Table I. Thioformamides HC(=S)NRR'

R	R'	yield,[a] %	mp, °C (bp)	lit.
n-C_4H_9	n-C_4H_9	72	(105-112 [0.9 Torr])	(153 [12 Torr])[10]
$-CH_2CH_2OCH_2CH_2-$		66	68-69	67-68[10]
$-(CH_2)_4-$		58	(70-100 [1.1 Torr])	(100-110 [1 Torr])[11]
n-C_4H_9	H	63	(85-108 [1.1 Torr])	(160-172 [25 Torr])[12]
t-C_4H_9	H	63	123.5-125	124-125[12]
C_6H_5	H	73	139-140	137-139[12]

[a] Yield for two steps based on ethyl orthoformate.

procedure, both steps are carried out in a single flask, affording thioformamides from primary or secondary amines quickly, under mild conditions, and in superior overall yields (Table I).

Experimental Section

Ethyl Thioformate. Approximately 150 mg of 70% perchloric acid was placed in a 100-mL round-bottom flask equipped with magnetic stirring and a two-way stopcock with a balloon reservoir. The flask was evacuated, and then hydrogen sulfide gas from a lecture bottle was introduced via the balloon. Triethyl orthoformate (7.5 mL, 6.7 g, 0.045 mol) was injected through a septum and stirring begun at ambient temperature. The liquid soon became yellow. After 3 h, gas absorption ceased, as noted by balloon shrinkage. The excess H_2S was evacuated briefly and replaced with nitrogen. ^1H NMR analysis of the liquid showed a 77-83% yield of ethyl thioformate (δ 9.68, s) along with 5-21% ethyl formate (δ 7.95, s) plus ethanol. This solution was used directly without separation in the preparation of thioformamides.

Thioformamides. General Procedure. The primary or secondary amine (0.045 mol) was added dropwise to the ethyl thioformate with stirring. The solution became warm and brown. After 30 min, the ethanol was evaporated under vacuum and the residue was distilled, sublimed, or recrystallized.

Registry No. S=CHN(C_4H_9)$_2$, 13749-55-8; S=CHN(CH_2CH_2)$_2$O, 5780-30-3; S=CHN(CH_2)$_4$, 2474-33-1; S=CHNHC_4H_9, 60448-30-8; S=CHNHC_4H_9-t, 20278-31-3; S=CHNHC_6H_5, 637-51-4; NH(C_4H_9)$_2$, 111-92-2; HN(CH_2CH_2)$_2$O, 110-91-8; HN(CH_2)$_4$, 123-75-1; $H_2NC_4H_9$, 109-73-9; $H_2NC_4H_9$-t, 75-64-9; $H_2NC_6H_5$, 62-53-3; triethyl orthoformate, 122-51-0; ethyl thioformate, 29392-46-9.

(9) Walter, W.; Schaumann, E. *Chem. Ber.* **1971**, *104*, 3361.
(10) Walter, W.; Maerten, G. *Justus Liebigs Ann. Chem.* **1963**, *669*, 66.
(11) Maier, L. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 141.
(12) deBenneville, P. L.; Strong, J. S.; Elkind, V. T. *J. Org. Chem.* **1956**, *21*, 772.

N-Iodosuccinimide-Mediated Conversion of Aldehydes to Methyl Esters

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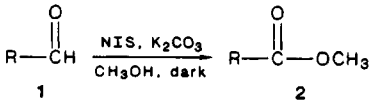
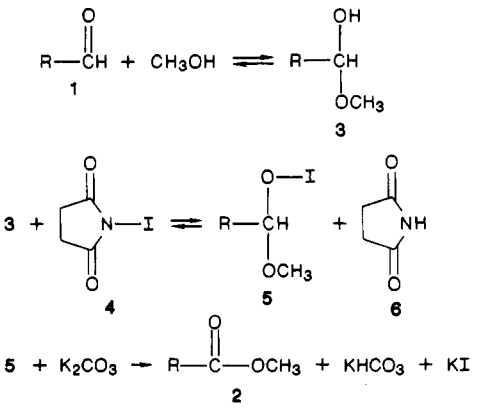
The conversion of aldehydes to esters has traditionally been accomplished by a two-step reaction sequence (oxidation followed by esterification). Results in this laboratory indicate that *N*-iodosuccinimide (NIS, **4**) can oxidize a wide variety of aldehydes to the corresponding methyl esters with high efficiency in a single step.[1,2] The reaction



