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Facile synthesis of 3,4-diiododihydrothiophenes via electrophilic iodocyclization

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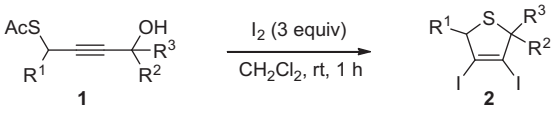
ABSTRACT

A facile, efficient, and general synthetic method for the construction of 3,4-diiododihydrothiophenes has been developed via the electrophilic iodocyclization of various *S*-hydroxy-2-butynyl ethanethioates. Application of the resulting iodine-containing products in organic transformations has been investigated.

Dihydrothiophenes are one of the most important classes of heterocycles which are used as versatile intermediates in the synthesis of natural and unnatural molecules with diverse biological activities and optoelectronic properties.[1–3] While the synthesis of functionalized dihydrothiophenes have attracted much less attention comparing to thiophenes and tetrahydrothiophenes, some efficient methodologies have been developed. The earliest approaches such as McIntosh cycloaddition of mercapto ketons or aldehydes with vinyl Wittig reagents,[4] modified McMurry cyclization of diketo sulfides,[5] and Birch reduction of thiophenes[6] still remains the most common approaches. Recently, new preparative methods have been reported, for example, copper-catalyzed ring expansion of vinyl thiiranes,[2a] gold-catalyzed hydrothiolation of allenes,[7] and olefin metathesis.[8] However, these approaches represent important general methods for the synthesis of dihydrothiophene derivatives, each of them suffers from either harsh conditions or limited scope of applications. Thus, the development of a facile and efficient methodology for the synthesis of the multifunctionalized dihydrothiophenes would be highly desirable.

The electrophilic iodocyclization is one of the most powerful methods for the efficient synthesis of a variety of functionalized carbocycles and heterocycles under mild conditions.[9–14] Furthermore, the corresponding iodine-containing products can be readily derived to the interesting structurally elaborated compounds by using transition metal-catalyzed transformations. While iodocyclizations for the preparation of O- and N-containing heterocycles have been well studied, iodocyclizations for the construction of S-containing heterocycles such as dihydrothiophenes or thiophenes have not been well explored.[12] In 1937, Kruglov reported an interesting iodocyclization of acetylene glycols, producing 3,4-diiododihydrofuran derivatives efficiently.[13] In the continuation of our interest in the development of efficient synthetic methods of heterocycles[15] and in iodocyclization chemistry,[14] we envisioned that if one of hydroxyl groups in acetylene glycols is replaced with a suitable sulfide group, 3,4-diiododihydrothiophene derivatives might be produced via an intramolecular iodocyclization. Herein, we report for the first time a facile and efficient synthesis of 3,4-diiododihydrothiophenes by the electrophilic iodocyclization of various substituted *S*-4-hydroxy-2-butynyl ethanethioates [Eq. 1]. This communication provides not only a new protocol for the construction of dihydrothiophenes but also an alternative avenue for the synthesis of the highly functionalized thiophene derivatives.



1 2 (1)

In the preliminary studies, we investigated the effect of solvents on the iodine-mediated electrophilic cyclization of **1a** for the formation of the 3,4-diiododihydrothiophene **2a**. The use of CH_3CN and CH_3NO_2 led to good yields of **2a** (~80%), while the use of a protic solvent MeOH resulted in decomposition of **1a**. CH_2Cl_2 was

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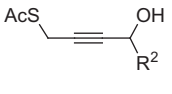
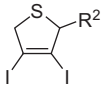
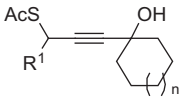
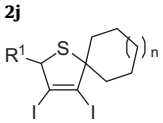
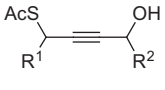
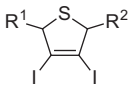
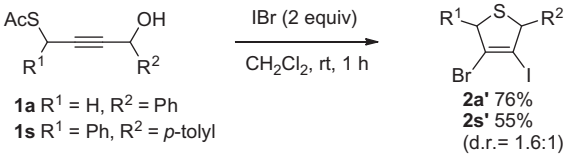
Table 1
Synthesis of 3,4-diiododihydrothiophenes by iodocyclization[a]

Entry	Substrate **1**	Product **2**	Yield[b] (%)
			
1	**1a** R^2 = Ph	**2a**	89
2	**1b** R^2 = 4-Me–C_6H_4	**2b**	93
3	**1c** R^2 = 2-Me–C_6H_4	**2c**	93
4	**1d** R^2 = 4-Cl–C_6H_4	**2d**	85
5	**1e** R^2 = 4-CO_2Me–C_6H_4	**2e**	71
6	**1f** R^2 = (*E*)–CH=CHC_6H_5	**2f**	91
7	**1g** R^2 = *n*-C_5H_{11}	**2g**	39
8	**1h** R^2 = 2-thienyl	**2h**	96
9	**1i** R^2 = 2-furanyl	**2i**	78
10	**1j** R^2 = 2-(1-tosyl)pyrrolyl	**2j**	98
			
