VILNIUS UNIVERSITY

STATE RESEARCH INSTITUTE CENTER FOR PHYSICAL SCIENCES AND TECHNOLOGY

RITA MAŽEIKAITĖ

SEARCH FOR SYNTHETIC METHODS OF COMPOUNDS CONTAINING THIOPHENE, INDOLE AND PYRAZOLE FRAMEWORK

SUMMARY OF DOCTORAL DISSERTATION

Physical sciences, chemistry (03P)

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The research was accomplished in State research institute Center for Physical Sciences and Technology in period of 2010 – 2014.

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VILNIAUS UNIVERSITETAS

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RITA MAŽEIKAITĖ

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Contents

Introduction 6

Results and discussion 10

Synthesis of 2,3-disubstituted thiophene derivatives 10

Synthesis of substituted 4-(1H-indol-3-yl)butylpiperazine derivatives 12

Synthesis of substituted pyridine moiety containing compounds for further modification of 1*H*-pyrazole derivatives 17

Synthesis of substituted *1H*-pyrazole derivatives 19

Results and conclusions 29

Santrauka 31

List of publications 33

Curriculum vitae 35

Introduction

Compounds containing thiophene, indole and pyrazole framework often possess important properties that are widely applied in practice. Substituted thiophene derivatives containing electron-withdrawing substituents and pyrazole complexes with metals represent classes of active optical materials, such as organic light emitting diodes. Moreover, thiophene, indole and pyrazole frameworks can be often found in various biologically active compounds. For example, some time ago, a non-selective histone deacetylase inhibitor (HDAC) Panobinostat (LBH-589) bearing indole moiety and hydroxamic acid functionality was developed. Synthesis of functionally substituted thiophene, indole and pyrazole derivatives is a highlighting task, since this modification opens possibility for construction of new heterocyclic systems.

In these investigations we put our attention on the development of efficient synthetic methods for preparation of 2,3-disubstituted thiophenes, substituted 3-[4-(piperazin-1-yl)butyl]-1*H*-indoles and 3-substituted pyrazoles. First, we envisioned three main problems associated with the synthesis of these classes' compounds and their plausible solutions:

1. 2,3-Disubstituted thiophenes are usually synthesized from 3-halogeno-2-substituted thiophene derivatives obtained by modification of the 2nd thiophene ring position of corresponding 3-substituted thiophenes. But it should be noted that this methodology is not very selective and sometimes modification at the 5th position takes place. Having an ortho orienting group at 3rd position of thiophene ring, a selective modification of the second position becomes possible by direct lithiation. Synthesis of 2,3-disubstituted thiophenes from 2-halogenothiophene derivatives by protecting the 5th position and then selective introduction of nitro functional group at 3rd position, looks much more acceptable and allows further modification of both 2nd and 3th positions of thiophene ring.

2. 3-[(Piperazin-1-yl)alkyl]-1*H*-indole derivatives are often synthesized by modification of mono-substituted piperazine with 1*H*-indol-3-yl-alkyl halides, mesylates or tosylates. But availability of mono-substituted piperazine derivatives is limited and their synthesis is rather complicated. Our main focus was in 3-[4-(piperazin-1-yl)butyl]-1*H*-

indole derivatives, because of not only for their structural similarity to Panobinostat (LBH-589), but also the synthesis of 3-[(piperazin-1-yl)alkyl]-1*H*-indoles with longer than propyl chain is not fully investigated. Thus, we chosed commercially available 4-(1*H*-indol-3-yl)butanoic acid as starting material for the synthesis of 3-[4-(piperazin-1-yl)butyl]-1*H*-indole. And by further modification of free NH group of piperazine ring, higher variety of substituted 3-[4-(piperazin-1-yl)butyl]-1*H*-indole derivatives can be synthesized.

3. Electrophilic substitution of pyrazole ring usually occurs at the 4th position. Thus, one of the most common approaches for the synthesis of 3-substituted pyrazoles is based on formation of the pyrazole ring via condensation reaction of substituted 1,3-dicarbonyl derivatives with hydrazine. Unfortunately, this method usually generates mixture of regioisomers and cause problems with isolation of products. Moreover, only limited number of dicarbonyl compounds are readily available. Another approach for the synthesis of 3-substituted pyrazoles is by transition metal catalyzed cross-coupling reactions of 3-halogeno or 3-organometalic pyrazole derivatives. 3-Br(Cl or I)-1*H*-pyrazole derivatives are commercial available but very expensive and availability of 3-halogen-1*H*-pyrazole derivatives with substituents at the 4th or 5th positions is very limited due to their complicated synthesis. Pyrazoles readily form complexes with transition metals so before performing cross-coupling reactions of 3-halogeno-1*H*-pyrazoles, it is necessary to protect free NH group. Thus, transition metal-catalyzed cross-coupling reactions are usually carried out using *N*-alkyl-, *N*-aryl or *N*-benzylpyrazoles. We decided to find simple and effective method for the synthesis of 4- or 5-substituted 3-halo-1*H*-pyrazoles protected by easy removable *tert*-butyloxycarbonyl (Boc), 2-ethoxyethyl-(EtOEt) or 2-tetrahydro-2*H*-pyranyl (THP) groups, because it can open possibilities for the synthesis of substituted pyrazoles with free NH group.

Considering the problems associated with synthesis of 2,3-disubstituted thiophenes, substituted 3-[4-(piperazin-1-yl)butyl]-1*H*-indoles and 3-, 4- and/or 5-substituted-1*H*-pyrazoles we have formulated the following main goals and tasks of this work:

The main goal of the present work:

To find new or to improve already known methods of the synthesis of 2,3-disubstituted thiophene, 3-[4-(piperazin-1-yl)butyl]-1*H*-indole and substituted 1*H*-pyrazle derivatives.

Main tasks for the achievement of the aims:

1. To find new or to improve already known methods for the synthesis of 2-halogeno-3-nitrothiophene derivatives and adapt them for the synthesis of 4*H*-thieno[3,2-*b*]indole via Suzuki-Miyaura cross-coupling reaction.

2. To create an universal method for the synthesis of 3-[4-(piperazin-1-yl)butyl]-1*H*-indole and, by functionalization of free piperazine ring NH group, to synthesize a series of *N*-substituted 3-[4-(piperazin-1-yl)butyl]-1*H*-indoles for antitumor activity studies.

3. To synthesize a set of substituted 2-halogenopyridine derivatives for investigation of cross-coupling reactions of pyrazole derivatives.

4. To find effective methods for the synthesis of substituted 3- and 4-halogeno-1*H*-pyrazoles. To select an appropriate protecting group for the pyrazole ring free NH group and to synthesize a set of *N*-protected 3-halogeno-1*H*-pyrazole derivatives for the further modification of the pyrazole ring.

5. To apply a palladium catalyzed cross-coupling reactions for effective synthesis of 3-substituted 1*H*-pyrazole derivatives.

Scientific novelty and practical advantage:

1. Synthetic method of 2-halogeno-3-nitrothiophene as well as Suzuki-Miyaura cross-coupling reaction of 2-bromo-3-nitrothiopfene with phenylboronic acid was optimized. By-product of the synthesis of 4*H*-thieno[3,2-b]indole was investigated.

2. Synthetic method of 3-[4-(1-piperazinyl)butyl]-1*H*-indole was optimized. Alkylation possibilities of free NH group of piperazine ring in 3-[4-(1-piperazinyl)butyl]-1*H*-indole were demonstrated.

3. For the evaluation of antitumor activity a series of hydroxamic acids were prepared from 3-[4-(1-piperazinyl)butyl]-1*H*-indole *N*-alkyl esters.

4. Selective and effective synthetic methods of 3-iodo(bromo or nitro)-4-bromo(iodo or nitro)-*1H*-pyrazole derivatives as well as 1-ethoxyethyl- 3-, 4- or 5-1*H*-pyrazole carbaldehydes were discovered.

5. It was found that ethoxyethyl protecting group selectively protects N-H bond of the pyrazole ring and products may be used in cross-coupling, Grignard and *ortho*-lithiation reactions. During protection reaction of 3,4- or 3,4,5-substituted pyrazoles, migration of the protecting group by forming most stable position isomer was observed. Optimal rearrangement of 4-substituted 1-ethoxyethyl-1*H*-pyrazole-5-carbaldehydes to 4-substituted 1-ethoxyethyl-1*H*-pyrazole-3-carbaldehydes conditions were determined.

6. It was found that during Grignard reaction of 1-(1-ethoxyethyl)-3,4-diiodo-1*H*-pyrazole with ethylmagnesium bromide at -10 ºC, iodo-magnesium exchange reaction mainly occurs at 4th position of the pyrazole ring.

7. Sonogashira cross-coupling reaction was applied for substituted 1-ethoxyethyl-3-iodo-1*H*-pyrazole derivatives. The scope and limitations of this methodology were determined.

8. Possibilities of synthesis of 2-(1*H*-pyrazol-5-yl)pyridine derivatives via Negishi cross-coupling reaction using 1-ethoxyethyl-1*H*-pyrazole or pyridine zinc organic compounds were examined.

9. Synthetic possibilities of *N*-protected and containing free NH group 3-aryl and 3-alkynylpyrazole derivatives were extended.

Main statements for the defense:

1. Negishi and Sonogashira cross-coupling reactions for the synthesis of 3-substituted 1*H*-pyrazole derivatives from corresponding *N*-protected 1*H*-pyrazole derivatives can be applied.

