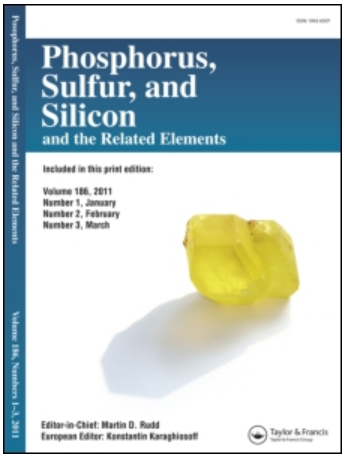

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Synthesis of Sulphur Compounds: Regioselective Synthesis of Thieno[2,3-*b*]thiophenes by Sulfoxide Rearrangement

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A number of thieno[2,3-b]thiophenes have been successfully synthesized in a 50–55% yield by m-chloroperoxybenzoic acid–mediated tandem cyclization involving [2, 3] and [3, 3] sigmatropic rearrangements and an intramolecular Michael addition.

Keywords [2,3] Sigmatropic rearrangement; [3,3] sigmatropic rearrangement; Sulfoxide rearrangement; thieno[2,3-*b*]thiophene

INTRODUCTION

Thieno[2,3-*b*]thiophenes have been synthesized[1] for different purposes in the pharmaceutical field and were tested as potential antiviral,[2] antibiotic,[3] antiglucoma,[4] analgesic, and antipyretic[5] drugs. A tandem cyclization methodology for the synthesis of benzo[*b*]thiophene and indole derivatives was reported by Majumdar and Thyagrajan[6a,6b] and El-Osta et al.[6c] Later this methodology was successfully utilized for the synthesis of some heterocyclic systems.[7] The methodology involves two consecutive sigmatropic rearrangements—a [2,3] shift followed by a [3,3] shift in arylprop-2-ynyl sulphoxides.[8] The sulfoxide rearrangements usually demand relatively high activation energy and require reaction conditions at r.t. to refluxing carbon tetrachloride (78°C). The same protocol was also applied to arylpropynyl amine oxide for the synthesis of fused pyrroles.[9] In continuation of our work in the area of

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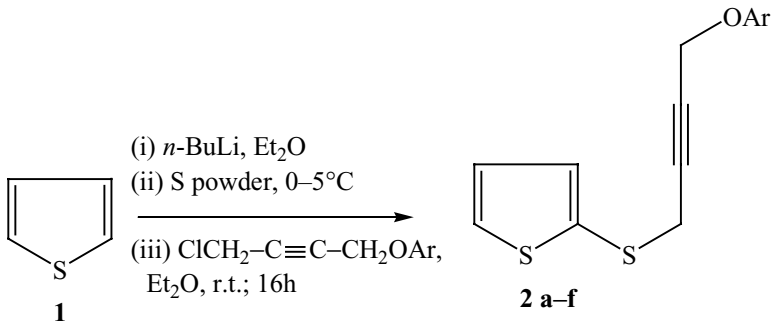
annulated heterocycles,[10] we became interested in exploring the viability of synthesizing thieno[2,3-*b*]thiophene derivatives by the application of the aforementioned tandem reaction, the sulfoxide rearrangement.

RESULTS AND DISCUSSION

The starting material for this study, 2-[4-aryloxybut-2-ynylsulfonyl]thiophenes **2**, were prepared in 75–85% yields by the reaction of thiophene, *n*-butyl lithium, sulphur powder, and 1-aryloxy-4- chlorobut-2-yne under a nitrogen atmosphere[11] (Scheme 1).

