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Synthesis of 4,6-dimethyl-tetrahydro- and hexahydro-dibenzothiophene

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Abstract

2-Bromo-3-methylcyclohexanone was synthesized by conjugate addition of trimethylaluminium to 2-bromo-2-cyclohexen-1-one with copper bromide as catalyst, coupled with 2-methylthiophenol and annulated with the aid of polyphosphoric acid to 4,6-dimethyl-1,2,3,4-tetrahydrodibenzothiophene. The latter was hydrogenated to 4,6-dimethyl-1,2,3,4,4a,9b-hexahydrodibenzothiophene, another intermediate in the hydrodesulfurization of 4,6-dimethyldibenzothiophene, by zinc and trifluoroacetic acid, and dehydrogenated to 4,6-dimethyldibenzothiophene.

Keywords: Conjugate addition; 2-Bromo-3-methylcyclohexanone; Tilak annulation; 4,6-Dimethyldibenzothiophene

Polyaromatic sulfur compounds and their substituted derivatives are present in oil fractions such as naphtha (the precursor for gasoline) and diesel fuels. Environmental regulations in many countries demand that the maximum amount of sulfur in fuels be reduced to 10–15 ppm by 2010. Derivatives of dibenzothiophene with the alkyl substituents in the 4- and 6-positions on the aromatic ring, adjacent to the sulfur atom, are the most refractory compounds in the hydrodesulfurization (HDS) process that is industrially used to remove sulfur from fuel.[1] Therefore, 4,6-dimethyldibenzothiophene (4,6-DMDBT) is often used as a model compound in HDS studies.[2] The HDS of 4,6-DMDBT occurs mainly by hydrogenation to partially and totally hydrogenated intermediates, followed by the breaking of the C–S bonds to form 3,3′-dimethylcyclohexylbenzene and 3,3′-dimethylbicyclohexyl.[3]

To achieve a low level of sulfur in fuels, a detailed knowledge of the mechanism of the HDS reaction and of the behaviour of the reaction intermediates is required. Three hydrogenated intermediates play a role in the HDS of 4,6-DMDBT: 4,6-dimethyl-1,2,3,4-tetrahydrodibenzothiophene (4,6-DM-THDBT), 4,6-dimethyl-1,2,3,4,4a,9b-hexahydrodibenzothiophene (4,6-DM-HHDBT) and 4,6-dimethyl-dodecahydrodibenzothiophene (4,6-DM-DHDBT). These intermediates have been synthesized by hydrogenation of 4,6-DMDBT,[4] but this method is inefficient, because the conversion of 4,6-DMDBT must be kept low to avoid further reaction of the hydrogenated intermediates to desulfurized hydrocarbons. As a consequence, laborious column-chromatographic separations of the product mixture and recyclcling of unreacted 4,6-DMDBT have to be performed. In addition, commercial 4,6-DMDBT is expensive. It can be synthesized in two steps from DBT by lithiation of the 4- and 6-positions of DBT and subsequent reaction with methyl iodide, but for safety reasons one should not make more than a few grams per batch. However, in the synthesis of 10 g of 4,6-DM-THDBT and 4,6-DM-HHDBT from 4,6-DMDBT, one needs about 50 g 4,6-DMDBT. 4,6-DMDBT has also been synthesized from 2-bromo-3-nitrotoluene and 2-methylthiophenol (*o*-thiocresol) by reduction of the nitro group followed by diazotation and ring closure by the Pschorr reaction, in which the diazonium group attacks the *ortho* carbon atom on the other phenyl ring.[5] The yield of this cyclization step was, however, low (26%). A future method for synthesizing 4,6-DMDBT could be a Pd-catalyzed domino cyclization

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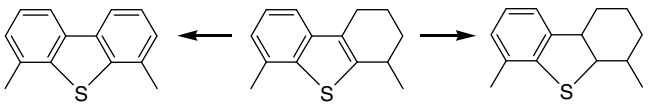
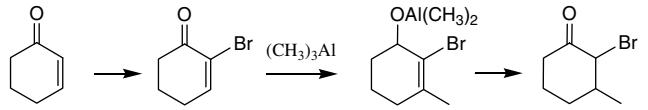
reaction of 2-chloro-6-methylthiophenol with 2-bromotoluene, analogous to the domino reaction of anilines and 1,2-dihaloarenes to carbazoles.[6] We did not explore this reaction, first because 2-chloro-6-methylthiophenol and even 2-chloro-6-methylphenol are not commercially available, and second because we were not only interested in synthesizing 4,6-DMDBT in an efficient way and on a sizeable scale (10–30 g), but also the hydrogenated 4,6-TH-DMDBT and 4,6-HH-DMDBT intermediates.

