PREPARATION OF 1-DIMETHYLAMINOMETHYLENE-3-ALKENYLINDOLES

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Abstract -- A one-pot synthesis of 1-dimethylaminomethylene-3-acylindoles is described, as well as their conversion to the corresponding 3-alkenylindoles.

3-Alkenylindoles are finding increased use in the field of heterocyclic chemistry, as exemplified most notably by the work of Pindur.[1] Indeed, several indole and carbazole derivatives have been prepared using 3-alkenylindoles as key intermediates.[2] The use of protecting groups on the indole nitrogen which facilitate α-lithiation (and thus allow introduction of electrophiles at *C*-2) further enhances the versatility of these compounds.

3-Alkenylindoles are typically prepared from 3-acylindoles, olefination being achieved most commonly through the use of the Wittig reaction,[3] although treatment of acylindoles with organometallic reagents and dehydration of the resulting alcohols

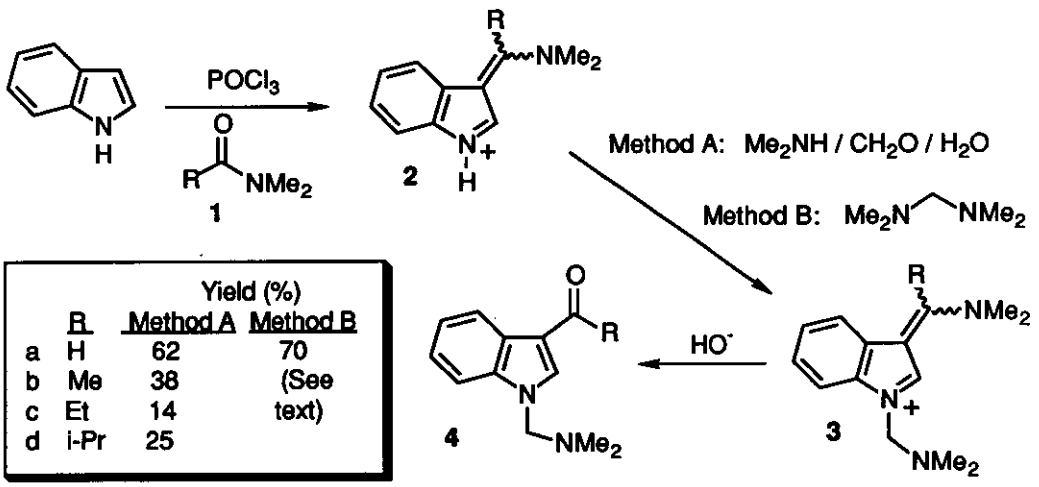
has also been demonstrated.[4] As part of a project directed toward the synthesis of β-carbolines, we required the preparation of 3-alkenylindoles possessing a metalation-directing protecting group on nitrogen. This in turn necessitated the preparation of the corresponding *N*-protected 3-acylindoles.

One of the most common protecting groups for indole nitrogens is the phenylsulfonyl group. Though useful in facilitating α-lithiation, this group was not suitable for our purposes, as we hoped to react the α-lithiated indoles with nitriles (as a means of introducing *N*-2 of the β-carboline ring system), and the phenylsulfonyl group is known to be removed under such conditions.[5] Instead, we chose to investigate the use of the dimethylaminomethylene group, recently described by Hlasta as a metalation-directing protecting group.[6]

Surprisingly, while examples of 1-phenylsulfonyl-3-acylindoles abound, only one of the 1-dimethylaminomethylene-3-acylindoles shown in Figure 1, compound (**4a**), has previously been reported. The only literature reference to this compound describes its preparation from indole-3-carboxaldehyde, which yields the product as a "brown oil."[7] These authors did not purify or characterize aldehyde (**4a**) itself, but instead treated it with methyl iodide to yield the corresponding quaternary ammonium iodide. We reasoned that 1-dimethylaminomethylene-3-acylindoles (**4**) could be prepared more easily if the Mannich reaction was conducted on enamine intermediates **2** (in their deprotonated form) rather than on the corresponding 3-acylindoles, owing to the greater nucleophilicity of the former species relative to the latter. (Enamine **2a** is a

