating of the imines **9a** and **9b** in hot dimethylformamide did not lead to the formation of cyclization products. Cyclization was successful only in the presence of an equivalent of *tert*–butylamine in DMF. From these results it seems that the thermal cyclization of 4–substituted 6–arylethynyl–2–methylthiopyrimidine–5–carbaldehydes with *tert*–butylamine could proceed via *N*–(*tert*–butyl)–*N*–{4–[(*Z*)–2–aryl–2–(*tert*–butylamino)vinyl]pyrimidin–5–yl}methyleneamines **10**. The possible reaction mechanism is presented in Scheme below.



Scheme. Possible mechanism of the thermal cyclization of 4–substituted 6–arylethynyl–2–methylthiopyrimidine–5–carbaldehydes with *tert*–butylamine.

We assumed, that intermediate adducts **10** underwent electrocyclic reaction to form six membered ring **B**. The aromatization of cyclic adduct, lead to elimination of *tert*–butylamine and 2–methylpropene molecules.

Thus, according to the present methodology, we have prepared various 4–substituted 7–aryl–2–methylthiopyrido[4,3–*d*]pyrimidines **11a–e**. The results are summarized in Table 5. On the other hand, heating of the corresponding 4–anilino–6–phenylethynyl–2–methylthiopyrimidine–5–carbaldehyde **2j** with an excess of *tert*–butylamine in sealed tubes at 120–130 ^{o}C did not lead to the formation of 4–anilino–7–phenyl–2–methylthiopyrido[4,3–*d*]pyrimidine, but formation of the intermediate **10j** was observed. To our pleasant surprise, when solutions of compounds **2j–l** and *tert*–butylamine in dimethylformamide were irradiated in a domestic microwave oven, after 10–60 min a high–yielding formation of 4–substituted 7–aryl–2–methylthiopyrido[4,3–*d*]–pyrimidines **11f–h** was observed. Thus, we have optimized an efficient, concise, and high–yielding method of synthesis of 4–substituted 7–aryl–2–methylthiopyrido[4,3–*d*]pyrimidines**11a–h** from 4–substituted 6–arylethynyl–2–methylthiopyridopyrimidines and *tert*–butylamine.

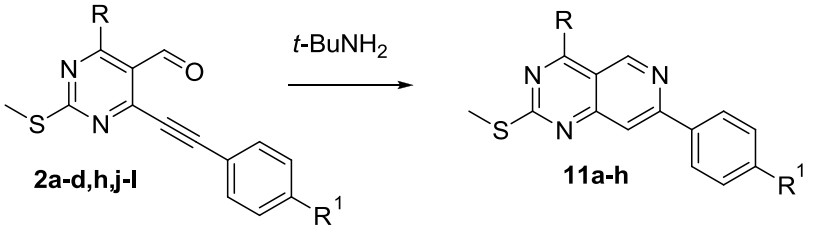


Table 5. Data of the synthesis of 4–substituted 7–aryl–2–methylthiopyrido[4,3–*d*]pyrimidines **11a–h.**

Entry	Starting compound	R	Product	R^1	Method A[a]	Method B[b]
					Yield, %	Yield, %
1	**2a**	NH_2	**11a**	H	25	95
2	**2b**	NH_2	**11b**	C_2H_5	18	90
3	**2c**	$NHCH_3$	**11c**	H	80	91
4	**2d**	$N(CH_3)_2$	**11d**	H	92	100
5	**2h**	$N(CH_2)_4O$	**11e**	H	92	97
6	**2j**	NHC_6H_5	**11f**	H	0[c]	97
7	**2k**	3–$CF_3C_6H_4NH$	**11g**	H	0	80
8	**2l**	3–BrC_6H_4NH	**11h**	H	0	97

[a] Method A: *tert*–butylamine, 120 – 130°C sealed tube 24 – 28 h.
[b] Method B: *tert*–butylamine (10 equiv.), DMF, MW, 600W, 10 – 60 min.
[c] Intermediate compound **10j**.

It is noteworthy that *tert*–butylamine is the only reagent which can be used in this transformation. Other amines such as propylamine, diethylamine, ammonia, and hydrazine did not cause cyclization of the starting compounds to pyrido[4,3–*d*]pyrimidine derivatives. It is noteworthy that the reaction rates depend on the nature of the substituent in position 4 of the pyrimidine ring. Thus, the shortest reaction times were for the bulky 4–*N*,*N*–dialkylamino derivatives, and the longest for the 4–anilino derivatives. We have studied the influence of solvent on cyclization rates of intermediates **10x,h,j**. The results are summarized in Table 6.

Table 6. Rates of the intramolecular cyclizations of *N*–(*tert*–butyl)–*N*–{4–[(*Z*)–2–aryl–2–(*tert*–butylamino)vinyl]pyrimidin–5–yl}methyleneamines **10** under various conditions.

Entry	Imine	*t*–$BuNH_2$, 120°C	DMF, 120°C	2–PrOH, reflux	Xylene, reflux	DMF, MW, 500W
1	**10x**	10h	30min	6h	3h	20min
2	**10h**	3h	10min	3h	1,5h	5min
3	**10j**	n.r.	n.r.	n.r.	n.r.	40min

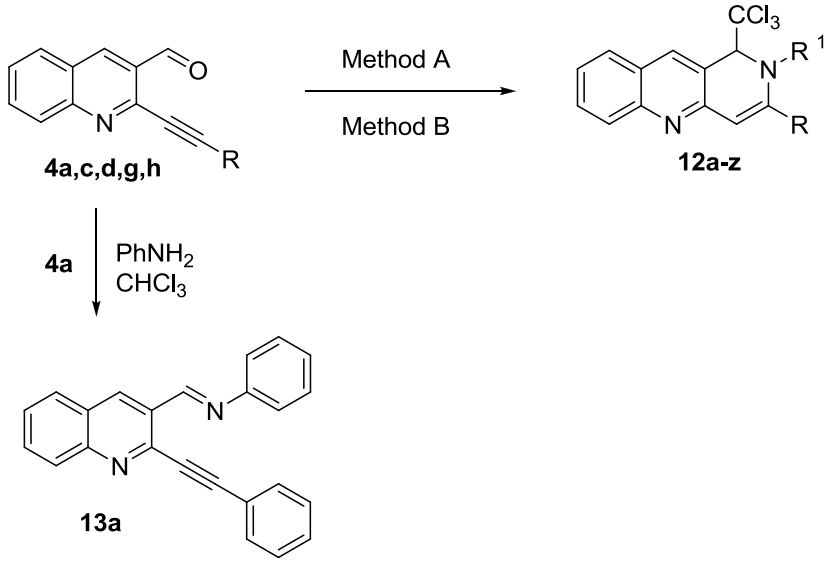
The most suitable solvent for the cyclization of the intermediates **10** under either convectional or microwave–induced heating was dimethylformamide, followed by p–xylene. On the other hand, 2–propanol and *tert*–butylamine seemed to be less effective. It should be noted that the cyclization of the intermediate adduct **10j** bearing an anilino substituent in position 4 of the pyrimidine ring did not undergo cyclization

into 4–anilino–2–methylthio–7–phenylpyrido[4,3–*d*]pyrimidine **11f** under thermal heating conditions. The satisfactory result was obtained only when compound **10j** was dissolved in dimethylformamide and heated using microwave irradiation.

2.3 Synthesis of 1,2–dihydrobenzo[*b*][1,6]naphthyridines *via* three–component reaction

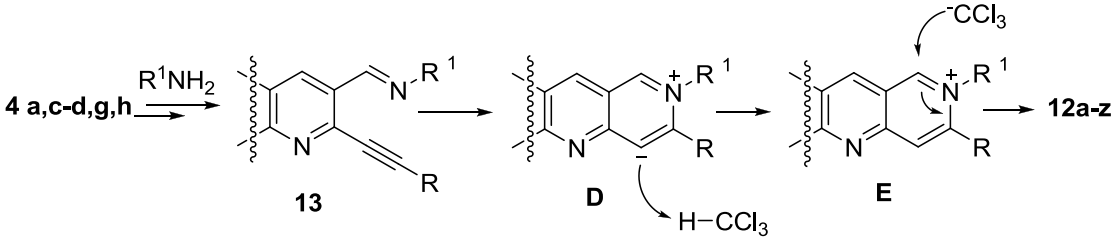
Multicomponent reactions belong to the most efficient methods for preparation of organic compounds, allowing the formation of several bonds and the construction of complex molecular architectures from simple precursors in a single synthetic operation without the need for isolation of intermediates. Continuing our research on the use of ethynylazines in the synthesis of fused nitrogen nucleus–containing heterocycles, we decided to explore the scope of the three–component reactions of 2–alkynylquinoline–3–carbaldehydes, primary amines, and *C*–pronucleophiles and the use of this method for the preparation of 1,2–dihydrobenzo[*b*][1,6]naphthyridines. First, we turned our attention to the multicomponent reaction among the substrates **4a,h**, amines, and chloroform. However, upon the treatment of compounds **4a,h** with amines in chloroform in the presence of 3 Å molecular sieves at room temperature, the conversions of the starting compounds were incomplete and mixtures of various products were formed. Heating under reflux of aldehydes **4a,h** with 1,2 equivalents of the corresponding amine in chloroform and in the presence of the molecular sieves furnished the target compounds **12a–d,t,u**. It should be noted that refluxing took 24 – 48 h, and the conversions of the starting compounds were still incomplete. Moreover, the reaction between **4a** and bulky cyclopentanamine in chloroform was unsuccessful, as no product was observed by thin–layer chromatography (TLC) after 48 h of heating. On the other hand, 2–hexynylquinoline–3–carbaldehyde **4d** was completely inert toward benzylamine and butylamine in refluxing chloroform.

To shorten the long reaction times, microwave–assisted chemistry was used. When the mixtures of the starting compounds **4a,c,d,g,h**, amines, chloroform, and molecular sieves in 1,2–dichloroethane were placed in closed vessels and irradiated in a domestic microwave oven for 5 – 60 min, the target 1–trichloromethyl–1,2–dihydrobenzo[*b*][1,6]naphthyridines **12a–z** formed. The method tolerates well aliphatic amines. In the case of bulky cyclopentanamine, the reaction time is longer and the yields are slightly lower. An attempted reaction of the starting quinoline **4a** with aniline was unsuccessful, and the formation of a stable Schiff base **13a** as a sole reaction product was observed (Scheme below).



Scheme. Method A: R^1NH_2 (1.2 equiv.), 3 Å molecular sieves, $CHCl_3$, reflux. Method B: R^1NH_2 (1.2 equiv.), 3 Å molecular sieves, $CHCl_3$ (3 equiv.) in 1,2–dichloroethane, microwave irradiation, 600 W.

We believe that at the beginning, the formation of imines **13** from the starting substrates and amines takes place. Nucleophilic attack of the imine nitrogen at the triple bond would lead to the formation of zwitterion salt **D.** Abstraction of proton from chloroform and subsequent attack of trichloromethyl anion would produce the final compounds **12a–z** (Scheme below). A similar mechanism was proposed by Asao et al. (2006) for *o*–alkynylbenzenecarbaldehydes.



Scheme. The plausible mechanism of the three–component reaction.

So, according to the optimal reaction conditions 1–trichloromethyl–1,2–dihydrobenzo[*b*][1,6]naphthyridines **12a–z** were synthesized (Table 7).

Table 7. Data of synthesis 2,3–disubstituted–1–trichlormethyl–1,2–dihydrobenzo[*b*][1,6]naphtyridines **12a–z.**

Entry	Starting compound **4**, R	Amine R^1NH_2, R^1	Reaction time	Product	Yield, %	
					Method A[a]	Method B[b]
1	**4a** R = Ph	$PhCH_2$	24 h[A] 12 min[B]	**12a**	48	81
2	**4a**	$PhCH_2CH_2$	24 h[A] 15 min[B]	**12b**	56	84

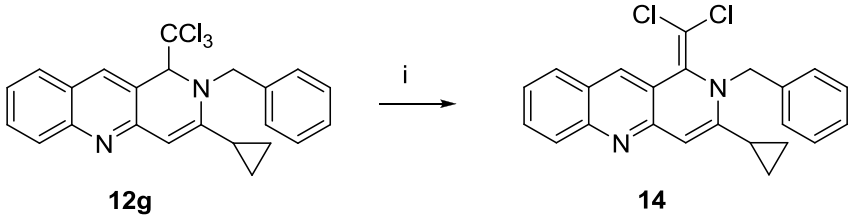
3	**4a**	CH_2=$CHCH_2$	24 h[A] 15 min[B]	**12c**	60	89
4	**4a**	*n*–C_4H_9	48 h[A] 30 min[B]	**12d**	39	70
5	**4a**	$CH(CH_2)_4$	48 h[A] 60 min[B]	**12e**	n.r.	45
6	**4a**	*n*–C_8H_{17}	60 min[B]	**12f**		42
7	**4c** R = $CH(CH_2)_2$	$PhCH_2$	6 min[B]	**12g**		65
8	**4c**	$PhCH_2CH_2$	11 min[B]	**12h**		71
9	**4c**	CH_2=$CHCH_2$	5 min[B]	**12i**		64
10	**4c**	*n*–C_4H_9	8 min[B]	**12y**		57
11	**4c**	$CH(CH_2)_4$	29 min[B]	**12j**		72
12	**4d** R = *n*–C_4H_9	$PhCH_2$	48 h[A] 40 min[B]	**12k**	n.r.	64
13	**4d**	$PhCH_2CH_2$	35 min[B]	**12l**		62
14	**4d**	CH_2=$CHCH_2$	25 min[B]	**12m**		58
15	**4d**	*n*–C_4H_9	48 h[A] 23 min[B]	**12n**	n.r.	48
16	**4d**	$CH(CH_2)_4$	46 min[B]	**12o**		38
17	**4g** R=CH_2OCOCH_3	*n*–C_4H_9	5 min[B]	**12p**		52
18	**4h** R = H	$PhCH_2$	18 min[B]	**12r**		71
19	**4h**	$PhCH_2CH_2$	15 min[B]	**12s**		76
20	**4h**	CH_2=$CHCH_2$	24 h[A] 15 min[B]	**12t**	16	75
21	**4h**	*n*–C_4H_9	48 h[A] 10 min[B]	**12u**	45	85
22	**4h**	$CH(CH_2)_4$	5 min[B]	**12v**		75
23	**4h**	*n*–C_8H_{17}	6 min[B]	**12z**		63
24	**4a** R = Ph	Ph	20 h[A] 10 min[B]	**13a**	98	100

Method A: R^1NH_2 (1.2 equiv.), 3Å molecular sieves, $CHCl_3$, reflux.
Method B: R^1NH_2 (1.2 equiv.), 3Å molecular sieves, $CHCl_3$ (3 equiv.), DCE, MW, 600W.
n.r: no reaction

The examination of the results suggests that there are several factors affecting the successful cyclization. These include steric factors (hindrance or geometrical alignment of substituents on alkynyl and imine moieties), stability of the intermediate products, and reaction conditions. The observed failure of the attempted reaction of aniline can be explained in two ways. First, the imine nitrogen in compound **13a** is relatively non–nucleophilic due to conjugation with the aromatic ring. And secondary, there is a steric hindrance between two planar phenyl rings in compound **13a**, thus the formation of intermediate **D** becomes impossible. Moreover, this reaction is highly regioselective in that only the formation of 6–*endo*–dig cyclization products is observed.

