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Sterically shielded secondary *N*-tritylamines and *N*-tritylamide bases, readily available and useful synthetic reagents

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Abstract

t-Butyltritylamine (**1**) and lithium *t*-butyltritylamide (**2**) are introduced as readily available and useful superhindered bases.

Amide bases such as lithium diisopropylamide and lithium 2,2,6,6-tetramethylpiperidide have been much used and exceedingly valuable bases in synthesis because of their solubility, basicity and steric bulk.[1] They are the principal reagents used for the stereoselective conversion of monosubstituted acetate esters RCH_2COOR' into *transoid* lithium enolates (R and OLi *trans*) and derived silyl ethers. The more bulky the dialkylamide base, the greater is the predominance of the *transoid* product, with the highest selectivities attained using the reagents lithium di-*t*-butylamide and *t*-octyl-*t*-butylamide (typically 98:2, *transoid*:*cisoid*).[2,3] Surprisingly, these last two bases, although highly selective and readily made, have not come into common use — possibly because they are not commercially available. We describe herein the synthesis of a new series of hindered amide bases incorporating the triphenylmethyl (trityl) group which can be made very simply and economically in a single step and which are potentially cheap commercial reagents.

The trityl group is a unique carbogenic substituent in the sense that it has the largest 'cone angle' compared to common tertiary groups and is readily introduced as the trityl cation at a nucleophilic site. It was astonishing to us that *N*-trityl derivatives of *t*-alkylamines apparently have never been reported. In contrast, ditrityl ether (C–O–C angle, 128°)[4] and ditritylmethane (C–CH_2–C angle, 129°)[5] are both known as geared molecules from X-ray studies which indicate substantial sterically-induced broadening of the key central angle from the normal values for ROR or RCH_2R.

N-*t*-Butyl-*N*-tritylamine (TBTA) (**1**) was synthesized simply and in good yield by reaction of trityl chloride and *t*-butylamine at room temperature in chloroform and obtained as crystalline solid, mp 90–91°C.[6] X-Ray diffraction analysis revealed the structure shown in Fig. 1. As expected the C–N–C angle of **1** was enlarged (to 125°) and there was gearing of methyl and phenyl groups. Reaction of **1**

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with *n*-butyllithium (1 equiv.) in THF produced a solution of lithium *t*-butyltritylamide (LTBTA) (**2**). Sequential treatment of **2** in THF at −78°C with trimethylsilyl chloride and a series of α-substituted acetic esters produced selectively the *E*-trimethylsilyl ketene acetals (**3**) as summarized in Table 1, which includes α-aryloxyacetic esters that normally show a strong tendency to form *cisoid* enolates.[7]

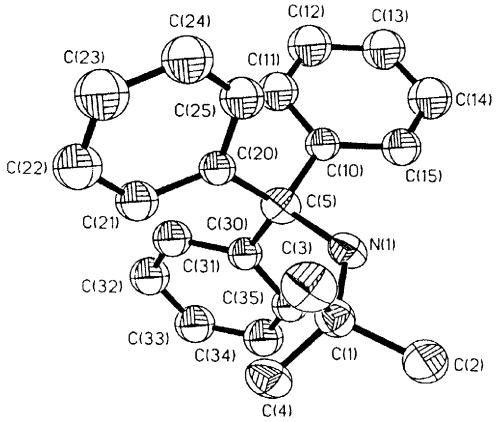
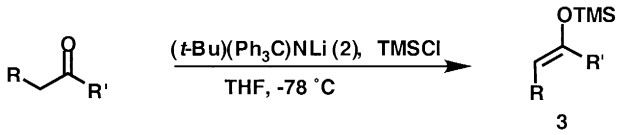
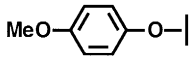
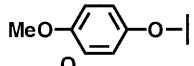
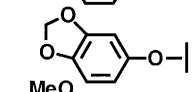
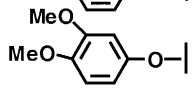
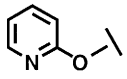


Fig. 1.

