Article

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ACS Comb. Sci., **Just Accepted Manuscript** • DOI: 10.1021/co5001376 • Publication Date (Web): 19 Jun 2015

A New Convenient Strategy for Annulation of Pyrimidines to Thiophenes or Furans via the One-pot Multistep Cascade Reaction of 1*H*-Tetrazoles with Aliphatic Amines

Nazariy T. Pokhodylo,* Olga Ya. Shyyka, Vasyl S. Matiychuk, Mykola D. Obushak

Department of Organic Chemistry, Ivan Franko National University of Lviv, Kyryla i Mefodiya St. 6, Lviv 79005, Ukraine.
E-mail: pokhodylo@gmail.com

Abstract — A versatile, convenient, efficient and high-yield synthetic method for 2-R^3,R^4-amino-5-R^1-6-R^2-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones, 2-R^3,R^4-amino-5-R^1-6-R^2-thieno[3,2-*d*]pyrimidin-4(3*H*)-ones and benzofuro[3,2-*d*]pyrimidin-4(3*H*)-ones preparation has been developed. The reaction proceeded without using solvents and included several steps. A variety of thieno[2,3-*d*]pyrimidine and thieno[3,2-*d*]pyrimidine derivatives with substituents of different nature were obtained in high yields from substituted alkyl 2-(1*H*-tetrazol-1-yl)thiophene-3-carboxylates, 3-(1*H*-tetrazol-1-yl)thiophene-2-carboxylates and 3-(1*H*-tetrazol-1-yl)benzofuran-2-carboxylate after their treatment with aliphatic amines.

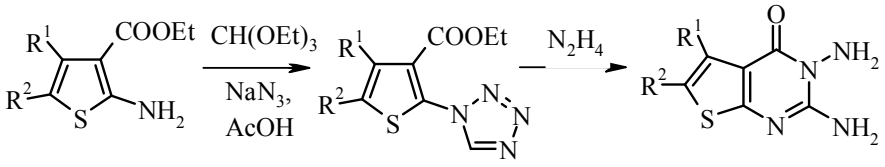
Keywords: tetrazole, thieno[2,3-*d*]pyrimidin-4(3*H*)-one, thieno[3,2-*d*]pyrimidin-4(3*H*)-one, benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one, heterocyclization.

Introduction

Thienopyrimidine derivatives have attracted considerable interest in pharmaceutical discovery in cancer and antivirus research.[1-9] Therefore, the development of new efficient and mild syntheses of the thienopyrimidine framework is a useful task, particularly when one-step procedures from readily-available reagents can be employed.[11]

The Gewald thiophenes[12] are used as starting materials in many routes to thieno[2,3-*d*]pyrimidines.[13-20] We have recently reported that alkyl 2-(1*H*-tetrazol-1-yl)-4-R^1-5-R^2-thiophene-3-carboxylates, obtained from alkyl 2-amino-thiophene-3-carboxylates by the reaction with triethyl orthoformate and sodium azide under conditions of hydrazinolyzation of the ester group, underwent recyclization including cleavage of the tetrazole ring, elimination of the nitrogen molecule and annulation of the pyrimidinone core (Scheme 1).[21] This simple and convenient synthetic path opened access to 2,3-diaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones and allowed us to presume that the tetrazole ring cleavage and loss of nitrogen could proceed under mild conditions (hydrazine solution). The ready access to the cyanamide moiety makes alkyl 2-(1*H*-tetrazol-1-yl)-4-R^1-5-R^2-thiophene-3-carboxylates the potentially useful precursors to a range of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones, a transformation elaborated here.

Scheme 1. 2,3-Diaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones synthesis

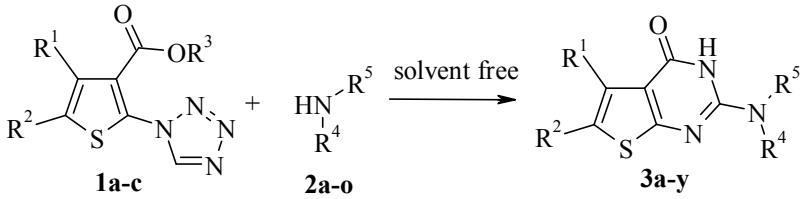


Results and Discussion

As a continuation of our work on the tetrazole ring cleavage *via* nucleophilic attack, we examined a number of amines in such a reaction to find its scope and limitations. Replacement of hydrazine by basic amines led to the same type of reaction (Scheme 2), which could be performed without solvent by simple heating to 80-90 °C in a small excess of amine. The reaction time depended on the basicity and nucleophility of amine. Monitoring of the reaction progress was performed using TLC on Silufol plates and IR spectroscopy, noting a characteristic shift of the carbonyl

absorption band from 1710-1725 cm^{-1} in the initial tetrazoles to 1660-1680 cm^{-1} in the target thienopyrimidines.

