The Direct Bradsher Reaction. Part III.[1] A New Method for the Benzologation of Heterocycles [2]

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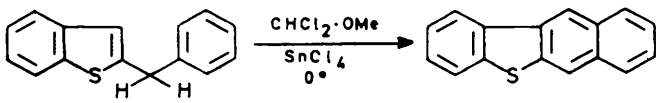
The action of dichloromethyl alkyl ethers and tin(IV) chloride on 2-(allyl- or substituted allyl)benzo[*b*]thiophens or benzo[*b*]furans gives rise to the corresponding unsubstituted or 3-substituted derivatives of dibenzothiophen or dibenzofuran. In particular, the use of ethyl dichloro(ethoxy)acetate gives derivatives containing a 1-ethoxycarbonyl substituent. A range of novel 1-substituted dibenzothiophens has thus been prepared.

THE most general primary synthesis of substituted dibenzothiophens was developed independently by Tilak [3] and McCall,[4] and involves the condensation of a substituted benzenethiol with α-chlorocyclohexanone followed by cyclodehydration and aromatization. This procedure has proved efficient in the synthesis of 2- or 4-substituted dibenzothiophens, but the literature indicates that the use of *meta*-substituted benzenethiols gives mixtures containing both 1- and 3-substituted dibenzothiophens.[5]

In order to functionalize the 1- and 3-positions of dibenzothiophen it has, therefore, usually been found necessary to proceed *via* the corresponding bromo-compounds.[5] 1-Bromodibenzothiophen is formed by the action of ethanolic hydrogen bromide on 2-acetamido-1-nitrodibenzothiophen, itself formed by a four-stage synthesis from dibenzothiophen [6] (14% overall yield). 3-Bromodibenzothiophen is formed by Sandmeyer conversion of the relatively inaccessible 3-aminodibenzothiophen (13% overall yield).[7,8] Both compounds are tedious to prepare but are useful starting materials for subsequent transformations by way of the lithio-derivatives.[8] As a consequence of these difficulties, relatively few dibenzothiophens containing aliphatic substituents in the 1- or the 3-position have been described.

We have demonstrated previously [1] the utility of the formylating agent dichloromethyl methyl ether in the construction of linear thiophenic polycycles by direct



(1) (2)

mid-ring formation, as illustrated by the conversion (1) ⟶ (2). The prerequisite for this reaction is a nucleus activated in such a way that the initial formylation will occur *ortho* to the methylene bridge. We anticipated that cyclization of allyl rather than benzyl

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[1] Part II, J. Ashby, M. Ayad, and O. Meth-Cohn, *J.C.S. Perkin I*, 1973, 1104.

[2] Preliminary communication, J. Ashby, M. Ayad, and O. Meth-Cohn, *Chem. Comm.*, 1971, 1251.

[3] K. Rabindran and B. D. Tilak, *Current Sci.*, 1951, **20**, 207.

[4] E. B. McCall, B.P. 701,267/1953 (*Chem. Abs.*, 1955, **49**, 4027).

[5] J. Ashby and C. C. Cook, *Adv. Heterocyclic Chem.*, 1974, **16**, 181.

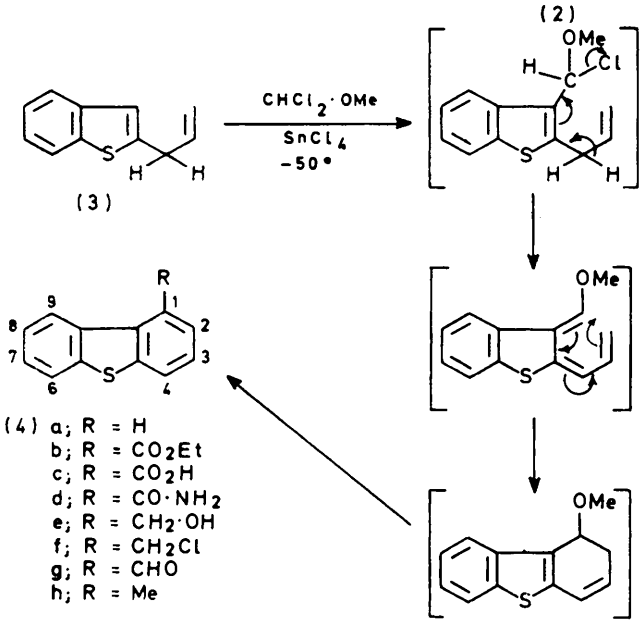
[6] H. Gilman and G. R. Wilder, *J. Amer. Chem. Soc.*, 1954, **76**, 2906.

