Synthesis of 4-(4-Alkyl-2-morpholinyl)indoles

Robin D. Clark

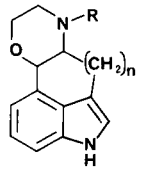
Institute of Organic Chemistry, Syntex Research,
Palo Alto, CA 94304

Received April 4, 1983

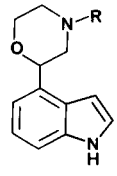
N-substituted 4-(2-morpholinyl)indoles were prepared from 1-(*t*-butoxycarbonyl)-4-acetylindole (**7**) which was itself prepared from 4-cyanoindole. Bromination of ketone **7**, followed by reaction with amines and subsequent sodium borohydride reduction, gave amino alcohols. These were converted to α-chloro amides that were cyclized to lactams. Lithium aluminum hydride reduction served both to remove the *t*-BOC protecting group and to reduce the lactams to the 4-(2-morpholinyl)indoles.

J. Heterocyclic Chem., **20**, 1393 (1983).

Syntheses of the 9-oxaergoline **1** [2] and the C-homo-oxaergoline **2** [3], as well as the dopaminergic properties thereof [4,5], have been reported. A recent patent which discloses 4-(2-morpholinyl)indoles (**3**) [6] prompts us to describe our independent preparation of several alkylated derivatives of this heterocycle.



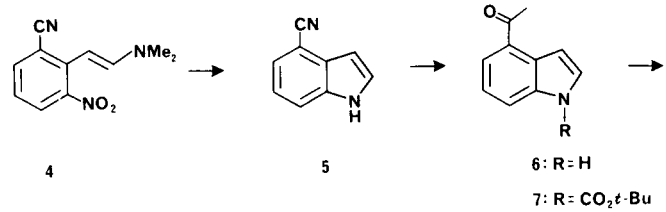
1: n=1
2: n=2



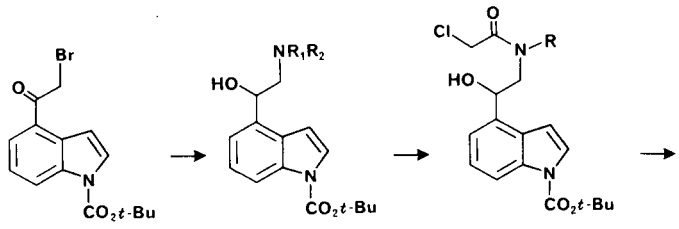
3

4-Cyanoindole (**5**) was efficiently prepared in 70% yield by the Leimgruber-Batcho indole synthesis [7] which involved hydrogenation of *trans*-2-cyano-6-nitro-β-dimethylaminostyrene (**4**) using 10% palladium on carbon in methanol [8]. This procedure offers a considerable improvement, both in terms of manipulation and product isolation, over the iron-acetic acid reduction reported by Ponticello [9]. Treatment of nitrile **5** with excess methyllithium in ether, followed by brief aqueous hydrochloric acid treatment, afforded 4-acetylindole (**6**) in greater than 90% yield. Conversion of **6** to *t*-BOC derivative **7** was effected with di-*t*-butyl dicarbonate and a catalytic amount of potassium *t*-butoxide (76% yield). Bromination of **7** with 2-pyrrolidinone hydrotribromide gave bromo ketone **8** in 77% yield.

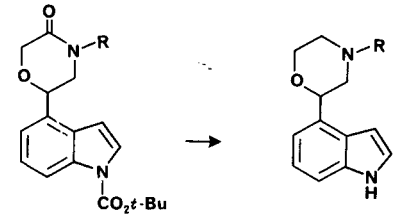
Reaction of **8** with *N*-benzylmethylamine, followed by sodium borohydride reduction of the amino ketone thus obtained, gave the amino alcohol **9** in 61% yield. Hydrogenolysis of the benzyl group to give **10** was accompanied by substantial (~40%) reduction to the indoline. This mixture was carried through subsequent transformations. Thus, treatment with chloroacetyl chloride gave the α-chloroamides that were cyclized to the lactams (**16** and the corresponding indoline) with potassium *t*-butoxide. Reduction with lithium aluminum hydride gave 4-(4-meth-



