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SYNTHESIS OF DI-t-ALKYLAMINES

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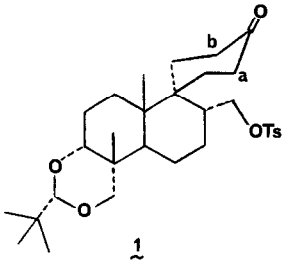
Summary: Di-t-alkylamines can be synthesized efficiently by a three-step process: (1) oxidation of a t-alkylamine to a t-alkylnitroso compound with peracetic acid in ethyl acetate (2) conversion of the t-alkylnitroso compound to a tri-t-alkylhydroxylamine by successive trapping of two t-butyl radicals and (3) sodium naphthalide reduction to the di-t-alkylamine.

A key step in a recent total synthesis of aphidicolin was the internal enolate alkylation of 1, the course of which was found to be dependent on the nature of the base.[1] The ratio of desired alkylation at carbon a to that at carbon b, as shown in the accompanying

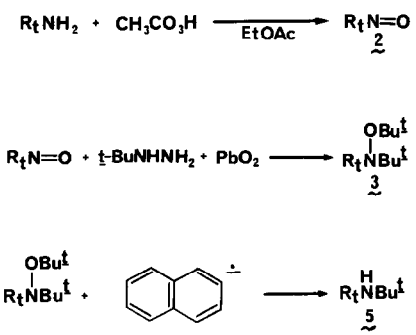


1

base	alkylation, a:b
NaOMe	0 : 100
LDA	55 : 45
LiTMP[2]	65 : 35
LiN(t-Bu)$_2$	91 : 9

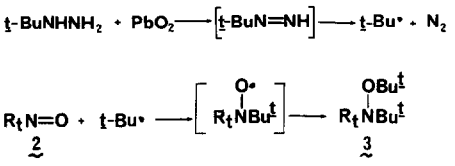
table, was most favorable for LiN(t-Bu)$_2$.[3] However, difficulties were encountered in the synthesis of di-t-butylamine, which prompted us to develop an efficient, general synthesis of di-t-alkylamines with the results reported herein.

The new synthesis of di-t-alkylamines proceeds in three steps according to the following reaction scheme.

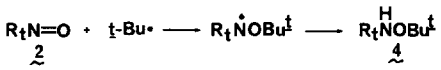


The conversion of the t-alkylamine to the t-alkylnitroso compound was accomplished efficiently using peracetic acid in ethyl acetate.[4] The following yields of nitroso compound, 2, were realized: 2, R=t-butyl, 86%; 2, R=t-octyl,[5] 94%; 2, R=1-adamantyl, 95%. (The nitroso compounds had been previously synthesized in poor yield via oxidation of the respective amines with hydrogen peroxide/sodium tungstate.[6]) In general the oxidation was carried out by addition of a solution of peracetic acid in ethyl acetate to a five-fold excess of the t-alkylamine in ethyl acetate at 0°. The characteristic blue color of the nitroso monomer developed immediately. After consumption of the peracid, unreacted amine was removed and recovered by acid extraction. In practice the nitroso compound was not isolated but was directly used in ethyl acetate solution for the next reaction.

The nitroso compound was then converted to a tri-t-alkylhydroxylamine, 3, via sequential trapping of two t-butyl radicals. An excellent new preparative method of generating t-butyl radicals was developed involving the oxidation of commercially available t-butylhydrazine with PbO_2 as follows:



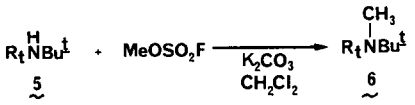
t-Butylhydrazine was added to the nitroso compound and lead dioxide in hexane/ethyl acetate at 15° to give brisk but controlled nitrogen evolution. Discharge of the blue nitroso monomer color indicated completion of the reaction. The radical trapping was very efficient with only 2.5-3.0 equivalents of t-butylhydrazine being necessary to yield the tri-t-alkylhydroxylamine. The product was isolated simply by filtration through Celite to remove lead oxides and removal of solvent. The only by-product in the reaction was the corresponding O-t-butylhydroxylamine, 4, presumably arising from initial trapping of a t-butyl radical on oxygen followed by proton abstraction. The yields of compound 3 were: 3, R=t-butyl, 92%; 3, R=t-octyl, 84%; 3, R=1-adamantyl, 90% with the balance in each case being compound 4.



