($\overline{OCH_2CH^+}$) and 330 kJ mol^{-1} less stable than the acetyl cation ($CH_3C{\equiv}O^+$) to which it collapses without an energy barrier. However, by charge reversal of the enolates of acetaldehyde and acetone Lehman et al.[14] have produced the formyl methyl and acetyl methyl carbocations and have shown that they give distinctive fragment ion spectra although this requires only a very short lifetime of the carbocations. Further experiments are in progress in an attempt to characterize the gaseous ion structures more completely.

Finally, the behavior of mandelonitrile in the gas phase is at variance with its solution behavior. In the gas phase protonated mandelonitrile fragments, entirely by elimination of HCN, to give the stable hydroxybenzyl (or hydroxytropylium) carbocation, while in solution mandelonitrile[15] or its mesylate[16] when treated with strong acids form the electron-deficient carbocation Ph^+CHCN. The reasons for this difference are not clear.

Experimental Section

The chemical ionization mass spectra were obtained on a DuPont 21-490 mass spectrometer equipped with a high-pressure source using methane as reagent gas at ~0.3-torr pressure. Source temperatures of 50–100 °C were employed and samples were introduced through a heated inlet system (100–110 °C) for liquids or by direct insertion probe for solids. The spectra reported are the averages of at least three runs on each sample.

All the compounds investigated, except the methyl esters **2**, **6**, and **10**, were commercial samples, the purities of which were checked by gas chromatography. The methyl esters were prepared by esterifying the corresponding acid with methanol using standard procedures and were purified by distillation.

Acknowledgment. We are indebted to the Natural Science and Engineering Research Council of Canada for financial support.

Registry No. 1, 50-21-5; 2, 547-64-8; 3, 2043-43-8; 4, 513-86-0; 5, 90-64-2; 6, 771-90-4; 7, 4410-31-5; 8, 119-53-9; 9, 76-93-7; 10, 76-89-1; 11, 3524-62-7; 12, 532-28-5; 13, 103-82-2; 14, 117-34-0.

(14) Lehman, J. A.; Bursey, M. M.; Hass, J. R. *Org. Mass Spectrom.* **1983**, *18*, 373.
(15) Olah, G. A.; Prakash, G. K. S.; Arvanghi, M. *J. Am. Chem. Soc.* **1980**, *102*, 6640.
(16) Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 12149

Chloromethylation of 1-Bromo-2-methoxynaphthalene. A Revised Structure for the Product

James R. McCarthy*

Medicinal Chemistry, Merrell Dow Research Institute, Indianapolis, Indiana 46268

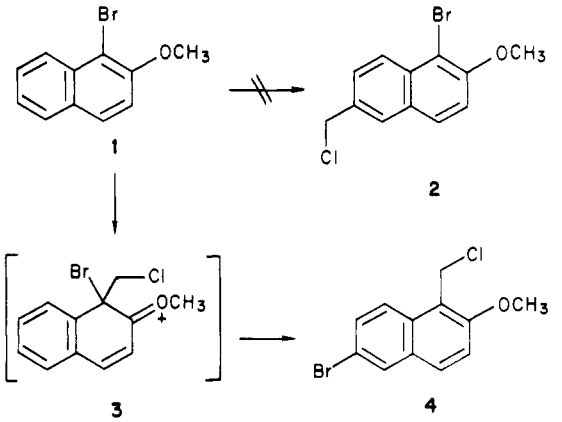
John C. Huffman

Molecular Structure Center, Chemistry Department, Indiana University, Bloomington, Indiana 47405