11	**1k** *n* = 1, R^1 = H	**2k**	86
12	**1l** *n* = 1, R^1 = Me	**2l**	71
13	**1m** *n* = 1, R^1 = Ph	**2m**	63
14	**1n** *n* = 2, R^1 = H	**2n**	89
15	**1o** *n* = 3, R^1 = H	**2o**	54
			
16[c]	**1p** R^1 = Me, R^2 = Ph	**2p**	67[d]
17	**1q** R^1 = Ph, R^2 = Ph	**2q**	76[e]
18	**1r** R^1 = 2-thienyl, R^2 = 2-thienyl	**2r**	48[f]

Ac = acetyl, Ph = phenyl, Me = methyl, tosyl = toluenesulfonyl.
[a] Reaction conditions: **1** (0.2 mmol), I_2 (0.6 mmol), anhydrous CH_2Cl_2 (0.1 M), room temperature, 1 h.
[b] Isolated yields.
[c] Diastereomeric ratio (d.r.) of **1p** is 20:1.
[d] d.r. is 1.5:1.
[e] d.r. is 1.4:1.
[f] d.r. is 1.3:1.

observed as a best choice of solvents, giving **2a** in 89% yield (Table 1, entry 1). This iodocyclization was extended to the various substituted *S*-4-hydroxy-2-butynyl ethanethioates **1** to examine the methodology for general utility for the synthesis of functionalized 3,4-diiododihydrothiophenes. The reactions of substrates **1b–e** bearing an electron-donating and an electron-withdrawing aromatic group (R^2) at the propargyl alcoholic carbon produced the corresponding tri-substituted dihydrothiophenes **2b–e** in good to high yields (entries 2–5). Remarkably, the presence of a double bond in substrate **1f** was also tolerated; the desired dihydrothiophene **2f** was obtained in 91% yield (entry 6). In the case of **1g** having an alkyl substituent at R^2, the product **2g** was formed in moderate yield (entry 7). Substrates **1h–j** having heteroaromatic rings such as thienyl, furanyl, and pyrrolyl, showed a high compatibility with the present reaction conditions, producing **2h–j** in high yields (entries 8–10). Interestingly, cyclic tertiary alcohols (**1k–o**) with a cyclohexyl, cycloheptyl, or cyclooctyl ring were transformed into the expected [4.n]thiaspirocycles **2k–o** in good yields (entries 11–15). The reaction also worked well with the substrates **1p–r** having two substituents at the both propargylic carbons, furnishing the expected tetrasubstituted dihydrothiophenes **2p–r** as a mixture of two diastereomers, respectively (entries 16–18).

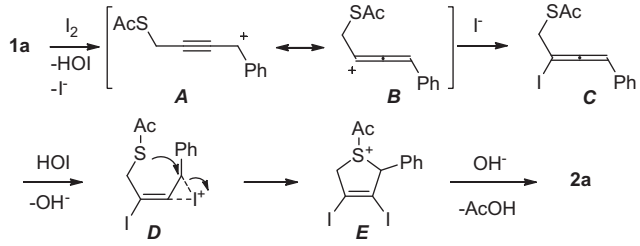
We further tested this iodocyclization with IBr electrophile instead of iodine. Fortunately, in the presence of 2 equiv of IBr, substrates **1a** and **1s** underwent the electrophilic iodocyclization smoothly to afford the corresponding 3-bromo-4-iodo-dihydrothiophenes **2a′** and **2s′** in good yields as a single regioisomer, in which **2s′** was obtained as a 1.6:1 diastereomeric mixture [Eq. 2].



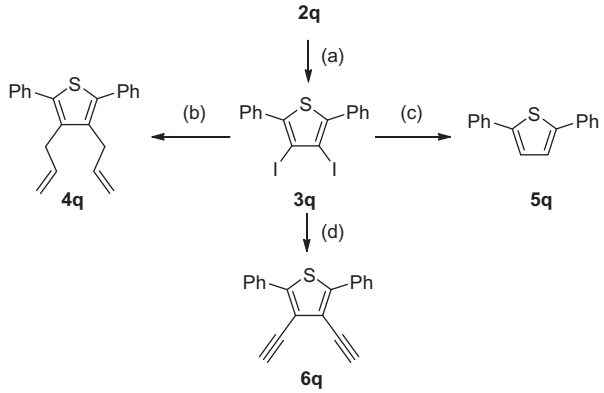
(2)

Based on these observations, the present iodocyclization mechanism is proposed as shown in Scheme 1. Presumably, initial activation of the propargyl hydroxyl group of **1a** with a Lewis acidic iodine[16] leads to the propargyl carbocation intermediate **A** or allene cation **B**[17] along with an unstable hypoiodous acid (HOI) and an iodine anion. Attack of the iodine anion onto γ-position of **A** or the cation in **B** affords iodoallene **C** which will react with hypoiodous acid to form an iodonium intermediate **D**.[18] Subsequent intramolecular nucleophilic addition of sulfide atom to the activated allene followed by deprotection of acetyl group produces **2a** and acetic acid.

