Further Derivatives of 4-Methoxydibenzothiophene (1)

John Ashby (2) and David Griffiths

Imperial Chemical Industries Limited, Pharmaceuticals, Division, Alderley Park, Macclesfield, Cheshire, SK10 4TG, U.K.

Received April 11, 1975

Gilman (3) has described the nitration of 4-methoxydibenzothiophene (Ia) which was assumed to yield a mixture of mono-nitro compounds. Reduction of this mixture with stannous chloride in 11*N* hydrochloric acid gave predominantly 1-amino-4-methoxydibenzothiophene (Ib) and a small amount of a by-product which was assumed to be 3-amino-4-methoxydibenzothiophene. We recently described a repetition of this nitration reaction in which we were unable to detect any isomer other than the 1-nitro compound (Ic) (by 100 MHz nmr, glc and tlc) (1). We have now repeated the reduction of 1-nitro-4-methoxydibenzothiophene (Ic) as described by Gilman and isolated the expected 1-amino-4-methoxydibenzothiophene as the major product. We also isolated a small amount of a product whose melting point and solubility characteristics agree with those of the alleged 3-amino-4-methoxydibenzothiophene described by Gilman (3).

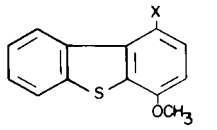
The elemental analysis and spectral data on this product are consistent with structure II rather than the suggested 3-amino-4-methoxydibenzothiophene. It is likely that II arises by chlorination of the activated A ring during reduction of the nitro group (4). The nmr spectrum of II showed a sharp singlet at δ 6.84 for either II-2 or II-3. Unfortunately, the resonances of II-2 and II-3 in the precursor Ib were almost coincident forming two sharp doublets at δ 6.67 and 6.7, thus it is not possible to define, by elimination, the position of the chlorine atom in II. It therefore seems likely that nitration of 4-methoxydibenzothiophene occurs exclusively in the 1-position.

Functionalization of dibenzothiophenes in the 1-position is comparatively rare (5,6) and we have therefore utilized the readily accessible 1-bromo-4-methoxydibenzothiophene (Id) (1) to prepare several 1-substituted dibenzothiophenes.

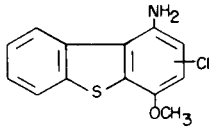
Translithiation of the 1-bromo compound (Id) with butyllithium followed by carbonation gave 4-methoxydibenzothiophene-1-carboxylic acid (Ie) which was esterified to the corresponding methyl ester (If). LAH reduction of this ester gave, as well as the expected alcohol (Ig) (32%) a low yield (9%) of the oxydimethylene compound (IIIa). The isolation of this ether was repeatable and it presumably arose by intermolecular dehydration of the initially formed alcohol (Ig).

An attempt to chloromethylate (Ia) with formalin in the presence of zinc chloride-hydrochloric acid resulted in the formation of 4,4′-dimethoxy-1,1′-methylenebis(dibenzothiophene) (IIIb).

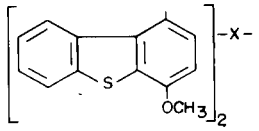
In all of the above compounds, 1-substitution was readily established by the presence of a high field doublet for II-3 in their nmr spectra.



(I) a, X = H c, X = CO_2H
b, X = NH_2 f, X = CO_2Me
e, X = NO_2 g, X = CH_2OH
d, X = Br



(II)



(III) a, X = CH_2OCH_2
b, X = CH_2

EXPERIMENTAL

Nmr spectra were determined on an HA100 spectrometer with TMS as internal reference. Unless otherwise stated the solvent was deuteriochloroform. Mass spectra were measured on either an AEI MS12 or MS9 spectrometer. The drying agent used was magnesium sulfate.

The Reduction of 1-Nitro-4-methoxydibenzothiophene.

The reduction was carried out as described by Gilman (3) (0.017 mole scale). The crude precipitate (8 g.) was stirred with 25% aqueous sodium hydroxide and chloroform (100 ml.). The chloroform layer was separated and the aqueous phase extracted again with chloroform (100 ml.). The combined extracts were dried and evaporated to leave the crude reduction product (3 g., 78% based on Ib formation) m.p. 90-96°. Upon crystallization from ethanol a dark grey solid was obtained which was further recrystallized from ethanol (0.15 g., 3%) m.p. 134-136° and identified

as 1-amino-2(or 3)chloro-4-methoxydibenzothiophene (Il); nmr: δ 3.88 (s, OCH_3), 4.3 (broad s, NH_2), 6.84 (s, H-2 or 3), 7.4 (m, H-7,8), 7.85 (m, H-6) and 8.23 (m, H-9); ms: m/e 263 (M^+) 248 (M^+-CH_3; m* 233.8).

Anal. Calcd. for $C_{13}H_{10}ClNOS$: C, 59.20; H, 3.82; N, 5.31. Found: C, 59.5; H, 4.1; N, 5.0.

Freezing the combined liquors from the above crystallizations gave authentic 1-amino-4-methoxydibenzothiophene (Ib) (1.3 g., 34%) m.p. 97-101° [Lit (3) m.p. 101-102°]; nmr: δ 3.87 (s, OCH_3), 6.67 and 6.70 (sharp d's, H-2,3), 7.4 (m, H-7,8), 7.86 (m, H-6) and 8.28 (m, H-9); ms: m/e 229 (M^+).

4-Methoxydibenzothiophene-1-carboxylic Acid (Ie).

