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Synthesis of 3-iodothiophenes via iodocyclization of (*Z*)-thiobutenynes

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ABSTRACT

A simple synthesis of 3-iodothiophenes was demonstrated using a wide range of (*Z*)-thioenynes. The key step in the iodocyclofunctionalization was the selective reduction of the triple bond in (*Z*)-thioenynes by the addition of iodine as an electrophilic agent. The 3-iodothiophenes were obtained in good to excellent yields of 61–92%. The 3-iodothiophenes were used as substrates in Sonogashira cross-coupling reactions to obtain thiophene acetylenes.

Organochalcogen compounds have been investigated in recent decades because of their many applications in synthetic organic chemistry,[1] preparation of new materials[2] and medicinal chemistry.[3]

Chalcogen atoms such as S, Se and Te can be easily introduced into organic molecules via nucleophilic and electrophilic addition reactions.[1] These organochalcogens have been widely used in the formation of new carbon–carbon bonds in palladium-catalyzed Suzuki-,[4] Negishi-,[5] and Sonogashira-type[6] cross-coupling reactions.

The most studied organochalcogen species are organosulfur compounds.[1d,7] For example, the thiophene moiety is found in various chemical compounds, with a broad range of applications in the electronics industry to produce electroluminescent diodes (OLED), organic field effect transistors (OFET), photovoltaic cells, sensors, semiconductors, liquid crystals and displays.[2,8] Organosulfur compounds also play an important role in medicinal chemistry[3] because of their lower toxicity compared to organoselenium and organotellurium reagents.[1c,3d,9,10]

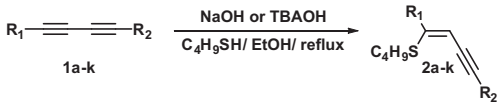
Because of the great interest in developing new and effective drugs containing thiophene groups, the aim of this systematic study was the preparation of 3-iodothiophenes **3** (Scheme 2) through the electrophilic cyclization reactions[11] of (*Z*)-thiobutenynes **2a–k**.

The (*Z*)-thiobutenynes **2a–k** were synthesized by the addition of organothiolate anions to diacetylenes **1a–k** using $C_4H_9SSC_4H_9$/$NaBH_4$ or C_4H_9SH/bases as a reducing system (Scheme 1).[12,13]

Synthesizing the (*Z*)-thiobutenynes **2** with C_4H_9SH/TBAOH as a reducing system resulted in improved efficiency compared with C_4H_9SH/NaOH because TBAOH provided a phase-transfer catalyst that increased the solubility and reactivity of the butylthiolate anion (Scheme 1).[13]

The studies involving the electrophilic cyclization reactions were focused on optimizing the reaction conditions to prepare 3-iodothiophenes **3** in high yields.

Initially, we tested the cyclization reaction using (*Z*)-thiobutenyne **2a** as the starting material in several solvents, such as CH_2Cl_2,[13] THF, MeCN, and EtOH, followed by the addition of I_2 (1.1 equiv) or ICl (1.1 equiv) as electrophilic agents.



Scheme 1.

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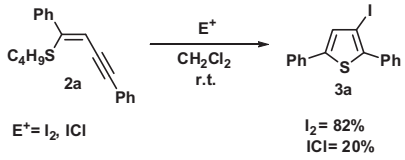
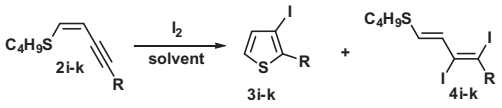


Scheme 2.

