Steric Limits in the Reactions of Amines with in Situ Generated α-Lactams: The Synthesis of Extremely Sterically Hindered Tertiary Amines†

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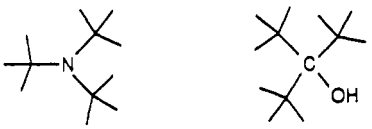
Sterically hindered amines are very important in a variety of applications. They are particularly useful as proton scavengers in synthesis.[1-5] Their metal salts have been invaluable reagents in selective alkylation reactions of carbonyl compounds.[6-11] Industrially, sterically hindered amines are precursors to persistent nitroxyl radicals, important as polymer photostabilizers.[12-15] Hindered amines are also important agents for removal of carbon dioxide from gas streams.[16] Theoretically, sterically hindered amines have proved to be quite interesting. The effect of steric hindrance on the basicity of amines has been intensely studied,[17-28] as have steric effects on NMR parameters.[29-32]

Because of these factors, with our continued interest in the chemistry of extremely sterically hindered molecules, we were particularly intrigued by March's observation that although the extremely hindered tri-*tert*-butylamine, 1, has not been prepared to date, the even more hindered tri-*tert*-butylcarbinol, 2, can be readily synthesized.[33] It appeared that there should be no insurmountable structural barrier to the preparation of 1, or the preparations of related tri-*tert*-alkylamines, assuming suitable synthetic methodology could be developed.[34]



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Although there are numerous methods for the preparation of hindered secondary amines, there are relatively few general methods available for the synthesis of extremely hindered tertiary amines. These include the alkylative amination route of Seebach,[35] direct methylation of di-*tert*-alkylamines,[36] and the reduction of sterically hindered formamides[37] or 2-chloroalkanamides.[38] Each of these methods is limited to the preparation of hindered amines where one or more substituents was methyl or a primary alkyl group.[39]

Another general method for the preparation of hindered secondary amines which appeared to be applicable to the synthesis of hindered tertiary amines was initially reported by Lai.[40] This involved the reaction of a primary amine with an α-halo amide in the presence of base, affording extremely hindered amino amides. Hydrolysis of the amide followed by reduction would afford the desired hindered amine (Scheme I).

The amine-forming reaction presumably involves an intermediate α-lactam. The key to the success of this reaction was the observation by Sheehan and Lengyel[41] that protonic nucleophiles (water, alcohols, thiols, and amines) react with α-lactams via alkyl–nitrogen bond cleavage. In contrast, aprotic nucleophiles (e.g. alkoxides) react with α-lactams via acyl–nitrogen bond cleavage (Scheme II).[42]

Lai prepared the α-lactam intermediates in situ from the reaction of an α-bromo amide with powdered sodium hydroxide at room temperature in the presence of excess primary amine as a solvent. Using this route Lai was able to prepare a variety of hindered secondary amino amides; however, he did not investigate the steric limits of this reaction. In particular he did not attempt reactions with sterically hindered secondary amines.

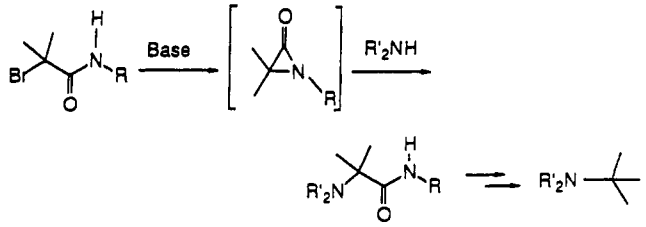
In attempts at optimizing Lai's reaction conditions for the preparation of very hindered secondary amines, we found that if the initial in situ α-lactam formation was carried out below room temperature, the yields of the hindered amine derivatives could be routinely improved. For example when the preparation of *N'-tert*-butyl-2-(*N*-

† Dedicated to the memory of Professor John C. Sheehan.