Butyllithium (21% solution in hexane, 38.6 ml., 0.0615 mole) was added at 0° to a suspension of the 1-bromo compound (Id) (1) (18 g., 0.0615 mole) in dry ether (180 ml.), under nitrogen with stirring. Dry carbon dioxide gas was then passed through the mixture for 1 hour at 0°. The resultant solid was filtered, washed with ether, suspended in water and acidified with hydrochloric acid (2*N*). This suspension was extracted with chloroform (1500 ml.) and the chloroform solution extracted with warm, aqueous sodium hydroxide (1*N*, 2 x 500 ml.). Acidification of this alkaline solution gave the product (11.9 g., 75%) m.p. 244-246°, unaffected by recrystallization from aqueous ethanol; nmr (deuteriochloroform/DMSO-d_6): δ 4.08 (s, OCH_3), 6.95 (d, J 8 Hz, H-3), 7.5 and 7.9 (m, H6-9) and 7.94 (d, J 8 Hz, H-2); ms: m/e 258 (M^+) and 243 (M^+-CH_3, m* 228.9).

Anal. Calcd. for $C_{14}H_{10}O_3S.½H_2O$: C, 62.90; H, 4.15. Found: C, 63.2; H, 3.9.

Methyl 4-Methoxydibenzothiophene-1-carboxylate (If).

To a solution of the carboxylic acid (Ie) (5.7 g., 0.022 mole) in methanol (130 ml.) was added concentrated sulfuric acid (11.4 ml.) (*CAUTION*) and the mixture refluxed for 48 hours. After evaporation the resulting product was washed with water and collected (5.8 g., 96%), m.p. 98-100°. An analytical sample from methanol had m.p. 104-105°; nmr: δ 4.0 and 4.3 (singlets, OCH_3 and ester CH_3), 6.87 (d, J 8.5 Hz, H-3), 7.34 (m, H-7,8), 7.88 (m, H-6), 7.88 (d, J 8.5 Hz, H-2), and 8.65 (m, H-9); ms: m/e 272 (M^+).

Anal. Calcd. for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44. Found: C, 66.3; H, 4.6.

The Reduction of Methyl 4-Methoxydibenzothiophene-2-carboxylate (If).

A solution of the ester (If) (7.6 g., 0.028 mole) in dry THF (75 ml.) was added dropwise at 40° to a suspension of LAH (3.0 g.) in dry THF (50 ml.) and the mixture refluxed for 18 hours. Excess LAH was destroyed in the cooled mixture by the dropwise addition of ethyl acetate followed by hydrochloric acid (2*N*, 10 ml.). The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic extracts were dried and evaporated to yield an oil which was crystallized from ethanol-water (10:1; 250 ml.). The solid was collected and recrystallized from ethanol (1.2 g., 9%), m.p. 167-168° identified as 4,4'-dimethoxy-1,1'-oxydimethylene(dibenzothiophene) (IIIa); nmr: δ 3.92 (s, OCH_3), 5.06 (s, CH_2), 6.76 (d, J 8 Hz, H-3), 7.1 (m, H-7,8), 7.34 (d, J 8 Hz, H-2), 7.82 (dd, $J_{6,7}$ 8 Hz, $J_{6,8}$ 1 Hz, H-6), 8.26 (dd, $J_{9,8}$ 8 Hz, $J_{9,7}$ 1 Hz, H-9); ms: m/e 470 (M^+).

Anal. Calcd. for $C_{28}H_{22}O_3S_2$: C, 71.46; H, 4.71. Found: C, 71.0; H, 5.0.

Evaporation of the above ethanolic liquors gave a brown solid which was crystallized from aqueous ethanol (1:1) to give 4-methoxy-1-hydroxymethyldibenzothiophene (Ig) m.p. 101-104° (2.2 g., 32%); nmr: δ 3.9 (s, OCH_3), 5.05 (s, CH_2), 6.75 (d, J 9 Hz, H-3), 7.28 (d, J 9 Hz, H-2), 7.32 (m, H-7,8), 7.88 (m, H-6) and 8.38 (m, H-9); ms: m/e 244 (M^+).

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.8; H, 4.95. Found: C, 68.7; H, 5.1.

4,4'-Dimethoxy-1,1'-methylenebis(dibenzothiophene) (IIIb).

Hydrogen chloride was passed through a stirred mixture of 4-methoxydibenzothiophene (0.85 g., 0.004 mole), 40% aqueous formaldehyde solution (4 ml.) and zinc chloride (0.5 g.) for 2 hours at 0°. The temperature was then allowed to rise to 25° and the reaction stirred for 1 hour when water was added and the resultant gum extracted into ether. The ether extract was washed with aqueous sodium bicarbonate, water, dried and evaporated to give an oil which slowly crystallized (0.7 g.). Extraction of this solid with hot ethanol left the product (0.2 g., 22%), m.p. 278°; nmr (pyridine d_6): δ 3.82 (s, OCH_3), 5.3 (s, CH_2), 6.8 (d, J 8 Hz, H-3,3'), 7.3 (m, H-7,7'; H-8,8'), 7.36 (d, J 8 Hz, H-2,2'), 8.05 (m, H-6,6') and 8.4 (m, H-9,9'); ms: m/e 440 (M^+).

Anal. Calcd. for $C_{27}H_{20}O_2S_2$: C, 73.6; H, 4.5. Found: C, 73.1; H, 4.7.

REFERENCES

(1) E. Campaigne, L. Hewitt and J. Ashby, *J. Heterocyclic Chem.*, 7, 753 (1969).

(2) To whom correspondence should be addressed.

(3) H. Gilman and S. Avakian, *J. Am. Chem. Soc.*, 68, 1514 (1946).

(4) L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopfenstein and D. R. McCoy, *J. Heterocyclic Chem.*, 7, 373 (1970).

(5) J. Ashby and C. C. Cook, *Adv. Heterocyclic Chem.*, 16, 181 (1974).

(6) J. Ashby, M. Ayad and O. Meth-Cohn, *J. Chem. Soc. (Perkin I)*, 1744 (1974).