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Routes to highly substituted thiophenol derivatives

Gary Nicholson, Jon D. Silversides and Stephen J. Archibald*

Department of Chemistry, University of Hull, Cottingham Road, Hull HU6 7RX, UK

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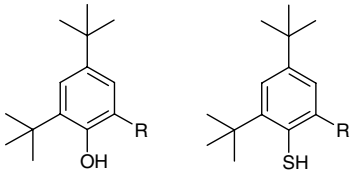
Abstract—Syntheses of highly substituted thiophenol derivatives that incorporate steric bulk into the ligand framework via *ortho* and *para tert*-butyl substituents are reported. *S*-Benzyl and trityl protection were investigated and the effects of substituents on the Newman–Kwart rearrangement of the thiocarbamate discussed. Single crystal X-ray structures are reported for three compounds and demonstrate the role of hydrogen bonding in stabilising the thiophenol to oxidation.

There is current interest in stabilising and characterising radical species of biochemical significance.[1–3] There are very few examples in the literature of stabilised thiyl radicals. Thiyl radicals (cysteine) may be intermediates in the catalytic cycles of ribonucleotide reductases and Ni–Fe hydrogenases.[4,5] Small molecule mimics incorporating a metal bound phenylthiyl radical offer a more complex synthetic challenge than the analogous phenoxyl radical species due to the potential for oxidation to form disulfide bonds.



1 **2**

The non-substituted phenylthiyl radical is estimated to decay with head-to-head dimerisation at $9.6 \times 10^9\ M^{-1}\ s^{-1}$.[6] S-Oxygenation can also occur as an unwanted side reaction to form sulfoxy compounds.[7,8] A further problem can be the harsh conditions which are often required for protection and deprotection steps that can be incompatible with the required functional groups.[9] Bulky (preferably *tert*-butyl) substituents *ortho* and *para* to the phenol, **1**, have been shown to increase the lifetime of metal bound phenoxyl radicals. Bulky substituents suppress radical coupling reactions and increase the lifetime of the radical species to allow characterisation using a variety of spectroscopic techniques.[10]

We aim to produce a variety of highly substituted functionalised thiophenolates, **2**, that may be incorporated into chelate ligands. There are very few published routes to highly substituted thiophenols. The route we initially attempted was a Newman–Kwart rearrangement of dimethylthiocarbamates. Brooker et al. and Schröder and co-workers used dimethylthiocarbamates to incorporate the thiophenol into a chelate ligand framework, providing rare examples of efficient SH protection throughout the syntheses.[11,12] The formyl substituted phenol derivatives were converted into *O*-dimethylthiocarbamates, **4**, by reaction with DABCO and dimethylthiocarbamoyl chloride followed by a Newman–Kwart rearrangement to give the more thermodynamically stable *S*-dimethylthiocarbamate, **5**, using $BF_3{\cdot}OEt_2$ in toluene at 85 °C. Subsequent cleavage with KOH produces the thiophenol. These conditions were used in an attempted synthesis of the *O*-2,4-di-*tert*-butyl-6-formylphenyl dimethylthiocarbamate but the rearrangement did not occur. The route was adapted to provide more forcing conditions using vapour phase flash vacuum pyrolysis (Scheme 1). This has been shown to effect the rearrangement in sterically constrained systems.[13] Compound **3** was subjected to furnace temperatures ranging from 200 to 500 °C under an inert atmosphere but no rearrangement was observed and only the starting material was recovered. Both steric and electronic factors contribute to the lowered reactivity.

Wieghardt and co-workers have used a benzyl group to protect the thiophenol in the synthesis of a highly

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* Corresponding author. Tel.: +44 1482465488; fax: +44 1482466410; e-mail: s.j.archibald@hull.ac.uk