[7] G. Illuminati, J. Nobis, and H. Gilman, *J. Amer. Chem. Soc.*, 1951, **73**, 5887.

[8] E. Campaigne and J. Ashby, *J. Heterocyclic Chem.*, 1969, **6**, 517.

derivatives would lead to dibenzothiophens containing various 1- or 3-substituents.

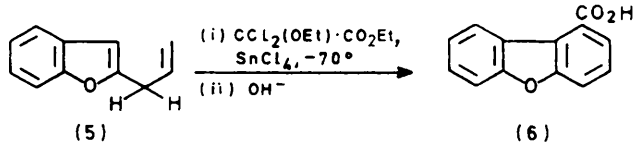
2-Allylbenzo[*b*]thiophen (3), readily prepared by the action of allyl bromide on 2-lithiobenzo[*b*]thiophen, reacted with dichloromethyl methyl ether and anhydrous tin(IV) chloride in methylene chloride at −50° to give dibenzothiophen(4a) in 55% yield, as shown in Scheme 1.[9]



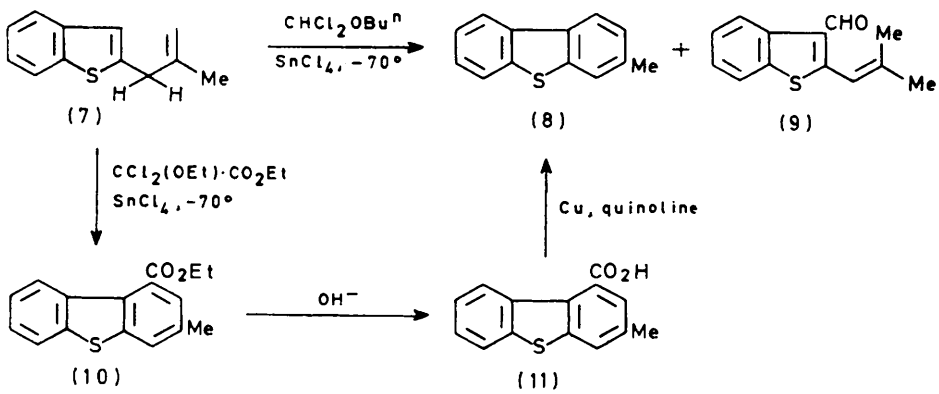
SCHEME 1

Similarly, use of the more reactive ethyl dichloro(ethoxy)acetate (prepared from diethyl oxalate phosphorus pentachloride[10]) gave ethyl dibenzothiophen-1-carboxylate (4b) (61%), which was converted into the known[11] 1-acid (4c) (94%) and the derived amide (4d) (74%). Reduction of the ester (4b) with lithium aluminium hydride gave the 1-alcohol (4e) (97%), which was transformed into the 1-chloromethyl compound (4f) by treatment with thionyl chloride (70%). A Duff reaction with compound (4f) yielded the corresponding 1-aldehyde (4g), characterized as its 2,4-dinitrophenylhydrazone (23%). The reductive silylation procedure of Benkeser and his co-workers[12] was employed to prepare 1-methyldibenzothiophen (4h) from the corresponding 1-acid (4c) (70%).

The analogous transformation of 2-allylbenzo[*b*]furan (5) into ethyl dibenzofuran-1-carboxylate proceeded in lower yield (32%), hydrolysis yielding the known[13] but difficult to prepare carboxylic acid (6).