1 2

Scheme I



is thought to proceed as indicated in Scheme I. The initially formed methyl hemiacetal (**3**) is oxidized by NIS to the corresponding hemiacetal hypoiodite (**5**).[3] Subsequent elimination of hydrogen iodide produces the observed product.[4] We believe the mechanism to be ionic in nature since a moderately strong base was shown to be required (substitution of potassium bicarbonate for potassium carrbonate stopped the reaction), the reaction proceeded faster in polar solvents, and light (or oxygen) had no positive effect on either the reaction rate or ultimate yield of the product. The success of this reaction is dependent upon the selective oxidation of the methyl hemiacetal hydroxyl moiety in the presence of a much higher concentration of methanol. Such selectivity appears reasonable since it is known that more subsitituted alcohols are oxidized at significantly faster rates by NIS. In a competition experiment, NIS oxidized 2-undecanol (via a secondary hypoiodite) six times faster than 1-tetradecanol (via a primary hypoiodite).[5,6]

The results of our studies are shown in Table I. The reaction is typically carried out by treating the aldehyde (0.1 M in methanol) with 2.5 equiv of both NIS and potassium carbonate at room temperature (method A). The reaction is performed in the dark to prevent the light-induced homolytic decomposition of the intermediate hypoiodite.[7] Under these conditions straight-chain aliphatic, branched aliphatic, and conjugated aldehydes can all be oxidized to the corresponding methyl esters in good to excellent yields. This conversion can also be carried out in acetonitrile by treating a 0.1 M solution of the aldehyde with 2.5 equiv of NIS, 2.5 equiv of potassium carbonate,

(1) Preliminary results were disclosed at the Second National Conference on Undergraduate Research, University of North Carolina at Asheville, April 21-23, 1988.
(2) For other single-step procedures for the oxidation of aldehydes to esters, see: (a) Okimoto, M.; Chiba, T. *J. Org. Chem.* **1988**, *53*, 218. (b) Stevens, R.; Chapman, K.; Stubbs, C.; Tam, W.; Albizati, K. *Tetrahedron Lett.* **1982**, *23*, 4647. (c) Sundararaman, P.; Walker, E.; Djerassi, C. *Tetrahedron Lett.* **1978**, *19*, 1627.
(3) The oxidation of alcohols to hypoiodites is well known, see: (a) Meystere, C.; Heusler, K.; Kalvoda, J.; Wieland, P.; Anner, G.; Wettstein, A. *Experientia* **1961**, *17*, 475. (b) Beebe, T.; Barnes, B.; Bender, K.; Halbert, A.; Miller, R.; Ramsay, M.; Ridenour, M. *J. Org. Chem.* **1975**, *40*, 1992.
(4) The conversion of alcohols to aldehydes and ketones via presumed hypohalite intermediates has been reported, see: (a) Filler, R. *Chem. Rev.* **1963**, *63*, 21. (b) Beebe, T.; Hensley, V.; Ng, F.; Noe, R.; Scott, D. *J. Org. Chem.* **1985**, *50*, 3015.
(5) The greater rate of decomposition of more highly substituted hypochlorites and hypobromites has also been reported. See ref 2b and Filler, R. *Chem. Rev.* **1963**, *63*, 21.
(6) A reviewer suggested an alternative mechanism involving direct electrophilic attack by NIS on the aldehyde to produce RC(O-I)H$^+$. This carbocation would then be trapped by methanol to produce hemiacetal hypoiodite **5**.
(7) Heusler, K.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525.