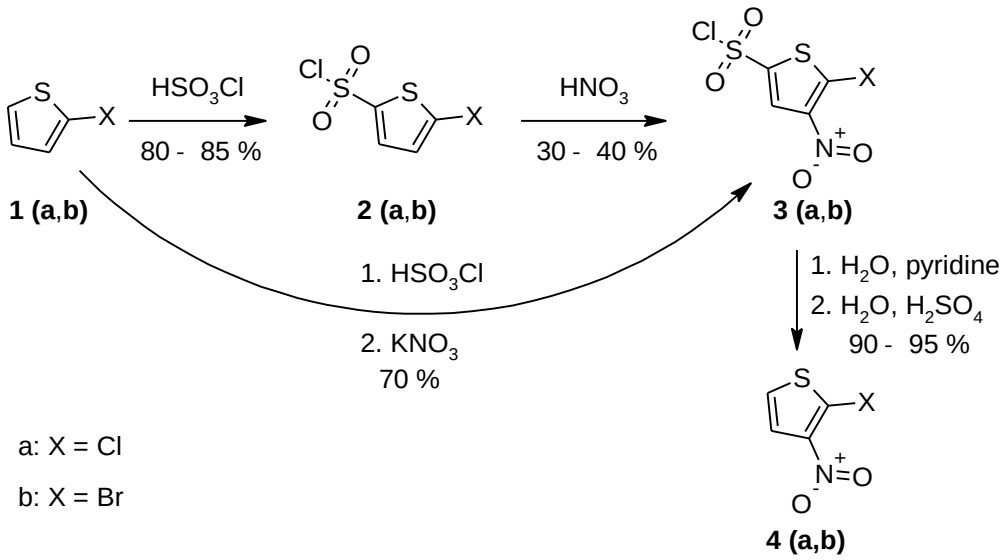
2. Ethoxyethyl group can be used for protection of 1*H*-pyrazole derivatives in the cross-coupling reactions, Grignard reactions and reaction with lithium organic compounds. The employment of ethoxyethyl group enables the synthesis of new substituted 1*H*-pyrazole derivatives containing free NH group.

3. Ethoxyethyl protecting group of 1*H*-pyrazole derivatives tends to migrate in mild acidic conditions by forming most stable position isomer. This migration happens in presence of catalytic amount of trifluoroacetic acid and 0,1 equivalent of ethyl vinyl ether, almost quantitatively and opens the ways for the synthesis of new 3,5-disubstituted-1*H*-pyrazole derivatives.

Results and discussion

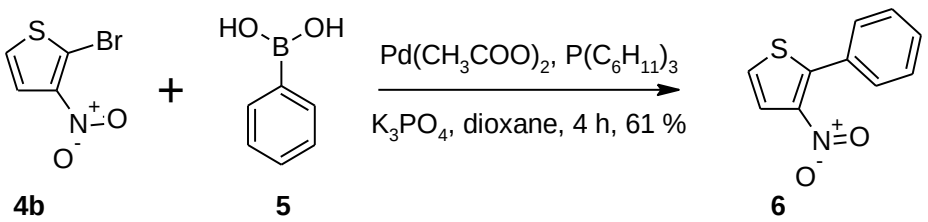
Synthesis of 2,3-disubstituted thiophene derivatives

Synthesis of 5-chloro(bromo)-4-nitrothiophene-2-sulfonyl chlorides **3a,b**, starting from 2-chloro(bromo)thiophenes **1a,b** was improved. It was found that by adding solid KNO_3 to chlorosulfonation reaction mixture, products **3a,b** were isolated in 70 % yield during one step synthesis without isolation of intermediates **2a** or **2b**. The desulfonation reaction resulted in formation of 2-chloro(bromo)-3-nitrothiopenes **4a,b** in high yields.



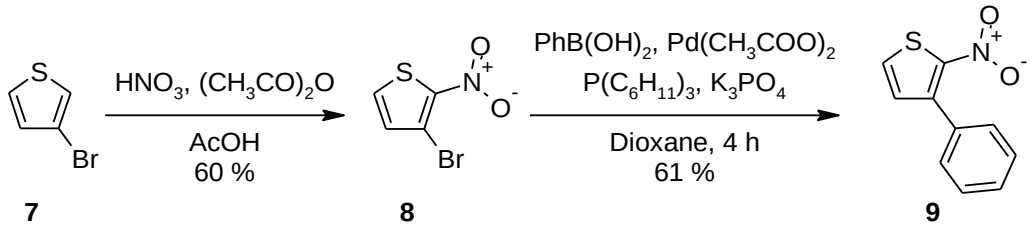
Scheme 1

The synthesis of 3-nitro-2-phenylthiophene (**6**) via Suzuki-Miyaura cross-coupling reaction starting from 2-bromo-3-nitrothiophene (**4b**) was improved.



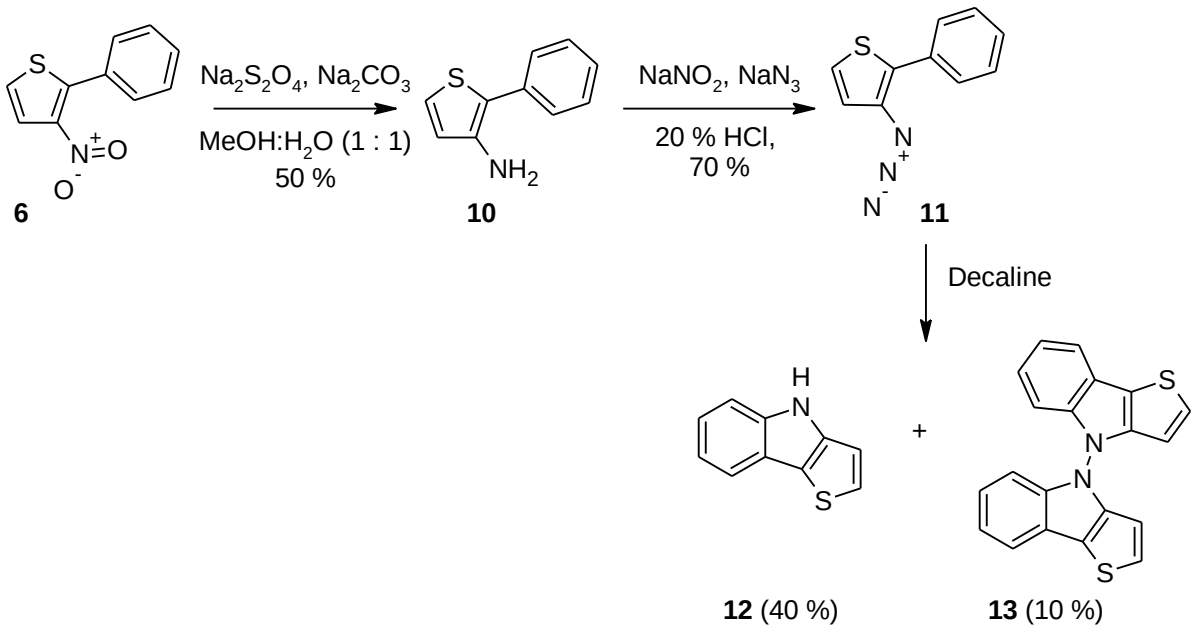
Scheme 1

3-Bromo-2-nitrothiophene (**8**) was synthesized by direct nitration of 3-bromothiophene (**7**) at the 2nd position of thiophene ring and applied in cross-coupling reaction with phenylboronic acid (**5**) resulting 2-nitro-3-phenyltiophene (**9**).



Scheme 2

Nitro group of 3-nitro-2-phenylthiophene (**6**) was reduced in mixture of methanol and water using sodium dithionite with sodium carbonate. Obtained 3-amino-2-phenylthiophene (**10**) was converted to azide **11** using standard Sandmeyer reaction procedure. Cyclization reaction of 3-azido-2-phenylthiophene (**11**) was performed in boiling decaline. Unfortunately, along with expected 4*H*-thieno[3,2-*b*]indole (**12**) its dimerization product **13** was formed. Due to the end of project further investigations of thiophene derivatives were suspended.

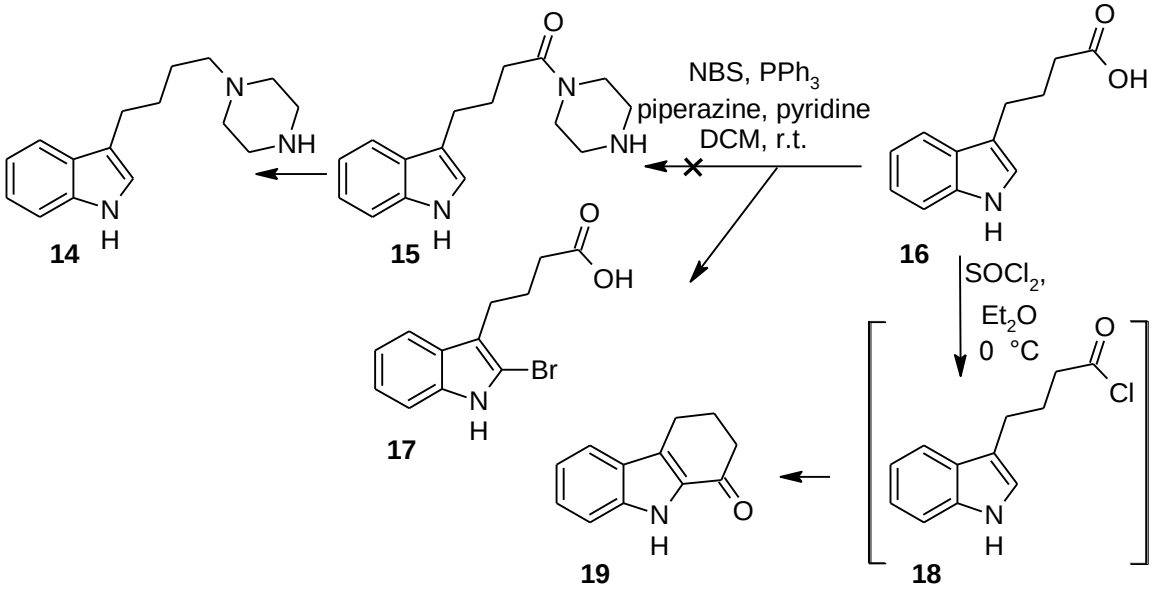


Scheme 3

In collaboration with Vilniaus University professor's Dr. I. Čikotienė laboratory, 2-bromo-3-nitrothiophene was used for Sonogashira cross-coupling reaction and the products have been applied for new thieno[2,3-c]isoxazole moiety-containing heterocyclic compounds synthesis.

