SODIUM BENZYL OXYCARBONYL THIOSULPHATE: A WATER-SOLUBLE ACYLATING REAGENT*

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Ito recently described the synthesis of sodium benzoyl thiosulphate from benzoyl chloride and sodium thiosulphate. We have now prepared sodium benzyl oxy carbonyl thiosulphate from benzyl oxy carbonyl chloride in a similar manner. Whereas sodium benzoyl thiosulphate hydrolyses rapidly, sodium benzyl oxy carbonyl thiosulphate is stable in neutral aqueous solution, but hydrolyses slowly at pH 9-10 at room temperature.

Amines and amino acids react readily with the Bunte salt in aqueous solution at pH 6-9, giving benzyl oxy carbonyl derivatives in 19-95% yield (see Table 1). Reaction of sodium benzyl oxy carbonyl thiosulphate and 4-amino phenol at either pH 6 or 9 gave only the N-benzyl oxy carbonyl derivative. This contrasts with Ito's observation that sodium benzoyl thiosulphate and 4-amino phenol gave the N-benzoyl derivative at pH 4-5, but the O-benzoyl derivative at pH 8-4.

2-Naphthol reacted slowly with sodium benzyl oxy carbonyl thiosulphate, even at pH 10, giving benzy l 2-naphthyl carbonate; appreciable loss of reagent by hydrolysis occurs under these conditions.

Sodium benzyl oxy carbonyl thiosulphate undergoes reactions typical of a Bunte salt, rather than an acylating reagent, with thiols. Thus, naphthalene-2-thiol gave 2,2'-dinaphthyl disulphide, presumably by disproportionation of the first-formed benzyl oxy carbonyl 2-naphthyl disulphide; no S-benzyl oxy carbonyl derivative of the thiol was obtained. Similarly toluene-ω-thiol gave dibenzyl disulphide.

In general there seems to be no advantage in using sodium benzyl oxy carbonyl thiosulphate rather than benzyl oxy carbonyl chloride unless one wishes to acylate an amine or phenol in homogeneous aqueous solution.

Experimental

Sodium Benzyl Oxy Carbonyl Thiosulphate

Ice-cold solutions of sodium thiosulphate pentahydrate (50 g) in water (100 ml) and benzyl oxy carbonyl chloride (34.1 g) in ethanol (100 ml) were stirred together for 3 hr at 6°, and then allowed to warm to room temperature. After 3 hr the mixture was cooled again, and the Bunte salt (27.7 g, 51%) was filtered off, washed with a little ethanol, then with ether, and air-dried. After recrystallization from ethanol, it had m.p. 215-218° (dec.) (Found: C, 36.0; H, 2.9; S, 23.6. C12H8NaO6S2 requires C, 35.7; H, 2.6; S, 23.7%).

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Reaction of Sodium Benzyloxy carbonyl Thiocarbonate with Thiols

(i) Equimolar proportions of sodium benzyloxy carbonyl thiosulphate and naphthalene-2-thiol were stirred in aqueous suspension at pH 9 for 2 hr, giving 2,2'-dinaphthyl disulphide (92%), plates (from chloroform), m.p. 142° (lit. m.p. 139°). An authentic sample of benzyloxy carbonyl 2-naphthyl sulphide was prepared by treating naphthalene-2-thiol with benzyloxy carbonyl chloride in aqueous alkali. It crystallized from ethanol as needles, m.p. 88° (Found: C, 73.3; H, 5.1; S, 11.4. C₁₈H₁₄O₃S requires C, 73.4; H, 4.8; S, 10.9%).

(ii) Equimolar proportions of sodium benzyloxy carbonyl thiosulphate and toluene-ω-thiol were allowed to react at pH 8 for 1 hr. The crude product, isolated by extraction with ethyl acetate, was dissolved in light petroleum and chromatographed on alumina. Dibenzyl disulphide (44%) and benzyl alcohol (identified as its p-nitrobenzoate) were obtained.

PREPARATION OF BENZYLOXYCARBONYL DERIVATIVES OF AMINES AND PHENOLS

All reactions were carried out in aqueous solution at 20-25° using 1 equiv. of sodium benzyloxy carbonyl thiosulphate, unless otherwise stated.

<table>
<thead>
<tr>
<th>Reactant</th>
<th>pH</th>
<th>Time (hr)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>M.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aniline</td>
<td>9</td>
<td>2</td>
<td>N-phenyl O-benzyl carbamate</td>
<td>88</td>
<td>77°</td>
</tr>
<tr>
<td>Cyclohexylamine</td>
<td>9</td>
<td>3</td>
<td>N-cyclohexyl O-benzyl carbamate</td>
<td>76</td>
<td>90–91°</td>
</tr>
<tr>
<td>4-Aminophenol</td>
<td>6</td>
<td>2</td>
<td>N-(4-hydroxyphenyl) O-benzyl carbamate</td>
<td>95</td>
<td>150–160°</td>
</tr>
<tr>
<td>Glycine</td>
<td>9</td>
<td>2</td>
<td>N-benzyloxy carbonyl glycine</td>
<td>66</td>
<td>118–120°</td>
</tr>
<tr>
<td>L-Tyrosine</td>
<td>10–12</td>
<td>4</td>
<td>N-benzyloxy carbonyl-L-tyrosine</td>
<td>19</td>
<td>270–273°</td>
</tr>
<tr>
<td>L-Lysine</td>
<td>7.5</td>
<td>3</td>
<td>N⁵-benzyloxy carbonyl-L-lysine</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N⁵,N⁵-di(benzyloxy carbonyl)-L-lysine</td>
<td>19</td>
<td>270–273°</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N⁵,N⁵-di(benzyloxy carbonyl)-L-lysine</td>
<td>72</td>
<td>2</td>
</tr>
</tbody>
</table>

*b Colourless plates (from aqueous ethanol) (Found: C, 71.9; H, 7.9; N, 6.2. C₁₄H₁₄NO₄ requires C, 72.1; H, 8.2; N, 6.0%).
+ Using 2.5 equiv. of sodium benzyloxy carbonyl thiosulphate.
* Unchanged 2-naphthol (35%) was recovered.
* Colourless plates (from methanol) (Found: C, 77.9; H, 5.1. C₁₈H₁₄O₃ requires C, 77.7; H, 5.1%).
* Bergmann, M., and Zervas, L. (Ber. dt. chem. Ges., 1932, 65, 1192) give 120°.
* Unchanged L-tyrosine (58%) was recovered.
* Isolated as the dicyclohexylammonium salt, prisms (from acetone/ethanol), [α]D₂⁰ +8.0° (c, 2% in ethanol) (Found: C, 68.4; H, 8.2; N, 7.1. Calc. for C₁₈H₁₆N₂O₄: C, 68.5; H, 8.3; N, 7.1%); m.p. 130–132°, Klieger, Schröder, and Gibian (see) give 124–127°.