0022-3263/89/1954-1213$01.50/0

Table I. Synthesis of Methyl Esters

entry	aldehyde	method[a]	NIS, equiv	time, h	product yield,[b] %
1	nonanal	A	2.5	4.0	80
2	nonanal	B	3.0	7.0	81[c]
3	dodecanal	A	2.5	3.5	93
4	dodecanal	B	3.0	9.0	77
5	tetradecanal	A	2.5	3.5	82
6	cyclohexanecarbaldehyde	A	2.5	2.5	70
7	cyclohexanecarbaldehyde	B	3.0	6.0	92[c]
8	2-phenylethanal	A	2.5	3.0	69
9	5-hexenal	A	2.5	3.5	72
10	benzaldehyde	A	2.5	3.0	89
11	benzaldehyde	B	3.0	22.0	42
12	3-pyridinecarbaldehyde	A	2.5	3.0	83
13	3-pyridinecarbaldehyde	B	3.0	15.0	80
14	3-nitrobenzaldehyde	A	2.5	4.0	88
15	*trans*-cinnamaldehyde	A	2.8	23.0	62
16	*trans*-cinnamaldehyde	B	3.0	24.0	0
17	2-methylbenzaldehyde	A	3.5	29.0	66
18	2-methylbenzaldehyde	B	3.0	22.0	15[c]

[a] A: reactions were performed using 1 mmol of aldehyde (0.1 M in methanol) with 1 equiv K_2CO_3 per equivalent of NIS at room temperature. B: reactions were performed using 1 mmol of aldehyde (0.1 M in acetonitrile) with 5 mmol of CH_3OH and 1 equiv of K_2CO_3 per equivalent NIS at room temperature. [b] Isolated yields except where noted. [c] Yield determined by GC.

and 5 equiv of methanol (method B). The range of aldehydes amenable to this oxidation procedure is much more limited.

It is our belief that cases in which long reaction times or low yields result can be attributed to an unfavorable equilibrium for the formation of the requisite hemiactal in step 1 of the proposed mechanism. This unfavorable equilibrium can result from either disruption of conjugation or increased steric strain upon addition of methanol. Both factors are clearly important in the oxidation of 2-methylbenzaldehyde (entries 17 and 18). Unhindered aliphatic aldehydes and electron-poor aromatic aldehydes react well under both sets of conditions.

It is interesting to note the behavior of the related halo imides NCS and NBS in this transformation. *N*-Chlorosuccinimide did not oxidize aldehydes to esters to any significant extent. Straight chain aldehydes are susceptible to oxidation by NBS under the indicated conditions. Rather vigorous conditions were required to oxidize conjugated aldehydes with NBS.[8]

$$CH_3(CH_2)_7CHO \xrightarrow[CH_3OH\ (0.1\ M),\ 60\ °C,\ dark,\ 24\ h]{2.5\ equiv\ of\ NCS,\ 2.5\ equiv\ of\ K_2CO_3} CH_3(CH_2)_7CO_2CH_3 \quad 1\%$$

$$CH_3(CH_2)_7CHO \xrightarrow[CH_3OH\ (0.1\ M),\ room\ temperature,\ dark,\ 8\ h]{2.5\ equiv\ of\ NBS,\ 2.5\ equiv\ of\ K_2CO_3} CH_3(CH_2)_7CO_2CH_3 \quad 65\%$$

$$PhCHO \xrightarrow[CH_3OH\ (0.1\ M),\ 37\ °C,\ dark,\ 24\ h]{5.0\ equiv\ of\ NBS,\ 5.0\ equiv\ of\ K_2CO_3} PhCO_2CH_3 \quad 52\%$$

In summary, a mild procedure for the one-step oxidation of aldehydes to methyl esters has been uncovered. Extension of this methodology to the conversion of primary alcohols to methyl esters is currently under investigation.

Experimental Section

Reactions were performed in oven-dried, foil-wrapped glassware under a nitrogen atmosphere. The aldehydes were purchased from Aldrich and distilled prior to use. Acetonitrile was distilled from calcium hydride, and methanol was distilled from oven-dried 3A molecular sieves prior to use. *N*-Iodosuccinimide was synthesized by the method of Vankar[9] and purified by stirring in acetone (dried over molecular sieves) at 0 °C followed by vacuum filtration. The white cyrstalline material was washed with several small quantities of acetone and dried under vacuum; mp 195–200 °C dec (lit.[10] mp 193–199 °C dec). Reaction products were identified by comparison of ^1H NMR, IR, and GC or melting point with that of authentic material. ^1H NMR spectra were recorded on a Varian EM-360L spectrophotometer in $CDCl_3$ using tetramethylsilane as an internal reference. IR spectra were recorded on a Mattson Polaris. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected: GC analyses were performed on a Perkin-Elmer 3700A instrument equipped with an OV-17 column, 12 ft × 0.25 in., glass. Either chlorobenzene or bromobenzene was used as an internal standard in the reactions monitored by GC. Crude products were purified by Kugelrohr distillation or column chromatography (Kieselgel 60, 70–230 mesh).

