SCIENTIFIC PAPERS
OF THE UNIVERSITY OF PARDUBICE
Series A
Faculty of Chemical Technology
20 (2014)

REACTIONS OF *S*-, *N*-AMBIDENT NUCLEOPHILES WITH POLARIZED ETHYLENES GIVING PYRIMIDINES AND 1,3-THIAZINES

Denisa TARABOVÁ and Jiří HANUSEK[1]
Institute of Organic Chemistry and Technology,
The University of Pardubice, CZ–532 10 Pardubice

Received March 31, 2014

The review is focused on a diverse use of polarized ethylenes bearing an alkoxy, halogen or amino group in the reaction with S-, N- ambident nucleophiles (thioamides, thioureas, thiosemicarbazides, thiocarbamates, dithiocarbamates) to give pyrimidine and 1,3-thiazine ring. Other possibilities of synthesis of these heterocyclic scaffolds are also reported.

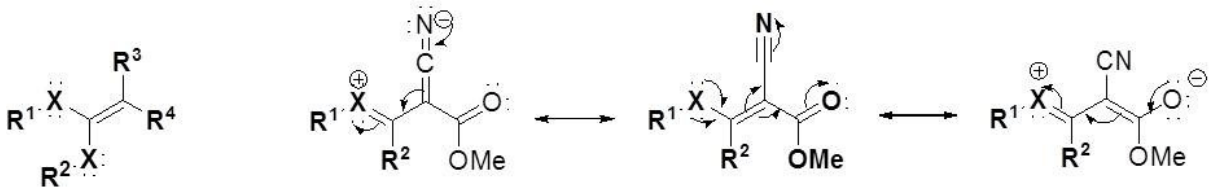
Contents

[1] To whom correspondence should be addressed.

1 Introduction

1.1 Polarized Alkenes

Activated alkenes, also known as polarized ethylenes, represent compounds with the general formula depicted in Fig.1. Here belong, e.g., (thio)enolethers and enamines where a heteroatom (O, S or NH) donates free electron pair and another group in β-position of the double bond is able to withdraw it (push-pull system). (Fig. 1).



R^1,**R**^{2} = H, alkyl, aryl (Me, Ph, cycloalkyl...), alkoxy, alkylthio
R^3,**R**^{4} = $COCX_3$, COR (R = alkyl, aryl), CN
X = O, S, NH, halogen

Fig.1

Such enolethers bearing alkoxy group and strong electron-withdrawing groups (alkoxycarbonyl/aryloxycarbonyl, cyano, acetyl, benzoyl, nitro, sulfonyl or formyl) in the β-position of the double bond are very reactive towards nucleophiles and play an important role in the synthesis of various heterocyclic compounds [1]. For example:

a) *N*-nucleophiles (anilines) give *via* S_NV and Gould–Jacobs reaction quinolones [2] and kynurenic acids;
b) amidines [3] give pyrimidines;
c) hydrazines [4] give pyrazoles;
d) *O*, *N*-binucleophiles, e.g., hydroxylamine, give 1,3-oxazole derivatives [5];
e) *O*, *S*-binucleophiles, e.g., 2-aminoethanethiole, form 1,4-oxathiepinones [6];
f) *S*, *N*-binucleophiles, e. g., 2-hydroxyethanethiol, give 1,4-thiazepinones [7];

and 2-aminobenzenethiols give benzothiazoles [8].

1.2 Occurrence and Biological Activity of Polarized Ethylenes

Some of the polarized ethylenes display significant biological activity. From among naturally occuring alkoxymethylidenes, we can mention strobillurine and oudemansine or rhynkofyline, mytraghinine and korynoxine, respectively [9] (Fig. 2). Oudemansine A was isolated from *Oudemansiella mucida* and acts fungicidally, antibiotically and shows mild activity against tumors [10]. Strobilurine A/Mucidine, Mucidermine were isolated from *Strobilurus tenacellus, Oudemansiella mucida, Bolinea lutea* [11] and other fungi. They also display fungicidal activity based on inhibition of plant respiration. 9-Methoxystrobilurine was isolated from bazidomycethes *Favolaschia pustulosa* [12] and displays some cytostatic activity.

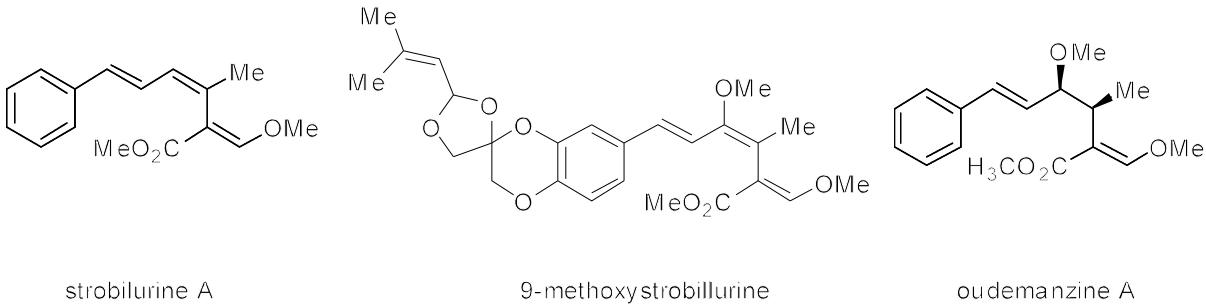
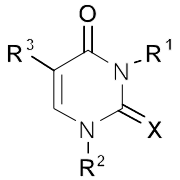


Fig. 2 Examples of biologically active alkoxymethylidenes

1.3 Biological Activity of Pyrimidines and 1,3-Thiazines

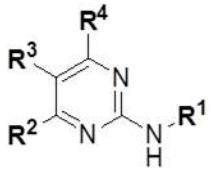
The most important heterocyclic compounds formed after the reactions of polarized alkenes with *O*-, *S*-, and *N*-nucleophiles, are 1,3-thiazines and pyrimidines. These heterocycles are present in nucleic acids as nucleobases cytosine (C), thymine (T), and uracil (U) and have a broad-spectrum biological activity [13]. The most important examples are depicted in Figs 3 and 4.

From the newest literature there is also known that bis-aryl-aminopyrimidine displays an excellent activity as inhibitors of tubulin polymerization [14], and they have an excellent antiproliferative activity. A new class of chalcone and pyrimidine derivatives [15] were also synthesized and evaluated as antitubercular agents. These compounds exhibited promising antitubercular activities against *Mycobacterium tuberculosis*, and new arylazo derivatives [16] of pyrimidines showed some cytotoxic, antibacterial and micro-



Generic name	***R*^{1}**	***R*^{2}**	***R*^{3}**	***X***	*Biological effect*
fluorouracil	H	H	F	O	Cytostaticum
Azidothymidine	H	$HOCH_2C_4H_6ON_3$	Me	O	HIV drug
Methylphenobarbital	Me	H	Et, Ph	O	Antiepilepticum

Fig. 3



Generic name	***R*^{1}**	***R*^{2}**	***R*^{3}**	***R*^{4}**	*Biological effect*
Pyrimethamine	H	C_2H_5	4-ClC_6H_4	NH_2	Antimalarial drug
Trimethoprim	H	H	3,4,5-$(MeO)_3C_6H_2CH_2$	NH_2	Antimalarial drug
Minodixil	H	NH_2	H	$C_5H_{10}N$	Antihypertensivum
Sulfadiazine	SO_2PhNH_2	H	H	H	Chemoterapeutics

Fig. 4

biological activity. As another example of active compounds containing pyrimidine skeleton can be mentioned 2-pyrido[2,3-*d*]pyrimidines which show diuretic activity [17], anticonvulsant [18] and antioxidant activity.

Potent pharmacological activity of 1,3-thiazine derivatives was recently described in several reviews [19,20]. Their antimicrobial and antibacterial activity was also studied by Haider *et al*. [21]. They found that the presence of phenolic group, sulphur or nitrogen atom in substituents associated with an increasing number of heteroatoms showed the best results for testing of antimicrobial activity for all types of Gram-positive and Gram-negative bacteria.