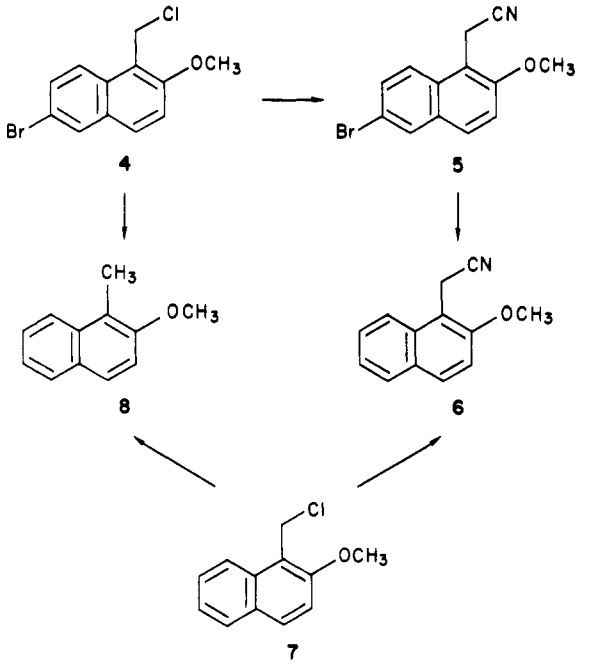
Received May 1, 1984

During the course of synthesizing metabolites of napactidine (DL-588) (**12a**),[1] a potential antidepressant agent, a sample of 6-methoxy-2-naphthaleneacetonitrile (**11a**) was required for subsequent demethylation[2] and conversion to the 6-hydroxy metabolite **12b**.[1b] The route initially chosen to prepare **11** utilized 1-bromo-6-(chloromethyl)-2-methoxynaphthalene (**2**)[3] as an intermeidate. On repetition of the procedure of Sy and Oiry[3] for the preparation of **2**, (see Scheme I) a compound was isolated in the same yield, with the same melting point and IR spectrum as those reported. The chloromethylation product (shown to be **4**; vide infra) (see below) was treated with sodium cyanide under

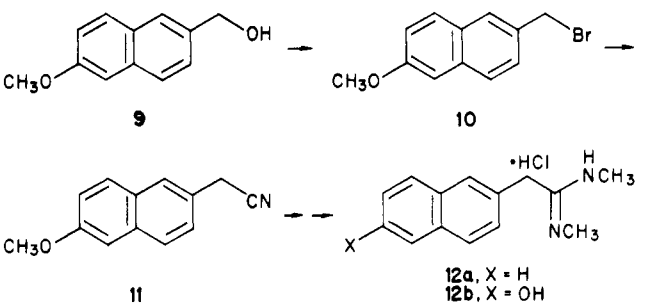
Scheme I



Scheme II



Scheme III



(1) (a) McCarthy, J. R. (The Dow Chemical Company) U. S. Patent 3 903 163; *Chem. Abstr.* **1975**, *83*, 192933q. (b) McCarthy, J. R.; Wright, D. L.; Schuster, A. J.; Abdullah, A. H.; Shea, P. J., manuscript in preparation. (c) Goralski, C. T.; McCarthy, J. R.; Linowski, J. W.; Nyquist, R. A.; Putzig, C. L. *J. Labelled Compds. Radiopharm.* **1981**, *18*, 1047.

(2) McCarthy, J. R.; Moore, J. L.; Cregge, R. L. *Tetrahedron Lett.* **1978**, 5183.
(3) Sy, M; Oiry, J. *Bull. Soc. Chim. Fr.* **1967**, 3759.

0022-3263/84/1949-4995$01.50/0

phase-transfer conditions (see Scheme II) and the bromine from the resulting bromomethoxy nitrile **5** was removed with tributyltin hydride. The IR spectrum of the isolated methoxynaphthaleneacetonitrile **6** contained out of plane bending bands for a 1,2-disubstituted naphthalene at 800 cm^{-1} (two adjacent H) and 750 cm^{-1} (four adjacent H). The inconsistency of the IR spectrum for this derivative of the chloromethylation product with the reported structure led to the preparation of 6-methoxy-2-naphthaleneacetonitrile (**11**) by an unambiguous route outlined in Scheme III. 2-(Hydroxymethyl)-6-methoxynaphthalene (**9**)[4] was carefully converted to the bromomethyl compound **10** with hydrogen bromide and the highly reactive intermediate **10** was treated with sodium cyanide to provide 6-methoxy-2-naphthaleneacetonitrile (**11**) in good yield. We first reported this compound, without experimental details, as an example for our procedure for deblocking aromatic methyl esters[2]. An alternate synthesis of **11** has recently been published.[5] The melting point of **11** (mp 103–104 °C) was almost identical with that of **6** (mp 100–103 °C). However, the IR spectrum of **11** was considerably different from that of the methoxynaphthaleneacetonitrile **6** prepared from the chloromethylation product **4**. The IR spectrum of **11** displayed bands at 855 cm^{-1} (isolated H) and 820 cm^{-1} (2 adjacent H), consistent with the assigned structure. Hydrogenation of the chloromethylation product described by Sy and Oiry[3] gave 1-methyl-2-methoxynaphthalene (**8**) (Scheme II), identical with the product obtained from the hydrogenation of 1-(chloromethyl)-2-methoxynaphthalene (**7**).[6] Additional proof for the entry of the chloromethyl group at the 1-position of 1-bromo-2-methoxynaphthalene (**1**), to form **3**, followed by the migration of the bromine was obtained by a two-step conversion of this product (**4**) to 2-methoxy-1-naphthaleneacetonitrile (**6**) (see Scheme II). This material was identical with the nitrile obtained from 1-(chloromethyl)-2-methoxynaphthalene.[6]

