A new approach to reductive deprotection of thioethers with a low-valent titanium reagent†

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Low-valent titanium mediated cleavage of carbon-sulphur bond is reported. This has resulted in an efficient and mild protocol for the deprotection of allyl/benzyl thioethers under reductive condition and with good yields. Deprotection can be performed regio- and chemo-selectively in the presence of acid, ester and N-benzylation functionality and is general for aliphatic and aromatic precursors.

Low-valent titanium reagents have occupied pride of place in organic synthesis1-3. These have been successfully used for the construction of cycloalkanes, heterocycles, macrocyclic rings as well for the synthesis of several complex natural products4-6. In view of the importance, several new variants of the LVT reagents3,7 including instant5 and catalytic formulations18 have also been developed. Considering the utility of selective cleavage of carbon-heteroatom (O, N, S) bonds in organic synthesis, several useful synthetic methodologies involving C-O and C-N bond cleavage have been reported10-12 from our laboratory. These include deprotection of alcohols/phenols10 and amines11, reductive cleavage of acetals12 etc. Although many methods are available13 for the cleavage of C-O and C-N bonds, the C-S bond cleavage in thioethers has received scanty attention. Protection of thiols finds innumerable applications in multistep organic syntheses, particularly in protein chemistry including the synthesis of coenzyme A. Of the two classes of protections, viz ester and ether types, the latter is preferred because of their inertness to nucleophilic, acidic or basic reaction conditions. For thiols, deprotection under a reducing environment would be of importance over oxidative approach due to the inherent tendency of thiol towards dimerization. Amongst the thioethers, the S-benzyl derivatives are most frequently used, although very few methods are known for their deprotection15. These include both photolytic14 and some chemical routes. Amongst the latter, the more frequently used protocol13,15 with Na/NH3 is not selective, while reagents like Hg(II)/HCl16 are not of general utility. Use of corrosive and strong acid viz. HF in combination with scavangers produces17 side products due to drastic conditions, thereby, limiting their synthetic utility for sensitive polyfunctional compounds. Therefore, a need for a better and selective strategy for this transformation was felt. To this end, we have developed a convenient approach for the selective removal of allyl/benzyl thioethers to the corresponding thiols via a LVT mediated single electron transfer (SET) reaction (Scheme I).

In a model experiment, the reaction was carried out by refluxing a mixture of S-benzyl-2-aminothiophenol 1a and LVT, prepared from TiCl4/Li in THF. The reaction was complete (cf TLC) in 20 hr under refluxing condition affording 2-aminothiophenol 1b in good yield (Table I, entry 1). The scope of the methodology has been illustrated (Table I) by the deprotection of a variety of S-allyl and S-benzyl thioethers of both

†Dedicated to Prof. U.R. Ghatak on his 70th birthday
aromatic (entries 1-6 and 9) and aliphatic (entries 10-12) origins. Selective protection of polyfunctional molecule constitutes a challenging task in organic synthesis. In the present study, both chemo- and regio-selectives were achieved. In general, the method was very effective for the cleavage of the S-benzyl and S-allyl bonds but did not affect S-alkyl groups (entries 7 and 8). Hence, the former can be cleaved selectively in presence of the latter. Allyl group appeared to be removed easily (entry 2) as compared to the benzyl counterpart. Hence, to study any selectivity of cleavage between S-allyl and S-Bn, a model reaction was carried out with a mixture (1:1 molar preparations) of S-allyl and S-benzyl-2-aminothiophenols 1a and 2a with LVT. The S-allyl bond was found to be cleaved even at room temperature along with the quantitative recovery of 1a (entry 3). In addition, the reagent ensured chemo-selective deprotection of both allyl and benzyl thiocarboxylic acids in preference to the N-benzyl and N-allyl bonds thus, allowing selective protection of aminoalkylthiols (entries 4 and 5).

The lability of the S-C bond cleavage was further augmented by replacing the benzyl group with the cinnamyl component. In fact, S-cinnamyl group was cleaved in 18 hr at room temperature (entry 6) compared to S-benzyl group which required 20 hr at reflux temperature. The preferential cleavage of S-cinnamyl > S-benzyl > S-alkyl groups is in tune with the relative stabilities of the respective radicals generated in the cleavage. In case of the cleavage of S-benzyl bond, bibenzyl was also isolated (Equation 1) which is indicative of an electron transfer process. Since most of the above chosen substrates possessed a protected or free amino functionality ortho to the thioether group, it was of interest to investigate any influence of the former on the course of the deprotection route. For this, the reaction was also carried out with a simple unsubstituted aryl thioether, 8a. This furnished the expected thiol 8b and in identical yield (entry 9) as that of the corresponding ortho-amino compound 1a. Thus, the method appeared to have general applicability with a wide substrate tolerance.

