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Research Article

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Synthesis of 2,5-Asymmetrically Substituted 3,4-Diaminothieno[2,3-*b*]thiophenes by Domino Reaction

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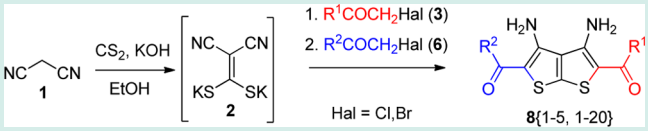
Supporting Information

ABSTRACT: A convenient one pot synthesis of 2,5-asymmetrically substituted thieno[2,3-*b*]thiophenes is developed. The method is based on consecutive domino reactions (S_N2 reaction → Thorpe−Ziegler reaction) using malononitrile and carbon disulfide as starting materials with the generation of potassium 2,2-dicyanoethene-1,1-bis(thiolate) in a solution. The high yield of the target thienothiophenes was achieved using the Ziegler dilution effect.



KEYWORDS: *thieno[2,3-b]thiophenes, domino reaction, combinatorial synthesis, one pot synthesis, Ziegler dilution effect*

INTRODUCTION

Since the first report by Rudolf Gompper,[1] the chemistry of 3,4-diaminothieno[2,3-*b*]thiophenes has been intensively developed.[1−15] This is due to the simplicity of the synthesis of these compounds via double alkylation of potassium 2,2-dicyanoethene-1,1-bis(thiolate). As a rule, derivatives of bromoacetophenone, bromoacetic acid esters, chloroacetonitrile are used as alkylating agents. The subsequent double Thorpe−Ziegler heterocyclization results in the target compounds.

On the other hand, these compounds contain several reactive groups thus allowing the synthesis of hetaryl-substituted thienothiophenes and poly fused heterocyclic systems. Futhermore, diaminothienothiophenes and their derivatives show biological activity, that is, antiallergenic.[3] The compounds are also effective in vitro against *Escherichia coli, Staphylococcus aureus, Aspergillus flavus*, and *Fusarium axysporium*.[8] The basic steps of thienothiophenes chemistry development and their practical use were described in a review.[16] However, the diversity of these compounds is not large enough, and consequently their biological activity is insufficiently investigated.

First of all, it is due to a limited set of methylene-active alkylating agents. Moreover, in most cases thieno[2,3-*b*]-thiophenes are obtained by bis-alkylation of 2,2-dicyanoethene-1,1-bis(thiolate) yielding only 2,5-symmetrically substituted thienothiophenes. Only a few thienothiophenes, containing different substituents in positions 2- and 5- have been described.[3,8,12]

Generally, the synthesis of these compounds is multistep, requires isolation of intermediates and total yields do not exceed 50%. To increase yields of target compounds at large scale, high dilution and long reagent addition times must be used. This method described for synthesis of macrocycles[17−19] to increase yields of products of intramolecular reactions. We found that the method increased the regio-selectivity of the intermolecular alkylation of 2,2-dicyanoethene-1,1-bis(thiolate).

RESULTS AND DISCUSSION

The basic problem in synthesis of asymmetrically substituted thienothiophenes, using various alkylating agents, is the bis-alkylation reaction, lowering yields of target products and affording a mixture of 2,5-substituted thieno[2,3-*b*]thiophenes which are difficult to separate.

The present work is aimed at developing an effective method of synthesis 2,5-asymmetrically substituted 3,4-diaminothieno-[2,3-*b*]thiophenes without isolation of intermediates. Originally, we tried to use standard methods[1] for synthesis of asymmetrically substituted thienothiophenes. As starting compounds, malononitrile, carbon disulfide and bromacetophenone were used. To the diluted aqueous ethanolic solution of potassium 2,2-dicyanoethene-1,1-bis(thiolate), obtained by the described technique,[20] a solution of an equimolar amount of bromacetophenone in a minimal quantity of ethanol was added within 30 min. Then an equimolar amount of KOH was added, and the reaction mixture was heated to boiling, diluted with water and acidified by an equimolar amount of HBr. During the reaction both mono- and bis-alkylation of the dipotassium salt occurs. However, in the first case a soluble monopotassium salt of 5-mercaptothiophene is formed, while the product of bis-alkylation is transformed in insoluble symmetric thienothiophene. Yields of the byproduct (symmetric thienothiophene) is 30−35%, however it can be filtered off, and the mother solution is used for reaction with another alkylating reagent. The subsequent cyclization results in target asymmetrical thienothiophenes, however their yields are only moderate (about 50%). Attempts of using the monopotassium salt, instead of the dipotassium one, did not improve the situation because the yields of symmetric thienothiophenes were 45−50%.