The complete structure of the chloromethyl product orginally assigned as **2** by Sy and Oiry[3] was established as 6-bromo-1-(chloromethyl)-2-methoxynaphthalene (**4**) by X-ray crystallographic analysis. An ORTEP drawing of **4** is included in the supplementary material section. To our knowledge, this represents a novel rearrangement of a 1-halo-2-methoxynaphthalene on treatment with an electrophile.[7] However, this type of rearrangement is not without precedent. Perrin[8] has reported that the product obtained on treatment of 1-chloro-2-naphthol with 90% nitric acid, 1-chloro-1-nitronaphthalene-2(1*H*)-one, provides 1-chloro-6-nitro-2-naphthol on acid-catalyzed rearrangement.

No halogen migration was noted when 1-chloro-2-methoxynaphthalene was treated under chloromethylation conditions as reported by Sy and Oiry[3]. However, 1-iodo-2-methoxynaphthalene under these conditions gave a dark purple reaction solution that was a multicomponent mixture as judged by TLC. As we[9] and others[10] have observed, bromine has a greater propensity for migration than chlorine. Studies on the mechanism of this rearrangement are in progress.

Experimental Section

All melting points are uncorrected. The IR spectra were recorded with a Perkin-Elmer Model 727 spectrophotometer. NMR spectra were determined with a Varian T-60 and a Perkin-Elmer R32 (90 MHz) instrument. Thin layer chromatography (TLC) was run with Quantum Q1F silia gel plates using the following solvent systems: (1) chloroform-methanol (9:1), (2) chloroform–hexane (1:1), (3) methanol–40% aqueous methylamine (98:2), (4) chloroform. TLC solvent systems are given in parentheses.

6-Bromo-1-(chloromethyl)-2-methoxynaphthalene (4). The precedure of Sy and Oiry[3] used to prepare the compound they assigned 1-bromo-6-(chloromethyl)-2-methoxynaphthalene (**2**) was followed. 1-Bromo-2-methoxynaphthalene (**1**) (60 g, 0.25 mol), glacial acetic acid (175 mL), 37% aqueous formaldehyde (32.5 g, 0.4 mol), and 125 ml of concentrated hydrochloride acid were added to a three–necked 1-L round-bottomed flask with overhead stirrer, thermometer, and gas inlet tube. The mixture was warmed to 45 °C with a stream bath, and HCl gas was bubbled into the mixture. The reaction warmed to 60 °C and all the starting material went into solution and a light purple material crystallized out of the reaction. After 1 h the reaction started to cool and could be worked up at this point; however, the addition of HCl gas was continued an additional 2.5 h, and the reaction temperature was kept above 50 °C with a steam bath as in the procedure of Sy and Oiry[3]. The product was collected on a sintered glass Buchner funnel and washed with water. Recrystallization from 250 mL of acetone gave 41 g (57.5%) of product. An analytical sample of **4** was obtained by recrystallization from acetone: mp 139–140 °C (lit.[3] mp 144 °C); NMR (Me_2SO-d_6) δ 4.0 (s, 3, OCH_3), 5.2 (s, 2, CH_2Cl), 7.4–8.5 (m, 5); IR (nujol) 2240, 880, 800 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}OBrCl$: C, 50.47; H, 3.53. Found: C, 50.31; H, 3.36.