In the synthesis of biologically important cystein-based compounds, the thiol group is often protected by benzylation. Hence, we attempted regeneration of the thiol group from two benzylated cystein esters with the above reagent. It was gratifying to note that deprotection of S-benzyl thiocarboxylic acids 9a and 10a proceeded smoothly even in the presence of the reducible ester functionality in the substrates (entries 10 and 11). In the case of the cystein derivatives, 9b and 10b, the product recovery was poor possibly due to their high solubility in water. Hence, the yield is reported based on the amount of equimolar proportion of bibenzyl isolated. Finally, the reaction was also applicable with aliphatic thiocarboxylic acids as is reflected with result with the substrate 11a (entry 12).

In conclusion, an efficient and selective protocol for the deprotection of allyl and benzyl derivatives of thiols has been developed with LVT. The S-benzyl bond can be cleaved chemo-selectively in the presence of N-benzyl, N-allyl, S-alkyl and ester functionalities and is general for both aliphatic and aromatic precursors. Regioselective cleavage of S-allyl bond in preference to their benzyl counterpart is an additional feature of the method.

Experimental Section
Reagents are used as received. The LVT reactions were carried out under Ar atmosphere and using freshly dried solvent. Lithium rods cut into small pieces were used for the reduction of titanium chloride. All the extracts were dried over anhyd. Na₂SO₄. The IR spectra were scanned with a Nicolet FT-IR spectrophotometer model 410 and only pertinent values are shown. The 1H NMR spectra were recorded with a Bruker AC-200 200 MHz spectrometer using CDCl₃ as the solvent. The GLC analyses were carried out with a Shimadzu GC-16A chromatogram.

Preparation of the substrates
Alkylation of thiols. A suspension of the thiol (0.016 mole), suitable halide (0.018 mole) and K₂CO₃ (0.064 mole) in anhyd. EtOH (25 mL) was stirred at

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Table I—Deprotection of thioethers with LVT

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temp (°C)/ time</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>reflux/20</td>
<td>1b</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>25/2</td>
<td>1b</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>1a + 2a</td>
<td>25/18</td>
<td>1a + 1b</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>25/22</td>
<td>3b</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>4a</td>
<td>25/18</td>
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<td>45</td>
</tr>
<tr>
<td>6</td>
<td>5a</td>
<td>25/18</td>
<td>1b</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>6a</td>
<td>reflux/22</td>
<td>-</td>
<td>-²</td>
</tr>
<tr>
<td>8</td>
<td>7a</td>
<td>reflux/22</td>
<td>-</td>
<td>-²</td>
</tr>
<tr>
<td>9</td>
<td>8a</td>
<td>25/16</td>
<td>8b</td>
<td>55</td>
</tr>
<tr>
<td>10</td>
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<td>20</td>
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<td>11</td>
<td>10a</td>
<td>2.5/25</td>
<td>10b</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>11a</td>
<td>18/25</td>
<td>11b</td>
<td>94²</td>
</tr>
</tbody>
</table>

*The starting materials were recovered quantitatively.

¹Yield based on GLC.
0 °C till the reaction was complete (cf. TLC). The reaction mixture was filtered, the filtrate concentrated in vacuo and the residue dissolved in ether. The ether extract was washed with water and brine and dried (Na₂SO₄). Removal of solvent followed by column chromatography (silica gel) gave the pure product.

2-Amino-S-benzylthiophenol 1a: Yield 68%; ¹H NMR: δ 3.73 (s, 2H, SCH₂), 4.1 (bs, 2H, D₂O exchangeable, NH₂), 6.3-7.1 (m, 9H, ArH).

2-Amino-S-allylthiophenol 2a: Yield 58%; ¹H NMR: δ 3.6 (d, J = 6 Hz, 2H, SCH₂), 4.2 (bs, 2H, D₂O exchangeable, NH₂), 4.88 (d, J = 4 Hz, 2H, olefinic CH₂), 5.6-6.25 (m, 1H, olefinic CH), 7.0-7.47 (m, 4H, ArH).

2-Amino-S-cinnamylthiophenol 5a: In this case, the alkylation was carried out at 25 °C. Yield: 41%; ¹H NMR: δ 3.52 (d, J = 6 Hz, 2H, SCH₂), 4.2 (bs, 2H, D₂O exchangeable, NH₂), 6.23-6.37 (m, 3H, CH=CH₂), 6.78-7.47 (m, 9H, ArH).