The Tilak annulation of thiophenol with 2-halocyclohexanone is an established reaction that leads in two easy steps to TH-DBT.[7] Analogously, one could react *o*-thiocresol (2-methylthiophenol) with 2-halo-3-methylcyclohexanone and obtain TH-DMDBT (Scheme 1); this, in turn, could be hydrogenated to HH-DMDBT and dehydrogenated to DMDBT (Scheme 2). *o*-Thiocresol is commercially available or can easily be made from cheap *o*-cresol by the Newman–Kwart reaction.[8] 2-Bromo-3-methyl- and 2-chloro-3-methylcyclohexanone are unfortunately not commercially available. Several methods for synthesizing 2-bromo-3-methylcyclohexanone were considered and some of them were tried. Aromatic molecules are more reactive than aliphatic molecules and, therefore, we first considered synthesis routes via aromatic substitution reactions. However, first synthesizing 2-bromo-3-methylphenol and then hydrogenating it to 2-bromo-3-methylcyclohexanone had to be rejected because the literature gives no hope that a phenyl ring can be hydrogenated without the loss of the halogen atom.

Instead of aromatic precursors, aliphatic cyclohexane educts can be used. We first tried the bromination and iodination of 3-methylcyclohexanone. This reaction is easy to perform and the literature even promised that 2-iodo-3-methylcyclohexanone would be formed preferentially.[9] Unfortunately, but not surprisingly, this turned out not to be the case and the reaction, both for bromine and iodine, quantitatively led to a mixture of four isomers (*cis* and *trans* 2-halo-3-methyl- and 2-halo-5-methylcyclohexanone), that proved too difficult to separate. Of the two commercially available molecules with the cyclohexenone structure (2-cyclohexen-1-one and 3-ethoxy-2-cyclohexen-1-one), we tried 2-cyclohexen-1-one, because it promised to give 2-bromo-3-methylcyclohexanone in only three steps (Scheme 3). While the first step, the bromination of 2-cyclohexen-1-one, and the last step, the hydrolysis of the aluminium–oxygen bond, are easy, the second step, the conjugate addition of trimethylaluminium to 2-bromo-2-cyclohexen-1-one,[10] needs more precaution. We were able to obtain complete conversion of 2-bromo-2-cyclohexen-1-one and better than 90% yield of the desired product 2-bromo-3-methylcyclohexanone by using CuBr as a catalyst, triphenylphosphine as a ligand, toluene as a solvent and controlling the temperature below −30 °C.[11] A drawback of this method is that, because of safety precautions, we could only make small batches (2 g) at the time.



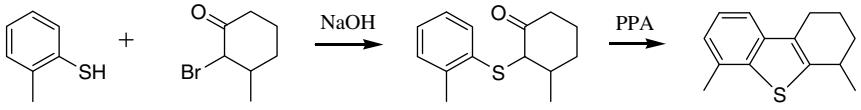
Scheme 2.



Scheme 3.

With the thus obtained 2-bromo-3-methylcyclohexanone cis/trans mixture and *o*-thiocresol we were able to synthesize 4,6-DM-THDBT without any problem (Scheme 1).[12] We tried to synthesize 4,6-DM-HHDBT in a similar way by reducing 2-bromo-3-methylcyclohexanone with $NaBH_4$ to 2-bromo-3-methylcyclohexanol and reacting the latter with *o*-thiocresol in the presence of polyphosphoric acid (PPA). While the reduction of ketone and the subsequent coupling of thiol with 2-bromo-3-methylcyclohexanol to 2-(2-methylthiophenolate)-3-methylcyclohexanol proceeded smoothly, the final ring closure by the reaction of the OH group with the *ortho* carbon atom of the phenyl ring was not successful. As an alternative, we reacted 2-(2-methylthiophenolate)-3-methylcyclohexanol to 2-(2-methylthiophenolate)-3-methylcyclohexanechloride and tried to cyclize the latter molecule with the aid of $AlCl_3$ or $ZnCl_2$. However, also this last step was not successful. Apparently, Friedel–Crafts reactions are not only difficult for phenols, but also for thiophenols. We successfully synthesized 4,6-DM-HHDBT instead by the reduction of 4,6-DM-THDBT with the Zn–trifluoroacetic acid couple.[13] Alternatively, 4,6-DM-THDBT can be hydrogenated by transfer hydrogenation with a secondary alcohol, as in the dehydrogenation of secondary alcohols with styrene over a Cu catalyst.[14] 4,6-DM-THDBT can be easily dehydrogenated to 4,6-DMDBT by reaction with sulfur, selenium or a Pd catalyst, or by transfer dehydrogenation (Scheme 2).