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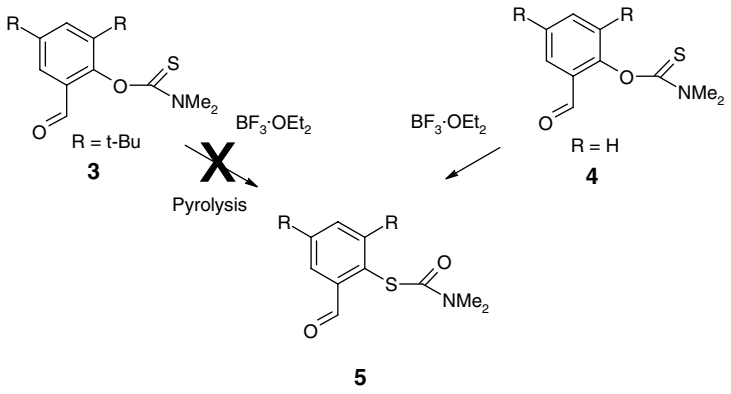
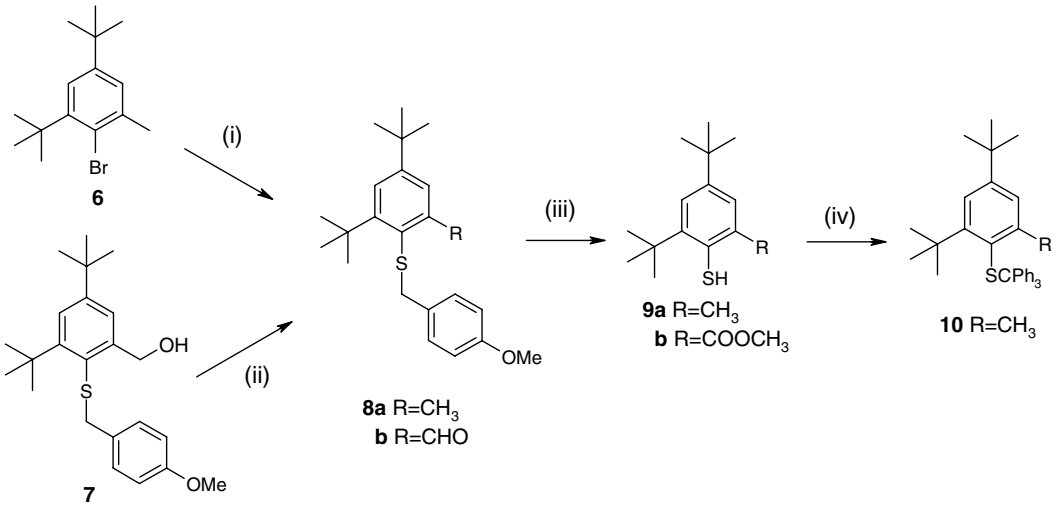


Scheme 1.

substituted derivative that has subsequently been incorporated into a triazacyclononane chelator framework.[14] We exploited the *para*-methoxybenzyl protecting group in the synthesis of novel substituted phenylthiol compounds. 1,3-Di-*tert*-butyl-5-methylbenzene was used as a starting material and the compounds were synthesised via adaptations of the experimental procedures of Wieghardt and co-workers and Shibata et al.[14,15] The *S*-benzyl protected compound **8a**[16] was synthesised from toluene-4-thiosulfonic acid *S*-(4-methoxybenzyl)ester using a related procedure (Scheme 2). The methyl group offers a potential site for further functionalisation of thiophenolates while the sulfur is protected. The synthesis of a benzylic bromide compound from **6** has previously been reported using NBS and the radical initiator AIBN.[14] Single crystals of **8a** were grown by evaporation of an *n*-hexane solution and X-ray crystallographic analysis confirmed the structural assignment (Fig. 1).

Oxidation of the alcohol group in **7** to the aldehyde was carried out using $BaMnO_4$. Compound **8b**[17] was synthesised over 48 h initially using a five-fold excess by mass of $BaMnO_4$ and stirring the reaction at room temperature, further $BaMnO_4$ was added after 24 h. Precipitated solids were removed by filtration and washed with CH_2Cl_2. Use of a 10-fold excess by mass of the reagent over 24 h resulted in only a partially oxidised product. The crude product was purified by column chromatography to give **8b** in 53% yield.

The 4-methoxybenzyl S-protecting group can be removed using mercury(II) acetate in DCM, then passing hydrogen sulfide through the solution to produce solid mercury(II) sulfide which is filtered off and the desired product isolated. Compound **8a** was subjected to this cleavage reaction and the product isolated was the expected 2-thio-2,4-di-*tert*-butyl-6-methyl thiophenol derivative **9a**.[18] This was purified by column chromatography using *n*-hexane as an eluent to give 83% yield. Again, single crystals were grown by slow evaporation of the hexane solution in air. X-ray crystallographic analysis revealed that air oxidation had occurred during the crystallisation process resulting in formation of the disulfide linked compound (Fig. 2). The Cambridge Structural Database shows only four examples of 2,4,6-trisubstituted disulfide linked thiophenyl compounds and none with the *tert*-butyl group.[19] The S–S



Scheme 2. Reagents and conditions: (i) *n*-BuLi, Et_2O, 0 °C, 10 min then rt, 3 h, Ar; toluene-4-thiosulfonic acid *S*-(4-methoxybenzyl) ester, Et_2O, −70 °C, 1 h then −30 °C, 4 h, Ar (65%) ; (ii) $BaMnO_4$, CH_2Cl_2, rt, 48 h (53%); (iii) $Hg(CH_3CO_2)_2$, 60 °C, 6 h then H_2S, 20 min, Ar (**9a** 83%, **9b** 68%) and (iv) trityl chloride, C_6H_6, 96 h, Ar (58%).

