

SODIUM BENZYLOXYCARBONYL THIOSULPHATE: A WATER-SOLUBLE ACYLATING REAGENT*

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Ito¹ recently described the synthesis of sodium benzoyl thiosulphate from benzoyl chloride and sodium thiosulphate. We have now prepared sodium benzyloxycarbonyl thiosulphate from benzyloxycarbonyl chloride in a similar manner. Whereas sodium benzoyl thiosulphate hydrolyses rapidly, sodium benzyloxycarbonyl 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 benzyloxycarbonyl derivatives in 19–95% yield (see Table 1). Reaction of sodium benzyloxycarbonyl thiosulphate and 4-aminophenol at either pH 6 or 9 gave only the *N*-benzyloxycarbonyl derivative. This contrasts with Ito's² observation that sodium benzoyl thiosulphate and 4-aminophenol gave the *N*-benzoyl derivative at pH 4–5, but the *O*-benzoyl derivative at pH 8–4.

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

Sodium benzyloxycarbonyl thiosulphate undergoes reactions typical of a Bunte salt,³ rather than an acylating reagent, with thiols. Thus, naphthalene-2-thiol gave 2,2'-dinaphthyl disulphide, presumably by disproportionation of the first-formed benzyloxycarbonyl 2-naphthyl disulphide; no *S*-benzyloxycarbonyl derivative of the thiol was obtained. Similarly toluene- ω -thiol gave dibenzyl disulphide.

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

Experimental

Sodium Benzyloxycarbonyl Thiosulphate

Ice-cold solutions of sodium thiosulphate pentahydrate (50 g) in water (100 ml) and benzyloxycarbonyl chloride (34.1 g) in ethanol (100 ml) were stirred together for 3 hr at 0°, 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. C₈H₇NaO₆S₂ requires C, 35.7; H, 2.6; S, 23.7%).

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¹ Ito, A., *Yakugaku Zasshi*, 1962, **82**, 866.

² Ito, A., *Yakugaku Zasshi*, 1962, **82**, 875.

³ Milligan, B., and Swan, J. M., *Rev. Pure Appl. Chem.*, 1962, **12**, 72.

Reaction of Sodium Benzyloxycarbonyl Thiosulphate with Thiols

(i) Equimolar proportions of sodium benzyloxycarbonyl 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.⁴ m.p. 139°). An authentic sample of *benzyloxycarbonyl 2-naphthyl sulphide* was prepared by treating naphthalene-2-thiol with benzyloxycarbonyl chloride in aqueous alkali. It crystallized from ethanol as needles, m.p. 88° (Found: C, 73.3; H, 5.1; S, 11.4. $C_{18}H_{14}O_2S$ requires C, 73.4; H, 4.8; S, 10.9%).

(ii) Equimolar proportions of sodium benzyloxycarbonyl thiosulphate and toluene- ω -thiol were stirred 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.

TABLE I

PREPARATION OF BENZYLOXYCARBONYL DERIVATIVES OF AMINES AND PHENOLS

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

Reactant	pH	Time (hr)	Product	Yield (%)	M.P.
Aniline	9	2	<i>N</i> -phenyl <i>O</i> -benzyl carbamate	88	77° ^a
Cyclohexylamine	9	3	<i>N</i> -cyclohexyl <i>O</i> -benzyl carbamate	76	90–91° ^b
4-Aminophenol	6	2	<i>N</i> -(4-hydroxyphenyl) <i>O</i> -benzyl carbamate	95	159–160° ^c
	9 ^d	24	<i>N</i> -(4-hydroxyphenyl) <i>O</i> -benzyl carbamate	95	156–157°
2-Naphthol	10	3	benzyl 2-naphthyl carbonate	63° ^e	71–71.5° ^f
Glycine	9	2	<i>N</i> -benzyloxycarbonylglycine	66	118–120° ^g
L-Tyrosine	10–12	4	<i>N</i> -benzyloxycarbonyl-L-tyrosine	19 ^h	ⁱ
L-Lysine	7.5	3	<i>N</i> ^ε -benzyloxycarbonyl-L-lysine	16	270–273° ^j
			<i>N</i> ^α , <i>N</i> ^ε -di(benzyloxycarbonyl)-L-lysine	19	^k
			<i>N</i> ^α , <i>N</i> ^ε -di(benzyloxycarbonyl)-L-lysine	72	^k

^a Bergstrom, N. C., and Martell, A. E. (*J. Am. Chem. Soc.*, 1945, **67**, 494) give 77°.

^b Colourless plates (from aqueous ethanol) (Found: C, 71.9; H, 7.9; N, 6.2. $C_{14}H_{19}NO_2$ requires C, 72.1; H, 8.2; N, 6.0%).

^c Chabrier, P., Najer, H., and Giudicelli, R. (*Bull. Soc. Chim. Fr.*, 1955, 1353) give 160°.

^d Using 2.5 equiv. of sodium benzyloxycarbonyl thiosulphate.

^e Unchanged 2-naphthol (35%) was recovered.

^f Colourless plates (from methanol) (Found: C, 77.9; H, 5.1. $C_{18}H_{14}O_3$ requires C, 77.7; H, 5.1%).

^g Bergmann, M., and Zervas, L. (*Ber. dt. chem. Ges.*, 1932, **65**, 1192) give 120°.

^h Unchanged L-tyrosine (58%) was recovered.

ⁱ Isolated as the dicyclohexylammonium salt, plates (from ether/ethanol), $[\alpha]_D^{22} + 38.5^\circ$ (c, 2% in ethanol) (Found: N, 5.5. Calc. for $C_{29}H_{40}N_2O_5$: N, 5.6%); m.p. 113–115°, Klieger, E., Schröder, E., and Gibian, H. (*Liebigs Ann.*, 1961, **640**, 157) give 114–115°.

^j Ledger, R., and Stewart, F. H. C. (*Aust. J. Chem.*, 1965, **18**, 933) give 278–280°. Plates (from water), $[\alpha]_D^{22} + 18.4^\circ$ (c, 2%; 2N HCl) (Found: N, 9.6. Calc. for $C_{14}H_{20}N_2O_4$: N, 10.0%).

^k Isolated as the dicyclohexylammonium salt, prisms (from acetone/ethanol), $[\alpha]_D^{22} + 8.0^\circ$ (c, 2% in ethanol) (Found: C, 68.4; H, 8.2; N, 7.1. Calc. for $C_{34}H_{49}N_3O_6$: C, 68.5; H, 8.3; N, 7.1%); m.p. 130–132°, Klieger, Schröder, and Gibian (see¹) give 124–127°.

⁴ Cleve, P. T., *Ber. dt. chem. Ges.*, 1888, **21**, 1099.