Pyrimidines and 1,3-thiazines can be synthesized by a number of methods [22-57] from which those starting from polarized ethylenes represent a good alternative. Such synthetic approaches are described in the next chapters.

2 Reactions of Polarized Alkenes with *S*-, *N*-nucleophiles

From the polarized ethylenes, diethyl ethoxymethylidenemalonate **(1a)**, ethoxymethylidene malononitrile **(1b)** and others **1c-p (**Fig. 5**)** are the most frequent starting materials for the synthesis of various heterocycles.

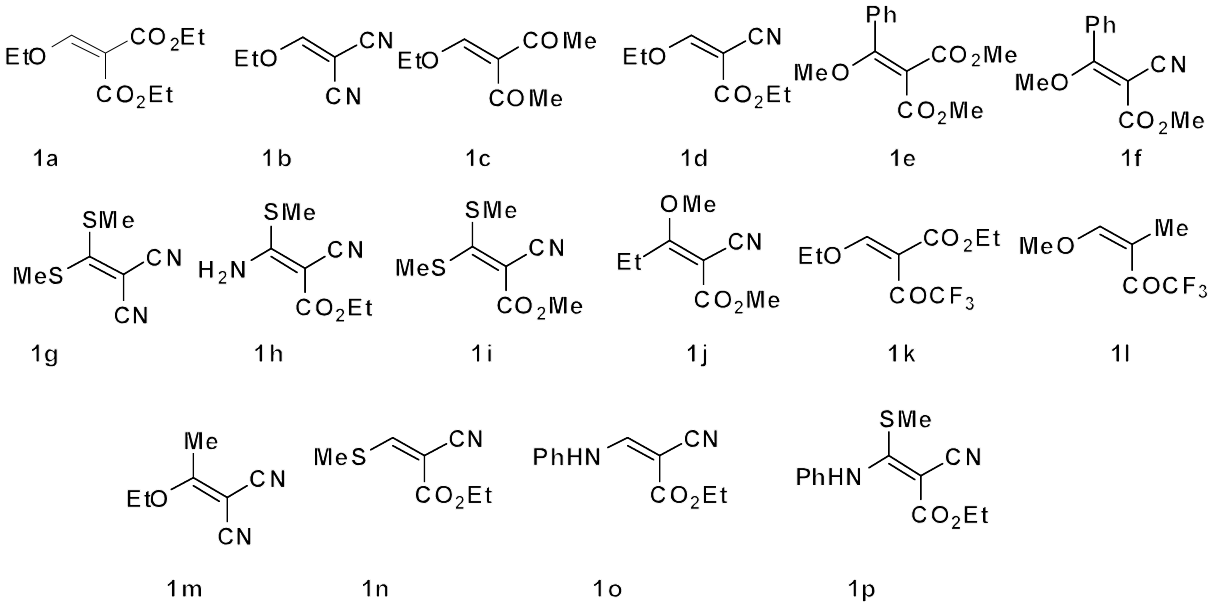
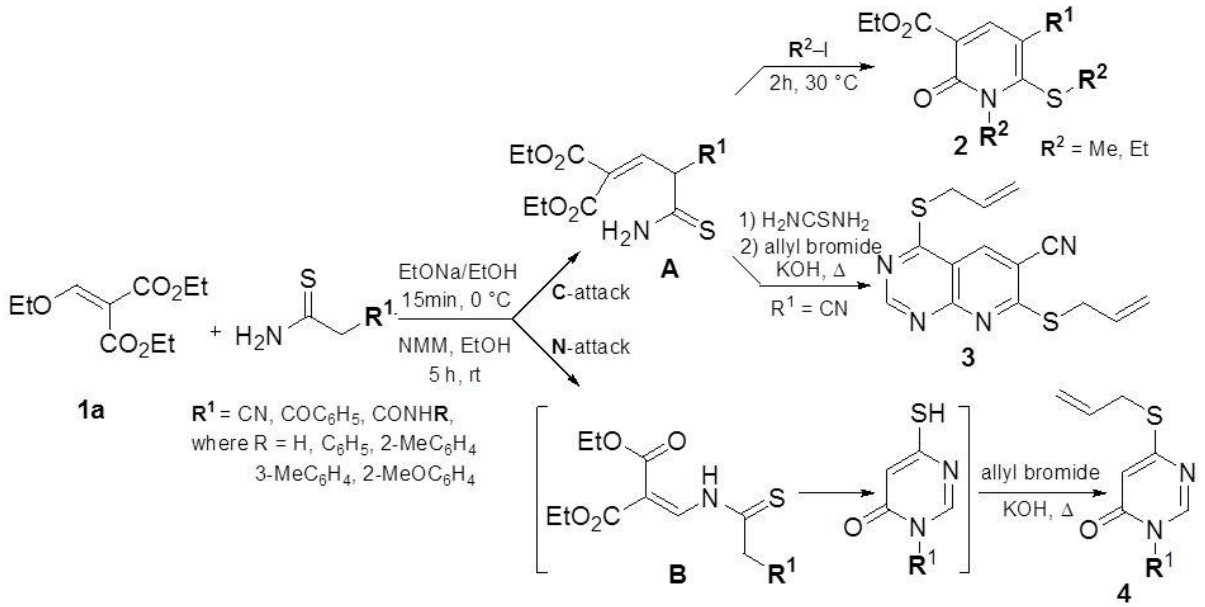


Fig. 5

2.1 Thioamides

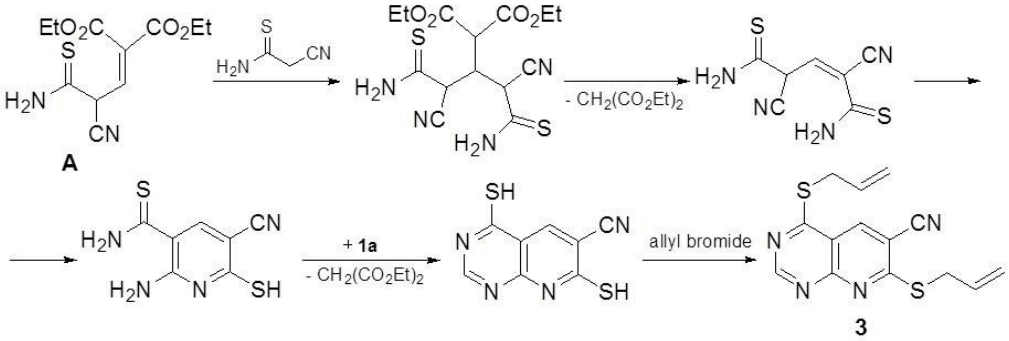
The first synthesis starting from enolether **1a** involves reaction with α-substituted thioacetamides (Scheme 1) under moderate or strongly basic conditions (ethanolic morpholine or ethanolic sodium ethoxide) [58-60] at ambient or reduced temperature and affords corresponding 6-sulfanyl-2-pyridones (**2**) as the main products. The formation of 2-pyridone skeleton involves nucleophilic vinylic substitution (S_NV) in which α-substituted thioacetamide behaves as *C*-nucleophile,



Scheme 1

and intermediate **A** is formed. Then almost spontaneous ring closure of this intermediate **A** takes place to give 6-sulfanyl-2-pyridone which can be subsequently *S*-alkylated [61] with appropriate alkyl halide.

