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Efficient One-Pot Synthesis of Polyfunctionalized Thiophenes via an Amine-Mediated Ring Opening of EWG-Activated 2-Methylene-1,3-dithioles

Fushun Liang,* Dazhi Li, Lei Zhang, Jingjie Gao, and Qun Liu*

Department of Chemistry, Northeast Normal University, Changchun 130024, China

liangfs112@nenu.edu.cn

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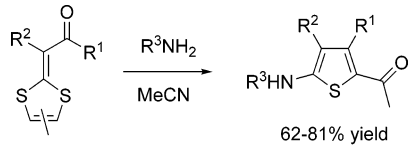
ABSTRACT



R^1 = H, Me, Ph; R^2 = EWGs; R^3 = alkyl

An amine-mediated ring-opening reaction of EWG-activated 2-methylene-1,3-dithioles (EWG = electron-withdrawing group) was disclosed, and a new route to highly substituted thiophenes was developed via the ring opening of 1,3-dithioles and subsequent intramolecular annulation and amine substitution. This one-pot reaction could proceed efficiently under mild conditions.

Thiophenes are widespread in nature, and a variety of multisubstituted thiophenes form an internal part of numerous products[1] and pharmaceuticals.[2] Thiophene derivatives also find broad applications as functional materials in dyes, liquid crystals, molecular wires, organic light-emitting diodes, field-effect transistors, organic solar cells, etc.[3] Moreover, multi-substituted thiophenes represent extremely versatile organic intermediates.[4] In view of their vast application in the areas of biology, materials science, and chemistry, it is of great importance to develop efficient synthetic methods toward multisubstituted thiophenes, especially polyfunctionalized thiophenes. There are two general methods that have been reported in the literature. One is the direct functionalization of the thiophene ring (usually α-metalation or *β*-halogenation).[5] The other is via the annulation reactions of suitably substituted open chain precursors.[6] The latter may allow regioselective preparation of the thiophene derivatives and thus represents an attractive but less developed methodology.

Over the past decades, the utility of α-oxo ketene-(*S*,*S*)-acetals as versatile intermediates in organic synthesis has been recognized.[7] In our research on the chemistry of functionalized ketene-(*S*,*S*)-acetals,[8] the fragmentation of the 1,3-dithiolane moiety was reported in the presence of protic solvents,[9a,b] primary amines,[9c] or Cu(II) catalysts[9d] based on different mechanisms. Recently, we turned to the study of

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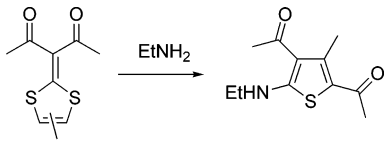
the fragmentation reaction of 2-methylene-1,3-dithioles. A *N*,*S*-heterotetracyclic thieno[2,3-*b*]thiopyran fused imidazo-[1,2-*a*]pyridine/pyrido[1,2-*a*]pyrimidines has been successfully constructed via a domino process of 4-(4-methyl-1,3-dithiol-2-ylidene)-1,7-bis(aryl/heteroaryl)hepta-1,6-diene-3,5-diones and diamines under mild conditions.[10] With the aim to further clarify the mechanism of this reaction, we simplified the reaction model, and the one-pot reaction of EWG-activated 2-methylene-1,3-dithioles with monoamines was performed. As a result, highly substituted thiophenes were obtained in good to high yields via ring opening and subsequent ring closure, which represents a new and alternative method for the preparation of multisubstitued thiophenes. We wish to report the preliminary result in this letter.

In the initial study for the ring-opening reaction of 1,3-dithioles with amines, a model reaction between 3-(4-methyl-1,3-dithiol-2-ylidene)pentane-2,4-dione **1a** with ethylamine was first examined to optimize the reaction conditions.[11] Thus, the variation of the solvents (CH_2Cl_2, DMF, CH_3CN, and CH_3CH_2OH), the amount of the amines, and temperature (room temperature to 80 °C) were investigated in detail. Some of the results were shown in Table 1. After optimization, treatment of **1a** (1.0 mmol) with ethylamine (2.5 mmol) in CH_3CN at 80 °C for 2.5 h, multisubstituted thiophene **2a** was isolated as a sole product with a 79% yield (entry 5). The structure was characterized on the basis of its spectra and analytical data, as well as X-ray diffraction analysis (Figure 1).[12]

