Notes

Reaction of Trialkylboranes with Nitrones: A Novel Route to α-Alkylated Hydroxylamines

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Trialkylboranes have been shown to function effectively as alkylating agents in reactions with a variety of substrates[1] (nitrogen and sulfur ylides, carbon monoxide, hydroperoxide, haloamines, halogenated carbanions, etc.). Such reactions are believed to proceed via substrate attack on the electrophilic boron with subsequent rearrangement of the resulting intermediate through migration of an alkyl group. We have recently been able to exploit such reactivity in the conversion of nitrones to α-alkylated hydroxylamines. Similar conversions in which Grignard reagents, organolithium reagents, and other organometallics function as alkylating agents have been reported.[2] N,N-Disubstituted hydroxylamines have received attention in recent years as precursors to nitroxide radicals which can be used as spin labels.[2d] Hydroxylamines can also be easily reduced, making this methodology appropriate to the preparation of α-alkylated amines as well.

α,*N*-Diphenyl nitrone **1** and 2,3,4,5-tetrahydropyridine *N*-oxide **2** were prepared by modifying previously reported syntheses.[3-6] Specific modifications are related in the Experimental Section. Three trialkylboranes, triethyl-, tributyl-, and tri-*sec*-butylborane, were selected to react with nitrones **1** and **2** in our studies. The alkylation process is shown in Scheme 1. In theory, up to three alkyl groups are available for transfer from each borane, but only *in situ* intermediates **3** and **4** have been observed in the reaction mixture prior to hydrolysis.

A summary of results is presented in Table 1. The reactions were carried out at 110 °C in sealed tubes, and the progress of the reactions was monitored by GC. Total disappearance of nitrone after 5 h indicated completion of reaction. At lower temperatures, consumption of nitrone was considerably retarded, and yields of the desired products were reduced. Hydrolysis of the crude product mixture was accomplished by adding 3 M NaOH and stirring for an additional 3 h. Yields for this two-step process ranged from 60 to 100%. The α-alkylated hydroxylamines thus generated were purified via preparative GC and were characterized by a variety of spectral methods (see Experimental Section).

An ideal stoichiometry of 3:1 nitrone:borane is suggested. In practice, this ratio was 2:1 in the case of nitrone **2**, but efficient conversion of nitrone **1** occurred only when the ratio was reduced to 1:1. This outcome could be the result of the less electrophilic nature of the α-carbon in nitrone **1**, decreased electrophilicity of boron as bound oxygens increase, increased stability of possible "ate" intermediates as oxygen substitution at boron increases, or increased nonbonded interactions arising in the attack of each subsequent equivalent of nitrone. Also noteworthy is the comparatively low yield which results when the alkyl group transferred is secondary (entries 3 and 6 in Table 1).

In conclusion, this methodology, which is experimentally facile, should provide a new means to synthesize a wide variety of α-alkylated hydroxylamines and with subsequent reduction the corresponding α-alkylated amines.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Analytical GC was performed using an OV-1 capillary column (12 m length, 0.20 mm diameter, 0.33 μm film thickness) coupled to a mass-selective detector. Preparative GC was carried out using an OV-17 column (8 ft length, 4 mm diameter) fitted with a TC detector. Elemental analyses were performed by Galbraith Laboratories, Inc. The trialkylbornaes were purchased from Aldrich Chemical Co. as solutions in hexane or THF. Yellow HgO was freshly prepared before each use by known protocol.

***N*-Phenylhydroxylamine.** Modification of Kamm's protocol[3] as outlined below provided hydroxylamine of higher purity and in greater yield. After carrying out the zinc reduction of nitrobenzene in aqueous ammonium chloride and filtering the hot solution which results, the filtrate was cooled to 5 °C and saturated with NaCl. This aqueous solution was extracted with 3 × 100 mL of CH_2Cl_2. The solvent was removed *in vacuo* from the combined organic extracts, and the resulting yellow solid was recrystallized from CH_2Cl_2 and hexanes.

α,*N*-Diphenyl Nitrone (1). Modification of Huisgen's procedure[4] in the manner below generated the desired material in significantly higher yield. To a solution of 9.50 g (87.1 mmol) of *N*-phenylhydroxylamine in 10 mL of absolute ethanol at 23 °C was added 9.24 g (87.1 mmol) of freshly distilled benzaldehyde dropwise over a period of 10 min. The resulting mixture was swirled briefly, stoppered, and placed in the freezer for 16 h. The white crystalline product (16.3 g, 82.7 mmol, 95% yield, mp 112–113 °C) was collected, washed with 20 mL of ice-chilled diethyl ether, and finally dried *in vacuo*.

***N*-Hydroxypiperidine.** The procedure of Handford[5] called for H_2O_2 oxidation of *N*-ethylpiperidine to proceed for 5 d. No decrease in yield was observed when the reaction was stopped after 3 d.