Oxidation of Dodecanal by NIS in Methanol (Method A). To a solution of dodecanal (191 mg, 1.04 mmol) in methanol (10.4 mL) were added NIS (585 mg, 2.60 mmol) and K_2CO_3 (359 mg, 2.60 mmol). The resultant dark mixture was stirred for 2.5 h, at which time GC analysis indicated complete consumption of starting material. Water (5 mL) and $Na_2S_2O_3 \cdot 5H_2O$ (0.5 g) were added to destroy any remaining NIS or hypoiodite species. The resultant mixture was extracted with 4 × 10 mL of a solution of 50% ether in hexane. The combined organic extracts were washed with brine (5 mL), and the solvent was removed under reduced pressure. The crude residue was chromatographed on a 35 × 1 cm column of silica gel with 1% ethyl acetate in hexane, yielding 207 mg (93%) of methyl dodecanoate as a colorless liquid.

Oxidation of Dodecanal by NIS in Acetonitrile (Method B). To a solution of dodecanal (176 mg, 0.957 mmol) in acetonitrile (9.6 mL) were added NIS (646 mg, 2.87 mmol), K_2CO_3 (396 mg, 2.87 mmol), and CH_3OH (194 μL, 4.79 mmol). The resultant mixture was stirred until GC analysis indicated complete consumption of starting material. Product isolation was performed as described above, affording 158 mg (77%) of methyl dodecanoate as a colorless liquid.

Oxidation of Nonanal by NBS in Methanol. To a solution of nonanal (127 mg, 0.894 mmol) in methanol (8.9 mL) were added NBS (398 mg, 2.24 mmol) and K_2CO_3 (308 mg, 2.24 mmol). This mixture was stirred until GC analysis indicated complete consumption of starting material. Water (5 mL) and $Na_2S_2O_3 \cdot H_2O$ (0.5 g) were added. The resultant mixture was extracted with 4 × 10 mL of a solution of 50% ether in hexane. The combined organic extracts were washed with brine (5 mL), and the solvent was removed by distillation through a Vigreux column. The crude

(8) Attempted oxidation of nonanal by NBS in acetonitrile with 5 equiv of methanol resulted in a 35% GC yield of methyl nonanoate after 24 h at 60 °C.

(9) Vankar, Y.; Kumaravel, G. *Tetraheron Lett.* **1984**, *26*, 233.
(10) Benson, W.; McBee, E.; Rand, L. *Org. Synth.* **1962**, *42*, 73.

product was chromatographed on a 35 × 1 cm column of silica gel with 1% ethyl acetate in hexane, yielding 100 mg (65%) of methyl nonanoate as a colorless liquid.

Acknowledgment. This work was supported by a Whitaker Foundation Grant of Research Corporation.

Registry No. NIS, 516-12-1; nonanal, 124-19-6; methyl nonanoate, 1731-84-6; dodecanal, 112-54-9; methyl dodecanoate, 111-82-0; tetradecanal, 124-25-4; methyl tetradecanoate, 124-10-7; cyclohexanecarbaldehyde, 2043-61-0; methyl cyclohexanecarboxylate, 4630-82-4; 2-phenylethanal, 122-78-1; benzeneacetic acid methyl ester, 101-41-7; 5-hexenal, 764-59-0; methyl hexenoate, 2396-80-7; benzaldehyde, 100-52-7; methyl benzoate, 93-58-3; 3-pyridinecarbaldehyde, 500-22-1; methyl 3-pyridinecarboxylate, 93-60-7; 3-nitrobenzaldehyde, 99-61-6; methyl 3-nitrobenzoate, 618-95-1; *trans*-cinnamaldehyde, 14371-10-9; *trans*-cinnamic acid methyl ester, 1754-62-7; 2-methylbenzaldehyde, 529-20-4; methyl 2-methylbenzoate, 89-71-4.