Table 1. Reaction of **1a** with Ethylamine under Different Conditions



1a **2a**

entry	**1a** (mmol)	$EtNH_2$ (mmol)	*T* (°C)	solvent	time (h)	**2a** yield[a] (%)
1	1.0	2.5	rt	CH_2Cl_2	5.0	0
2	1.0	2.5	rt	DMF	1.0	*b*
3	1.0	2.5	rt	CH_3CN	4.0	0
4	1.0	2.5	40	CH_3CN	5.0	16
5	1.0	2.5	80	CH_3CN	2.5	79
6	1.0	1.2	80	CH_3CN	5.0	*c*
7	1.0	2.5	reflux	CH_3CH_2OH	5.0	0

[a] Isolated yields after column chromatography. [b] Complicated products were observed. [c] The reaction was incomplete, with the substrate remaining.

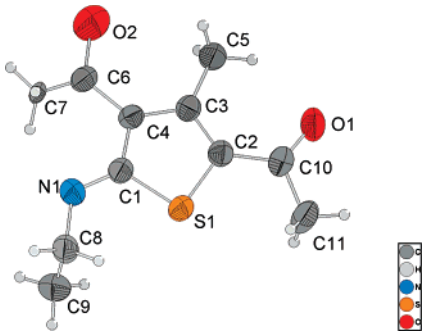


Figure 1. ORTEP drawing of **2a**.

Under the optimized conditions described above, a range of reactions between EWG-containing 1,3-dithioles **1** (1.0 mmol) and amines (2.5 mmol) were carried out at 80 °C in CH_3CN (Table 2). The 1,3-dithiole substrates **1** were prepared according to our previously reported methods.[10] In particular, when the electron-withdrawing R^2 group of the substrates **1** was benzoyl, methoxycarbonyl, ethoxycarbonyl, and *N*-phenylcarbamoyl, the ring-opening and ring-closure reactions proceeded smoothly and the corresponding multisubstituted thiophenes **2b**−**e** (R^1 = CH_3) were obtained in

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(6) For representative reports on the synthesis of substituted thiophenes from open chain precursors, see: (a) Bartolo, G.; Giuseppe, S.; Alessia, F. *Org. Lett.* **2000**, *2*, 351−352. (b) Fazio, A.; Gabriele, B.; Salerno, G.; Destri, S.; *Tetrahedron* **1999**, *55*, 485−503. (c) Ong, C. W.; Chen, C. M.; Wang, L. F.; Shieh, P. C. *Tetrahedron Lett.* **1998**, *39*, 9191−9192. (d) Stephensen, H.; Zaragoza, F. *J. Org. Chem.* **1997**, *62*, 6096−6097. (e) Marshall, J. A.; DuBay, W. J. *Synlett* **1993**, 209−210. (f) Wang, M.; Ai, L.; Zhang, J.-Y.; Liu, Q.; Gao, L.-X. *Chin. J. Chem.* **2002**, *20*, 1591−1597.

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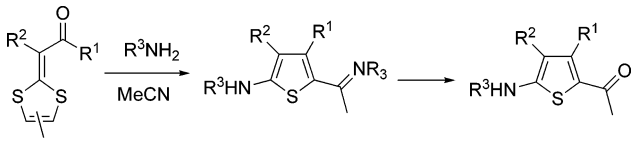
(11) Actually, bases such as K_2CO_3 and NaOH were also tried to examine the feasibility of the ring-opening reaction of EWG-activated 2-methylene-1,3-dithioles. When K_2CO_3 was used as the base, no reaction occurred, with the substrate recovered in almost quantitative yield. When NaOH was used, a few faint spots were detected by TLC, but no desired product was observed.

(12) X-ray diffraction data for **2a** has been deposited in the Cambridge Crystallographic Data Centre with supplementary publication number of CCDC 634141. The CIF file is also available in the Supporting Information.