So we decided to investigate chemical properties of compound **12g**. Compound **12g** was refluxed in methanol with iron (III) chloride, potassium *tert*–

butoxide or hydrochloric acid. In all cases after the work–up the starting compound was recovered. When **12g** was refluxed in methanol and water mixture with sodium hydroxide, the elimination reaction took place and 2–benzyl–1–dichloromethylene–3–cyclopropyl–1,2–dihydrobenzo[*b*][1,6]naphthyridine **14** was formed (Scheme).

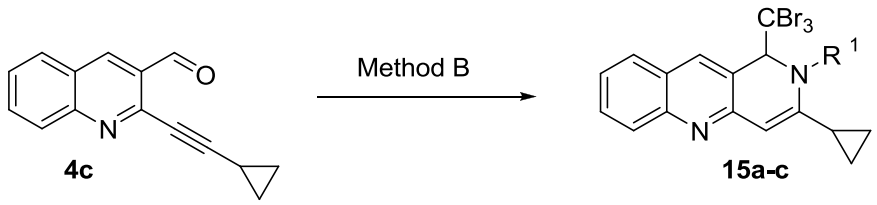


12g **14**

i: CH_3OH/H_2O (4:1), 2% (NaOHaq), 48 h., r. t.

Scheme. Reaction of **12g** with $NaOH_{(aq)}$.

Analogously reactions between 2–cyclopropylethynylquinoline–3–carbaldehide **4c,** amines and bromoform were performed. Compounds **15a–c** were synthesized by the optimal three–component reaction conditions (Table 8).



4c **15a-c**

Table 8 Data of synthesis 2,3–disubstituted 1–tribromomethyl–1,2–dihydrobenzo[*b*][1,6]naphtyridines **15a–c.**

Entry	Starting compound **4c**	Amine R^1NH_2, R^1	Reaction time	Product	Yield, %
1	**4c**	CH_2Ph	20 min	**15a**	42
2	**4c**	$CH{=}CHCH_2$	6 min	**15b**	38
3	**4c**	$C{\equiv}CCH_2$	5 min	**15c**	42

As an extension of this work, similar three–component reactions with other *C*–pronucleophiles, such as nitromethane, diethylmalonate, phenylacetylene, and trimethoxymethane, were attempted. In all cases, mixtures of various undefined products were formed.

It is known that in some cases phosphites can be also used as pronucleofiles. 2–Alkynylquinoline–3–carbaldehydes **4a,c,d,e** where treated with various aromatic amines and dimethylphosphite in dichloroethane. When the consumption of the starting materials were observed by TLC, the catalytic amount of copper (I) iodide was added. After the stirring of the reaction mixtures at room temperature for several hours compounds **16a–k** were formed.

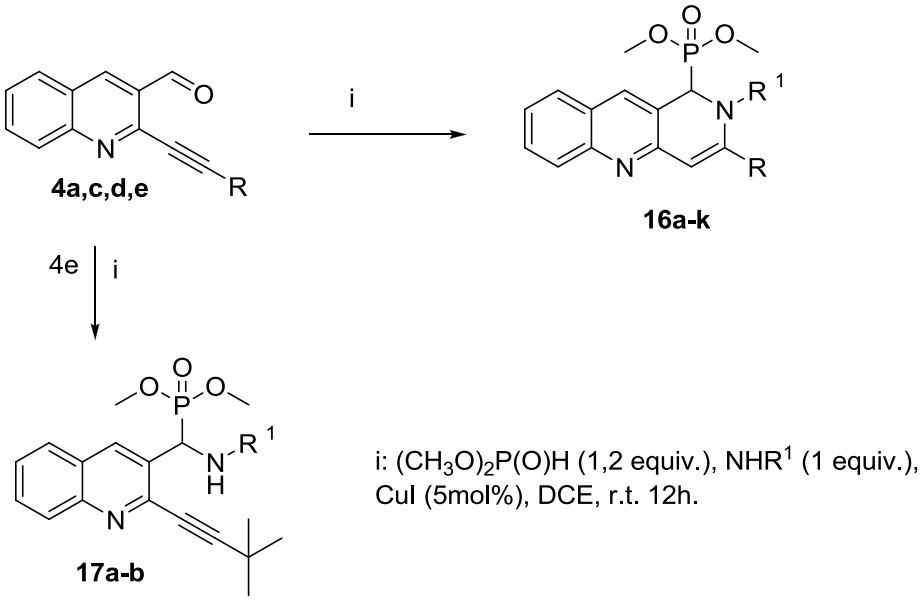


Table 9. Data of synthesis of dimethyl–2,3–disubstituted–1,2–dihydrobenzo[*b*][1,6]naphtyridine–1–ylphosphonates.

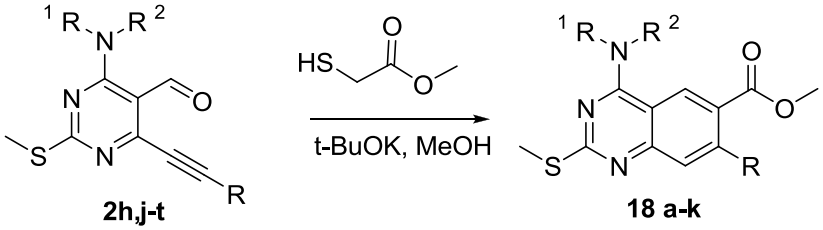
Entry	Starting compound **4c**	Amine R^1NH_2, R^1	Product	Yield, %
1	**4a**	4–$CH_3OC_6H_4$	**16a**	49
2	**4c**	C_6H_5	**16b**	52
3	**4c**	4–$CH_3OC_6H_4$	**16c**	67
4	**4c**	4–$C_2H_5OC_6H_4$	**16d**	56
5	**4c**	4–ClC_6H_4	**16e**	48
6	**4c**	4–FC_6H_4	**16f**	67
7	**4d**	C_6H_5	**16g**	48
8	**4d**	4–$CH_3OC_6H_4$	**16h**	45
9	**4d**	4–$C_2H_5OC_6H_4$	**16i**	42
10	**4d**	4–ClC_6H_4	**16j**	51
11	**4d**	4–FC_6H_4	**16k**	52
12	**4e**	4–$CH_3OC_6H_4$	**16l**	0
13	**4e**	4–$CH_3OC_6H_4$	**17a**	47
14	**4e**	4–$C_2H_5OC_6H_4$	**17b**	42

Reaction between 2–phenylethynylquinoline–3–carbaldehyde **4a,** dimethylphosphite and aniline produces cyclization product (it was observed by TLC as characteristic yellow spot). However, purification of cyclization product from aniline traces was very complicated, neither column chromatography, nor extraction in mild acidic conditions did not worked. On the other hand, the reaction of 2–(3,3–dimethylbut–1–ynyl)quinoline–3–carbaldehyde **4e** with *p*–methoxy or *p*–ethoxyaniline and dimethylphosphite was incomplete, and the formation of only Kabachnik – Fields reaction products **17a,b** were observed. Cyclization of **17a,b** did not proceed during either refluxing reaction mixture or heating in the microwave oven. We speculate that due to bulky *tert*–butyl group the formation of intramolecular cyclization product **16** becomes impossible.

It is noteworthy, that these reactions can be successful only with aromatic amines, and aliphatic amines (butylamine, alylamine, benzylamine) did not participate in these three – component reactions.

2.4 Novel [5+1] benzannulation reaction with methyl mercaptoacetate

We have shown that compounds bearing formyl and ethynyl groups in close proximity to each other undergo reactions with *N*–nucleophiles, therefore these compounds are versatile and useful intermediates for the synthesis of pyridine ring containing heterosystems. These results logically led us to investigate the reactions of starting compounds with sulphur nucleophiles. Reaction of 6–phenylethynylpyrimidine–5–carbaldehyde with an equivalent of sodium salt of methyl mercaptoacetate in methanol at room temperature led to formation of compound **18a.** Neither IR spectra nor ^{13}C NMR spectra of **18a** showed the presence of C≡C or formyl groups in molecules. In the ^{1}H NMR spectra of obtained products two new singlets at 7.73 ppm and 8.37 ppm along with the singlet of methoxy group at 3.67 ppm were observed. These data indicated that not only conjugate addition of thiolate moiety to the C≡C bond, but also condensation of activated methylene group with formyl functionality had taken place. So 2–methylthio–4–morpholino–6–phenyletinylpyrimidine–5–carbaldehyde **2h** during reaction with sodium salt of methyl mercaptoacetate at room temperature gave 6–methoxycarbonyl–2–methylthio–4–morpholine–7–phenylquinazoline **18a**. Encouraged by these results we decided to perform the reactions of the other 4–substituted 2–methythio–6–alkynylpyrimidine–5–carbaldehydes **2h,j–t**. It is noteworthy, that in case of insoluble starting materials, the reaction rate is diminished leading to decreased yield of the target compound. Heating the reaction mixture in methanol moderately increased the yields for the benzannulation for 2–methylthio–6–phenylethynylpyrimidine–5–carbaldehydes **2k–t.** The results of the synthesis of 7–aryl–6–methoxycarbonylquinazolines **18a–k** are summarized in Table 10.



Tabale 10. Data of synthesis of 4,7–disubstituted 6–methoxycarbonyl–2–methyltioquinazolines **18a–k.**

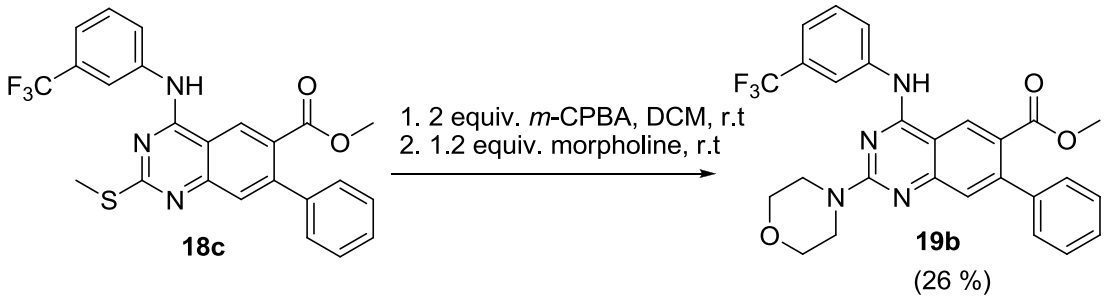
Entry	Starting compound	R	NR^1R^2		Product	Yield, %
			R^1	R^2		
1	**2h**	Ph	$N(CH_2)_4O$		**18a**	85[a]; 90[b]
2	**2j**	Ph	Ph	H	**18b**	98[a,b]
3	**2k**	Ph	3–$CF_3C_6H_4$	H	**18c**	79[b]
4	**2l**	Ph	3–BrC_6H_4	H	**18d**	80[b]

5	**2m**	Ph	4–$CH_3OC_6H_5$	H	**18e**	50[b]
6	**2n**	Ph	4–$C_2H_5OC_6H_4$	H	**18f**	45[b]
7	**2o**	*n*–C_4H_9	Ph	H	**18g**	81[b]
8	**2p**	*n*–C_4H_9	3–$CF_3C_6H_4$	H	**18h**	73[b]
9	**2r**	*n*–C_4H_9	3–BrC_6H_4	H	**18i**	82[b]
10	**2s**	$Si(CH_3)_3$	3–$CF_3C_6H_4$	H	**18j**	47[b]
11	**2t**	$Si(CH_3)_3$	3–BrC_6H_4	H	**18k** (R: H)	35[b]

[a] Reaction was performed at room temperature.
[b] Reaction was performed at reflux temperature.

In the case of compound **2t** cyclization occurred together with the concomitant loss of the TMS group (Table 10, entry 11).

We decided to modify methylthio moiety at the 2nd position of 6–methoxycarbonylquinazolines by oxidation with *m*–chloroperbenzoic acid and replacement by nucleophilic substitution. 6–Methoxycarbonylquinazoline **18c** was treated by *m*–CPBA in dichloromethane at room temperature. After the stirring of reaction mixture for 1–2 hours at room temperature an excess of secondary amine morpholine was added. 2–Morpholino–7–phenyl–4–[3–(trifluoromethyl)phenylamino]–6–methoxycarbonylquinazoline **19b** was obtained in low 26% yield after the complicated purification of reaction mixture.



Thus, we decided to modify the starting 6–arylethynylpyrimidine–5–carbaldehydes **2j–l** first and then perform the cyclization with methyl mercaptoacetate. The results of the synthesis of 2,4–disubstituted 6–arylethynylpyrimidine–5–carbaldehydes **20a–e** are summarized in Table 11.

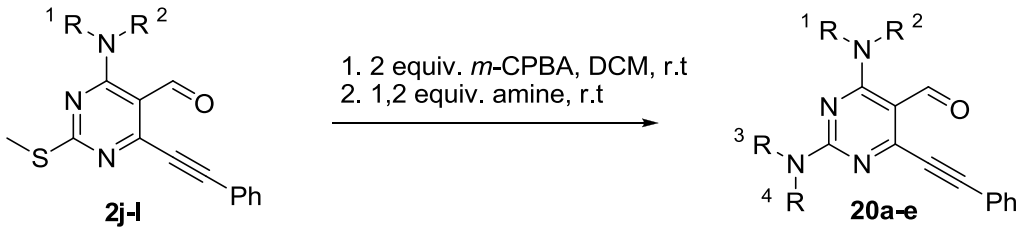


Table 11. Data of synthesis 2,4–disubstituted 6–phenylethynyl–5–pyrimidinecarbaldehides **20a–e**.

