New Heterocyclic Scaffolds with Thiophene and 1,2,4-triazole Rings

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Abstract – Some chemical modifications of the Gewald 2-amino-thiophenes and 3-aminothiophenes were established. A number of new substituted thienotriazolopyrimidines, thienotriazoles and thiophenyl-triazolothiadiazine were obtained. This study provides new approaches to the construction of substituted 1H-1,2,4-triazoles bearing thiophene core and allows to use data in medical chemistry for further drug discovery.

Keywords – 2-aminothiophene, 3-aminothiophene, 1,2,4-triazoles, aminohydrazones, thienotriazolopyrimidines, triazolothiadiazines.

I.Introduction

Recently, special attention is paid to the research in medicine, particularly to the synthetic drugs development for the treatment of serious diseases such as cancer. Fused heterocyclic derivatives with thiophene core continue to attract considerable attention because of their great practical usefulness, primarily, due to a very wide spectrum of biological activities. In particular, thiophenes have been reported to possess anticancer activity [1]. Among all heterocycles, the heterocycle-fused 1,2,4-triazole scaffold has been identified as one of the privileged structures in drug discovery. New literature data suggest that compounds with both: thiophene and 1,2,4-triasole rings are actively investigated for anticancer activity [2]. Among them thieno[3,2-*e*][1,2,4]triazolo [4,3-*a*]pyrimidines [3], thieno[3,2-*d*][1,2,4]triazolo[1,5-*a*] pyrimidines [4] and [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazines [5] are predisposed to antitumor activity.

Therefore, based on the combination of both thiophene and 1,2,4 triazole rings, an extended structure-activity investigation focusing on drug-like properties should be performed and the development of new efficient and mild syntheses of such compounds is a useful task, particularly when versatile procedures from readily available reagents can be employed.

II. Results and discussion

Synthesis of diverse heterocyclic molecules from the readily available starting materials in a cost and time-effective manner is an enduring challenge for organic chemists. Thus, functionalized Gewald 2-aminothiophenes and 3-aminothiophenes were used as starting material for this research.

In order to obtain 1*H*-1,2,4-triazole derivatives aminothiophenes **1a-c** were transformed at first into reactive thienyl clorohydrazones **3a-c** in high yields through the diazotation reaction. Obtained chlorohydrazones with active chlorine atom could easily react with ammonia giving corresponding aminohydrazones in quantitative yields. It should be mentioned, that in case of Gewald aminothiophene, the diazotization step was carried out in the sulfate acid, since the use of concentrated hydrochloric acid leads to a rapid decomposition of such labile diazosalts.

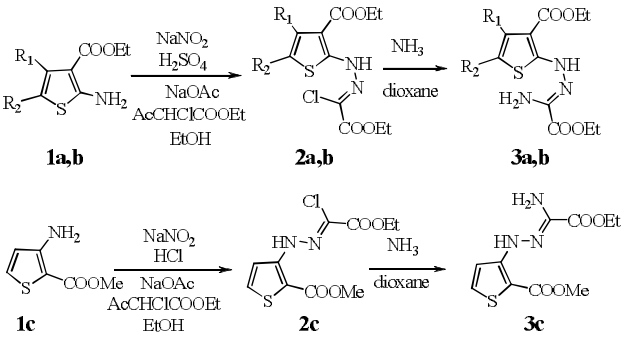


Fig. 1 Synthesis of thienyl aminohydrazones **3 a-c**

Aminohydrazones **3** as a versatile reagents with several nucleophilic centers were studied in the cyclization reactions. Special attention was paid to the formation of 1*H*-1,2,4-triazole derivatives. We found that aminoethenylhydrazones **3a-c** do not react with carbodiimidazole, even with prolonged heating and excess of reagents. Cyclic derivative **6** was obtained only during prolonged heating of aminohydrazones with acetic anhydride in moderate yield. The cyclization reaction is most easily achieved by the formation of similar thienyl triazoles **5a,c** while heating aminohydrazones **3** with orthoester in acetic acid using toluenesulphonic acid as a catalyst. The target product is formed with a good yield.