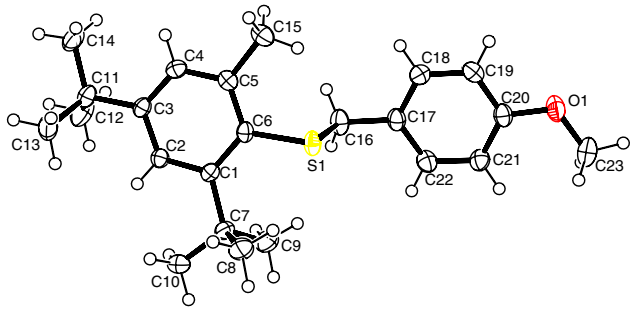


Figure 1. ORTEP plot of the X-ray crystal structure of **8a**.

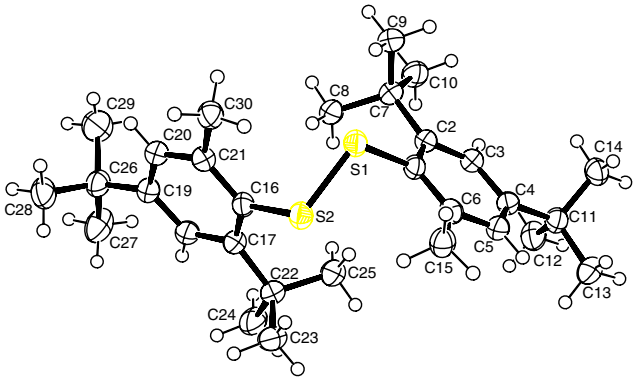


Figure 2. ORTEP plot of the X-ray crystal structure of the air oxidation product from **9a**.

bond length of 2.059(1) Å does not appear to be affected by the steric bulk as it is similar to the overall average for thiophenyl compounds of 2.052 Å from 157 structures with S-coordinated compounds excluded.

The cleavage of the benzyl group from **8b** was attempted under the same conditions employed for **8a**. However, the aldehyde product was not isolated and the product identity was confirmed by X-ray crystallography (Fig. 3). Crystals were grown by slow evaporation of an *n*-hexane/CH_2Cl_2 solution in air. The product contains a free thiol but the aldehyde has been transformed to a methyl ester. This can be accounted for by the presence of a small amount of methanol required to solubilise the mercury acetate, with the esterification catalysed by mercury(II). The methyl ester substituted thiol **9b**[18] was isolated in 68% yield using gradient column chromatography with *n*-hexane/ CH_2Cl_2 as eluent. The X-ray structural data give an insight into the stabilisation of the thiophenol by formation of an intramolecular H-bond (Fig. 3). The crystals were grown in air but did not show oxidation to the disulfide linked compound. The key difference is the presence of the ester which forms an intramolecular H-bond with thiophenol, thus inhibiting the oxidation process and disulfide bond formation.

The applicability of a further S-protecting group to highly substituted thiophenols that may be cleaved under mild conditions was investigated. The trityl group has been used to protect thiophenols but there are no

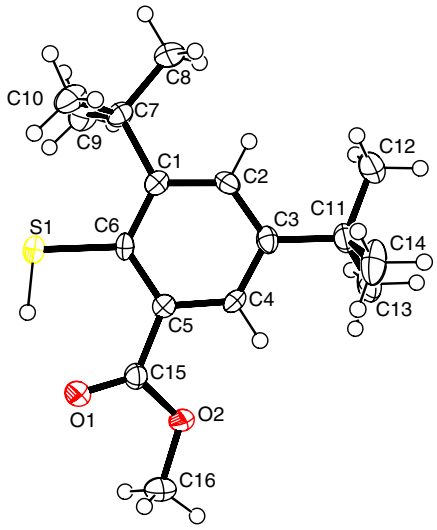


Figure 3. ORTEP plot of the X-ray crystal structure of **9b**.

reports with highly substituted derivatives. It was thought that the steric repulsion may be too great to accommodate this protecting group. The conditions given for unsubstituted thiophenol in the literature suggest that the reaction with trityl chloride, performed at reflux in benzene, is complete after 1 h. However, considerably longer reaction times were required to protect 2,4-di-*tert*-butyl-6-methyl thiophenol. The reaction was monitored by TLC and stopped after 96 h. Purification was carried out using column chromatography with hexane as an eluent to give **10**[18] in 58% yield. Despite the reaction being carried out under an argon atmosphere, a considerable amount of disulfide linked starting material was also recovered. This protecting group provides an option that may be useful due to the very mild conditions for cleavage.