Entry	Starting compound	NR^1R^2		Product	NR^3R^4		Yield, %
		R^1	R^2		R^3	R^4	
1	**2j**	Ph	H	**20a**	CH_2=$CHCH_2$	H	49
2	**2k**	3–$CF_3C_6H_4$	H	**20b**	$N(CH_2)_4O$		64
4	**2k**	3–$CF_3C_6H_4$	H	**20c**	CH_2=$CHCH_2$	H	66

5	**2k**	3–$CF_3C_6H_4$	H	**20d**	$PhCH_2$	H	59
7	**2l**	3–BrC_6H_4	H	**20e**	CH_2=$CHCH_2$	H	50

After we had prepared the substrates **20a–e,** the methyl mercaptoacetate triggered benzannulation reaction was applied. However, the solubility of compounds **20a–e** was remarkably low in methanol and the benzannulations took longer heating times. In the case of starting substrate **20b**, we isolated the intermediate of the benzannulation reaction the product of conjugate addition of methyl mercaptoacetate to triple bond **21.** In order to solve these problems we decided to take advantage of microwave–assisted chemistry. To our pleasant surprise, when solutions of compounds **20a–e** and potassium salt of methyl mercaptoacetate in methanol were irradiated in a microwave oven, after 1–3 min the high–yielding formation of quinazolines **19a–e** took place. Reactions were performed in domestic microwave oven in closed pressure resistant vessel. Results are summarized in Table 12.

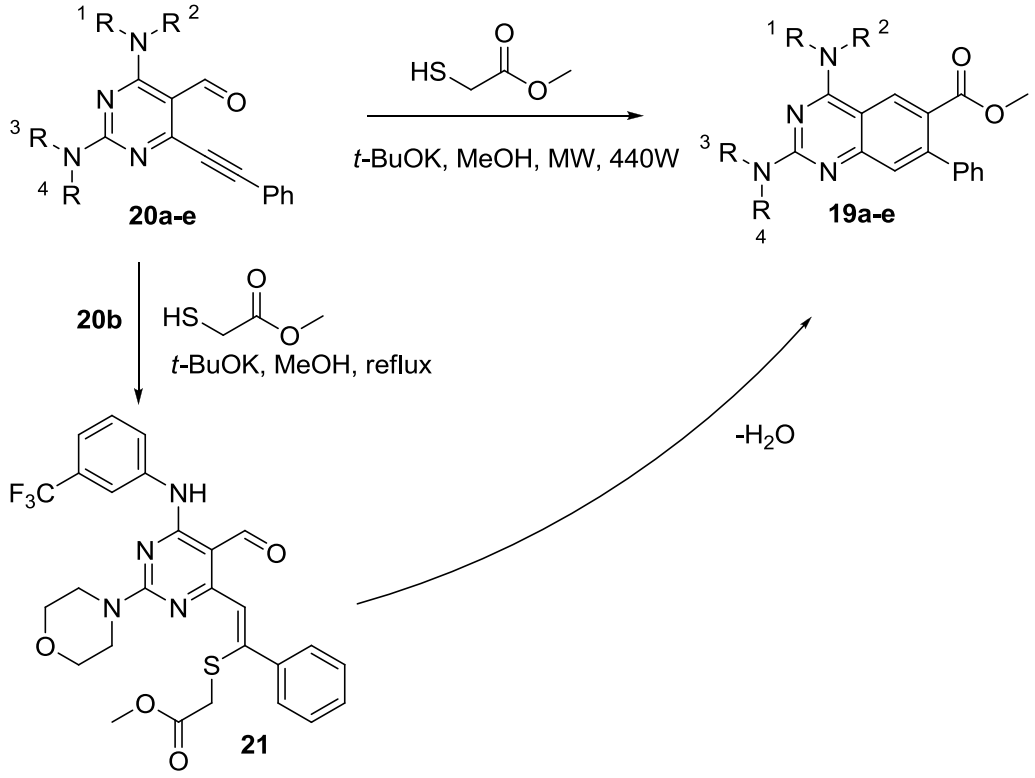
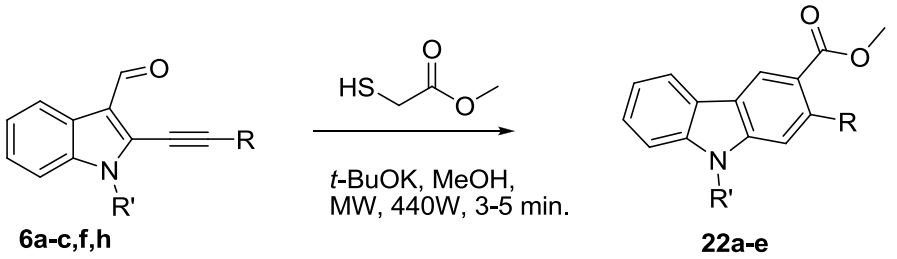


Table 12. Data of synthesis 2,4–disubstituted 6–methoxycarbonyl–7–phenylquinazolines **19a–e**

Entry	Starting compound	NR^1R^2		NR^3R^4		Product	Yield, %
		R^1	R^2	R^3	R^4		
1	**20a**	Ph	H	CH_2=$CHCH_2$	H	**19a**	63
2	**20b**	3–$CF_3C_6H_4$	H	$N(CH_2)_4O$		**19b**	86
4	**20c**	3–$CF_3C_6H_4$	H	CH_2=$CHCH_2$	H	**19c**	71
5	**20d**	3–$CF_3C_6H_4$	H	$PhCH_2$	H	**19d**	54
7	**20e**	3–BrC_6H_4	H	CH_2=$CHCH_2$	H	**19e**	65

In these cases, the substituents in positions 2 and 4 of the pyrimidine ring did not have any effect.

At this stage of the investigation, it appeared that activation of the triple bond by the electron–withdrawing pyrimidine nucleus played an important role in enabling a successful and regioselective nucleophilic addition of methyl mercaptoacetate to the C≡C moiety and following benzannulation. Nevertheless, we decided to examine the generality of our method and turned our attention to electron rich substrates (e.g., indole, thiophene derivatives). To our pleasant surprise, the starting compounds bearing electron–donating heterocycle indole **6a–c,f,h** reacted with the potassium salt of methyl mercaptoacetate in methanol and formed the desired carbazoles **22a–e** (Table 13) in high yields after irradiation of reaction mixtures in a microwave oven.

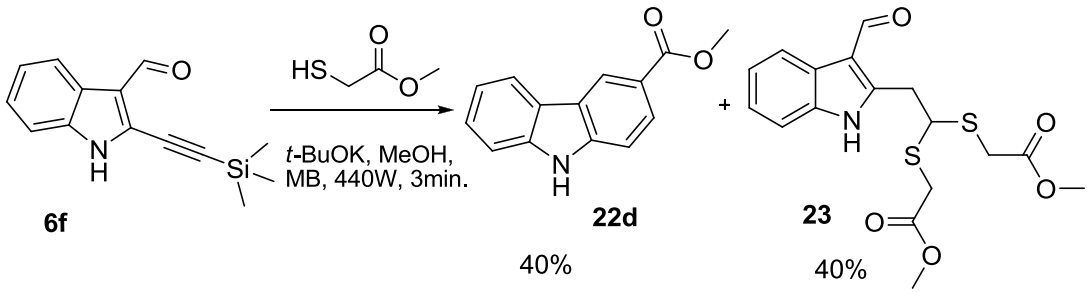


6a-c,f,h **22a-e**

Table 13. Data of synthesis 2,9–disubstituted 3–methoxycarbonylcarbazoles **22a–e**.

Entry	Starting compound	R	R^1	Product	Yield, %
1	**6a**	C_6H_5	H	**22a**	80
2	**6b**	4–$CH_3C_6H_4$	H	**22b**	62
3	**6c**	4–$C_2H_5C_6H_4$	H	**22c**	79
4	**6f**	$Si(CH_3)_3$	H	**22d** (R: H) **23**	40/40
5	**6h**	$CH(CH_2)_2$	$CH_2C_6H_5$	**22e**	70

It is noteworthy, that in case of compound **6f** cyclization occurred together with the concomitant loss of the TMS group and product **22d** was formed. We have also isolate side product **23**.



6f **22d** 40% **23** 40%

Moreover it is noteworthy, that there was no need to protect the NH moiety on indole ring (something that is usually recommended under basic reaction conditions).

Analogously, the one–step benzannulation reaction was suitable for the preparation of benzo[*b*]thiophenes **24a–e** from thiophene derivatives **8a–e**. In the case of 2–trimethylsilylethynylthiophene–3–carbaldehyde **8d**, cyclization occurred together with the concomitant loss of the TMS group (Table 14).

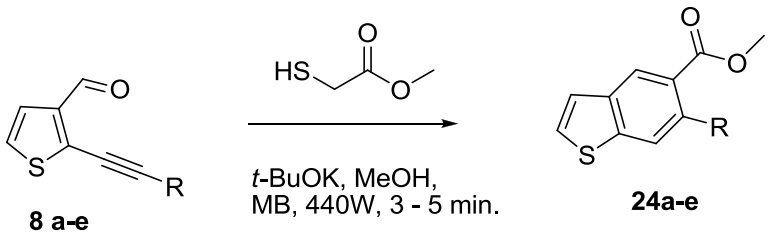
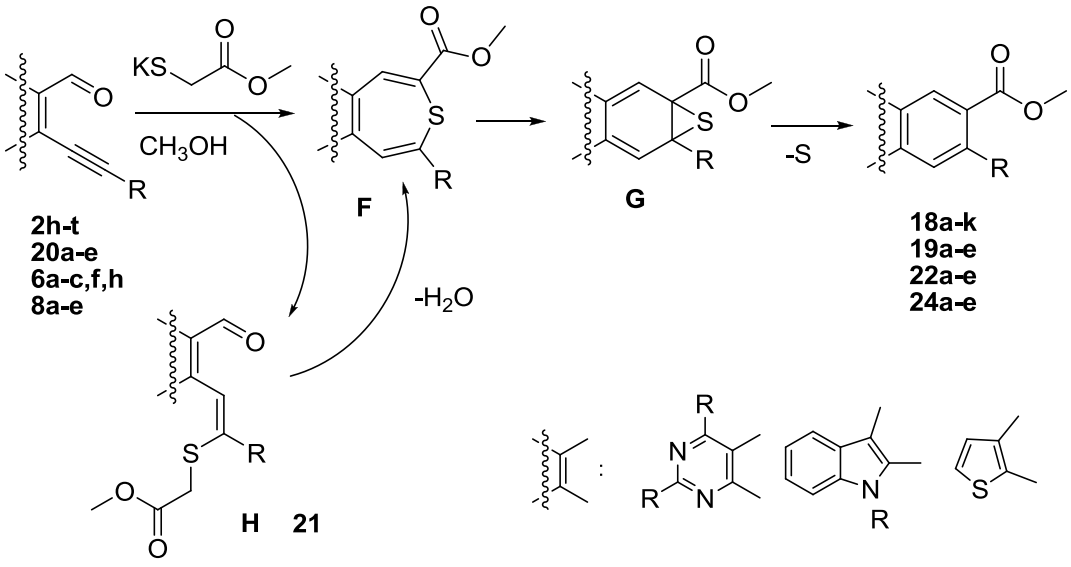


Table 14. Data of synthesis 6–substituted–5–methoxycarbonylbenzo[*b*]thiophenes **24a–e**.

Entry	Starting compound	R	Product	Yield, %
1	**8a**	C_6H_5	**24a**	60
2	**8b**	4–$CH_3C_6H_4$	**24b**	60
3	**8c**	4–$C_2H_5C_6H_4$	**24c**	64
4	**8d**	$Si(CH_3)_3$	**24d** (R = H)	78
5	**8e**	*n*–C_4H_9	**24e**	81

The present benzannulation process is believed to proceed *via* an antiaromatic thiepine **F** as outlined in Scheme below. We suppose that during the reaction of starting compounds with potassium salt of methyl mercaptoacetate the conjugated nucleophilic addition to C≡C moiety together with Dieckmann type condensation took place and intermediate **I** formed. Intermediates **F** due to their anti–aromaticity underwent smooth electrocyclic ring closure (intermediates **G**) and following aromatization with elimination of sulphur to form the corresponding benzo–annealed heterocycles.



Scheme. Possible mechanism for the benzannulation reactions

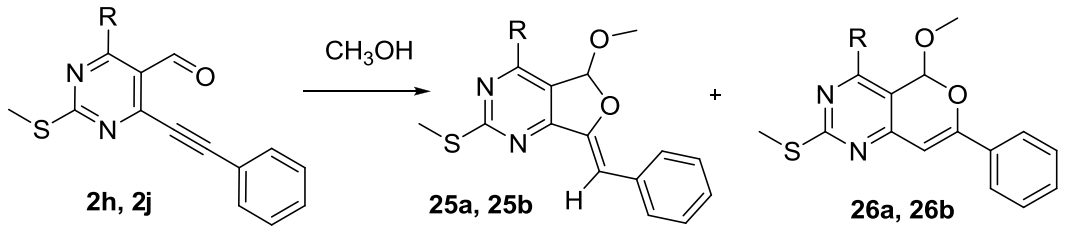
Analogous transformation from benzothiepine to naphthalene derivatives was reported earlier in literature, so our proposed mechanism seems to be reasonable. Unfortunately, we did not succeed to isolate antiaromatic thiepines **F** from the reaction mixtures. But on the other hand, another intermediate methyl (*Z*)–2–[5–formyl–2–morpholino–6–(3–trifluoromethyl)anilino–4–pyrimidinyl–1–phenylethenyl]thioacetate

21 after the resubmission to the reaction conditions also formed the final benzoannelated product **19b**. The only one logical speculation about the latter result can be intramolecular condensation of intermediates **H** to form thiepines **F** and following rearrangements as described above.

