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Intermolecular heterocyclization of alkynones with 2-mercaptoacetaldehyde under metal-free conditions: synthesis of 2,3-disubstituted thiophenes

Erol Can Vatansever [a], Kübra Kılıç [a,b], Merve Sinem Özer [a], Gani Koza [b], Nurettin Menges [a,c,*], Metin Balci [a,*]

[a] Chemistry Department, Middle East Technical University, 06800 Ankara, Turkey
[b] Chemistry Department, Ahi Evran University, Kırşehir, Turkey
[c] Pharmacy Faculty, Yüzüncü Yil University, 65100 Van, Turkey

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ABSTRACT

A concise and regioselective approach for the synthesis of 2,3-disubstituted thiophene derivatives has been developed. The synthetic strategy relies on the reaction of an in situ generated 2-mercaptoacetaldehyde with various alkynones. Furthermore, we calculated the energy gap between the HOMO and the LUMO orbitals of all compounds and observed that the introduction of a strong electron-withdrawing group decreased the HOMO–LUMO energy gap.

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Sulfur-containing heteroaromatic compounds are very important due to their abundance in various natural products.[1] Included in these compounds are thiophenes which are widely distributed in nature and incorporated in several pharmacologically active compounds.[2] The benzene ring of biologically active compounds may be replaced by a thiophene group without the loss of activity as was observed in the example of the NSAID piroxicam and its thiophene analog lornoxicam.[3] Thiophene containing compounds have also been shown to possess protein inhibition and anticancer activities.[4] In the last decade, thiophene-based materials have also found widespread use in electronic and optoelectronic devices[5] as well as solar cells.[6,7] Solar cells, which directly convert sunlight into electrical energy, are interesting structures for energy generation.[8] Dye-sensitized solar cells (DSSCs) based on organic and organometallic complexes have also attracted considerable attention.[9] Organic dyes are considered as an alternative to organometallic complexes, as they are easily accessible.[10] To date, the highest photoconversion efficiency of organic dye-sensitized solar cells has not exceeded 9%.[11]

To reach higher photoconversion efficiency, polymer-based organic solar cell materials such as polythiophene (PT) have rapidly become the subject of considerable interest.[12] Due to the varied potential applications of thiophene derivatives in organic chemistry and pharmaceutical science, the development of efficient methods for thiophene synthesis has continued to attract the attention of chemists. Thiophenes are classically synthesized from 1,4-dicarbonyl compounds using reagents such as P_4S_{10}, and Lawesson's reagent, or via the Gewald reaction.[13a,b] Recently, new methodologies have been applied to the synthesis of various thiophene derivatives.[13c,d,14] However, there are few Letters on the synthesis of 2,3-disubstituted thiophene derivatives.[15] Recently, Müller and co-workers reported the synthesis of substituted thiophene derivatives using thiophene-aroyl chlorides, alkynes, and ethyl 2-mercaptoacetate as starting materials.[14a]

A widely used strategy to lower the LUMO energy is the introduction of an electron-withdrawing moiety such as a carbonyl or cyano group onto the organic framework.[16] Hence, thiophenes containing a carbonyl group might be good candidates for organic solar cells due to a reduction in their LUMO energy. In this respect, Brisset and co-workers reported a thiophene derivative **1** (Fig. 1) with a carbonyl group attached to the C-3 atom, which showed a positive shift of reduction potential, indicating an increase in

* Corresponding authors. Tel.: +90 312 210 5140; fax: +90 312 210 3200.
E-mail addresses: nurettinmenges@gmail.com (N. Menges), mbalci@metu.edu.tr (M. Balci).

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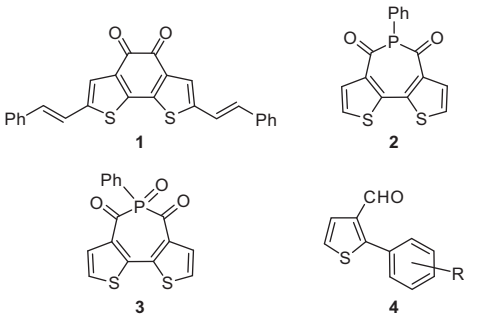


Figure 1. Selected thiophene derivatives with carbonyl groups at the C-3 position.