We have shown that the synthesis of some highly substituted thiophenolate functionalised derivatives is possible using both benzylic and trityl protecting groups. However, such syntheses can be challenging due to slower reaction times or no reaction via established routes for unsubstituted thiophenols. Hydrogen bonding was demonstrated to have an important role in stabilising the thiophenol to disulfide bond formation. These routes should contribute to the synthesis of chelate systems for the characterisation of metal bound thiyl radicals.

CCDC Nos. 296458, 296459 and 604270 contain the supplementary crystallographic data for compounds **8a**, **9a** and **9b**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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16. (2,4-Di-*tert*-butyl-6-methylphenyl)(4-methoxybenzyl) sulfane **8a**; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9H), 1.63 (s, 9H), 2.77 (s, 3H), 3.82 (s, 2H), 3.83 (s, 3H), 6.87 (m, 2H), 7.25 (d, 1H, $J = 2.3$ Hz), 7.27 (m, 2H), 7.40 (d, 1H, $J = 2.3$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 31.3, 31.6 , 34.7, 37.6, 40.9, 55.2, 113.9, 121.9, 125.8, 129.5, 130.1, 130.6, 144.2, 150.6, 153.1, 158.8. MS (EI)$m/z = 356$ (M^+).
17. 3,5-Di-*tert*-butyl-2-(4-methoxybenzylthio)benzaldehyde **8b**. Barium manganate (15 g) was added to a stirred solution of **7** (2.97 g, 8.03 mmol) in CH_2Cl_2 (50 mL). The resulting suspension was stirred at room temperature for 48 h with further barium manganate (15 g) added after 24 h. The solids were separated by filtration of the reaction mixture through a filter agent (Hyflo) and washed thoroughly with CH_2Cl_2. The combined CH_2Cl_2 washings were dried over $MgSO_4$ and concentrated in vacuo. The pale green/yellow crude solid was purified by column chromatography to yield a light yellow powder **8b**. (Silica gel 60, eluent: *n*-hexane/ Et_2O 85/15 (v/v)). R_f: 0.38. Yield 1.58 g (53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 9H), 1.55 (s, 9H), 3.77 (s, 2H), 3.78 (s, 3H), 6.78 (m, 2H), 7.03 (m, 2H), 7.71 (d, 1H, $J = 2.2$ Hz), 7.78 (d, 1H, $J = 2.2$ Hz), 10.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1, 31.5, 35.1, 37.4, 45.2, 55.3, 114.0, 123.8, 128.4, 129.3, 130.2, 135.7, 139.9, 151.5, 153.7, 159.1, 194.3. HRMS (ESI) calcd $[M+H]^+$ for $C_{23}H_{31}O_2S$: 371.2039; found 371.2039. IR ν_{max}: 1685 cm^{-1} (C=O).
18. 2,4-Di-*tert*-butyl-6-methylbenzenethiol **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 1.65 (s, 9H), 2.51 (s, 3H), 3.35 (s, 1H), 7.24 (d, 1H, $J = 2.2$ Hz), 7.45 (d, 1H, $J = 2.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 30.3, 31.4, 34.5, 36.7, 122.1, 125.5, 126.3, 137.7, 147.9, 148.2. MS (EI)$m/z = 470$ (dimer), 235 (M^+). Methyl 3,5-di-*tert*-butyl-2-mercaptobenzoate **9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 9H), 1.52 (s, 9H), 3.90 (s, 3H), 6.46 (s, 1H), 7.54 (d, 1H, $J = 2.2$ Hz), 7.61 (d, 1H, $J = 2.2$ Hz). MS (EI)$m/z = 281$ (M^++H), 266 (M^+–CH_3), 250 (M^+–OCH_3). IR ν_{max}: 1700 cm^{-1} (C=O). (2,4-Di-*tert*-butyl-6-methylphenyl)(trityl) sulfane **10**; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 18H), 2.51 (br s, 3H), 7.15 (d, 1H, $J = 2.0$ Hz), 7.23 (d, 1H, $J = 2.0$ Hz), 7.25–7.32 (m, 15H). MS (EI)$m/z = 478$ (M^+).
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