6-Bromo-2-methoxy-1-naphthaleneacetonitrile (5). A solution of 6-bromo-1-(chloromethyl)-2-methoxynaphthalene (**4**) (5.7 g, 0.02 mol) CH_2Cl_2 (30 ml) and benzyltriethylammonium chloride (0.45 g, 1 mmol) was treated with an aqueous solution (5 mL) of KCN (2.6 g, 0.04 mol) at a gentle reflux for 2.5 h. The reaction was monitored by TLC (SS2) and showed one spot that ran different than the starting material. The organic layer was washed with water (3 × 50 mL), dried (Na_2SO_4), and evaporated to a solid. The solid was recrystallized from 60 mL of CCl_4; yielding white crystals of the nitrile **5** (4.0 g, 73%): mp 140–3 °C; NMR ($CDCl_3$–Me_2SO-d_6) δ 4.0 (s, 3, OCH_3), 4.1 (s, 2, CH_2CN), 7.0–8.0 (7, 5); IR (Nujol) 2250, 895, 800 cm^{-1}.

2-Methoxy-1-naphthaleneacetonitrile (6).[11] **Method A.** A mixture of 6-bromo-2-methoxy-1-naphthaleneacetonitrile (**5**) (2.76 g, 0.01 mol) and tributyltin hydride (4.5 g, 0.015 mol) were heated with stirring in an oil bath at 140 °C under a nitrogen atmosphere. The reaction was monitored by gas chromatography (5 ft 5% SE 30 column). After 4 h the reaction was partially cooled and hexane (30 mL) was added. The mixture was cooled in an ice bath, and the off-white crystals were collected by filtration. The product was recrystallized from 100 mL of hexane, yielding white crystals of **6** (1.0 g, 50%): mp 100–3 °C, softens at 97 °C; NMR ($CDCl_3$) δ 3.93 (s, 3, OCH_3), 4.07 (s, 2, CH_2CN), 7.0–8.0 (m, 6); IR (Nujol) 2250, 800, 750 cm^{-1}.

Method B. The procedure of Cook et al.[11] was followed. 1-(Chloromethyl)-2-methoxynaphthalene (**7**)[6] (18 g, 0.087 mol) was dissolved in warm (35 °C) acetone (600 mL), filtering the mixture to remove a small amount on insoluble material. The solution was stirred for 1 h with an aqueous solution (300 mL) of KCN (12 g, 0.18 mol) at 30–35 °C. The reaction was concentrated to one-third of its original volume and diluted with water. After standing for 1 h the white crystals were collected by filtration. Recrystallization from acetone–water (175 mL–50 mL) gave fluffy white crystals of **6** (10.6 g, 61%), mp 106–8 °C (lit.[11] mp 111 °C) identical with TLC, IR and NMR to the product prepared by method A.

(4) Schreiber, K. C.; Byers, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 859. 6-Bromo-2-methoxynaphthalene was converted into 6-methoxy-2-naphthoic acid via a Grignard reaction (CO_2 quench) and subsequently reduced to **9** with $LiAlH_4$.

(5) Eriguchi, A.; Takegoshi, T. *Chem. Pharm. Bull.* **1982**, *30*, 428.

(6) Badger, G. M.; Carrathers, W.; Cook, J. W. *J. Chem. Soc.* **1949**, 1768.

(7) For a review on the chloromethylation of aromatic compounds, see: Olah, G. A.; Tolgyesi, W. S. "Friedel-Crafts and Related Reactions"; Olah, G. A., Ed.; Interscience: New York, 1963; Vol. 2, pp 659–784. To our knowledge this represents the first example of $ClCH_2^+$ displacing a group other than hydrogen on an aromatic ring.

(8) Perrin, C. L. *J. Org. Chem.* **1971**, *36*, 420.

(9) Reinke, C. E.; McCarthy, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 6376.

(10) Peterson, P. E.; Boron, W. F. *J. Am. Chem. Soc.* **1971**, *93*, 4076.

(11) Cook, A. H.; Dowher, J.; Hornuhg, B. *J. Chem. Soc.* **1941**, 502.

2-Methoxy-1-methylnaphthalene (8).[12] **Method A.** 1-(Chloromethyl)-2-methoxynaphthalene (**7**)[6] (4.2 g, 0.02 mol) was dissolved in 200 mL of room temperature ethyl acetate and filtered from a small amount of insoluble material. Calcium carbonate (4 g) and 5% Pd/C (0.7 g) was added to the solution, and the mixture was hydrogenated at 50 psi for 2 h. The reaction was filtered through a Celite pad, and the filtrate was evaporated to dryness. The resulting oil was extracted with hot hexane (50 mL). The extracts were evaporated to an oil that formed white crystals of **8** (3.0 g, 87%) on cooling in an ice bath. Recrystallization from 12 mL of methanol gave analytically pure crystals (1.6 g): mp 39–39.5 °C (lit.[12] mp 39 °C); IR (thin film) 800, 740 cm^{-1}.

