Oxidative S-Dealkylation of *tert*-Butyl Aryl Sulphides: A Novel Route to 3-Substituted-3*H*-1,2-benzodithioles[1]

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Substituted 3*H*-1,2-benzodithioles are readily synthesized by an oxidative S-dealkylation reaction of mercapto *tert*-butyl sulphides **8** with *N*-bromosuccinimide in acetonitrile without prior deprotection of the *tert*-butyl group.

The 3*H*-1,2-benzodithioles **1** are a class of relatively unexplored sulphur heterocycles. The presence of a cyclic disulphide fused to a benzene ring in these molecules suggests that they may possess unusual redox properties. The strain associated with the five-membered cyclic disulphides, a consequence of the repulsion between the sulphur–sulphur lone pairs due to the geometric constraints of the ring, is reflected in the instability of these compounds.[2] As a result, it is not surprising that the only known member, **1** (R = H), of this class of interesting heterocycles is unstable at room temperature and has not been isolated in the pure state.[3]

As part of our research programme directed towards the design and synthesis of novel bio-compatible reducing agents, we require compounds that can be regenerated by endogenous redox enzyme systems. We were intrigued by the possibility of employing **1** for such purposes. It is expected that ring substitution at the 3-position would stabilize the cyclic disulphide and would also provide a convenient handle for attaching polar groups for binding. Since the synthetic route for the parent compound **1** (R = H)[3] is not readily adapted for preparing 3-substituted analogues, we have designed a general synthesis of these cyclic disulphides based on *ortho*-lithiated alkyl phenyl sulphides **2**. Ideally, the alkyl group should serve as a protecting group during the *ortho*-lithiation reaction and should spontaneously depart during subsequent oxidative cyclization so that deprotection would not be necessary (Scheme 1). The *tert*-butyl group does not undergo metallation and forms a stable carbocation or radical, making it suitable for this purpose.

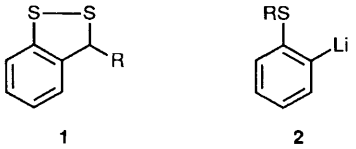
tert-Butyl phenyl sulphide **4**, readily synthesized from benzenethiol,[4] was lithiated at the *ortho* position by a modified literature method[5] [BuLi, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)–hexanes, 25 °C, 4 h]. The resulting anion was treated with aldehydes to give the alcohols **5** in good yields (Table 1). The alcohols **5** were smoothly converted into the corresponding mesylates **6**[6] which were then displaced with potassium *O*-ethyl xanthate to give the ethyl xanthates **7**. Treatment of the xanthate **7** with ethylenediamine[7] gave the thiols **8** in 60–70% overall yield from the alcohol (Scheme 2).

On treatment with *N*-bromosuccinimide (NBS) in acetonitrile‡ (0 °C), the mercapto sulphide **8a** indeed gave the cyclic disulphide **1a**§ as a yellow oil. Compound **1a** is stable at room temperature and has been stored at −10 °C for months without noticeable decomposition. The oxidation of **8a** has been studied in detail with a number of oxidizing agents in acetonitrile as solvent. NBS and 1,3-dibromo-5,5-dimethylhydantoin both gave good yields of **1a**. Other oxidizing agents including *tert*-butyl hydroperoxide, *N*-iodosuccinimide (NIS)

Table 1 Preparation of compounds **5** and **1**

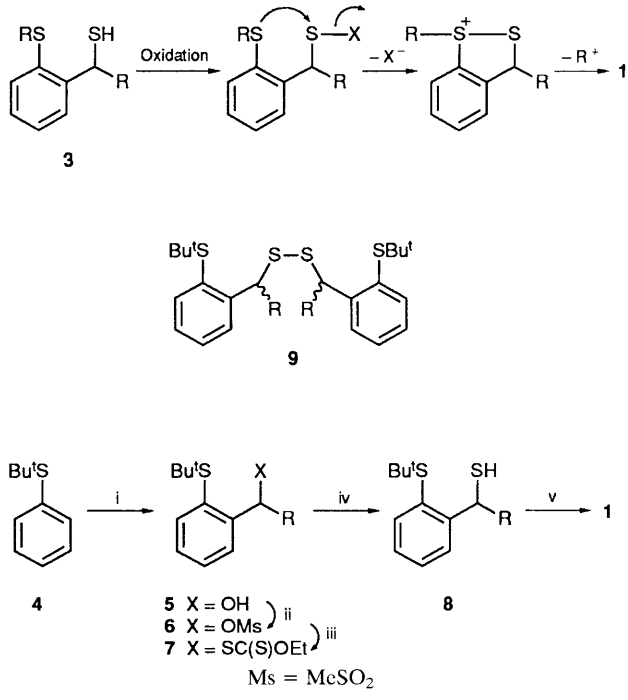
	R	Yield (%) 5	1
a	C_5H_{11}	87	81
b	C_9H_{19}	61	44[a]
c	$PhCH_2CH_2$	57	80
d	$Bu^tOCO(CH_2)_4$	33	42[a]
e	$CH_2{=}CH(CH_2)_8$	84	65

[a] Yields based on the alcohol **5**.