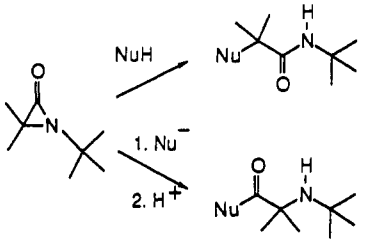
(1) Hünig, S.; Kiessel, M. *Chem. Ber.* **1958**, *91*, 380.
(2) Alder, R.; Goode, N.; Miller, N. *J. Chem. Soc., Chem. Commun.* **1978**, 89.
(3) Eisele, G.; Simchen, G. *Synthesis* **1978**, 757.
(4) Stang, P.; Treptow, W. *Synthesis* **1980**, 283.
(5) Wright, M.; Pulley, S. *J. Org. Chem.* **1989**, *54*, 2886.
(6) Podraza, K.; Bassfield, R. *J. Org. Chem.* **1988**, *53*, 2643.
(7) Kopka, I.; Fataftah, Z.; Rathke, M. *J. Org. Chem.* **1987**, *52*, 448.
(8) Rathke, M.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318.
(9) Rathke, M. *J. Am. Chem. Soc.* **1970**, *92*, 3222.
(10) Corey, E.; Gross, A. *Tetrahedron Lett.* **1984**, *25*, 491.
(11) Corey, E.; Gross, A. *Tetrahedron Lett.* **1984**, *25*, 495.
(12) Keana, J. F. *Chem. Rev.* **1978**, *78*, 37.
(13) Hoffmann, A.; Henderson, A. *J. Am. Chem. Soc.* **1961**, *83*, 4671.
(14) Carlsson, D.; Garton, A.; Wiles, D. *Developments in Polymer Stabilization-I*, Scott, G., Ed.; Applied Science Publishers: London, 1979; p 246.
(15) Tucker, R.; Susi, P. *ACS Symp. Ser.* **1985**, *280*, 139.
(16) Sartori, G.; Savage, D. W. *Ind. Eng. Chem. Fundam.* **1983**, *22*, 239.
(17) Smith, J. *The Chemistry of the Amino Group*; Patai, S., Ed.; Interscience: New York, 1968; pp 161-169.
(18) Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1953**, *75*, 3865.
(19) Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1966**, *88*, 986.
(20) Condon, F. *J. Am. Chem. Soc.* **1965**, *87*, 4481.
(21) Day, J. *J. Am. Chem. Soc.* **1981**, *103*, 7355.
(22) Condon, F. *J. Am. Chem. Soc.* **1965**, *87*, 4485.
(23) Hall, H. K. *J. Am. Chem. Soc.* **1957**, *79*, 5441.
(24) Brown, H. C. *Boranes in Organic Chemistry*; Cornell University Press: New York, 1972; pp 114-121.
(25) Brown, H. C.; Fletcher, R. *J. Am. Chem. Soc.* **1949**, *71*, 1845.
(26) Brauman, J.; Riveros, J.; Blair, L. *J. Am. Chem. Soc.* **1971**, *93*, 3914.
(27) Alder, R. *Chem. Rev.* **1989**, *89*, 1215.
(28) Hennion, G.; Hanzel, R. *J. Am. Chem. Soc.* **1960**, *82*, 4908.
(29) Witanowski, M.; Januszewski, H. *Can. J. Chem.* **1969**, *47*, 1321.
(30) Duthaler, R. O.; Roberts, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 3889.
(31) Duthaler, R. O.; Roberts, J. D. *J. Magn. Reson.* **1979**, *34*, 129.
(32) Gouesnard, J.-P.; Dorie, J. *Nouv. J. Chim.* **1982**, *6*, 143 and references therin.
(33) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; pp 139-140.
(34) Some unsuccessful approaches to 1 have been reported. Back, T.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 924.
(35) Seebach, D.; Schiess, M. *Helv. Chim. Acta* **1982**, *65*, 2598.
(36) Corey, E.; Gross, A. *J. Org. Chem.* **1985**, *50*, 5391.
(37) Audeh, C.; Fuller, S.; Hutchinson, R.; Smith, J. *J. Chem. Res. (S)* **1979**, 270.
(38) Susuki, K.; Okano, K.; Nakai, K.; Terao, Y.; Sekiya, M. *Synthesis* **1983**, 723.
(39) The synthesis of triisopropylamine, perhaps the most sterically hindered tertiary amine prepared to date, has been reported; however, the method used does not appear to be general. [Kuffner, F.; Koechlin, W. *Monatsh. Chem.* **1962**, *93*, 476. Kuffner, F.; Seifried, W. *Monatsh. Chem.* **1952**, *83*, 748.]
(40) Lai, J. T. *Tetrahedron Lett.* **1982**, *23*, 595.
(41) Sheehan, J. C.; Lengyel, I. *J. Am. Chem. Soc.* **1964**, *86*, 1356.
(42) An alternative explanation for this pattern of substitution in reactions of amines with α-bromo amides has been reported. [Scrimin, P.; D'Angeli, F.; Cavicchioni, G. *Synthesis* **1982**, 1092.]
(43) Rekker, R. F.; Nauta, W. *Recl. Trav. Chim. Pays Bas* **1951**, *70*, 241.

