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Thiophene Sulfoximides: 2,4- and 3,4-Di-*tert*-butyl-1-imino-1,1-dihydrothiophene 1-Oxides

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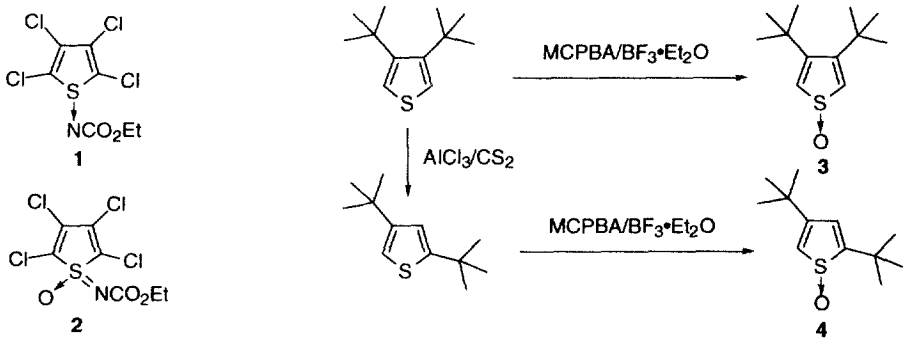
Abstract: Preparation of sulfoximide derivatives of monocyclic thiophenes is reported. Treatment of 2,4–di-*tert*-butylthiophene 1-oxide (**4**) with *N*-[(*p*-toluenesulfonyl)imino]-phenyliodinane (TsN=IPh) in the presence of $Cu(MeCN)_4PF_6$ in MeCN at room temperature provided 2,4-di-*tert*-butyl-1-[(*p*-toluenesulfonyl)imino]-1,1-dihydrothiophene 1-oxide (**8**) in 81% yield. Hydrolysis of **8** with concentrated H_2SO_4 at room temperature furnished 2,4-di-*tert*-butyl-1-imino-1,1-dihydrothiophene 1-oxide (**9**) in 89% yield. Optical resolution of a pair of enantiomers of **9** was performed by HPLC on a chiral column and their absolute configuration was determined by an X-ray crystallographic analysis.

A great number of sulfoximides have been synthesized and their chemistry has been attracting a good deal of interest and activity from a variety of standpoints such as structures, stereochemistry, reactivities, and applications to organic syntheses.[1] However, synthetic study of sulfoximide derivatives of thiophenes has been surprisingly limited, whereas the chemistry of thiophene 1,1-dioxides has been a matter of most extensive investigation. To our knowledge, the sulfoximide (**2**),[2] which was obtained by MCPBA oxidation of the sulfinylimide (**1**), is the only monocyclic sulfoximide derivative of a thiophene ever synthesized.[3] This is probably owing to the expected thermal instability of thiophene sulfoximides and the nonavailablity of suitable precursor compounds. Recently, kinetically stabilized, isolably stable thiophene 1-oxides (**3**) and (**4**),[4] which might serve as the precursor for sulfoximides, were obtained by oxidation of the corresponding thiophenes in the presence of BF_3•Et_2O.[5]



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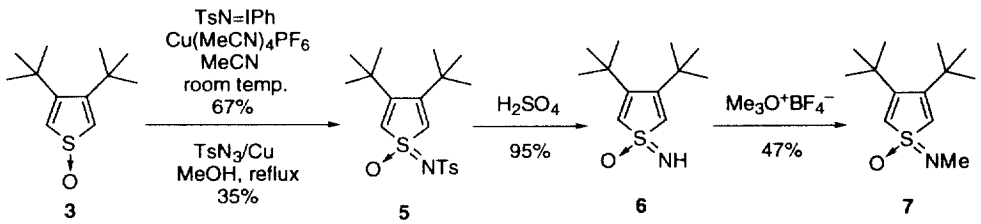
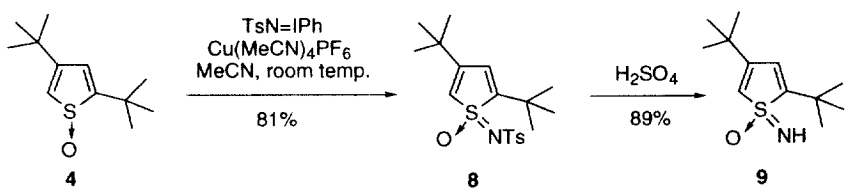
The present paper describes i) preparation of sulfoximide derivatives from **3** and **4**, ii) optical resolution of a pair of enantiomers derived from **4**, iii) and determination of absolute configuration of the enantiomers by an X-ray crystallographic analysis.