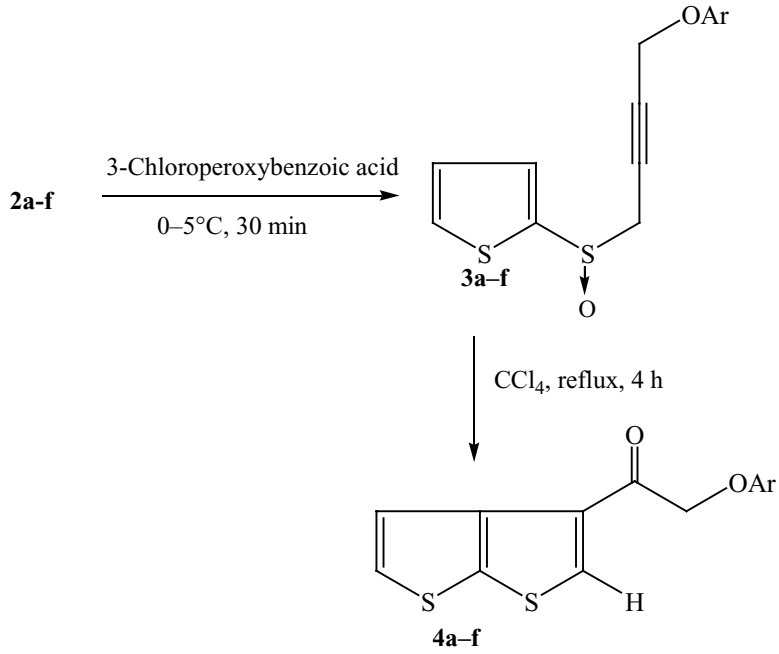


2 a Ar = 4-ClC_6H_4
b Ar = 4-MeC_6H_4
c Ar = -C_6H_5
d Ar = 4-*t*-BuC_6H_4
e Ar = 3,5-$Me_2C_6H_3$
f Ar = 4-$MeOC_6H_4$

SCHEME 1

Substrates **2a–f** are endowed with an aryloxy propynyl and a thioprop-2-ynyl moiety. In order to form thiophene annulated heterocycles, substrate **2a** was treated with one equivalent of *m*–chloroperoxybenzoic acid in chloroform at 0–5°C. TLC indicated the formation of the highly polar sulfoxide **3a**. Compound **2a** was completely converted to the new sulfoxide **3a** in 30 min. During hydrolytic work-up, another new spot appeared on TLC, but the conversion was only partial. As sulfoxide is labile, no attempt was made to isolate it in pure form. The solvent was removed, and the crude **3a** was refluxed in CCl_4 for a period of 4 h (Scheme 2).

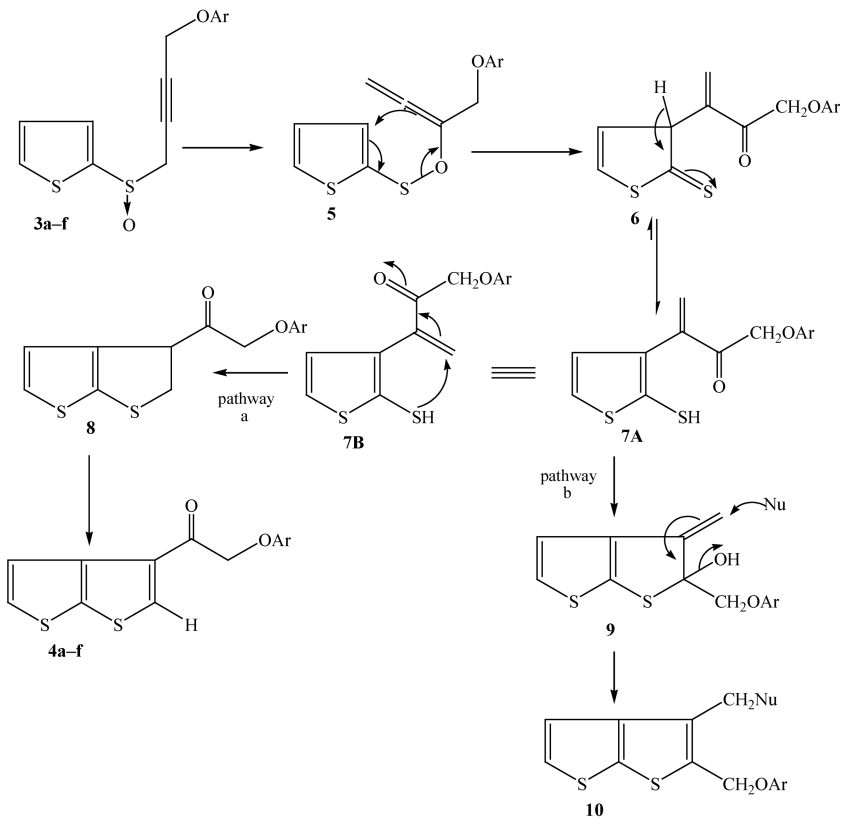
A colorless solid (55%), m.p. 86°C, was obtained. This was shown to be 2-(4-chlorophenoxy)-1[thieno-[2,3-*b*]thiophene-3-yl]ethanone **4a** by its elemental analysis and spectral data. The ^{1}H NMR spectrum of