Scheme 2. Synthesis of novel thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **3**.



1a: $R^1=R^2=Me$
1b: $R^1=R^2=-(CH_2)_2-$
1c: $R^1=Ph$, $R^2=H$

We examined a number of different amines, shown in Figure 1. The results, summarized in Table 1 and shown in detail in Table 2, revealed three main outcomes. Interestingly, aqueous ammonia was found to be unreactive, perhaps due to a great decrease in the solubility of NH_3 (11.1 g per 100 g of water) at the temperature of the reaction (70 °C). In case of other reagents, a good correlation between the basicity of amines and the ability to form thienopyrimidines was found. The target thienopyrimidines **3a-y** were easily prepared in excellent yield from thienotetrazoles and a wide range of basic and nucleophilic amine reagents, giving more than 30 new compounds of this class, was found. In contrast, weakly basic amines **2q-v** ($pK_a < 6$) were unreactive in this protocol. Since good nucleophiles in this category (hydrazines and an aminoether) were also ineffective, it is rather basicity than nucleophilicity that is the most important. Diisopropylamine **2p** was found to be sufficiently basic to generate cyanamides **4a-c**, but too hindered to add to these electrophiles. Intermediate cyanamides **4a** and **4b** were also easily obtained in quantitative yields by the addition of tetrazole **1** to sodium methoxide in methanol at room temperature.

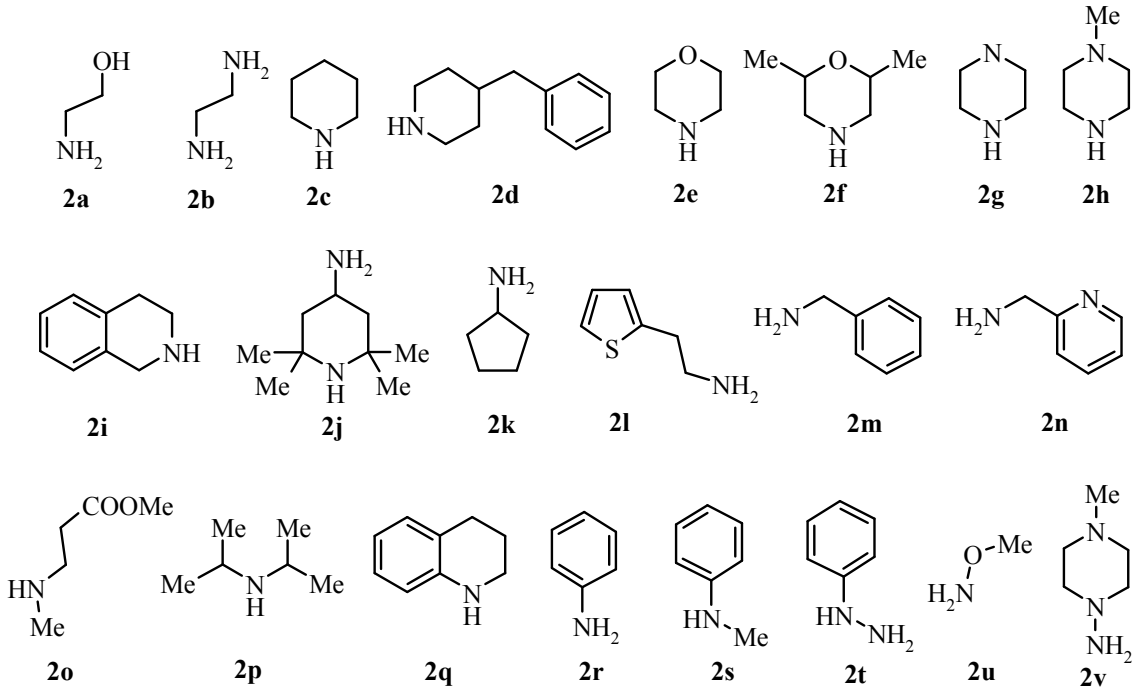


Figure 1. Amines tested in the reaction.