A Highly Stereoselective and Iterative Approach to Isoprenoid Chains: Synthesis of Homogeraniol, Homofarnesol, and Homogeranylgeraniol

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We recently described a highly stereoselective synthesis of trisubstituted homoallylic alcohols based on the Ni(0)-catalyzed coupling of Grignard reagents with 5-alkyl-2,3-dihydrofurans[1] first reported by Wenkert and coworkers.[2] The reaction is easy to do on a substantial scale and generally gives good yields. In this note we show how the procedure can be applied in an iterative sense to the synthesis of the isoprenoids homogeraniol (**5**),[3] homofarnesol (**8**), and homogeranylgeraniol (**11**). Each turn of the cycle requires the alkylation of 5-lithio-2,3-dihydrofuran (**2**) with a homoallylic iodide followed by the Ni(0)-catalyzed coupling with methylmagnesium bromide as shown in Scheme I. The resultant homoallylic alcohol can then be converted to the corresponding iodide and the cycle repeated.

All of the reagents used in the scheme are comparatively cheap and readily available. The Ni(0) catalyst, of which only 2 mol % is required, is generated in situ by the reaction of MeMgBr with $[Ph_3P]_2NiCl_2$, giving the thermally unstable $[Ph_3P]_2NiMe_2$ which loses ethane to give the active dark red catalyst. The yields at every stage are uniformly good. However, the salient feature of the sequence is the very high stereoselectivity of the three coupling steps. Analysis of the alcohols **5**, **8** and **11** by high-field ^1H and ^{13}C NMR and capillary gas chromatography indicated a purity of ≥97% in each case.

In conclusion this sequence compares favorably with analogous iterative isoprenoid syntheses[4] by virtue of its economy, experimental ease, and high stereoselectivity. The various homoprenols should prove useful as precursors to other higher terpenoids via coupling to appropriate C_4 components.

Experimental Section

2,3-Dihydrofuran (**1**) was obtained from Aldrich and freshly distilled. 1-Iodo-4-methylpent-3-ene (**3**) was prepared from the corresponding bromide by a Finkelstein reaction in the usual way, using NaI in acetone, and then freshly distilled. Benzene, Et_2O, and THF were freshly distilled from Na wire. ^1H (270 MHz) and ^{13}C (67.5 MHz) NMR spectra were recorded with a JEOL GX 270 spectrometer in the solvent specified with Me_4Si as an internal standard. Coupling constants (J) are reported in hertz. All IR spectra were recorded as thin films. Capillary gas chromatography was performed on a Packard 436 machine using a Chrompack 220 μ CP WAX 52 column. The purity of compounds **4**, **6**, **7**, **9**, and **10** was shown to be >94% by ^1H NMR and capillary GC.

5-(4-Methylpent-3-enyl)-2,3-dihydrofuran (4). A solution of *tert*-butyllithium in pentanes (81.2 mL, 130 mmol) was added dropwise to a solution of 2,3-dihydrofuran (8.4 g, 120 mmol) in dry tetrahydrofuran (33 mL) cooled to −50 °C under argon. The resulting yellow suspension was allowed to warm to 0 °C and was stirred for a further 30 min. The mixture was then cooled to −30 °C and a solution of 1-iodo-4-methylpent-3-ene (**3**) (20.0 g, 95 mmol) in dry tetrahydrofuran (40 mL) was added. The mixture was allowed to warm to room temperature and was stirred for 18 h. The white suspension so obtained was poured into a solution of saturated ammonium hydroxide (10 mL) in saturated ammonium chloride (90 mL) and the organic products were extracted with ether. The combined extracts were dried briefly ($MgSO_4$) and evaporated to leave a yellow oil. Bulb-to-bulb distillation gave the desired dihydrofuran **4** (14.0 g, 97%) as a colorless oil: bp 90 °C (bath)/15 mmHg; IR 2980 s, 2920 s, 2860 s, 1670 s, 1450 s, 1380 s, 1180 s, 1165 s, 1010 s, 930 s cm^{-1}; ^1H NMR (acetone-d_6) δ 5.11 (m, 1 H, J = 1.2, 6.0), 4.55 (m, 1 H), 4.20 (t, 2 H, J = 9.4), 2.52 (tdd, 2 H, J = 1.9, 1.9, 9.4), 2.17–1.99 (m, 4 H), 1.63 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR (acetone-d_6) δ 159.8 (s), 132.7 (s), 125.0 (d), 94.6 (d), 70.5 (t), 31.0 (t), 29.2 (t), 26.4 (t), 26.2 (q), 18.1 (q); MS m/z 152 (M^+, 76), 135 (38), 111 (21), 109 (23), 108 (23), 97 (16), 95 (24), 93 (18), 84 (62), 83 (25), 67 (100); high resolution EIMS m/z 152.1201 ($C_{10}H_{16}O$ = 152.1198).

