Chemistry of Hindered Amines: Synthesis and Properties of Di-t-Butylamine and Related Compounds

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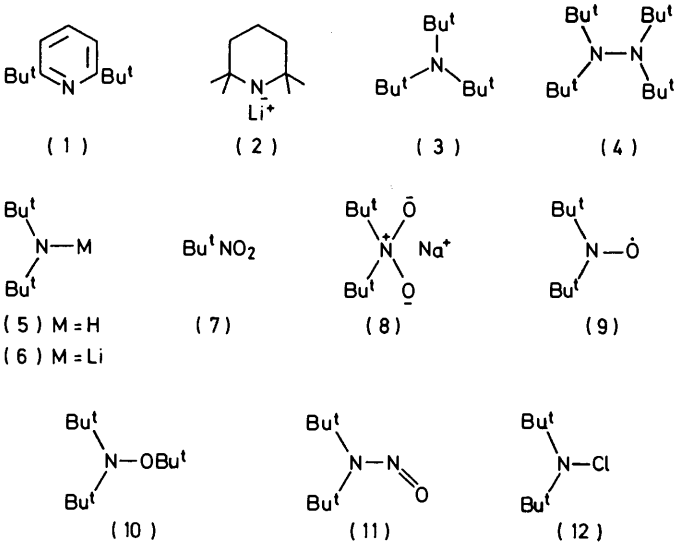
Di-t-butylamine was prepared from 2-methyl-2-nitropropane by an improved method in 54% yield, and was in turn converted into *N*-nitroso- and *N*-chloro-di-t-butylamine in yields of 89 and 90%, respectively. Di-t-butylamine is a non-nucleophilic base which is inert to benzoyl chloride. It reacts with acetyl chloride and with *O*-mesitylsulphonylhydroxylamine to form di-t-butylammonium chloride and mesitylenesulphonate rather than *NN*-di-t-butylacetamide and 1,1-di-t-butylhydrazine respectively. The *N*-chloro-amine was reduced to di-t-butylamine with sodium. The *N*-nitroso-amine reacted with methyl fluorosulphate to generate an unstable *O*-alkyl intermediate. The properties of tri-t-butylhydroxylamine, a by-product in the preparation of di-t-butylamine, are also described. Possible routes to tri-t-butylamine are discussed.

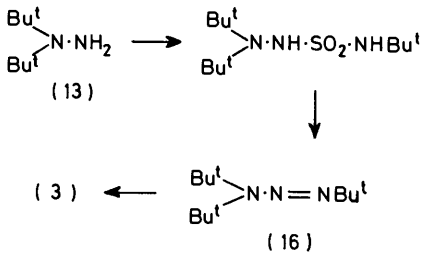
BASES which are efficient proton abstractors but poor nucleophiles are of value for synthetic work. Certain sterically hindered amines and their lithio-derivatives are of particular interest in this respect. For example, 2,6-di-t-butylpyridine [1] (1), lithium 2,2,6,6-tetramethylpiperidide [2] (2), and a variety of compounds of structure $LiNR_2$[2,3] (where R is a bulky substituent) are effective as non-nucleophilic bases. Furthermore, the absence of α-hydrogen atoms is desirable in hindered amine bases as hydride transfer to suitable acceptors is thereby precluded. Hence compounds such as tri-t-butylamine (3) and tetra-t-butylhydrazine (4) would be ideal reagents in many situations. However, no viable synthetic routes to these compounds have as yet been described. Di-t-butylamine (5) and its lithio-derivative [2] (6) are also potentially useful non-nucleophilic bases, but their widespread application has awaited a more convenient method for their preparation. To date, the most efficient synthesis of the amine (5) involves the reaction of 2-methyl-2-nitropropane (7) with sodium to generate the presumed intermediate (8), which is hydrolysed to di-t-butyl nitroxide [4] (9). The latter compound is then best converted into the amine by the method of Kornblum and Pinnick,[5] which employs a reducing mixture of sodium sulphide nonahydrate and sulphur in *NN*-dimethylformamide in the presence of light. Di-t-butylamine is thus obtained in an overall yield of 25%. We now report that direct reduction of the intermediate (8) by the method of Kornblum and Pinnick affords di-t-butylamine in an improved yield of 54% and eliminates the need to isolate and purify the nitroxide (9). Thus, di-t-butylamine is rendered accessible through a convenient, one-step process and becomes a practical candidate for synthetic applications. The known tri-t-butylhydroxylamine [4] (10) was obtained as a by-product in 20% yield.