It is noteworthy that methyl mercaptoacetate is the most efficient reagent for this transformation. Other thiols, such as 1–butanethiol and benzylthiol did not trigger the benzannulation process. The unique role of mercaptoacetic acid ester is due to active methylene group and also due to soft nucleophilicity of thiole moiety.

2.5 Tandem 5–*exo*–dig, 6–*endo*–dig cyclization reactions

A literature survey revealed that cyclization of the carbonyl group on alkynes of *o*–alkynylbenzencarbaldehydes could undergo transition metal–catalyzed or electrophile induced 5–*exo*–dig and/or 6–*endo*–dig cyclization reactions. During continuation of our research aimed on the use of 6–arylethynylpyrimidines in the synthesis of fused pyrimidine derivatives (2.2 paragraph, 8 page) we have found that 2–methylthio–4–morpholine–6–phenylethynylpyrimidine–5–carbaldehyde **2h** underwent cyclization reaction during refluxing in methanol in the presence of base to form cyclization product **25a**. We were intrigued that 2–methylthio–4–morpholine–6–phenylethynylpyrimidine–5–carbaldehyde **2h** reacts with an equivalent of *tert*–butylamine in boiling methanol and instead of expected imine formation the unexpected product **25a** was formed. Neither IR nor ^{13}C NMR spectra of **25a** showed the presence of C≡C or C=O group in the molecule. In the ^{1}H NMR spectra of the obtained product two new singlets at 6.52 and 6.63 ppm along with a singlet of methoxy group at 3.44 ppm were observed. These data indicated that the 5–*exo*–dig or 6–*endo*–dig cyclization took place. As evidence the crystallographic data of similar compound which was synthesized in our laboratory showed that 5–*exo*–dig cyclization took place. So during refluxing of the compound **2h** in methanol in the presence of *tert*–butylamine the formation of (7*Z*)–7–benzylidene–5–methoxy–2–methylthio–4–morpholine–5,7–dihydrofuro[3,4–*d*]pyrimidine **25a** took place. Formation of compound **25a** was long and low yielded because of weak base *tert*–butylamine. In order to study the generality and regioselectivity of the acetalisation/cyclization reaction two starting compounds bearing morpholino **2h** and anilino **2j** moieties in position 4 of the pyrimidine ring were chosen and their reactions with methanol under the different conditions were studied. The results are summarized in Table 15.



2h, 25a, 26a R: $N(CH_2)_4O$
2j, 25b, 26b R: NHC_6H_5

Table 15. Optimization of the acetalisation/5–*exo*–dig or 6–*endo*–dig cyclization reactions of 4–substituted 2–methylthio–6–phenylethynylpyrimidine–5–carbaldehydes **2j,h** with methanol

Entry	R	Base	Catalyst	Conditions	5–*egzo*–dig product (**25**)	6–*endo*–dig product (**26**)
1	$N(CH_2)_4O$	K_2CO_3	–	CH_3OH, reflux 2h	72%[a]	–
2	$N(CH_2)_4O$	$NaOCH_3$	–	CH_3OH, reflux 1h	92%[a]	–
3	**$N(CH_2)_4O$**	**$KOCH_3$**	–	**CH_3OH, reflux 0,5h**	**98%[a]**	–
4	$N(CH_2)_4O$	–	CuI	CH_3OH, reflux 20h	n.r.[b]	
5	$N(CH_2)_4O$	–	$Cu(OTf)_2$	CH_3OH, reflux 5h	0.73[c]	0.27[c]
6	$N(CH_2)_4O$	–	$PdCl_2$	CH_3OH, reflux 5h	60%[a]	–
7	$N(CH_2)_4O$	–	$PdCl_2(PPh_3)_2$	CH_3OH, reflux 5h	0,26[c]	0,74[c]
8	$N(CH_2)_4O$	–	$AuCl_3$	CH_3OH, reflux 5h	n.r.[b]	
9	$N(CH_2)_4O$	–	Ag_2O	CH_3OH, reflux 40h	39%[a]	–
10	$N(CH_2)_4O$	–	$AgNO_3$	CH_3OH, reflux 4h	0.41[c]	0.59[c]
11	$N(CH_2)_4O$	–	CF_3CO_2Ag	CH_3OH, reflux 4h	0.49[c]	0.51[c]
12	**$N(CH_2)_4O$**	–	**$AgNO_3$**	**CH_3OH/DCM, MW, 600W, 5min**	–	**96%[a]**
13	$N(CH_2)_4O$	–	CF_3CO_2Ag	CH_3OH/DCM, MW, 600W, 5min	0.04[c]	0.96[c]
14	$N(CH_2)_4O$	$KOCH_3$	$AgNO_3$	CH_3OH/DCM, MW, 600W, 5min	93%[a]	–
15	NHC_6H_5	$KOCH_3$	–	CH_3OH, reflux 20h	n.r.[b]	
16	NHC_6H_5	$KOCH_3$	–	CH_3OH, MW, 600W, 30min	n.r.[b]	
17	NHC_6H_5	–	Ag_2O	CH_3OH, reflux 24h	n.r.[b]	
18	NHC_6H_5	$KOCH_3$	$AgNO_3$	CH_3OH/DCM, r.t. 48h	79%[a]	–
19	**NHC_6H_5**	**$KOCH_3$**	**CF_3CO_2Ag**	**CH_3OH/DCM, r.t. 48h**	**82%[a]**	–
20	NHC_6H_5	–	$AgNO_3$	CH_3OH, reflux 4h	–	85%[a]
21	NHC_6H_5	–	CF_3CO_2Ag	CH_3OH, reflux 4h	–	87%[a]
22	NHC_6H_5	–	$AgNO_3$	CH_3OH/DCM, MW, 600W, 10min	–	96%[a]
23	**NHC_6H_5**	–	**CF_3CO_2Ag**	**CH_3OH/DCM, MW, 600W, 10min**	–	**98%[a]**

[a] Isolated yield.
[b] No reaction, starting material recovered.
[c] Ratio estimated by ^1H NMR analysis.

First of all, we studied the reactivity of 2–methylthio–4–morpholino–6–phenylethynylpyrimidine–5–carbaldehyde **2h** with methanol under the different

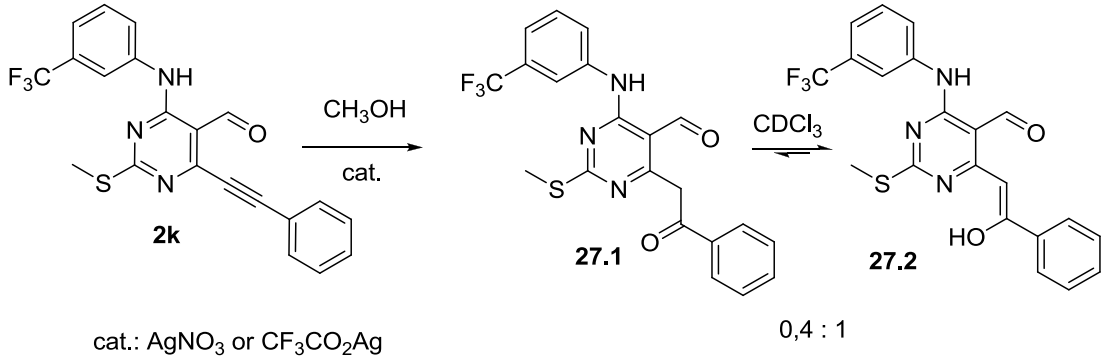
conditions. During heating a solution of the starting compound in methanol in the presence of bases, the regioselective formation of (*Z*)–7–benzylidene–5–methoxy–4–morpholino–5,7–dihydrofuro[3,4–*d*]pyrimidine **25a** took place. Reaction proceeded smoothly and provided high yields of **2h** when 1 equiv. of sodium or potassium methoxide was used (Table 15, entries 2, 3). Then we tried to change the regioselectivity of ring–closure and for this purpose we used catalytic amounts of different transition metals salts in order to form π–complexes between triple bond and metal ion. As shown in Table 15, CuI and $AuCl_3$ (Table 15, entries 4, 8) were ineffective. After the long heating and work up of the reaction mixtures, the initial compound was recovered. Using 5 mol % of palladium (II) chloride or silver (I) oxide led to the formation of only 5–*exo*–dig cyclization product **25a** (Table 15, entries 6, 9). However, the reaction of **2h** with methanol in the presence of $Cu(OTf)_2$, $PdCl_2(PPh_3)_2$, $AgNO_3$ or CF_3CO_2Ag proceeded with poor regioselectivity and the formation of mixtures of **25a** and **26a** was observed in these cases (Table 15, entries 5, 7, 10, 11). We were pleasantly surprised when during heating of solution of **2h** in 1,2–dichloroethane in the presence of 3 equiv. of methanol and 5 mol % of $AgNO_3$ in microwave oven after 5 min a high–yielding regioselective formation of 6–*endo*–dig cyclization product **26a** was observed (Table 15, entry 12). Using CF_3CO_2Ag at the same conditions provided slightly lower regioselectivity (Table 15, entry 13). However, irradiation of the reaction mixture in the presence of a catalytic amount of silver (I) nitrate together with an equivalent of potassium methoxide completely reversed the regioselectivity and high–yielding formation of **25a** was observed (Table 15, entry 14).

The next compound that we chose was 4–anilino–2–methylthio–6–phenylethynylpyrimidine–5–carbaldehyde **2j**. It is noteworthy, that compound **2j** treated by sodium methoxide in methanol did not undergo acetalisation/cyclization reactions (Table 15, entries 15, 16). Moreover silver (I) oxide also did not catalyzed the formation of furo[3,4–*d*]pyrimidine **25b** or pyrano[4,3–*d*]pyrimidine **26b** (Table 15, entry 17). In all these cases after the work up of the reaction mixtures the initial compound **2j** was recovered. On the other hand, using a catalytic amount of silver (I) salts together with potassium methoxide gave slow but regioselective acetalisation/5–*exo*–dig cyclization (Table 15, entries 18, 19). Interestingly, when we used only silver catalysts without addition of bases, we observed regioselective formation of 6–*endo*–dig cyclization product **26b**. The same result was obtained even during convectional or microwave heating (Table 15, entries 20–24).

So, we have found that the optimal acetalisation/5–*exo*–dig cyclization of 4–*N*,*N*–dialkylamino–6–phenylethynylpyrimidine–5–carbaldehydes conditions are: an equivalent of potassium alkoxides in alcohols, convectional or microwave heating. The best conditions for the acetalisation/5–*exo*–dig cyclization of 6–phenylethynylpyrimidine–5–carbaldehydes bearing amino, alkylamino or arylamino groups in position 4 of the pyrimidine ring are: an equivalent of potassium alkoxide, alcohol (3 equiv.), 5 mol % of silver (I) nitrate or silver (I) trifluoroacetate in

dichloromethane at room temperature. The optimal acetalisation/6–*endo*–dig cyclization of 4–*N*,*N*–dialkylamino–6–phenylethynylpyrimidine–5–carbaldehydes conditions are: alcohol (3 equiv.), 1,2–dichloroethane, 5 mol % of silver (I) nitrate, irradiation of the reaction mixture in microwave oven (600 W) for 5 min. The best conditions for the acetalisation/6–*endo*–dig cyclization of 6–phenylethynylpyrimidine–5–carbaldehydes bearing amino, alkylamino or arylamino groups in position 4 of the pyrimidine ring are: alcohol (3 equiv.), 1,2–dichloroethane, 5 mol % of silver (I) nitrate or silver (I) trifluoroacetate convectional heating for 4 h or irradiation of the reaction mixture in microwave oven (600 W) for 10 min.

During these reactions we have also found, that in the presence of silver (I) salts, addition of water to the triple bond of 6–phenylethynylpyrimidine–5–carbaldehydes takes place, so use of anhydrous solvents is strongly recommended. Isolated compound **27** exists in two tautomeric forms **27.1** and **27.2** in the solutions. ^{1}H NMR spectra in chloroform of compound **27** showed, that major tautomeric form is **27.2.**



Thus, 5,7–dihydrofuro[3,4–*d*]pyrimidines **25a,b** and 5*H*–pyrano[4,3–*d*]pyrimidines **26a,b** were synthesized (Tables 16, 17).

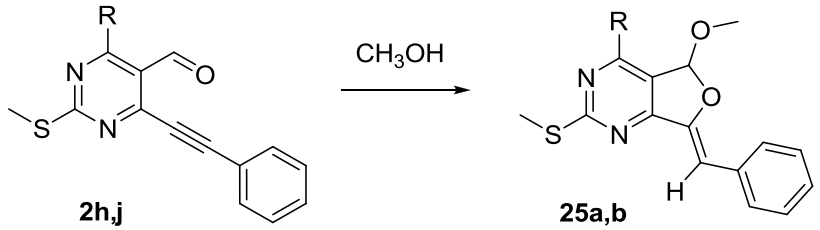


Table 16. Data of the synthesis of 4–substituted 2–methylthio–5–methoxy–(*Z*)–7–benzylidene–5,7–dihydrofuro[3,4–*d*]pyrimidines **25a,b.**

Entry	Starting compound	R	Product	Method	Yield, %
1	**2h**	$N(CH_2)_4O$	**25a**	A[a]	93
2	**2h**	$N(CH_2)_4O$	**25a**	B[b]	100
3	**2j**	NHC_6H_5	**25b**	C[c]	82

[a] Method A: potassium alkoxide (1 equiv), alcohol, reflux, 0.5–3 h.
[b] Metodas B: potassium alkoxide (1 equiv), alcohol (3 equiv), 1,2–dichloroethane, microwave oven, 600 W, 5 min.
[c] Method C: potassium alkoxide (1 equiv), alcohol (3 equiv), CF_3CO_2Ag (5 mol %), dichloromethane, r.t 24–48 h.

