

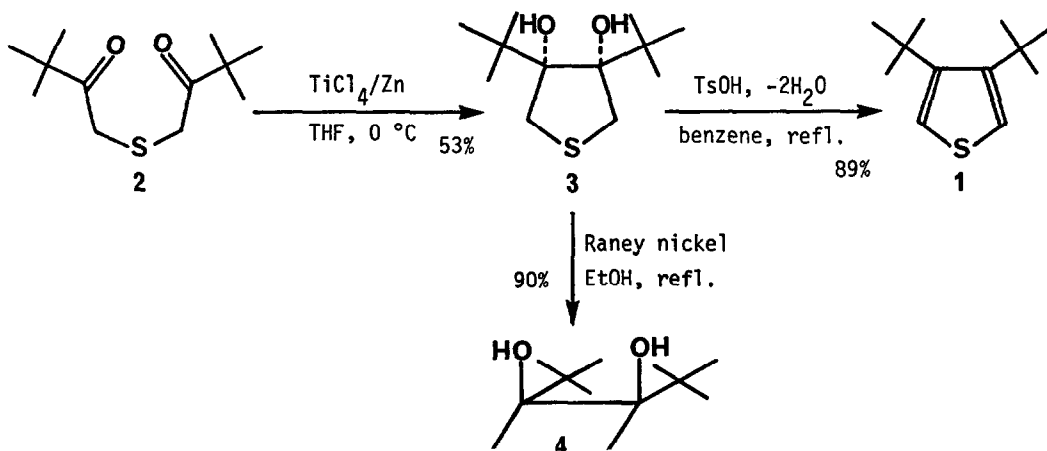
SYNTHESIS AND REACTIONS OF 3,4-DI-*t*-BUTYLTHIOPHENE

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Abstract: 3,4-Di-*t*-butylthiophene (1) was surprisingly easily synthesized from readily accessible bis(2-*t*-butyl-2-oxoethyl) sulfide (2). Reactions of 1 with a variety of electrophiles were examined.

Sterically overcrowded 3,4-di-*t*-butylthiophene (1) was first synthesized in 1980¹ after numerous unsuccessful attempts.² X-Ray crystal-structure determination shows that the internal strain in this molecule is appreciable.³ Although this provokes an interest in the reactivities of this compound, such study has not appeared. Herein we report a surprisingly facile synthesis of 1 and its reactions with a variety of electrophiles.

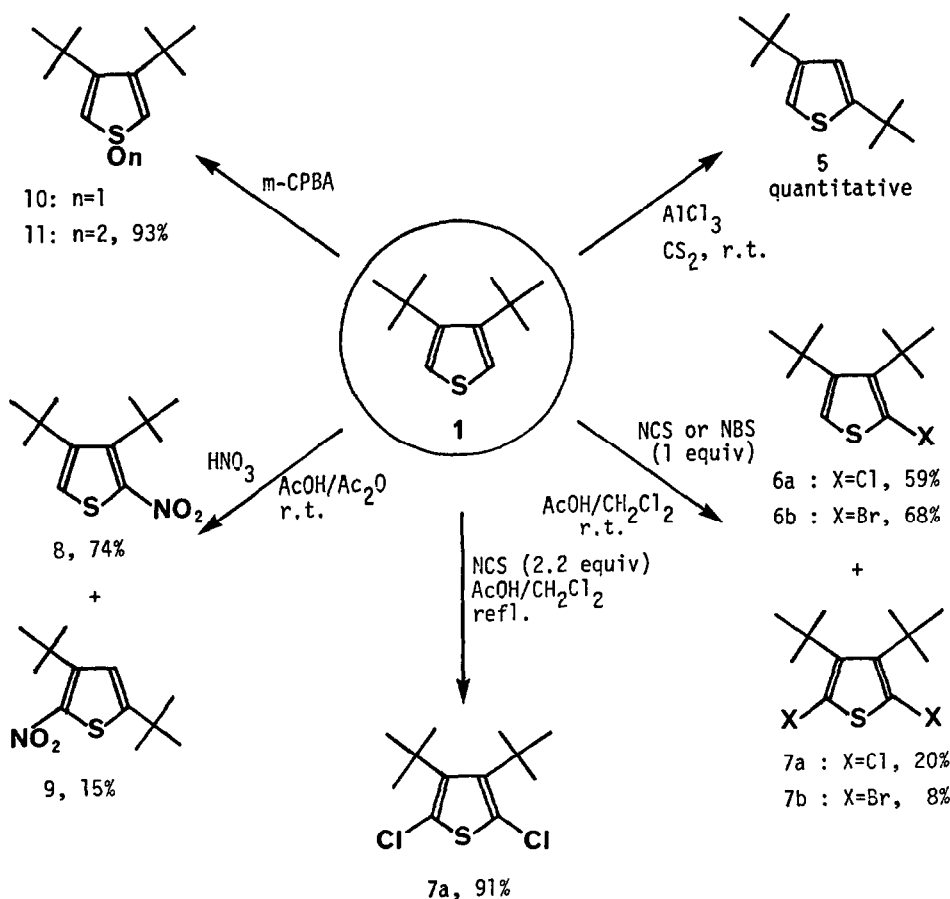
We have recently developed a new thiophene synthesis, which involves intramolecular reductive coupling of α, α' -diketo sulfides and the acid-catalyzed dehydration of the resulting 3,4-dihydroxythiolanes.⁴ Application of this thiophene synthesis to readily obtainable bis(2-*t*-butyl-2-oxoethyl) sulfide (2)⁵ allows a simple synthesis of 1. Thus, treatment of 2 with a low-valent titanium reagent, prepared from titanium(IV) chloride and zinc powder, in tetrahydrofuran (THF) affords *cis*-3,4-di-*t*-butyl-3,4-dihydroxythiolane (3)⁷ in 53% yield.⁸ The *cis*-configuration of this diol was established by X-ray



