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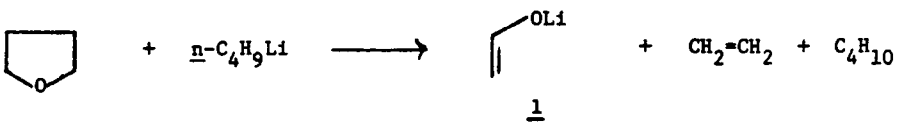
A FACILE PREPARATION OF A VOC REAGENT: VINYL PHENYLTHIOCARBONATE

Angelina J. Duggan* and F. Edward Roberts
Merck Sharp and Dohme Research Laboratories
Rahway, New Jersey 07065

The vinyloxycarbonyl unit has been demonstrated by Olofson to be a useful moiety in the N-dealkylation of tertiary amines,[1] N-protection of amino acids[2], and in the protection of phenols.[1c] However, its introduction via vinyl chloroformate (5), VOC-Cl, suffers from the difficulty in preparing pure vinyl chloroformate from either the gas phase decomposition of ethylene glycol bis(chloroformate)[3], or by acylation of enolates with phosgene.[4] Herein, we describe the synthesis and utility of vinyl phenylthiocarbonate, VOC-SPh, a useful alternative for the introduction of the VOC protective group into amino acids.

Bates[5] has shown that the lithium enolate of acetaldehyde (1) is formed by the action of n-butyllithium on tetrahydrofuran at room temperature. Ethylene and butane are generated as by-products.



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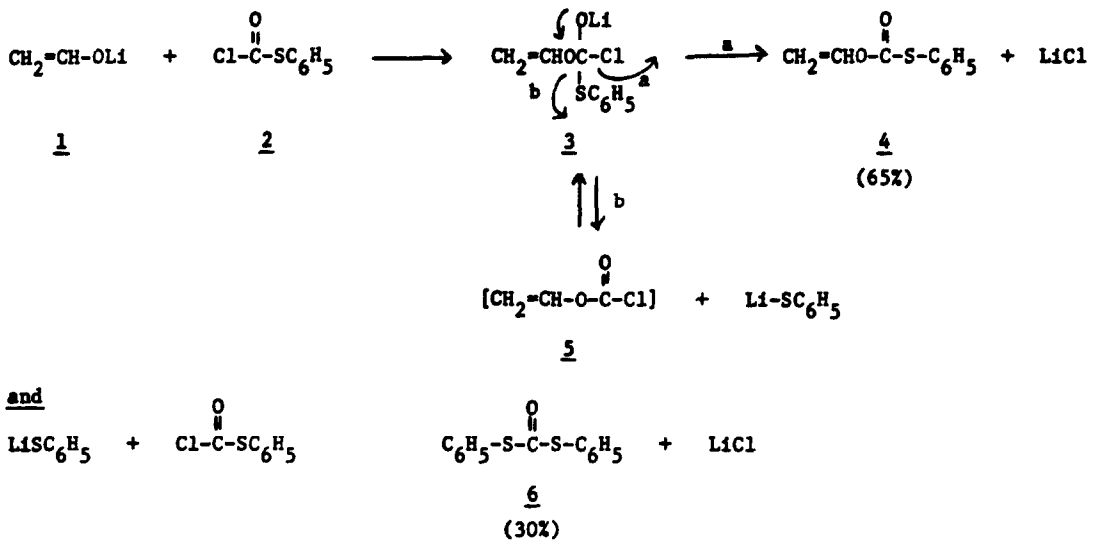
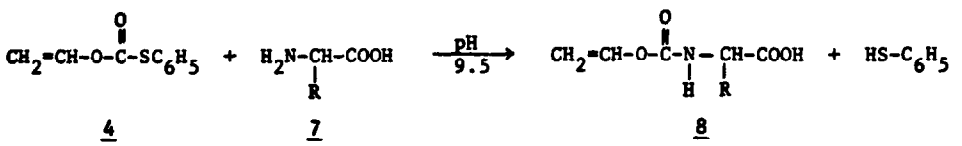
Recently Jung has demonstrated that the acetaldehyde enolate, generated in the manner of Bates, can be utilized to effect either alkylation or acylation.[6] Similarly, we have found that acylation with phenyl thiochloroformate (2) affords vinyl phenylthiocarbonate (4) in 65% isolated yield. A major but not serious side-product, diphenylthiocarbonate (6),[7] is formed in 30% during the reaction. A possible mechanism for the formation of 4 and 6 is illustrated below:



Neat vinyl phenylthiocarbonate does not polymerize at room temperature or upon distillation. It is stable towards light and no decomposition was observed in deuterochloroform solution (NMR) after one week. Although the reagent is stable to aqueous base, it reacts readily with amino acids at pH 9.5. The preferred leaving group in the nitrogen displacement reaction is the -SPh, not the $-OCH=CH_2$. The only products isolated were thiophenol and a vinyl carbamate, i.e. a VOC-AA (8)[8] in good yield. Table I illustrates the preparation of some representative VOC-AA's.

TABLE I

Preparation of VOC AA From Vinyl Phenylthiocarbonate



Amino Acid	Product	Yield[a,b]
Glycine (7a)	VOC-glycine (8a)	80%
L-Phenylalanine (7b)	VOC-Phenylalanine (8b)	60%
L-Proline (7c)	VOC-Proline (8c)	77%
Glycylglycine (7d)	VOC-glycylglycine (8d)	50%

a. Each product was one spot on TLC. IR, NMR and MS data were in accord with the proposed structure. b. The reaction was performed in 2:1 dioxane-water, maintained at pH 9.5 with $N(Et)_3$.

The reaction proceeds most efficiently[9] in solvent systems, such as dioxane-water or DMF-water, which afford the proper polarity for concurrent solubility of the VOC-SPhenyl and the amino acid. Bases such as triethylamine were found to be superior to aqueous buffer (tetraborate pH 9.7).

Studies are in progress to further assess the reactivity of vinyl phenylthiocarbonate.

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Experimental

Vinyl phenylthiocarbonate (4). n-Butyllithium (0.173 mol, 71 mL of a 2.45 M solution in hexane) was added rapidly at < 35°C to dry THF (130 mL) maintained under N_2. The reaction was heated at 35°C for 2 h cooled at room temp for 1 h, and transferred rapidly via a cannula to 28.5 g (0.165 mol) of phenyl thiochloroformate/80 mL of THF (which contained a few crystals of hydroquinone) at -40 to -45°C. The reaction was stirred at -45° for 1 h, quenched with 100 mL of saturated NaCl, and warmed to room temperature. The aqueous layer was extracted with 50 mL of hexane and the combined organic layers were dried over Na_2SO_4 and concentrated to afford 29.3 g of a yellow oil which was a ∿ 2:1 mixture of 4:6. Distillation, 67-69°C (.4 torr), afforded 19.3 g (65%) of 4 as a colorless oil. 4: IR ($CHCl_3$): 3100, 2975, 1740, 1650 cm^{-1}; NMR (100 HMz, $CDCl_3$): δ 4.65 (1 H, d, d, J = 4 and J = 1 Hz), 4.85 (1 H, d, d, J = 7 and J = 1 hz), 7.25 (1 H, d, d, J = 7 and J = 3 Hz), 7.67-7.40 (5 H, m); MS: 180, 109, 137, 43.

Anal. calcd for $C_9H_8O_2S$: C, 59.98; H, 4.47; S, 17.79. Found: C, 59.39; H, 4.52; S, 17.79.