Table 1
Optimization of reaction conditions for **3i–k** synthesis[a]



Entry	R	*T* (°C)	Solvent	Time (h)	Yield[b] (%)	
					3	**4**
1	C_6H_{13}	rt	CH_2Cl_2	6	0	35
2	C_6H_{13}	rt	CH_2Cl_2	48	0	30
3	C_4H_9	rt	CH_2Cl_2	24	0	35
4	Ph	rt	CH_2Cl_2	0.5	25	25
5	Ph	rt	CH_2Cl_2	48	45	0[c]
6	Ph	40	CH_2Cl_2	72	60	0[c]
7	Ph	rt	$CHCl_3$	48	25	0[c]
8	Ph	60	$CHCl_3$	48	45	0[c]
9	Ph	70[d]	1,2-$(CH_2Cl)_2$	1	80	0[c]
10	C_6H_{13}	70[d]	1,2-$(CH_2Cl)_2$	2	68	0[c]

[a] Reaction conditions: compound **2i-k** (1.0 mmol), I_2 (1.1 mmol), appropriate solvent (14 ml).
[b] Ratio detected by ^1H NMR (300 MHz) of the crude products.
[c] Yields of isolated products.
[d] Addition of electrophile at 70 °C.

The best result was achieved when compound **2a** (1.0 mmol) in CH_2Cl_2 reacted for 5 min with I_2 (1.1 equiv) at room temperature, producing 2,5-diphenyl-3-iodo-thiophene **3a** in 82% yield (Scheme 2). Using ICl instead of I_2 as the electrophile, the cyclization gave an unsatisfactory yield of 20% for thiophene **3a**.

However, the synthesis of disubstituted 3-iodothiophene **3i** failed under identical reaction conditions of iodocyclization in Scheme 2 (Table 1, entry 1). This led us to study other reaction conditions to prepare 3-iodothiophenes **3i–k** (Table 1).

The reaction of (*Z*)-thiobutenynes **2i–k** with I_2, using dichloromethane as the solvent, gave exclusively diiodobutadienes **4i**, **j** in low yields (Table 1, entries 1–3). By using (*Z*)-thiobutenyne **2k**, a mixture containing a 1:1 ratio of 3-iodothiophene **3k** and diiodobutadiene **4k** was obtained (Table 1, entry 4).

The reaction of (*Z*)-thiobutenyne **2k** and I_2/CH_2Cl_2 at room temperature (48 h) and under reflux at 40 °C (72 h) gave 3-iodothiophene **3k** exclusively in 45% and 60% yields, respectively (Table 1, entries 5 and 6). No improvement in synthesizing 3-iodothiophene **3k** was observed when $CHCl_3$ was used as the solvent (Table 1, entries 7 and 8).

However, when using 1,2-dichloroethane as the solvent at 70 °C, a high yield of 80% for 3-iodothiophene **3k** was obtained in 1 h (Table 1, entry 9) and a yield of 68% was obtained for 3-iodothiophene **3i** after 2 h (Table 1, entry 10).

Given these excellent results, we synthesized a wide range of 3-iodothiophenes to further investigate the scope and limitations of the iodocyclization reactions, as shown in Table 2.

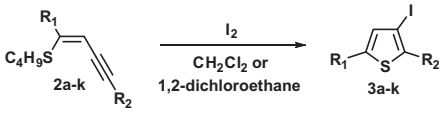
The iodocyclization of **2a–c** containing phenyl and aromatic activating *p*-OMe groups occurred in 5 min, leading to 3-iodothiophenes **3a–c** in yields ranging from 82% to 92% (Table 2, entries 1–3). Compounds **3d–h** were obtained in 15–30 min, in yields ranging from 61% to 84% (Table 2, entries 4–8).

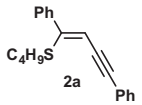
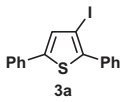
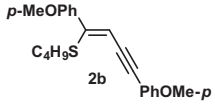
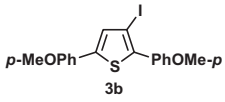
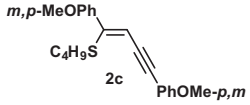
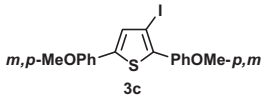
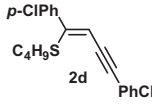
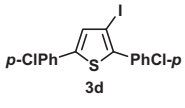
The disubstituted 3-iodothiophenes **3i–k** (Table 2, entries 9–11) were obtained in 1–2 h and in good yields (65–80%), using 1,2-dichloroethane as the solvent.