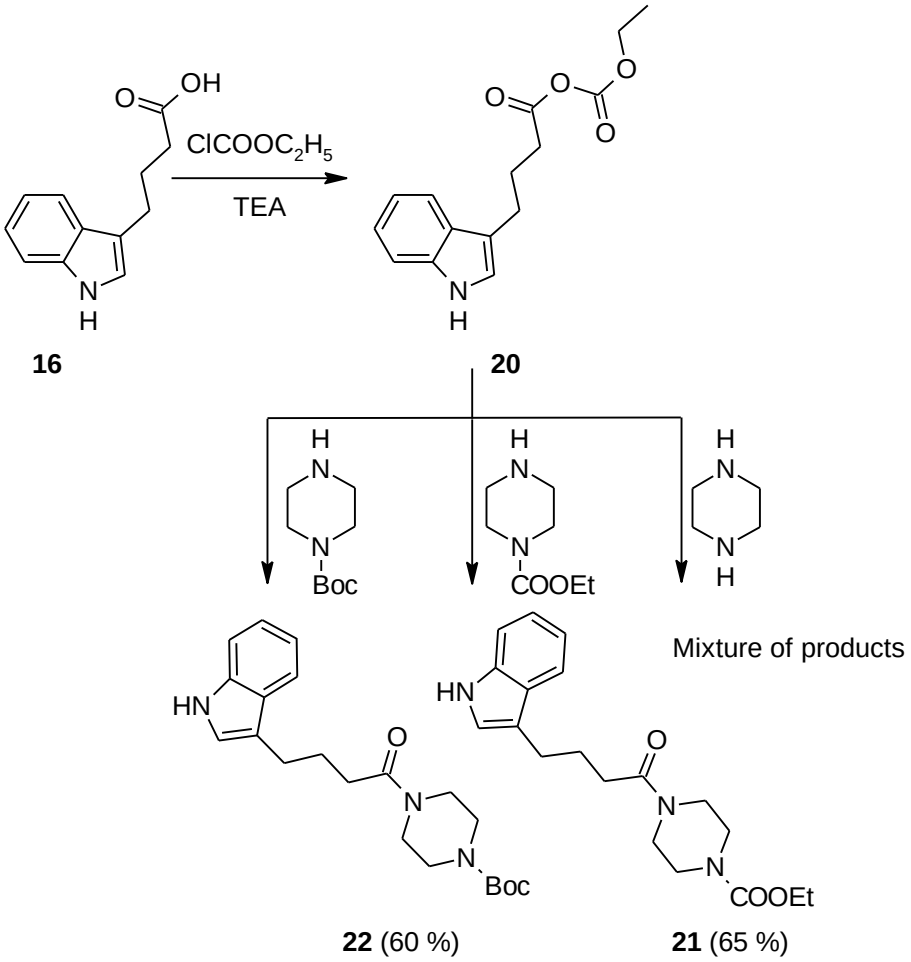
Synthesis of substituted 4-(1H-indol-3-yl)butylpiperazine derivatives

Several strategies for the synthesis of 4-(1*H*-indol-3-yl)butylpiperazine (**14**) were tested using 4-(1*H*-indol-3-yl)butanoic acid (**16**) as starting material. One of well-known methods for the synthesis of mono-acylpiperazine is the reaction of corresponding acids with excess of piperazine using *N*-bromosuccinimide (NBS) and triphenylphosphine. However, instead of expected 3-(4-oxo-4-piperazin-1-yl-butyl)-1*H*-indole (**15**) the product of bromination (4-(2-bromo-1*H*-indol-3-yl)butanoic acid) was isolated (**17**). Thus, another methodology, which involves the reaction between acyl chlorides with an excess of piperazine, was applied. The 4-(1*H*-indol-3-yl)butanoyl chloride (**18**) appeared to be quite unstable under reaction conditions and immediately participated in intramolecular acylation by forming 2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**19**).



Scheme 5

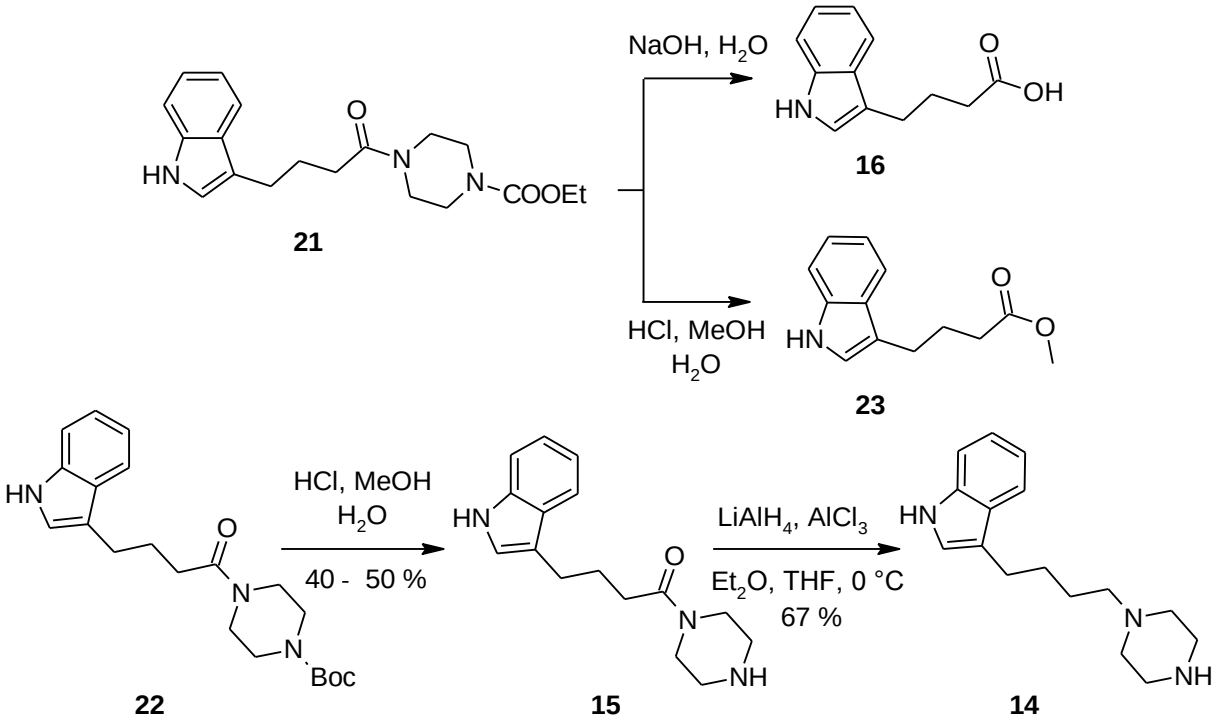
Therefore another active compound – ethyl 4-(1*H*-indol-3-yl)butanoyl carbonate (**20**) was synthesized by treating 4-(1*H*-indol-3-yl)butanoic acid (**16**) with ethylchloroformate and triethylamine. Treatment of compound **20** with the triple excess of piperazine resulted the formation of an inseparable mixture of products. Since product mixture did not contain even traces of target mono-acylpiperazine, protected piperazines were used in further investigations. Reaction of compound **20** with ethylpiperazine-1-carboxylate or *t*-butylpiperazine-1-carboxylate led to the formation of 1-protected 4-[4-(1*H*-indol-3-yl)butyl]piperazines **21** and **22** in moderate yields.



Scheme 6

Unfortunately, the hydrolysis of compound **21** both under basic and acidic conditions led to the formation of initial acid **16** or its methyl ester **23** and significant amount of tar-like side products. In contrast, the hydrolysis of *t*-butyl-4-[4-(1*H*-indol-3-yl)butanoyl]piperazine-1-carboxylate (**22**) was accomplished successfully. The hydrolysis

