On the Metalation of 2,6-Dimethyl-4-*tert*-butyl-thiophenol

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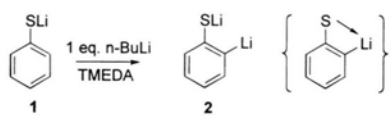
Z. Naturforsch. **53b,** 1239–1240 (1998); received August 5, 1998

Metalation, 2,6-Dimethyl-4-*tert*-butyl-thiophenol, Lithium, Sulfur

Metalation of 2,6-Dimethyl-4-*tert*-butyl-thiophenol (**6**) with *n*-BuLi/TMEDA in THF occurs regioselectively at the benzylic positions to produce lithium 2,6-di(lithiomethyl)-4-*tert*-butyl-benzenethiolate (**7**). Treatment of compound **7** with elemental sulfur followed by iodine-oxidation affords an oxidation product **9a** of bis(sulfanylmethyl)-4-*tert*-butyl-thiophenol (**5**).

The sulfanyl group belongs to a group of activating substituents which facilitate ortho-lithiation of aromatic compounds [1, 2]. The directed lithiation of lithium thiophenolate (**1**), *e.g.*, gives lithium 2-lithio-benzenethiolate (**2**) which has been proven to be very useful as an intermediate in the synthesis of a variety of sulfur containing compounds [3, 4]. The regioselectivity of this reaction is due to the fact that, prior to metalation, complexation occurs between the substituent group and the metalating agent. Intramolecular coordination by the substituent groups also stabilizes the metalated intermediates.



Scheme 1.

One might expect that the sulfanyl group in the arenethiolate compound **3** similarly facilitates metalation at a benzylic position and stabilizes the corresponding lithiated derivative **4** by formation of a five-membered chelate ring. It has been our goal to use reactions of this kind for the preparation of the tridentate thiol compound **5**, for which general syntheses are not available [5, 6].

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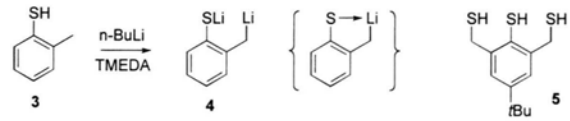


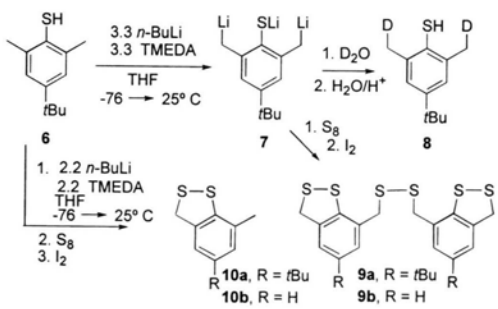
Scheme 2.

We here describe that metalation of 2,6-dimethyl-4-*tert*-butyl-thiophenol (**6**) by use of *n*-butyllithium in the presence of *N,N,N′,N′*-tetramethylethylenediamine occurs at the benzylic positions and that the reaction of the lithiated intermediate with elemental sulfur affords compound **9a**, which is an oxidation product of the trithiol compound **5**.

Results

Metalation of compound **6** at both benzylic positions proceeds with the use of 3.3 equivalents of *n*-butyllithium and 3.3 equivalents of *N,N,N′,N′*-tetramethylethylenediamine in THF. The reagents are simply mixed at −76 °C, and then the reaction mixture is allowed to warm up to r.t., where it is further maintained for 2 h. Reaction with D_2O at this stage produces **8** in > 95% yields, indicating that metalation of **6** to the intermediate lithium 2,6-di(lithiomethyl)-4-*tert*-butyl-benzenethiolate **7** is complete within 2–3 h.

Reaction of **7** with elemental sulfur followed by oxidation with iodine gives compound **9a**, which is an oxidation product of **5**. The NMR spectral properties of **9a** are very similar to those of **9b**, with singlets at $\delta = 3.63$ and 3.36 for two sets of inequivalent benzylic protons [6]. When **6** is treated with less than 3.3 equivalents for *n*-BuLi, only one benzylic position is metalated. Reaction of this monometalated intermediate with S_8 and subsequent oxidation by I_2 affords the cyclic disulfide **10a**.



Scheme 3.

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Although we have not optimized the conditions to obtain maximum yields of **9a**, this method provides a convenient alternative to the traditional routes to **9b** and **10b** [6]. We will report on the reduction of **9a** and of corresponding metal complexes in due course [7].

Experimental

Compound **6** was prepared by reduction of 2,6-dimethyl-4-*tert*-butyl-benzenesulfonylchloride with $LiAlH_4$ in THF [8]. The sulfonylchloride was obtained from commercially available 5-*tert*-butyl-meta-xylene and chlorosulfonic acid. All reactions were carried out under an atmosphere of dry nitrogen with standard Schlenk techniques. THF was distilled from sodium benzophenone ketyl prior to use. CHN-Analyses: Perkin Elmer Elemental Analyzer 240. ^1H NMR, $^{13}C\{^1H\}$ NMR: Bruker AC 200 spectrometer.