Table 2. Reactions of EWG-Containing Dithioles **1** with Amines Leading to Polyfunctionalized Thiophenes **2**



entry	substrate	R^1	R^2	R^3NH_2	time (h)	product	yield[a] (%) **2**
1	**1b**	Me	COPh	$EtNH_2$	3.0	**2b**	73
2	**1c**	Me	CO_2Me	$EtNH_2$	2.5	**2c**	75
3	**1d**	Me	CO_2Et	$EtNH_2$	2.5	**2d**	73
4	**1e**	Me	CONHPh	$EtNH_2$	3.5	**2e**	62
5	**1f**	Ph	CO_2Et	$EtNH_2$	3.0	**2f**	69
6	**1g**	4-OMePh	CO_2Et	$EtNH_2$	3.0	**2g**	68
7	**1h**	H	COPh	$EtNH_2$	2.5	**2h**	81
8	**1i**	Me	COMe	n-$PrNH_2$	2.5	**2i**	75
9	**1a**	Me	COMe	*n*-$BuNH_2$	3.0	**2j**	78
10	**1a**	Me	COMe	$BnNH_2$	2.0	**2k′**[b]	76
11	**1a**	Me	COMe	$OH(CH_2)_2NH_2$	2.0	**2l**	73
12	**1a**	Me	COMe	NH_4OAc	4.0	**2m**	*c*
13	**1a**	Me	COMe	Et_2NH	4.0	**2n**	*c*
14	**1a**	Me	COMe	Et_3N	4.0	**2o**	*c*
15	**1a**	Me	COMe	aniline	4.0	**2p**	*c*

[a] Isolated yield. [b] **2k′** was obtained as the sole product and no **2k** was detected. [c] No reaction.

high to excellent yields (62−75%, Table 1, entries 1−4). When R^1 was varied to aryl, aryl-substituted thiophenes would be prepared. Thus, benzoyl and 4-methoxybenzoyl substituted substrates **1f** and **1g** were subjected to the reaction sequences and 3-phenyl and 3-(4-methoxyphenyl) substituted thiophenes **2f** and **2g** were successfully obtained in 69% and 68% yield, respectively (entries 5 and 6). Such type of asymmetric biaryls were generally prepared via metal-catalyzed crossing-coupling reactions, and the direct preparation of such molecules via a C−C bond-formation process can be limited when functional group compatibility complicates the synthetic approach.[13] When R^1 is hydrogen, partly substituted thiophene **2h** was obtained in high yield (81%, entry 7). Hence, the method developed here not only provides a new route to fully/partly substituted thiophenes but also furnishes an alternative to the aryl-thienyl compounds.

Next, with the aim to explore the scope of the amines in the ring-opening/ring-closure reaction, acetylacetone counterpart **1a** was selected to react with a variety of amines under the identical conditions as described above. In addition to ethylamine, other primary aliphatic amines such as *n*-butylamine, *tert*-butylamine, benzylamine, and ethanolamine are also efficient for the tandem ring-opening and ring-closure reaction. As a result, alkylamino-substituted thiophenes **2i**−**l** were obtained in 73−78% yields (entries 8−11). It should be noted that in the reaction of **1a** with benzylamine (entry 10), the corresponding imine product **2k′** was proved to be the main product (76% yield) and no corresponding **2k** was observed. The reason for this is unclear presently. It was reasonable to conclude, based on this result, that products **2** were produced from the hydrolysis of the imines **2′**. In our experiment, it was found that ammonium acetate and secondary and tertiary aliphatic amines are inert to the ring opening of 1,3-dithioles (entries 12−14). Aromatic amines such as aniline were also tried, but the ring-opening reaction could not occur under identical conditions (entry 15). The thiophenes **2** and/or **2′** with ariable R^1, R^2, and R^3 groups indicated the efficiency of this ring-opening/ring-closure reaction and the molecular versatility, which not only provides potential applications in biological and materials areas but also meets the need for library synthesis.

The scope of the 1,3-dithioles was further examined, and the experimental results revealed that structures of type **5** with one EWG and one EDG (electron-donating group) and type **6** with only one EWG were inactive to the reaction explored here (Figure 2). Actually, we are also interested in the exploration on the reaction of a structure like **7** (without a methyl substituent on the dithiole ring). Unfortunately, such