Table 1. General results of reactions with the use of amines shown in Figure 1 with tetrazoles **1a-c**.

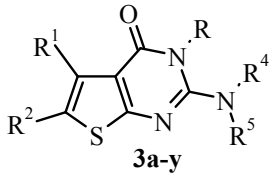
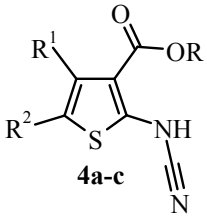
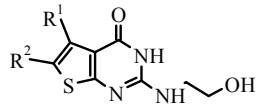
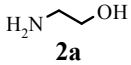
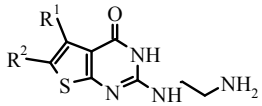
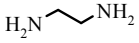
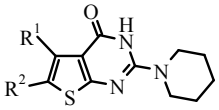
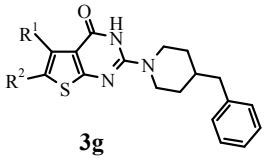
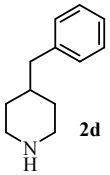
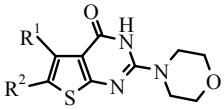
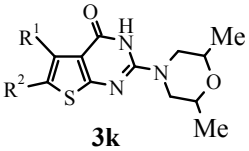
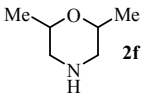
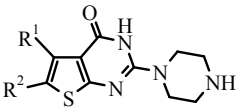
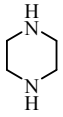
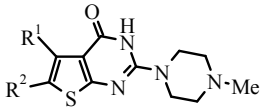
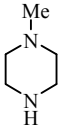
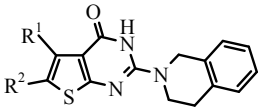
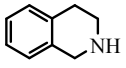
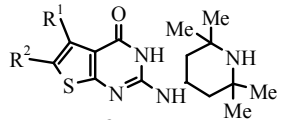
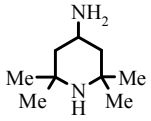
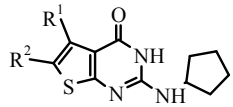
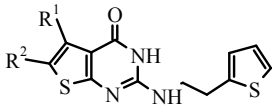
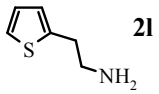
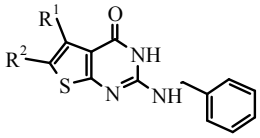
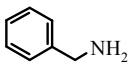
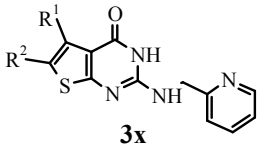
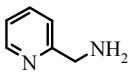
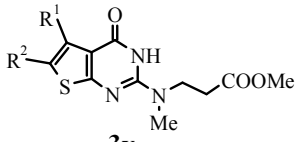
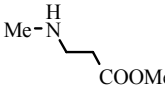
Type of amines	Result
1) strong base, strong nucleophile **2a-o**	Complete formation of the expected thienopyrimidin-4(3*H*)-ones; isolated yields >88%  **3a-y**
2) strong base, weak nucleophile **2p**	Isolation of intermediate cyanamide in >98% yield  **4a-c**
3) weak base **2q-v**	No reaction, with recovery of initial reagents, for reactions up to 20 h at 160°C in case of aniline

Table 2. Detailed results of the reactions of tetrazoles **1a-c** with amines **2a-o**.