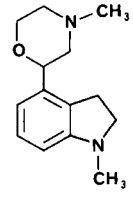
4 5 6: R=H 7: R=CO$_2$*t*-Bu



8 9: R$_1$=CH$_3$, R$_2$=CH$_2$Ph 10: R$_1$=CH$_3$, R$_2$=H 11: R$_1$=H, R$_2$=CH$_2$CH$_3$ 12: R$_1$=H, R$_2$=CH$_2$CH$_2$CH$_3$ 13: R=CH$_3$ 14: R=CH$_2$CH$_3$ 15: R=CH$_2$CH$_2$CH$_3$



16: R=CH$_3$ 17: R=CH$_2$CH$_3$ 18: R=CH$_2$CH$_2$CH$_3$ 19: R=CH$_3$ 20: R=CH$_2$CH$_3$ 21: R=CH$_2$CH$_2$CH$_3$



22

yl-2-morpholinyl)indole (**19**) and indoline **22** that were separated chromatographically. The cleavage of the *t*-BOC group from the indole involves, at least partially, the intermediacy of the 1-hydroxymethylindole that is observed by tlc analysis. The hydroxymethyl group is cleaved under the basic reaction conditions to the observed indole product.

For the preparation of the N-ethyl and N-propyl compounds **20** and **21**, **8** was treated with ethylamine and propylamine respectively, and the resulting amino ketones were, without isolation, reduced with sodium borohydride to give **11** and **12**. Thus, the necessity of removal of benzyl protecting groups was avoided by using the primary amines. Treatment of **11** and **12** with chloroacetyl chloride, followed by cyclization with potassium *t*-butoxide and lithium aluminum hydride reduction gave **20** and **21**.

Compound **19** was converted to the hydrochloride salt that proved to be hygroscopic and rather unstable. Compounds **20** and **21** were converted to the more stable monohydrogen fumarate salts.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded with Varian A-60 and Bruker WM 300 instruments and are reported in ppm δ downfield from an internal standard of tetramethylsilane. Microanalyses were performed by Syntex Analytical Department. Reactions were monitored by thin layer chromatography on 250μ layers of silica gel GF on glass plates. Silica gel column chromatography was performed using 70-230 mesh (Merck) silica gel. Melting points are uncorrected. The ir spectra were measured with a Perkin-Elmer Model 237 grating infrared spectrometer.

4-Cyanoindole (**5**).

A solution of 10.85 g (50 mmoles) of 2-cyano-6-nitro-*trans*-β-dimethylaminostyrene [9] and 2.7 of 10% palladium on carbon in 250 ml of methanol was hydrogenated on a Parr apparatus at 65 psi for 45 minutes. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between ether and dilute hydrochloric acid, and the ether was washed with water and brine, and evaporated to a solid. Purification by chromatography on silica gel (1% methanol-dichloromethane) afforded 5.0 g (70%) of product, mp 119-120°, lit [10] mp 120-121°.

Anal. Calcd. for $C_9H_6N_2$: C, 76.08; H, 4.26; N, 19.70. Found: C, 75.93; H, 3.95; N, 19.48.

4-Acetylindole (**6**).

A solution of 33 g (230 mmoles) of **5** was added to a stirred mixture of 277 ml of 1.8 *M* ethereal methyllithium and 200 ml of tetrahydrofuran at such a rate as to maintain a gentle reflux. After the addition was complete, the heterogeneous mixture was heated at reflux for 2 hours. Ice cold dilute hydrochloric acid was cautiously added, and the resulting solution was heated on a steam bath for 5 minutes. The cooled mixture was extracted three times with ether, and the ether extract was dried (sodium sulfate) and evaporated to 34 g (93%) of crude **6** as a tan solid. This material was used in the next step without further purification. An analytical sample was obtained by column chromatography on silica gel (25% ether-hexane), mp 159-160°, lit [1] mp 163-164°.