Table 1



3

Entry	R	R'	3, *E* / *Z*[a]	Yield (%)[b]
1		O*t*-Bu	14 / 1	62
2		NMe_2	4 / 1	70
3		O*t*-Bu	15 / 1	70
4		O*t*-Bu	12 / 1	68
5		O*t*-Bu	<2 / 98	61[c]
6	$(BnS)_2C{=}CH$-	O*t*-Bu	10 / 1	74
7	Ph_2CH-O-	O*t*-Bu	10 / 1	59
8	Me-	Et	>98 / 2	70[d]
9	$PhCH_2$-	OEt	>98 / 2	85[d]
10	Et-	OMe	>98 / 2	56[d,e]

(a) *E* / *Z* ratios were determined by 1H-NMR with integration. The stereochemistry of the major isomers was determined by one dimensional nOe experiments. (b) Isolated yields. Products were separated from the amine **1** as described in footnote 7 unless otherwise noted. (c) This product can be prepared in 85% yield by using LDA in place of **2**. (d) Isolated by bulb-to-bulb distillation. (e) Replacing TMSCl with phenyldimethylsilyl chloride resulted in a 81% yield of the corresponding *E*-silyl ketene acetal.

In contrast to the results which are detailed in Table 1, relatively poor *E*/*Z* selectivities were observed even at −100°C with lithium diisopropylamide (LDA) or lithium tetramethylpiperidide (LTMP) and *t*-butyl 4-methoxyphenylacetate (**4**) as shown in Table 2. In fact, the use of the still bulkier base lithium *t*-butyl-*t*-octylamide produced **5** with an *E*/*Z* ratio of only 5/1. It is clear that with oxyacetate esters such as **4** and the analogous substrates listed in Table 1 have an inherent tendency to form *Z*-silyl ketene acetals because of the availability of a chelation control pathway (see Fig. 2). This tendency is much less suppressed by the bases listed in Table 2 (LDA and LTMP) than with lithium *t*-butyltritylamide (**2**), a clear measure of the superior effective bulk of **2**. Here it should be noted that with *t*-butyl 2-pyridyloxyacetate, the substrate in entry 5 of Table 1, the tendency to react via the chelation pathway is so strong that it cannot be overcome even with **2** as base, with the result that a *Z*/*E* ratio of silyl ketene acetals of >50/1 is produced.

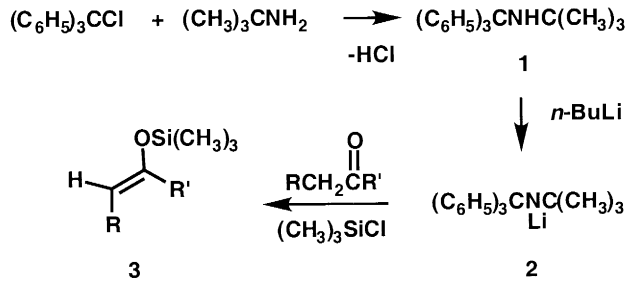
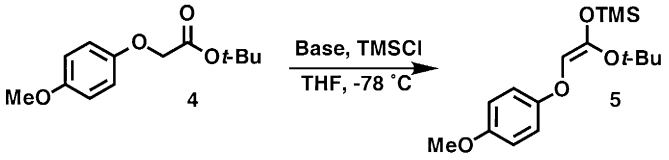
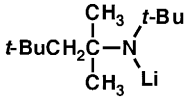


Table 2



Base	*E* / *Z*
LDA	2 / 1
LTMP	3.5 / 1
	5 / 1[a]

(a) The reaction was conducted at -100 °C.

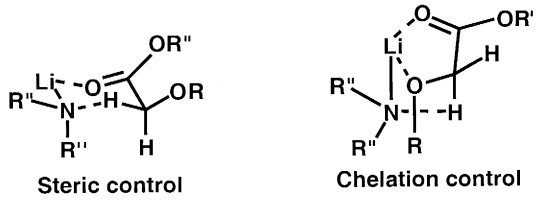
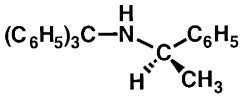


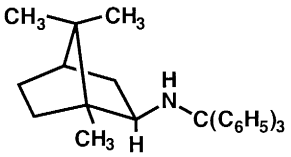
Fig. 2.