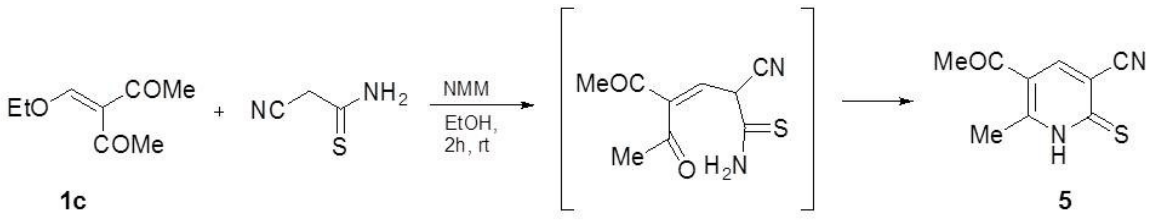
In the case of reaction of **1a** with 2-cyanothioacetamide, an unexpected product — i.e., 4,7-bis-(allylsulfanyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (**3**) — was also isolated after treatment with allyl bromide [61]. The most probable mechanism of its formation from intermediate **A** is depicted in Scheme 2



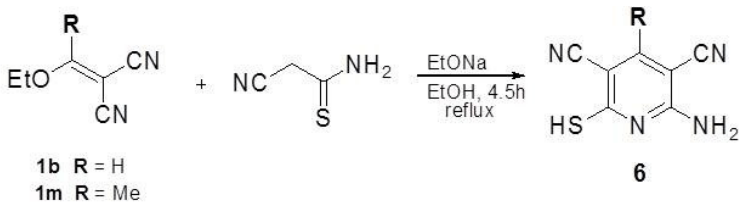
Scheme 2

Individual steps in Scheme 2 include Michael addition of the second molecule of 2-cyanothioacetamide to intermediate **A**, subsequent elimination of diethyl malonate and spontaneous ring closure to give 2-amino-5-cyano-6-sulfanylpyridine-thiocarboxamide. This compound reacts with diethyl ethoxymethylidenemalonate **(1a)** again and then undergoes ring closure and elimination of a second molecule of diethyl malonate. Finally, double alkylation with allyl bromide provides substituted pyrido[2,3-*d*]pyrimidine **3** [61].

However, α-substituted thioacetamides also contain another nucleophilic centre — i.e., nitrogen of thioamide group. If this nitrogen acts as nucleophile in nucleophilic vinylic substitution (S_NV), then intermediate **B** is formed whose ring closure gives corresponding alkylsulfanylpyrimidinones **4** [61] (Scheme 1). Similar base-catalyzed reaction of 2-cyanothioacetamide with ethoxymethylidene-acetylacetone [62] (**1c**) and ethoxymethylidenemalononitrile (**1b**) [63-65] was also described in the literature. It was found that the reaction gives either 5-acetyl-3-cyano-6-methylpyridine-2(1*H*)-thione (**5**) (Scheme 3) or pentasubstituted pyridines **6** (Scheme 4).

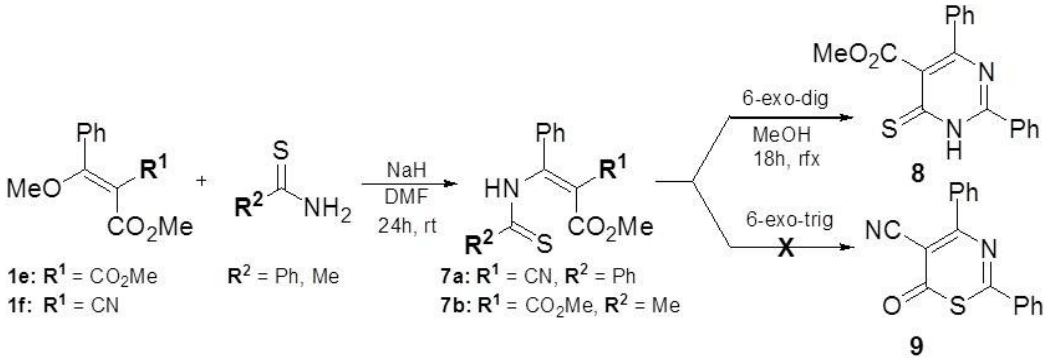


Scheme 3



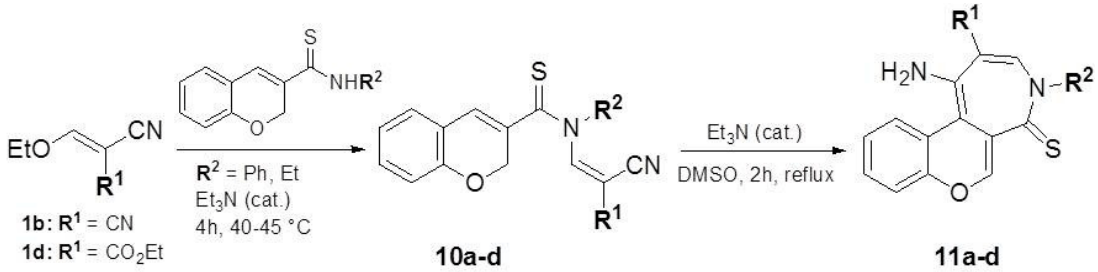
Scheme 4

Except α-substituted thioacetamides, base-catalyzed reactions of thiobenzamide with methyl 2-cyano-3-methoxy-3-phenylpropenoate (**1d**) and thioacetamide with dimethyl 1-methoxy-1-phenylmethylidenemalonate (**1e**) were studied at room temperature by Lorente *et al*. [66]. In both cases it was possible to isolate corresponding intermediates **7a,b** (S_NV). If these intermediates were refluxed in methanol, then methyl 2,6-diphenyl-4-thioxo-3,4-dihydropyrimidine-5-carboxylate **8** was formed from **7a** *via* 6-exo-dig cyclization, whereas no reaction occurred with **7b** (Scheme 5). The mechanism of transformation of **7a** to **8** is not known. Surprisingly, the formation of thiazine **9** which could be also formed *via* favorable 6-exo-trig cyclization of **7a** was not observed.



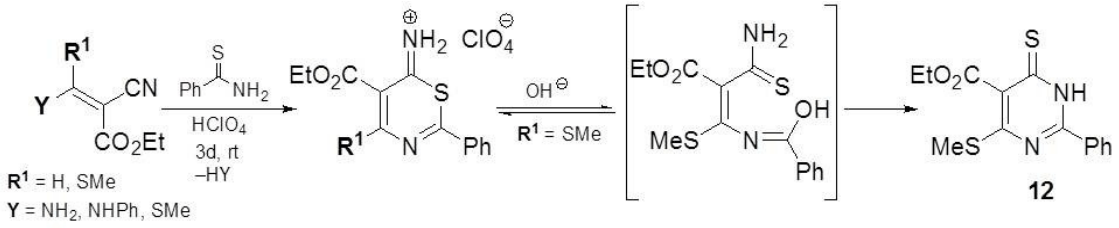
Scheme 5

In the case of *N*-ethyl- and *N*-phenyl-2*H*-chromene-3-carbothioamides, the first step of reaction with ethoxymethylidene malononitrile **(1b)** and ethyl ethoxymethylidene cyanoacetate (**1d**) gives analogous S_NV intermediate **10a-d**. However the subsequent triethylamine-catalyzed cyclization in DMSO gives neither 4-thioxo-3,4-dihydropyrimidine [67] nor 1,3-thiazine derivative, but a new seven-membered ring is formed (Scheme 6).