0022-3263/93/1958-1604$04.00/0

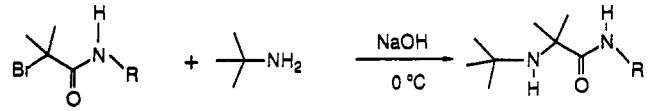
Scheme I



Scheme II



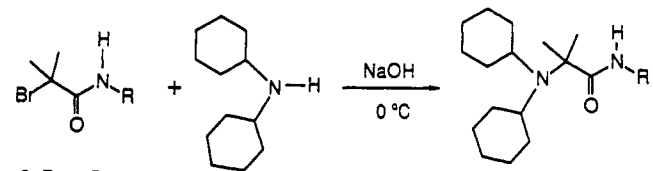
tert-butylamino)-2-methylpropanamide, **4**, was carried out starting with bromo amide **3** and *tert*-butylamine using these modified conditions, the yield improved from 65% to 82%. The corresponding *N*-methyl derivative **6** could be prepared similarly in 86% yield. These optimized conditions were then used for investigating the corresponding reactions with hindered secondary amines.



3, R = t-Bu
5, R = CH_3

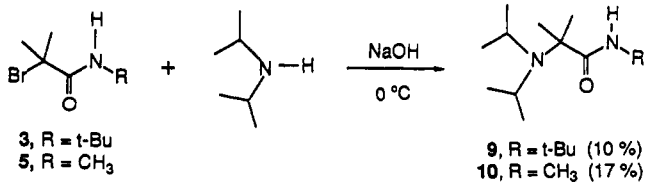
4, R = t-Bu (82%)
6, R = CH_3 (86%)

Treatment of **3** in excess dicyclohexylamine with powdered sodium hydroxide at 0 °C, followed by reflux afforded *N'-tert*-butyl-2-(*N,N*-dicyclohexylamino)-2-methylpropanamide, **7**, although in only 12% yield. The corresponding *N,N*-diisopropyl derivative **9** could be prepared in 10% yield. Changing the starting α-bromo amide to the *N*-methyl derivative **5** afforded the corresponding tertiary amino amides **8** and **10** in yields of 7 and 17%, respectively. In each case the major significant byproducts



3, R = t-Bu
5, R = CH_3

7, R = t-Bu (12%)
8, R = CH_3 (7%)

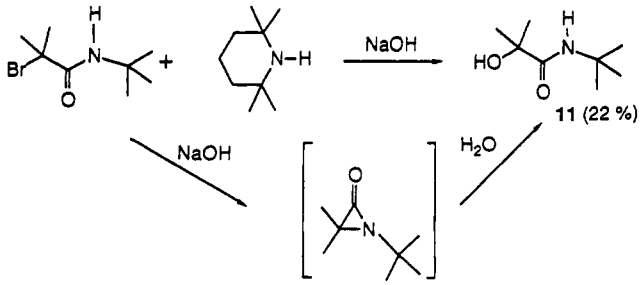


3, R = t-Bu
5, R = CH_3

9, R = t-Bu (10%)
10, R = CH_3 (17%)

observed were the amino acids formed by nucleophilic reaction of hydroxide with the intermediate α-lactam. Clearly the increasing steric hindrance in going even from a hindered primary amine to a secondary amine profoundly influences the course of the reaction. While

Scheme III



the yields of extremely hindered tertiary amines are quite low, these compounds are among the most hindered tertiary amine derivatives as yet prepared.