SCHEME 2

compound **4a** displayed a singlet at δ 5.10 for OC**H**$_2$ protons. The aromatic protons appeared as two multiplets, one at δ 6.87–6.91 and another at δ 7.21–7.26. For the thiophene protons, three signals were observed: a doublet of doublets at δ 7.48 ($J = 5.2$, 1.0 Hz), a doublet at δ 7.79 ($J = 5.2$ Hz), and a doublet at δ 8.38 Hz ($J = 1.0$ Hz). The IR spectrum of compound **4a** displayed ν_{max} at 1685 cm^{-1} for the side chain carbonyl group. The mass spectrum of the compound showed molecular ion peaks at m/z 308 and 310. Sulfoxides **3b–f** obtained from **2b–f** in an analogous way were treated similarly to give products **4b–f** in 50–55% yields (Scheme 2).

The formation of thieno[2,3-*b*]thiophenes **4** from sulfoxides **3** may be mechanistically rationalized as shown in Scheme 3. A [2,3] sigmatropic rearrangement of sulfoxides **3** may give allenyl sulphenate derivatives **5**. An instantaneous [3,3] sigmatropic rearrangement through two heteroatoms, oxygen and sulphur, may generate intermediates **6**, which may then undergo tautomerization to **7**. Intermediates **7** possess a nucleophilic –SH functionality favorably situated to a α,β-enone moiety to allow an intramolecular Michael–type addition to afford compounds **4** (pathway a, Scheme 3). Another mode of cyclization (pathway b) could



SCHEME 3

also have occurred in intermediates **7**. Thus –SH could have delivered its nucleophilic attack to the carbonyl carbon of the enone moiety leading to allylic alcohols **9**. The S_N2' attack of water or *m*-chlorobenzoate ion on **9** could have produced compounds **10**. However, we could not detect compound **10** in any of the cases studied so far. The reaction displayed generality and regioselectivity. This is a mild and direct method for the synthesis of thieno[2,3-*b*]thiophene derivatives.

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded with a Perkin-Elmer L 120-000A spectrometer (ν_{max} in cm^{-1}). UV absorption spectra were recorded in EtOH

with a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^{1}H NMR (300 MHz, 500 MHz) and ^{13}C NMR (125.7 MHz) spectra were recorded with a Bruker DPX-300 and Bruker DPX-500 spectrometer in $CDCl_3$ with TMS as an internal standard. Elemental analyses and mass spectra were recorded on a Perkin Elmer 2400 Series-II CHN analyzer and a JEOL JMS-600 instrument. Silica gel ([60–120 mesh]), Spectrochem)] was used for chromatographic separation. Silica gel G [(E-Merck)] was used for TLC. Petroleum ether refers to the fraction boiling between 60°C and 80°C.