Anal. Calcd. for $C_{10}H_9NO$: C, 75.46; H, 5.70; N, 8.80. Found: C, 75.21; H, 5.75; N, 8.74.

1-(*t*-Butoxycarbonyl)-4-acetylindole (**7**),

A solution of 34 g (214 mmoles) of crude **6**, 46 g (211 mmoles) of di-*t*-butyl dicarbonate, and 1.68 g (15 mmoles) of potassium *t*-butoxide in 400 ml of tetrahydrofuran was heated at reflux for 3 hours. The cooled solution was diluted with water, extracted with ether, and the ether extract was washed with water and brine, dried (sodium sulfate), and evaporated. Chromatography of the residue on silica gel (20% ether-hexane) afforded 45 g (76% from **6**) of **7**, mp 65-66°; nmr (deuteriochloroform): δ 1.67 (s, 9H), 2.68 (s, 3H), 7.34 (dd, 1H, J = 8, 8 Hz), 7.43 (dd, 1H, J = 3.8, 0.7 Hz), 7.70 (d, 1H, J = 3.8 Hz), 7.78 (dd, 1H, J = 8, 1 Hz), 8.41 (broad d, 1H, J = 8 Hz); ir (potassium bromide): 1720, 1670 cm^{-1}.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.73; H, 6.42; N, 5.39.

4-Bromoacetyl-1-(*t*-butoxycarbonyl)indole (**8**).

A mixture of 45 g (174 mmoles) of ketone **6**, 90.4 g (183 mmoles) of 2-pyrrolidinone hydrotribromide, and 15.6 g (183 mmoles) of 2-pyrrolidinone in 500 ml of tetrahydrofuran was heated at reflux for 3 hours. The mixture was filter while warm and concentrated under reduced pressure. Recrystallization of the solid thus obtained from ethanol-water gave 45 g (77%) of **8** as a tan solid, mp 105-107°; nmr (deuteriochloroform): δ 1.68 (s, 9H), 4.57 (s, 2H), 7.37 (dd, 1H, J = 8, 8 Hz), 7.40 (dd, 1H, J = 3.8, 0.7 Hz), 7.75 (d, 1H, J = 8 Hz), 7.79 (dd, 1H, J = 8, 0.8 Hz), 8.45 (broad d, 1H, J = 8 Hz); ir (potassium bromide): 1730, 1710 cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.05; H, 4.82; N, 4.06.

1-(*t*-Butoxycarbonyl)-4-[1-hydroxy-2-(benzylmethylamino)ethyl]indole (**9**).

To an ice-cooled solution of 18.2 g (150 mmoles) of benzylmethylamine in 50 ml of tetrahydrofuran was added dropwise a solution of 25 g (74 mmoles) of bromoketone **8** in 200 ml of tetrahydrofuran. The resulting mixture was stirred in the ice-bath for 1 hour and was then concentrated under reduced pressure at 30-40°. The residue was dissolved in 250 ml of methanol and the mixture was cooled in an ice-bath. Sodium borohydride was added in small portions until tlc analysis (20% ethyl acetate-hexane) showed complete conversion of the ketone (rf 0.4) to the alcohol (rf 0.2). The mixture was added to water and extracted with ether. The ether extract was washed with brine, dried (sodium sulfate), and evaporated and the residue was purified by silica gel chromatography (40% ethyl acetate-hexane) to give 17 g (61%) of **9** as a thick, colorless oil: nmr (deuteriochloroform): δ 1.65 (s, 9H), 2.38 (s, 3H), 2.56 (dd, 1H, J = 12, 3.5 Hz), 2.75 (dd, 1H, J = 12, 11 Hz), 3.64 (AB, 2H, J = 13 Hz), 5.08 (dd, 1H, J = 11, 3.5 Hz), 6.52 (dd, 1H, J = 3.8, 0.7 Hz), 7.20-7.40 (m, 7H), 7.54 (d, 1H, J = 3.8 Hz), 8.06 (broad t, 1H); ir (film): 3600-3200, 1740 cm^{-1}.