Vinyloxycarbonylglycine (8a): Vinyl phenylthiocarbonate (4), 4.43 g (0.0246 mol)/50 mL dioxane, was added to 1.85 g (0.0246 mol) of glycine/40 mL H_2O. The pH was maintained at 9.5 with $N(Et)_3$ for 16 h at room temperature. The reaction was acidified to pH 5.8 with 5N HCl and extracted 4 x 30 mL of hexane to remove the thiophenol. The aqueous was then acidified to pH 2, saturated with NaCl, and stirred to remove the thiophenol. The aqueous was then acidified to pH 2, saturated with NaCl, and stirred 15 min with 3 x 50 mL of EtOAc. The combined EtOAc extracts were dried over Na_2SO_4 and concentrated to afford 2.89 g (78%) of the VOC glycine (8a), m.p. 90-91°C (Lit[2] 95-96°C). Recrystallization from CH_2Cl_2-hexane afforded crystals, m.p. 94-96°C. 8a: IR ($CHCl_3$): 3500, 3400, 2975, 1750, 1700, 1575, 1550 cm^{-1}; NMR (100 MHz, d_6DMSO): δ 3.65 (2 H, d, J = 3 Hz), 4.45 (1 H, d, d, J = 3 and J = 1 Hz), 4.75 (1 H, d, d, J = 7 and J = 1 Hz), 7.08 (1 H, d, d, J = 7 and J = 3 Hz), CIMS:203 (M + 1), 159, 128.

Anal. calcd for $C_5H_7O_4N$: C, 41.38; H, 4.88; N, 9.65. Found: C, 41.56; H, 4.94; N, 9.33.

References and Notes

1. (a) R. A. Olofson, R. C. Schnur, L. Bunes and J. P. Pepe, Tetrahedron Lett., 1567 (1977). (b) R. A. Olofson and J. P. Pepe, Tetrahedron Lett., 1575 (1977) and (c) R. A. Olofson and R. C. Schnur, Tetrahedron Lett., 1571 (1977).

2. R. A. Olofson, Y. S. Yamamoto, and D. J. Wancowicz, Tetrahedron Lett., 1563 (1977).

3. (a) F. E. Kung, U. S. Patent 2,377,085 (1945) and (b) L.-H. Lee, J. Org. Chem., 30, 3943 (1965). Ethylene glycol bis (chloroformate) is pyrolyzed in a nitrogen stream at 480°C[3a] to afford a complex mixture of products: vinyl chloride; 1,1-dichloroethane; 1,2-dichloroethane; 1-chloroethyl chloroformate; 2-chloroethyl chloroformate; the desired product vinyl chloroformate (5), and unreacted ethylene glycol bis (chloroformate). The vinyl chloroformate, a lacrymator, (yield 30-40%, b.p. 67-69°C) is separated from the other pyrolyses components after repeated distillation of the low boiling fractions.

4. Although isopropenyl chloroformate has been prepared (86% distilled pure) from phosgene and diacetonyl mercury, only impure solutions containing some VOC-Cl could be obtained from the similar acylation of mercuridiacetaldehyde. Treatment of either sodium or lithium enolates of ketones and aldehydes with phosgene did not afford enol chloroformates.

5. R. B. Bates, L. M. Kroposki and D. E. Potter, J. Org. Chem., 37, 560 (1972) and references cited therein.

6. M. E. Jung, R. B. Blum, Tetrahedron Letters, 3791 (1977).

7. The diphenylthiocarbonate, which was not present in the phenyl thiochloroformate, is readily separated from the more volatile and less polar vinyl phenylthiocarbonate by either distillation or column chromatography on silica gel (eluting with ether-hexane mixtures).

8. A detailed discussion of VOC deprotection is described in reference 2. The action of either HCl, HBr, or Br_2 on VOC-AA generates an unstable saturated adduct which upon treatment with alcohol liberates the amino acid salt, CO_2 and the acylal.

9. The reaction proceeds in $\sim$ 16 h at ambient temperatures. At warmer temperatures (30-35°C) the reaction is complete in a few hours.

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