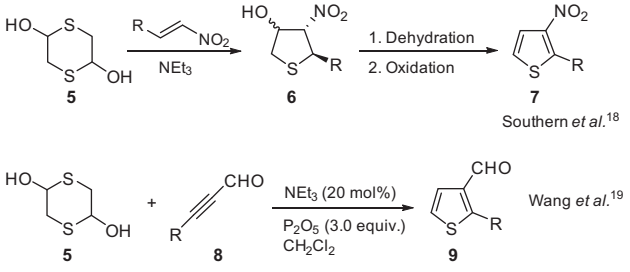
electroaffinity.[17] Furthermore, Baumgartner and co-workers have reported thiophene derivatives, **2** and **3** with carbonyl groups at the C-3 position which exhibit promising electron-accepting character.[16]

Recently, Southern and co-workers[18] developed two approaches for the synthesis of 3-nitro-2-substituted thiophenes **7**, by the reaction of 1,4-dithane-2,5-diol **5** with nitroalkenes in the presence of triethylamine proceeding via compound **6**. Wang and co-workers reported the application of this methodology to the synthesis of 2-substituted thiophenes-3-carboxyaldehydes **4** by the cycloaddition of 1,4-dithiane-2,5-diols to ynals in the presence of Lewis bases (Scheme 1).[19] In addition to the base, they also required P_2O_5 in 3 mol equiv for this reaction.

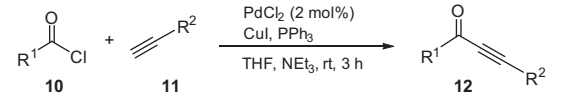
The recent publication by Wang and co-workers[19] prompted us to communicate our preliminary results on the synthesis of 2,3-disubstituted thiophene derivatives containing a carbonyl group at the C-3 position and our investigation into the HOMO–LUMO energy gaps by theoretical calculations.

Herein, we report the cyclization of activated alkynes with in situ generated 2-mercaptoethanal for the construction of 2,3-disubstituted thiophene derivatives. Alkynones **12**, formed from the Sonogashira cross-coupling reaction of readily available acyl chlorides **10** and terminal acetylene derivatives **11**, were used as starting materials[20] (Scheme 2).[21]

The reaction of alkynones **12a–m** with 2,5-dihydroxy-1,4-dithiane **5** in the presence of NEt_3 followed by treatment with silica gel or HCl yielded 2,3-disubstituted thiophene derivatives **14a–m** in good to excellent yields (Table 1). The formation of the 2,3-disubstituted thiophene ring was easily detected by measuring the coupling constant (J) between the thiophene protons which had characteristic values of approximately 5.3 Hz.[22] The presence of intermediates **13** was detected in the crude products, however these were not stable and underwent slow dehydration upon standing in chloroform. Chromatography using silica gel or treatment with HCl caused dehydration to give the desired thiophene derivatives **14a–m**.



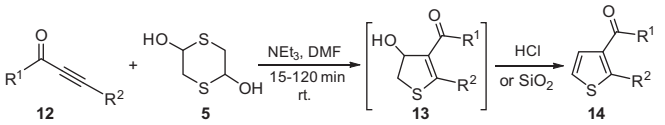
Scheme 1. Synthesis of thiophene derivatives using 1,4-dithiane-2,5-diol.