The data presented above shows that *t*-butyltritylamine (**1**) and lithium *t*-butyltritylamide (**2**) are readily available, relatively inexpensive,[8] superhindered bases which could be widely useful in synthesis. The method used for the synthesis of **1** was also applied to the synthesis of other potentially valuable bulky *N*-tritylamines. Thus, the chiral secondary amines **6** and **7** were readily prepared as colorless crystalline

solids from trityl chloride and (*R*)-1-phenylethylamine and *exo*-isobornylamine. X-Ray crystallographic analysis of single crystals of **6** and **7** revealed C–N–C angles of 118° and 120.7°, respectively, i.e. about 5° smaller than for the ditertiary amine **1**.[9,10]



6



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References

1. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: New York, pp. 3096–3104 and pp. 3166–3172, respectively.
2. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495 and *Org. Synth. Coll. Vol. VIII*, 93.
3. Lithium tetramethylpiperidide has also been found to produce *E*-silyl ketene acetals via the corresponding *transoid* enolates provided that a bulky silylating agent is used, e.g. triisopropyl silyl chloride; see Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3099.
4. Glidewell, C.; Liles, D. C. *Acta Crystallogr.* **1978**, *B34*, 696.
5. Blount, J. F.; Gutiérrez, A.; Mislow, K. *J. Org. Chem.* **1982**, *47*, 4359.
6. Experimental details for preparation of *t*-butyltritylamine (**1**). To a solution of trityl chloride (48.3 g, 0.17 mol) in dry, ethanol-free $CHCl_3$ (100 mL) was added *t*-butylamine (44.5 mL, 0.43 mol). The reaction mixture was stirred at room temperature for 12 h, diluted with CH_2Cl_2 and washed with 2N NaOH, water and brine. The aqueous layers were extracted with CH_2Cl_2 and the extract was dried over $MgSO_4$. The solvent was removed in vacuo and the solid residue was recrystallized twice from MeOH (using charcoal for decolorization) yielding 33.0 g of a colorless crystalline solid, mp 90–91°C. The combined mother liquors yielded an additional 11.4 g resulting in a total yield of 45.4 g (85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J*=7.4 Hz, 6H), 7.23 (t, *J*=7.4 Hz, 6H), 7.13 (t, *J*=7.4 Hz, 3H), 0.81 (s, 9H) ppm.
7. Preparation of ketene acetals using lithium *t*-butyltritylamide. (Typical procedure): *t*-butyltritylamine (1.20 g, 3.81 mmol) was dissolved in 3 mL THF, and the solution was dried over 4 Å molecular sieves and transferred to the reaction flask. After cooling to 0°C, *n*-BuLi (2.34 mL, 3.81 mmol) was added dropwise and the reaction mixture was stirred at 0°C for 45 min. The resulting solution of **2** was cooled to −78°C and TMSCl (0.73 mL, 5.81 mmol) was added dropwise. *p*-Methoxyphenoxyacetic acid *t*-butyl ester (758 mg, 3.18 mmol) was dissolved in 2 mL THF and the solution was dried over 4 Å molecular sieves and transferred dropwise after cooling to −78°C to the reaction mixture. The reaction mixture was stirred at −78°C for 1.5 h and concentrated to remove solvent and excess TMSCl. The crude product was dissolved in dry pentane and LiCl was removed by filtration through a Teflon filter. The pentane solution was concentrated, cooled to −20°C and then seeded with a crystal of *t*-butyltritylamine. Following crystallization of **1**, the supernatant was removed via cannula and the solution was concentrated in vacuo yielding 612 mg (62%) of the ketene acetal **3**. The product, which contained approx. 9% *t*-butyltritylamine as determined by ^{1}H NMR integration can be further purified by short-path distillation in vacuo. ^{1}H NMR and one dimensional NOE experiments showed that the *E*/*Z* ratio was 14/1. Data for the *E*-isomer: ^{1}H NMR (400 MHz, benzene-d_6) δ 6.95 (d, *J*=9.0 Hz, 2H), 6.69 (d, *J*=9.0 Hz, 2H), 5.89 (s, 1H), 3.26 (s, 3H), 1.28 (s, 9H), 0.28 (s, 9H) ppm.
8. Approximate prices of precursor materials (Aldrich 1999): trityl chloride, 100 g, $ 22.45; *t*-butylamine, 100 mL, $ 23.55.
9. Detailed X-ray crystallographic data for **1**, **6** and **7** are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.
10. We are grateful to Drs. Georgios Sarakinos and Axel Fischer for experimental assistance and to the National Institutes of Health and Pfizer Inc for financial assistance.