known intermediate in the Vilsmeier-Haack formylation of indole).[8] Additionally, the sequence depicted in Figure 1 offers the advantage of being a one-pot procedure starting from indole. Indeed, treatment of indole with DMF and $POCl_3$, followed by an aqueous solution of dimethylamine and formaldehyde provided *N*-dimethylamino-methyleneindole-3-carboxaldehyde (**4a**) in 76% yield as a tan solid. One recrystallization from diisopropyl ether provided analytically pure material in 62% isolated yield. The other 1-dimethylaminomethylene-3-acylindoles were prepared in an analogous manner in the yields shown.

Figure 1



	R	Yield (%) Method A	Method B
a	H	62	70
b	Me	38	(See
c	Et	14	text)
d	i-Pr	25	

As can be seen, yields were noticeably lower when the R group possessed an α-hydrogen. In the case of **4b** and **4c**, this was due in part to contamination by product which had been aminomethylated on the side chain as well as the indole

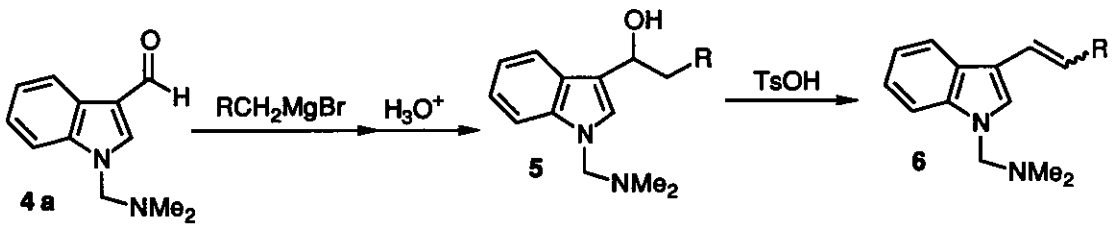
nitrogen. In the preparation of **4c**, 1,3-dipropionylindole was also obtained in 22% yield. The yields of **4b-d** have not been optimized.

Alternately, the Mannich reaction could be carried out under non-aqueous conditions by reacting the product of the Vilsmeier reaction directly with tetramethyldiaminomethane. Use of this procedure raised the crude yield of **4a** to 87% and allowed a purified yield of 70% to be obtained. Crude yields of the other acylindoles were similarly improved, but the products were contaminated with unidentified impurities which proved impossible to remove by either recrystallization or column chromatography.

Having developed a convenient, one-pot method of preparing 1-dimethylaminomethylene-3-acylindoles, we next turned our attention to elaboration of these compounds into the corresponding 3-alkenylindoles, focusing on using formyl derivative **4a** as the substrate. While literature precedent, and indeed, results obtained in this laboratory using 1-phenylsulfonylindole-3-carboxaldehyde as a substrate, indicated that Wittig olefination would be an effective method of achieving this transformation, in our hands Wittig olefination of **4a** was quite disappointing (yields in the range of 10%). We believe replacement of the electron-withdrawing phenylsulfonyl group with the electron-donating dimethylaminomethylene group allows greater delocalization of electron density from the indole nitrogen onto the aldehyde, thus reducing the electrophilicity of the carbonyl group.

We then investigated the reaction of **4a** with Grignard reagents and dehydration of the resulting alcohols. As shown in Figure 2, excellent yields of alcohols (**5**) were obtained. Dehydration of these compounds to alkenes (**6**), however, proved to be surprisingly difficult. Of several methods investigated, (MsCl/base,[9] $DMF/SOCl_2/Et_3N$, $POCl_3/Et_3N$, DCC/CuI, $BF_3 \cdot Et_2O$, and *p*-TsOH on SiO_2), the most effective was found to be refluxing a solution of the alcohol in toluene with a catalytic amount of *p*-TsOH. The crude products were purified by column chromatography (SiO_2) to give the isolated yields of the products shown in Figure 2.