12a R^1 = Me R^2 = Ph 45% **12h** R^1 = 4-MeC_6H_4 R^2 = Ph 83%
12b R^1 = *t*-Bu R^2 = *n*-Bu 35% **12i** R^1 = 4-$NO_2C_6H_4$ R^2 = Ph 73%
12c R^1 = *t*-Bu R^2 = Ph 82% **12j** R^1 = β-Naphthyl R^2 = Ph 74%
12d R^1 = Ph R^2 = *n*-Bu 78% **12k** R^1 = furan-2-yl R^2 = Ph 98%
12e R^1 = Ph R^2 = TMS 70% **12l** R^1 = pyrrol-2-yl R^2 = Ph 30%
12f R^1 = Ph R^2 = Ph 85% **12m** R^1 = thiophen-2-yl R^2 = Ph 56%
12g R^1 = 4-MeC_6H_4 R^2 = *n*-Bu 82%

Scheme 2. Synthesis of alkynones **12a–m**.

Table 1
Synthesis of 2,3-disubstituted thiophene derivatives



Entry	R^1	R^2	Product	Time (min)	Yield (%)
1	Me	Ph	**14a**	20	75
2	*t*-Bu	*n*-Bu	**14b**	15	87
3	*t*-Bu	Ph	**14c**	15	79
4	Ph	*n*-Bu	**14d**	15	91
5	Ph	TMS	**14e**[a]	120	80
6	Ph	Ph	**14f**	15	91
7	4-Me-C_6H_4	*n*-Bu	**14g**	15	88
8	4-Me-C_6H_4	Ph	**14h**	15	90
9	4-NO_2-C_6H_4	Ph	**14i**	15	75
10	β-Naphthyl	Ph	**14j**	15	89
11	Furan-2-yl	Ph	**14k**	15	89
12	Pyrrol-2-yl	Ph	**14l**	20	83
13	Thiophen-2-yl	Ph	**14m**	15	70

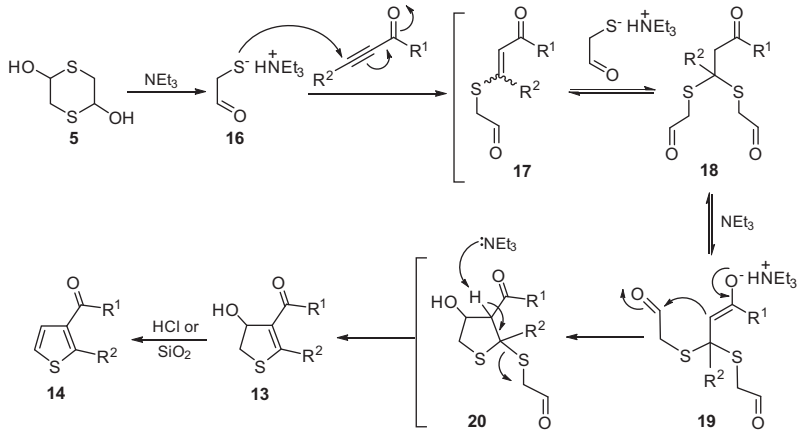
[a] **15** was formed as a side product in 8% yield.

Compound **14e** bearing a trimethylsilyl group was partially hydrolyzed under the reaction conditions to give 3-benzoyl thiophene **15**.

A tentative mechanism for the formation of **13** is outlined in Scheme 3. It is proposed that the first step is the formation of ammonium 2-oxoethanethiolate **16**. Nucleophilic attack at the β-carbon atom of the alkynone **12** by the thiolate anion **16** furnishes intermediate **17** which undergoes attack of a second thiolate anion at the β-carbon atom of thioenol ether **17** to give thioacetal **18**.

Enolate **19** then undergoes an intramolecular aldol type condensation reaction to yield **20**. Since the thiolate anion is a good leaving group, NEt_3-promoted elimination gives the relatively stable alcohol **13** and regenerates the thiolate anion **16**. Recently, Joshi and Anslyn[23] reported that thiols could reversibly add to β-sulfido-α,β-unsaturated carbonyl groups forming a thioketal possessing a structure similar to compound **18** which supports our mechanistic proposal.

