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A FACILE SYNTHESIS OF PRIMARY AMINES FROM CARBOXYLIC ACIDS BY THE CURTIUS REARRANGEMENT

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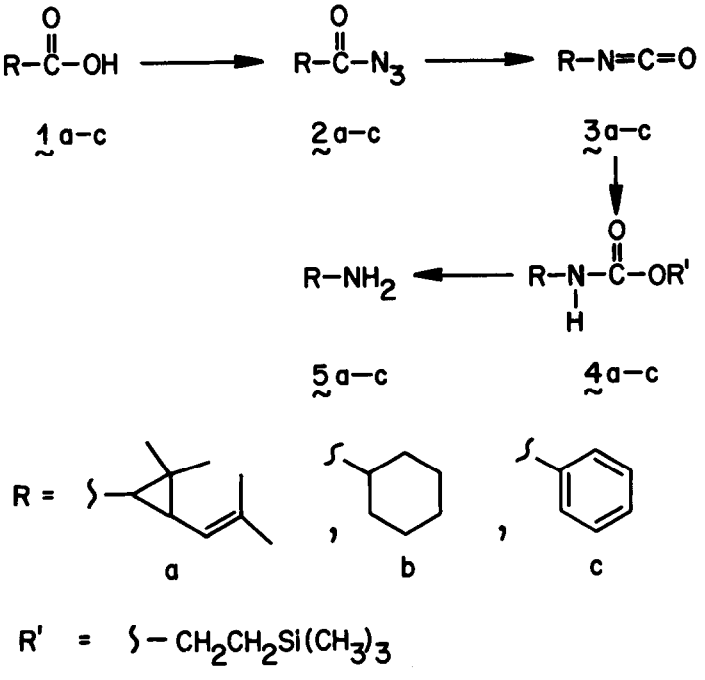
Abstract. 2-Trimethylsilylethanol was used to trap isocyanates produced by the Curtius rearrangement of acyl azides and the resulting trimethylsilylethyl carbamates were readily cleaved with tetra-n-butylammonium fluoride to liberate the primary amines.

The Curtius rearrangement is a commonly used reaction for the synthesis of primary amines from carboxylic acids by the general sequence of reactions shown below.[1] Although many



successful examples are known, problems are often encountered during the conversion of penultimate carbamate 4 to the final product, especially when the R-group is not compatible with the vigorous conditions needed to hydrolyze 4 or R contains unsaturation that precludes cleavage by hydrogenolysis when R' is benzyl. During the synthesis of amines to be used as reactive intermediate inhibitors of enzymes in the isoprenoid biosynthetic pathway,[2] we encountered considerable difficulty with cyclopropyl and polyunsaturated systems. Base catalyzed hydrolysis gave substantial amounts of N-substituted ureas and treatment with acidic reagents including trimethylsilyl halides,[3,4] resulted in low recoveries of the desired amines for a variety of R' derivatives. We were also unsuccessful in removing the benzyl moiety from olefinic carbamates using a variety of procedures, including transfer hydrogenation,[5] without some concommittant reduction of double bonds.

The procedure we now report is based on work by Carpino and co-workers in which the trimethylsilylethyl moiety in carbamate-containing polymers was cleaved to give polyamines.[6] Carboxylic acids 1a-c were converted to isocyanates by the standard acid → acid chloride → acyl azide → isocyanate three-step sequence or by the more convenient one-pot procedure reported by Shioiri, Ninomiya, and Yamada.[7] Addition of trimethylsilylethanol, followed by heating at 80°, gave carbamates 4a-c in good yields after purification by flash chromatography on silica gel.[8] The carbamates were cleaved with tetra-n-butylammonium fluoride at 50°C, and the amines were isolated directly or as hydrochloride salts. Overall yields from carboxylic acids to primary amines ranged from 68% to 85%. All new compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and combustion analysis. The results are summarized in Table I. The procedures described for 4a - 5a in the following paragraphs are typical.