Figure 2



	R	Yield (%)
a	H	93
b	Me	86
c	Et	95
d	Pr	93
e	Ph	97

	R	Yield (%)
a	H	0
b	Me	26
c	Et	48
d	Pr	43
e	Ph	38

We suspect that at least some of the product is lost due to polymerization during the dehydration, though use of shorter reaction times resulted in incomplete conversion, and return of some starting material. Additional product is lost upon purification due not only to polymerization, but also partial loss of the dimethylaminomethylene

protecting group. (For example, a 21% yield of 3-styrylindole was obtained along with compound (6e).) Efforts are still being made to improve the yields of this step.

In summary, an efficient, one-pot synthesis of 1-dimethylaminomethylene-3-acylindoles has been developed, and conversion of 1-dimethylaminomethylene-indole-3-carbaldehyde into a series of alkenylindoles demonstrated. Efforts directed toward the elaboration of these compounds into a series of β-carboline derivatives are currently underway.

EXPERIMENTAL

1-Dimethylaminomethyleneindole-3-carboxaldehyde (4a)

(Method A): Dimethylformamide (DMF) (41.06 g, 561.7 mmol) was placed in a 500 ml two-neck flask fitted with a mechanical stirrer and a $CaSO_4$ drying tube.[10] The flask was cooled in an ice-salt bath for 1 h, after which time the drying tube was replaced with an addition funnel containing phosphorus oxychloride (27.40 g, 178.7 mmol). The $POCl_3$ was added dropwise with stirring over 30 min. A solution of indole (15.00 g, 127.7 mmol) in DMF (12.13 g, 165.9 mmol), was then added dropwise over 1 h. The resulting syrup was heated to 35 °C and stirred until a thick yellow paste formed. Ice (130 g) was added to the paste and the mixture was stirred for 20-25 min. The solution was transferred to a 500 ml round-bottom flask, and treated with 37% aqueous formaldehyde (41 ml, 510 mmol) and 40% aqueous dimethylamine (57 ml, 510 mmol). After 4 h of heating at reflux, the solution was cooled to room

temperature, brought to pH 8 with 9M NaOH, and extracted with ether (2 x 150 ml). The combined ether extracts were washed with water (2 x 75 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a tan solid (19.58 g, 76% yield). The crude product was recrystallized from diisopropyl ether (200 ml) to give white crystals (16.02 g, 62% yield) mp 60-60.5 °C. ^1H Nmr ($CDCl_3$, 400 MHz) δ 9.99 (s, 1H), 8.30 (d, J = 6.3 Hz, 1H), 7.75 (s, 1H), 7.48 (d, J = 6.7 Hz, 1H), 7.34-7.26 (m, 2H), 4.78 (s, 2H), 2.33 (s, 6H); ^{13}C nmr ($CDCl_3$, 100 MHz) δ 184.8, 138.8, 137.8, 125.2, 124.0, 122.9, 121.8, 118.2, 110.7, 69.6, 42.6; ir (KBr) 3095, 2940, 1643, 1530 cm-1; LRms (EI, 70eV) 202 (M^+, 2), 144 (8), 58 (100); HRms (CI, M + 1) calcd for $C_{12}H_{15}N_2O$: 203.1184, found 203.1185; Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.16; H, 7.02; N, 13.76.

Method B: Method A was followed up to the point prior to addition of ice. Four equivalents of tetramethyldiaminomethane were added, and the solution was heated at 80 °C for 4 h. The work-up (basification with NaOH, *etc.*) was the same as described for Method A.