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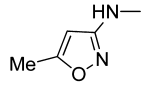
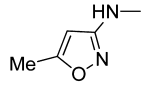
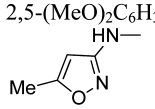
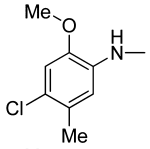
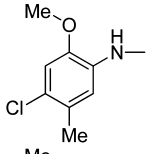
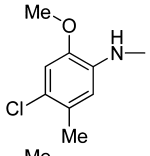
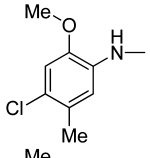
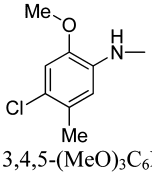
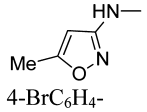
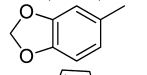
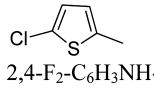
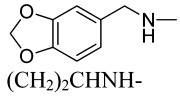
Table 1. Thieno[2,3-*b*]thiophenes 8

Entry	Product	R^1	R^2	Yield, %
1	**8**{1, 6}	Ph	4-F-C_6H_4-	70
2	**8**{1, 7}	Ph		59
3	**8**{1, 8}	Ph	Me	59
4	**8**{2, 6}	4-MeC_6H_4-	4-F-C_6H_4-	77
5	**8**{2, 9}	4-MeC_6H_4-	3,4-$(MeO)_2C_6H_3$-	84
6	**8**{2, 8}	4-MeC_6H_4-	Me	73
7	**8**{2, 7}	4-MeC_6H_4-		59
8	**8**{2, 10}	4-MeC_6H_4-	3,4-Me_2-C_6H_3NH-	76
9	**8**{2, 11}	4-MeC_6H_4-	2,5-$(MeO)_2C_6H_3NH$-	59
10	**8**{3, 7}	4-BrC_6H_4-		53
11	**8**{3, 1}	4-BrC_6H_4-	Ph	77
12	**8**{3, 2}	4-BrC_6H_4-	4-MeC_6H_4-	76
13	**8**{4, 12}		$(CH_2)_2CHNH$-	49
14	**8**{4, 11}		2,5-$(MeO)_2C_6H_3NH$-	63
15	**8**{4, 13}		4-$(MeCO)C_6H_4NH$-	80
16	**8**{4, 14}		3-Cl-C_6H_4NH-	73
17	**8**{4, 15}		4-F-C_6H_4NH-	74
18	**8**{5, 1}	3,4,5-$(MeO)_3C_6H_2$-	Ph	79
19	**8**{5, 7}	3,4,5-$(MeO)_3C_6H_2$-		59
20	**8**{5, 3}	3,4,5-$(MeO)_3C_6H_2$-	4-BrC_6H_4-	81
21	**8**{5, 16}	3,4,5-$(MeO)_3C_6H_2$-	4-$(MeO)C_6H_4$-	74
22	**8**{5, 9}	3,4,5-$(MeO)_3C_6H_2$-	3,4-$(MeO)_2C_6H_3$-	71
23	**8**{5, 17}	3,4,5-$(MeO)_3C_6H_2$-		78
24	**8**{5, 18}	3,4,5-$(MeO)_3C_6H_2$-		81
25	**8**{5, 19}	3,4,5-$(MeO)_3C_6H_2$-	2,4-F_2-C_6H_3NH-	68
26	**8**{5, 20}	3,4,5-$(MeO)_3C_6H_2$-		77
27	**8**{5, 12}	3,4,5-$(MeO)_3C_6H_2$-	$(CH_2)_2CHNH$-	51