The reaction of thiophene 1-oxide **3** with *N*-[(*p*-toluenesulfonyl)imino]phenyliodinane (TsN=IPh)[6] (1.2 equiv) proceeded smoothly in the presence of a copper(I) catalyst [Cu(MeCN)$_4$PF$_6$][7] in acetonitrile at room temperature and formed the expected thiophene sulfoximide (**5**)[8,9] in 67% yield. A conventional method, which employs *p*-toluenesulfonyl azide (3 equiv) in the presence of an activated copper powder in refluxing methanol,[10] worked only in a sluggish way to produce **5** in a moderate yield of 35%. The *p*-toluenesulfonyl group was eliminated from **5** by hydrolysis with concentrated H_2SO_4[11] to form the parent sulfoximide (**6**)[8,9] in 95% yield. Treatment of **6** with $Me_3O^+BF_4^-$ gave the *N*-methylated compound (**7**)[8,9] in 47% yield with recovery of **6** in 44% yield.



Similarly, treatment of the unsymmetrically substituted thiophene 1-oxide **4** with TsN=IPh (1.2 equiv) in the presence of the copper(I) catalyst gave the sulfoximide (**8**)[8,9] in 81% yield. The compound **8** was then converted to the parent sulfoximide (**9**)[8,9] in 89% yield by treatment with concentrated H_2SO_4.



Both **6** and **9** are not very stable thermally; **9** decomposed completely, when heated in boiling toluene for several hours, to give at least ten products.

The tetra-coordinated sulfur atom of **9** is chiral, thus an effort was made to separate a pair of enantiomers. HPLC on a chiral column[12] gave the two well-separated peaks due to a pair of enantiomers and allowed us their easy separation.[13] The both enantiomers, on slow evaporation of a hexane solution, provided good crystals for an X-ray crystallographic analysis. The analysis disclosed, with the η value defined by Rogers[14] being 1.03(6), that the second-eluted enantiomer has an (*S*)-configuration.[15,16] (*R*)-Configuration is therefore assigned to the first-eluted enantiomer. An ORTEP diagram of (*S*)-**9** is given in Figure 1 along with the relevant bond lengths and bond angles data. The thiophene ring of the compound is planar as so with most thiophene 1,1-dioxides.[17] The bond length data (1.32 Å for C2-C3 and C4-C5, 1.49 Å for C3-C4) are indicative of bond fixing, that is, nonaromaticity of the thiophene ring. The S-O and S-N bond lengths are 1.45 and 1.54 Å, respectively, and are comparable with those of other sulfoximides.[1c,16] The O-S-N bond angle of 119° is larger than those of acyclic sulfoximides.[16]

(*R*)-**9** and (*S*)-**9** both had a melting point of 114-115 °C, which is much higher than that of the racemate **9** (mp 82.5-83.5 °C), and showed specific rotations of –48.6 ° and +48.6 ° (*c* 0.10 g/100 ml, $CHCl_3$, 26 °C), respectively. The UV/Vis spectrum of the racemate **9** showed absorption maxima at ca. 315 (sh), 279, and 245 nm (Figure 2). Thus (–)-(*R*)-**9** showed the negative first Cotton effect at 315, the positive second one at 279, and the negative third one at 236 nm in the circular dichroism (CD) spectrum, while (+)-(*S*)-**9** gave the quite reverse pattern (Figure 2).

In conclusion, the present study provides first example that the chirality was introduced to the sulfur atom of the thiophene ring,[13] and optical resolution and determination of the absolute configuration of a pair of enantiomers were accomplished successfully.

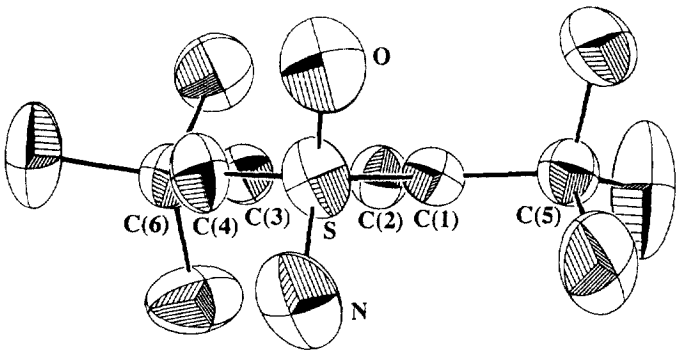


Figure 1. ORTEP diagram of (+)-(*S*)-**9**. Selected bond lengths: S-O, 1.445(3); S-N, 1.536(3); S-C1, 1.796(3); S-C4, 1.739(3); C1-C2, 1.321(3); C2-C3, 1.492(3); C3-C4, 1.319(4); C1-C5, 1.520(4); C3-C6, 1.507(4) Å. Bond angles: O-S-N, 119.3(2); C1-S-C4, 92.9(2); S-C1-C2, 107.3; C1-C2-C3, 116.4(2); C2-C3-C4, 111.5(3), C3-C4-S, 111.9(2); S-C1-C5, 123.2(2); C2-C3-C6, 121.5(2)°.