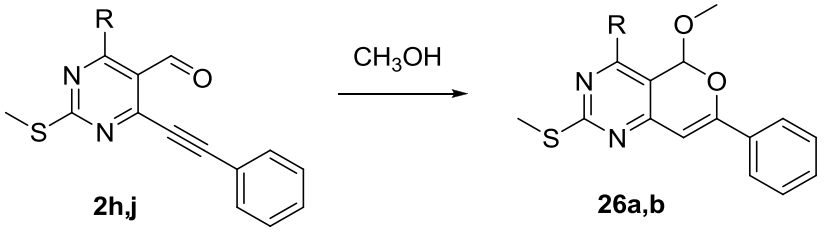


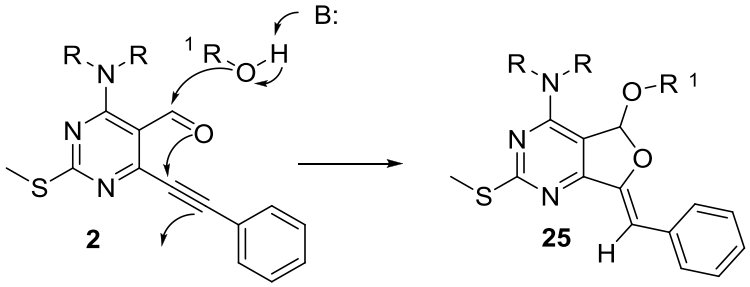
Table 17. Data of the synthesis of 4–substituted 2–methylthio–5–methoxy–7–phenyl–5*H*–pyrano[4,3–*d*]pyrimidines **26a,b.**

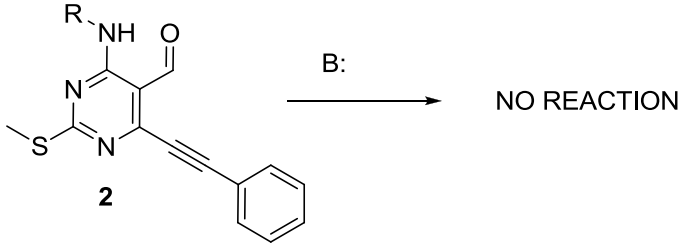
Entry	Starting compound	R	R^1	Product	Method	Yield, %
1	**2h**	$N(CH_2)_4O$	CH_3	**26a**	D[a]	93
2	**2h**	$N(CH_2)_4O$	CH_3	**26a**	E[b]	96
3	**2j**	NHC_6H_5	CH_3	**26b**	D	96

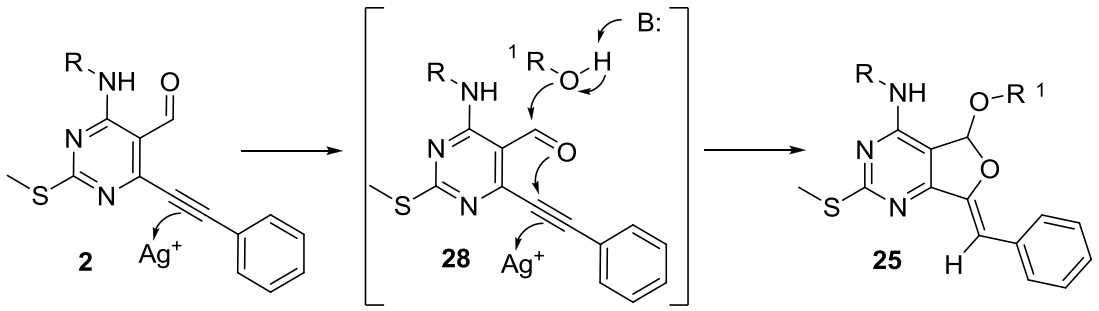
[a] Method D: methanol, $AgNO_3$ (5 mol%) reflux, 4 h.
[b] Method E: methanol (3 equiv.), $AgNO_3$ (5 mol%), 1,2–dichloroethane, MW, 600W, 5 min.

According to the presented methodologies, in our laboratory we have prepared more derivatives of 5,7–dihydrofuro[3,4–*d*]pyrimidines and 5*H*–pyrano[4,3–*d*]pyrimidines.

From these results we can propose three possible mechanistic pathways for the acetalisation/cyclization reactions. We believe that base–induced acetalisation/5–*exo*–dig cyclization proceeds by a tandem type reaction: formation of an intermediate hemiacetal and immediate nucleophilic cyclization to form the 5,7–dihydrofuran ring. We speculate that 6–phenylethynylpyrimidine–5–carbaldehydes bearing an NHR moiety in the position 4 of the pyrimidine ring, exist in an unfavorable conformation where the carbonyl group is turned towards the NHR moiety to form an intramolecular hydrogen bond and directed away from the C≡C bond, therefore tandem reactions become impossible. Using a catalytic amount of silver nitrate or silver trifluoroacetate resulted the complexation of Ag^+ with C≡C bond (intermediate **28**), thus making rotation of C=O to the activated triple bond more favorable.

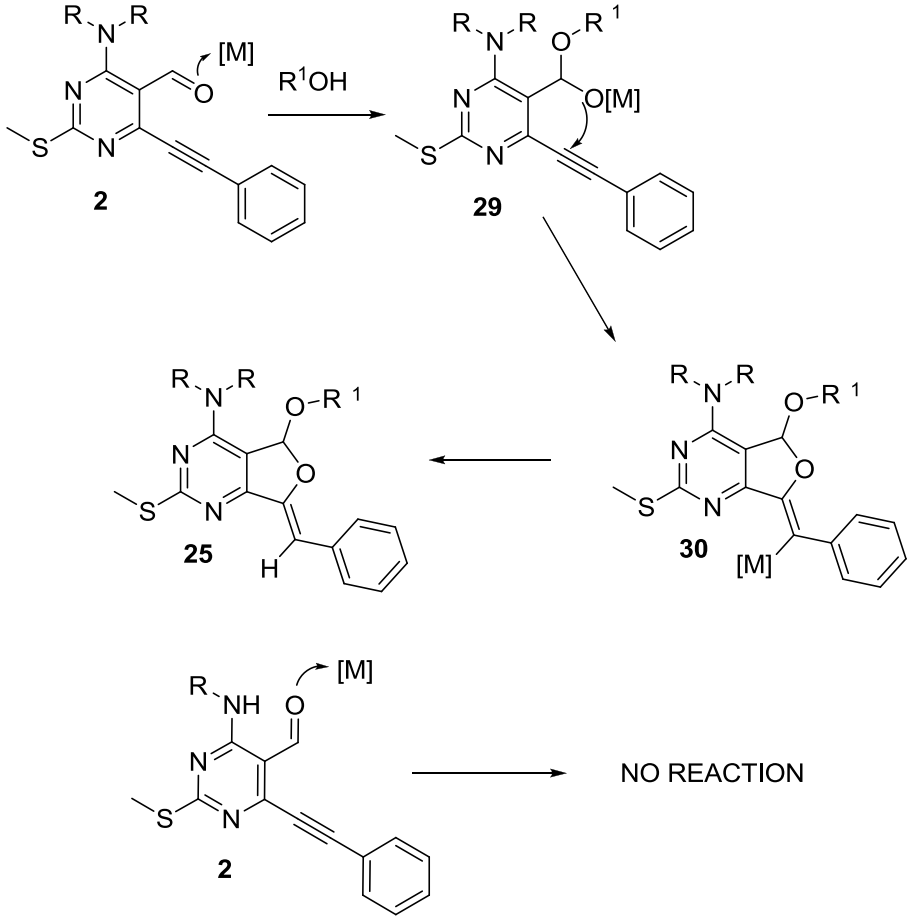






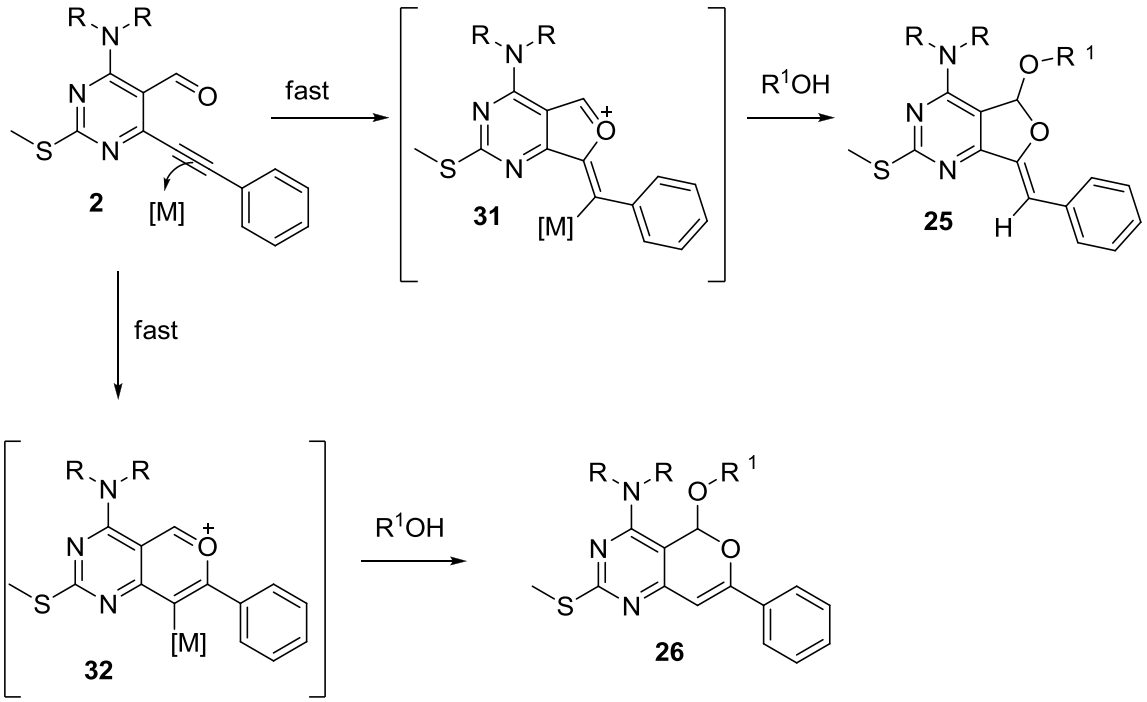
Scheme. Mechanistic pathway A.

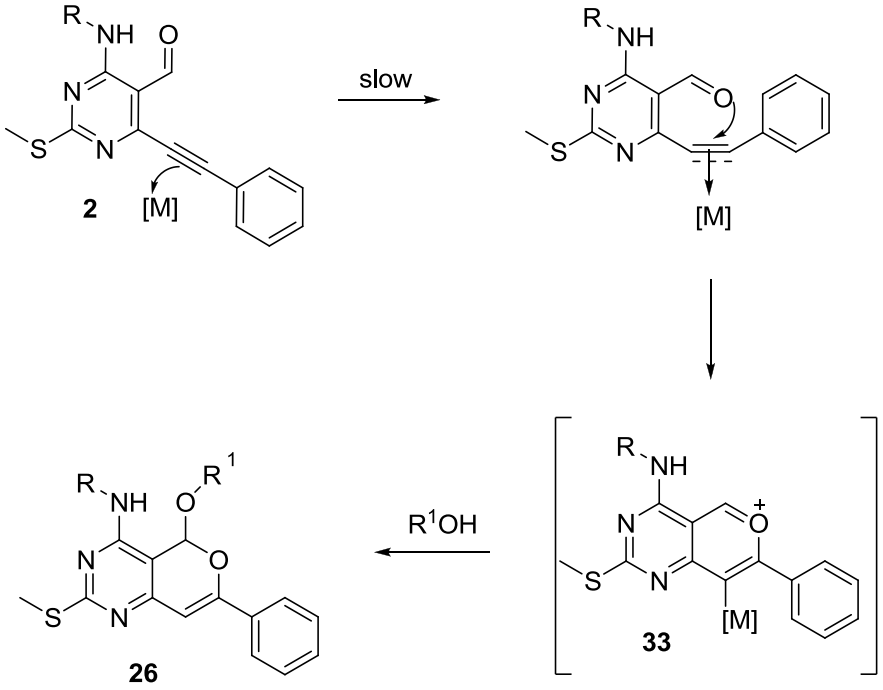
Two of our investigated catalysts – silver (I) oxide and palladium (II) chloride also led to the acetalisation/5–*exo*–dig cyclizations, so we suppose that these species coordinate with the oxygen of the carbonyl moiety of the starting compounds. Thus, intermediate acetal derivative **29** cyclizes to give complex **30** and, after catalyst recycling, yields the 5–*exo*–dig product **27**. Moreover, it is important to note again, that 6–phenylethynylpyrimidine–5–carbaldehydes bearing an NHR moiety in the position 4 of the pyrimidine ring adopt an unfavorable conformation and do not undergo acetalisation/5–*exo*–dig cyclization without formation of π–complexes between the triple bond and catalysts (Scheme).



Scheme. Mechanistic pathway B.

The path C (Scheme below) accounts for the $Cu(OTf)_2$, $PdCl_2(PPh_3)_2$, $AgNO_3$ and CF_3CO_2Ag catalysts without using bases (Table 15, entries 5, 7, 10–13, 20–24), for which upon coordination of the triple bond of **2**, the enhancement of electrophilicity of the alkyne gives rise to subsequent nucleophilic attack of the carbonyl oxygen atom on the electron deficient alkyne to yield the intermediate complexes **31** and/or **32**. The solvent/nucleophile alcohol can then attack intermediates **31** and **32** and lead to catalyst recycling and liberation of the products **25** and/or **26**. It is noteworthy that 4–dialkylamino–6–phenylethynylpyrimidine–5–carbaldehydes during refluxing in alcohols in the presence of catalysts gave mixture of 5–*exo*–dig and 6–*endo*–dig cyclization products **25** and **26**. This could be explained by the conformation of starting compounds, we believe that carbonyl group is turned away from *N*,*N*–dialkylamino moiety and it is close to the C≡C bond. So, after the complexation the nucleophilic attack by the carbonyl oxygen occurs very quickly and control of regioselectivity is lost. Fortunately, microwave heating of the reaction mixture led to better 6–*endo*–dig regiochemistry. On the other hand, 6–phenylethynylpyrimidine–5–carbaldehydes bearing NHR moiety in the position 4 of the pyrimidine ring exist in a different conformation where the carbonyl group is turned towards the NHR moiety to form an intramolecular hydrogen bond and directed away from the C≡C bond. Thus, after the complexation the carbonyl group rotates to the triple bond slowly and only after the rotation the cyclization process can take place. During this slower process we obtain high regioselectivity.





Scheme. Mechanistic pathway C.

2–Alkynylquinoline–3–carbaldehydes analogously react with alcohol according to the optimal 5–*exo*–dig/6–*endo*–dig cyclization reactions conditions and 1,3–dihydrofuro[3,4–*b*]quinolines **34a–c** (Table 18) and 1*H*–pyrano[4,3–*b*]quinolines **35a–j** (Table 19) were formed.