The use of a substituted allyl side-chain in benzo[*b*]-thiophen facilitated the synthesis of 3-substituted and 1,3-disubstituted derivatives of dibenzothiophen. Thus the β-methylallyl derivative (7) gave 3-methyldibenzothiophen[14] (8) upon treatment with dichloromethyl butyl ether, although in poor yield (10%), the major product in this case being the aldehyde (9). Acid-catalysed rearrangement of the allyl double bond prevented cyclization to (8) (Scheme 2). In contrast, reaction of (7) with ethyl dichloro(ethoxy)acetate gave ethyl 3-methyldibenzothiophen-1-carboxylate (10) in 40% yield. The quantitative hydrolysis of (10) to (11) followed by copper-catalysed decarbonylation gave 3-methyldibenzothiophen (8) in 40% overall yield. The five-stage synthesis of this compound from dibenzothiophen *via* 3-lithiodibenzothiophen proceeds in an overall yield of 6%.[14] The ester substituent in (10) could readily be transformed as described for compound (4b); for example, reduction with lithium aluminium hydride gave 1-hydroxymethyl-3-methyldibenzothiophen (75%).



SCHEME 2

The n.m.r. spectrum of 1-methyldibenzothiophen showed the 1-methyl resonance as a singlet at δ 2·82,

After completion of this manuscript a paper appeared based on ref. 2: P. Cagniant, N. Bellinger, and D. Cagniant, *Compt. rend.*, 1973, **277***C*, 383.

[9] R. G. Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 5168.

[10] H. Gilman and A. L. Jacoby, *J. Org. Chem.*, 1938, **3**, 108.

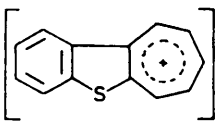
[12] R. A. Benkeser, K. N. Foley, J. M. Gaul, and G. S. Li, *J. Amer. Chem. Soc.*, 1970, **92**, 3232.

[13] H. Gilman and P. R. van Ess, *J. Amer. Chem. Soc.*, 1939, **61**, 1365.

[14] H. Gilman and G. R. Wilder, *J. Org. Chem.*, 1957, **22**, 523.

ca. 0·4 p.p.m. to lower field than the corresponding resonances of 2-, 3-, and 4-methyldibenzothiophen, which occur between δ 2·42 and 2·48. This is consistent with the deshielding generally observed for protons in the 1-position of dibenzothiophen and its derivatives.[5] The spectrum of 1,3,7,9-tetramethyldibenzothiophen has been recorded elsewhere;[15,16] however, in view of the foregoing observation the resonance reported for this compound at δ 2·7 must be associated with the 1- and 9-methyl groups and that at δ 2·4 with the 3- and 7-methyl groups (the assignment reported is the reverse of this).

The mass spectral fragmentation of alkyldibenzothiophens has not been described previously. 1-Methyldibenzothiophen gave an intense molecular ion peak at *m/e* 198 and a further intense peak at *m/e* 197 (*M* − 1), presumably associated with the tropylium ion (12), by analogy with the fragmentation pathway of toluene.[5]



(12)
m/e 197

Further significant ions at *m/e* 165, 164, and 153 probably arise by the loss of S, SH, and CS respectively from (12); these are generally observed features of the fragmentation of dibenzothiophens.[5] A metastable peak at *m** 118·9 indicates that loss of CS takes place from the tropylium ion (12) rather than from the molecular ion.

EXPERIMENTAL

N.m.r. spectra were obtained with a Varian A60A or HA-100 spectrometer (tetramethylsilane as internal standard), mass spectra with an A.E.I. MS902 instrument, and i.r. spectra with a Perkin-Elmer 257 spectrometer (for either Nujol mulls or films).