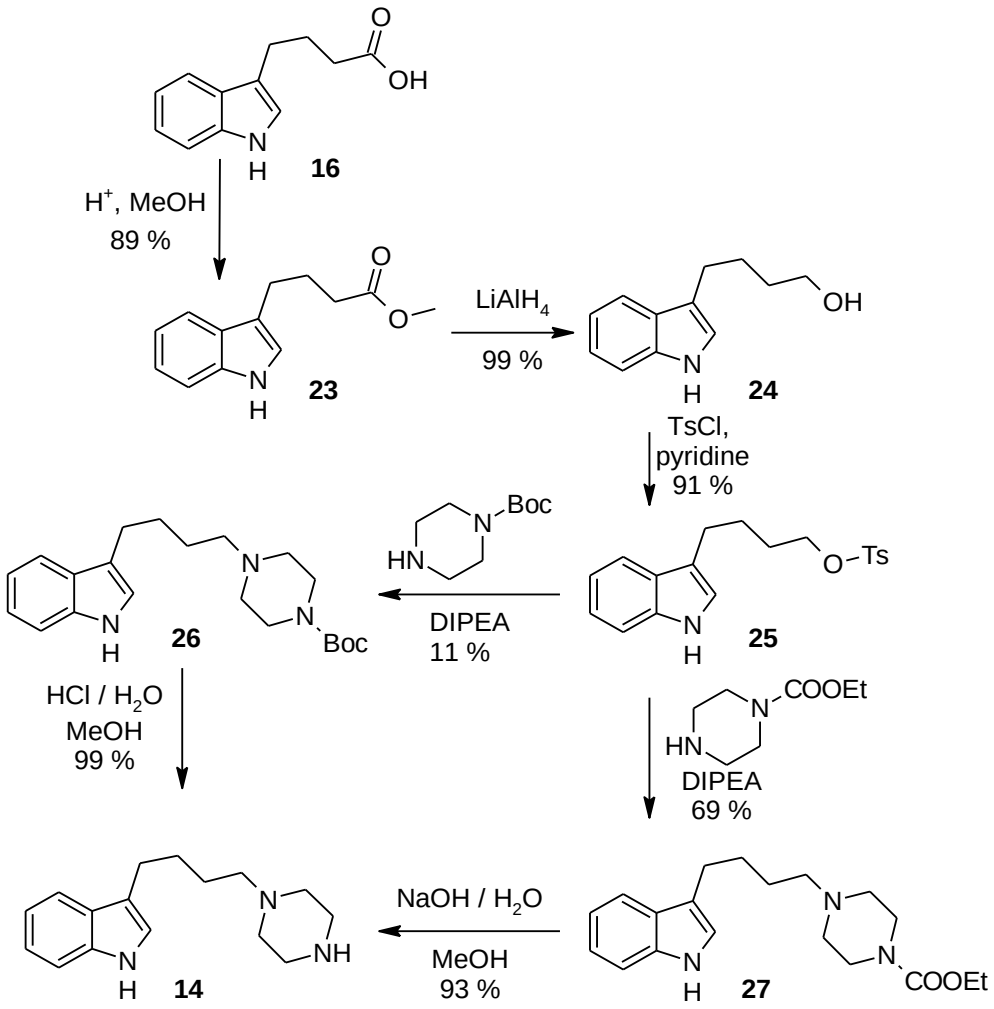
using catalytic amount of hydrochloric acid in methanol resulted quantitative yield of target 3-(4-oxo-4-piperazin-1-ylbutyl)-1*H*-indole (**15**) in milligram scale. The same reaction carried out in multi-gram scale yielded only 50 % of target compound **15**. Significant amount of the starting 4-(1*H*-indol-3-yl)butanoic acid (**16**) was isolated from the mixture. The reduction of compound **15** using lithium aluminum hydride was improved by adding equimolar amount of aluminum chloride. 3-[4-(1-Piperazinyl)butyl]-1*H*-indole (**14**) was isolated with 67 % yield (52 % yield without $AlCl_3$).



Scheme 7

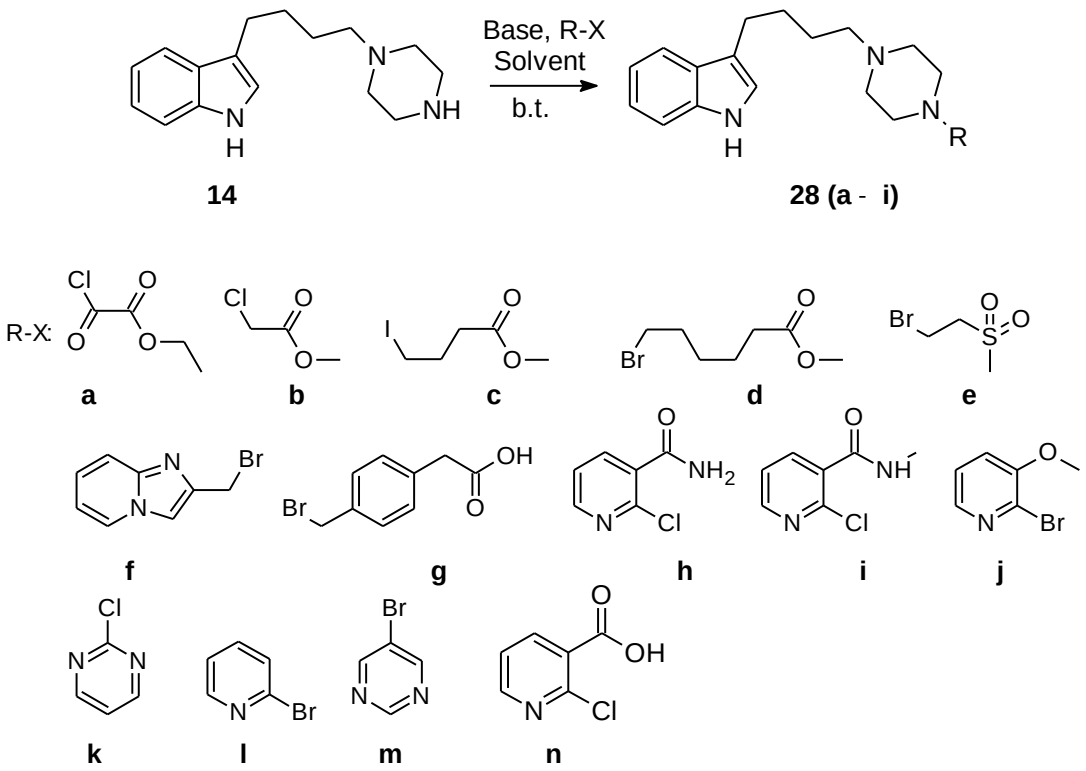
Since the overall yield of product **14** counting from 4-(1*H*-indol-3-yl)butanoic acid (**16**) was unsatisfying (20 %) and the hydrolysis step was inconsistent, an alternative route involving modification of 4-(1*H*-indol-3-yl)butan-1-ol (**24**) was employed. The starting alcohol **24** was synthesized by esterification of 4-(1*H*-indol-3-yl)butanoic acid (**16**) to methyl 4-(1*H*-indol-3-yl)butanoate (**23**), which was subsequently reduced with lithium aluminum hydride. Alcohol **24** was tosylated in ethyl acetate using pyridine as a base. The resulting product **25** was used for alkylation of *N*-protected piperazines. Unfortunately, the yield of *t*-butyl 4-[4-(1*H*-indol-3-yl)butyl]piperazine-1-carboxylate (**26**) was very low

(11 %), while ethyl 4-[4-(1*H*-indol-3-yl)butyl]piperazine-1-carboxylate (**27**) was isolated in good yield (69 %). Both compounds **26** and **27** were hydrolyzed to piperazine derivative **14** in high yields. This alternative method allows to synthesize target 3-[4-(1-piperazinyl)butyl]-1*H*-indole (**14**) in overall 52 % yield.



Scheme 8

Further alkylation of 4-(1*H*-indol-3-yl)butyl]piperazine (**14**) with various alkyl halides was carried out in acetonitrile in the presence of base (*N*,*N*-diisopropylethyl amine (DIPEA) or potassium carbonate) and gave desired products **28a-g** in high yields (Table 1). In contrast, arylation with various pyridine or pyrimidine halides was inconsistent, target products were not formed (compounds **28j-n**) or formed in very low yields (compounds **28h**,**i**) even if copper or palladium catalysis was applied.

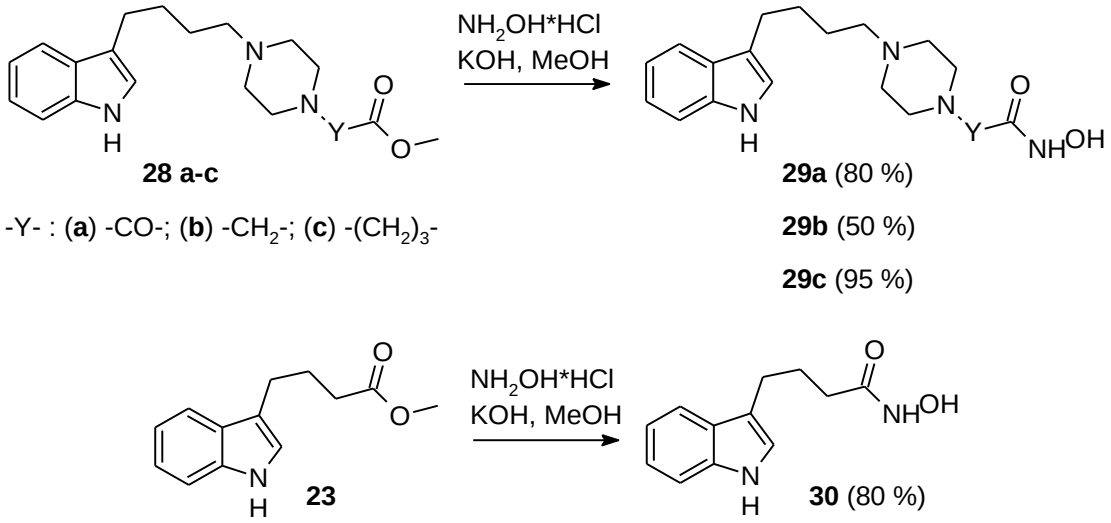


Scheme 9

Table 1. Data of alkylation and arylation of 4-(1*H*-indol-3-yl)butyl]piperazine (14).

R-X	Solvent	Base	Time	Product	Yield, %
a	CH_3CN	DIPEA	3 h	**28a**	95
b	CH_3CN	DIPEA	3 h	**28b**	70
	CH_3CN	K_2CO_3	5 h	**28b**	80
c	CH_3CN	K_2CO_3	4 h	**28c**	95
d	CH_3CN	K_2CO_3	6 h	**28d**	96
e	CH_3CN	K_2CO_3,	4 h	**28e**	90
f	CH_3CN	DIPEA	4 h	**28f**	95
g	CH_3CN	K_2CO_3	10 h	**28g**	80
h	CH_3CN	DIPEA	30 h	**28h**	31
i	CH_3CN	DIPEA	30 h	**28i**	22

Esters **23** and **28a-c** were treated with hydroxylamine hydrochloride at room temperature and converted to corresponding hydroxamic acids **29a-c** and **30** in moderate to good yields.