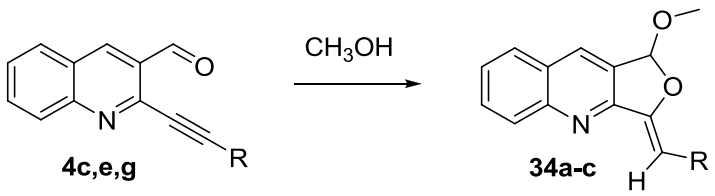


Table 18. Data of the synthesis of 3(*Z*)–alkynyliden–1–methoxy–1,3–dihydrofuro[3,4–*b*]quinolines **35a–c.**

Entry	Starting compound	R	Product	Method	Yield, %
1	**4c**	$CH(CH_2)_2$	**34a**	A[a]	71
2	**4e**	$C(CH_3)_3$	**34b**	A	88
3	**4g**	CH_2OCOCH_3	**34c** (R = CH_2OH)	A	51

[a] Method A: potassium methoxide (1 equiv.), methanol, reflux.

In the case of compound **4g** cyclization occurred together with the hydrolysis of acetyl group.

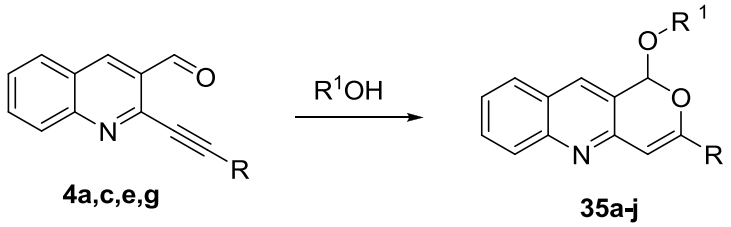


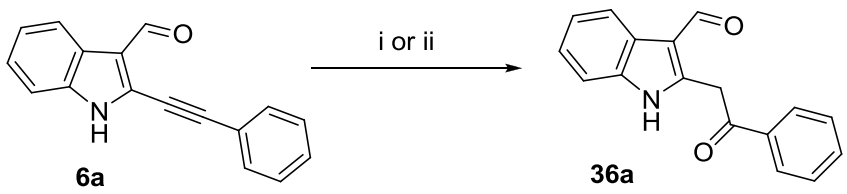
Table 19. Data of the synthesis of 3–substituted 1–alkoxy–1*H*–pyrano[4,3–*b*]quinolines **35a–j.**

Entry	Starting comp.	R	R^1	Product	Method	Yield, %
1	**4a**	C_6H_5	CH_3	**35a**	D[a]	57
2	**4a**	C_6H_5	$CH_2C_6H_5$	**35b**	E[b]	72
3	**4a**	C_6H_5	$CH(CH_2)_5$	**35c**	E	87
4	**4a**	C_6H_5	$CH_2(CH_2)_{14}CH_3$	**35d**	E	62
5	**4a**	C_6H_5	CH_2CH_2OH	**35e**	E	67
6	**4a**	C_6H_5	$CH_2CH=CH_2$	**35f**	E	67
7	**4a**	C_6H_5	$CH_2CH(CH_3)_2$	**35g**	E	77
8	**4c**	$CH(CH_2)_2$	CH_3	**35h**	E	97
9	**4e**	$C(CH_3)_3$	CH_3	**35i**	E	53
10	**4g**	CH_2OCOCH_3	CH_3	**35j**	E	58

[a] Method D: alcohol, $AgNO_3$ (5 mol%) reflux, 4 h.
[b] Method E: alcohol (3 equiv.), $AgNO_3$ (5mol%), 1,2–dichloroethane, MW, 600W, 5 min.

In summary, pyrimidine and quinoline derivatives bearing formyl and ethynyl groups in close proximity to each other undergo 5–*exo*–dig cyclization reactions with methanol in basic conditions and 6–*endo*–dig cyclization reactions takes place in presence of transition metal catalysts in neutral reaction conditions.

These results logically led us to investigate the analogous reactions with 2–alkynylindol–3–carbaldehydes and methanol. It should be noted that 2–phenylethynyl–1*H*–indole–3–carbaldehyde **6a** treated with sodium or potassium methoxide in methanol did not undergo acetalisation–cyclization reactions. This result can be explained by the fact that the triple bond is electron–rich due to the neighboring electron–donating indole ring, so tandem cyclization becomes impossible. However, no changes of the starting material were observed by TLC when we used a catalytic amount of silver nitrate or trifluoroacetate as a catalyst under the same reaction conditions: boiling methanol and basic medium (1 equiv. of sodium or potassium methoxide). On the other hand, the reaction of **6a** with methanol only in the presence of $AgNO_3$ or $AgCF_3CO_2$ proceeded smoothly, and formation of one major product was observed by TLC. We were intrigued that the NMR, IR, and microanalysis data of the isolated product did not correspond to any of the expected structures – (*Z*)–3–benzylidene–3,4–dihydro–1–methoxy–1*H*–furo[3,4–*b*]indole or 1,5–dihydro–1–methoxy–3–phenylpyrano[4,3–*b*]indole. The analytical data showed that during the reaction of the starting compound with methanol in the presence of silver salts 2–(2–oxo–2–phenylethyl)–1*H*–indole–3–carbaldehyde **36a** was formed as the sole product (Scheme). The same reaction result was obtained from heating of a solution of **6a** in 1,2–dichloroethane in the presence of 2 equivalents of methanol and 5 mol% of $AgCF_3CO_2$ in a microwave oven. The results are summarized in table 20.



i: CH_3OH,CF_3CO_2Ag (5 mol%), reflux
ii: CH_3OH (2 equiv.), CF_3CO_2Ag (5 mol%), DCE, MW, 600W.

Table 20. Reaction Conditions for the Synthesis of 2–(2–oxo–2–phenylethyl)–1*H*–indole–3–carbaldehyde **36a** from 2–phenylethynyl–1*H*–indole–3–carbaldehyde **6a**.

Entry	Reaction conditions	Time	Conversion, %	Yield, **36a** %
1	CH_3OH, reflux	12 h.	0[a]	0
2	CH_3OH, $NaOCH_3$ (1 equiv.), reflux	12 h.	0[a]	0
3	CH_3OH, $KOCH_3$ (1 equiv.), reflux	12 h.	0[a]	0
4	CH_3OH, $KOCH_3$ (1 equiv.), $AgCF_3CO_2$ (5mol%), reflux	12 h.	0[a]	0
5	CH_3OH, CF_3CO_2Ag (5 mol%), reflux	3 h.	75	43
6	CH_3OH, CF_3CO_2Ag (5 mol%), DCE, MW, 600W	15 min.	100	84
7	CH_3OH, $AgNO_3$ (5 mol%), DCE, MW, 600W	20 min.	100	71
8	CH_3OH, CuI (10 mol%), DCE, MW, 600W	40 min.	50	23
9	CH_3OH, $Cu(OTf)_2$ (10 mol%), DCE, MW, 600W	40 min.	80	44
10	C_2H_5OH, CF_3CO_2Ag (5 mol%), DCE, MW, 600W	20 min.	100	70
11	$(CH_3)_2CHOH$, CF_3CO_2Ag (5 mol%), DCE, MW, 600W	35 min.	80	62
12	C_4H_9OH, CF_3CO_2Ag (5mol%), DCE, MW, 600W	45 min.	70	52
13	CH_3OH (10 mol%), CF_3CO_2Ag (5 mol%), DCE, MW, 600W	20 min.	100	80
14	H_2O, CF_3CO_2Ag (5 mol%), DCE, MW, 600W	1 h.	0[a]	0

[a] Starting material **6a** was isolated.

It was noted that the use of 2 equivalents of methanol, silver trifluoroacetate (5 mol%) in dichloroethane, and the heating of the reaction mixture in a close vessel in a domestic microwave oven gave the best result (Table 20, entry 5). While use of silver nitrate or ethanol provided a slightly lower yield of the desired product **36a** (Table 20, entries 6, 9), refluxing of the reaction mixture in methanol, as well as the use of catalytic amounts of CuI and $Cu(OTf)_2$, proved to be far less effective (Table 20, entries 4, 7–8). The formation of **36a** was slower, and the conversion was not complete when 1–propanol or 1–butanol were used (Table 1, entries 10, 11). However, the use of a catalytic amount of methanol is also suitable for the synthesis of **36a** (Table 20, entry

12). On the other hand, absence of alcohol inhibited the reaction, so it can be concluded that direct addition of water to the triple bond of the starting compound does not take place (Table 20, entry 13).

Encouraged by these results we decided to perform the synthesis of a range of 2–(2–oxoethyl)–1*H*–indole–3–carbaldehydes **36**. The results are summarized in Table 21.

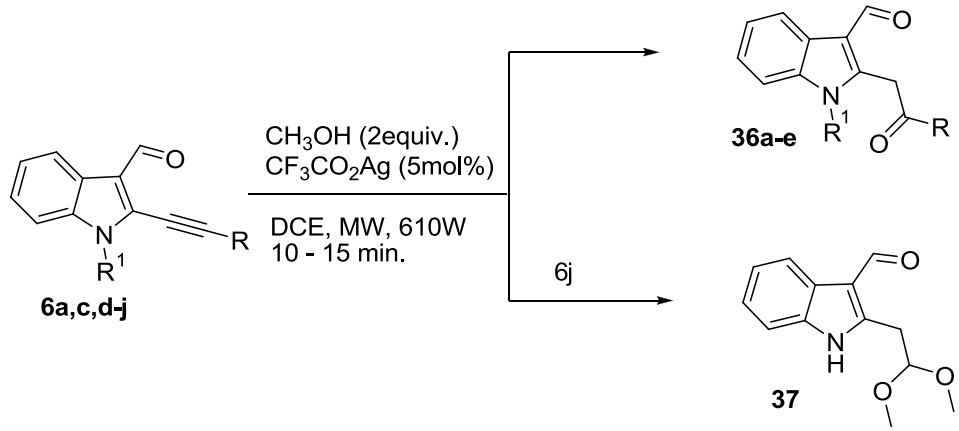


Table 21. Synthesis of 2–(2–oxoethyl)–1*H*–indole–3–carbaldehydes

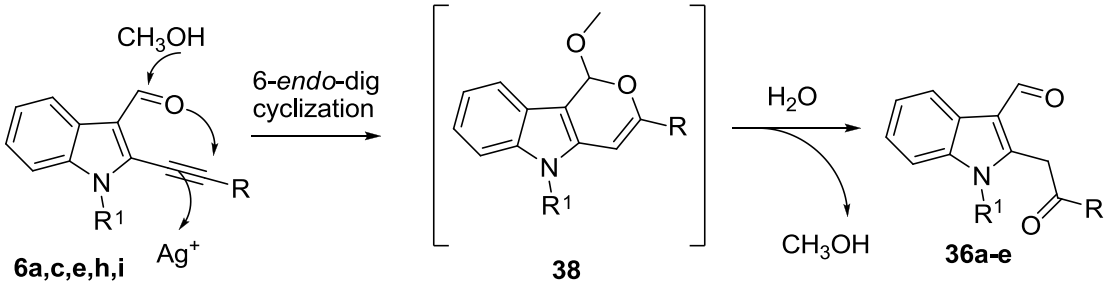
Entry	Starting compound	R	R^1	Product	Yield, %
1	**6a**	Ph	H	**36a**	84
2	**6c**	4–$C_2H_5C_6H_4$	H	**36b**	77
3	**6d**	2–pyridyl	H	-	n.r.[a]
4	**6e**	*n*–C_4H_9	H	**36c**	66
5	**6f**	$Si(CH_3)_3$	H	**37**	48
6	**6g**	2–pyridyl	Bn	-	n.r.[a]
7	**6h**	$CH(CH_2)_2$	Bn	**36d**	76
8	**6i**	$C(CH_3)_3$	Bn	**36e**	67
9	**6j**	H	H	**37**	78

[a] No reaction, the starting material was isolated after the workup of the reaction mixture.

It is noteworthy, that the nature of the alkynyl substituent normally does not have a strong influence on the result of the reaction. In the case of 2–arylethynyl–1*H*–indole–3–carbaldehydes and 2–alkynyl–1*H*–indole–3–carbaldehydes, the formation of the dicarbonyl compounds took place (Table 21, entries 1, 2, and 5–7). However, when the substituent on the alkynyl moiety contains a basic pyridine type nitrogen (compounds **6c**,**g**, Table 21, entries 3 and 4) no changes of the starting materials were observed under the reaction conditions. This 'nitrogen–effect' can be explained by complexation of the pyridine moiety with silver ion or by the pyridine substituent acting as a base and inhibiting the process. In the case of 2–trimethylsilylethynyl–1*H*–indole–3–carbaldehyde **6f** and 2–ethynyl–1*H*–indole–3–carbaldehyde **6j**, the formation of the same product 2–(2,2–dimethoxyethyl)–1*H*–indole–3–carbaldehyde **37** was observed (Table 21, entries 8 and 9). Probably, the expected reaction product 3–formyl–1*H*–indole–2–acetaldehyde reacted with methanol to give the dimethyl acetal.

In Scheme below the possible mechanism of formation of 2–(2–oxoethyl)–1*H*–indole–3–carbaldehydes **36** is depicted. We propose that, after the complexation of

the metal with the triple bond, intramolecular 6–*endo*–dig cyclization reaction takes place. The intermediate 1,5–dihydro–1–methoxypyrano[4,3–*b*]indole **38** should be unstable due to the electron–donating indole ring and therefore undergo smooth hydrolytic cleavage with traces of water leading to the formation of final dicarbonyl compounds **36**.



Scheme. Possible mechanism of formation of 2–(2–oxoethyl)–1*H*–indole–3–carbaldehydes **36**.

In conclusion, we have developed a short and efficient synthesis of 2–(2–oxoethyl)–1*H*–indole–3–carbaldehydes *via* a tandem 6–*endo*–dig cyclization process followed by smooth hydrolysis.