1-Dimethylaminomethylene-3-acetylindole (4b)

Prepared as described above for Method A, except that the Vilsmeier complex was formed by heating dimethylacetamide with $POCl_3$ for 2 h at 85 °C. The product was purified by recrystallization from diisopropyl ether. ^1H Nmr ($CDCl_3$, 250 MHz) δ 8.39-8.36 (m, 1H), 7.77 (s, 1H), 7.47-7.43 (m, 1H), 7.29-7.26 (m, 2H), 4.73 (s, 2H), 2.51 (s, 3H), 2.31 (s, 6H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 192.9, 137.5, 134.9, 126.3, 123.3,

122.4, 122.3, 117.3, 110.3, 69.4, 42.6, 27.5; HRms (EI, M +) calcd for $C_{13}H_{16}N_2O$: 216.1262, found 216.1263.

1-Dimethylaminomethylene-3-propionylindole (4c)

Prepared as described above for Method A, except that the Vilsmeier complex was formed by heating dimethylpropionamide with $POCl_3$ for 2 h at 85 °C. The product obtained was contaminated by dimethylpropionamide and a small amount of an unidentified compound. ^1H Nmr ($CDCl_3$, 250 MHz) δ 8.45 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.40-7.20 (m, 2H), 4.80 (s, 2H), 2.34 (q, J = 7.4 Hz, 2H), 2.24 (s, 6H), 1.13 (t, J = 7.4 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 198.5, 137.4, 134.4, 126.3, 123.1, 122.4, 122.1, 116.0, 110.1, 69.1, 45.6, 42.3, 16.9; HRms (EI, M +) calcd for $C_{14}H_{18}N_2O$: 230.1419, found 230.1420.

1-Dimethylaminomethylene-3-isobutyrylindole (4d)

Prepared as described above for Method A, except that the Vilsmeier complex was formed by heating dimethylisobutyramide with $POCl_3$ for 2 h at 85 °C. The product was purified by recrystallization from ether, and was contaminated with a small amount of an unidentified compound. ^1H Nmr ($CDCl_3$, 250 MHz) δ 8.40-8.45 (m, 1H), 7.84 (s, 1H), 7.50-7.45 (m, 1H), 7.30-7.25 (m, 2H), 4.79 (s, 2H), 3.36 (sept, J = 6.8 Hz, 1H), 2.34 (s, 6H), 1.26 (d, J = 6.8 Hz, 6H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 200.6, 137.6, 131.0, 126.7, 123.4, 122.6, 122.5, 115.6, 110.4, 69.4, 42.7, 37.2, 19.7; HRms (CI, M + 1) calcd for $C_{15}H_{21}N_2O$: 245.1654, found 245.1649.

General Procedure for Preparation of Alcohols (5)

To a solution of formylindole **4a** (7.5 mmol in 25 ml dry THF) at 0 °C was added 1.2 equivalents of the Grignard reagent dropwise. The solution was stirred for 45 min at room temperature (at 40 °C in the case of **5a** and **5e**), then treated with water. The solution was extracted with ether (3 x 30 ml), the combined extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The alcohols thus obtained were essentially pure (as judged by nmr) and were used in subsequent steps without further purification.

1-Dimethylaminomethylene-3-(1-hydroxyethyl)indole (5a)

^1H Nmr ($CDCl_3$, 250 MHz) δ 7.74 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 10 Hz, 1H), 7.23-7.08 (m, 2H), 7.06 (s, 1H), 5.19 (q, J = 9.5 Hz, 1H), 4.62 (s, 2H), 2.49 (br s, 1H), 2.21 (s, 6H), 1.63 (d, J = 9.5 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 137.5, 126.3, 124.9, 122.0, 120.2, 119.6, 119.4, 110.0, 68.4, 63.9, 42.6, 23.7; HRms (EI, M +) calcd for $C_{13}H_{18}N_2O$: 218.1419, found 218.1420.

1-Dimethylaminomethylene-3-(1-hydroxypropyl)indole (5b)

^1H Nmr ($CDCl_3$, 250 MHz) δ 7.50 (d, J = 9.1 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.25-7.09 (m, 3H), 4.91 (t, J = 6.7 Hz, 1H), 4.69 (s, 2H), 2.28 (s, 6H), 2.22-1.93 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 137.6, 126.4, 125.6, 121.9, 119.7, 119.3, 118.8, 109.9, 69.6, 67.8, 42.5, 30.4, 10.4; HRms (EI, M +) calcd for $C_{14}H_{20}N_2O$: 232.1576, found 232.1575.