Scheme 6

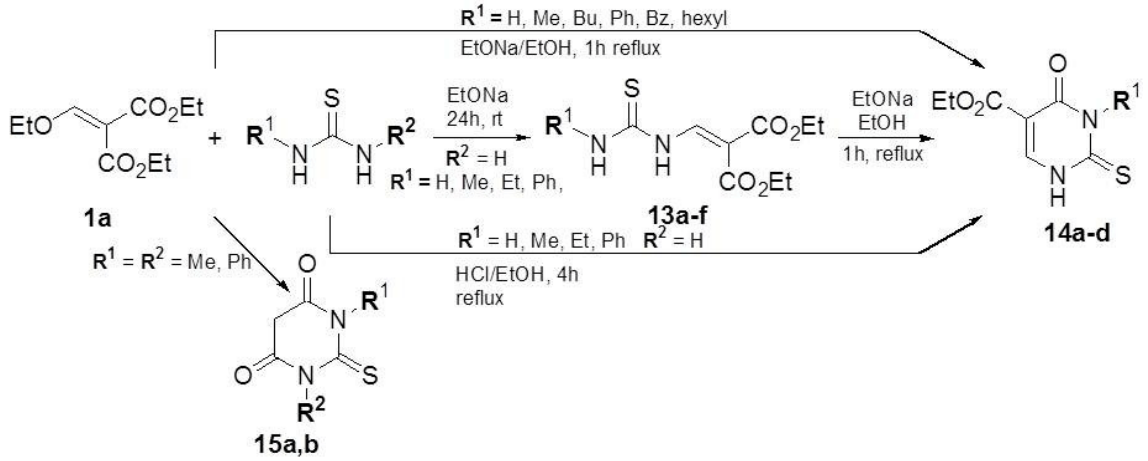
Finally, the reaction of enolthioethers with thiobenzamide in strong acid medium (perchloric acid) gives corresponding 1,3-thiazine hydroperchlorates which under basic conditions [68,69] undergo ring opening to thioacrylamides or to 4-thioxopyrimidine (**12**). (Scheme 7)



Scheme 7

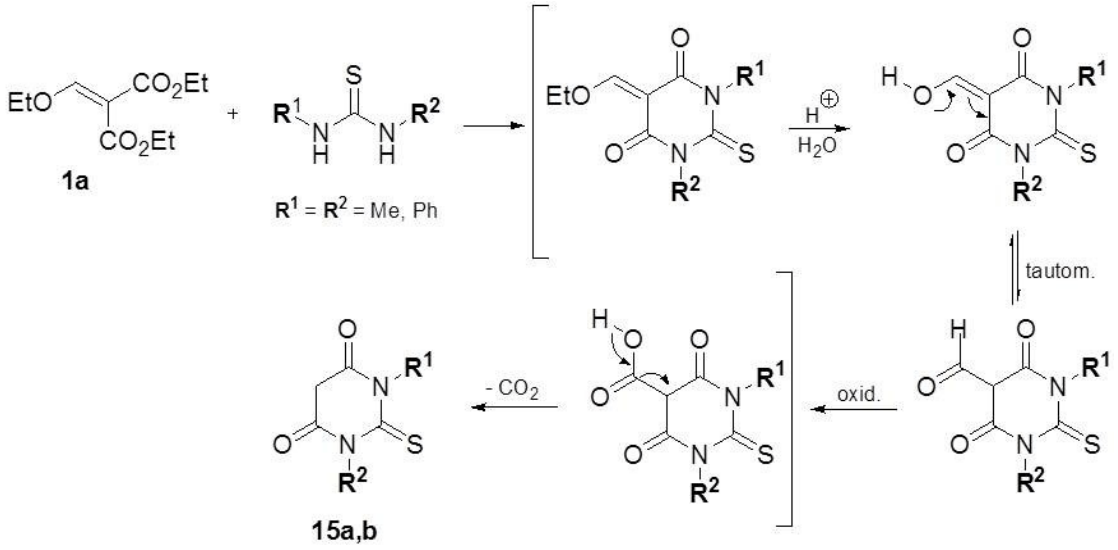
2.2 Thioureas

As early as in 1907, Wheller *et al*. [70] reported that diethyl ethoxymethylidene-malonate **(1a)** is not suitable for reaction with thiourea in the synthesis of pyrimidine. Unfortunately, these authors suggested quite harsh reaction conditions — alkali medium and heating at 140 °C. Later, Ballard and Johnson and many others found that **1a** smoothly reacts with thiourea to give pyrimidine (thiouracile derivative) **14a-d** in the presence of ethanolic sodium ethoxide under reflux (Scheme 8). Similar results were also obtained with *N*-alkyl- and *N*-aryl- thioureas **15a**, **b** [71-73]



Scheme 8

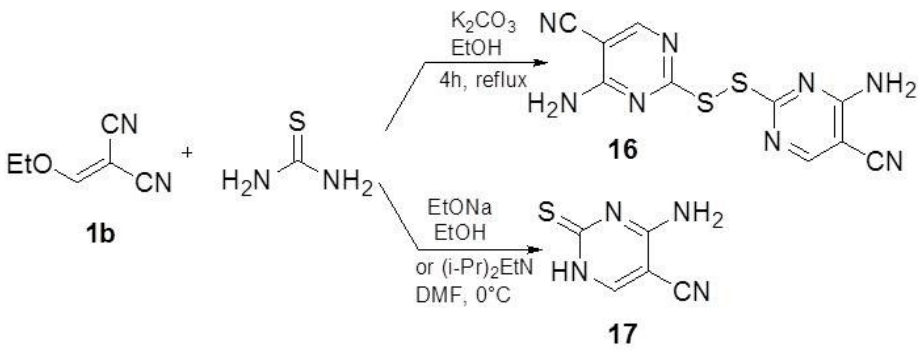
The formation of derivatives **15a**, **b** from polarized ethylene **1a** and 1,3-disubstituted thioureas is illustrated in Scheme 9.



Scheme 9

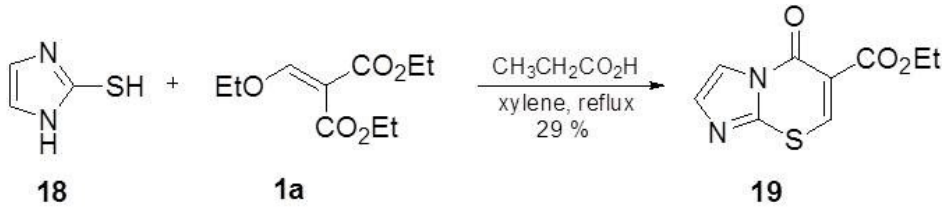
In 2007, Botsi *et al*. [73] developed a new method based on acid catalysis allowing easier separation of intermediates from thiouracil derivatives. Therefore, the reaction involves one or two steps. The first step involves nucleophilic vinylic substitution of protonated ethoxy group (better leaving group) and the second step involves intramolecular nucleophilic attack by the amino group of thiourea. While condensation of thiourea with **1a** provided tetrahydropyrimidine derivative, substituted thioureas gave at room temperature under acid catalysis mainly alkylureidomethylidenemalonates **13a-f**. These compounds can easily be transformed to the corresponding thiouracils **14a-d** under acid or base conditions. In the case of 1,3-disubstituted thioureas (methyl, phenyl), corresponding thiobarbituric acids **15a**, **b** were surprisingly formed (Scheme 9) [73].

Similar reaction takes place when ethoxymethylidene malononitrile (**1b)** is treated with thiourea. Under basic conditions such as sodium ethoxide in ethanol or diisopropyl(ethyl)amine in DMF, 4-amino-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (**17**) is formed. (Scheme 10) [72,75-77].



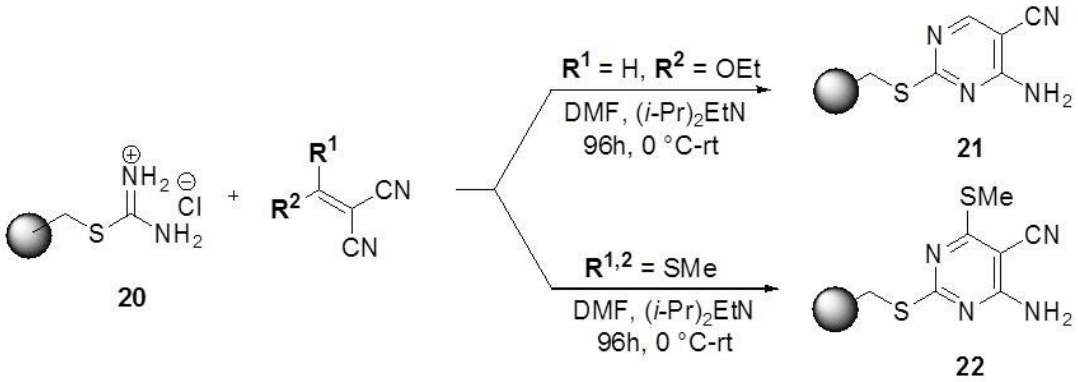
Scheme 10

Clayton *et al*. used 2-sulfanylimidazol (**18**) as a cyclic form of isothiourea in the reaction with **1a** [74] under reflux and isolated imidazo[2,1-*b*][1,3]thiazine derivative **19** in low 29% yield.



