

The β -(Trimethylsilyl)ethoxycarbonyl Amino-protecting Group

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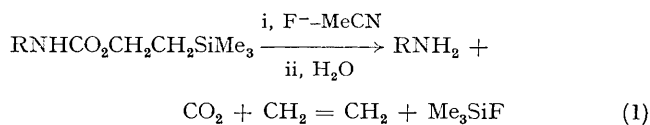
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Summary The β -(trimethylsilyl)ethoxycarbonyl amino-protecting group is de-blocked in acetonitrile at 50 °C by the specific reagent tetraethylammonium fluoride with the formation of gaseous by-products.

We report the first of a new family of novel amino-protecting groups based on the specific fluoride ion-induced fragmentation of the β -(trimethylsilyl)ethoxycarbonyl (TEOC) group. Most base-sensitive¹ amino-protecting groups generate high molecular weight by-products, the removal of which can, in some cases, present tedious separation problems.

Among acid-sensitive groups the t-butoxycarbonyl (t-BOC) group¹ is unique in generating a stream of volatile by-products and this, aside from the mildness of the de-blocking conditions required, is one of its major advantages over related alkoxy carbonyl functions. We have now developed a base-sensitive group which gives an analogous stream of gaseous by-products on cleavage.

In dipolar aprotic solvents the TEOC group suffers fragmentation on treatment with fluoride ion [equation (1)].^{2†} The most convenient solvent proved to be acetonitrile although other solvents such as Me₂SO, hexamethyl-



phosphoric triamide, dimethylformamide, and tetrahydrofuran could be used. Initially the carbamate RNHCO₂⁻ (1) is formed which is spontaneously decomposed by the addition of water. Introduction of the TEOC group is easily carried out *via* the known chloroformate³ Me₃Si-CH₂CH₂O₂CX (2; X=Cl) or the azidoformate (2; X=N₃) which can be obtained by the standard technique from β -trimethylsilylethanol.‡

† The gases evolved were shown to consist of trimethylsilyl fluoride, b.p. 16 °C, which was identified by its i.r. and n.m.r. spectra and ethylene identified as 1,2-dibromoethane.

‡ The general method previously developed for t-butyl azidoformate (L. A. Carpino, P. J. Crowley, C. A. Giza, and P. H. Terry, *Org. Synth.*, Coll. Vol. 5, 1973, 157) was adapted for the preparation of (2; X=N₃), b.p. 83.5 °C at 15 mmHg; ¹H n.m.r. (CCl₄): δ 0.0 (s, 9H, Me₃Si); 0.95 (t, 2H, CH₂Si), and 4.25 (t, 2H, CH₂O). Because the chloroformate decomposed on standing, the azidoformate was more generally useful as an acylating agent. The latter reacted normally with glycine and ethyl glycinate.

TABLE. Cleavage of $p\text{-ClC}_6\text{H}_4\text{NHCO}_2\text{CH}_2\text{CH}_2\text{SiMe}_3$.^a

Reagent	Solvent	Temp./°C	Time/h	Yield of $p\text{-ClC}_6\text{H}_4\text{NH}_2$ /%
Et ₄ NF ^b	MeCN	50—55	4	94
Et ₄ NF ^b	MeCN	25	64	88
KF	Me ₂ SO	56	12	70
KF	Me ₂ SO	25	68	50
MeCO ₂ H	—	25	264	0
CF ₃ CO ₂ H	—	25	0.08	100
HCl	MeNO ₂	25	0.033	100
H ₂ -Pd(C)	MeOH-HOAc	25	24	0

^a Prepared by treatment of p -chlorophenyl isocyanate with β -trimethylsilylethanol or reaction of β -trimethylsilylethyl chloroformate or the corresponding azidoformate with p -chloroaniline, m.p. 103—103.5 °C. ^b Commercial tetraethylammonium fluoride hydrate (Eastman Kodak Co.) was dried over P₂O₅ before use.

To date the most efficient source of fluoride ion has proved to be tetraethylammonium fluoride in acetonitrile (4—5 h at *ca.* 50 °C; if desired the reaction can be carried out at room temperature over a longer period).