1-Dimethylaminomethylene-3-(1-hydroxybutyl)indole (5c)

^{1}H Nmr ($CDCl_3$, 250 MHz) δ 7.75 (d, J = 7.9 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.23-7.10 (m, 2H), 7.08 (s, 1H), 4.99 (t, J = 6.7 Hz, 1H), 4.67 (s, 2H), 2.26 (s, 6H), 2.01-1.89 (m, 2H), 1.53-1.32 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 137.6, 126.5, 125.5, 122.0, 119.7, 119.4, 119.2, 110.1, 68.6, 68.0, 42.6, 39.8, 19.4, 13.9; HRms (EI, M +) calcd for $C_{15}H_{22}N_2O$: 246.1732, found 246.1736.

1-Dimethylaminomethylene-3-(1-hydroxypentyl)indole (5d)

^{1}H Nmr ($CDCl_3$, 250 MHz) δ 7.74 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.22-7.11 (m, 2H), 7.09 (s, 1H), 4.98 (t, J = 6.7 Hz, 1H), 4.68 (s, 2H), 2.27 (s, 6H), 2.01-1.93 (m, 2H), 1.78-1.33 (m, 4H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 137.6, 126.4, 125.6, 122.0, 119.7, 119.4, 119.1, 110.1, 68.6, 68.3, 42.7, 37.3, 28.4, 22.6, 14.1; HRms (EI, M +) calcd for $C_{16}H_{24}N_2O$: 260.1889, found 260.1891.

1-Dimethylaminomethylene-3-(1-hydroxy-2-phenylethyl)indole (5e)

^{1}H Nmr ($CDCl_3$, 250 MHz) δ 7.76 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 9.1 Hz, 1H) 7.35-7.10 (m, 7H), 6.99 (s, 1H), 5.20 (dd, J = 8.0, 5.3 Hz, 1H), 4.61 (s, 2H), 3.33-3.15 (m, 2H), 2.41 (br s, 1H), 2.19 (s, 6H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 138.6, 137.5, 129.5, 128.3, 126.3, 126.2, 125.8, 122.1, 119.7, 119.5, 117.9, 110.2, 69.5, 68.5, 44.3, 42.6; HRms (EI, M +) calcd for $C_{19}H_{22}N_2O$: 294.1732, found 294.1730.

General Procedure for Preparation of Alkenes (6)

A solution of hydroxyalkylindole **5** (5 mmol in 50 ml toluene) was treated with a catalytic amount of *p*-TsOH and refluxed with a Dean-Stark trap for 4-5 h. The solvent was removed under reduced pressure, the residue was taken up in 20 ml of 2% NaOH, and extracted with ether (2 x 25 ml). The combined ether extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the crude product, which was then purified by column chromatography (SiO_2, ether/pet. ether).

1-Dimethylaminomethylene-3-vinylindole (6a)

Product polymerized, and was never isolated in pure form.

1-Dimethylaminomethylene-3-(1-propenyl)indole (6b)

(Mixture of cis and trans isomers, data for cis isomer given). ^{1}H Nmr ($CDCl_3$, 250 MHz) δ 7.81 (d, J = 7.7 Hz, 1H), 7.41-7.37 (m,1H), 7.24-7.09 (m, 2H), 7.08 (s, 1H), 6.60-6.51 (m, 1H), 6.26-6.12 (m, 1H), 4.65 (s, 2H), 2.57 (s, 6H), 1.90 (d, J = 6.6 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 137.6, 126.7, 126.2, 123.1, 122.5, 121.9, 119.9, 119.7, 114.5, 109.9, 68.4, 42.5, 18.9; HRms (EI, M +) calcd for $C_{14}H_{18}N_2$: 214.1470, found 214.1471.

