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SILICON IN SYNTHESIS: STABASE ADDUCTS - A NEW PRIMARY AMINE PROTECTING GROUP: ALKYLATION OF ETHYL GLYCINATE

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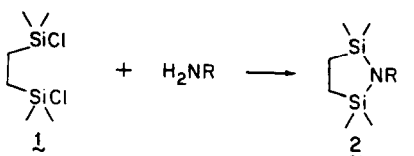
Summary. A new silicon-based protecting group for primary amines has been developed. Its usefulness is illustrated in a simple synthesis of an alkylated amino acid derivative.

As part of a study of alkaloid synthesis we required a protecting group for a primary amine that was stable to organolithium reagents and amide bases, yet could be removed to expose the primary amino group under extremely mild conditions. We reasoned that ideally a cyclic version of hexamethyldisilazane could fulfil the above requirements, in particular a cyclic array would benefit entropically, and consequently be more stable than hexamethyldisilazane systems.[1] To achieve the synthesis of cyclic disilazanes (tied back hexamethyldisilazane derivatives) we required the disilyl reagent 1,1,4,4,-tetramethyl-1,4-dichlorodisilethylene 1. Fortunately, this reagent is readily available since it has been used as a cross-linking agent in polymer chemistry.[2]

Here we report the use of this crystalline reagent for the synthesis of tetramethyldisilylazacyclopentane adducts 2; conveniently abbreviated to STABASE adducts,[3] and some of their properties.

For primary amines with pKa's in the range 10-11, it is sufficient to treat the amine with 1 in dichloromethane, in the presence of triethylamine (2 equiv.) at room temperature, followed by work-up with aqueous sodium dihydrogen phosphate, to give the stabase adducts 2, in excellent yields.



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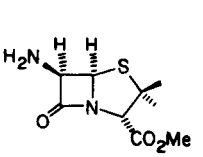

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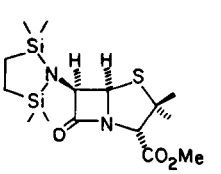

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AMINE (RNH_2)/ADDUCT(2)	YIELD(%)	bp/mp
R = cyclohexyl	95	8-12°C
R = benzyl	90	94-98°C (0.035 mm)
R = morpholino	91	114°C (0.25mmHg)
R = n-butyl	85	109-111°C (0.15mm Hg)
R = N,N-dimethylamino	100(ca 5% impure)	Ref. 4
R = p-IC_6H_4	89	viscous oil
R = $-CH_2CO_2Et$	92	80-2°C (0.25mm Hg)

For less basic primary amines pKa 4-5 more vigorous conditions are required to form the stabase adducts (n-BuLi / Et_2O / -78°C).

AMINE (RNH_2)/ADDUCT(2)	YIELD(%)	bp/mp
R = p-MeC_6H_4	60	mp 20-24°C
R = o-MeC_6H_4	72	153°C (0.2 mmHg)
R = p-BrC_6H_4	74	160°C (0.4 mmHg)
R = p-$MeOC_6H_4$	77	137-140°C (0.07mm Hg)
R = m-MeC_6H_4	79	128-131°C (0.07mmHg)

Representative Experimental Procedures

a) Triethylamine as base

A solution of 1,1,4,4-tetramethyl-1,4-dichlorosilethylene (1.8 g, 8 mmol) in anhydrous dichloromethane (3 cm^3) was added via a syringe to a stirred solution of ethyl glycinate (0.75 g, 8 mmol) in dichloromethane (5 cm^3) containing triethylamine (2 equiv.). The mixture was stirred, under argon at room temperature for 2 hours and then poured into aqueous sodium dihydrogen phosphate (5 cm^3).[9] The pure stabase adduct was obtained by distillation 1.86 g, (92%), bp. 80-82°C (0.25 mm Hg). NMR δ (CCl_4) 4.1 (2H, q, $-\underline{CH_2}CH_3$), 3.5 (2H, s, $-\underline{CH_2}-N$), 1.3 (3H, t, $-CH_2\underline{CH_3}$), 0.7 (2H, s, $-Si-\underline{CH_2}-$), 0.0 (12H, s, $-Si-\underline{CH_3}$). IR (tf) 1725, 1250 and 800 cm^{-1}. M.S. calculated for $C_{10}H_{23}NO_2Si_2$ 245.126, found 245.127. Anal. found: C, 48.76; H, 9.59; N, 5.50. $C_{10}H_{23}NO_2Si_2$ required C, 49.0; H, 9.4; N, 5.7.