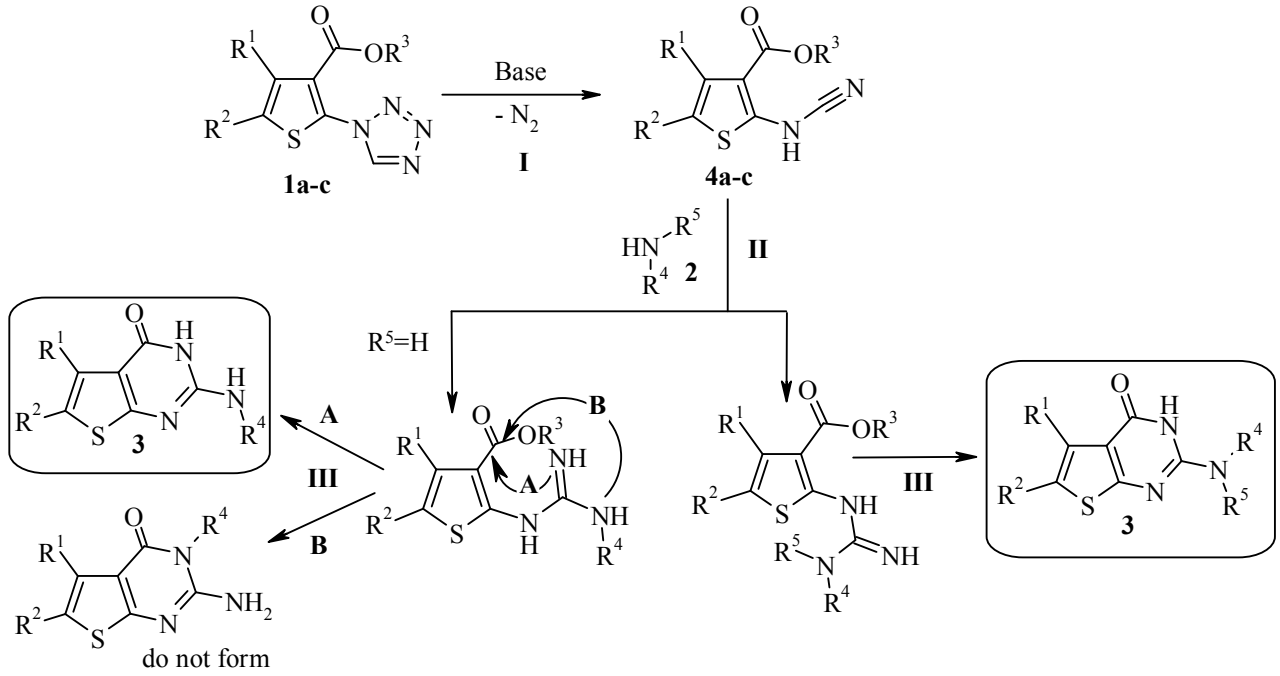
Product	Base-nucleophile	Tetrazole involved in reaction	Reaction time, minutes	Yield, %[a] (product number)		
				R^1=R^2=Me	R^1+R^2= -$(CH_2)_2$-	R^1=Ph, R^2=H
3a-y	**2a-q**	**1a-c**				
 **3a,b**	 **2a**	**1a,1b**	30	95 (**3a**)	96 (**3b**)	N/A[b]
 **3c,d**	 **2b**	**1a,1c**	45	95 (**3c**)	N/A	93 (**3d**)
 **3e,f**	 **2c**	**1a,1c**	60	96 (**3e**)	N/A	92 (**3f**)
 **3g**	 **2d**	**1a**	45	95 (**3g**)	N/A	N/A
 **3h-j**	 **2e**	**1a-c**	30	93 (**3h**)	94 (**3i**)	93 (**3j**)
 **3k**	 **2f**	**1a**	30	94 (**3k**)	N/A	N/A
 **3l**	 **2g**	**1a**	30	93 (**3l**)	N/A	N/A
 **3m-o**	 **2h**	**1a-c**	30	95 (**3m**)	95 (**3n**)	93 (**3o**)
 **3p-r**	 **2i**	**1a-c**	45	89 (**3p**)	89 (**3q**)	88 (**3r**)

 **3s,t**	 **2j**	**1a,1b**	30	90 (**3s**)	91 (**3t**)	N/A
 **3u**	 **2k**	**1a**	30	96 (**3u**)	N/A	N/A
 **3v**	 **2l**	**1a**	60	90 (**3v**)	N/A	N/A
 **3w**	 **2m**	**1a**	60	90 (**3w**)	N/A	N/A
 **3x**	 **2n**	**1a**	60	90 (**3x**)	N/A	N/A
 **3y**	 **2o**	**1a**	30	91 (**3y**)	N/A	N/A

[a] Yields of compounds after isolation and purification in a single experiment are given.
[b] N/A – reactions are not studied.