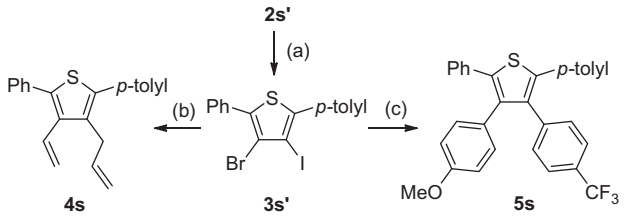
As shown in Schemes 2 and 3, dihydrothiophenes **2q** and **2s′** were readily converted to the corresponding thiophenes **3q** and **3s′** by DDQ aromatization. Aiming at examining the potential application in synthesis of highly functionalized thiophenes possessing interesting photophysical and electrochemical properties, transformations of **3q** and **3s** to the synthesis of 2,3,4,5-tetrasubstituted thiophenes have been investigated. For example, in the case of **3q**, double Pd-catalyzed Still couplings, *n*-BuLi-mediated deiodination, and double Sonogashira couplings have afforded the corresponding symmetric thiophenes **4q**, **5q**, and **6q** in 97%, 95%, and 81% yields, respectively (Scheme 2). Similarly, in the case of **3s**, sequence Still couplings and Suzuki–Miyaura couplings have furnished the corresponding unsymmetric thiophenes **4s** and **5s**[19] in 88% and 66% yields, respectively (Scheme 3).



Scheme 1. Proposed reaction mechanism for the formation of 3,4-diiododihydrothiophenes.



Scheme 2. Reagents and conditions: (a) DDQ (3 equiv), toluene, reflux, 93%; (b) $Pd(PPh_3)_4$ (20 mol %), LiCl, DMF, allyltributylstannane, 100 °C, 97%; (c) ^{n}BuLi (2 equiv), THF, −78 °C then H_2O, 95%; (d) (i) $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), DIPA, THF, 60 °C, ethynyltrimethylsilane; (ii) K_2CO_3, MeOH/THF, rt, 81% for two-steps. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIPA = diisopropylamine, ^{n}Bu = *n*-butyl.



Scheme 3. Reagents and conditions: (a) DDQ (3 equiv), toluene, reflux, 98%; (b) (i) $Pd(PPh_3)_4$ (10 mol %), LiCl, DMF, allyltributylstannane, 100 °C, 24 h; (ii) $Pd(PPh_3)_4$ (10 mol %), LiCl, DMF, tributylvinylstannane, 100 °C, 24 h, 88% for two-steps; (c) (i) $Pd(PPh_3)_4$ (3 mol %), PPh_3, K_2CO_3, THF, 4-(trifluoromethyl)phenylboronic acid, 80 °C, 12 h; (ii) $Pd(PPh_3)_4$ (6 mol %), K_3PO_4, toluene/dioxane, 4-methoxyphenylboronic acid, 100 °C, 12 h, 66% for two-steps. DMF = dimethylforamide, THF = tetrahydrofuran.

In conclusion, we have developed a facile, efficient, and general method for the synthesis of dihydrothiophenes through the electrophilic iodocyclization. This methodology accommodates a wide range of functional groups and affords various highly substituted 3,4-diiododihydrothiophenes efficiently under mild reaction conditions. The resulting iodine-containing products can be readily transferred to the more complex thiophenes by using known organic transformations. Investigation into the extension of the present methodology to the construction of other heterocycles and application to the synthesis of useful optoelectronic materials are in progress.

General procedure: I_2 (0.6 mmol, 152 mg) was added to a solution of *S*-hydroxy-4-phenylbut-2-ynyl ethanethioate **1a** (0.2 mmol, 44 mg) in dichloromethane (2 mL), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with 10 mL dichloromethane, washed with saturated sodium thiosulfate. The organic layer was dried with anhydrous $MgSO_4$. After concentration of the filtrate, the residue was purified by chromatography on silica gel to afford 3,4-diiodo-2-phenyldihydrothiophenes **2a** (73.6 mg, 89%) as a slight yellow solid.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.075.

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