It is known, that dimethylphosphite can also be used as nucleophile in some intramolecular cyclization reactions. So we decided to study the reactions of various starting alkynylaldehydes containing quinoline and pyrimidine rings with dimethylphosphite in basic media. When the mixtures of compounds **4a,c**–**e,h**, dimethylphosphite and 2 equiv. of potassium *tert*–butoxide were stirred at 50^{o}C temperature, we observed the quick and selective conversions of the starting materials by TLC. The spectral elucidation of purified products **40a,c**–**e,h** let us to conclude that under the reaction conditions the Pudovik reaction and phosphonate–phosphate rearrangement sequences took place. In the ^{1}H NMR spectra of isolated products **40a,c-e,h** there were doublets of equivalent methoxy groups at 3.75 – 3.79 ppm and doublets of doublets of methylene groups at 5.32 – 5.48 ppm with the coupling constants 7.2 – 7.8 Hz and 0.9 Hz, respectively. The smaller couplings were due to splitting of methylene groups to the proton at the 4th quinoline ring position, what was well – seen from the H,H–correlation spectra and multiplicity of C(4)–H (d, J = 0.9 Hz). In the ^{13}C NMR spectra of **40a,c–e,h** there were two signals at 73.1 – 86.0 and 94.9 – 104.9 ppm regions, peculiar to the carbons of C≡C bonds. And finally, the presence of alkynyl moiety in the products was proved by IR spectra, where we found the sharp absorption peaks at 2212 – 2233 cm^{-1}. The intermediates **39a,c** were isolated and fully characterized when we used 1 equivalent of base. Reactions results are summarized in Table 22.

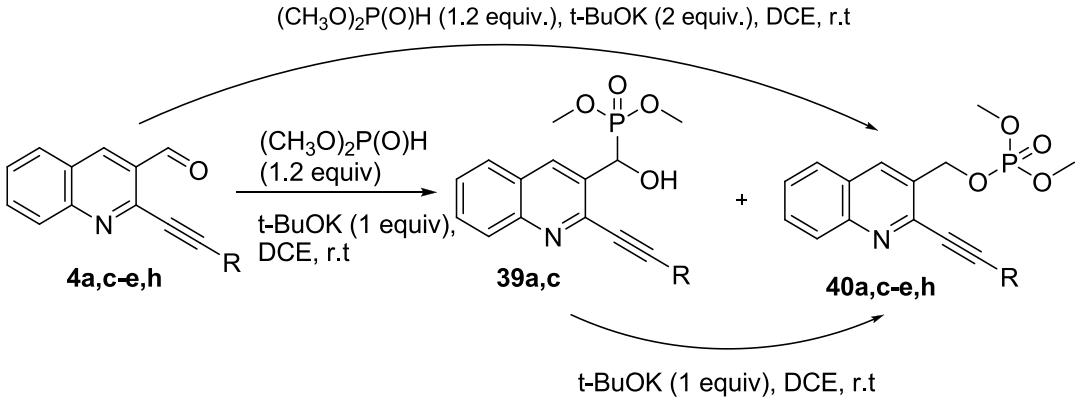
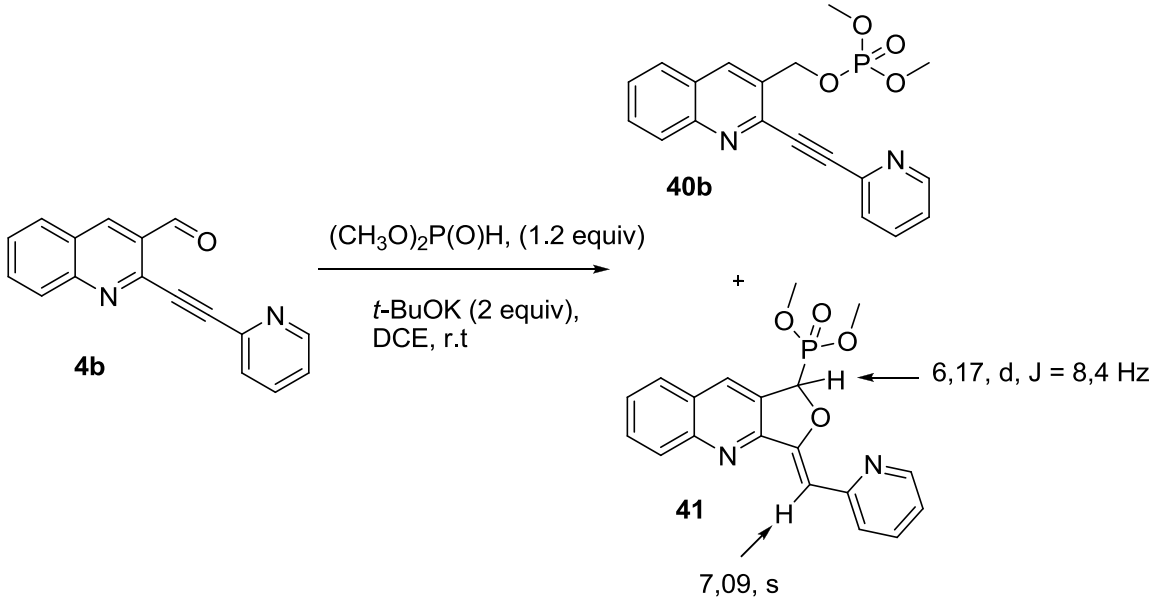


Table 22. Reaction of 2–alkynylquinoline–3–carbaldehydes with dimethylphosphite.

Entry	Starting compound	Product		Yield, %	
		addition	rearrangement	**39**	**40**
1	**4a**	**39a**	**40a**	85[a]	55[b]
3	**4c**	**39c**	**40c**	40[a]	75
4	**4d**	–	**40d**	–	50
5	**4e**	–	**40e**	–	70
6	**4h**	–	**40f**	–	45

[a] $(CH_3O)_2P(O)H$ (1.2 equiv.), *t*–BuOK (1 equiv.), DCE, r.t. 10min.
[b] Compounds **39a,c** treated with *t*–BuOK(1 equiv.), DCE, r.t. 10min.
[c] $(CH_3O)_2P(O)H$ (1.2 equiv.), *t*–BuOK (2 equiv.), DCE, r.t. 10min.

However, to our pleasant surprise, when 2–(2–pyridinylethynyl)quinoline–3–carbaldehyde **4b** was treated by dimethylphosphite in the presence of potassium *tert*–butoxide in dichloroethane at room temperature the formation of cyclized product **41** took place. We also observed the formation of small amount of phosphonate–phosphate rearrangement **40b** (less than 10 %).

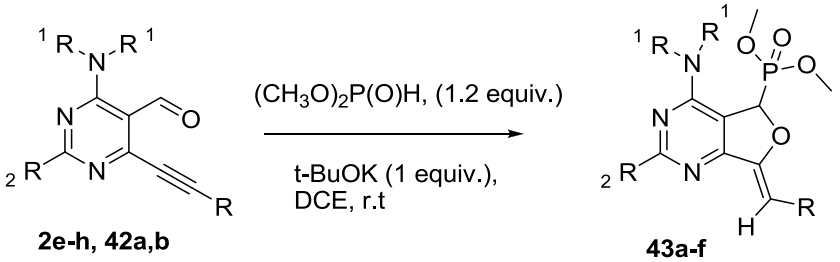


In the ^{1}H NMR spectrum of **41** there were two doublets of diastereotopic methoxy groups at 3.64 and 3.93 ppm, respectively. The signal of proton at C–1 of dihydrofurane ring appeared as doublet at 6.17 ppm with coupling constant 8.4 Hz. The proton of ethene moiety appeared as a singlet at 7.09 ppm. Neither ^{13}C NMR, nor IR spectra showed the presence of C≡C bond. These data together with HSQC, HMBC, TOCSY spectra and molecular formula obtained by HRMS confirmed the structure of **41**.

Therefore, we assumed that activation of the triple bond by electron withdrawing quinoline and pyridine moieties in the starting compound **4b** is sufficient for enabling tandem cyclization reaction.

It is obvious, that the triple bond of the starting pyrimidine substrates **2** is more activated due to the electron deficient pyrimidine moiety and its formyl group, so we envisioned that the pyrimidines **2** could be able to undergo the smooth tandem cyclization process with dimethylphosphite in basic media. Indeed, after the treatment of starting compounds **2e-h, 42a,b** with dimethylphosphite and potassium *tert*–butoxide in dichloroethane at room temperature, the smooth and regioselective reactions were observed by TLC. Transformations of starting compounds completed in 30 min. when 1 equiv. of base was used. Moreover, we did not succeed to isolate the Pudovik addition intermediates from the reaction mixtures. This fact indicated that during the treatment of 6–alkynylpyrimidine–5–carbaldehydes **2e**–**h, 42a,b** with dimethylphosphite in basic media, the tandem nucleophilic addition – cyclizations reactions took place. Results are summarized in Table 23.

In the ^{1}H NMR spectra of compound **43b** there were a singlet at 5.93 ppm and a doublet at 6.52 ppm (J = 3.6 Hz) along with two doublets of nonequivalent methoxy groups at 3.58 ppm and 3.83 ppm. ^{13}C NMR, IR and HRMS spectra also confirmed these results. Moreover slow crystallization of **43b** from chloroform provided single crystals suitable for the X–ray crystallographic analysis, which enabled the outcome of the reaction to be elucidated unambiguously (Figure 1).



2e-h, 42a,b **43a-f**

Table 23. Data of synthesis of 2,4–disubstituted (*Z*)–dimethyl–7–benzylidene–5,7–dihydrofuro[3,4–*d*]pyrimidin–5–ylphosphonate **43a–f.**

Entry	Starting compound				Product	Yield, %
		R	R^1	R^2		
1	**2e**	Ph	$N(C_2H_5)_2$	SCH_3	**43a**	**55**
2	**2f**	4–$CH_3C_6H_4$	$N(C_2H_5)_2$	SCH_3	**43b**	**46**
3	**2g**	4–$C_2H_5C_6H_4$	$N(C_2H_5)_2$	SCH_3	**43c**	**60**
4	**2h**	Ph	$N(CH_2)_2O$	SCH_3	**43d**	**80**

5	**42a***	Ph	$N(CH_2)_2O$	H	**43e**	**71**
6	**42b***	Ph	$N(CH_2)_4$	H	**43f**	**75**

*Compounds **42a** and **42b** where synthesized in our laboratory.

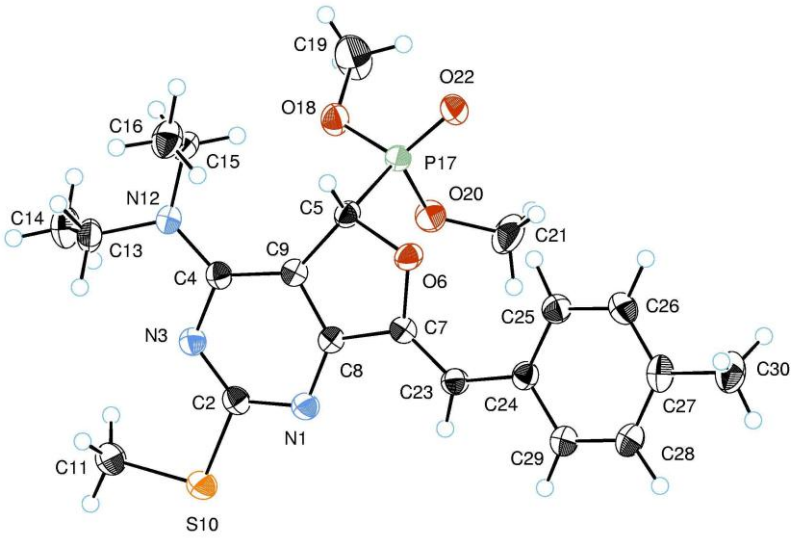


Figure 1. ORTEP drawing of compound **43b**.

It is noteworthy, that compound **2j** bearing secondary ethylamino or anilino group in position 4 of the pyrimidine ring did not undergo cyclization reactions with dimethylphosphite. In both these cases the starting materials were recovered after the work–up of reaction mixtures. We suppose, that compound **2j** exists in the unfavorable conformation where carbonyl group is turned towards the NHR moiety to form intramolecular hydrogen bond and directed away from the C≡C bond, therefore tandem reactions become impossible. The same consistent pattern we observed during investigation of tandem reactions of 4–alkynylpyrimidine–5–carbaldehydes with alcohols in basic media.

So it can be concluded that the outcome of the reactions between dimethylphospite and 3–alkynylquinoline–2–carbaldehydes or 6–arylethynylpyrimidine–5–carbaldehydes is dictated by the electron density on the alkyne moiety. Electron rich substrates undergo classic Pudovik reaction followed by phoshonate – phosphate rearrangement. On the other hand, when the triple bond of the starting materials is activated by electron withdrawing heterocycles, the novel tandem 5–*exo*–dig cyclization reactions take place.

Conclusions

1. A novel, concise, and environmentally friendly synthetic method of pyrido[4,3–*d*]pyrimidine framework *via* thermal or microwave–induced cyclization of 2,4–disubstituted 6–arylethynylpyrimidine–5–carbaldehydes with *tert*–butylamine was developed.

2. A novel and fast synthetic method for preparation of 2,3–disubstituted 1,2–dihydro–1–(trichlormethyl/tribrommethyl)benzo[*b*][1,6]naphthyridines by means of a three–component reaction between 2–alkynylquinoline–3–carbaldehydes, primary amines and chloroform/bromoform was proposed. Moreover, 2–alkynylquinoline–3–carbaldehydes react with dimethylphosphite and aromatic amines in the presence of copper (I) iodide and the corresponding dimethyl 2,3–disubstituted 1,2–dihydrobenzo[*b*][1,6]naphthyridin–1–ylphosphonates formed.

3. A novel, efficient and powerful methyl mercaptoacetate triggered benzannulation reaction was described**.** The reaction does not require metal–catalysts and moreover – it is really unique method of the synthesis of benzoannelated heterocycles, since the key step is formation of benzene ring instead of usual heterocyclic ring formation.