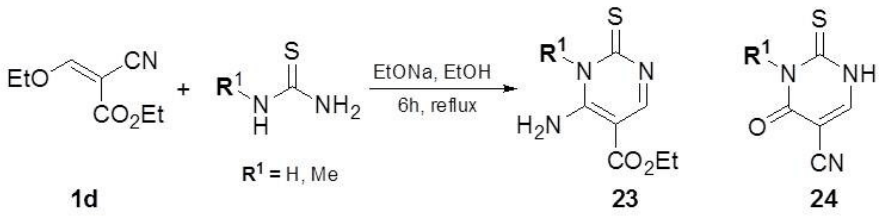
Scheme 11

Merrifield combinatorial solid phase [78] synthesis of isothiouronium salts **20** with **1b** or its bis(methylthio) derivative in the DMF provided polymer-bound (alkylthio) pyrimidines **21**, **22** in high yields and purity (Scheme 12). Further, El-Agrody *et al*. described a synthesis of bis-(4-amino-5-cyano-pyrimidine-2-yl)disulfide (**16**) from **1b** and thiourea in boiling K_2CO_3 ethanolic solution. It is obvious that this reaction involves the formation of compound **17** which in air undergoes subsequent oxidative S–S coupling which is connected with favorable aromatization of pyrimidine ring. (Scheme 10)



Scheme 12

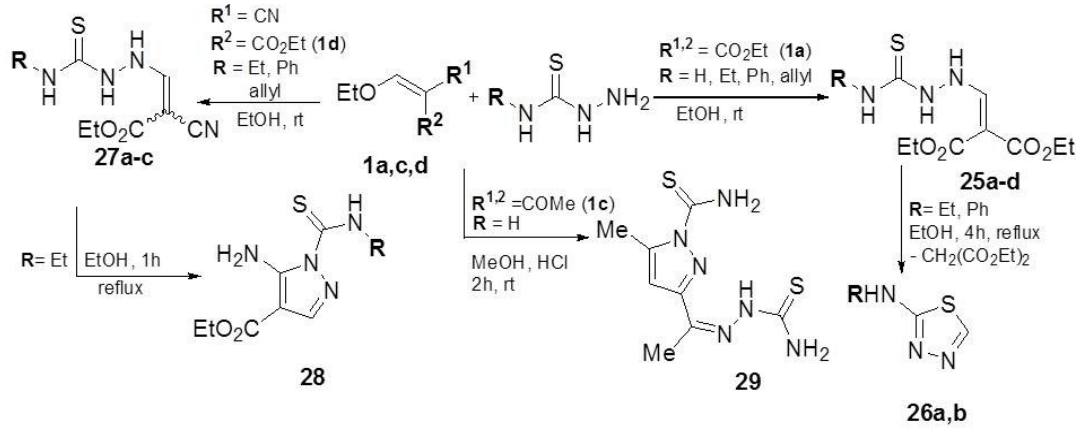
Access to the preparation of 5-amino substituted pyrimidines **23**, **24** was attained by the reaction of ethyl (ethoxymethylidene)cyanoacetate (**1d**) with substituted thioureas under basic conditions (sodium ethoxide). In the case of parent thiourea and its monosubstituted derivatives, two products **23** and **24** were formed. Compound **23** was always the major component [72,79-82] of this mixture because internal nucleophilic attack of cyano group is favorable. (Scheme 13)



Scheme 13

2.3 Thiosemicarbazides

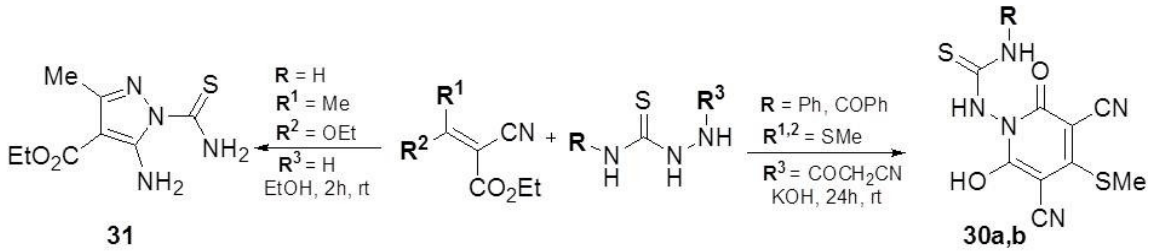
Thiosemicarbazides represent another type of ambident *S*- and *N*-nucleophiles/binucleophiles which can react with alkoxymethylidene compounds to give predominantly products of S_NV reaction, i.e., thiosemicarbazidomethyli-denes **25a-d**, **27a-c**. This reaction takes place in EtOH at room temperature. The first synthesis [83,84] was carried out in 1964 with **1a** or **1f** and unsubstituted thiosemicarbazide. Later, alkyl- and arylsubstituted thiosemicarbazides were also submitted to the reaction with **1a** and **1f**. In all the cases, S_NV products **25a-d**, **27a-c** were formed at room temperature which after heating under reflux for 4h gave 1,3,4-thiadiazoles **26a**, **b** in good yields [82]. Ethyl thiosemicarbazido-2-cyanoacrylate was also smoothly transformed to corresponding 5-aminopyrazole **28** under similar reaction conditions. Analogous result was achieved in the case of **1c**. Compound **1c** reacts with two equivalents of thiosemicarbazide in methanolic hydrochloric acid [85] to give 4-acetyl-5-methyl-1-thiocarbamoyl-pyrazol thiosemicarbazone (**29**) (Scheme 14).



Scheme 14

Many attempts were made with the aim to synthesize new biologically active purine derivatives where ketene dithioacetals, e.g., bis(methylthio) analogues of **1b** and **1d**, serve as a suitable starting material. These compounds

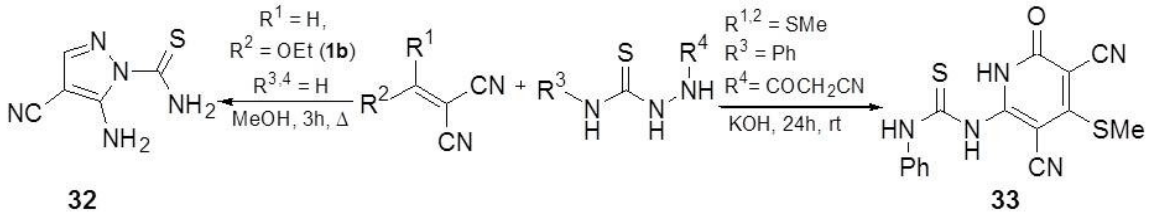
were submitted to the reaction with 4-substituted 1-cyanoacetylthiosemicarbazides [86] and gave *N*-substituted amino-4-methylsulfanyl-2-pyridones **30a**, **b** (Scheme 15). It is worth mentioning that with the methyl analogue of **1d**, the corresponding 1-thiocarbamoyl substituted pyrazole **31** [87] was isolated as the main reaction product (*cf*. Scheme 14).



Scheme 15

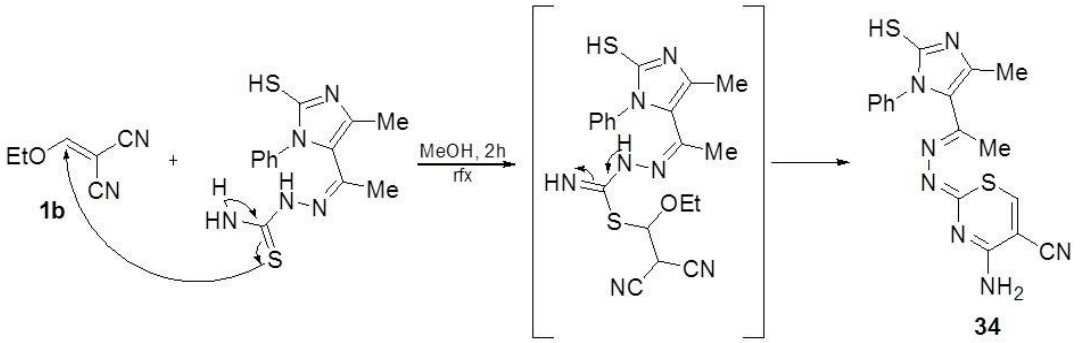
The formation of derivatives **30a**, **b** involves S_NV reaction in which 1-cyanoacetylthiosemicarbazide acts as *C*-nucleophile and methanethiol as leaving group. Then subsequent cyclization of this intermediate to the ester group takes place [86].