When the reaction was attempted with a more hindered amine, 2,2,6,6-tetramethylpiperidine, no tertiary amine product was obtained. The only identifiable new product was the known *N-tert*-butyl-2-hydroxy-2-methylpropanamide, **11**.[43] The formation of this product may be explained by the nucleophilic reaction of water on the α-lactam (Scheme III). Note that hydroxide attack would have afforded the previously described isomeric N-substituted α-amino acid. Subsequent examination of the crude reaction products in the preparation of tertiary amines **7–10** indicated that **11** was formed as a minor byproduct in each case. The identification of these byproducts of nucleophilic attack on the in situ generated α-lactam indicates that the reaction may be significantly improved if isolated α-lactams are used as substrates in the reaction. Investigations in this area and into further functionalization of the amino amides are currently being carried out.

Experimental Section

General experimental conditions used are as those recently reported.[44]

***N-tert*-Butyl-2-(*N-tert*-butylamino)-2-methylpropanamide (4).** A mixture of *tert*-butylamine (450 mmol, 47.3 mL) and *N-tert*-butyl-2-bromo-2-methylpropanamide (**3**)[41] (22.5 mmol, 5.0 g) was cooled with an ice–water bath, and powdered sodium hydroxide (1.8 g, 45 mmol) was added in one portion. The mixture was allowed to come to room temperature and then heated to reflux for 4 h. The reaction was cooled to room temperature, and water was added (10 mL). The solution was extracted with ether and dried over sodium sulfate. Concentration afforded amino amide **4** as colorless crystals: 3.96 g, 82% yield; mp 71–73 °C [lit.[40] mp 70–72 °C]; ^{1}H NMR ($CDCl_3$) δ 7.55 (bs, 1 H), 1.34 (s, 15 H), 1.16 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 177.86 (s), 58.5 (s), 51.8 (s), 49.9 (s), 31.8 (q), 28.7 (q), 18.6 (q); IR ($CHCl_3$) 3336, 2973, 1660, 1514 cm^{-1}; MS *m/e* 114 (t-BuNH$C_3H_6^+$), 98 ($C_6H_{12}N^+$), 58 ($C_3H_8N^+$).

***N*,2-Dimethyl-2-bromopropanamide (5).** A well-stirred solution of dichloromethane (20 mL) and aqueous methylamine (130.5 mmol, 11.22 mL of a 40% solution) was cooled to −10 °C by means of a dry ice–acetone bath. The 2-bromo-2-methylpropionyl bromide (43.5 mmol, 10.0 g, 5.38 mL) was added dropwise, keeping the reaction temperature about −10 °C. When addition was complete, the mixture was allowed to come to room temperature and water (10 mL) was added. The phases were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 1 N sodium bicarbonate, 1 N hydrochloric acid, and water and dried over sodium sulfate. Filtration and evaporation of solvent afforded bromo amide **5** as colorless crystals: 6.01 g, 85% yield; mp 59–61 °C [lit.[45] mp 59–60 °C]; ^{1}H NMR ($CDCl_3$) δ 7.00 (bs, 1 H), 2.86 (d, 3 H), 1.96 (s, 6 H); IR ($CHCl_3$) 3436, 3012, 1665, 1533 cm^{-1}.

(44) Guziec, F. S., Jr.; Wei, D. *J. Org. Chem.* **1992**, *57*, 3772.
(45) Quast, H.; Frank, R.; Freudenreich, B.; Schafer, P.; Schmitt, E. *Ann. Chem.* **1979**, 74.