Representative Procedure for Preparation of α-Alkylated Hydroxylamines from Trialkylboranes and Nitrones. To an open tube under N_2 at rt was added 1.30 g (0.0131 mol) of nitrone **2** and subsequently 4.4 mL of a 1.0 M solution of triethylborane in THF via syringe. After sealing the tube, the mixture was heated with stirring at 110 °C for 5 h. The resulting mixture was allowed to cool to rt, and 5 mL of 3 M NaOH was

(1) (a) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press Limited: London, 1988. (b) Pelter, A.; Smith, K. Triorganylboranes. In *Comprehensive Organic Chemistry: The Synthesis and Reactions of Organic Compounds*; Barton, D., Ollis, W. D., Jones, D. N., Eds.; Pergamon Press Inc.; New York, 1979; Vol. 3, pp 687–940.

(2) (a) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press Inc.: New York, 1993; pp 391–393. (b) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473. (c) Delpierre, G. R.; Lamchen, M. *Quart. Rev.* **1965**, *19*, 329. (d) Breuer, E.; Aurich, H. G.; Nielsen, A. *Nitrones, Nitronates, and Nitroxides*; John Wiley & Sons: New York, 1989; pp 212–216.

(3) Kamm, O. *Organic Syntheses*; Wiley: New York, 1932; Collect. Vol. 1, p 435.

(4) Bruning, I.; Grashey, R.; Hauck, H.; Huisgen, R.; Seidl, H. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 1124.

(5) Handford, B. O.; Jones, J. H.; Young, G. T. *J. Chem. Soc.* **1965**, 6814–6827.

(6) Iwashita, T.; Kusumi, T.; Kakisawa, H. *J. Org. Chem.* **1982**, *47*, 230–233.

0022-3263/94/1959-3485$04.50/0

Scheme 1

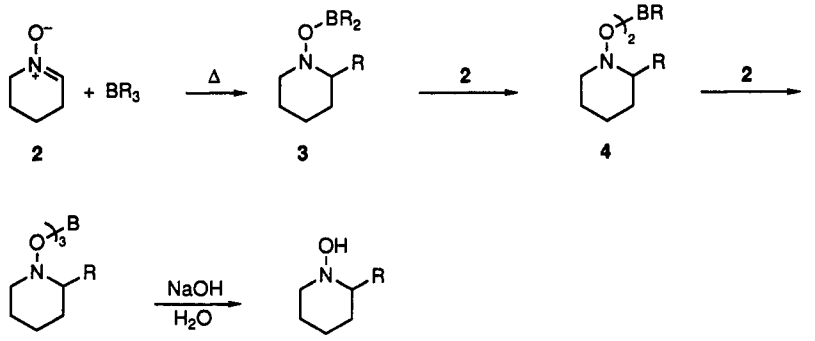
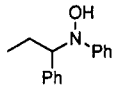
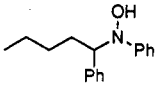
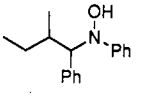
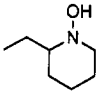
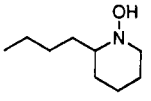
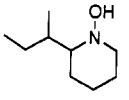


Table 1. Production of α-Alkylated *N*-Hydroxylamines by Reaction of Trialkylboranes with Nitrones

entry	nitrone	trialkylborane	product	% yield[a]
1	1	Et_3B		84
2	1	Bu_3B		74
3	1	*s*-Bu_3B		65[b]
4	2	Et_3B		97
5	2	Bu_3B		99
6	2	*s*-Bu_3B		63[b]

[a] Yields reported are GC yields using an internal standard with known response factors. [b] 1:1 Mixture of diastereomers.

added. Hydrolysis was complete after stirring for an additional 3 h. The solution was saturated with NaCl and extracted with 3 × 10 mL of CH_2Cl_2. After drying the combined organic extract with anhydrous Na_2SO_4 and removing the volatiles under reduced pressure, the crude product was isolated as a brown oil. A 96% yield of 2-ethyl-*N*-hydroxypiperidine was determined. Similar conditions were utilized for the reactions involving nitrone **1**, but the nitrone:borane ratio was set at 2:1. Yields were ascertained by analytical GC using tetradecane as an internal standard; relative response factors were experimentally determined. Pure samples of the product hydroxylamines were obtained via preparative GC.