General Procedure for the Preparation of Compounds 2a–f

1.6 M *n*-BuLi solution in heptane (6.2 mL, 9.92 mmol) was added to thiophene (0.83 g, 9.92 mmol) in anhydrous ether at r.t. under a nitrogen atmosphere. The reaction mixture was then refluxed for 30 min, and sulphur powder (0.32 g, 9.92 mmol) was added portionwise at 0–5°C. The reaction mixture was then allowed to attain r.t., 1-aryloxy-4-chlorobut-2-yne (9.92 mmol) in ether was added during 30 min, and the mixture was stirred overnight. The reaction mixture was poured into NH_4Cl solution (50 mL). The organic layer was washed with water (2 × 50 mL), brine (50 mL), and dried (Na_2SO_4). Evaporation of the solvent left a gummy residue, which was subjected to column chromatography. Elution of the column with EtOAc/petroleum ether (1:50) afforded compounds **2a–f**.

2-[4-(4-Chlorophenoxy)but-2-ynylsulfanyl]thiophene (2a)

Yield 83%; viscous liquid; UV (EtOH) λ_{max}: 229, 250, 257, 267 nm; IR (neat) ν_{max}: 1218, 1489, 1594, 2225 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.50 (t, $J = 2.0$ Hz, 2H, SC**H**$_2$), 4.67 (t, $J = 2$ Hz, 2H, OC**H**$_2$), 6.83–7.41 (m, 7H, Ar**H**); MS m/z 294, 296 (M^+); anal. calcd for $C_{14}H_{11}OS_2Cl$: C, 57.03; H, 3.76; found; C, 57.30; H, 3.63%.

2-[4-(*p*-Tolyloxy)but-2-ynylsulfanyl]thiophene (2b)

Yield 77%; viscous liquid; UV (EtOH) λ_{max}: 228, 250, 257, 267 nm; IR (neat) ν_{max}: 1216, 1509, 1610, 2224 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H, C**H**$_3$), 3.50 (t, $J = 2.0$ Hz, 2H, SC**H**$_2$), 4.67 (t, $J = 2.0$ Hz, 2H, OC**H**$_2$), 6.81–7.40 (m, 7H, Ar**H**); MS m/z 274 (M^+); anal. calcd. for $C_{15}H_{14}OS_2$: C, 65.66; H, 5.14; found; C, 65.42; H, 4.88%.

2-[4-Phenoxybut-2-ynylsulfanyl]thiophene (2c)

Yield 80%; viscous liquid; UV (EtOH) λ_{max}: 220, 237, 262, 269 nm; IR (neat) ν_{max}: 1215, 1494, 1598, 2225 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.51 (t, $J = 2.0$ Hz, 2H, SCH_2), 4.70 (t, $J = 2.0$ Hz, 2H, OCH_2), 6.93–7.40 (m, 8H, ArH); MS m/z 260 (M^+); anal. calcd for $C_{14}H_{12}OS_2$: C, 64.58; H, 4.65; found; C, 64.80; H, 4.78%.

2-[4-(4-*tert*-Butylphenoxy)but-2-ynylsulfanyl]thiophene (2d)

Yield 85%; viscous liquid; UV (EtOH) λ_{max}: 226, 250, 257, 267 nm; IR (neat) ν_{max}: 1222, 1512, 1608, 2224 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.23 (s, 9H, C**H**$_3$), 3.43 (t, $J = 2.1$ Hz, 2H, SC**H**$_2$), 4.60 (t, $J = 2.1$ Hz, 2H, OC**H**$_2$), 6.77–7.30 (m, 7H, Ar**H**); MS m/z 316 (M^+); anal. calcd. for $C_{18}H_{20}OS_2$: C, 68.31; H, 6.37; found; C, 68.52; H, 6.48%.

2-[4-(3,5-Dimethylphenoxy)but-2-ynylsulfanyl]thiophene (2e)

Yield 75%; viscous liquid; UV (EtOH) λ_{max}: 231, 250, 257, 267 nm; IR (neat) ν_{max}: 1217, 1471, 1613, 2224 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.31 (s, 6H, C**H**$_3$), 3.52 (t, $J = 1.9$ Hz, 2H, SC**H**$_2$), 4.68 (t, $J = 1.9$ Hz, 2H, OC**H**$_2$), 6.59–7.40 (m, 7H, Ar**H**); MS m/z 288 (M^+); anal. calcd. for $C_{16}H_{16}OS_2$: C, 66.63; H, 5.59; found; C, 66.89; H, 5.77%.