Anal. Calcd. for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 73.05; H, 6.99; N, 7.30.

4-(4-Methyl-2-morpholinyl)indole (**19**) and 1-Methyl-4-(4-methyl-2-morpholinyl)indoline (**22**).

A mixture of 12.5 g (32.9 mmoles) of **9** and 2.5 g of 10% palladium on carbon in 200 ml of methanol was hydrogenated at 60 psi for 16 hours. The mixture was filtered and evaporated to afford 8.9 g (93%) of a white foam. Analysis (tlc, 20% methanol-dichloromethane) showed the major product **10** (rf 0.5) to be contaminated with the corresponding indoline (rf 0.4). This material was partitioned between 250 ml of ethyl acetate and 250 ml of water containing 20 g of sodium carbonate, cooled in an ice bath, and treated slowly with 5.7 g (50 mmoles) of chloroacetyl chloride. The ethyl acetate layer was dried (sodium sulfate) and evaporated and the residue of crude **13** (and the indoline) was dissolved in 200 ml of tetrahydrofuran. Potassium *t*-butoxide (3.92 g, 35 mmoles) was added and the solution was stirred at room temperature for 15 minutes, concentrated under reduced pressure, diluted with water and extracted with ether. After drying, the ether was evaporated to afford 5.8 g of **16** and the indoline (85% from **10**). This material was dissolved in 50 ml of tetrahydrofuran and was added slowly to 1.5 g of lithium aluminum hydride in 100 ml of tetrahydrofuran. The mixture was heated under reflux for 12 hours and was then cooled in an ice bath and treated sequentially with 1.5 ml of water, 1.5 ml of 15% sodium hydroxide, and 3.0 ml of water. The white solid was filtered off and the filtrate was evaporated. Chromatography of the residue on silica gel (10% methanol-dichloromethane,

1% *t*-butylamine) afforded 2.1 g of **19** (30% from **9**) as the first compound eluted, followed by 1.4 g (19%) of **22.** Both compounds were obtained as viscous oils. Compound **19** had nmr (deuteriochloroform): δ 2.23-2.40 (m, 2H), 2.32 (s, 3H), 2.78 (broad d, 1H, J = 11 Hz), 3.02 (broad d, 1H, J = 11 Hz), 3.95 (ddd, 1H, J = 11, 11, 2 Hz), 4.12 (broad d, 1H, J = 11 Hz), 5.02 (dd, 1H, J = 11, 2 Hz), 6.61 (broad s, 1H), 7.06 (m, 1H), 7.10-7.26 (m, 3H), 8.90 (s, 1H, *N*H). Compound **22** had (deuteriochloroform): δ 2.10 (dd, 1H, J = 11, 11 Hz), 2.24 (ddd, 1H, J = 11, 11, 2 Hz), 2.68-2.85 (m, 2H), 2.73 (s, 3H), 2.90-3.05 (m, 2H), 3.20-3.26 (m, 2H), 3.81 (ddd, 1H, J = 11, 11, 2 Hz), 4.02 (dd, 1H, J = 11, 2 Hz), 6.40 (d, 1H, J = 7.5 Hz), 6.74 (d, 1H, J = 7.5 Hz), 7.08 (dd, 1H, J = 7.5, 7.5 Hz).

The hydrochloride salt of **19** was obtained from methanolic hydrogen chloride by precipitation with ether and was a hygroscopic foam.

Anal. Calcd. for $C_{13}H_{17}ClN_2O \cdot 0.25\ H_2O$: C, 60.70; H, 6.86; N, 10.89. Found: C, 60.63; H, 6.96; N, 10.65.

The dihydrochloride salt of **22** crystallized from methanol, mp 208-210°.

Anal. Calcd. for $C_{14}H_{22}Cl_2N_2O$: C, 55.08; H, 7.27; N, 9.18. Found C, 54.85; H, 7.22; N, 8.89.

1-(*t*-Butoxycarbonyl)-4-[2-(*N*-chloroacetyl-*N*-ethyl)amino-1-hydroxyethyl]indole (**14**).