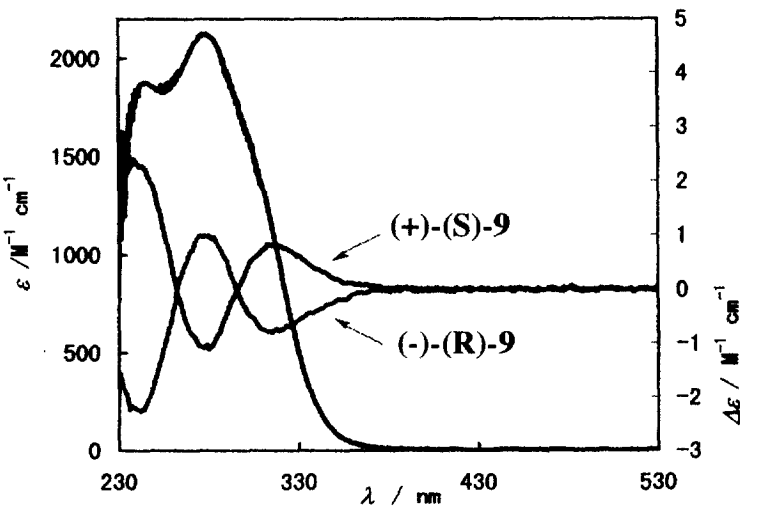


Figure 2. CD spectra of (–)-(*R*)- and (+)-(*S*)-**9** (*c* 0.010 g/100 ml, CH_2Cl_2) and UV/Vis spectrum of the racemate **9** (CH_2Cl_2)

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[8] All new compounds gave satisfactory elemental analysis results.

[9] **5**: mp 140.0-140.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (18H, s), 2.41 (3H, s), 6.92 (2H, s), 7.29 (2H, d, J = 8.2 Hz), 7.89 (2H, d, J = 8.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5, 31.5, 36.2, 126.6, 126.7, 129.4, 140.5, 143.0, 158.9. **6**: mp 95.5-96.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (18H, s), 2.97 (1H, broad s, NH), 6.53 (2H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.6, 35.4, 129.4, 155.0. **7**: mp 117-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (18H, s), 2.95 (3H, s), 6.57 (2H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.1, 31.7, 35.5, 126.5, 155.4. **8**: mp 124.5-126.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (9H, s), 1.36 (9H, s), 2.42 (3H, s), 6.55 (1H, d, J = 1.3 Hz), 6.96 (1H, d, J = 1.3 Hz), 7.29 (2H, d, J = 8.2 Hz), 7.89 (2H, d, J = 8.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5, 27.6, 29.5, 33.7, 35.6, 121.3, 124.9, 126.5, 129.3, 141.0, 142.7, 153.3, 153.9. **9** (racemate): mp 82.5-83.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (9H, s), 1.42 (9H, s), 2.96 (1H, broad s, NH), 6.12 (1H, d, J = 1.4 Hz), 6.29 (1H, d, J = 1.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.7, 29.6, 33.1, 35.1, 120.1, 122.8, 152.7, 156.0.

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[12] CHIRALPAK AD (4.6 mm i.d. x 250 mm; Daicel Chemical Industries, Ltd) was used with hexane/ethanol (98.5/1.5) as the eluent (flow rate: 1.0 ml/min, detector: UV, 254 nm).

[13] The sulfur atom of the sulfoxide **4** is also chiral. However, the pyramidal inversion energy of thiophene 1-oxides is not sufficiently large that optical resolution of a pair of enantiomers at room temperature must be impossible: calculated and experimental pyramidal inversion energies are 13.3 and 14.8 kcal/mol for 2,5-dimethylthiophene and 2,5-di-*tert*-octylthiophene 1-oxides, respectively; a) J. D. Andose, A. Rauk, R. Tang, and K. Mislow, *Int. J. Sulfur Chem.*, **1971**, *A1*, 66; b) W. L. Mock, *J. Am. Chem. Soc.*, **1970**, *92*, 7610. Indeed, attempted isolation of a pair of enantiomers of **4** by HPLC on a chiral column failed.

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[15] Crystal structure data for (*S*)-**9**: $C_{12}H_{21}NOS$, M_r = 227.40, orthorhombic, $P2_12_12_1$, a = 13.491(3), b = 17.019(4), c = 5.802(1) Å, V = 1332.2(5) Å^3, Z = 4, D_c = 1.133 M gm^{-3}, μ(Cu K_α) = 19.246 mm^{-1}, λ = 1.54178 Å, T = 298 K, crystal dimensions (0.58 x 0.16 x 0.10 mm), Mac Science MXC3K diffractometer, 1361 observed reflections, R = 0.055, wR = 0.065, S = 1.526. Data collection and cell refinement, MXC (Mac Science); data reduction, program used to solve and refine structure, and molecular graphics, CRYSTAN. The assignment of the oxygen and nitrogen atoms was based on the distance from the sulfur atom since the position of the imide hydrogen atom could not be determined.[16]

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[18] We thank Dr. T. Fujihara for his help in determination of the CD spectra.