***N*,2-Dimethyl-2-(*N-tert*-butylamino)propanamide (6).** A mixture of *tert*-butylamine (117 mL) and *N*,2-dimethyl-2-bromopropanamide (**5**) (10.0 g, 55.2 mmol) was stirred under nitrogen until completely dissolved. The mixture was cooled in an ice–water bath, powdered sodium hydroxide (4.46 g) was added, and the mixture was allowed to come to room temperature and stirred for 5 days. Water (100 mL) was added, and the mixture was extracted with ether and dried over sodium sulfate. After removal of solvent the excess amine was removed under reduced pressure overnight affording amino amide **6**: 8.27 g, 86% yield; mp 52–55 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (bs, 1 H), 2.78 (d, 3 H), 1.37 (s, 6 H), 1.14 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 179.5 (s), 58.2 (s), 51.7 (s), 31.7 (q), 28.8 (q), 25.9 (q); IR ($CHCl_3$) 3378, 2994, 1658, 1523 cm^{-1}. Anal. Calcd for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26. Found: C, 62.61; H, 12.00; N, 16.31.

***N-tert*-Butyl-2-(*N,N*-dicyclohexylamino)-2-methylpropanamide (7).** A mixture of 2-bromo-2-methyl-*N-tert*-butylpropanamide (**3**) (1.0 g, 4.5 mmol) and dicyclohexylamine (12.7 mL) was stirred under positive nitrogen pressure until completely dissolved. The stirred mixture was cooled in an ice–water bath, powdered sodium hydroxide (0.36 g) was added, and the mixture was allowed to come to room temperature and stirred for 5 days. Water (15 mL) was added, and the mixture was extracted with ether and dried over sodium sulfate. After removal of solvent the excess amine was removed via Kugelrohr distillation under reduced pressure. The resulting solid was recrystallized from an ethanol–water mixture to afford amino amide **7** as colorless crystals: 0.17 g, 12% yield; mp 83–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (bs, 1 H), 2.45 (m, 2 H), 1.86–1.00 (m, 20 H), 1.37 (s, 9 H), 1.33 (s, 6 H); IR ($CHCl_3$) 3350, 2932, 1656, 1508 cm^{-1}. Anal. Calcd for $C_{20}H_{38}N_2O$: C, 74.48; H, 11.88; N, 8.69. Found: C, 74.54; H, 12.22; N, 8.39.

***N*,2-Dimethyl-2-(*N,N*-dicyclohexylamino)propanamide (8).** A mixture of *N*,2-dimethyl-2-bromopropanamide (**5**) (1.0 g, 5.6 mmol) and dicyclohexylamine (12.7 mL) was stirred under positive nitrogen pressure until completely dissolved. The mixture was cooled in an ice–water bath, powdered sodium hydroxide (0.44 g) was added, and the mixture was allowed to come to room temperature and stirred for 5 days. Water (15 mL) was added, and the mixture was extracted with ether and dried over sodium sulfate. After removal of solvent the excess amine was removed via Kugelrohr distillation under reduced pressure. The resulting solid was recrystallized from an ethanol/water mixture to afford amino amide **8** as colorless crystals: 0.11 g, 7% yield; mp 177–179 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (bs, 1 H), 2.79 (d, 3 H), 2.44 (m, 2 H), 1.84–0.97 (m, 20 H), 1.40 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 180.2 (s), 66.8 (s), 59.4 (d), 35.2 (t), 27.3, 26.23, 26.13, 25.93 (t); IR ($CHCl_3$) 3385, 3016, 2932, 2855, 1658, 1518, 1220 cm^{-1}. Anal. Calcd for $C_{17}H_{32}N_2O$: C, 72.81; H, 11.50; N, 9.99. Found: C, 72.69; H, 11.55; N, 10.18.