Method B. 6-Bromo-1-(chloromethyl)-2-methoxynaphthalene (**4**) (5.7 g, 0.02 mol) was dissolved in 125 mL of warm ethyl acetate. Triethylamine (5 mL) and 5% Pd/C (500 mg) were added, and the mixture was hydrogenated as in method A. The reaction was worked up as above and the white crystals of **8** (3.3 g, 96%); mp 35–7 °C, were identical by IR and NMR with the product prepared by method A.

2-(Hydroxymethyl)-6-methoxynaphthalene (9).[14] 6-Methoxy-2-naphthoic acid[13] (202 g, 1 mol) was dissolved in 1 L of dry THF (warm) and added dropwise to a mixture of dry THF (2 L) and 40 g (1 mol) of $LiAlH_4$ while cooling the reaction with an ice bath. The reaction mixture was stirred overnight at room temperature; cooled in an ice bath, and quenched by the consecutive dropwise addition of 40 mL of water, 40 mL of 15% aqueous NaOH, and 120 mL of water. The mixture was filtered and the precipitate washed with hot THF. The light yellow filtrate was evaporated to dryness and the solid was recrystallized from 800 mL of ethanol, yielding white crystals of **9** (137 g, 73%): mp 116–118 °C (lit.[14] mp 116–117 °C); NMR (Me_2SO-d_6) δ 3.85 (s, 3, OCH_3), 4.65 (d, 2, J = 5 Hz, CH_2), 5.23 (t, 1, J = 5 Hz, OH), 7.1–7.9 (m, 6).

2-(Bromomethyl)-6-methoxynaphthalene (10).[4] In a 1-L three-necked round-bottomed with football stirrer, gas inlet tube, and drying tube was added 56.4 g (0.3 mol) of finely powdered 2-(hydroxymethyl)-6-methoxynaphthalene (**9**). The mixture was stirred and kept between 15 °C and 20 °C in an ice bath while HBr gas was bubbled into the mixture. Hydrogen bromide addition was terminated when a homogenous light green solution was obtained. The reaction was poured over 500 mL of ice-cold 10% aqueous Na_2CO_3, and the organic layer was washed with water (300 mL), dried (Na_2SO_4), and evaporated to dryness (warm water bath). The resulting white solid was recrystallized from 250 mL of hexane by cooling to −10 °C; and the crystals of **10** were collected by filtration: mp 84–5 °C (lit.[4] mp 79–80 °C); TLC (SS2) showed one fast moving spot. The filter cake was air-dried for 2 min and used directly for the preparation of the nitrile **11**.

6-Methoxy-2-naphthaleneacetonitrile (11). The 2-(bromomethyl)-6-methoxynaphthalene (**10**) from the above reaction (assumed 0.3 mol) was dissolved in 500 mL of CH_2Cl_2. Benzyltriethylammonium chloride (13.7 g. 0.06 mol) and NaCN (45 g, 0.9 mol) dissolved in 75 mL of hot water were added to the reaction. The two-phase system was heated gently with a steam bath and stirred (overhead stirrer). The reaction was monitored by TLC (SS2). After 20 h the organic layer was washed with brine (3 × 100 mL), dried (Na_2SO_4), evaporated, and the residue was recrystallized from 600 mL of ethanol to give a 76% yield (45.0 g) of nitrile **11**: mp 102–3 °C. Recrystallization of 500 mg from 8 mL of ethanol gave an analytical sample: mp 103–4 °C; IR (KBr) 2230, 855, 820 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.97; H, 5.76; N, 7.05.

Registry No. **1**, 3401-47-6; **4**, 92643-16-8; **5**, 92643-17-9; **6**, 71056-97-8; **7**, 67367-39-9; **8**, 1130-80-9; **9**, 60201-22-1; **10**, 73022-40-9; **11a**, 71056-96-7; 6-methoxy-2-naphthoic acid, 2471-70-7.

Supplementary Material Available: (a) Crystallography methods discussion, (b) Figure 1, ORTEP drawing of **4**, (c) Table I, crystal data summary for **4**, (d) line drawing of **4** showing numbering scheme, (e) Table II listing fractional coordinates for atoms in **4**, (f) Table III listing angles in degrees for **4**, (g) Table IV listing bond distances in angstroms for **4**, (h) Table V listing anisotropic thermal parameters (7 pages). Ordering information is given on any current masthead page.