The non-nucleophilic nature of di-t-butylamine was demonstrated by its inability to undergo benzoylation or acetylation. It was inert to benzoyl chloride at 150 °C and reacted with acetyl chloride by proton abstraction (presumably generating keten) to form the amine hydrochloride instead of the corresponding amide. It has also been reported [6] that di-t-butylamine does not react with phosgene. Treatment of di-t-butylamine with an excess of nitrosyl chloride in pyridine provided *N*-nitrosodi-t-butylamine (11) in 89% yield. Nitrous acid did not bring about this transformation. The *N*-nitroso-amine had previously been prepared by Klages and Sitz [7] in 23% yield by employing 2 equiv. of the amine (5) and ether as solvent. These authors also reported [7] the formation of 17% of *N*-chlorodi-t-butylamine (12) from the reaction of the amine (5) with sodium hypochlorite. We have found that *N*-chlorosuccinimide is a far more effective reagent for this transformation, providing compound (12) in 90% yield. The *N*-chloro-amine was reduced by sodium to di-t-butylamine. Formation of tetra-t-butylhydrazine (4) was not observed.



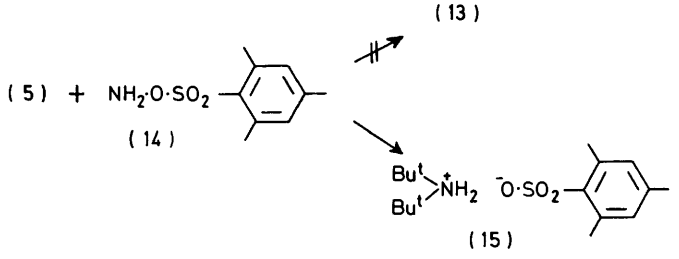
[1] H. C. Brown and B. Kanner, *J. Amer. Chem. Soc.*, 1966, **88**, 986; F. R. Jensen and R. A. Neese, *J. Org. Chem.*, 1972, **37**, 3037.
[2] R. A. Olofson and C. M. Dougherty, *J. Amer. Chem. Soc.*, 1973, **95**, 581, 582; R. A. Olofson, K. D. Lotts, and G. N. Barber, *Tetrahedron Letters*, 1976, 3779.
[3] For example, M. Hamell and R. Levine, *J. Org. Chem.*, 1950, **15**, 162; D. H. R. Barton, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Comm.*, 1969, 1497; M. Tanabe and D. F. Crowe, *ibid.*, p. 1498.
[4] A. K. Hoffmann and A. T. Henderson, *J. Amer. Chem. Soc.*, 1961, **83**, 4671; A. K. Hoffmann, A. M. Feldman, E. Gelblum and W. G. Hodgson, *ibid.*, 1964, **86**, 639.
[5] N. Kornblum and H. W. Pinnick, *J. Org. Chem.*, 1972, **37**, 2050.
[6] P. S. Bailey, J. E. Keller, and T. P. Carter, jun., *J. Org. Chem.*, 1970, **35**, 2777.
[7] F. Klages and H. Sitz, *Chem. Ber.*, 1963, **96**, 2394.

During our investigations of hindered amines, we also considered the possibility of preparing tri-t-butylamine by the route shown in Scheme 1. Preparation of the



SCHEME 1

required precursor 1,1-di-t-butylhydrazine (13) was attempted by subjecting *N*-nitrosodi-t-butylamine to a variety of standard reducing conditions. However, no significant quantities of (13) were obtained in this manner. The synthesis of (13) was also attempted by amination of di-t-butylamine with *O*-mesitylsulphonylhydroxylamine [8] (MSH) (14) (Scheme 2). Di-t-butylammonium mesitylenesulphonate (15) was obtained in high yield instead of the desired hydrazine (13); the



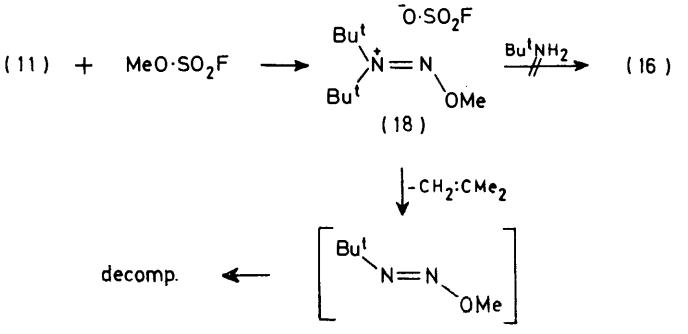
SCHEME 2

product was identical with an authentic sample prepared from the amine and mesitylenesulphonic acid. This indicates that elimination is favoured over nucleophilic attack by the amine, presumably with concomitant generation of di-imide. Precedent for this reaction lies in the preparation of di-imide from hydroxylamine-*O*-sulphonic acid in alkaline medium.[9] Triphenylphosphine reacted with MSH in methylene chloride to afford a product with m.p. 137—138° and an elemental analysis consistent with structure (17). This procedure has been reported [8] to give a hydrate with m.p. 154—155°.