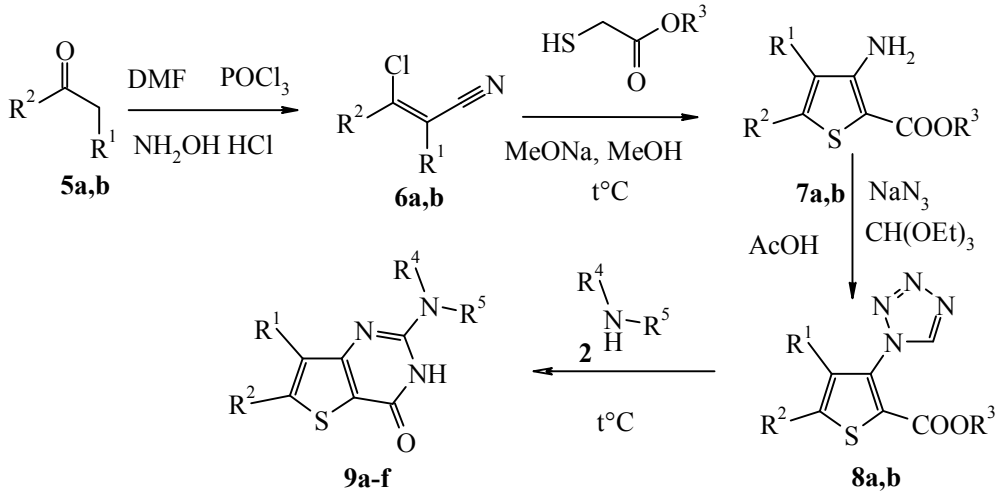
Consistent with these observations is the proposed three-step reaction mechanism shown in Scheme 3, involving the tetrazole ring cleavage, nucleophilic addition, and intramolecular cyclization. The action of base is thought to be crucial to the first step to induce proton elimination from the tetrazole ring to generate the tetrazolyl anion, which opens being accompanied by elimination of dinitrogen. Addition of the corresponding amines to the resulting cyanamide provides a guanidine moiety that undergoes rapid annulation to the pyrimidine ring. The reaction occurs regioselectively, with ^{1}H NMR confirming the formation of only one thienopyrimidine product in each case, having the substituent at the exocyclic nitrogen atom. The purity of all compounds was established by liquid chromatography with UV and mass detection.

Scheme 3. Proposed reaction mechanism.



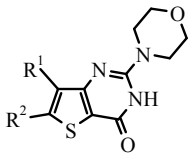
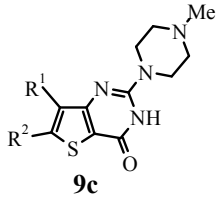
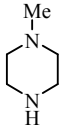
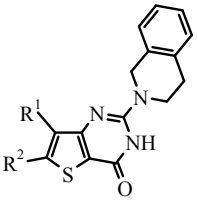
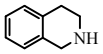
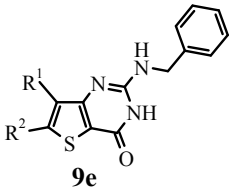
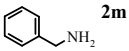
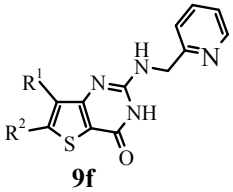
Recently, in the frame to broaden the applicability of the proposed thienopyrimidine formation approach, we have used alkyl 3-(1*H*-tetrazol-1-yl)-4-R^1-5-R^2-thiophene-2-carboxylates **9** in such a protocol, which were prepared *via* known procedures[24,25] from commercially available starting materials (Scheme 4).

Scheme 4. 2-R^3,R^4-amino-5-R^1-6-R^2-thieno[3,2-*d*]pyrimidine-4(3*H*)-ones synthesis.



The reaction of tetrazoles **8** with amines **2** was carried out under the same conditions by heating to 80-90°C without a solvent. The target substituted 2-R^3,R^4-amino-5-R^1-6-R^2-thieno[3,2-*d*]pyrimidine-4(3*H*)-ones **9e-f** were isolated in high yields. The results are summarized and shown in detail in Table 3.