2-Allylbenzo[b]*thiophen* (3).—Butyl-lithium (0·1 mol in hexane) was added to a solution of benzo[*b*]thiophen (13·4 g, 0·1 mol) in dry ether at 0°. To this stirred solution, allyl bromide (12·1 g, 0·1 mol) was added dropwise over 40 min. The mixture was stirred at 0° for 4 h and at room temperature for a further 18 h. Water (200 ml) was added and the organic phase was separated. The aqueous phase was extracted with ether (3 × 100 ml) and the combined extracts were washed with water, dried, and evaporated. The residue was distilled *in vacuo* to afford the *product* (9·5 g, 53%), b.p. 104° at 2·5 mmHg (Found: C, 75·8; H, 5·65. $C_{11}H_{10}S$ requires C, 75·9; H, 5·8%), δ (neat) 3·3 (m, CH_2), 5·09 (m, C=CH_2), 5·6—6·3 (m, CH), 6·7 (s, 3-H), and 7·12—7·77 (m, aromatic), $\nu_{max.}$ 1690 cm^{-1} (C=C).

Dibenzothiophen (4a).—Anhydrous tin(v) chloride (6·5 g, 0·025 mol) was added to a stirred solution of 2-allylbenzo[*b*]-thiophen (1·74 g, 0·01 mol) in methylene chloride (25 ml) at −50°. To the resultant, stirred mixture was added dichloromethyl methyl ether[17] (1·14 g, 0·01 mol) during 15 min. The temperature was allowed to rise slowly to 0°. Stirring was continued at this temperature for 30 min and for a further 15 h at room temperature, and the solution was then poured onto ice. The organic phase was separated and the aqueous phase extracted with more methylene chloride (50 ml). The combined extracts were washed with aqueous sodium hydrogen carbonate and water and dried. Evaporation left an oil which was chromatographed on alumina. Elution with light petroleum (b.p. 60—80°) gave the product (1·0 g, 55%), identified by comparison with an authentic sample. When the above reaction was conducted at 0° throughout the yield was only 11%.

Ethyl Dibenzothiophen-1-carboxylate (4b).—Anhydrous tin(IV) chloride (3·3 g, 0·0128 mol) was added to a stirred solution of 2-allylbenzo[*b*]thiophen (1·74 g, 0·01 mol) in methylene chloride (25 ml) at −50°. To the resultant mixture was added ethyl dichloro(ethoxy)acetate[10] (2 g, 0·01 mol), and stirring was continued for 30 min. The mixture was then allowed to warm to room temperature, stirred overnight, and worked up as for (4a); the residue was chromatographed on alumina. Light petroleum–benzene (3 : 1) eluted the *ester* (1·56 g, 61%), which afforded needles, m.p. 62·5° (from aqueous methanol) (Found: C, 70·9; H, 4·95. $C_{15}H_{12}O_2S$ requires C, 70·4; H, 4·7%), $\nu_{max.}$ 1735 cm^{-1} (ester C=O). The corresponding acid (4c) was obtained by hydrolysis with 10% sodium hydroxide in ethanol; yield 94%, m.p. 176—177° (lit.,[11] 176—177°).

Dibenzothiophen-1-carboxamide (4d).—Successive treatment of the acid (4c) with thionyl chloride and ammonium hydroxide (*d* 0·88) gave the *amide* (74%), m.p. 258° (from aqueous ethanol) (Found: C, 68·6; H, 3·85. $C_{13}H_9NOS$ requires C, 68·7; H, 4·0%).

1-Hydroxymethyl- (4e) *and 1-Chloromethyl-dibenzothiophen* (4f).—Reduction of the ester (4b) with an excess of lithium aluminium hydride ether gave the *alcohol* (97%), m.p. 105—107° (from aqueous ethanol) (Found: C, 72·9; H, 4·65. $C_{13}H_{10}OS$ requires C, 72·8; H, 4·7%), treatment of which with thionyl chloride at room temperature gave the *chloride* (70%), m.p. 99—100° (from aqueous ethanol) (Found: C, 67·05; H, 3·7. $C_{13}H_9ClS$ requires C, 67·1; H, 3·9%).

Dibenzothiophen-1-carbaldehyde (4g).—A mixture of the chloro-derivative (4f) (1 g, 0·0043 mol) and hexamethylenetetramine (1·2 g) was dissolved in acetic acid (3·6 ml; 1 : 1) and refluxed for 2 h. Hydrochloric acid (5 ml; 36%) was then added and the mixture was refluxed for a further 15 min, cooled, and extracted with ether (2 × 250 ml). The combined extracts were washed with aqueous sodium hydrogen carbonate (10%) and water, dried, and evaporated, yielding an oil which did not crystallize. The *2,4-dinitrophenylhydrazone* formed needles (0·38 g, 23%), m.p. 283—284° (Found: C, 59·2; H, 3·1. $C_{19}H_{12}N_4O_4S$ requires C, 58·1; H, 3·1%).