Another synthetic approach (Scheme 3) to tri-t-butylamine (3) was envisaged, involving *O*-alkylation of *N*-nitrosodi-t-butylamine (11) followed by reaction of the expected intermediate with t-butylamine to provide tri-t-butyltriazene (16). However, when the *N*-nitroso-amine was treated with methyl fluorosulphate at −80 °C, and subsequently with t-butylamine, only the latter compound underwent alkylation while the *N*-nitroso-amine remained unchanged. When a mixture of compound (11) and methyl fluorosulphate was warmed to room temperature, vigorous gas evolution and the absence of non-volatile products demonstrated rapid collapse of the *O*-methyl intermediate (18). Hence, *N*-nitrosodi-t-butylamine is inert to methyl fluorosulphate at −80 °C. It is alkylated only at higher temperatures to form the labile intermediate (18), which decomposes faster than it reacts with t-butylamine. This behaviour is attributed to relief of steric compression in (18).

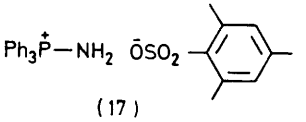
The properties of tri-t-butylhydroxylamine (10) as a hindered base were also studied. Compound (10) reacts with perchloric acid to form tri-t-butylhydroxylammonium perchlorate (19). This contrasts with its behaviour towards anhydrous hydrogen chloride,[4] which effects C–O bond cleavage to furnish *N*-hydroxy-di-t-butylammonium chloride (20).

Tri-t-butylhydroxylamine was treated with trityl perchlorate in methylene chloride solution to determine

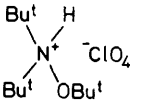


SCHEME 3

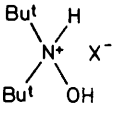
whether hydride transfer would occur. After 15 min at room temperature, no reaction was observed and the hydroxylamine was recovered intact. Prolonged reaction times resulted in loss of the *O*-t-butyl group as evidenced by formation of *N*-hydroxydi-t-butylammonium perchlorate (21). Clearly, tri-t-butylhydroxylamine could be used as a proton-binding base in the presence of hydride-abstracting species.



(17)



(19)



(20) X = Cl
(21) X = ClO_4

EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 257 spectrometer and n.m.r. spectra with a Varian T60 instrument (tetramethylsilane as internal reference). Mass spectra were recorded with an A.E.I. MS9 instrument. ' Light petroleum ' refers to the fraction with b.p. 30—40° and ' petroleum ' to the fraction with b.p. 60—80°.

[8] Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.*, 1973, **38**, 1239.

[9] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, vol. 1, p. 482.

Di-t-butylamine (5) *and Tri-t-butylhydroxylamine* (10).—Sodium (3.5 g), cut into small pieces, was added to 2-methyl-2-nitropropane [10] (15.5 g) in dry 1,2-dimethoxyethane (60 ml). After being stirred vigorously under nitrogen for 48 h the resulting white slurry was added to a stirred mixture of sodium sulphide nonahydrate (100 g), sulphur (2 g), and *NN*-dimethylformamide (150 ml), and irradiated for 75 min with a 100 W lamp (tungsten filament). Longer reaction times gave lower yields of di-t-butylamine. The mixture was poured into water (500 ml), basified with potassium carbonate, and extracted with light petroleum (5 × 100 ml). The petroleum layer was washed with water (5 × 50 ml), dried (Na_2SO_4), and distilled through a Vigreux column to give three fractions. The first had b.p. lower than 57 °C at 130 mmHg and was treated with anhydrous hydrogen chloride to afford *di-t-butylammonium chloride* (15%), m.p. 250—260° (subl. from 220°; m.p. dependent on rate of heating). A sample prepared by repeated recrystallisation from chloroform–ether had m.p. 260—270° (subl.) (Found: C, 57.9; H, 12.0; N, 8.2. $C_8H_{20}ClN$ requires C, 58.0; H, 12.2; N, 8.5%). The free amine could be liberated by treatment of an aqueous solution of the hydrochloride with potassium carbonate.

The second fraction contained di-t-butylamine (39%; total 54%) and a trace of dimethoxyethane, b.p. 57—59° at 130 mmHg, δ (CCl_4) 1.14 (18 H, s) and 0.5br (1 H) [lit.,[5] b.p. 119—120°, δ(CCl_4) 1.18 (18 H, s) and 0.45br (1 H)].