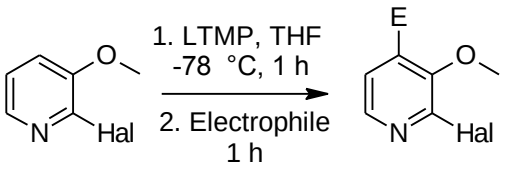
Scheme 10

Due to the structural similarity of compounds **29 – 30** with Panobinostat (LBH-589) we expected their possible anti-cancer activity. Thus the antiproliferative activity of these compounds was tested *in vitro*. Unfortunately, all compounds were inactive against tested human solid tumor cancer cell lines (HeLa (cervix), Ishikawa (endometrial), SW1573 (non-small cell lung), T-47D (breast), and WiDr (colon). Due to the end of project further investigations of 4-(1*H*-indol-3-yl)butyl]piperazine derivatives were suspended.

Synthesis of substituted pyridine moiety containing compounds for further modification of 1*H*-pyrazole derivatives

It was found that lithium tetramethylpiperidide (LTMP) is much more suitable base than lithium diisopropylamide (LDA) for the lithiation reaction of 2-chloro(bromo)-3-methoxy pyridines **31a,b** at the 4th pyridine ring position. Pyridines **31a,b** were treated with freshly prepared LTMP, then subsequently quenched with corresponding

electrophiles. 2-Bromo(chloro)-3-methoxy-4-substituted pyridine derivatives **32a,b** – **35a,b** and **36b** have been formed in good to high yields.



31a: Hal = Br

31b: Hal = Cl

32a – **35a, 36b**

32b – **35b**

32a: Electrophile: DMF; E = CHO (50 %)

32b: Electrophile: DMF; E = CHO (54 %)

33a: Electrophile: CO_2; E = COOH (51 %)

33b: Electrophile: CO_2; E = COOH (58 %)

34a: Electrophile: $B(OMe)_3$ then AcOOH; E = OH (88 %)

34b: Electrophile: $B(OMe)_3$ then AcOOH; E = OH (92 %)

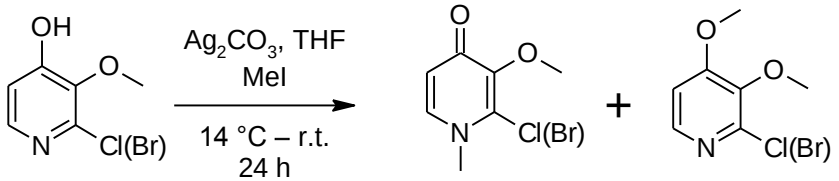
35a: Electrophile: $B(OMe)_3$; E = $B(OH)_2$ (59 %)

35b: Electrophile: $B(OMe)_3$; E = $B(OH)_2$ (66 %)

36b: Electrophile: $(SMe)_2$; E = SMe (60 %)

Scheme 11

Methylation of hydroxy group was performed using methyl iodide and silver carbonate in tetrahydrofurane. 2-Bromo(chloro)-3,4-dimethoxy pyridines **38a** and **38b** were isolated in good yields, however a significant amounts of *N*-methyl derivatives **37a** and **37b** were also isolated from reaction mixtures.



34a (Br)

34b (Cl)

37a (10 %)

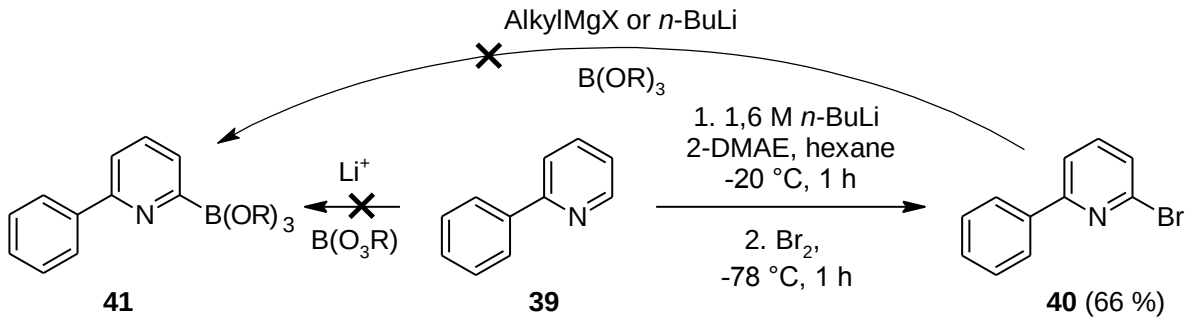
37b (15 %)

38a (64 %)

38b (55 %)

Scheme 12

2-Bromo-6-phenylpyridine (**40**) was synthesized by lithiation of 2-phenylpyridine (**39**) in good yield using *n*-BuLi with 2-dimethylaminoethanol and bromine as electrophile.

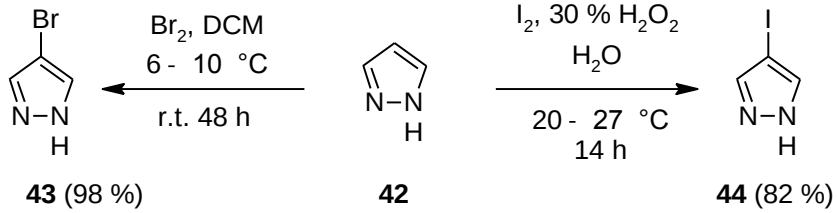


Scheme 13

Unfortunately, the synthesis of boronic acid **41** via direct lithiation reaction of compound **39** or via 2-bromo-6-phenyl pyridine (**40**) halogen-lithium or halogen-magnesium exchange reactions was unsuccessful.

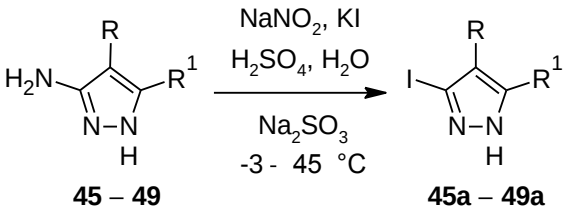
Synthesis of substituted *1H*-pyrazole derivatives

4-Bromo(iodo)-1*H*-pyrazole derivatives **43** and **44** were synthesized by direct halogenation of 1*H*-pyrazole (**42**) via slightly modified procedures described in literature. Halogenated products **43** and **44** were isolated in the same or higher yields that described in literature (98 % and 82 % yields instead of 100 % and 63 %, respectively).



Scheme 14

Substituted 3-iodo-1*H*-pyrazole derivatives **45a** – **49a** were synthesized from the corresponding substituted 3-amino-1*H*-pyrazoles **45** – **49**. Sandmeyer type reaction was performed in sulfuric acid using potassium iodide as halogen source.



45 – **49** **45a** – **49a**

45a: R = R^1 = H (70 %)

46a: R = COOEt, R^1 = H (75 %)

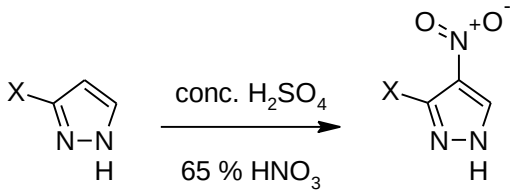
47a: R = Me, R^1 = H (50 %)

48a: R = H, R^1 = CF_3 (60 %)

49: R = H, R^1 = Me (48 %)

Scheme 15

3,4-Disubstituted 1*H*-pyrazoles were synthesized from 3-substituted 1*H*-pyrazoles by functionalization of the 4th ring position. Nitration of 3-iodo(bromo)-1*H*-pyrazole derivatives **45a** and **45b** was performed in sulfuric acid with 65 % nitric acid, obtaining 3-iodo(bromo)-4-nitro-1*H*-pyrazole derivatives **50a** and **50b** in high yields.

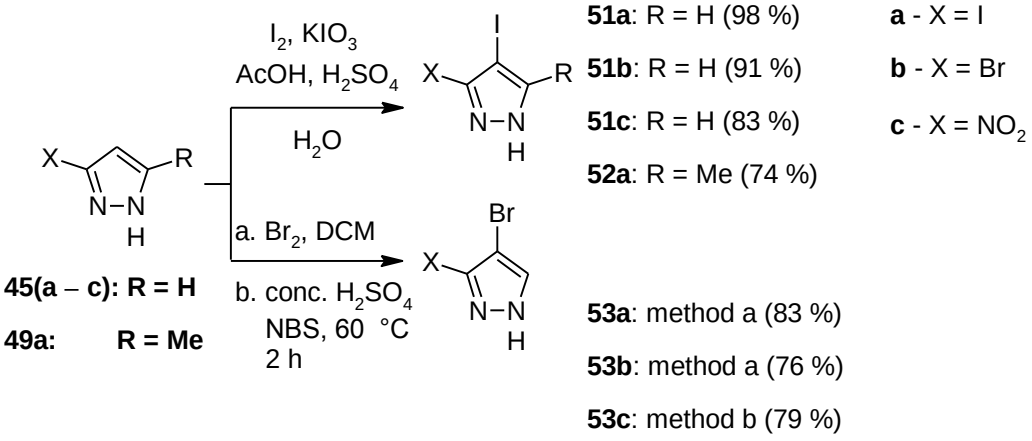


45a: X = I **50a** (81 %)

45b: X = Br **50b** (70 %)

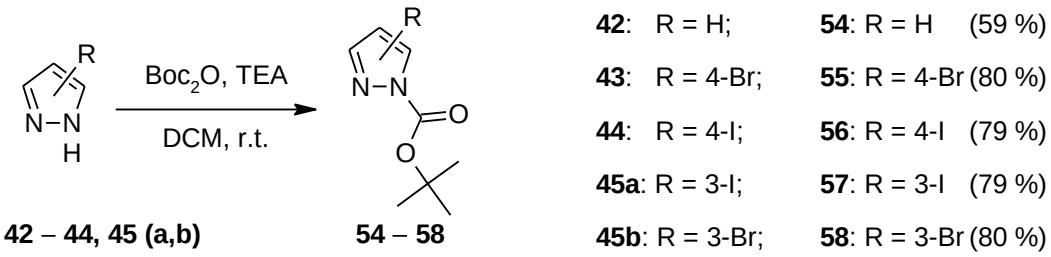
Scheme 16

3-Substituted pyrazole derivatives **45a-c** and **49a** were iodinated at the 4th pyrazole ring position by slightly modified procedure described in literature. We have also showed that this method could be successfully adapted for the 1*H*-pyrazole derivatives with substituents at both 3th and 5th positions. 3-Iodo(bromo)-1*H*-pyrazole derivatives **45a,b** were brominated at the 4th position with bromine in dichloromethane. Bromination of 3-nitro-1*H*-pyrazole (**45c**) was carried out under harsher conditions, using *N*-bromosuccinimide in concentrated sulfuric acid at 60 ºC temperature.