b) n-Butyl lithium as base

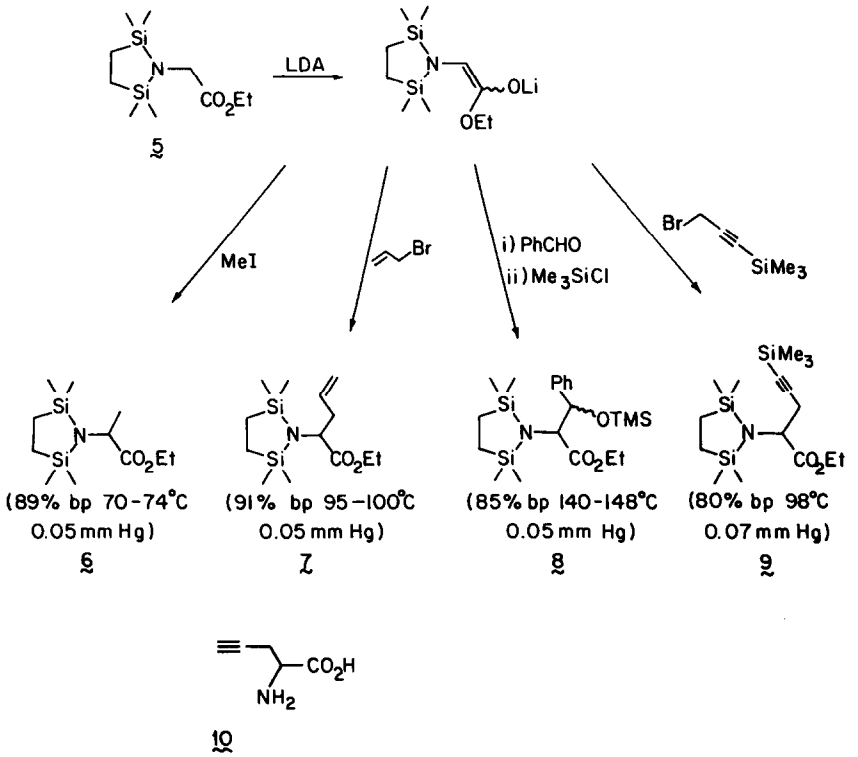
A solution of n-butyl lithium in hexane (1.5 M, 2.1 cm^3, 2.1 equiv.) was added via a syringe to a stirred solution of p-toluidine (0.5 g, 4.66 mmol) in anhydrous THF (10 cm^3) under argon. The reaction mixture was warmed to -40°C and then recooled to -78°C. A solution of 1,1,4,4-tetramethyl-1,4-dichlorosilethylene (1.0 g, 4.66 mmol) in THF (10 cm^3) was then added slowly to the reaction mixture. The reaction mixture was then allowed to warm slowly to room temperature and then poured into water. The solution was diluted with ether (20 cm^3) and the ether layer separated. The aqueous layer was washed with two further portions of ether (2x15 cm^3) and the ethereal extracts combined. Evaporation of the dried (Na_2SO_4) solvent in vacuo afforded a yellow oil which NMR showed to be > 95% pure. Yield 60%. The oil could be crystallized from petroleum ether (30°-40°C) and sublimed at 0.15 torr (25°C). NMR δ (CCl_4, PhH as internal standard) 6.74 (4H, aromatic Hs), 2.35 (s, 3H), 0.93 (s, 4H), 0.23 (s, 12H). IR (tf) 1230, 960 and 920 cm^{-1}. M/e calculated 249.1368, observed 249.1375.