The third fraction furnished tri-t-butylhydroxylamine (20%) b.p. 90—92° at 10 mmHg (lit.,[4] b.p. 85° at 11 mmHg), δ(CCl_4) 1.25 (9 H, s) and 1.20 (18 H, s) (lit.,[4] τ 8.75 and 8.83 in ratio 1 : 2).

Attempted Benzoylation of Di-t-butylamine (5).—Di-t-butylamine (129 mg), benzoyl chloride (140 mg), and pyridine (79 mg) were refluxed in benzene (1 ml) and remained unchanged after 63 h (n.m.r.). An excess of benzoyl chloride (280 mg) was added and the mixture heated at 150 °C in a sealed glass tube for 15 h. N.m.r. still showed no change.

Reaction of Di-t-butylamine with Acetyl Chloride.—The amine (151 mg) and acetyl chloride (92 mg) were stirred for 30 min in dry benzene (2 ml) under nitrogen. N.m.r. then showed the presence of mostly starting material. The mixture was refluxed for 22 h and evaporated under reduced pressure to afford pure di-t-butylammonium chloride (80%), m.p. 255—265° (subl.), n.m.r. spectrum identical with that of an authentic sample; the i.r. spectrum showed no amide carbonyl band.

N-*Nitroso-di-t-butylamine* (11).—Nitrosyl chloride was passed into a solution of di-t-butylamine (646 mg) in pyridine (5 ml) until a red colour persisted. An exothermic reaction was observed. After 10 min, the mixture was poured into water (25 ml) and extracted with ether (3 × 20 ml). The extract was washed repeatedly with water and evaporated under reduced pressure. The resulting oil still contained pyridine and was taken up in light petroleum; this solution was washed thoroughly with water, dried (Na_2SO_4), and evaporated *in vacuo* to furnish a yellow oil (89%) which solidified on cooling; m.p. 25—27° (lit.[7] 29°), δ(CCl_4) 1.67 (9 H, s) and 1.47 (9 H, s).

The *N*-nitroso-compound was not obtained by heating di-t-butylamine with a mixture of hydrochloric acid and sodium nitrite. Instead, the amine hydrochloride was recovered (62%).

N-*Chloro-di-t-butylamine* (12).—Di-t-butylamine (262 mg) and *N*-chlorosuccinimide (280 mg) were stirred during 4 h in methylene chloride (5 ml) at room temperature. The solvent was then evaporated off at 0 °C and 100 mmHg and the residue was distilled at 0.5 mmHg into a solid CO_2–acetone trap to provide *N*-chlorodi-t-butylamine (90%), δ(CCl_4) 1.33 (s), *m/e* 163 (M^+).

Reaction of N-*Chlorodi-t-butylamine with Sodium.*—The *N*-chloro-amine (130 mg) and sodium (100 mg) were refluxed for 15 h in petroleum (2 ml). Water was then cautiously added to destroy the excess of sodium and the mixture was poured into water (7 ml) and extracted with ether (2 × 10 ml). The organic layer was dried (Na_2SO_4) and evaporated at room temperature and 100 mmHg to afford di-t-butylamine (78%), having the same n.m.r. spectrum as an authentic sample. To confirm its identity, a portion was treated with nitrosyl chloride in pyridine, thereby effecting quantitative conversion into *N*-nitrosodi-t-butylamine (n.m.r., t.l.c.).

Amination of Triphenylphosphine with O-*Mesitylsulphonylhydroxylamine* (MSH).—MSH [8] (107 mg) was added to triphenylphosphine (131 mg) in methylene chloride (2 ml) at 0 °C. After 10 min, the product was crystallized by addition of ether at low temperature; yield 82%, m.p. 134—137° (decomp.). It was recrystallized from methylene chloride–ether; m.p. 137—138° (decomp.) (lit.,[8] 154—155° for monohydrate) (Found: C, 67.85; H, 5.8; N, 2.9. $C_{27}H_{28}NO_3PS$ requires C, 67.9; H, 5.9; N, 2.9%). The product was dissolved in acetone–water; the solution was evaporated *in vacuo* and the residue crystallized from methylene chloride–ether to give a product with m.p. 129—134° (decomp.).