Scheme 17

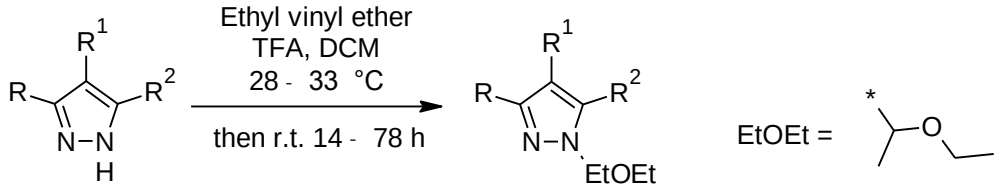
1*H*-pyrazoles **42** – **45** were protected using Boc anhydride. *N*-Boc protected 1*H*-pyrazoles **54 – 58** were obtained in good to excellent yields. Unfortunately, Boc protecting group was not stable enough both in reactions with lithium organic compounds and during GC-MS analysis.



Scheme 18

Usually, protection reaction of 1*H*-pyrazole ring with EtOEt or THP groups is performed by heating reaction mixture of starting pyrazole with ethyl vinyl ether or dihydropyran and catalytic amount of acid at 40 – 50 °C degree temperature. We found that the exothermic effect of addition of ethyl vinyl ether to N-H bond is quite significant in larger scale (up to 1 kg) syntheses. In higher temperatures the reaction tends to accelerate and can get out of control. The control of reaction can be achieved by portionwise addition of ethyl vinyl ether to the reaction mixture at 28 – 33 ºC temperature in dichloromethane, with catalytic amount of trifluoroacetic acid (TFA). By adapting this

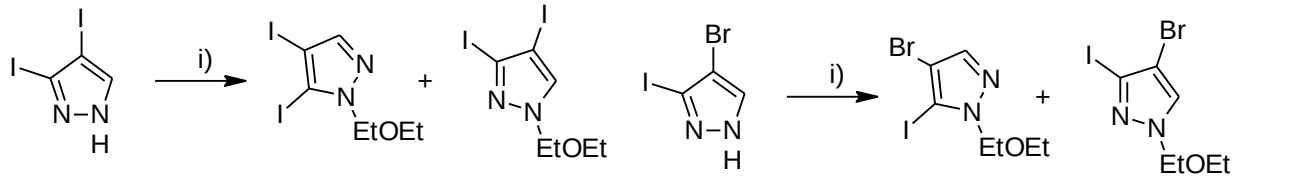
modified method *N*-ethoxyethyl protected 1*H*-pyrazole derivatives **59** – **70** were synthesized in good to excellent yields.



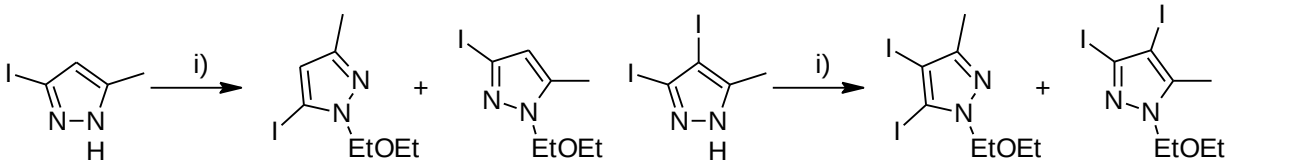
42: R = R^1 = R^2 = H	**59** (93 %)
43: R^1 = Br; R = R^2 = H	**60** (73 %)
44: R^1 = I; R = R^2 = H	**61** (93 %)
45a: R = I; R^1 = R^2 = H	**62** (92 %)
45b: R = Br; R^1 = R^2 = H	**63** (86 %)
46a: R = I; R^1 = COOEt; R^2 = H	**64** (43 %)
46b: R = Br; R^1 = COOEt; R^2 = H	**65** (83 %)
47a: R = I; R^1 = Me; R^2 = H	**66** (80 %)
48a: R = I; R^1 = H; R^2 = CF_3	**67** (75 %)
50a: R = I; R^1 = NO_2; R^2 = H	**68** (77 %)
50b: R = Br; R^1 = NO_2; R^2 = H	**69** (75 %)
51c: R = NO_2; R^1 = I; R^2 = H	**70** (80 %)

Scheme 19

The monitoring (using GC-MS, TLC and BMR analysis) of protection reaction of 3,4-diiodo-1*H*-pyrazole (**51a**) and 4-bromo-3-iodo-1*H*-pyrazole (**53a**) with ethyl vinyl ether indicated the migration of EtOEt group in acidic conditions. After stirring the reaction mixture at room temperature for 2 h, full conversion of starting material was achieved, but in both cases mixtures of isomers were detected. After stirring the reaction mixtures at room temperature for prolonged period of time (20 – 78 hours) only traces of 5-iodo isomers **71** and **73** were detected. 4-Bromo(iodo)-1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazoles **72** and **74** were isolated in excellent yields. However, only partial migration of EtOEt group in case of 5-methylpyrazoles **49a** and **52a** was observed. Additional reflux for 5 hours did not change the ratio of isomers.



51a	**71**	**72**	**53a**	**73**	**74**
r.t. 2 h	50 %*	50 %	r.t. 2 h	50 %*	50 %
r.t. 20 h	20 %	80 %	r.t. 20 h	20 %	80 %
r.t. 78 h	3 %	97 % (86 %)**	r.t. 78 h	3 %	97 % (79 %)**



49a	**75**	**76**	**52a**	**77**	**78**
r.t. 2 h	43 %*	57 %	r.t. 2 h	31 %*	69 %
r.t. 20 h	12 %	88 %	r.t. 20 h	28 %	72 %
r.t. 78 h	13 %	87 % (57 %)**	r.t. 120 h	20 % (18 %)**	80 % (69 %)**

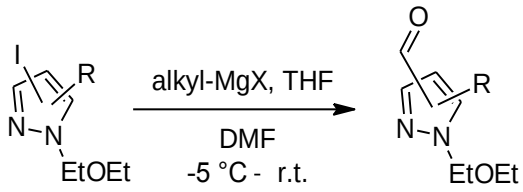
i) Ethyl vinyl ether, DCM, TFA, 28 - 33 °C → r.t.

* GC-MS data

** Isolated yield

Scheme 20

It was found that 1-(1-ethoxyethyl)-4-bromo-1*H*-pyrazole (**60**) was inactive in Grignard type reaction with ethylmagnesium bromide, but it's analog 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole (**61**) participated in this reaction. Also we successfully applied Grignard type reaction for substituted 3-iodo-pyrazole derivatives **62** and **76** using 2-propylmagnesium chloride. Unfortunately, 3-iodo-4-methyl-1*H*-pyrazole (**66**) was unreactive under all tested reaction conditions.



61, 62, 66, 76 → **79** – **81**

61: 4-I, R = H; Et-MgBr; Product Nr.: **79** (72 %)

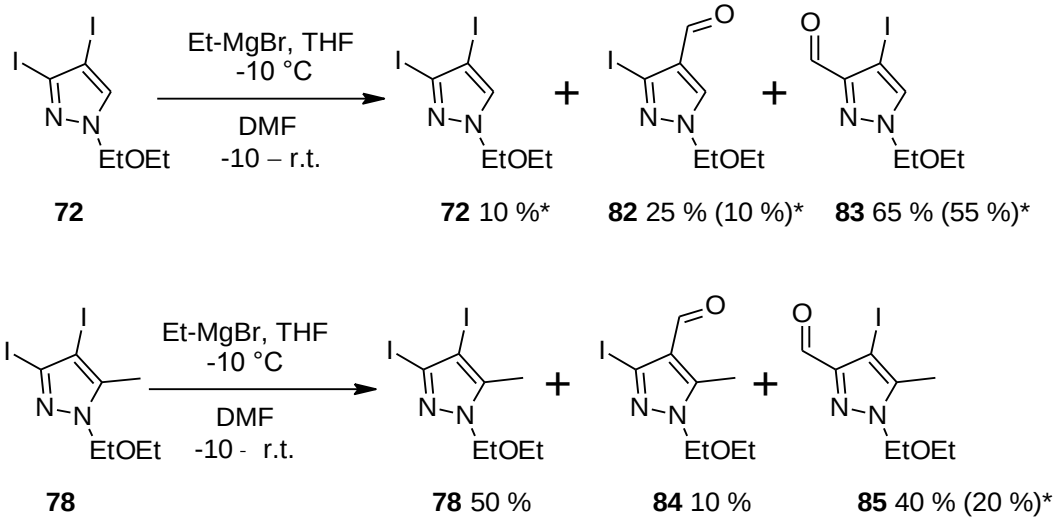
62: 3-I, R = H; *i*Pr-MgCl; Product Nr.: **80** (65 %)

76: 3-I, R = 5-Me; *i*Pr-MgCl; Product Nr.: **81** (54 %)

66: 3-I, R = 4-Me; *i*Pr-MgCl; No reaction

Scheme 21

Since 3-iodo derivative **62** did not react with ethylmagnesium bromide, we expected that EtMgBr could selectively react with iodo substituent at the 4th position of 3,4-diiodo derivative **72**. Full conversion of **72** was achieved within 30 minutes at +5 °C, however the formation of both available isomers – 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole-3-carbaldehyde (**83**) and 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole-4-carbaldehyde (**82**) in ratio 1 : 1 was observed. Decreasing of reaction temperature increases selectivity of substitution (at -10 °C ratio of **83** to **82** is 1 to 2, at -40 °C ratio reaches 1 to 4). However the starting compound has not fully reacted at lower temperatures. Performing iodo-EtMgBr exchange reaction at -10 °C degrees after 2 hours – 10 % (at -40 °C – 30 %) of **72** has left. Surprisingly, 1-(1-ethoxyethyl)-3,4-diiodo-5-methyl-1*H*-pyrazole (**78**) reacted in different way. Performing this reaction at -10 °C, conversion of the starting material was reached only 50 % and iodo-EtMgBr exchange reaction took place at the 3th position of pyrazole ring.