If (di)substituted methylidene malononitriles are submitted to the reaction with parent thiosemicarbazide or its cyanoacetyl derivative, then analogous pyrazole **32** or 4-sulfanyl pyridone **33** [86] is formed (Scheme 16).

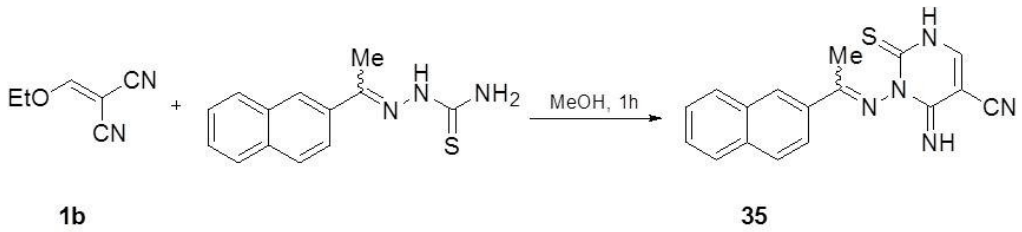


Scheme 16

On the other hand, thiosemicarbazones [88-90] react with **1b** in refluxing MeOH to give corresponding 1,3-thiazine **34** (Scheme 17) or pyrimidine **35** (Scheme 18).



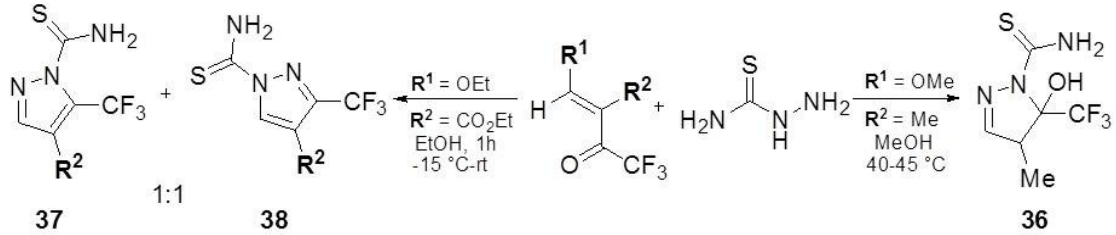
Scheme 17



1b **35**

Scheme 18

The last reported reaction of thiosemicarbazide involves its cyclo-condensation with β-alkoxyvinyl(trifluoromethyl)ketone in methanol under mild reaction conditions [91] to give pyrazolethiocarboxamide **36**. Similar reaction was also used for preparation of a new class of compounds inhibiting fibrinogen-mediated platelet aggregation. In this case, the synthesis started from ethyl (ethoxymethy1idene)trifluoroacetoacetate and gave an equimolar mixture of 3- and 5-substituted pyrazoles **37** and **38** [92] (Scheme 19).



37 **38** **36**

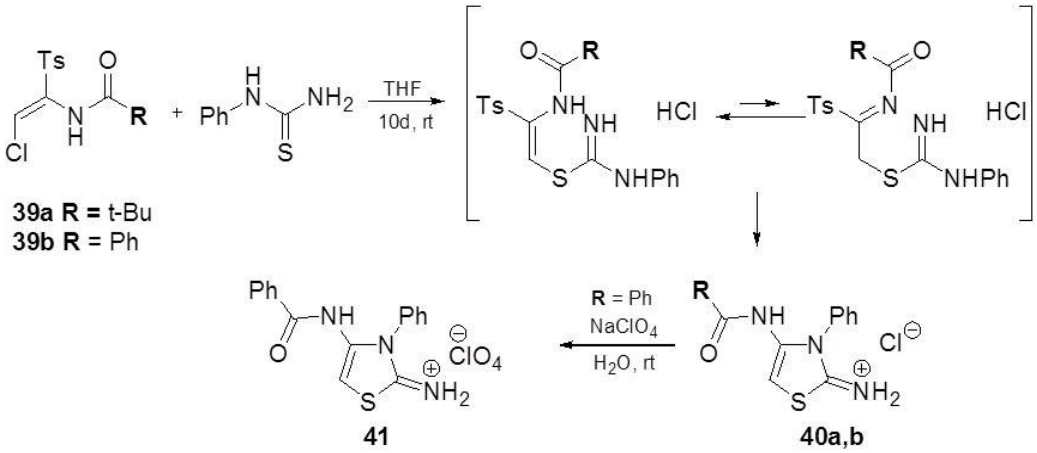
Scheme 19

3 Reaction of Halogenomethylidenes with *S*-nucleophiles — Thioamides, Thioureas, Thiosemicarbazides

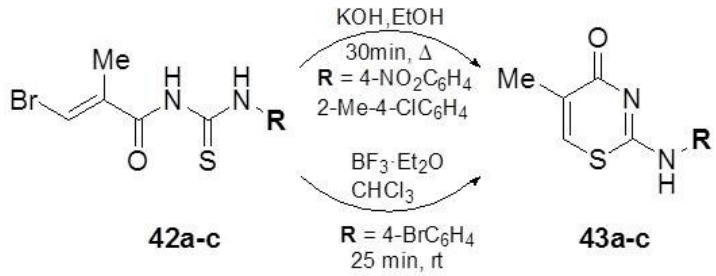
If a (thio)alkoxy group in a molecule of polarized alkene is replaced by the halogen group (e.g., bromide, chloride), the reactivity towards nucleophiles increases due to better leaving group.

Kharchenko in 1999 studied the reaction of *N*-[2-chloro-1-(tosylvinyl)]benz-amide (**39a**, **b**) with phenyl- and *tert*-butylthiourea to give thiazolidinones **41** (Scheme 20) after 10 days in THF at room temperature [93,94].

Bromoethylidene derivatives **42a-c** [95] represent a special type of polarized ethylenes, because they contain both the nucleophilic atom and polarized double bond. They undergo base- or Lewis acid-catalyzed cyclization to give corresponding 1,3-thiazine derivatives **43a-c** (Scheme 21**)**

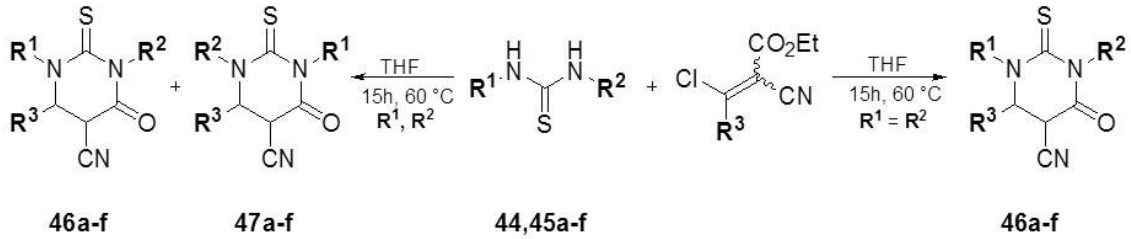


Scheme 20



Scheme 21

Nucleophilic vinylic substitutions of (*E,Z*)-mixture of ethyl 3-aryl-3-chloro-2-cyanopropenoates with (un)symmetrically substituted thioureas **44**, **45a-f** afforded, after spontaneous cyclization, 1,3-dialkyl- and 1,3-diaryl-5-cyano-2-thiouracils [96] (**46**, **47a-f**) derivatives as one or a mixture two compounds (Scheme 22)