The adducts 2 are stable to the following reagents - n-BuLi (THF -25°C), s-BuLi (Et_2O -25°C); lithium diisopropylamine; saturated aqueous ammonium chloride; H_2O; MeOH; 2N $NaHCO_3$; pyridinium dichromate/CH_2Cl_2; KF. $2H_2O$/THF/H_2O; saturated aqueous sodium dihydrogen phosphate.

The adducts 2 are unstable to the following reagents - 0•1N HCl, 1N KOH, 75% aqueous AcOH, 0•1N AcOH, $NaBH_4$/EtOH, pyridinium chlorochromate/CH_2Cl_2.

6-Aminopenicillanic acid methyl ester 3[5] required prolonged treatment (15 h.) with 1, in the presence of triethylamine to form the adduct 4 (75%). Interestingly, the H^1 NMR of 4 showed that the methyl and methylene groups attached to the Si- atoms to be non-equivalent at 25°C. Free rotation about the bulky 6-stabase group is prohibited.

To illustrate the synthetic utility of the methodology developed above, the stabase adduct with ethyl glycinate 5 was treated with lithium diisopropylamine/THF/-78°C, and the resulting ester enolate quenched with various electrophiles to furnish the amino ester derivatives 6-9 listed below (Scheme).[6] It should be noted that the stabase adducts can be isolated intact from the aqueous work-up, and purified by distillation.



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As an example of the synthetic utility of the stabase adduct, the acetylenic glycinate 9 was treated with 10% aqueous potassium hydroxide in methanol at reflux for 24 h., and the crude product chromatographed over the cation exchange resin A9 50W-X4 (200-400 mesh) eluting first with water, then 20% aqueous pyridine, to give racemic 2-amino-4-pentynoic acid 10,[7] m.p. 235°-237°C (dec.) (from aqueous EtOH/Acetone),(identical, ir, ms, tlc with an authentic sample), an antimetabolite of L-methionine and L-leucine.[8]

We anticipate that the reagent 1 will find other uses in synthesis.

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References

1. See, for example, King, F. D.; and Walton, D. R. M.; J.C.S. Chem. Commun., 1974, 256.

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4. The stabase adduct of N,N-dimethylhydrazine decomposed upon attempted distillation.

5. We thank Eli Lilly and Co. for a sample of 6-APA and Dr. R. Cooper for details of the preparation of 6-APA methyl ester from 6-APA.

6. For examples of aminoacid-ester alkyation see-Shanzer, A.; Somekh, L.; and Butina, D.; J. Org. Chem., 1979, 44, 3967; Ruehlmann, K.: Kaufmann, K. D.; and Ickert, K.; Z. Chem., 1970, 10, 393; For references to the alkylation of protected amino acid ester enolates see: Stork, G.; Leong, A. Y. W.; and Touzin, A. M.; J. Org. Chem., 1976, 41, 3491; Fitt, J. J.; and Gschwend, H. W.; Ibid., 1977, 42, 2639; Oguri, T.; Shioiri, T.; and Yamada, S.; Chem. and Pharm. Bull. (Japan), 1977, 25, 2287; Bey, P.; and Vevert, J. P., Tetrahedron Letters, 1977, 1455; Yamada, S. I.; Oguri, T.; and Shioiri, T.; J.C.S. Chem. Commun., 1976, 136; For other alkylation methods see: Krapcho, A. P.; and Dundulis, E. Q.; Tetrahedron Letters, 1976, 2205; Schollkopf, U.; and Hoppe, D.; Angew. Chem. Int. Ed., 1970, 9, 459.

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9. An alternative (and very convenient) method of work-up involved the filtering of the reaction mixture through sintered glass followed by evaporation of the solvent in vacuo. The residue was taken up into light petroleum (15 cm^3), refiltered and the solvent removed to afford almost pure stabase adduct.

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