Metalation of **6**: A 2.5 M solution of *n*-BuLi in hexane (13.2 ml, 33.0 mmol) in THF (50 ml) was added dropwise to a solution of **6** (1.94 g, 10.0 mmol) and TMEDA (3.83 g, 33.0 mmol) in THF (30 ml) at −76 °C. The reaction mixture was allowed to warm up to r.t. and stirring was continued for 2 h. This solution was used without further purification in one of the next steps.

Compound **8**: Compound **6** was metalated as described above. To a 2 ml aliquot of the reaction mixture was added D_2O (1 ml) and then H_2O (5 ml). The pH was adjusted to 1 by addition of concentrated HCl, and the resulting solution was extracted with CH_2Cl_2 (3×20 ml). The combined organic phases were dried with $MgSO_4$, filtered, and the solvent was removed in a vacuum. ^1H NMR ($CDCl_3$): δ = 7.09 (s, 2H, Ar*H*), 3.16 (s, 1H, S*H*), 2.34 (t, ^1J(D,H) = 2 Hz, 4H, CH_2D), 1.31 (s, 9H, CH_3).

Compound **9a**: After compound **6** was metalated as described above, sulfur (673 mg, 21.0 mmol) was added in small portions at −76 °C. The reaction mixture was stirred for 30 min at −76 °C and then for 24 h at 25 °C. A solution of iodine (3.81 g, 15.0 mmol) in methanol (25 ml) was carefully added and the resulting brown solution was stirred for 6 h, diluted with 100 ml of water, acidified with conc. HCl to a final pH of 1, and extracted with CH_2Cl_2 (3×100 ml). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was removed in a vacuum to give a dark brown oil. Column chromatography on silica gel gave 1.10 g (43%) of **9a** as a pale yellow oil. R_f (SiO_2, CH_2Cl_2/C_6H_{12} (1:4)) = 0.31. ^1H NMR ($CDCl_3$): δ = 7.15 (d, ^4J(H,H) = 2 Hz, 2H, Ar*H*), 7.00 (d, ^4J(H,H) = 2 Hz, 2H, Ar*H*), 4.36 (s, 4H, CH_2S), 3.63 (s, 4H, CH_2S), 1.23 (s. 18H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 149.3, 140.4, 138.9, 131.8, 126.2, 121.0, 43.9, 42.5, 34.5, 31.4.

$C_{24}H_{30}S_6$ (510.86)
Calcd C 56.43 H 5.92%,
Found C 56.23 H 5.86%.

Compound **10a**: Compound **10a** was prepared as described above from **6** (1.94 g, 10.0 mmol), *n*-BuLi (8.80 ml, 22.0 mmol), TMEDA (2.56 g, 22.0 mmol), S_8 (352 mg, 11.0 mmol), and I_2 (1.40 g, 5.50 mmol). The product was purified by chromatography (SiO_2, C_6H_{12}). Yellow crystals, m.p. 80–81 °C. R_f (SiO_2, C_6H_{12}) = 0.39. ^1H NMR ($CDCl_3$): δ = 7.03 (d, ^4J(H,H) = 2 Hz, 1H, Ar*H*), 6.89 (d, ^4J(H,H) = 2 Hz, 1H, Ar*H*), 4.35 (s, 2H, CH_2S), 2.20 (s, 3H, CH_3), 1.23 (s, 9H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 149.0, 138.7, 138.3, 131.8, 125.5, 119.2, 44.2, 34.3, 31.4, 21.4.

$C_{12}H_{16}S_2$ (224.38)
Calcd C 64.24 H 7.19%,
Found C 64.13 H 7.04%.

Acknowledgements

The author thanks Prof. Dr. H. Vahrenkamp for his generous support. This work was supported by Deutsche Forschungsgemeinschaft.

[1] H. W. Gschwend, H. R. Rodriguez, Org. React. **26,** 1 (1979).
[2] P. Beak, V. Snieckus, Acc. Chem. Res. **15,** 306 (1982).
[3] a) G. D. Figuly, C. K. Loop, J. C. Martin, J. Am. Chem. Soc. **111,** 654 (1989);
b) E. Block, V. Eswarakrishnan, M. Gernon, G. Ofori-Okai, C. Saha, K. Tang, J. Zubieta, J. Am. Chem. Soc. **111,** 658 (1989);
c) K. Smith, C. M. Lindsay, G. J. Pritchard, J. Am. Chem. Soc. **111,** 665 (1989);
d) E. Block, G. Ofori-Okai, J. Zubieta, J. Am. Chem. Soc. **111,** 2327 (1989).
[4] F. E. Hahn, W. W. Seidel, Angew. Chem. **107,** 2938 (1995), Angew. Chem., Int. Ed. Engl. **34,** 2700 (1995).
[5] A. Lüttringhaus, K. Hägele, Angew. Chem. **67,** 304 (1955).
[6] H. Fujihara, J.-J. Chiu, N. Furukawa, Bull. Chem. Soc. Jpn. **64,** 699 (1991).
[7] a) B. Kersting, D. Siebert, Inorg. Chem. **37,** 3820 (1998);
b) G. Steinfeld, B. Kersting, unpublished results.
[8] ^1H NMR ($CDCl_3$): δ = 7.10 (s, 2H, Ar*H*), 3.17 (s, 1H, S*H*), 2.37 (s, 6H, CH_3), 1.31 (s, 9H, CH_3).