(12) Fries, K.; Huber, B, *Chem. Ber.* **1906**, *39*, 442.
(13) Tard, C.; Lapin, H.; Horean, A. *C. R. Hebd. Seances Akad. Sci.* **1958**, *246*, 3644.
(14) Ferns, R. T.; Hamer, D., *J. Chem. Soc.* **1961**, 1409.

A New Synthesis of Medium and Large Membered Lactones via Denitration of Nitro Lactones

Noboru Ono,* Hideyoshi Miyake, and Aritsune Kaji*

Department of Chemistry, Faculty of Science, Kyoto University, Kyoto 606, Japan

Received September 22, 1983

Although a number of methods for preparing macrolides have been reported,[1] the recent method based on ring expansion of 2-(3-hydroxypropyl)-2-nitrocyclohexanones **1** to nitro lactones **2** as in Scheme I is very attractive, for **2** can be prepared in good yields from readily available materials and without requirement of tedious procedures such as high dilution and/or very slow mixing of reactants.[2,3] It was originally reported that **2** could be converted into keto lactones by the Nef reaction, but we felt that conversion of **2** into nitro-free lactones **3** via direct replacement of the nitro group by hydrogen would be highly desirable for preparing macrolides. In this paper we report the realization of this conversion by treatment of **2** with tributyltin hydride, (Bu_3SnH).

We have reported that aliphatic nitro groups are efficiently replaced by hydrogen without affecting other functional groups on treatment with Bu_3SnH (1.3 equiv) in the presence of azobis(isobutyronitrile) (AIBN, 0.3 equiv) at 80 °C for 1–2 h.[4] This reaction is now being used as a useful strategy for organic synthesis.[5] However, this procedure cannot be applied to the denitrohydrogenation of all kinds of nitroalkanes. In general, primary and secondary nitro groups are not replaced by hydrogen in good yields by this procedure.[6] For example, heating a mixture of 6-nitro-9-nonanolide (**2a**), Bu_3SnH (1.3 equiv), and AIBN (0.3 equiv) in benzene for 2 h at 80 °C gave only a trace amount of 9-nonanolide (**3a**). And unidentified products were mainly obtained. The use of Bu_3SnH in large excess improved the yield of **3a**. Heating a mixture of **2a**, Bu_3SnH (5 equiv), and AIBN (0.8 equiv) in toluene at 110 °C for 30 min gave **3a** in 26% yield. Similarly, 12-nitro-15-pentadecanolide (**2b**, n = 10) was converted into 15-pentadecanolide (**3a**) in 25% yield.

The present denitration was applied to the synthesis of 9-decanolide (**3c**) (Scheme II), which is a natural product

(1) See the following reviews: (a) Nicolaou, K. C. *Tetrahedron* **1977**, 683. (b) Masamune, S.; Bates, G. S.; Corcoran, I. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (c) Back, T. G. *Tetrahedron* **1977**, 3041.
(2) Cookson, R. C.; Ray, P. S. *Tetrahedron Lett.* **1982**, *23*, 3521.
(3) (a) Kostova, K.; Lorenzi-Riatsch, A.; Nakashita, Y.; Hesse, M. *Helv. Chim. Acta* **1982**, *65*, 249. (b) Kostova, K.; Hesse, M. *Ibid.* **1983**, *66*, 741. (c) Nakashita, Y.; Hesse, M. *Ibid.* **1983**, *66*, 845.
(4) Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1982**, *23*, 2957.
(5) (a) Ono, N.; Miyake, H.; Kaji, A. *J. Chem. Soc., Chem. Commun.*, **1982**, 33. (b) Ono, N.; Miyake, H.; Fujii, M.; Kaji, A. *Tetrahedron Lett.* **1983**, *24*, 3477, and references therein.
(6) The nitro group of the following secondary nitro compounds is replaced by hydrogen in good yields by this procedure, i.e., benzylic and allylic nitro compounds, α-nitro ketones, and α-nitro esters.[4] The reason for this difficulty for denitration of secondary nitro compounds is not clear yet, but probably nitro compounds are reduced to the nitrogen derivatives on treatment with Bu_3SnH when the carbon–nitrogen bond is hard to break.

0022-3263/84/1949-4997$01.50/0