## 5-BENZYLTHIOTHIAZOLONE AS A PROTECTING REAGENT FOR AMINES

## F. Edward Roberts

Merck Sharp & Dohme Research Laboratories Division of Merck & Co., Inc. Rahway, New Jersey 07065

5-Benzythiothiazolone ( $\underline{2}$ ) has been found to be an excellent protecting reagent for amines. The compound is easily prepared, reacts in high yield with amines and is removed under mild conditions. Cook, et  $\underline{al}^1$ , first described the synthesis of  $\underline{2}$  and its reactivity with amines. The discovery of a facile cleavage of the amine product ( $\underline{3}$ ) with trifluoroacetic acid makes possible the use of the thiazolone as a protecting group.

When  $\underline{1}$  (one mole) is slurried in ether in the presence of 2 moles of trifluoroacetic anhydride for 1 hr at room temperature 5-benzylthiothiazolone ( $\underline{2}$ ) is formed in high yield. The ether solution is washed with 5% sodium acetate solution to remove trifluoroacetic and the reagent is ready to use<sup>2</sup>.

When the ether solution of  $\underline{2}$  is treated with one mole of amine at room temperature the amide product ( $\underline{3}$ ) crystallizes out after a few minutes. The yield from  $\underline{1}$  to  $\underline{3}$  is in the range of 83-86%. Table I contains a summary of yields for representative amines.

Removal of the protecting group is achieved by dissolving the amide  $\underline{3}$  (1 g) in trifluoro-acetic acid (10 ml) at room temperature<sup>3</sup> for 2 hr. The amide is cleaved and 5-benzylthio-thiazolone  $\underline{2}$  and the amine are regenerated as their trifluoroacetate salts.

$$\emptyset \text{CH}_2 \text{S-C-NHCH}_2 - \text{C-N} \\ R_2 \\ \text{Erifluoroacetic} \\ \text{acid} \\ \text{OCH}_2 \text{S} \\ \text{CH}_2 \\ \text{CH}_2 \\ \text{CH}_2 \\ \text{CH}_2 \\ \text{CH}_2 \\ \text{CH}_2 \\ \text{R}_2 \\ \text{CH}_2 \\ \text{R}_2 \\ \text{CH}_2 \\ \text{R}_2 \\ \text{CH}_2 \\ \text{R}_2 \\ \text{CH}_2 \\$$

Yields for the cleavage step, based on isolation of the amine are shown in the Table. Because of the easy recombination of  $\underline{2}$  and the amine to  $\underline{3}$  upon removal of the trifluoroacetic acid, methanol in ether is added to convert  $\underline{2}$  to the neutral methyl ester  $\underline{4}$ . The amine is then extracted with dilute aqueous hydrochloride acid.

The benzylthiothiazolone reagent has wide applicability and can be used as a protecting reagent for simple amino acids as well as more complex amino acids such as the cephalosporins and the cephanycins.

Table I. Reaction of 5-Benzylthiothiazolone with Amines			
Amine		Yield 1 to $3^4$	Cleavage 3 to Amine
R <sub>1</sub>	$^{R}_{2}$		
ØСН <sub>2</sub>	Н	86%	77% <sup>5a</sup>
CH <sub>2</sub> CO <sub>3</sub> Et	Н	86%	95% <sup>5</sup> b
<u>p</u> -c1ø	Н	86%	93% <sup>5C</sup>
ØCH <sub>2</sub>	Øсн <sub>2</sub>	83%	75 <sup>5d</sup>

## References and Notes

- 1. A. H. Cook, G. Harris, I. Heilbron and G. Shaw, <u>J. Chem. Soc.</u>, (1948), 1056.
- 2. Although ether solutions of 2 were stable for several days, Cook, et al. (See reference 1) report 5-benzylthiothiazolone as an unstable solid (m.p. 45°) which darkens and decomposes on exposure to air.
- 3. The amide from p-chloroaniline required warming to  $40-50^{\circ}$  to effect solution.
- All new compounds had correct elemental analysis and gave nmr and mass spectral data in accord with the structures listed.
- 5. (a) Isolated and identified as its benzoyl derivative; (b) isolated and identified as glycine hydrochloride; (c) isolated as the free amine; (d) isolated as free amine and identified as the hydrochloride.
- 6. Unpublished results from these laboratories.

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