1-Methyldibenzothiophen (4h).—A suspension of the acid (4c) (1·65 g, 0·0073 mol) and trichlorosilane (0·99 g) in acetonitrile (6 ml) was refluxed for 1 h. The suspension was cooled and tripropylamine (3·8 g) was added at 15°. The suspension was again refluxed and further trichlorosilane added to produce a clear solution; refluxing was then continued for a further 18 h. Ether (50 ml) was added to the cooled solution and tripropylamine hydrochloride was filtered off. The filtrate was evaporated to give an oil, which was dissolved in methanol (4 ml) and refluxed for 1 h. A solution of potassium hydroxide (4·1 g) in methanol (7 ml) and water (2 ml) was then added to the refluxing solution and heating was continued for 19 h.

[15] P. Canonne and J. Gourier, *Compt. rend.*, 1969, **268***C*, 2319.
[16] J. Gourier and P. Canonne, *Canad. J. Chem.*, 1970, **48**, 2587.
[17] A. Rieche, H. Gross, and E. Hoft, *Chem. Ber.*, 1960, **93**, 88; G. N. Taylor and K. B. Wiberg, *Org. Synth.*, 1967, **47**, 47.

The reaction solution was poured into water and extracted with ether (3 × 50 ml), and the extracts were evaporated to give an oil which crystallized from aqueous ethanol, affording the product as needles (0·97 g, 70%), m.p. 70—71° (lit.,[14] 67—68°), δ ($CDCl_3$) 2·82 (s, CH_3), 7·3 (m, H-2, -3, -7, -8), 7·7 (m, H-4, -6), and 8·3 (m, H-9), *m/e* 198 (M^+, 100%), 197 (M − H, 84%), 165 (197 − S, 28%), 164 (197 − HS, 6%), 153 (197 − CS, 8%, *m** 118·9), and 152 (153 − H), 16%).

2-(2-*Methylallyl*)*benzo*[b]*thiophen* (7).—A 0·1M-solution of 2-lithiobenzo[*b*]thiophen, prepared as described earlier, was treated with stirring at 0° with 2-methylallyl bromide (13·5 g, 0·1 mol) over 50 min. Stirring was continued at 0° for 4 h and at room temperature overnight, after which the solution was refluxed for 1 h. The resulting mixture was worked up as for 2-allylbenzo[*b*]thiophen, giving the *product* (7·8 g, 42%), b.p. 135—136° at 7·5 mmHg (Found: C, 76·4; H, 6·4. $C_{12}H_{12}S$ requires C, 76·5; H, 6·4%), δ (neat) 1·62 (s, CH_3), 3·36 (s, CH_2), 4·85 (s, $C{=}CH_2$), 6·88 (s, 3-H), and 7—7·6 (m, aromatic), $\nu_{max.}$ 1544 cm^{-1} (C=C).

Reaction of 2-(2-*Methylallyl*)*benzo*[b]*thiophen with Dichloromethyl Butyl Ether*.—Anhydrous tin(IV) chloride (2·6 g, 0·01 mol) was added with stirring to a solution of 2-(2-methylallyl)benzo[*b*]thiophen (1·88 g, 0·01 mol) in methylene chloride (20 ml). The solution was cooled to −70° and dichloromethyl butyl ether[17] (1·50 g, 0·01 mol) was added during 15 min. The mixture was stirred at that temperature for 2·5 h and then the temperature was allowed to rise slowly to −5°. The mixture was then stirred for 15 min, set aside overnight, and treated in the usual manner. The residue was chromatographed on alumina. 3-Methyldibenzothiophen (8) (0·2 g, 10%), m.p. 78° (lit.,[14] 77—79°), was eluted with light petroleum (b.p. 60—80°). Further elution with the same solvent gave yellow needles of 2-(2-*methylprop*-1-*enyl*)*benzothiophen*-3-*carbaldehyde* (9) (0·3 g, 14%), m.p. 47—48° (Found: C, 72·6; H, 5·8. $C_{13}H_{12}OS$ requires C, 72·2; H, 5·6%), δ ($CDCl_3$) 1·88 (s, CH_3), 1·93 (s, CH_3), 6·74 (m, CH), 7·27—7·77 (m, aromatic), and 10·19 (s, CHO), $\nu_{max.}$ 1680 cm^{-1} (C=O).