crystal-structure analysis.⁹ The occurrence of cis-oriented cyclization, even in a system leading to an overcrowded molecule such as 3, is particularly noteworthy.¹⁰ Desulfurization of 3 with Raney nickel afforded meso-2,3-di-t-butyl-2,3-dihydroxybutane (4)¹¹ in 90% yield. Finally acid-catalyzed dehydration of 3 leading to 1 occurs quite smoothly; heating of 3 with a catalytic amount of p-toluenesulfonic acid in refluxing benzene for 1 h affords 1¹² in 89% yield.

The method developed here allows the preparation of 1 in a large quantity and thus enables to examine the reactivities of 1 toward a variety of reagents.

The thiophene 1, on treatment with aluminum chloride at room temperature in carbon disulfide, quantitatively rearranges to 2,4-di-t-butylthiophene (5).¹³ Such rearrangement was also observed with nitration of 1 as described later. Chlorination of 1 with 1 equiv of N-chlorosuccinimide (NCS) in a mixture of acetic acid and methylene chloride (1:1) at room temperature affords the monochloro derivative 6a¹⁴ (59%) and the dichloro derivative 7a¹⁴ (20%) with recovery of 1 in 20% yield, while the use of 2.2 equiv of NCS under refluxing conditions gives 7a exclusively in 91% yield. Bromination with 1



equiv of N-bromosuccinimide (NBS) under similar conditions affords the mono-bromo derivative 6b¹⁴ (68%), dibromo derivative 7b¹⁴ (8%), and 1 (20%).¹⁵ Nitration of 1 affords mononitro derivatives 8¹⁴ (74%) and 9¹⁴ (15%). The latter compound was independently obtained by nitration of 5. The Vilsmeier reagent prepared from N,N-dimethylformamide and phosphorus oxychloride failed to react with 1 because of steric hindrance. The reactivities of 1 observed above are rather normal and similar to those of simple alkyl thiophenes,¹⁶ except that facile rearrangement to 5 and failure of Vilsmeier formylation give a positive proof of the influence of t-butyl group.

Oxidation of 1 with excess m-chloroperoxybenzoic acid (m-CPBA) at room temperature cleanly afforded the sulfone 11¹⁷ in 93% yield. Oxidation of thiophenes to the corresponding sulfones is usually accompanied by side reactions including dimerization of unstable sulfoxide intermediates, and thus yields of sulfones are generally moderate to low.¹⁶ The excellent yield attained in the present case indicates that side reactions are effectively suppressed by bulky t-butyl groups. Even the use of 1 equiv of m-CPBA could not stop the oxidation at the stage of the sulfoxide 10, 11 being the sole product.^{18,19}