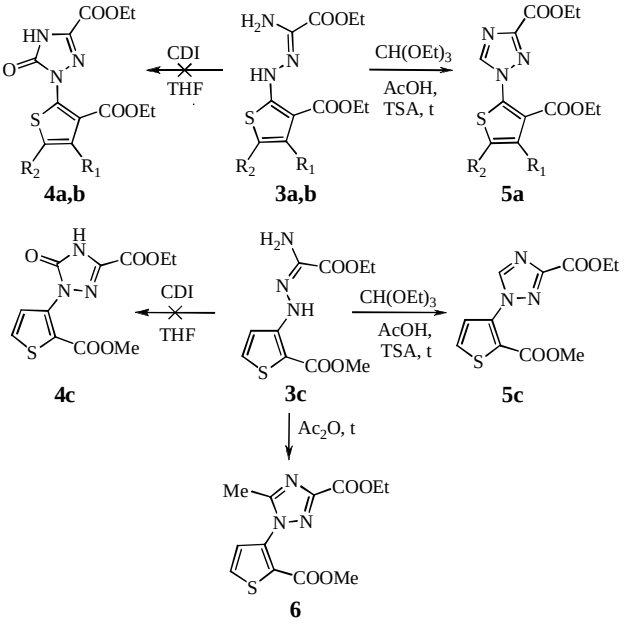
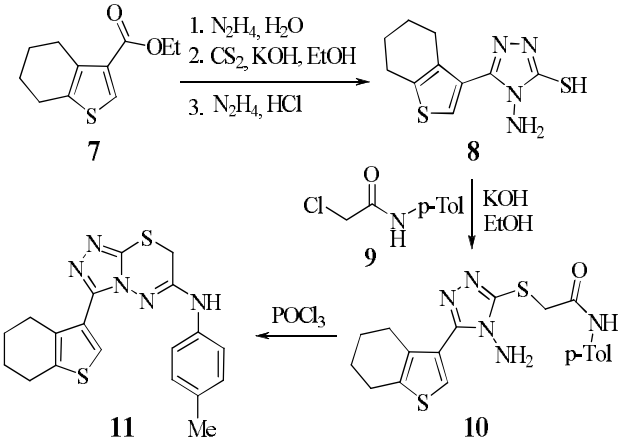


Fig. 2 Transformation of thienyl aminohydrazones **3 a-c**

The etyl thiophene-3-carboxylate **7**, formed in Gewald aminothiophene deamination reaction, was converted to

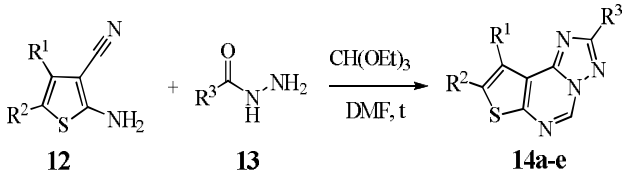
4-amino-[1,2,4]triazole-3-thiol **8** according to the well-known method [6]. Alkylation of the compound **8** with chloroacetamide **9** and subsequent cyclization of the product in excess of $POCl_3$ resulted in the previously unknown thienyl substituted [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine **11**.



7 **8** **9** **10** **11**

Fig. 3 Synthesis of triazolothiadiazine **11**.

Moreover, Gewald's aminothiophenes were studied in a three-component reaction with hydrazides and orthoester. Thus, 2-aminothiophene **12** reacting with triethylorthoformiate forms an appropriate ethoxymethylene-aminothiophene, which undergoes an attack by the nucleophilic nitrogen atom of the hydrazide molecule. Further cascade cyclization lead to the formation of thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine **14a-e**.



12 **13** **14a-e**

Fig. 4 Synthesis of thienotriazolopyrimidines **14a-e**.

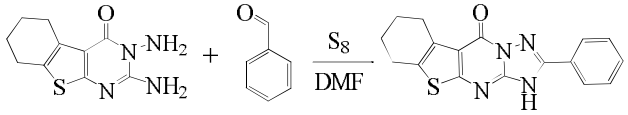
The method has been tested on a number of hydrazides and allows to obtain large combinatorial libraries of the not enough studied tricyclic fused systems of thiophene. Yields of compounds **14a-e** are shown in Table 1.

TABLE 1

YIELDS OF THIENOTRIAZOLOPYRIMIDINES **14a-e**.

	R^1, R^2	R^3	YIELD, %
14a	R^1+ R^2= -(CH_2)-	Ph	81
14b	R^1= R^2=Me	4-NO_2-C_6H_4	84
14c	R^1= R^2=Me	3-Me-C_6H_4	80
14d	R^1= R^2=Me	CH_2CN	79
14e	R^1+ R^2= -(CH_2)-	CH_2CN	79

Investigating the properties of previously obtained by us thienopyrimidines [7], we found that when heating a mixture of 2,3-diaminothieno[2,3-*d*]pyrimidine **15** with benzaldehyde and sulfur in DMF, a thieno[2,3-*d*][1,2,4] triazolo[1,5-*a*]pyrimidine **17** is formed. This result opens the way for the synthesis of isomeric thienotriazolopyrimidines.



15 **16** **17**

Fig 5. Synthesis of thienotriazolopyrimidine **17**.

Conclusion

A number of new substituted thienyl 1,2,4-triazoles, 3-(thiopen-3-yl)-triazolo[3,4-*b*][1,3,4]thiadiazines, thieno [2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines, thieno[2,3-*d*] [1,2,4]triazolo[1,5-*a*]pyrimidine were obtained. The resulting compounds have significant potential for biological research, in particular, to find new anticancer drugs.

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