The mixture of 3 and 4 was not separated but rather was directly reduced to yield the desired di-t-alkylamine. In each case the primary amine arising from 4 was readily removed by distillation. The reduction could be achieved with sodium in 1:1 tetrahydrofuran (THF)/ammonia but the insolubility of the hydrophobic substrates made this process difficult. The reduction was more conveniently performed with sodium naphthalide in THF.[7] Simply stirring the substrate, naphthalene, and sodium in THF under an inert atmosphere followed by extractive workup afforded the desired amine in excellent yield.[8] The yields of the di-t-alkylamines 5 were: 5, R=t-butyl, 93%; 5, R=t-octyl, 91%; 5, R=1-adamantyl, 90%.

The three step sequence leading to the di-t-alkylamines is readily operable on a multigram scale. The nitroso and tri-t-alkylhydroxylamine intermediates need not be purified but can be used directly in the subsequent reaction. The reactions themselves are easily monitored and need no special precautions. Indeed, only the final reduction required even exclusion of air and moisture. The efficacy of this procedure was demonstrated in the preparation of a doubly-distilled ten gram sample of t-octyl-t-butylamine in 73% overall yield in little more than a day.

The extreme hindrance of the di-t-alkylamines was demonstrated by their resistance to methylation and metalation.[3,9] The amines, 5, are inert to methyl iodide and dimethyl sulfate at 25°, but treatment with methyl fluorosulfate at 0° in methylene chloride with potassium carbonate as a proton scavenger afforded the N-methyl amines, 6, in good yields: 6, R=t-butyl, 70%; 6, R=t-octyl, 95%; 6, R=1-adamantyl, 84%. The amines, 5, could be metalated with MeLi but reacted sluggishly, if at all, with n-BuLi. Interestingly, the amines are inert to molten potassium metal in refluxing dimethoxyethane.



The preparation of t-octyl-t-butylamine, 5, R=t-octyl, is described below.

Nitroso-t-octane (2, R=t-octyl). Peracetic acid in ethyl acetate (3.15 M sol'n., 51 ml., 160 mmol) was added dropwise to a 0° solution of t-octylamine (51.7 g, 400 mmol) in 50 ml. of 1:1 water/ethyl acetate. After 2 h the absence of peracid was indicated by starch-iodide paper. Unreacted t-octylamine was removed by extraction with 4 N HCl and the ethyl acetate solution containing nitroso alkane was dried over sodium sulfate.[10]

N-t-octyl-N-t-butyl-O-t-butylhydroxylamine (3, R=t-octyl). The nitroso solution and lead dioxide (57.5 g, 240 mmol) were placed in a 1-liter, 3-necked flask fitted with dropping funnel, mechanical stirrer, and gas inlet. t-Butylhydrazine (21.2 g, 240 mmol) was added dropwise so as to give brisk but controlled nitrogen evolution. Cooling was provided so that the reaction temperature did not exceed 25°. After complete discharge of the blue nitroso monomer color the reaction mixture was filtered through Celite to remove lead oxides. Removal of solvent gave a 6:1 mixture of 3 and 4, R=t-octyl, respectively. Compound 3, R=t-octyl; PMR ($CDCl_3$) (δ) 1.76 (s, 2H); 1.31 (s, 9H, O-t-butyl); 1.30 (s, 3H, N-C-CH_3); 1.26 (s, 12H, N-C-CH_3 and N-t-butyl); 1.00 (s, 9H). Compound 4, R=t-octyl; PMR ($CDCl_3$) (δ) 4.44 (s, 1H); 1.40 (s, 2H); 1.15 (s, 9H); 1.12 (s, 6H); 1.01 (s, 9H).

t-Octyl-t-butylamine (5, R=t-octyl). To a dry 250 ml. flask under nitrogen was added naphthalene (12.8 g, 100 mmol), 150 ml. THF, and sodium (5.4 g, 234 mmol) and the solution was stirred 0.5 h. To the blue-green solution was added the mixture of 3 and 4, R=t-octyl, from above. After 4 h analytical thin layer chromatography showed the absence of starting material. The reaction mixture was decanted from unreacted sodium and carefully quenched with isopropyl alcohol. The product was extracted into 1 N HCl, the acid extracts were neutralized, and were extracted with ether. Removal of solvent and distillation (68-70°; 15 mm Hg) afforded t-octyl-t-butylamine (10.8 g, 58.4 mmol, 73% based on peracetic acid). PMR ($CDCl_3$) (δ):1.43 (s, 2H); 1.23 (s, 6H); 1.18 (s, 9H); 1.01 (s, 9H).

References and Notes

1. E. J. Corey, M. A. Tius, and J. Das, J. Am. Chem. Soc., 102, 1742 (1980).
2. LiTMP=lithium 2,2,6,6-tetramethylpiperidide.
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4. Peracetic acid in ethyl acetate (25%) was supplied by the Union Carbide Co.
5. t-Octyl=1,1,3,3-tetramethylbutyl.
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