References and Notes

1. L. Brandsma, J. Meijer, H. D. Verkruisje, G. Bokkers, A. J. M. Duisenberg, and J. Kroon, J. Chem. Soc., Chem. Commun., 922 (1980).
2. H. Wynberg, Acc. Chem. Res., 4, 65 (1971).
3. G. Bokkers, A. J. M. Duisenberg, J. Kroon, and L. Brandsma, Cryst. Struct. Chem., 10, 361 (1981).
4. J. Nakayama, H. Machida, R. Saito, and M. Hoshino, Tetrahedron Lett., 26, 1983 (1985).
5. Y. Miyahara, J. Heterocycl. Chem., 16, 1147 (1976).
6. T. Mukaiyama, T. Sato, and J. Hanna, Chem. Lett., 1041 (1973).
7. 3: mp 108.5-110 °C; IR (nujol) 3408, 3398 cm⁻¹, (CCl₄) 3532 cm⁻¹ (OH); ¹H-NMR (CDCl₃) δ 1.23 (18H, s, t-Bu), 2.75 (2H, d, J=13 Hz, methylene), 3.29 (2H, d, J=13 Hz, methylene), 3.29 (2H, s, OH); ¹³C-NMR (CDCl₃) δ 28.4 (q), 37.4 (t), 38.2 (s), 91.0 (s).
8. The yield based on a 1.7-mmol scale reaction. The yield may decrease in a larger scale reaction. The following is typical procedure of a relatively large scale reaction. To a stirred mixture of 2 (23.0 g, 0.1 mol) and zinc powder (44.0 g, 0.67 mol) in THF (650 ml) was added titanium(IV) chloride (37 ml, 0.34 mol) at -10 °C over a period of 1 h under nitrogen. The mixture was stirred for 0.5 h, warmed to 0 °C, and stirred for 4.5 h. The resulting mixture was poured onto a two-phase mixture of hexane (1000 ml) and 10% aqueous sodium carbonate (800 ml) (cracked ice was added to maintain the temperature at about 0 °C). The mixture was stirred for 1 h and the insoluble material was removed by filtration through Celite. The hexane layer was separated and the aqueous layer was extracted with hexane (200 ml x 2). The combined hexane extracts were washed with water, dried, and evaporated. The residue was recrystallized from pentane to give 7.4 g (32%) of 3. If required, chromatographic workup of the mother liquor gives an additional amount of 3.

9. X-Ray analysis work was done by Professor F. Iwasaki of University of Electro-Communication. Details of this work will be reported elsewhere.
10. J. Nakayama, S. Yamaoka, and M. Hoshino, Tetrahedron Lett., 28, 1799 (1987).
11. The present result provides a stereoselective synthesis of the meso-isomer of 2,3-di-t-butyl-2,3-dihydroxybutane; cf. H. J. Backer and H. Bos, Recl. Trav. Chim. Pays-Bas, 57, 967 (1938).
12. 1: mp 43-43.5 °C (lit., ¹ mp 42 °C); bp 75 °C/4 mmHg (bulb-to-bulb distillation); ¹H-NMR (CDCl₃) δ 1.47 (18H, s), 7.16 (2H, s); ¹³C-NMR (CDCl₃) δ 33.5 (q), 35.3 (s), 122.3 (d), 150.6 (s).
13. H. Wynberg and U. E. Wiersum, J. Org. Chem., 30, 1058 (1965).
14. 6a: oil; ¹H-NMR (CDCl₃) δ 1.45 (9H, s), 1.61 (9H, s), 6.92 (1H, s).
⁶b: oil; ¹H-NMR (CDCl₃) δ 1.46 (9H, s), 1.64 (9H, s), 7.09 (1H, s).
⁷a: mp 45.5-46 °C; ¹H-NMR (CDCl₃) δ 1.58 (s); ¹³C-NMR (CDCl₃) δ 33.4, 37.7, 121.4, 146.4
⁷b: solid; ¹H-NMR (CDCl₃) δ 1.60 (s).
⁸: mp 32-32.5 °C; ¹H-NMR (CDCl₃) δ 1.50 (9H, s), 1.56 (9H, s), 7.32 (1H, s).
⁹: oil; ¹H-NMR (CDCl₃) δ 1.41 (9H, s), 1.47 (9H, s), 6.67 (1H, s).
15. Bromination with 3 equiv of NBS is rather complex. GC-MS analysis reveals that the reaction is accompanied by de-t-butylation, and thus a considerable amount of 2,4,5-tribromo-3-t-butylthiophene (or its positional isomer) is formed in addition to 7b.
16. a) R. Livingstone, "Rodd's Chemistry of Carbon Compounds," Vol. IV Part A, S. Coffey, Ed., Elsevier, Amsterdam, 1973, Chapter 3.
 b) G. R. Newkome and W. W. Paudler, "Contemporary Heterocyclic Chemistry," John Wiley, New York, 1982, Chapter 3.
 c) S. Rajappa, "Comprehensive Heterocyclic Chemistry," Vol. 4, C. W. Bird and G. W. H. Cheeseman, Eds., Pergamon Press, Oxford, 1984, p.741.
17. 11: mp 132.5-133 °C; ¹H-NMR (CDCl₃) δ 1.40 (18H, s), 6.40 (2H, s); IR (KBr) 1284, $\tilde{\nu}$ 1134 cm⁻¹ (SO₂).
18. 2,5-Di-t-butylthiophene-1-oxide is the only example that the sulfoxide of thiophene is satisfactorily isolated; W. L. Mock, J. Am. Chem. Soc., 92, 7610 (1970).
19. The thiophene 1 was not oxidized by sodium periodate in a refluxing mixture of methanol and water for 10 h. 1 also resisted S-methylation with methyl iodide in the presence of silver tetrafluoroborate in methylene chloride at room temperature for 2.5 d.

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