Synthesized thiophenes **14a–m** were optimized using Gaussian 09 at the B3LYP/6-311+G(d,p)[24,25] level of theory and the optimized structures were used to calculate their energy levels (Table 2). As discussed, thiophene derivatives represent good candidates for application in organic solar cells, and an important parameter is the energy level of the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO). Compounds with lower LUMO energy levels have high electron affinities and may increase electron transport. The introduction of substituents with electron-withdrawing capabilities to the thiophene ring should lower the energy level of the LUMO.



Scheme 3. Proposed mechanism for the formation of 2,3-disubstituted thiophene derivatives **14**.

Table 2
Energy gaps for thiophene derivatives

Compounds	**14i**	**14j**	**14m**	**14k**	**14l**	**14h**	**14f**
HOMO–LUMO gap (eV)	3.49	4.04	4.16	4.31	4.34	4.34	4.42
Compounds	**14d**	**14e**	**14g**	**14a**	**14c**	**15**	**14b**
HOMO–LUMO gap (eV)	4.60	4.61	4.64	4.89	4.89	5.0	5.04

The lowest energy gap (3.49 eV) was observed in **14i** which contained a good electron acceptor group due to the presence of a nitro group attached to the benzene ring. On the other hand, the highest energy gap (5.04 eV) was observed in **14b** due to the lack of conjugation between the thiophene ring and the *n*-Bu group.

Next, we plotted the HOMO and LUMO orbitals of selected derivatives (Fig. 2). The HOMO orbital of **14i** was localized primarily on the thiophene, and benzene rings, and less on the carbonyl group, whereas the LUMO orbital of **14i** was localized only on the nitro-benzoyl group. However in the case of **14f**, the LUMO orbital was distributed over the entire molecule. Localization of the LUMO on the nitrobenzene ring decreases the energy gap indicating that a strong electron acceptor group on the C-3 position of thiophene might decrease the energy gap of the molecule. Furthermore, we observed that alkyl groups attached to the thiophene ring had little or no effect on the HOMO and LUMO orbitals.

In conclusion, we have described a concise synthetic methodology for 2,3-disubstituted thiophene derivatives having electron-withdrawing substituents. The key feature of our method is the reaction between in situ generated 2-mercaptoacetaldehyde and various alkynones. Furthermore, we calculated the energy gap between the HOMO and the LUMO orbitals of all compounds. We observed that the introduction of a strong electron-withdrawing group decreased the energy gap.

This synthetic strategy also represents a reasonable methodology that would allow us to introduce various strong electron-withdrawing groups attached to the thiophene ring to further decrease the HOMO–LUMO energy gap further. Hence, the compounds synthesized under metal-free conditions might be useful for photovoltaic cells.

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Supplementary data

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.090.

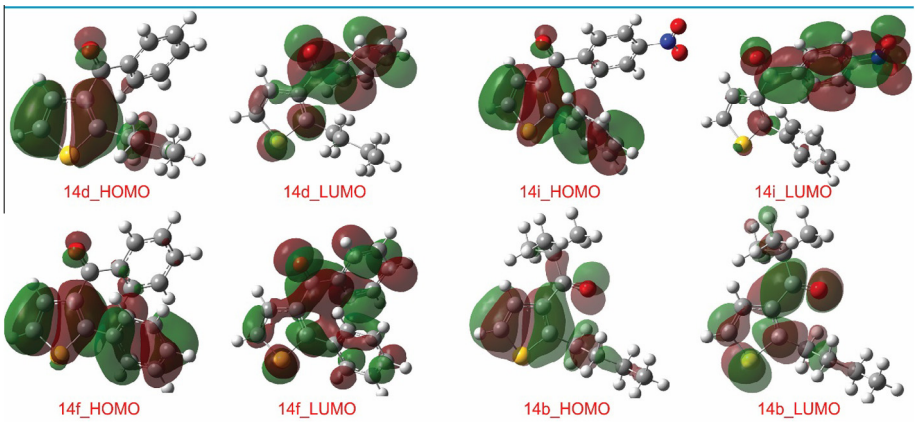

Figure 2. HOMO and LUMO orbitals for selected thiophene derivatives.

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