Ethyl 3-*Methyldibenzothiophen*-1-*carboxylate* (10).—Anhydrous tin(IV) chloride (10 g, 0·038 mol) was added to a stirred solution of 2-(2-methylallyl)benzo[*b*]thiophen (6·1 g, 0·0325 mol) in methylene chloride (50 ml) at −70°. To the resultant, stirred, red mixture was slowly added ethyl dichloro(ethoxy)acetate[10] (6·53 g, 0·032 5 mol), and the mixture was stirred at −70° for 105 min and at ambient temperature for a further 18 h. It was worked up as described for (4a) and the product chromatographed on alumina. Elution with petroleum (b.p. 40—60°) gave a little starting material; elution with light petroleum–benzene (3 : 1) gave the *ester* (3·58 g, 41%) as needles, m.p. 87—88° [from ethanol (carbon)] (Found: C, 71·0; H, 5·4. $C_{16}H_{14}O_2S$ requires C, 71·1; H, 5·2%), $\nu_{max.}$ 1720 cm^{-1} (C=O). Alkaline hydrolysis gave the *acid* (11) (100%), m.p. 199—200° (from ethanol) (Found: C, 68·7; H, 4·1. $C_{14}H_{10}O_2S$ requires C, 69·4; H, 4·2), $\nu_{max.}$ 1670 cm^{-1} (C=O), which was decarboxylated by refluxing in quinoline with copper bronze, yielding 3-methyldibenzothiophen (99%), identical with the previous sample.

1-*Hydroxymethyl*-3-*methyldibenzothiophen*.—Reduction of the ester (10) with an excess of lithium aluminium hydride gave the *alcohol* (90%), m.p. 115—116° (from ethanol) (Found: C, 73·9; H, 5·5. $C_{14}H_{12}OS$ requires C, 73·75; H, 5·3).

2-*Allylbenzo*[b]*furan* (5).—This was prepared as described for 2-allylbenzo[*b*]thiophen except that the reaction was conducted initially at −10° rather than 0°. Distillation gave the pure *product* (18%), b.p. 148—150° at 50 mmHg (Found: C, 83·8; H, 6·4. $C_{11}H_{10}O$ requires C, 83·5; H, 6·4%), δ (CCl_4) 3·33 (m, CH_2), 5·07 (m, $C{=}CH_2$), 5·6—6·1 (m, CH), 6·2 (s, 3-H), and 7·0—7·45 (m, aromatic), $\nu_{max.}$ 1686 cm^{-1} (C=C).

Dibenzofuran-1-*carboxylic Acid* (6).—Anhydrous tin(IV) chloride (5·0 g, 0·019 mol) was added to a solution of 2-allylbenzo[*b*]furan (2·5 g, 0·017 mol) in methylene chloride (30 ml) at −70°. To the resultant stirred solution was added ethyl dichloro(ethoxy)acetate[10] (3·7 g, 0·0184 mol) in methylene chloride (5 ml) during 30 min, and the mixture was stirred at −70° for 1 h and at room temperature for 19 h. The usual work-up gave an oil which was chromatographed on alumina. Elution with light petroleum–benzene (2 : 1) gave ethyl dibenzofuran-1-carboxylate as an oil (1·2 g, 32%), $\nu_{max.}$ 1725 cm^{-1} (C=O), M^+ 240. Alkaline hydrolysis gave the acid (95%), m.p. 232—233° (lit.,[13] 231—232°).

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