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A novel base-induced cyclization of selected benzyl alkynyl sulfides for the synthesis of 2-aryl-2,3-dihydrothiophenes

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Abstract

2-Halobenzyl 1-alkynyl sulfides undergo an unprecedented dihydrothiophene formation when treated with 2 equiv. of KO*t*Bu in CH_3CN. The reaction, believed to proceed via a 5-*endo-dig* cyclization, is sluggish or non-existent in the absence of the halogen.

Thiophenes and their derivatives have a myriad of uses in the fields of medicine, physical organic chemistry and materials chemistry.[1] Syntheses of a partially saturated version, the 2,3-dihydrothiophenes, have been the topic of a number of publications,[2–7] and among the newer approaches,[3–7] methods that involve the intramolecular cyclizations are particularly related to this work. Some recent strategies include reactions of sulfenyl iodides with intramolecularly disposed alkynes[4] and the intramolecular olefination of thiol esters using low valent titanium.[5] Similarly, these heterocycles are accessible through the cyclization reactions of photochemically generated radicals[6] and by a unimolecular Wittig reaction.[7]

Our contribution to the area of 2,3-dihydrothiophenes arises from synthetic studies directed towards allenyl benzyl sulfides for eventual cyclization to sulfur heterocycles. Through the exploration of established methods designed to isomerize triple bonds to allenes, it was found that 2-iodobenzyl 1-propynyl sulfide (**1a**) did react with 2 equiv. KO*t*Bu/THF/aq NH_4Cl (quench), but not to afford an allene. Rather, the material isolated was identified with the assistance of spectroscopic data to be 2-(2-iodophenyl)-2,3-dihydrothiophene (**2a**), a cyclic isomer of **1a** (56% yield; Scheme 1). The $^1H-^1H$ coupling constants of **2a** are consistent with those expected for related heterocycles[3d,8] and of particular note, each of the hydrogens on C-3 couples appreciably to all of the other protons in the heterocycle.

The conditions for the cyclization were idealized by varying parameters such as solvent, reaction temperature, amount and identity of base and substrate concentration. A selection of the results performed on sulfide **1a** is presented in Table 1 (entries 1–6). Other benzyl alkynyl sulfides were

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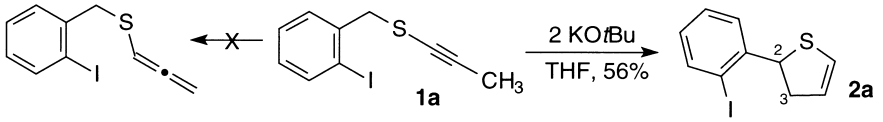
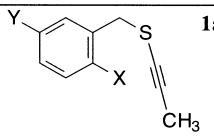
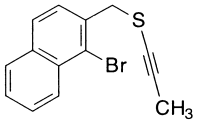


Scheme 1.

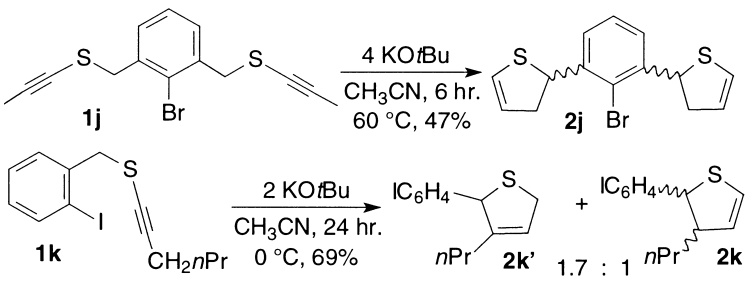
prepared[9] in order to probe the generality of the cyclization and the remainder of Table 1 indicates the propensity of those sulfides for cyclization.[10] On inspection of the table, it is readily noted that an *ortho* halogen group appears to be vital to a synthetically useful cyclization. In those cases where the substrate was lacking the *ortho* halogen, the reaction proved sluggish and the yield was lower. Harsher reaction conditions provided a small improvement in yield for some of those substrates.[11]