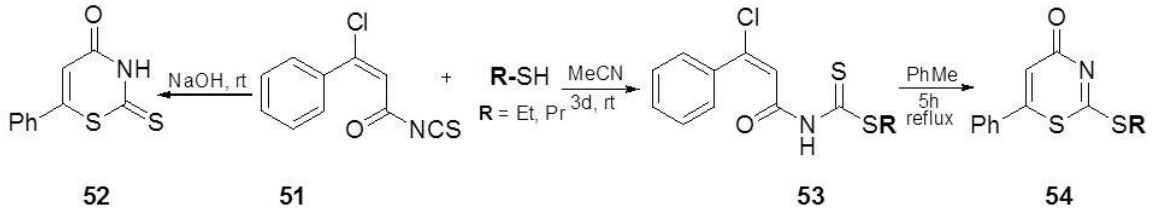


47a-f: R^1 = Ph, R^2 = Me, R^3 = Ph, 10 %
R^1 = Ph, R^2 = Me, R^3 = 4-MeC_6H_4, 10 %
R^1 = Ph, R^2 = Et, R^3 = Ph, 16 %
R^1 = $CH_2C_6H_5$, R^2 = Me, R^3 = Ph, 21 %
R^1 = $CH_2C_6H_5$, R^2 = Me, R^3 = 4-MeC_6H_4, 22 %
R^1 = Ph, R^2 = Et, R^3 = 4-MeC_6H_4, 15 %

46a-f: R^1 = R^2 = Ph, R^3 = Ph, 48 %
R^1 = R^2 = Me, R^3 = 4-MeC_6H_4, 52 %
R^1 = R^2 = Et, R^3 = Ph, 46 %
R^1 = R^2 = Et, R^3 = Ph, 41 %
R^1 = R^2 = allyl, R^3 = 4-MeC_6H_4, 37 %
R^1 = R^2 = allyl, R^3 = 4-MeC_6H_4, 36 %

Scheme 22

The paper by Imrich *et al*. [97] was dealing with application of 3-chloro-3-phenylpropenoyl isothiocyanate (**51**) in the reactions with ethyl, propyl and phenylmethanethiol which afforded the corresponding dithiourethanes **53**. By heating of these compounds in toluene, cyclization to 1,3-thiazine-4-ones (Scheme 23) took place. The structure of thiazines **54** was deduced from IR, UV, NMR and mass spectrometric data. Aiming to verify the foregoing observations, model substances with a fixed endocyclic C= N bond were synthesized.



52 51 53 54

Scheme 23

Acknowledgement

The Ministry of Education, Youth and Sports of the Czech Republic, Project CZ.1.07/2.3.00/30.0021 "Strengthening of Research and Development Teams at the University of Pardubice" financially supported this work.

References

[1] Milata V.: Ald Acta **34**, 20 (2001).
[2] Ressureicao A. S., Goncalves D., Sitoe A. R., Albuquerque I. S., Gut J., Góis A., Gonçalves L. M., Bronze M. R., Hanscheid T., Biagini G. A., Rosenthal P.J., Prudêncio M., O'Neill P., Mota M.M., Lopes F., Moreira R.: J. Med. Chem. **56**, 7679 (2013).
[3] Palanki M.S.S., Erdman P.E., Manning A.M., Ow A., Ransone L.J., Spooner Ch., Suto C., Suto M.: Bioorg. Med. Chem. Lett. **10**, 1645 (2000).
[4] Gerus I.I., Mironetz R.X.: Koudratov J.S., Bezdudny A.V., Dmytriv Y.V., Shishkin O.V., Starova V.S., Zaporozhets O.A., Tolmachev A.A., Mykhailiuk P.K.: J. Org. Chem. **77**, 47 (2012).
[5] Taylor E.C., Garcia E.E.: J. Org. Chem. **29**, 2116 (1964).
[6] Hunter G.A., Mc Nab H.: J. Chem. Soc. Perkin 1, 1209 (1995).
[7] Jourdain F., Pommelet J.C.: Synth. Commun. **27**, 483 (1997).
[8] Segelstein B.J., Chenard B.L., Macor J.E., Post R.J.: Tetrahedron Lett. **34**, 1897 (1993).
[9] Milata V.: Acta Chim. Slovaca **1**, 221 (2008).

[10] Musílek V., Černá J., Šašek M., Semerdžieva M., Vondráček M.: Folia Microbiol. **14**, 377 (1969).
[11] Anke T., Oberwinkler F., Steglich W., Scharmm G.: J. Antibiot. **30**, 1112 (1977).
[12] Aiba Y., Hasegawa D., Marunouchi T., Nagasawa K., Uchiro H., Kobayashi S.: Bioorg. Med. Chem. Lett. **11**, 2783 (2001).
[13] Lagoja I. M.: Chem. Biodivers. **2**, 1 (2005).
[14] Xie F., Zhao H., Li D., Chen H., Quan H., Shi X.,Lou L., Hu Y.: J. Med. Chem. **54**, 3200 (2011).
[15] Trivedi A. R., Dodiya D. K., Ravat N. R., Shah V. H.: Arkivoc **IX**, 131 (2008).
[16] Fathalla O. A., Radwan H. H., Awad S. M., Mohamed M. S.: Ind. J. Chem. **45B**, 980 (2006).
[17] Monge A., Martinez-Merino V., Sanmartin C., Fernandez F. J., Ochoa M. C., Bellver C., Artigas P., Fernandez-Alvarez E.: Eur. J. Med. Chem. **24**, 209 (1989).
[18] Mohana K.N., Basavapatna N., Kumar P., Mallesha L.: Drug Invention Today **5**, 216 (2013).
[19] Damanjit C.S.: Pharmacophore **4**, 70 (2013).
[20] Didwagh S.S., Piste P.B.: Int. J. Pharm. Sci. Res. **4**, 2045 (2013).
[21] Haider F, Haider Z.: J. Pharm. Chem. Res. **4**, 2263 (2012).
[22] Gayon M. Szymczyk H. Gérard E. Vrancken J.-M.: J. Org. Chem. **77**, 9205 (2012).
[23] Zhichkin D.J. Fairfax S.A. Eisenbein.: Synthesis, 720, (2002).
[24] Karpov A.S., Müller T.J.J. Synthesis, 2815 (2003).
[25] Movassaghi M., Hill M.D.: J. Am. Chem. Soc.**128**, 14254 (2006).
[26] Ahmad O.K. Hill M.D. Movassaghi M.: J. Org. Chem., **74**, 8460 (2009).
[27] Huang S., Pan Y., Wu A., Zhu Y.: Org. Lett. **7**, 3797 (2005).
[28] Rai V.K., Yadav B.S., Yadav L.D. S: Tetrahedron **65**, 1306 (2009).
[29] El-Taweel F.M.A.A., Elnagdi M.H.: J. Heterocycl. Chem. **38**, 981 (2001).
[30] Fu L., Li Y., Ye D., Yin S.: Chem. Nat. Compd. **46**, 169 (2010).
[31] Balenkova E.S., Nenajdenko V. G.: ARKIVOC, **I**, 246 (2011),
[32] Bhangale L.P., Sawant R.L., Wadekar J.B.: Int. J. Drug Design Dis. **2**, 637 (2011).
[33] Charjan A.P., Rajput P.R., Rathod S.P.: Rasayan J. Chem. **3**, 363 (2010).
[34] Al-Difar H.A., Elarfi M.J.: Sci. Revs. Chem. Commun. **2**, 103 (2012).
[35] Gowramma B., Jubie S., Kalirajan R., Sivakumar S.U. Suresh B.: Int. J. Chem. Tech. Res. **1**, 27(2009).
[36] Dighade A.S., Dighade S.R.: Pharm. Chem. **4**, 1863 (2012).
[37] Biehl Ed, Sathunuru R.: ARKIVOC **XIV**, 51 (2004).
[38] Hossaini Z., Nematpour M., Yavari, I.: Monatsh. Chem. **141**, 229 (2010).