In conclusion, the Tilak annulation is a convenient way to synthesize 4,6-dimethyl-1,2,3,4-tetrahydrodibenzothiophene, but requires the synthesis of 2-bromo-3-methylcyclohexanone. This can be achieved by the conjugate addition of trimethylaluminium to 2-bromo-2-cyclohexen-1-one with a copper salt as the catalyst. 4,6-Dimethyl-



Scheme 1.

1,2,3,4-tetrahydrodibenzothiophene can easily be hydrogenated to 4,6-dimethyl-1,2,3,4,4a,9b-hexahydrodibenzothiophene and dehydrogenated to 4,6-dimethyldibenzothiophene. The Tilak reaction thus provides easy access to 4,6-DMDBT and its hydrogenated intermediates, which are used as model molecules in hydrodesulfurization studies.[15]

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References and notes

1. (a) Kabe, T.; Ishihara, A.; Qian, W. *Hydrodesulfurization and Hydrodenitrogenation*; Kodansha Scientific, Wiley-VCH: New York, 1999; (b) Gates, B. C.; Topsøe, H. *Polyhedron* **1997**, *16*, 3213; (c) Whitehurst, D. D.; Isoda, T.; Mochida, I. *Adv. Catal.* **1998**, *48*, 345; (d) Girgis, M. J.; Gates, B. C. *Ind. Eng. Chem. Res.* **1991**, *30*, 2021.
2. (a) Houalla, M.; Nag, N. K.; Sapre, A. V.; Broderick, D. H.; Gates, B. C. *AIChE J.* **1978**, *24*, 1015; (b) Kabe, T.; Ishihara, A.; Zhang, Q. *Appl. Catal. A: Gen.* **1993**, *97*, L1; (c) Meille, V.; Schulz, E.; Lemaire, M.; Vrinat, M. *J. Catal.* **1997**, *170*, 29; (d) Macaud, M.; Milenkovic, A.; Schulz, E.; Lemaire, M.; Vrinat, M. *J. Catal.* **2000**, *193*, 255.
3. (a) Sakanishi, K.; Nagamatsu, T.; Mochida, I.; Whitehurst, D. D. *J. Mol. Catal. A: Chem.* **2000**, *155*, 101; (b) da Costa, P.; Potvin, C.; Manoli, J.-M.; Lemberton, J.-L.; Pérot, G.; Djéga-Mariadassou, G. *J. Mol. Catal. A: Chem.* **2002**, *184*, 323; (c) Bej, S. K.; Maity, S. K.; Turaga, U. T. *Energy Fuels* **2004**, *18*, 1227; (d) Ishihara, A.; Dumeignil, F.; Lee, J.; Mitsuhashi, K.; Qian, E. W.; Kabe, T. *Appl. Catal. A: Gen.* **2005**, *289*, 163.
4. Kukula, P.; Gramlich, V.; Prins, R. *Helv. Chim. Acta* **2006**, *89*, 1623.
5. Meille, V.; Schulz, E.; Lemaire, M.; Faure, R.; Vrinat, M. *Tetrahedron* **1996**, *52*, 3953.
6. (a) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627; (b) Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581; (c) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310.
7. (a) Rabindran, K.; Tilak, B. D. *Proc. Indian Acad. Sci., Sect. A* **1952**, *36*, 411; (b) Campaigne, E.; Hewitt, L.; Ashby, J. *J. Heterocycl. Chem.* **1969**, *6*, 553; (c) Tedjamulia, M. L.; Tominaga, Y.; Castle, R. N.; Lee, M. L. *J. Heterocycl. Chem.* **1983**, *20*, 1485; (d) DiCesare, J. C.; Thompson, L. B.; Andersen, R. J.; Nail, J. *Org. Prep. Proced. Int.* **2000**, *32*, 169.
8. (a) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410; (b) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980; (c) Moseley, J. D.; Lenden, P. *Tetrahedron* **2007**, *63*, 4120; (d) Fabbri, D.; Delogu, G.; De Lucchi, O. *J. Org. Chem.* **1993**, *58*, 1748.
9. (a) Horiuchi, C. A.; Kiji, S. *Chem. Lett.* **1988**, 31; (b) Horiuchi, C. A.; Satoh, J. Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 426; (c) Horiuchi, C. A.; Kiji, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 421.
10. (a) Li, K.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 5823; (b) Li, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7600; (c) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.