Table I. Synthesis of Amines from Carboxylic Acids

Acid	Acid → Carbamate (% yield)	Carbamate → Amine (% yield)	Overall (% yield)
1a	86[a], 97[b]	79	68[a], 77[b]
2a	91	93	85
3a	90	88	79

[a] Procedure a (see experimental) [b] Procedure b (see experimental)

N-Carboxytrimethylsilylethyl-N-[2,2-dimethyl-3-(2'-methyl-1'-propenyl)]cyclopropyl amine (4a). Procedure a. The one-pot conversion of acid 1a to carbamate 4a was based on the procedure reported by Shioiri and coworkers.[7] trans-Chrysanthemic acid (0.50 g, 3.0 mmol) was dissolved in 2 mL of toluene and 0.30 g (3.0 mmol) of triethylamine was added. A nitrogen atmosphere was used to exclude moisture from the flask. Diphenylphosphoryl azide (0.82 g, 3.0 mmol) was added, and the resulting solution was heated to 80°C with stirring. Evolution of nitrogen began immediately. After 2 h, 0.71 g (6.0 mmol) of 2-trimethylsilylethanol was added and stirring at 80° was continued for 6 h. Toluene was removed under reduced pressure. The residue was dissolved in 20 mL of diethyl ether and the resulting solution was extracted with dilute aqueous sodium hydroxide. The ether layer was dried over anhydrous magnesium sulfate and filtered. Solvent was removed at reduced pressure to afford a pale yellow oil. Purification by flash chromatography (7:3 hexanes:ether, Merck silica gel, grade 60) yielded 0.72 g (86%) of a clear, viscous oil; IR (neat) 3300, 2940, 2910, 1700, 1510, 1450, 1410, 1370, 1327, 1246, 1225, 1170, 1148, 1050, 940 (br), 852, 830, 765, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.1 (s, 9), 1.08 (s, 3), 1.1 (m, 3), 1.17 (s, 3), 1.73 (s, 3), 1.77 (s, 3), 2.3 (m, 1), 4.18 (t, 2, J = 8 Hz), 4.73 (s, 1), 4.89 (d, 1, J = 7.5 Hz).

Procedure b. trans-Chrysanthemic acid (0.51 g, 3.0 mmol) was dissolved in 5 mL of toluene. As described in procedure a, a nitrogen atmosphere was used to exclude moisture. The solution was stirred at room temperature while 0.46 g (3.6 mmol) of oxalyl chloride was added by syringe. After 30 min, evolution of gas had ceased and solvent was removed at reduced pressure. The residual pale yellow viscous oil was dissolved in 16 mL of anhydrous acetone, and the resulting solution was added dropwise to a rapidly stirred solution of 0.70 g (11 mmol) of sodium azide in 2.3 mL of water at 0°C. After 15 min, 20 mL of hexanes and 20 mL of water were added. The hexane layer was removed and the aqueous layer extracted again. The organic layer was dried over magnesium sulfate. After filtration and removal of solvent under reduced pressure, the acyl azide was dissolved in 6 mL of toluene. The solution was heated to 80°C with stirring. Evolution of nitrogen began immediately. After 1 h, 0.71 g (6 mmol) of 2-trimethylsilylethanol was added and stirring at 80°C was continued for 6 h. The toluene was removed under reduced pressure. The product was purified as described in procedure a to yield 0.78 g (91%) of carbamate 4a.

2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropyl amine (5a). Carbamate 4a (0.18 g, 0.64 mmol) was heated with 2.54 mL of 1 M tetra-n-butylammonium fluoride in tetrahydrofuran at 50°C for 30 min. The mixture was allowed to cool to room temperature and solvent was removed at reduced pressure. The residue was dissolved in 5 mL of pentane. Water (5 mL) was added and the layers were mixed by rapid stirring for 15 min. The pentane layer was extracted with saturated

ammonium chloride solution and dried over magnesium sulfate. After filtration, solvent was removed to yield 69 mg (79%) of a colorless oil; IR (neat) 3360, 3280, 2955, 2910, 2850, 1605, 1442, 1415, 1368, 1145, 1110, 960, 830 (br), and 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 3), 1.0 (m, 1), 1.16 (s, 3), 1.53 (s, 2), 1.66 (s, 6), 1.96 (d, 1, J = 3 Hz), 4.81 (d, 1, J = 7.5 Hz).

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