1 **2**

Scheme 1



Scheme 2 *Reagents*: i, BuLi, TMEDA, hexanes, 25 °C, 4 h, then RCHO, THF, −78 °C (see Table 1); ii, MsCl, Et_3N, CH_2Cl_2, 0 °C, 10–20 min.; iii, $EtOC(S)S^-K^+$, acetone, room temperature, 14 h; iv, ethylenediamine, CH_2Cl_2, 25 °C, 3–4 h, 60–70% overall from **5**; v, NBS (1 equiv.), MeCN–acetone (9 : 1, 0.05 mol dm^{-3}), 0 °C, 10 min (see Table 1)

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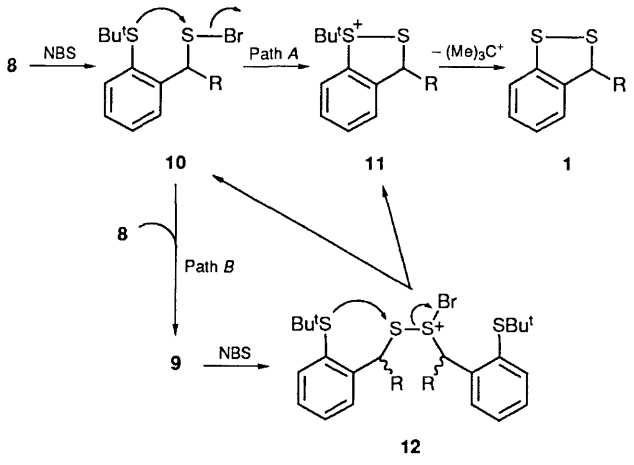
‡ Acetonitrile was selected as the solvent owing to its ability to capture carbocations which may otherwise cause undesirable side reactions. NBS, 2,4-dibromo-5,5-dimethylhydantoin and NIS were each added as a solution in acetone.

§ *Selected spectral data*: δ_H (300 MHz, $CDCl_3$) 7.05–7.48 (4H, m), 6.42 (1H, dd, *J* 4.6 and 9.6 Hz, -C*H*-S), 1.8–2.1 (2H, m, S-CH-CH_2-), 1.25–1.65 (6H, m) and 0.89 (3H, distorted t, *J* 7 Hz); δ_C (75 MHz, $CDCl_3$) 142.91 (C), 141.12 (C), 127.28 (CH), 125.14 (CH), 124.27 (CH), 122.74 (CH), 60.17 (CH-S), 34.78 (CH_2), 31.45 (CH_2), 27.73 (CH_2), 22.60 (CH_2) and 14.11 (CH_3); ν_{max}/cm^{-1} (neat): 1465, 1442 and 748; *m/z* 224 (M^+, 17%), 153 (M − C_5H_{11}, 100); found: 224.0707, required for $C_{12}H_{16}S_2$: 224.0693.



Scheme 3

and iodine were much less effective, giving the intermolecular disulphide **9**¶ as the major isolated product. Using NBS in dilute acetonitrile solutions (0.05 mol dm^{-3}) as the standard reaction condition, a number of 3-substituted-3*H*-1,2-benzodithioles **1** were synthesized in 60–84% yield (Table 1).

Mechanistically, two distinct pathways can be envisaged. The first pathway involves a direct oxidation of **8** to the disulphide **1** *via* the intermediate sulphenyl bromide **10** (Scheme 3, path *A*). In the second pathway, **8** is first converted into the intermolecular disulphide **9** which is then further oxidized to **1** (Scheme 3, path *B*). We tend to favour the latter for the following reasons:

(*i*) during the oxidation of **8a**, the characteristic yellow colour of **1** did not appear until more than 0.5 equivalent of NBS had been added; (*ii*) **9a** was isolated from the reaction of **8a** with 0.5 equivalent of NBS; (*iii*) further oxidation of **9a** under standard conditions gave **1a** in 78% yield. The failure of weaker oxidizing agents to give **1** can be rationalized by their inefficiency in further reacting with the intermolecular disulphide **9**.

In summary, the present procedure offers a rapid and effective entry into 3-substituted 3*H*-1,2-benzodithioles from benzenethiol, which is compatible with alkenes and *tert*-butyl esters. Unlike the parent, these 3-substituted 3*H*-1,2-benzodithioles are stable and isolable under normal conditions, and other compounds with substitution in the benzene ring should also be readily available. The biological effects of **1** will be reported elsewhere.

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References

1 Presented at the 1989 Pacific Conference on Chemistry and Spectroscopy, Pasadena, California, 18–21 October, 1989; abstract No. 181.
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¶ This compound exists as a pair of diastereoisomers (*R*R** and *R*S**): δ_H (300 MHz, $CDCl_3$) 7.60 (1H, distorted t, *J* 7 Hz), 7.45–7.50 (1H, m), 7.36 (1H, distorted t, *J* 7 Hz), 7.16–7.24 (1H, m), 5.04 (0.5H, dd, *J* 5.3 and 9.8 Hz, –C*H*–S), 4.91 (0.5H, dd, *J* 6.1 and 9.0 Hz, –C*H*–S), 2.1–2.4 (1H, m, CH_2–CH–S), 1.75–1.90 (1H, m, CH_2–CH–S), 1.38 and 1.34 (9H, 2 X s, Bu^t), 1.1–1.45 (6 H, m), 0.83 and 0.84 (3H, 2 X t, CH_3); δ_C (75 MHz, $CDCl_3$)146.65 (C), 145.86 (C), 138.83 (CH), 138.65 (CH), 133.45 (C), 133.19 (C), 129.33 (CH), 127.86 (CH), 126.96 (CH), 126.79 (CH), 51.87 (CH–S), 50.35 (CH–S), 47.10 (Me_3C–S), 47.06 (C, Me_3C–S), 35.19 (CH), 31.75 (CH), 31.61 (CH), 31.34 (CH_3), 31.29 (CH_3), 26.75 (CH_2), 26.70 (CH_2), 22.27 (CH_2) and 13.75 (CH_3).