4. 4–*N*,*N*–dialkylamino–2–methylthio–6–phenylethynylpyrimidine–5–carbaldehydes and 2–alkynylquinoline–3–carbaldehydes underwent smooth and regioselective 5–*exo*–dig acetalisation–cyclization reaction to 4–*N*,*N*–dialkylamino–5–methoxy–2–methylthio–(7*Z*)–7–benzylidene–5,7–dihydrofuro[3,4–*d*]pyrimidines and 3(*Z*)–alkynyliden–1–methoxy–1,3–dihydrofuro[3,4–*b*]quinolines in the presence of potassium alkoxide in methanol. 6–Phenylethynylpyrimidine–5–carbaldehydes bearing NHR group in position 4 of the pyrimidine ring undergo 5–*exo*–dig acetalisation–cyclization reaction only in the presence of an equivalent of base and 5 mol% of silver (I) nitrate or silver (I) trifluoroacetate.

5. 4–*N*,*N*–dialkylamino–2–methylthio–6–phenylethynylpyrimidine–5–carbaldehydes and 2–alkynylquinoline–3–carbaldehydes underwent smooth and regioselective 6–*endo*–dig acetalisation–cyclization reaction in the presence of 5 mol% of silver (I) nitrate in methanol. 6–Phenylethynylpyrimidine–5–carbaldehydes bearing NHR group in position 4 of the pyrimidine ring undergo 6–*endo*–dig acetalisation–cyclization reaction in the presence of 5 mol% of silver (I) nitrate or silver (I) trifluoroacetate in methanol.

6. A short and efficient synthesis of 2–(2–oxoethyl)–1*H*–indole–3–carbaldehydes *via* a tandem 6–*endo*–dig cyclization process followed by smooth hydrolysis from 2–alkynyl–1*H*–indole–3–carbaldehydes in the presence of 5 mol% $AgNO_3$ in methanol was developed.

7. It was found that 2–alkynylquinoline–3–carbaldehydes react with dimethylphosphite in basic media to produce dimethyl hydroxy–(2–alkynylquinolin–3–yl)methylphosphonates which can rearrange to dimethyl (2–alkynylquinolin–3–

yl)methyl phosphates. However 2–(pyridin–2–ylethynyl)quinoline–3–carbaldehyde and 2,4–disubstituted–6–arylethynylpyrimidine–5–carbaldehydes with dimethylphosphite in basic media underwent smooth and regioselective 5–*exo*–dig cyclization reaction.

THE LIST OF ORIGINAL PUBLICATIONS

Manuscripts in ISI journals:

1. R. Buksnaitiene, I. Cikotiene; A facile and efficient synthesis of 1–trichloromethyl–1,2–dihydrobenzo[*b*][1,6]naphthyridines *via* three–component reaction among 2–alkynylquinoline–3–carbaldehydes, primary amines, and chloroform. *Heterocycl. Commun.* **2012**, *18(2)*, 87 – 92.
2. R. Buksnaitiene, I. Cikotiene, Novel synthetic method of 2–(2–oxoethyl)–1*H*–indole–3–carbaldehydes; *Synlett*, **2011**, *17*, 2529–2532.
3. I. Cikotiene, R. Buksnaitiene, R. Sazinas, A. Nebylica; Rapid access to benzo–annelated heterocycles, naphthalenes and polysubstituted benzenes through a novel benzannulation reaction; *Tetrahedron*, **2011**, *67*, 706 – 717.
4. I. Cikotiene, R. Buksnaitiene, S. Rudys, M. Morkunas, D. Motiejaitis; Tandem reactions of 6–phenylethynylpyrimidine–5–carbaldehydes with alcohols: regioselective synthesis of 5–alkoxy–(7*Z*)–7–benzylidene–5,7–dihydrofuro[3,4–*d*]pyrimidines and 5–alkoxy–7–phenyl–5*H*–pyrano[4,3–*d*]pyrimidines, *Tetrahedron*, **2010**, *66*, 251 – 258.
5. I. Cikotienė, V. Kairys, R. Buksnaitiene, M. Morkunas, S. Rudys, A. Brukstus, M. X. Fernandes; Study on the cyclization of 6–arylethynylpyrimidine–5–carbaldehides with *tert*–butylamine: microwave versus thermal preparation of pyrido[4,3–*d*]pyrimidines., *Tetrahedron*, **2009**, *65*, 5752 – 5759.
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1. R. Buksnaitiene, R. Sazinas, A. Urbanaitė, I. Cikotiene, Synthesis of benzo–annelated heterocycles, naphthalenes and polysubstituted benzenes *via* methylmercaptoacetate triggered benzanullation reaction. In *"Balticum Organicum Syntheticum"* abstract, Estonia, Tallinn, **2012**, p.18
2. R. Buksnaitiene; I. Cikotiene; Synthesis of 1.2–dihidrobenzo[*b*][1,6]naphthyridines *via* multikomponent reactions between 2–alkynylquinoline–3–carbaldehides, primary amines and *pro*–nucleofiles., In *"14th Blue Danube Symposium on Heterocyclic Chemistry"*abstract, **2011**, Slovakia, Podbanske, p.44.
3. I. Cikotiene, R. Buksnaitiene, E. Pudziuvelyte, I. Zutautaite, R. Sazinas, D, Motiejaitis, A. Brukstus, Synthesis of different heterocycles *via*

transformations of functionally substituted alkynes. In *"24th European colloquium on Heterocyclic Chemistry"*abstract, **2010**, Austria, Vienna, OP – 8.

4. R. Buksnaitiene, A. Nebylica, A. Sazinas, I. Cikotiene; Synthesis of furane and pyrane nucleus containing heterocycles *via* tandem acetalisation–cycloisomerisation reactions., In *"Balticum Organicum Syntheticum"* abstact, **2010**, Latvia, Riga, p.65 (Thieme poster prize).

5. I. Cikotiene, R. Buksnaitiene, E. Pudziuvelyte, C. Ríos-Luci, L. G. León, J. M. Padrón, V. Lather and M. X. Fernandes, Intramolecular cyclizations of some alkynylazines and synthesis of novel antitumor compounds. In *"13th Blue Danube Symposium on Heterocyclic Chemistry"* abstract, **2009**, Slovenia, Bled, Oral Communication 4, p. 48.

6. I. Cikotiene, M. Morkunas, S. Rudys, R. Buksnaitienė, A. Brukstus; Novel and efficient synthesis of 7–arylpyrido[4,3–*d*]pyrimidines.,In *"Balticum Organicum Syntheticum"* abstract, **2008**, Lithuania, Vilnius p.73.

Abstracts of the national conferences

1. R. Bukšnaitienė; I. Čikotienė; Heterociklinių junginių, turinčių gretimose padėtyse etinil– ir formilfragmentus, intramolekulinės ciklizacijos reakcijos. In "*Organinė chemija*" abstract, Kaunas **2012**, p.12.

2. R. Bukšnaitienė; I. Čikotienė; 2–(2–Oksoetil)–1*H*–indol–3–il–karbaldehidų sintezė. In "*Organinė chemija*" abstract, Kaunas **2011**, p.43.

3. R. Bukšnaitienė, I. Čikotienė; Heterociklinių junginių, turinčių gretimose padėtyse etinil– ir formilfragmentus, ciklizacijos reakcijos., In*"Organinė chemija"* abstract, Kaunas, **2010**, p.33.

4. R. Bukšnaitienė, M. Morkūnas, I. Čikotienė; Nauja benzanuliavimo reakcija naudojant metilmerkaptoacetatą: efektyvi chinazolinų ir akridinų sintezė. In *"Organinė chemija"* abstract, Kaunas **2009**, p.13.

HETEROCIKLINIŲ JUNGINIŲ, GRETIMOSE PADĖTYSE TURINČIŲ ETINIL– IR FORMILFRAGMENTUS, CIKLIZACIJOS REAKCIJŲ TYRIMAS

Santrauka

Aromatiniai junginiai gretimose padėtyse turintys funkcines alkinil– ir formilgrupes yra vertingi įvairioms karbo– ir heterosistemoms sintetinti. Literatūroje aprašyta daug įvairių metodų leidžiančių sintetinti indolų, benzfuranų, benzpiranų, izokumarinų, indenonų, izochinolinų, policiklinių aromatinių angliavandenilių bei daugelio kitų ciklinių sistemų darinius. Dauguma tokių reakcijų vyksta esant pereinamųjų metalų katalizatoriams, kurie, sudarydami tarpinį C≡C ryšio ir metalo kompleksą, sumažina trigubojo ryšio elektronų tankį, dėl ko *orto*–padėtyje esanti funkcinė grupė gali nukleofiliškai atakuoti vieną iš C≡C ryšio anglies atomų.

Mūsų laboratorijoje anksčiau atlikti tyrimai parodė, kad kai kurie azinai turintys gretimose padėtyse funkcines alkinil– ir formil–, imino– arba nitrogrupes dalyvauja kiek neįprastose ciklizacijos reakcijose esant įvairiems nukleofiliniaims reagentams (aminams, alkoholiams, tioliams, *C*–pronukleofilams). Pastarosios reakcijos vyksta pakankamai švelniomis sąlygomis, o taip pat nenaudojant katalizatorių. Šis išskirtinis reakcijų bruožas, lyginant su *orto*–pakeistų alkinilbenzeno darinių chemija, gali būti paaiškintas elektronų akceptorinėmis azinų savybėmis, kurių dėka yra aktyvuojamas C≡C ryšys. Kita vertus, buvo pastebėta, kad katalizatoriaus panaudojimas gali iš esmės pakeisti reakcijos kryptį ir regioselektyvumą. Literatūroje duomenų apie heterociklinių junginių, gretimose padėtyse turinčių etinil– ir formilfragmentus, chemines savybes nėra labai daug. Šių priežasčių ir laboratorijoje gautų preliminarių tyrimų rezultatų paskatinti, nusprendėme nuodugniau ir plačiau ištirti heterociklinių junginių, turinčių gretimose padėtyse C≡C ryšį ir formilgrupes, intramolekulines bei multikomponentines ciklizacijos reakcijas. Atsižvelgiant į tai buvo suformuluotas *šio darbo tikslas* – ištirti heterociklinių junginių, gretimose padėtyse turinčių etinil– ir formilfragmentus, ciklizacijos reakcijas su įvairiais nukleofiliniais reagentais (aminais, alkoholiais, tioliais, *C*–pronukleofilais ir dimetilfosfitu), pasiūlyti galimus šių virsmų mechanizmus ir pritaikyti gautus dėsningumus kondensuotų heterociklinių junginių sintezėje.

Šio darbo metu rastas naujas ir efektyvus pirido[4,3–*d*]pirimidinų sintezės būdas kurio esmė yra 4–ariletinil–5–pirimidinkarbaldehidų terminė ar mikrobangų inicijuojama reakcija su *tret*–butilaminu be papildomų katalizatorių ar elektrofilinių iniciatorių.

Parodyta, kad 2–alkinilchinolin–3–karbaldehidai dalyvauja trikomponentinėse reakcijose su pirmininiais aminais ir *C*–pronukleofilais (chloroformu ir bromoformu) sudarydami 1,2–dihidrobenzo[*b*][1,6]naftiridinus. Taip pat 2–

alkinilchinolin–3–karbaldehidai reaguoja su dimetilfosfitu ir aromatiniais aminais, esant vario (I) jodido sudarydami 1,2–dihidrobenzo[*b*][1,6]naftiridin–1–ilfosfonatus.

Pasiūlytas naujas, universalus ir efektyvus būdas benzanuliuotoms sistemoms sintetinti panaudojant metilmerkaptoacetato kalio druską metanolyje.

Rasti regioselektyvūs būdai 5,7–dihidrofuro[3,4–*d*]pirimidinų ir 5(*H*)–pirano[4,3–*d*]pirimidinų sintezei iš 2,4–dipakeistų 6–alkinilpirimidin–5–karbaldehidų ir alkoholių tandeminių 5–*egzo*–dig ir 6–*endo*–dig ciklizacijos reakcijų pagalba. Analogiškų reakcijų metu regioselektyviai iš 2–alkinilchinolin–3–karbaldehidų ir alkoholių susintetinti 1,3–dihidrofuro[3,4–*b*]chinolinai ir 1*H*–pirano[4,3–*b*]chinolinai.

Rastas efektyvus būdas 2–(2–oksoetil)–1*H*–indol–3–karbaldehidams sintetinti iš 2–alkinil–1*H*–indol–3–karbaldehidų, būdo esmė – pradinių junginių sąveika su metanoliu, esant sidabro katalizatoriams.

Parodyta, kad 2–alkinilchinolin–3–karbaldehidai reaguodami su dimetilfosfitu bazinėje terpėje sudaro prisijungimo produktus dimetil–hidroksi–(2–(pakeistus)chinolin–3–il)metilfosfonatus. Pastarieji junginiai, esant bazės pertekliaus, persigrupuoja į atitinkamus dimetil–(2–(pakeistus)chinolin–3–il)metilfosfatus. Tuo tarpu elektronų akceptorinėmis savybėmis pasižymintys 2–(2–piridinil)etinilchinolin–3–karbaldehidas ir 6–ariletinilpirimidin–5–karbaldehidai reaguodami su dimetilfosfitu analogiškomis sąlygomis sudaro fosforą savo sudėtyje turinčius 5–*egzo*–dig ciklizacijos produktus.

CURRICULUM VITAE

Surname, name: Rita Bukšnaitienė

Birth date and place: 25 April, 1982, Panevėžys

Education:

2000 Graduation certificate of secondary school.

2000 – 2004 Faculty of chemistry, Vilnius University. Graduation thesis for *Bachelor degree*: "Novel synthetic way of 4–amino–7–aryl–2–methylthiopyrido[4,3–*d*]pyrimidines"

2004 – 2007 Faculty of chemistry, Vilnius University. Graduation thesis for *Master degree:* "Pyrido[4,3–*d*]pyrimidine synthesis from 4–aryethynylpyrimidine–5–carbaldehydes"

2008 – 2012 Department of Organic chemistry, Faculty of chemistry, Vilnius University. Doctoral studies.

Participation in research projects:

2009 *"Alkynylazines: investigation of intramolecular cyclizations and use in the synthesis of novel antitumour compounds"* The research was funded by the State Science and Studies Foundation. Grant No. T – 67/09.

2011 – 2015 *"An integrated discovery of novel anti – cancer compounds: from fundamental researches to purposeful modeling and synthesis"* The research was funded by the European Social Fund under the Global Grant measure. Grant No. VP1–3.1–SMM–07–K–01–002.

Other information:

Research areas: Synthesis of pyrimidine, quinoline, indole and thiophene derivatives, heterocyclic chemistry.

Foreign languages: Russian, English.