***N-tert*-Butyl-2-(*N,N*-diisopropylamino)-2-methylpropanamide (9).** A mixture of diisopropylamine (90 mmol, 12.6 mL) and *N-tert*-butyl-2-bromo-2-methylpropanamide (**3**) (1.0 g, 4.5 mmol) was cooled in ice–water bath, and powdered sodium hydroxide (0.36 g, 9.0 mmol) was added in one portion. The mixture was allowed to come to room temperature and heated to reflux overnight. The mixture was cooled to room temperature, water (10 mL) was added, and the mixture was extracted with ether. The organic layer was dried over sodium sulfate, and after removal of solvent 0.45 g of oily residue was recovered. Purification using flash chromatography (ether) afforded amino amide **9** as colorless crystals: 0.11 g, 10% yield; mp 39–40 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 (bs, 1 H), 3.09 (septet, 1 H), 1.38 (s, 6 H), 1.34 (s, 9 H), 1.18 (d, 12 H); ^{13}C NMR ($CDCl_3$) δ 178.7 (s), 67.2 (s), 49.9 (s), 48.4 (d), 28.6 (q), 25.3 (q), 23.9 (q); IR ($CHCl_3$) 3352, 2969, 1664, 1506, 1365 cm^{-1}; MS *m/e* 142 ($C_9H_{20}N^+$), 100 (t-BuNHCO$^+$), 98 ($C_6H_{12}N^+$), 84 ($C_5H_{10}N^+$). An analytically pure sample was obtained by sublimation (25 °C/0.1 Torr), mp 40–41 °C. Anal. Calcd for $C_{14}H_{30}N_2O$: C, 69.37; H, 12.47; N, 11.56. Found: C, 69.10; H, 12.64; N, 11.47.

***N*,2-Dimethyl-2-(*N,N*-diisopropylamino)propanamide (10).** A mixture of *N*,2-dimethyl-2-bromopropanamide (**5**) (10.0 g, 55.6 mmol) and diisopropylamine (157 mL) was stirred under nitrogen until completely dissolved. The mixture was cooled in an ice–water bath, powdered sodium hydroxide (4.45 g) was added, and the mixture was allowed to come to room temperature and stirred for 5 days. Water (100 mL) was added, and the mixture was extracted with ether and dried over sodium sulfate. After removal of solvent the excess amine was removed under reduced pressure overnight. The resulting solid was recrystallized from an ethanol/water mixture to afford amino amide **10** as coloreless crystals: 1.8 g, 17% yield; mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (bs, 1 H), 2.98 (septet, 2 H), 2.81 (d, 3 H), 1.41 (s, 6 H), 1.17 (d, 12 H); IR ($CHCl_3$) 3390, 2994, 1658, 1514 cm^{-1}. Anal. Calcd for $C_{11}H_{24}N_2O$: C, 65.95; H, 12.08; N, 13.98. Found: C, 66.02; H, 12.33; N, 13.92.

Attempted Preparation of *N-tert*-Butyl-2-[(2,2,6,6-tetramethylpiperidinyl)amino]-2-methylpropanamide. A mixture of 2-bromo-2-methyl-*N-tert*-butylpropanamide (**3**) (1.0 g, 4.5 mmol) and 2,2,6,6-tetramethylpiperidine (12.7 mL) was stirred under nitrogen until completely dissolved. The stirred mixture was cooled in an ice–water bath, powdered sodium hydroxide (0.36 g) was added, and the mixture was allowed to come to room temperature and stirred for 5 days. Water (15 mL) was added, and the mixture was extracted with ether and dried over sodium sulfate. After removal of solvent the excess amine was removed under reduced pressure overnight, and the residue was purified by flash chromatography (ethyl acetate) to afford *N-tert*-butyl-2-hydroxy-2-methylpropanamide (**11**) as a colorless solid: 0.16 g, 22% yield; mp 95–97 °C [lit.[43] 92–94 °C]; ^{1}H NMR ($CDCl_3$) δ 6.68 (bs, 1 H), 3.11 (bs, 1 H), 1.42 (s, 6 H), 1.36 (s, 9 H); IR ($CHCl_3$) 3610, 3413, 3019, 1666, 1519, 1366 cm^{-1}. No detectable amounts of the desired amino amide product was observed.

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