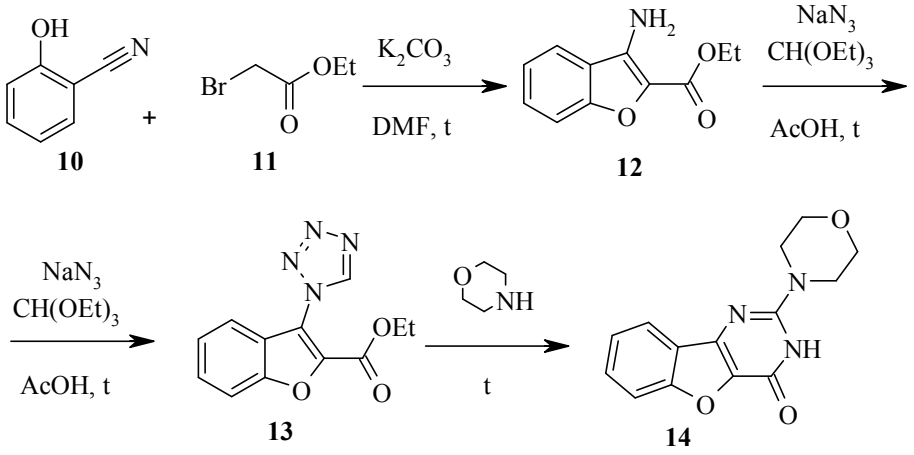
Table 3. Detailed results of the reactions of tetrazoles **8** with amines **2**

Product	Base-nucleophile	Tetrazole involved in reaction	Reaction time, minutes	Yield, %[a] (product number)	
				R^1+R^2= -$(CH_2)_2$-	R^1=H, R^2= Ph
9a-f	**2e,h,i,m,n**	**8a,b**			
 **9a,b**	 **2e**	**8a,8b**	45	95 (**9a**)	93 (**9b**)
 **9c**	 **2h**	**8a**	30	90 (**9c**)	N/A
 **9d**	 **2i**	**8a**	45	89 (**9d**)	N/A
 **9e**	 **2m**	**8a**	30	93(**9e**)	N/A
 **9f**	 **2n**	**8b**	45	N/A	92(**9f**)

[a] Yields of compounds after isolation and purification in a single experiment are given.
[b] N/A – reactions are not studied.

As a continuation of our work we examined a number of heterocyclic tetrazoles to prove the applicability of such a tetrazole ring cleavage method. For this purpose, at first, 3-amino-benzofuran derivative **12** was prepared (Scheme 5)[22]. Amine **12** was successfully transformed into the corresponding tetrazole **13** in the same way as the above described thienotetrazoles were obtained (Scheme 4). The treatment of tetrazoles **13** with moprholine **2e** under the tetrazole ring cleavege conditions gave benzofuro[3,2-*d*]pyrimidinone **14** in high yields.

Scheme 5. Benzofuro[3,2-*d*]pyrimidinone **14** preparation



Moreover, a variety of heterocyclic amines **15a-f** (Fig. 2) with the neighboring in ortho position ester/nitrile group were synthesized in our laboratory according to known procedures.[23-26] Nowadays, two synthetic pathways: a one-step procedure, as described for aminothiophenes and two-step protocol through isolation of the intermediate ethoxymethylene amino derivatives were tested for tetrazole ring closure reactions from the corresponding amines **15a-f**. It was found out that, these derivatives were relatively inert in such reactions, so methods for such heterocyclic tetrazoles construction and applicability of these tetrazoles in 2-N-substituted condensed pyrimidines synthesis are currently under investigation.

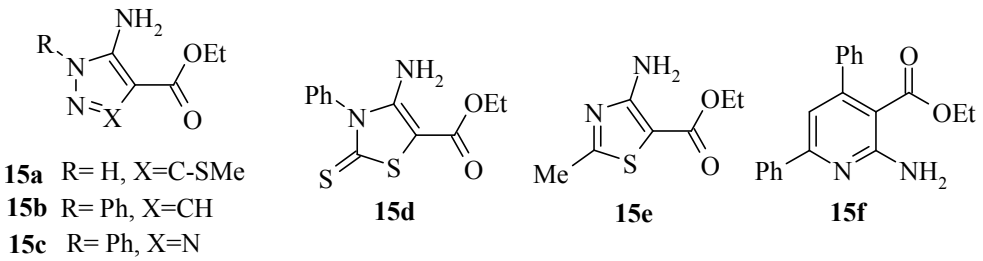


Figure 2. Heterocyclic amines **15a-f** with the neighboring in ortho position ester/nitrile group.

Conclusion

It was shown that thieno[2,3-*d*]pyrimidine as well as thieno[3,2-*d*]pyrimidine and benzofuro[3,2-*d*]pyrimidine derivatives could be easily obtained *via* a new solvent-free reaction of tetrazoles with amines. This simple reaction accommodates many different basic amines and proceeds in high yields under mild conditions. The pathway described here *via* the readily accessible 2-tetrazolylthiophene is more convenient than the related approach through 2-isothiocyanate derivatives[28] and complementary to the use of 2-aminothiophenes and secondary cyanamides.[27] Reactions of other types of tetrazoles and primary/secondary amines are currently under investigation in our group and will be reported in due course.