2-[4-(4-Methoxylphenoxy)but-2-ynylsulfanyl]thiophene (2f)

Yield 83%; viscous liquid; UV (EtOH) λ_{max}: 230, 250, 257, 267 nm; IR (neat) ν_{max}: 1207, 1509, 1610, 2224 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.50 (t, $J =$ 2.0 Hz, 2H, SC**H**$_2$), 3.77 (s, 3H, C**H**$_3$), 4.64 (t, $J = 2.0$ Hz, 2H, OC**H**$_2$), 6.80–7.39 (m, 7H, Ar**H**); MS m/z 290 (M^+); anal. calcd. for $C_{15}H_{14}O_2S_2$: C, 62.04; H, 4.86; found; C, 61.81; H, 5.01%.

General Procedure for the Oxidation and Subsequent Rearrangement of 2-[4-Aryloxybut-2-ynylsulfanyl]thiophenes (2a–f)

A solution of *m*-CPBA (2.43 mmol, 600 mg [70%]) in chloroform (30 mL) was slowly added to a well-stirred solution of sulphides **2a–f** (2.43 mmol) in chloroform (30 mL) at 0–5°C over a period of 15 min. The reaction mixture was stirred at r.t. for an additional 30 min. The resulting solution was then washed with 10% aq. Na_2CO_3 (3 × 25 mL), brine (25 mL), and dried (Na_2SO_4). Removal of the solvent gave a gummy mass, which was then dissolved in carbon tetrachloride and refluxed for 4 h.

After evaporation of the carbon tetrachloride, the crude product was purified by column chromatography. Elution of the column with 2% EtOAc/petroleum ether gave compounds **4a–f**.

2-(4-Chlorophenoxy)-1[thieno-[2,3-*b*]thiophene-3-yl]ethanone (4a)

Yield 50%; colorless solid, m.p. 86°C; UV (EtOH) λ_{max}: 229, 250, 256, 287 nm; IR (KBr) ν_{max}: 1187, 1429, 1490, 1583, 1685 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.14 (s, 2H, OCH_2), 6.87–6.91 (m, 2H, aryl-H), 7.21–7.26 (m, 2H, aryl-H), 7.48 (dd, $J = 5.2$, 1.0 Hz, 1H, thiophene-H), 7.79 (d, $J = 5.2$ Hz, 1H, thiophene-H), 8.38 (d, $J = 1.0$ Hz, 1H, thiophene-H); MS m/z 308, 310 (M^+); anal. calcd. for $C_{14}H_9O_2S_2Cl$: C, 54.45; H, 2.94; found; C, 54.60; H, 3.11%.

2-(*p*-Tolyloxy)-1[thieno-[2,3-*b*]thiophene-3-yl]ethanone (4b)

Yield 55%; colorless powder, m.p. 94°C; UV (EtOH) λ_{max}: 230, 251, 257, 286 nm; IR (KBr) ν_{max}: 1177, 1429, 1509, 1610, 1686 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.27 (s, 3H, C**H**$_3$), 5.11 (s, 2H, OC**H**$_2$), 6.84 (d, $J = 8.4$ Hz, 2H, aryl-H), 7.07 (d, $J = 8.4$ Hz, 2H, aryl-H), 7.46 (dd, $J = 5.2$, 1.0 Hz, 1H, thiophene-**H**), 7.80 (d, $J = 5.2$, Hz, 1H, thiophene-**H**), 8.43 (d, $J =$ 1.0 Hz, 1H, thiophene-**H**); ^{13}C NMR ($CDCl_3$): δ 20.8, 72.2, 114.9, 122.0, 130.4, 130.5, 131.1, 131.5, 137.8, 138.0, 145.7, 156.2, 189.6; MS m/z 288 (M^+); anal. calcd for $C_{15}H_{12}O_2S_2$: C, 62.47; H, 4.19; found; C, 62.73; H, 4.35%.