2-Amino-S-methylthiophenol 6a: Yield: 48%; ¹H NMR: δ 2.33 (s, 3H, CH₃), 4.1 (bs, 2H, D₂O exchangeable, NH), 2.47-3.47 (m, 4H, ArH).

2-Amino-S-ethylthiophenol 7a: Yield: 45%; ¹H NMR: δ 1.22 (t, J = 7.2 Hz, 3H, CH₃), 2.76 (q, J = 4.5 Hz, 2H, allylic CH₂), 4.36 (m, 2H, D₂O exchangeable, NH₂), 6.63-7.51 (m, 4H, ArH).

S-Alllylthiobutanal 11a: The alkylation was carried out at 25 °C using NaOH as the base. Yield 40%; ¹H NMR: δ 0.9 (dist. t, 3H, CH₃), 1.5 (m, 4H, CH₂CH₂), 2.4 (t, J = 6 Hz, 2H, CH₂), 3.1 (d, J = 4.5 Hz, 2H, allylic CH₂), 4.9-5.2 (m, 2H, olefinic CH₂), 5.5-6.2 (m, 1H, olefinic CH).

N-Alkylation of protected thiols

2-(N-Benzyl)Amino-S-benzylthiophenol 3a: A suspension of 1a (1.0 g, 4.7 mmole), BuBr (1.22 mL, 10.2 mmole) and NaOH (0.744 g, 18.6 mmole) in anhyd. toluene (25 mL) was refluxed for 48 hr. The reaction mixture was filtered, the filtrate concentrated in vacuo and the residue dissolved in ether. The ether extract was washed with water and brine and dried (Na₂SO₄). Removal of solvent followed by column chromatography (silica gel) gave pure 3a. Yield 0.5 g (35%); ¹H NMR: δ 3.73 (s, 2H, SCH₂), 4.03 (d, J = 6 Hz, NCH₂), 4.17 (bs, 1H, D₂O exchangeable, NH), 6.9-7.2 (m, 14H, ArH).

2-(N-Allyl)Amino-S-allylthiophenol 4a: A suspension of 2a (0.6 g, 3.7 mmole), allyl bromide (1.4 mL, 16.5 mmole) and NaOH (1.71 g, 29.3 mmole) in anhyd. benzene (25 mL) was refluxed for 48 hr. The reaction mixture was filtered, the filtrate concentrated in vacuo and the residue dissolved in ether. The ether extract was washed with water and brine and dried (Na₂SO₄). Removal of solvent followed by column chromatography (silica gel) gave pure 4a, yield 0.25 g (33%); ¹H NMR: δ 3.33 (d, J = 4 Hz, 2H, SCH₂), 3.7 (m, 3H, partially D₂O exchangeable, NCH₂, NH), 4.7 (d, J = 4 Hz, 2H, olefinic CH₂), 4.83 (d, J = 4 Hz, 2H, olefinic CH₂), 5.1-6.3 (m, 2H, olefinic CH), 6.43-7.47 (m, 4H, ArH).

General procedure for deprotection of thioureas. A dry argon-filled three-necked round-bottom flask was charged with anhyd. THF (70 mL), TiCl₃ (11.2 mmole) and Li (37 mmole). The mixture was refluxed for 3 hr with stirring, during which the colour of the reaction mixture changed from violet to black. To the LVT reagent thus prepared, was added the appropriate thiophenol (2.5 mmole) in THF (5 mL) and the reaction mixture was stirred at suitable temperature for a specific period as mentioned in Table I. After the completion of the reaction (cf. TLC), the reaction mixture was diluted with petroleum ether-ethyl acetate mixture (3:2) and passed through Celite. The organic layer was washed with water and brine and dried (Na₂SO₄). Removal of solvent followed by preparative thin layer chromatography (silica gel) furnished the respective products.

2-Aminothiophenol 1b: ¹H NMR: δ 3.6 (bs, 3H, D₂O exchangeable, NH₂, SH), 6.4-7.4 (m, 4H, ArH).

2-(N-Allylamino)thiophenol 3b: ¹H NMR: δ 3.7 (m, 3H, partially D₂O exchangeable, NCH₂, SH), 4.23 (bs, 1H, D₂O exchangeable, NH), 4.83 (d, J = 4 Hz, 2H, olefinic CH₂), 6.33-6.7 (m, 1H, olefinic CH), 6.9-7.2 (m, 4H, ArH).

2-(N-Benzylamino)thiophenol 4b: ¹H NMR: δ 3.8 (s, 1H, D₂O exchangeable, SH), 4.23 (bs, 1H, D₂O exchangeable, NH), 4.36 (m, 2H, NCH₂), 6.4-7.3 (m, 9H, ArH).

References