Di-t-butylammonium Mesitylenesulphonate (15).—Di-t-butylamine (200 mg) and mesitylenesulphonic acid (200 mg) were stirred for 1 h in methylene chloride (3 ml). The solvent was then evaporated off *in vacuo* to provide the *amine salt* (89%), m.p. 220—223° (decomp.). Repeated recrystallization from chloroform–ether furnished a sample with m.p. 228.5—229.5° (decomp.) (Found: C, 62.1; H, 9.4; N, 4.2. $C_{17}H_{31}NO_3S$ requires C, 61.9; H, 9.45; N, 4.25%).

Reaction of Di-t-butylamine with MSH.—(*a*) Di-t-butylamine (70 mg) and MSH [8] (107 mg) were stirred for 5 h in methylene chloride (2 ml). The solvent was then evaporated off under reduced pressure to give a white solid (86%), m.p. 212—217° (decomp.), which had the same n.m.r. spectrum as an authentic sample of di-t-butylammonium mesitylenesulphonate. The product was recrystallized from chloroform–ether; m.p. and mixed m.p. 225—228° (decomp.).

(*b*) MSH [8] (40 mg) was dissolved in methylene chloride (10 ml) and added dropwise over 1.5 h to di-t-butylamine (26 mg) in methylene chloride (10 ml). After a further 0.5 h, the solvent was removed under reduced pressure to afford di-t-butylammonium mesitylenesulphonate (95%), identical with an authentic sample (m.p., mixed m.p., n.m.r.).

Alkylation of N-*Nitrosodi-t-butylamine.*—(*a*) Methyl fluorosulphate (125 mg) in methylene chloride (2 ml) was added dropwise to *N*-nitrosodi-t-butylamine (158 mg) in methylene chloride (3 ml) at −80 °C. On warming to room temperature, vigorous evolution of gas occurred. The solvent was removed by distillation, leaving only a trace of non-volatile material.

(*b*) The *N*-nitroso-amine and methyl fluorosulphate were

[10] N. Kornblum, R. J. Clutter, and W. J. Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 4003.

dissolved in methylene chloride at −80 °C as above. After 15 min t-butylamine (200 mg) was added and the mixture was slowly warmed to room temperature. N.m.r. analysis then revealed the presence of unchanged *N*-nitroso-amine as well as products also observed in the reaction of t-butylamine with methyl fluorosulphonate in a blank experiment.

Tri-t-butylhydroxylammonium Perchlorate (19).—(*a*) Tri-t-butylhydroxylamine (200 mg) was added to 60% perchloric acid (165 mg) in water (5 ml). The resulting white precipitate was filtered off, washed with a little water and dried under vacuum to afford *compound* (19) (17%), m.p. 193—194° (decomp.), δ($CDCl_3$) 1.70 (s) and 1.68 (s) (addition of K_2CO_3–D_2O regenerated the spectrum of tri-t-butylhydroxylamine) (Found: C, 47.9; H, 9.1; N, 4.8. $C_{12}H_{28}ClNO_5$ requires C, 47.7; H, 9.4; N, 4.6%).

(*b*) Alternatively, the tri-t-butylhydroxylamine was added to a vigorously stirred mixture of the perchloric acid in methylene chloride (10 ml). After 10 min, the mixture was dried (Na_2SO_4) and evaporated under vacuum to furnish the perchlorate (96%), m.p. 187—190° (decomp.).

Reaction of Tri-t-butylhydroxylamine with Trityl Perchlorate.—(*a*) Trityl perchlorate [11] (130 mg) and tri-t-butylhydroxylamine (76 mg) were stirred for 15 min at room temperature in methylene chloride (2 ml). Aqueous potassium carbonate was then added, the layers were separated, and the aqueous phase was extracted with methylene chloride. The combined organic layers were dried and evaporated under reduced pressure. The residue was triturated with petroleum (3 ml), the insoluble solid was filtered off, and the filtrate was evaporated *in vacuo* to afford tri-t-butylhydroxylamine (quantitative recovery), identified by its n.m.r. spectrum. The solid was triphenylmethanol (67%).

(*b*) Trityl perchlorate (87 mg) and tri-t-butylhydroxylamine (50 mg) were stirred 18 h at room temperature in methylene chloride (1 ml). Ether was then added and *N-hydroxydi-t-butylammonium perchlorate* crystallized out (67%); m.p. 195—196° (decomp.), $\nu_{max.}$ ($CHCl_3$) 3 580 cm^{-1}, δ($CDCl_3$) 1.47 (s). A sample recrystallized from chloroform–ether had m.p. 195—196° (decomp.) (Found: C, 39.15; H, 8.15; N, 6.1. $C_8H_{20}ClNO_5$ requires C, 39.1; H, 8.2; N, 5.7%).

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[11] H. J. Dauben, jun., L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, 1960, **25**, 1442