2-Phenoxy-1[thieno-[2,3-*b*]thiophene-3-yl]ethanone (4c)

Yield 55%; viscous liquid; UV (EtOH) λ_{max}: 217, 250, 256, 288 nm; IR (neat) ν_{max}: 1186, 1429, 1495, 1598, 1686 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.15 (s, 2H, OC**H**$_2$), 6.95–7.02 (m, 3H, aryl-**H**), 7.27–7.33 (m, 2H, aryl-**H**), 7.47 (dd, $J = 5.3$, 1.0 Hz, 1H, thiophene-H), 7.81 (d, $J = 5.3$ Hz, 1H, thiophene-H), 8.44 (d, $J = 1.0$ Hz, 1H, thiophene-H);MS m/z 274 (M^+); anal. calcd. for $C_{14}H_{10}O_2S_2$: C, 61.29; H, 3.67; found; C, 61.51; H, 3.39%.

2-(4-*tert*-Butylphenoxy)-1[thieno-[2,3-*b*]thiophene-3-yl]ethanone (4d)

Yield 52%; colorless powder, m.p. 100°C; UV (EtOH) λ_{max}: 225, 245, 250, 282 nm; IR (KBr) ν_{max}: 1183, 1429, 1512, 1608, 1686 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (s, 9H, C**H**$_3$), 5.11 (s, 2H, OCH_2), 6.87 (d, $J =$

8.8 Hz, 2H, aryl-**H**), 7.28 (d, $J = 8.8$ Hz, 2H, aryl-**H**), 7.45 (dd, $J = 5.2$, 0.9 Hz, 1H, thiophene-H), 7.80 (d, $J = 5.2$, Hz, 1H, thiophene-**H**), 8.43 (d, $J = 0.9$ Hz, 1H, thiophene-H); MS m/z 330 (M^+); anal. calcd. for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49; found; C, 65.63; H, 5.25%.

2-(3,5-Dimethylphenoxy)-1[thieno-[2,3-*b*]thiophene-3-yl]ethanone (4e)

Yield 50%; colorless powder, m.p. 78°C; UV (EtOH) λ_{max}: 234, 251, 257, 288 nm; IR (KBr) ν_{max}: 1169, 1429, 1504, 1594, 1686 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.28 (s, 6H, C**H**$_3$), 5.10 (s, 2H, O**CH**$_2$), 6.59 (s, 2H, aryl-**H**), 6.64 (s, 1H, aryl-**H**), 7.47 (dd, $J = 5.2$, 1.1 Hz, 1H, thiophene-H), 7.82 (d, $J = 5.2$ Hz, 1H, thiophene-H), 8.45 (d, $J = 1.1$ Hz, 1H, thiophene-H); MS m/z 302 (M^+); anal. calcd. for $C_{16}H_{14}O_2S_2$: C, 63.55; H, 4.67; found; C, 63.83; H, 4.46%.

2-(4-Methoxyphenoxy)-1[thieno-[2,3-*b*]thiophene-3-yl]ethanone (4f)

Yield 53%; viscous liquid; UV (EtOH) λ_{max}: 226, 250, 256, 288 nm; IR (neat) ν_{max}: 1185, 1430, 1506, 1594, 1687 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.76 (s, 3H, OC**H**$_3$) 5.09 (s, 2H, OC**H**$_2$), 6.81–6.86 (m, 2H, aryl-**H**), 6.87–6.93 (m, 2H, aryl-**H**), 7.47 (dd, $J = 5.2$, 1.1 Hz, 1H, thiophene-**H**), 7.81 (d, $J = 5.2$, Hz, 1H, thiophene-**H**), 8.44 (d, $J = 1.1$ Hz, 1H, thiophene-**H**); MS m/z 304 (M^+); anal. calcd. for $C_{15}H_{12}O_3S_2$: C, 59.19; H, 3.97; found; C, 59.37; H, 3.79%.

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