***N*-Phenyl-*N*-(1-phenylpropyl)-*N*-hydroxylamine**: yield 84%; IR (film) 3410, 3024, 2963, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, *J* = 7.4 Hz), 1.81 (m, 2H), 4.05 (br s, 1H), 4.21 (t, 1H, *J* = 6.7 Hz), 6.50 (d, 2H, *J* = 8.0 Hz), 6.62 (t, 1H, *J* = 7.3 Hz), 7.06 (t, 2H, *J* = 7.7 Hz) 7.19–7.33 (m, 5H); ^1H NMR (DMSO-d_6) δ 0.86 (t, 3H, *J* = 6.8 Hz), 1.77–1.97 (m, 1H), 1.97–2.17 (m, 1H), 4.54 (t, 1H, *J* = 6.8 Hz), 6.63–7.50 (m, 10H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.8, 31.6, 59.7, 113.2, 117.1, 126.5, 126.8, 128.5, 129.0, 143.9, 147.5; ^{13}C NMR (DMSO-d_6) δ 12.7 (q), 26.5 (t), 70.1 (d), 116.7 (d), 120.6 (d), 127.8 (d), 128.7 (d), 129.4 (d), 129.9 (d), 141.7 (s), 153.9 (s); MS *m/z* (rel intensity) 211 (M^+ – 16, 12), 182 (100), 104 (10), 91 (20), 77 (19). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26%; H, 7.54%; N, 6.16%. Found: C, 79.00%; H, 7.76%; N, 6.16%.

***N*-Phenyl-*N*-(1-phenylpentyl)-*N*-hydroxylamine**: yield 74%; IR (film) 3413, 3023, 2930, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* = 6.8 Hz), 1.35 (m, 4H), 1.76 (m, 2H), 4.05 (br s, 1H), 4.27 (t, 1H, *J* = 6.7 Hz), 6.49 (d, 2H, *J* = 7.4 Hz), 6.60 (t, 1H, *J* = 6.6 Hz), 7.06 (t, 2H, *J* = 7.0 Hz), 7.17–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 28.5, 38.6, 58.2, 113.2, 116.9, 126.3, 126.8, 128.5, 129.0, 144.3, 147.5; MS *m/z* (rel intensity) 239 (M^+ – 16, 8), 182 (100), 104 (12), 91 (20), 77 (21). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96%; H, 8.29%; N, 5.49%. Found: C, 78.98%; H, 7.99%; N, 5.22%.

***N*-Phenyl-*N*-(1-phenyl-2-methylbutyl)-*N*-hydroxylamine**: yield 65% as a 1:1 mixture of diastereomers; IR (film) 3427, 3023, 2961, 1601, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (m, 12H), 1.18 (m, 2H), 1.48 (m, 2H), 1.77 (m, 2H), 4.05 (s, 2H), 4.18 (d, 1H, *J* = 5.1 Hz), 4.27 (d, 1H, *J* = 4.5 Hz), 6.46–6.60 (m, 3H), 7.02–7.27 (m, 17H); ^{13}C NMR ($CDCl_3$) δ 11.7, 12.0, 14.4, 16.0, 25.3, 26.8, 41.5, 41.8, 61.4, 62.5, 113.12, 113.14, 116.9, 126.6, 126.7, 126.9, 127.2, 127.3, 128.1, 128.2, 128.9, 129.0, 142.3, 142.9, 147.7; MS *m/z* (rel intensity) 239 (M^+ – 16, 5), 182 (100), 104 (9), 91 (5), 77 (18), 51 (5). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96%; H, 8.29%; N, 5.49%. Found: C, 80.43%; H, 8.36%; N, 5.60%.

2-Ethyl-*N*-hydroxypiperidine: yield 97%; IR (film) 3205, 2934, 2244, 1443 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J* = 7.6 Hz), 1.03–2.25 (m, 9H), 2.50 (t, 1H, *J* = 11.4 Hz), 3.29 (d, 1H, *J* = 10.0 Hz), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.2, 23.8, 25.7, 25.9, 30.3, 59.8, 69.0; MS *m/z* (rel intensity) 129 (M^+, 4), 100 (100), 83 (4), 55 (11).

2-Butyl-*N*-hydroxypiperidine: yield 99%; IR (film), 3297, 2928, 2859, 1658, 1464 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H), 0.99–1.84 (m, 11H), 2.15 (m, 2H), 2.44 (m, 1H), 2.63 (dt, 1H, *J* = 2.6, 11.7 Hz), 3.09 (bd, 1H, *J* = 12.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 23.0, 24.7, 26.0, 28.2, 32.3, 36.6, 47.0, 57.2; MS *m/z* (rel intensity) 141 (M^+ – 16, 2), 84 (100), 56 (13).

2-(1-Methylpropyl)-*N*-hydroxypiperidine: yield 63% as a mixture of diastereomers; IR (film) 3374, 2944, 2862, 1456, 1374 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–1.14 (m, 12H), 1.22–1.60 (m, 14 H), 1.76–2.03 (m, 5H), 2.15–2.35 (m, 3H), 2.79–2.96 (m, 2H), 3.49–3.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 22.2, 22.8, 23.0, 23.1, 24.2, 25.9, 26.2, 29.7, 30.5, 30.7, 35.3, 37.3, 37.7, 45.9, 61.6, 62.4; MS *m/z* (rel intensity) 141 (M^+ – 16, 2), 84 (100), 56 (13).

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