11. *Synthesis of 2-bromocyclohexenone*: A solution of Br_2 (157.5 mmol, 9 ml) in 150 ml CH_2Cl_2 was added dropwise over a period of 3 h to a stirred, 0 °C solution of cyclohexenone (150 mmol, 15 ml) in 400 ml CH_2Cl_2. The solution was stirred at 0 °C for 3 h, then Et_3N (250 mmol, 35 ml) was added dropwise and the mixture was stirred at room temperature for another 3 h. It was washed with 3% HCl and brine, and dried over anhydrous $MgSO_4$. Recrystallization using hexane/ether gave the pure product (15 g, 60% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10–2.15 (m, 2H, CH_2), 2.48–2.52 (m, 2H, CH_2), 2.66–2.69 (t, 2H, CH_2), 7.46–7.48 (t, 1H, CH). ^{13}C NMR: δ 22.71, 28.40, 38.39, 123.92, 151.22, 191.32.
Synthesis of 2-bromo-3-methylcyclohexanone: To a mixture of CuBr (100 mg) and PPh_3 (300 mg) were added 50 ml of dry toluene under nitrogen. The solution was stirred at room temperature for 30 min and then cooled to −60 °C (acetone + dry ice). Trimethyl aluminium (12 ml, 2 M in toluene) was added dropwise, maintaining the temperature below −60 °C. The solution was stirred for 5 min and 3 g of 2-bromocyclohexenone in 50 ml toluene were added dropwise. The reaction mixture was stirred below −60 °C for 2 h and then allowed to warm to room temperature until all starting material was consumed. The solution was diluted with dimethyl ether, quenched with MeOH, and successively washed with 2 N HCl and brine. The organic layer was dried over anhydrous sodium sulfate. After evaporation, the product (2.4 g, 75% yield, cis/trans mixture) was obtained. This procedure was repeated five times to obtain 12 g product.
12. *Synthesis of 2-(o-tolylthio)-3-methylcyclohexanone*: *o*-Cresol (7.4 g) and 2.4 g of NaOH were dissolved in a solution of 15 ml of ethanol and 15 ml of water. 2-Bromo-3-methylcyclohexanone (12 g) dissolved in ethanol (20 ml) was added dropwise to this solution kept under a stream of nitrogen. The reaction mixture was stirred at room temperature for 30 min and then refluxed for 4 h. After cooling, 60 ml of water was added. The lower oily layer was removed and the aqueous phase was extracted with chloroform. The combined oily layer and the extract were dried over anhydrous sodium sulfate. After evaporation, the product (11 g, 75% yield, cis/trans mixture) was obtained.
Synthesis of 4,6-DM-THDBT: The 2-(*o*-tolylthio)-3-methylcyclohexanone sample (11 g) was poured into a round bottom flask containing 100 g of polyphosphoric acid and the mixture was slowly heated in an oil bath with continuous stirring for 3 h at 165 °C. After cooling, the mixture was poured onto ice. The oily layer was separated and the aqueous phase extracted with chloroform. The oily layer and the extracts were combined, dried over anhydrous sodium sulfate and the chloroform was distilled off, yielding 8 g (69%) of a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40–1.43 (CH_3-6, 3H), 1.50–2.09 (CH_2-7, CH_2-8, 4H), 2.57 (CH_3-4, 3H), 2.66–2.70 (CH_2-9, 2H), 2.70–2.99 (C*H*-6, 1H) 7.13–7.20 (H-3, 1H, Ar*H*), 7.21–7.34 (H-2, 1H, Ar*H*), 7.45–7.50 (H-1, 1H, Ar*H*). ^{13}C NMR: δ 20.04, 20.31, 21.48, 22.99, 24.11, 31.70, 32.80, 118.42, 123.98, 124.30, 126.71, 127.36, 128.71, 130.34.
13. Lyakhovetsky, Y.; Kalinkin, M.; Parnes, Z.; Latypova, F.; Kursanov, D. *Chem. Commun.* **1980**, 766.
14. (a) Zaccheria, F.; Ravasio, N.; Psaro, R.; Fusi, A. *Chem. Commun.* **2005**, 253; (b) Hindle, K. T.; Burch, R.; Crawford, P.; Hardacre, C.; Hu, P.; Kalirai, B.; Rooney, D. W. *J. Catal.* **2007**, *251*, 338.
15. Li, X.; Wang, A.; Egorova, M.; Prins, R. *J. Catal.* **2007**, *250*, 283.