The proposed mechanism presented here for the formation of 3-iodothiophenes **3a–k** (Fig. 1) is similar to the mechanism proposed by Dabdoub et al. for the formation of 3-iodotellurophenes.[14]

First, (*Z*)-thiobutenynes **2a–k** undergo an electrophilic addition of iodine at their corresponding triple bonds to give the intermediates **5**. *Pathway a* shows the attack of the electron pair of a sulfur on the α-carbon of the R_2 groups, leading to the formation of intermediates **6** and the subsequent elimination of iodobutane,

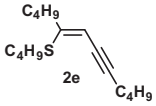
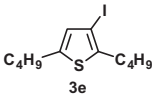
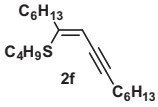
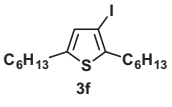
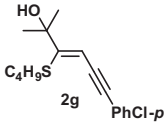
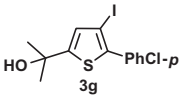
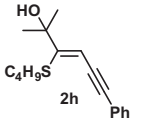
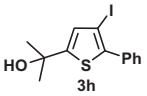
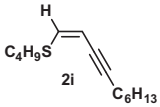
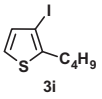
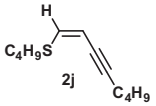
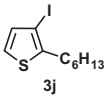
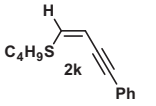
Table 2
Scope of iodocyclization of (*Z*)-thiobutenynes[a]



Entry	(*Z*)-Thiobutenyne	Solvent	Time (h/min)	T (°C)	Product	Yield (%)
1		CH_2Cl_2	5	rt		82
2		CH_2Cl_2	5	rt		92
3		CH_2Cl_2	5	rt		90
4		CH_2Cl_2	15	rt		77

(*continued on next page*)

Table 2 (*continued*)

Entry	(*Z*)-Thiobutenyne	Solvent	Time (h/min)	T (°C)	Product	Yield (%)
5	 2e	CH_2Cl_2	20	rt	 3e	65
6	 2f	CH_2Cl_2	20	rt	 3f	61
7	 2g	CH_2Cl_2	30	rt	 3g	78
8	 2h	CH_2Cl_2	30	rt	 3h	84
9	 2i	1,2-Dichloroethane	2	70[b]	 3i	68
10	 2j	1,2-Dichloroethane	2	70[b]	 3j	65
11	 2k	1,2-Dichloroethane	1	70[b]	 3k	80

[a] Reaction conditions: compound **2a-k** (2.0 mmol), dropwise addition of I_2 (2.2 mmol) in appropriate solvent (28 ml).
[b] Dropwise addition of I_2 at 70 °C.

generating the 3-iodothiophenes **3a–k**. Iodobutane was detected as a byproduct in all of the reactions listed in Table 2. On the other hand, diiodobutadienes **4i–k** (Fig. 1) are formed by the attack of the iodide anion (*pathway b*) on the α-carbon of the R_2 groups in **5**.[14] In this case, iodobutane was not detected as a byproduct when (*Z*)-thiobutenynes **2i**, **j** were used as starting materials in CH_2Cl_2.

We observed the formation of **3k**, diiodobutadiene **4k**, and a smaller proportion of iodobutane in the iodocyclization of (*Z*)-thiobutenyne **2k** in CH_2Cl_2 (Table 1, entry 4). Increases in reaction times and temperature (Table 1, entries 5–8) favored the formation of 3-iodothiophene **3k**.

A possible explanation for the formation of diiodobutadienes **4i–k** is that the distances between the sulfur and α-sp carbon bonded to R_2 groups are longer in **2i–k** than those of the sulfur and carbon in trisubstituted (*Z*)-thiobutenynes **2a–h**, thus favoring *pathway b*. Because of the steric hindrance effects between alkyl or aryl groups and C_4H_9S- group bonded in the same sp^2 carbon, this proximity in **2a–h** favors the attack of sulfur on the carbon containing the iodonium ion in intermediates **5**, leading to *pathway a* (Fig. 1) and the formation of aromatic trisubstituted 3-iodothiophenes **3a–h**.