[39] Fedoseev V.M., Mandrugin A.A., Trofimova T.P., Zefirova O.N.: Moscow Uni. Chem. B, **63**, 274 (2008).
[40] Batra S., Bhowmik S., Mishra A.: RSC Adv **1**, 1237 (2011).
[41] Sambhaji P.V., Shivraj B.S.: Org. Chem. Curr. Res.**1**, 1 (2012).
[42] Nagaraj A., Reddy C.S.: J. Iran Chem. Soc. **5**, 262 (2008).
[43] Glotova T.E., Kamarova T.N., Lopyrev V.A., Nakhmanovich A.S.: Russ. Chem. B+, **49**, 1917 (2000).
[44] Dzurilla M., Ficeri V., Koscik D., Kraus R., Kutschy P.: Chem. Papers **44**, 45 (1990).
[45] Fisyuk A. S., Peretokin N.V., Unkovsky B. V.: Chem. Heterocycl. Compd. **39**, 802 (2003).
[46] Jagodzinska E., Jagodzinski T. S., Rump S., Wesolowska A.: Acta Polomac Pharma- Drug Res. **60** , 67 (2003).
[47] Rai V.K., Yadav L.D.S., Yadav S.: Tetrahedron **61**, 10013 (2005).
[48] Siddiqui I.R., Singh J., Singh P.K., Srivastava V.: Indian J. Chem. **49B**, 512 (2010).
[49] Duburs G., Mishnev A., Ozols J., Vigante B. Chekavichus B.: Chem. Heterocycl. Compd. **36**, 862 (2000).
[50] Fedoseev V.M., Tkachenko S.E., Trofimova T.P.: Chem. Heterocycl. Compd. **38**, 1533 (2002).
[51] Kruithof A., Ploeger M.L., Janssen E., Helliwell M., de Kanter F.J.J., Ruijter F., Orru R.V.A.: Molecules **17**, 1675 (2012).
[52] Ali Tel S., El-Kazak A.M.: Eur. J. Chem. **1**, 6 (2010).
[53] Abdel-Latif F.F., Hassan A.A., Mostafa S.M., Nour El-Din A. M. Bräse S.: Chem. Papers **66**, 295 (2012).
[54] Legay R., Lohier J.F., Peudru F., Reboul V., Gulea M.: Tetrahedron **68**, 9016 (2012).
[55] Dabholkar V.V., Parab S.D.: **1**, 176 (2011). Available in: http://www.heteroletters.org.
[56] Ivin B.A., Moskvin A.V.,Yuskovets V.N.: Russ. J Gen. Chem. **74**, 312 (2004).
[57] Kleinpeter E., Markovic R., Rašovic A., Steel P.J.: Tetrahedron **63**, 1937 (2007).
[58] Yakunin Y.Y., Dyachenko V.D., Litvinov V.P.: Russ. Chem. Bull. **48**, 195 (1999).
[59] Britsun V.N., Esipenko A.N., Piroghenko V.V., Lozinskii M.O.: Chem. Heterocycl. Compd. **44,** 979 (2008).
[60] Dyachenko V.D., Tkacheva V.P., Dyachenko A.D., Tkachev R.P.: Russ. J. Gen. Chem. **80**, 1034 (2010).
[61] Tkachev R.P., Bityukova O.S., Dyachenko V.D., Tkacheva V.P., Dyachenko A.D.: Russ. J. Gen. Chem. **77**, 116 (2007).
[62] Yakunin Y.Y., Dyachenko V.D., Litvinov V.P.: Chem. Heterocycl. Compd.

37, 581 (2001).
[63] Shestopalov A.M., Sharanin Y.A., Litvinin V.P., Mortikov V.Y., Nesterov V.N.: J. Gen. Chem. (USSR) **57**, 959 (1987).
[64] Sharanin Y.A., Shestopalov A.M., Litvinin V.P., Klokol G.V., Mortikov V.Y., Demerkov A.S.: J. Org. Chem. (USSR), **24**, 771 (1988).
[65] Ibrahim D.A., Ismail N.S.M.: Eur. J. Med. Chem. **46**, 5825 (2011).
[66] Lorente A., Vaquerizo L., Martín A., Gómez-Sal P.: Heterocycles **41,** 71 (1995).
[67] El-Sayed A.M., Allah O.A.A.: Phosphorus, Sulfur Silicon Relat. Elem. **170**, 75 (2001).
[68] Briel D.: Heterocycles **60**, 2273 (2003).
[69] Briel D.: Heterocycles **63**, 2319 (2004).
[70] Wheeler H.L., Johnson C.O., Johns C.O.: Amer. Chem. J. **37**, 392 (1907).
[71] Ballard E., Johnson T.B.: J. Am. Chem. Soc. **64**, 794 (1942).
[72] Whitehead C.W., Traverso J.J.: J. Am. Chem. Soc. **78,** 5294 (1956).
[73] Botsi S., Tsolomytis A.: Heterocycl. Commun. **13**, 229 (2007).
[74] Clayton P.J., O'Hanlon P.J., King T.J.: J. Chem. Soc., Perkin Trans. 1, 1352 (1980).
[75] 1954 US Patent 2,698,326.
[76] Chatterjee S.K.: Anand J.: J. Sci. Ind. Res. **17B**, 63 (1958).
[77] Gottis S.G., Tieckelmann, H.: J. Org. Chem. **26**, 79 (1961).
[78] Masquelin T., Sprenger D., Baer R., Gerber F., Mercadal Y.: Helv. Chim. Acta **81**, 646 (1998).
[79] Johnson T.B., Ambler J.A.: J. Am. Chem. Soc., **33**, 978 (1911).
[80] Scherbina E.S., Dar´in D.V., Lobanov P.S.: Chem. Heterocycl. Compd. **46,** 1109 (2010).
[81] Ulbricht T.L.V., Price Ch.C.: J. Org. Chem. **21**, 567 (1956).
[82] Anderson G.W., Halverstadt I.F., Miller W.H., Roblin Jr. R.O.: J. Am. Chem. Soc. **67,** 2197 (1945).
[83] Santilli A.A., Bruce W.F., Osdene T.S.: J. Med. Chem. **7**, 68 (1964).
[84] Howe R.K., Boluyt S.C.: J. Org. Chem. **34**, 1713 (1969).
[85] Menichi G., Boutar M., Kokel B., Takagi K., Hubert- Habart M.: J. Heterocycl. Chem. **23**, 275 (1986).
[86] Elgemeie G.H., Elghandour A.H., Elzanate A.M., Masoud W.A.: J. Chem. Res. (S), 164 (1998).
[87] Kreutzman J.: Pharmazie **37**, 526 (1982).
[88] Gomha S.M., Riyadh S.M., Abbas I.M., Bauomi M.A.: Heterocycles **87**, 341 (2013).
[89] El-Dean J.: J. Chem. Res. (S) Miniprint **10**, 2255 (1997).
[90] Gomha S.M., Badrey M.G.: J. Chem. Res. **37**, 86 (2013).
[91] Bonacorso H.G., Wastowski A.D., Zanatta N., Martins M.A.P., Naue J.A.:

J. Fluor. Chem. **92**, 23 (1998).
[92] Sanfilippo P.J., Urbanski M.J., Beers K.N., Eckardt A., Falotico R., Ginsberg M.H., Offord S., Press J.B., Tighe J., Tomko K., Andrade-Gordon P.: J. Med. Chem. **38**, 34 (1995).
[93] Kharchenko A.V.: Zh. Obsch. Kh. **69**, 349 (1999).
[94] Kharchenko A.V.: Russ. J. Gen. Chem. **69**, 340 (1999).
[95] Koščík, D., Dzurilla, M., Kutschy, P.: Collect. Czech. Chem. Commun. **58**, 893 (1993).
[96] Jalander L.F., Lönnqvist J.E.: Heterocycles **48**, 743 (1998).
[97] Imrich J., Kristián P.: Collect. Czech. Chem. Commun. **47**, 3268 (1982).