Table 1
Base-induced cyclizations of benzyl 1-alkynyl sulfides

#	starting material	rxn conditions[a]	product: % yield[b]
1	 **1a**, X = I, Y=H	*t*BuOH, rt, 24h	**2a**: 0
2		THF, rt, 24h	56
3		DME, 0 °C, 24h	21[c]
4		CH_3CN, 0 °C, 24h	75
5		CH_3CN, 70 °C, 24h	51[c]
6		CH_3CN, -20 °C, 24h	56[c]
7	**1b**, X=Br, Y=H	CH_3CN, 0 °C, 24h	**2b**: 74
8	**1c**, X=Cl, Y=H	CH_3CN, 0 °C, 24h	**2c**: 74
9	**1d**, X=CH_3, Y=H	CH_3CN, reflux, 24h	**2d**: 0
10	**1e**, X=H, Y=H	CH_3CN, 0 °C, 24h	**2e**: 0
		CH_3CN, reflux, 24h	16(25)
11	**1f**, X=Ph, Y=H	CH_3CN, reflux, 8h	**2f**: 25(41)
12	**1g**, X=Y=OCH_3	CH_3CN, reflux, 24h	**2g**: 27(44)
13	**1h**, YC_6H_4X = 1-Naph[d]	CH_3CN, reflux, 24h	**2h**: 19(24)
14	 **1i**	CH_3CN, 0 °C, 24h	**2i**: 72

[a] Two equiv. of KO*t*Bu were used in all cases.
[b] Yield of reaction product. Yield in brackets is based on amount of recovered starting material.
[c] GC yield of a calibrated reaction mixture; see ref. 11.
[d] Compound **1h** is 1-(1-propynylthiomethyl)naphthalene.

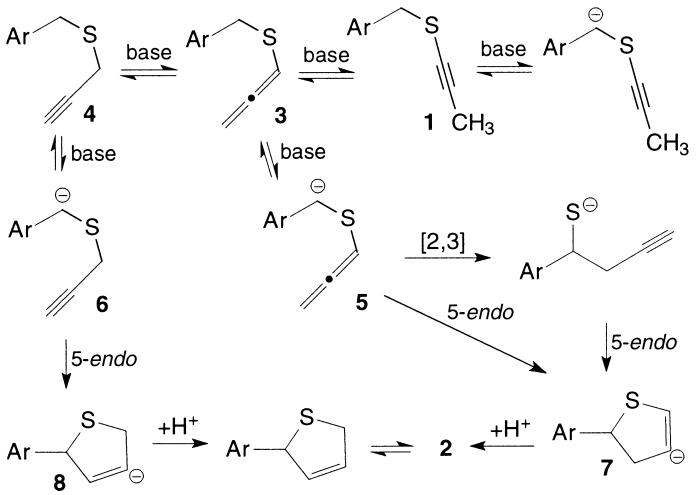
Additional noteworthy reactions are shown in Scheme 2. Bis-alkyne **1j** was treated with 4 equiv. KO*t*Bu/CH_3CN/60°C to afford product **2j** (47%, 1:1 *dr* by ^{13}C NMR). When the alkyl chain appended to the alkyne is longer than methyl in the starting material (**1k**), a mixture of dihydrothiophene isomers **2k** and **2k′** is obtained. The mixture can be separated and if **2k′** is re-exposed to the reaction conditions, the same ratio of double bond isomers is salvaged. It is suggested that the cyclization conditions may induce the isomerization of the double bond in any of the immediate cyclization products, to eventually provide the thermodynamically more stable reaction products.



Scheme 2.

Some preliminary mechanistic work has been accomplished. When **1a** labelled with a ^{13}C atom on the methyl group underwent cyclization, the label occupied position 3 exclusively in the product, suggesting that a direct attachment of atom 3 to the benzylic position is likely. Scrambling of the label may be expected from some sort of elimination/addition mechanism.[12] When the reaction of **1a** was performed in CD_3CN, the sample of **2a** obtained showed full deuteration at *all* of the heterocyclic ring positions (^1H and ^2H NMR). Subsequent control experiments indicated that there is substantial incorporation of deuterium in **1a** before cyclization.

Scheme 3 offers possible cyclization modes of alkyne **1** in CH_3CN. Our experiments and the literature indicate that there is probably an equilibrium comprised of the propynyl (**1**), allenyl (**3**) and propargyl (**4**) species, in addition to exchange at benzylic positions. Indeed, cyclization presumably requires a benzylic anion attacking the terminal carbon of the unsaturated chain which has assumed either the allenyl (**5**) or propargyl (**6**) tautomer. Alternatively, the benzylic anion could rearrange via a [2,3]-thia-Wittig-like sigmatropic rearrangement, with the eventual requirement of a thiolate to alkyne ring closure. The carbon anions formed (**7**, **8**) will be rapidly protonated by solvent and, as indicated above, tautomerization will furnish the thermodynamically more stable product.[13,14] Each of the cyclizations suggested herein are of the 5-*endo*-*dig* variety and as such are not predicted to readily occur. However, several precedents are available, including some that form sulfur heterocycles.[4,15]



Scheme 3.