(3*E*)-4,8-Dimethylnona-3,7-dien-1-ol (Homogeraniol) (5). A solution of methylmagnesium bromide in ether (69 mL, 0.2 mol) was added to a stirred suspension of bis(triphenylphosphine)nickel dichloride (2.25 g, 3.45 mmol) in dry benzene[5] (200 mL) under dry nitrogen. The resulting red solution was stirred at room temperature for 20 min, and a solution of 5-(4-methylpent-3-enyl)-2,3-dihydrofuran (**4**) (10.5 g, 69 mmol) in benzene (100 mL) was then added. The mixture was heated to reflux for 40 min, cooled to room temperature, and poured into saturated ammonium chloride solution (200 mL) with vigorous stirring. The mixture was stirred until decolorized and the organic material was extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated to leave a yellow oil. Column chromatography on silica gel (ether/petroleum ether, 1:4) and distillation gave homogeraniol (**5**) (10.3 g, 89%) as a colorless oil: bp 135 °C (bath)/15 mmHg; IR 3600–3100 m, 2980 s, 2930 s, 1670 w, 1460 s, 1380 s, 1060 s cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.14–5.05 (m, 2 H), 3.61 (t, 2 H, J = 6.5), 2.28 (dt, 2 H, J = 6.5, 7.1), 2.13–2.01 (m, 4 H + OH), 1.68, 1.64, 1.60 (s, 3 H each); ^{13}C NMR ($CDCl_3$) δ 138.9 (s), 131.1 (s), 124.2 (d), 119.9 (d), 62.4 (t), 39.8 (t), 31.5 (t), 26.6 (t), 25.7 (q), 17.7 (q), 16.2 (q). The IR and ^1H NMR spectra are in agreement with data reported by Leopold.[6]

(3*E*)-1-Iodo-4,8-dimethylnona-3,7-diene (6). Methanesulfonyl chloride (2.15 mL, 28 mmol) was added dropwise to a

(1) Wadman, S.; Whitby, R.; Yeates, C.; Kocieński, P.; Cooper, K. *J. Chem. Soc., Chem. Commun.* **1987**, 241. Kocieński, P.; Dixon, N. J.; Wadman, S. *Tetrahedron Lett.* **1988**, *29*, 2353. Kocieński, P.; Wadman, S.; Cooper, K. *Tetrahedron Lett.* **1988**, *29*, 2357. Kocieński, P.; Love, C.; Whitby, R.; Roberts, D. A. *Tetrahedron Lett.* **1988**, *29*, 2867.

(2) Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894.

(3) Kobayashi, M.; Valente, L. F.; Negishi, E. *Synthesis* **1980**, 1034.

(4) Carboalumination (review): Negishi, E.; Takahashi, T. *Synthesis* **1988**, *1*. Carbocupration (review): Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. Alkylcuprate coupling with alkenyl iodides: Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245. Alkylcuprate coupling with enol phosphates: Sum, F. W.; Weiler, L. *J. Am. Chem. Soc.* **1979**, *101*, 4401.

(5) Benzene can be replaced by toluene without incident.

(6) Leopold, E. L. *Org. Synth.* **1986**, *64*, 164.

0022-3263/89/1954-1215$01.50/0