Experimental Procedures

General

^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker instrument (500 MHz for ^{1}H, 125 MHz for ^{13}C). The ^{1}H and ^{13}C chemical shifts were reported in parts per million relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. IR spectra were recorded on a Specord 80 instrument in KBr tablets and in solution CCl_4.

General procedure for the synthesis of alkyl 3-(1*H*-tetrazol-1-yl)thiophene-2-carboxylates 8a,b and ethyl 3-(1*H*-tetrazol-1-yl)benzofuran-2-carboxylate 13

A suspension of 50 mmol of the required thiophene **7** or benzofurane **12**, triethyl orthoformate (37.9 mL, 0.23 mol), and sodium azide (3.9 g, 0.06 mol) in glacial acetic acid (40 mL) was stirred and heated at reflux for 2 h. The reaction mixture was cooled to room temperature and 7 mL of concd HCl was added. The solid was filtered off and the filtrate evaporated and the residue was recrystallized from ethanol.

General procedure for the synthesis of 2-R^3,R^4-amino-5-R^1-6-R^2-thieno[2,3-*d*]pyrimidine-4(3*H*)-ones 4,5, 2-R^3,R^4-amino-5-R^1-6-R^2-thieno[3,2-*d*]pyrimidine-4(3*H*)-ones 9, benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one 14

A suspension of an appropriate tetrazole **1a-c, 8a,b, 13** (1 mmol) in 0,7-1 mL of the corresponding amine **2a-p** was heated at 80-90 °C for 0,5-1 hour (mentioned in Tables 2, 3), then cooled and diluted with water. The solid was filtered and recrystallized from ethanol.

Supporting Information

Compound characterization data, ^{1}H NMR and ^{13}C NMR spectra for new compounds are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: *pokhodylo@gmail.com*

Notes

The authors declare no competing financial interest.

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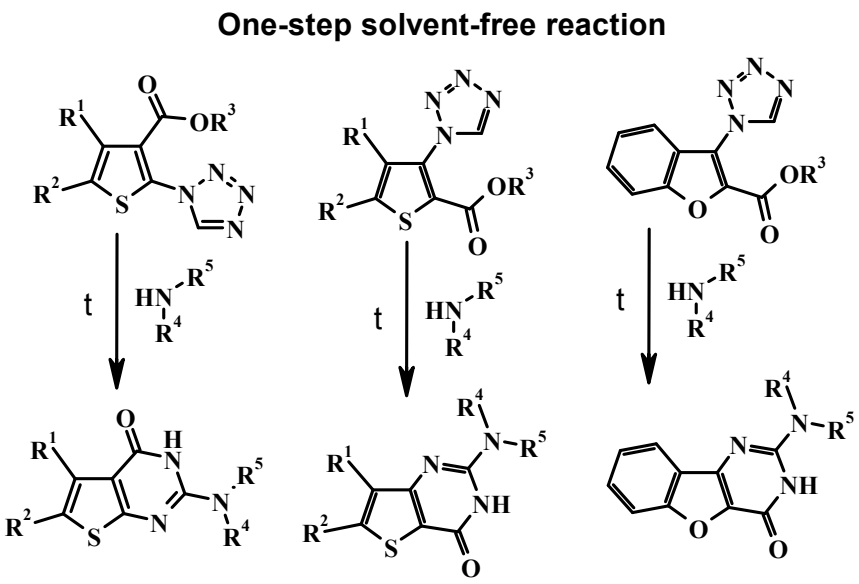
Graphical Abstract

A New Convenient Strategy for Annulation of Pyrimidines to Thiophenes or Furans via the One-pot Multistep Cascade Reaction of 1H-Tetrazoles with Aliphatic Amines

Nazariy T. Pokhodylo,* Olga Ya. Shyyka, Vasyl S. Matiychuk, Mykola D. Obushak

Department of Organic Chemistry, Ivan Franko National University of Lviv, Kyryla i Mefodiya St. 6, Lviv 79005, Ukraine



Keywords: tetrazole, thieno[2,3-*d*]pyrimidin-4(3*H*)-one, thieno[3,2-*d*]pyrimidin-4(3*H*)-one, benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one, heterocyclization.