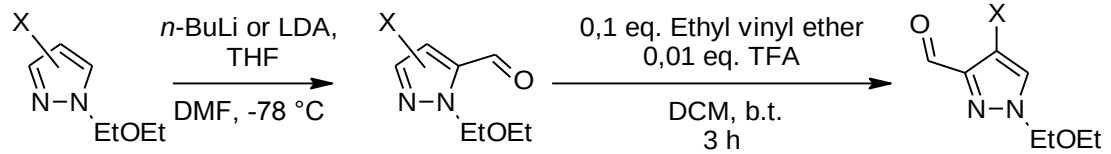
* GC-MS data (isolated yield)

Scheme 22

There are some suggestions for the synthesis of 1*H*-pyrazole derivatives in high yields via halogen-lithium exchange reaction. Usually such reactions are performed by direct lithiation at the 5th position or by halogen-lithium exchange of the halogen atom at the 4th or 5th positions of pyrazole ring. Our experiment has shown that *N*-EtOEt group acts as *ortho*-directing group. Thus, direct *ortho*-lithiation reaction of *N*-EtOEt protected

1*H*-pyrazoles was performed using *n*-BuLi (**59**) or LDA (**60 – 63**) as lithiating agents and therefore, pyrazole aldehydes **86** – **90** were synthesized in good yields. Also we noticed that by performing lithiation reaction of 3-bromo-1-(1-ethoxyethyl)-1*H*-pyrazole (**63**) with *n*-BuLi at -95 °C or -105 °C degree temperature, significant amount of direct lithiation product **87** at the 5th position was formed: 10 % at -95 °C (GC-MS data) and 16 % at -105 °C.

In order to reliably identify both position isomers (**82** and **83** scheme 23) and in order to compare their GC-MS and NMR spectra, compound **83** was synthesized in alternative way. Ethoxyethyl protecting group in compounds **86**, **88** and **89** appeared to be very sensitive to acidic conditions. The migration of protecting group was performed by heating 1-(1-ethoxyethyl)-1*H*-pyrazole-5-carbaldehyde (**86**), 4-bromo-1-(1-ethoxyethyl)-1*H*-pyrazole-5-carbaldehyde (**88**) or 1-(1-ethoxyethyl)-4-iodo-1*H*-pyrazole-5-carbaldehyde (**89**) in dichloromethane for 3 hours, using catalytic amount of trifluoroacetic acid and 5 % of ethyl vinyl ether for prevention of deprotection. Compounds **80**, **83** and **91** were synthesized in 73 – 84 % yields.



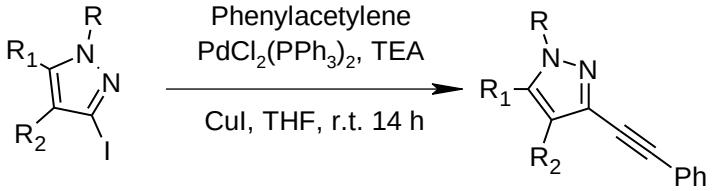
59: X = H
60: X = 4-Br
61: X = 4-I
62: X = 3-I
63: X = 3-Br

86: *n*-BuLi (65 %)
88: LDA (74 %)
89: LDA (68 %)
90: LDA (59 %)
87: LDA (70 %)

80 (84 %)
91 (74 %)
83 (73 %)

Scheme 23

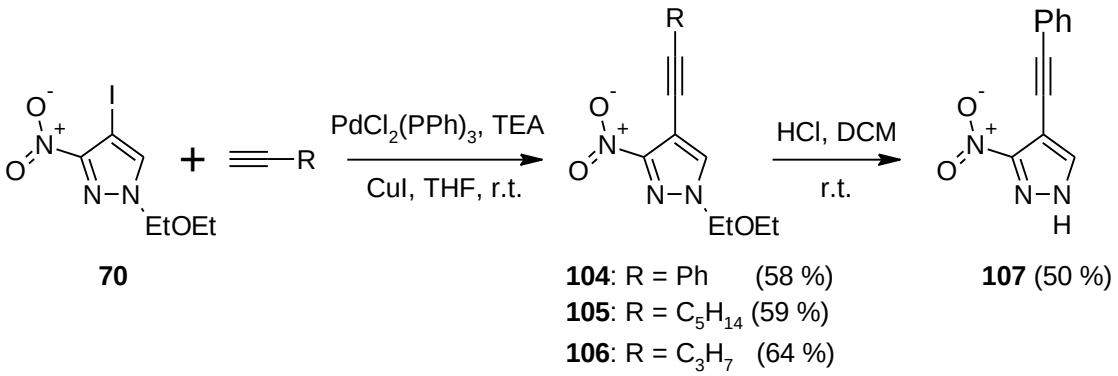
Sonogashira cross-coupling reactions of substituted 1-(1-protected)-3-iodo-1*H*-pyrazole derivatives **57**, **62**, **66**, **67**, **74**, **76**, **82**, **90** and **92** with phenyl acetylene were successfully performed at room temperature. Compounds **93** – **101** were synthesized in high yields.



57: R = Boc; R_1 = R_2 = H	**93** (65 %)
62: R = EtOEt; R_1 = R_2 = H	**94** (63 %)
66: R = EtOEt; R_1 = H; R_2 = Me	**95** (70 %)
67: R = EtOEt; R_1 = CF_3; R_2 = H	**96** (73 %)
74: R = EtOEt; R_1 = H; R_2 = Br	**97** (64 %)
76: R = EtOEt; R_1 = Me; R_2 = H	**98** (63 %)
82: R = EtOEt; R_1 = H; R_2 = CHO	**99** (87 %)
90: R = EtOEt; R_1 = CHO; R_2 = H	**100** (80 %)
92: R = Me; R_1 = R_2 = H	**101** (82 %)
64: R = EtOEt; R_1 = H; R_2 = COOEt	**102** (0 %)
68: R = EtOEt; R_1 = H; R_2 = NO_2	**103** (0 %)

Scheme 24

Unfortunately, protected 3- and 4-bromo as well as 3-iodo-1*H*-pyrazole derivatives bearing ethoxycarbonyl (**64**) or nitro (**68**) substituents at the 4th position of pyrazole ring were unreactive under various Sonogashira cross-coupling conditions. At the same time compound **70** (position isomer of compound **68**) has successfully reacted with different acetylenes at room temperature and final products were isolated in moderate yields. Deprotection of NH-bond was also performed and product **107** was isolated in 50 % yield.



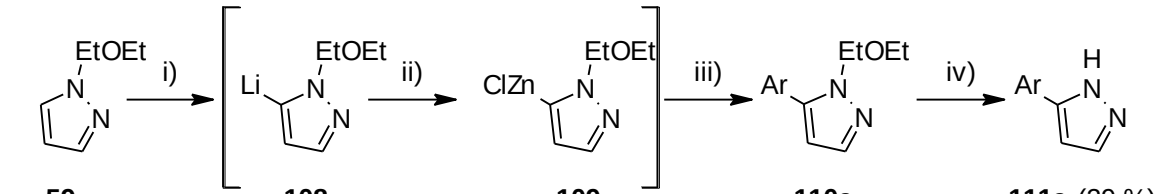
70

104: R = Ph (58 %)
105: R = C_5H_{14} (59 %)
106: R = C_3H_7 (64 %)

107 (50 %)

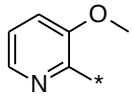
Scheme 25

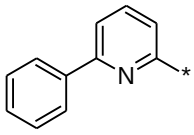
Since direct *ortho*-lithiation of 1-(1-ethoxyethyl)-1*H*-pyrazole (**59**) goes at the 5th position of pyrazole ring, we tried to apply this reaction for preparation of the intermediates for Negishi cross-coupling. Thus *N*-EtOE-5-arylpyrazoles **110a** and **110b** were synthesized by lithiating pyrazole **59** with *n*-BuLi to the 5th pyrazole ring position forming compound **108** which undergoes trans metalation then cross-coupling reaction with substituted 2-halogenopyridines **31a** or **40**. Unfortunately, the starting material was not fully consumed. In both experiments the conversion of starting material **59** was only 50 %. Both products **110a** and **110b** were deprotected using aq HCl solution, thus products **111a** and **111b** were isolated in lower yields.



59 **108** **109** **110a** **111a** (29 %)

110b **111b** (25 %)

a: Ar = 

b: Ar = 

i) 2,5 M *n*-BuLi in *n*-hexane, THF, -78 ^{o}C;

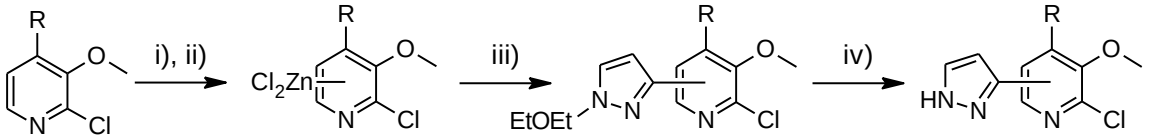
ii) 0,5 M $ZnCl_2$ in THF, -78 ^{o}C – r.t.;

iii) Comp. **31a** "**a**" or **40** "**b**", $PdCl_2(PPh_3)_2$, 80 ^{o}C;

iv) HCl, DCM;

Scheme 26

For the comparison of results, Negishi cross-coupling was performed using the reaction of pyridine-zinc organic compounds **112** or **113** with 1-(1-ethoxyethyl)-3-iodo-1*H*-pyrazole (**62**). Again, the conversion was not complete. Final deprotected products **112b** and **113b** were isolated in low yields.