Structure calculations for compounds **2a**, **2k** and intermediates **5a**, **5k** were performed using a computer modeling program.[15] The minimized structures showed that the distances between the sulfur atom and the α-sp carbon of the Ph group in (*Z*)-thiobutenynes **2a** and **2k** are 1.976 Å and 3.726 Å, respectively. The distances between the sulfur atom and the sp^2 carbon of iodonium intermediates **5a** and **5k** are 1.241 Å and 3.072 Å, respectively (Fig. 2).

The larger distances between the sulfur and sp carbon present in (*Z*)-thiobutenynes **2i–k** and their intermediates such as **5**

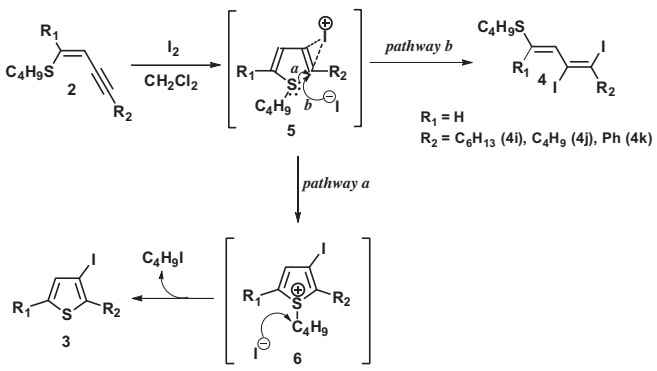


Figure 1. Proposed reaction mechanism.

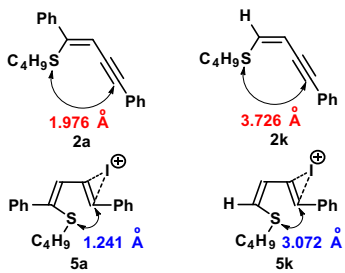
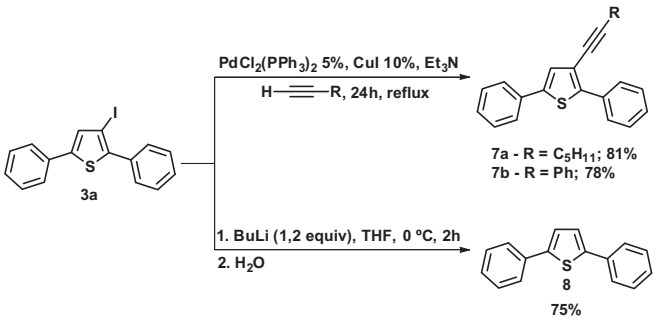


Figure 2. Calculation of distances between the sulfur and carbon atoms.



Scheme 3. Reactions of (*Z*)-thiobutenyne **3a**.

required changes in the reaction conditions, such as solvent exchange (1,2-dichloroethane) and increasing the temperature to 70 °C, to obtain good yields of the more thermodynamically stable 3-iodothiophenes **3i–k** (Table 2, entries 9–11).

Considering the possibility of new applications in organic synthesis, we investigated the cross-coupling reactions of 3-iodothiophene **3a** with terminal acetylenes in Sonogashira cross-coupling type reactions[16] and the removal of iodine by the reaction of compound **3a** with *n*-BuLi (Scheme 3).[17]

The formation of thiophene acetylenes **7a**, **b** occurred in 24 h in yields of 81% and 78%, respectively. The attack of the BuLi on the iodine atom gave thiophene **8** in 75% yield (Scheme 3).

We developed an efficient methodology for the synthesis of 3-iodothiophenes in good to excellent yields. We are currently studying the synthesis of other compounds via cross-coupling Sonogashira reactions[18] to increase the number of samples synthesized. Reactions with BuLi will be performed, and the lithium intermediate will be captured with other electrophiles (ketones or aldehydes) for the synthesis of new alcohol derivatives with potential activity against neglected diseases.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.118.

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