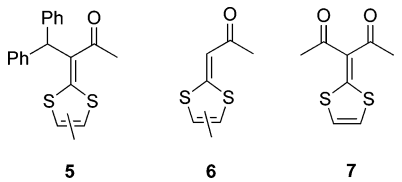


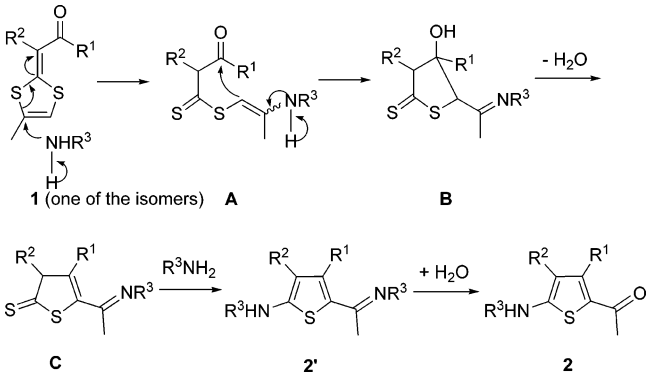
Figure 2. Scope of 1,3-dithioles in the explored amine-mediated ring-opening/ring-closure reaction.

(13) (a) Anastasia, L.; Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; p 311. (b) Jacqueline C. Bussolari, Diana C. Rehborn, *Org. Lett.* **1999**, *1*, 965−967.

substrates have not been successfully prepared in our laboratory.

On the basis of the above experimental results, a possible mechanism for the formation of thiophene derivatives **2** was proposed, as depicted in Scheme 1. Upon heating, a

Scheme 1. Possible Mechanism for the Formation of **2**



nucleophilic vinylic substitution (S_NV)[14] by the attack from the nitrogen atom of the amine to the vinylcarbon atom connected with the methyl group of 1,3-dithiole causes the ring opening of 1,3-dithioles take place, and enamine **A** is generated. It was noticeable that in all of the experiments, the amine always attacks at the vinylcarbon atom connected with the methyl group of 1,3-dithiole during this period of S_NV reaction. The reason for this was probably that this vinylcarbon atom is relatively more electrophilic than the other one without the methyl substituent (the electronic effect of the methyl group). Then an intramolecular nucleophilic addition of intermediate **A** gives rise to cyclic intermediate **B** with an imine group, followed by dehydration to give **C**. The addition−elimination of amine to the thiocarbonyl leads to the formation of thiophene **2′**. Finally, polyfunctionalized thiophenes **2** is formed via the hydrolysis of the imino group[15] of **2′**. As the key step toward the synthesis of thiophenes **2**, the ring opening of 1,3-dithioles under such mild conditions, to our best knowledge, was rare.[16] Indeed, the tandem reaction described here provides a novel and efficient method to construct polyfunctionalized thiophenes.

In summary, the ring-opening reaction of EWG-activated 2-methylene-1,3-dithioles is disclosed for the first time, and thus a new route to highly substituted thiophenes is developed via the amine-mediated ring-opening reaction and subsequent ring closure. The one-pot reaction features mild conditions, cheap reagents, and high efficiency and more importantly is metal-catalyst-free. A wide range of functional groups such as alkylamino, acetyl, alkoxycarbonyl, carbomoyl, etc. were included on the thiophene core, which provides potential for further modification to meet the need for various purposes. Work on the synthetic applications of the ring-opening reaction of EWG-activated 1,3-dithioles is in progress.

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Supporting Information Available: Experimental details and characterization for all new compounds and crystal structure data for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Based on the fact that more than 2.0 equiv of amine was required to drive the reaction to completion (Table 1, entry 3), it was concluded that the amine substitution may occur prior to the imine hydrolysis.

(16) For the fragmentation of 1,3-dithiolane, see: Luh, T.-Y.; Lee, C.-F. *Eur. J. Org. Chem.* **2005**, 3875−3885 and references therein. For the fragmentation of ketene dithioacetals containing 1,3-dithiolanes, see: Samuel, R.; Nair, S. K.; Asokan, C. V. *Synlett* **2001**, 1804−1806. In all cases, a strong base (e.g., sodium hydride, *n*-butyllithium, lithium diisopropylamide, etc.) was used. For an example with a weak base such as aliphatic primary amines, see ref 10, in which the double EWG-activated 1,3-dithiolane moiety was fragmented upon heating to 120 °C. For the fragmentation of 1,3-dithioles, see: Ogurtsov, V. A.; Rakitin, O. A.; Rees, C. W.; Smolentsev, A. A.; Belyakov, P. A.; Golovanov, D. G.; Lyssenko, K. A. *Org. lett.* **2005**, *7*, 791−794.