The less expensive reagent, KF, was ineffective in acetonitrile although in Me₂SO cleavage occurred slowly, even at room temperature. Specific conditions are presented in the Table. The de-blocking reaction could be easily followed kinetically by disappearance of the n.m.r. signal due to the trimethylsilyl group. Polymeric substrates protected by the TEOC group are deblocked by tetraethylammonium fluoride at rates only slightly less than those observed for low molecular weight compounds. For poly(β -trimethylsilylethyl- N -vinyl carbamate)[§] and the corresponding N -isopropyl analogue the half-lives in acetonitrile at 58 °C were *ca.* 45 and 30 min, respectively. In the case of the polymer no residual silicon could be detected by elemental analysis after 4 h. Previously, clean de-blocking of urethanes derived from polyvinylamine has only been possible under acidic conditions.⁴

Relative to conditions often employed to cleave the most

commonly used amino-protecting groups, the TEOC group is stable towards catalytic hydrogenation over palladium-carbon and towards common basic reagents (*e.g.*, piperidine, ethanolamine, and liquid ammonia)[¶] but is rapidly and cleanly de-blocked by trifluoroacetic acid. Although this sensitivity toward acids makes it impossible to use this group in conjunction with t -BOC and related acid-sensitive functions, if prior removal of the latter is desired, it is in itself remarkable that a urethane derived from a primary alcohol undergoes acid-induced cleavage as readily as the t -BOC system. Carbon-metal σ - π conjugation involving the β -silyl function is presumably responsible for this unusual effect.⁵

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[§] Treatment of vinyl isocyanate with β -trimethylsilylethanol gave the carbamate, m.p. 48—49 °C; ¹H n.m.r. (CCl₄): δ 0.0 (s, 9H), 0.9 (t, 2H), 4—4.5 (m, 4H), and 6.2—7 (m, 2H), which was polymerized in dioxan in the presence of 0.5 mol % azoisobutyronitrile. The resulting polymer, obtained as a colourless powder by precipitation from dioxan by the addition of water, was estimated from viscosity measurements to have a molecular weight of *ca.* 40,000.

[¶] Basic hydrolysis (KOH in HO-EtOH) is slow at room temperature but extensive after 2—3 days or at elevated temperatures.

¹ For a brief review, see: L. A. Carpino, *Accounts Chem. Res.*, 1973, **6**, 191; L. A. Carpino and G. Y. Han, *J. Org. Chem.*, 1972, **37**, 3404.

² Cf. E. J. Corey and B. B. Snider, *J. Amer. Chem. Soc.*, 1972, **94**, 2549; R. F. Cunico and E. M. Dexheimer, *J. Organometallic Chem.*, 1973, **59**, 153; *J. Amer. Chem. Soc.*, 1972, **94**, 2868; T. H. Chan and W. Mychajlowski, *Tetrahedron Letters*, 1974, **171**, 3479; S. S. Washburne, *J. Organometallic Chem.*, 1974, **83**, 155; G. I. Tesser, J. T. W. A. R. M. Buis, E. Th. M. Wolters, E. G. A. M. Bothe-Helmes, and G. Teutsch, *Tetrahedron*, 1976, **32**, 1069, 1971.

³ V. P. Kozukov, V. D. Sheludyakov, and V. F. Mironov, *Zhur Obshchei Khim.*, 1968, **38**, 1179. The β -trimethylsilylethanol was prepared by reduction [A. W. P. Jarvie, A. Holt, and J. Thompson, *J. Chem. Soc. (B)*, 1969, 852] of the corresponding silylacetate (R. J. Fessenden and J. S. Fessenden, *J. Org. Chem.*, 1967, **32**, 3535).

⁴ R. Hart, *Makromol. Chem.*, 1959, **32**, 51.

⁵ For a review of the unusual ' β -effect' of organosilicon compounds, see: A. W. P. Jarvie, *Organometallic Chem. Rev. (A)*, 1970, **6**, 153.