31b: R = H; **112**: 6-$ZnCl_2$; **112a** **112b** (21 %)

38b: R = OMe; **113**: 5-$ZnCl_2$; **113a** **113b** (13 %)

i) 2,5 M *n*-BuLi in *n*-hexane, THF, -78 ^oC;

ii) 0,5 M $ZnCl_2$ in THF, -78 ^oC – r.t.;

iii) Comp. **62**, $PdCl_2(PPh_3)_2$, 80 ^oC;

iv) HCl, DCM;

Scheme 27

As it was expected, lithiation of 2-chloro-3-methoxypyridine (**31b**) underwent at the 6th position of pyridine ring. Surprisingly, 2-chloro-3,4-dimethoxypyridine (**38b**) underwent *ortho*-lithiation reaction at the 5th position of pyridine ring. It seems like in this case the total directing effect of functional groups is stronger than that of nitrogen atom of pyridine ring.

Results and conclusions

1. Synthetic method of 2-halogeno-3-nitrothiophene as well as Suzuki-Miyaura cross-coupling reaction of 2-bromo-3-nitrothiophene with phenylboronic acid was optimized. 2-Phenyl-3-nitrothiophene was used as precursor for the 4*H*-thieno[3,2-b]indole synthesis. It was found that during cyclization reaction of 2-azido-2-phenylthiophene, significant amount of dimerization product 4,4'-bithieno[3,2-*b*]indole has formed from 4*H*-thieno[3,2-*b*]indole.
2. Synthetic method of 3-[4-(1-piperazinyl)butyl]-1*H*-indole was optimized. Alkylation possibilities of free piperazine ring NH group in 3-[4-(1-piperazinyl)butyl]-1*H*-indole were demonstrated.
3. A series of hydroxamic acids were synthesized from 3-[4-(1-piperazinyl)butyl]-1*H*-indole *N*-alkyl esters for evaluation of antitumor activity. It was found that synthesized hydroxamic acids were inactive against human solid tumor cancer cells.
4. Selective and efficient synthetic methods of 3-bromo(iodo or nitro)-4-bromo(iodo or nitro)-1*H*-pyrazole derivatives were discovered.
5. It was found that ethoxyethyl protecting group effectively protects N-H bond of the pyrazole ring. During protection reaction of 3,4- or 3,4,5-substituted pyrazole derivatives, migration reaction of the protecting group was observed by forming most stable position isomer.
6. Synthetic methods of 1-ethoxyethyl protected 3-, 4- or 5-1*H*-pyrazole carbaldehydes were investigated. Performing Grignard type reaction of 1-(1-ethoxyethyl)-3,4-diiodo-1*H*-pyrazole with ethylmagnesium bromide, at -10 ºC degrees, iodo-magnesium exchange reaction mainly took place at the 4th position of the pyrazole ring.
7. Optimal reaction conditions of 1-ethoxyethyl-1*H*-pyrazole with *n*-buthyllithium and lithium diisopropylamine were investigated. During lithiation reaction of 3-bromo-1-ethoxyethyl-1*H*-pyrazole with *n*-butyllithium at lower than -78 ºC degrees temperature, not only halogen lithium exchange but also a direct lithiathion reaction at the 5th pyrazole ring position was observed.

8. Synthetic method for the protecting group migration of 4-substituted 1-ethoxyethyl-1*H*-pyrazole-5-carbaldehydes forming 4-substituted 1-ethoxyethyl-1*H*-pyrazole-3-carbaldehydes was found.
9. Sonogashira cross-coupling reaction conditions for synthesis of substituted 1-ethoxyethyl-3-iodo-1*H*-pyrazole derivatives were applied. Cross-coupling reaction of 3-iodo-pyrazole derivatives with nitro and ethoxycarbonyl substituents at the 4th position did not occur.
10. It was shown that 2-(1*H*-pyrazol-5-yl)pyridine derivatives can be synthesized from either 1-ethoxyethyl-1*H*-pyrazole or pyridine zinc organic compounds using Negishi cross-coupling reaction.

Santrauka

Tiofeno, indolo, ir pirazolo ir fragmentus turintys dariniai dažnai pasižymi vertingomis praktikoje taikomomis savybėmis. Tiofeno, sujungto su elektrono akceptoriniais pakaitais pagrindu, konstruojami šviesą spinduliuojantys elementai (OLED). Tiofeno fragmentas pasitaiko ir biologiniu aktyvumu pasižyminčiuose junginiuose. Indolo fragmentą turinčių heterociklinių junginių pagrindu dažnai kuriami vaistai. Paskutiniu metu susidomėta hidroksamo rūgštimis, pavyzdžiui, Panobinostat (LBH-589) yra eksperimentinis preparatas, veikiantis kaip neselektyvus histadono deacilazės (HDAS) inhibitorius. Pirazolo fragmentas taip pat labai dažnai pasitaiko biologiniu aktyvumu pasižyminčių junginių, o jų metalų kompleksai gali būti panaudojami ne tik naujų kuriamų organinių šviesą spinduliuojančių medžiagų struktūrose, bet ir pereinamųjų metalų katalizuojamose C-C ryšio sudarymo reakcijose. 2-Formil- arba 2-nitroalkinildariniai yra labai vertingi naujų heterociklinių sistemų kūrimui arba gerai žinomų heterociklų, pvz., indolų arba chinolinų sintezei.

Šio darbo metu optimizuotas 2-halogen-3-nitrotiofenų sintezės metodas, o 2-brom-3-nitrotiofenas pritaikytas Suzuki-Miyaura kryžminio jungimosi reakcijai su fenilboronio rūgštimi. Susidaręs 2-fenil-3-nitrotiofenas panaudotas 4*H*-tieno[3,2-*b*]indolo sintezei. Nustatyta, kad vykdant terminę 3-azido-2-feniltiofeno ciklizaciją vyksta susidariusio 4*H*-tieno[3,2-*b*]indolo dimerizacija susidarant 4,4'-bitieno[3,2-*b*]indolui.

Tyrinėjant indolo darinių sintezę, optimizuotas 3-[4-(1-piperazinil)butil]-1*H*-indolo sintezės metodas. Ir parodytos 3-[4-(1-piperazinil)butil]-1*H*-indolo piperazino žiedo laisvos NH grupė alkilinimo galimybės įvairiais alkilhalogenidais. Iš susintetintų 3-[4-(1-piperazinil)butil]-1*H*-indolo *N*-alkilesterių susintetintos hidroksamo rūgštys, kurių ištirtas *in vitro* priešvėžinis aktyvumas. Nustatyta, kad susintetintos hidroksamo rūgštys neaktyvios prieš testuotas žmogaus kietojo auglio vėžinių ląstelių linijas.

Surasti selektyvūs ir efektyvūs 3-brom(jod arba nitro)-4-brom(jod arba nitro)-1*H*-pirazolo darinių sintezės metodai. Surasta tinkamiausia apsauginė grupė pirazolo žiedo laisvos NH grupei, leidžianti pritaikyti susintetintus pirazolo darinius reakcijoms su ličio organiniais junginiais ir kryžminio jungimosi reakcijoms. Nustatyta, kad apsaugant 3,4- arba 3,4,5-pakeistus 1*H*-pirazolo darinius vyksta apsauginės grupės migracija

susidarant stabiliausiam padėties izomerui. Tyrinėtos apsaugotų 1*H*-pirazolo halogendarinių reakcijos su alkilmagnio halogenidais ir ličio organiniais junginiais. Surasti efektyvūs metodai sintetinti halogenintus 1-etoksietilgrupe apsaugotus 3-, 4- arba 5-karbaldehidus. Parodyta, kad vykdant 1-(1-etoksietil)-3,4-dijod-1*H*-pirazolo Grignardo tipo reakciją su etilmagnio bromidu -10 ºC temperatūroje, pagrinde vyksta 4-ojoje pirazolo žiedo padėtyje esančio jodo atomo pakeitimas. O vykdant 3-brom-1-etoksietil-1*H*-pirazolo reakciją su *n*-butilličiu žemesnėje nei -78 ºC temperatūroje, vyksta ne tik ličio-halogeno apsikeitimo reakcija, bet ir tiesioginis litinimas į 5-ąją pirazolo žiedo padėtį. Pastebėta, kad 4-pakeistų 1-etoksietil-1*H*-pirazolo-5-karbaldehidų apsauginė grupė nėra stabili ir esant net silpnai rūgštinėms sąlygoms ir yra linkusi migruoti, susidarant 4-pakeistų 1-etoksietil-1*H*-pirazol-3-karbaldehidams. Todėl surasto apsauginės grupės pergrupavimo sąlygos panaudojant katalitinius kiekius etilvinileterio ir trifluoracto rūgšties. Susintetinti pakeisti 1-etoksietil-3-jod-1*H*-pirazolo dariniai pritaikyti Sonogashira kryžminio jungimosi reakcijai. Nustatyta, kad 4-ojoje pirazolo žiedo padėtyje esant nitro- arba etoksikarbonilgrupėms, minėta reakcija nevyksta, tačiau sėkmingai vyksta jodo atomui esant 4-ojoje padėtyje, o nitrogrupei – 3-ojoje. Taip pat parodytos 1-etoksietil-1*H*-pirazolo ir 1-etoksietil-3-jod-1*H*-pirazolo pritaikymo galimybės Negishi kryžminio jungimosi reakcijoje, panaudojant pirazolo arba piridino cinko organinius junginius.

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