1-Dimethylaminomethylene-3-(1-butenyl)indole (6c)

(Mixture of cis and trans isomers, data for trans isomer given). ^{1}H Nmr ($CDCl_3$, 250 MHz) δ 7.65 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.25-7.09 (m, 3H), 6.57 (d, J = 11.3 Hz, 1H), 5.67-5.59 (m, 1H), 4.72 (s, 2H), 2.38-2.27 (m, 2H), 2.30 (s, 6H), 1.11 (t, J = 7.5 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 136.5, 131.4, 128.1, 126.8, 122.0, 119.6,

118.9, 118.6, 112.8, 109.8, 68.7, 42.6, 23.1, 14.2; HRms (EI, M +) calcd for $C_{15}H_{20}N_2$: 228.1626, found 228.1628.

1-Dimethylaminomethylene-3-(1-pentenyl)indole (6d)

(Only trans isomer obtained). ^1H Nmr ($CDCl_3$, 250 MHz) δ 7.83 (d, J = 7.1 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.25-7.11 (m, 3H), 6.54 (d, J = 14.6 Hz, 1H), 6.25-6.13 (m, 1H), 4.69 (s, 2H), 2.33-2.15 (m, 2H), 2.29 (s, 6H), 1.56-1.45 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 137.7, 128.0, 126.44, 126.40, 122.1, 121.9, 119.9, 119.8, 114.6, 110.0, 68.6, 42.7, 35.7, 22.9, 13.8; HRms (CI, M + 1) calcd for $C_{16}H_{23}N_2$: 243.1861, found 243.1858.

1-Dimethylaminomethylene-3-styrylindole (6e)

(Only one isomer obtained, presumably trans). ^1H Nmr ($CDCl_3$, 250 MHz) δ 7.97 (d, J = 8.2 Hz, 1H), 7.53-7.15 (m, 11H), 4.73 (s, 2H), 2.31 (s, 6H); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ 138.6, 137.9, 128.62, 128.58, 128.56, 127.9, 126.5, 125.73, 125.71, 125.4, 122.4, 121.4, 120.3, 120.1, 68.8, 42.7; HRms (EI, M +) calcd for $C_{19}H_{20}N_2$: 276.1626, found 276.1628.

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REFERENCES

1. (a) U. Pindur, M.-H. Kim, M. Rogge, W. Massa, and M. Molinier, *J. Org. Chem.*, 1992, **57**, 910; (b) U. Pindur, *Heterocycles*, 1988, **27**, 1253; (c) E. Akgün and U. Pindur, *J. Heterocycl. Chem.*, 1985, **22**, 585.
2. See for example, B. Saroja and P. C. Srinivasan, *Synthesis*, 1986, 748, as well as reference 1b.
3. See for example, (a) U. Pindur and L. Pfeuffer, *Monatsh. Chem.*, 1989, **120**, 157, (b) R. Bergamasco, Q. N. Porter, and C. Yap, *Aust. J. Chem.*, 1977, **30**, 1531.
4. U. Pindur and L. Pfeuffer, *Monatsh. Chem.*, 1987, **118**, 1031.
5. R. J. Sundberg and H. F. Russell, *J. Org. Chem.*, 1973, **38**, 3324.
6. D. J. Hlasta and M. R. Bell, *Heterocycles*, 1989, **29**, 849. (The dimethylamino-methylene group can be removed using sodium borohydride. See A. R. Katritzky, P. Lue, and Y.-X. Chen, *J. Org. Chem.*, 1990, **55**, 3688).
7. J. Thesing and P. Binger, *Chem. Ber.*, 1957, **90**, 1419.
8. G. F. Smith, *J. Chem. Soc.*, 1954, 3842.
9. Some of the bases investigated were Et_3N, DBU, and t-BuOK.
10. The initial steps of this procedure, which produce intermediate **2**, are taken from P. N. James and H. R. Snyder, *Org. Synth., Coll. Vol. 4*, 1963, 539.

This paper is dedicated to Prof. Edward C. Taylor on the occasion of his 70th birthday.

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