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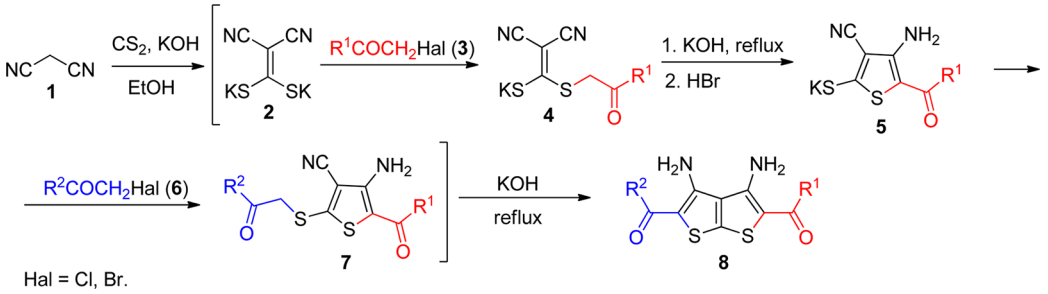
Scheme 1. Synthesis of 2,5-Asymmetrically Substituted Thieno[2,3-*b*]thiophenes 8



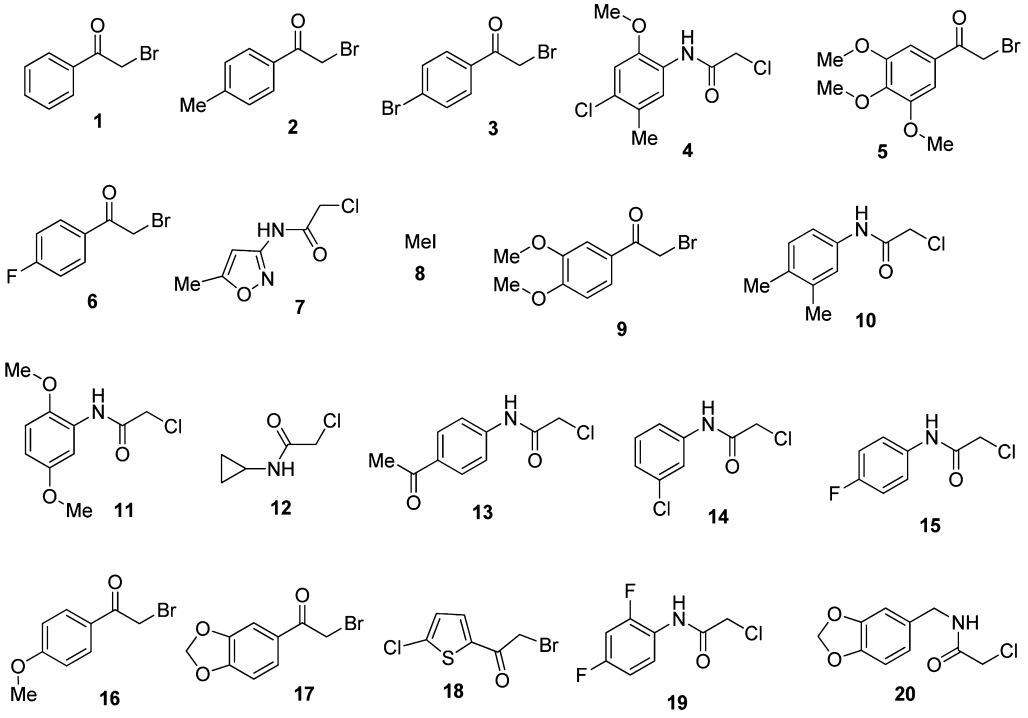


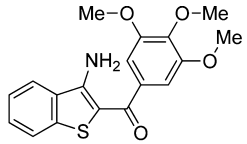
Figure 1. Diversity of α-halogenmethylcarbonyl compounds **3** and **6**.

To increase a regioselectivity of the first alkylation of dipotassium salt **2** we resorted to the dilution effect. It has been found, that use of the diluted solutions of dipotassium salt **2** and the α-halogenmethylcarbonyl compounds **3** and increasing the time of addition of the solution **3** up to 5−6 h for the first alkylation step reduced the formation of the byproduct to less than 10%. The yields of the targeted asymmetrical thienothiophenes increased to 60−85% (Scheme 1, Table 1).