The cyclization reaction is a useful protocol for preparing 2-(2-haloaryl) thiophene derivatives. Though apparently limiting, the *ortho* halogen does provide a handle for further elaboration of compounds **2** with applications in the growing areas of sulfur-containing organic materials[16,17] and in solid supported synthesis.[17] We are currently pursuing the synthetic scope and mechanism of this reaction, with particular attention being paid to the rate enhancing role played by the *ortho* halogen substituent.

Acknowledgements

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9. Alkynes **1** are prepared via the reaction of an acetylide anion with compounds $ArCH_2SX$ (X=CN and/or SO_2Tol; yields 55, 72, 79–95%). Similar displacement reactions are known; X=SO_2Tol: Takeda, H.; Shimada, S.; Ohnishi, S.; Nakanushi, F.; Matsuda, H. *Tetrahedron Lett.* **1998**, *39*, 3701–3704.; X=CN: Klein, T. R.; Bergemann, M.; Yehia, N. A. M.; Fanghänel, E. *J. Org. Chem.* **1998**, *63*, 4626–4631. The thiotosylates and thiocyanates are made through substitution reactions of $KSSO_2Tol$ and KSCN, respectively, with benzylic halides or mesylates. LiC≡C*n*Bu was made by LDA deprotonation of 1-hexyne, while LiC≡CMe was prepared as outlined in Suffert, J.; Toussaint, D. *J. Org. Chem.* **1995**, 60, 3550–3553. Compounds **1** and **2** were fully characterized by ^1H and ^{13}C NMR, IR and elemental analysis or MS.
10. The cyclization of **1b** is presented as an example of the general experimental procedure: To KO*t*Bu (1.73 mmol) in dry CH_3CN (10 mL) at 0°C, was added 2-bromobenzyl 1-propynyl sulfide (**1b**) (0.867 mmol) in dry CH_3CN (10 mL). The mixture was stirred at 0°C for 24 h and was quenched with H_2O. The layers were separated, and the aq. layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography on silica gel (100% hexanes) afforded pure 2-(2-bromophenyl)-2,3-dihydrothiophene (**2b**, 74%) as a yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 7.7, 1.6 Hz, 1H), 7.55 (dd, J = 7.7, 1.2 Hz, 1H), 7.29 (dt, J = 7.7, 1.2 Hz, 1H), 7.11 (dt, J = 7.7, 1.6 Hz, 1H), 6.24 (ddd, J = 6.0, 2.6, 1.7 Hz, 1H), 5.61 (dt, J = 6.0, 2.9 Hz, 1H), 5.27 (dd, J = 9.7, 4.9 Hz, 1H), 3.27 (ddt, J = 16.8, 9.7, 2.6 Hz, 1H), 2.86 (dddd, J = 16.8, 4.9, 2.9, 1.7 Hz, 1H). ^{13}C NMR δ 142.5, 132.7, 128.7, 128.1, 127.9, 125.4, 123.3, 120.4, 50.8, 42.3. IR (cm^{-1}) 3062, 2938, 2896, 2842, 1588, 1567, 1467, 1440, 1265, 1025. EIMS, *m*/*z* (%): 242 (20, M^+ for ^{81}Br), 128 (100); Analysis calcd for $C_{10}H_9BrS$: C, 49.81; H, 3.76. Found: C, 49.79; H, 3.88.

11. Compounds **2e**–**h** could not be successfully separated from the starting sulfide. Their structure was assigned by observation of the heterocycle's unique ^{1}H NMR splitting pattern, already established for isolated products **2a**–**c**, **i**–**k**. In one instance, the crude mixture containing **1e** and **2e** was oxidized (MCPBA) and the resulting *S,S*-dioxide of **2e** was isolated and fully characterized.
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13. The proposed mechanism(s) suggests that allenyl sulfides **3** and propargyl sulfides **4** should also be starting materials for the cyclization. Indeed upon exposure of **3a** and **4a** to the standard conditions, **2a** was obtained in 43 and 38% yields, respectively.
14. Quenching the mixtures with D_2O or MeI rather than aq. NH_4Cl gave the same product, indicating that anions such as **7** and **8** gain their H^+ from the reaction environs.
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