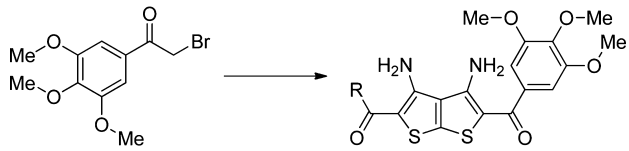
Thus, we have developed a convenient, highly selective method of synthesis of 2,5-asymmetrically substituted 3,4-diaminothieno[2,3-*b*]thiophenes **8**{*1*−*4*,*1*−*20*} using simple, readily available starting compounds without the isolation of any intermediates. As the primary alkylating agents **3**, bromoacetophenones **3**{*1*−*3*,*5*} and N-substituted chloroacetamide **3**{*4*} were used. α-Halogenmethylcarbonyl compounds **6**{*1*−*20*} with different substituents from compounds **3** were used as the second alkylating agents. The synthetic method developed is even more convenient since the solution obtained after filtration was used in a combinatorial synthesis of asymmetrical thienothiophenes.

It is known, that (3-aminothiophen-2-yl)(3,4,5-trimethoxyphenyl)-methanone derivatives, as heterocyclic analogues of phenstatin, show anticancer activity.[21−28] However, at present, analogous containing heterocycle fused to thiophene ring are not known.

Scheme 2. (3,4,5-Trimethoxyphenyl)methanones 8{*5*,*1*−*20*}



Murine leukemia L1210 cells; IC50 350 nmol/L
Molt4/C8 human T-lymphoblastoid cells; IC50 290 nmol/L



3{5}

8{5, 1-20}

Using the method developed, we synthesized (3,4-diamino-5-substituted-thieno[2,3-*b*]thiophen-2-yl)(3,4,5-trimethoxyphenyl)-methanones **8**{*5*,*1*−*20*} (Table 1), containing various substituents at 5 position in high yields (Scheme 2). Also, in the present work a method of synthesizing thienothiophenic analogous of phenstatin is reported for the first time.

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CONCLUSION

The convenient one pot method of synthesis of 2,5-asymmetrically substituted thieno[2,3-*b*]thiophenes is developed using two consecutive domino reactions (S_N2 reaction → Thorpe−Ziegler reaction). The potassium 2,2-dicyanoethene-1,1-bis(thiolate), generated in a solution from malononitrile and carbon disulfide is used as a starting reagent. High selectivity of synthesis of the target thienothiophenes was possible to achieve using the Ruggli−Ziegler dilution effect.

The combinatorial method developed allowed for easy preparation of a wide set of asymmetrically substituted thienothiophenes and has been used for the synthesis of thienothiophenic analogues of phenstatin.

EXPERIMENTAL PROCEDURES

The ^{1}H NMR spectra were recorded on a Bruker AM300 (300.13 MHz) using DMSO-d_6 as the solvent, a chemical shifts were reported in ppm (δ) and coupling constants (J) values were given in Hertz (Hz). The ^{13}C NMR spectra were recorded on a Bruker AM300 (75.47 MHz) and Bruker AV 600 (151 MHz) using DMSO-d_6 as the solvent. The IR spectra recorded on a Bruker Alpha in KBr pellets. Melting points measured on Kofler bench.

Synthesis of Thienothiophenes 8. *General Procedure.* To solution of 1.4 g (25 mmol) of KOH in 50 mL of EtOH at 10 °C the malononitrile (**1**) (1.65 g, 25 mmol) was added and stirred until dissolution. To the obtained solution, CS_2 (1.5 mL, 25 mmol) and then solution KOH (1.4 g, 25 mmol) in 50 mL of EtOH were added and stirred for 20 min. To the reaction mixture, 20 mL of H_2O was added to dissolve the precipitate. To the resulting solution (total volume 120 mL) 25 mmol of appropriate alkylating agent **3**{*1*−*5*} in 70 mL of EtOH was added dropwise over 5 h, then solution KOH (1.4 g, 25 mmol) in 10 mL of H_2O was added and heated up to reflux. To the cooled solution, 35 mL of H_2O and 2.8 mL (25 mmol) of concentrated HBr were added and stirred for 30 min before the precipitate was filtered off. The obtained solution was divided into 5 equal portions and to each portion an appropriate alkylhalogenide **6**{*1*−*20*} (4.7 mmol) was added and stirred for 10 min. To the solution 1.25 mL of 20% KOH in water was added and heated to reflux, then cooled down and the precipitate was filtered off. The thienothiophenes **8** were obtained as pure products, without additional purification, in 50−85% yields. (Table 1).

ASSOCIATED CONTENT

Supporting Information

Further details on the experimental procedures and spectra are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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