A solution of 3.4 g (10 mmoles) of **8** in 40 ml of tetrahydrofuran was added dropwise to an ice-cooled solution of 5 ml of 70% aqueous ethylamine in 25 ml of tetrahydrofuran and the resulting mixture was stirred at that temperature for 20 minutes. Methanol (100 ml) was added followed by 0.5 g of sodium borohydride in small protions, and the mixture was stirred for 15 minutes. The solution was concentrated at reduced pressure, diluted with water, and extracted with dichloromethane. Chromatography of the residue obtained upon evaporation (elution with 10% methanol-dichloromethane) afforded 2.0 g (67%) of amine **11** as a hygroscopic foam; nmr (deuteriochloroform): δ 1.10 (t, 3H, J = 7 Hz), 1.67 (s, 9H), 2.68 (ABX_3, 2H, J = 12, 7 Hz), 2.85 (dd, 1H, J = 12, 9 Hz), 2.94 (dd, 1H, J = 12, 4 Hz), 3.30 (s, 1H, OH), 5.16 (dd, 1H, J = 9, 4 Hz), 6.72 (dd, 1H, J = 3.8, 0.9 Hz), 7.25-7.34 (m, 2H), 7.58 (d, 1H, J = 3.8 Hz), 8.08 (m, 1H).

Amine **11** (1.9 g, 6 mmoles) was partitioned between 100 ml of ethyl acetate and 50 ml of water containing 2.8 g (20 mmoles) of potassium carbonate and the mixture was cooled in an ice bath while 1 ml (12.8 mmoles) of chloroacetyl chloride was added. After 5 minutes, the ethyl acetate layer was separated, washed with brine, dried (sodium sulfate) and evaporated to an oil that was crystallized from ether-hexane to afford 2.2 g (92%) of 14, mp 117-118°; nmr (deuteriochloroform): showed a 70-30 mixture of rotamers, δ 1.12 (t, 3H, J = 7 Hz), 1.67 (s, 9H), 3.24 (q, 2H, J = 7 Hz), 3.40-3.65 (m, 2H), 4.10 (s, 2H, major rotameter), 4.14 (AB, 2H, J = 12 Hz, minor), 5.21 (m, 1H, minor), 5.40 (broad d, 1H, major) 6.66 (d, 1H, J = 4 Hz, minor) 6.87 (d, 1H, J = 4 Hz, major), 7.20-7.36 (m, 2H), 7.58 (d, 1H, J = 4 Hz, major), 7.63 (d, 1H, J = 4 Hz, minor), 8.10 (m, 1H); ir (potassium bromide): 3600-3200, 1730, 1640 cm^{-1}.

Anal. Calcd. for $C_{19}H_{25}ClN_2O_4$: C, 59.92; H, 6.62; N, 7.35. Found: C, 59.70; H, 6.66; N, 7.13.

1-(*t*-Butoxycarbonyl)-4-(4-ethyl-5-oxo-2-morpholinyl)indole (**17**).

A solution of 2.0 g (5 mmoles) of **14** and 0.67 g (6 mmoles) of potassium *t*-butoxide in 50 ml of tetrahydrofuran was stirred at room temperature for 20 minutes, poured into water, and etracted with ether. The ether was washed with brine, dried (sodium sulfate) and evaporated to afford 1.8 g (87%) of **17** as a foam; nmr (deuteriochloroform: δ 1.10 (t, 3H, J = 7 Hz), 1.59 (s, 9H), 3.26-3.64 (m, 4H), 4.32 (AB, 2H, J = 16 Hz), 5.04 (dd, 1H, J = 10, 3 Hz), 6.62 (d, 1H, J = 3.5 Hz), 7.18 (d, 1H, J = 7 Hz), 7.24 (dd, 1H, J = 7.5, 7.5 Hz), 7.56 (d, 1H, J = 3.5 Hz), 8.08 (d, 1H, J = 7.5 Hz); ir (potassium bromide): 1730, 1650 cm^{-1}.

Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.27; H, 7.28; N, 8.30.

4-(-Ethyl-2-morpholinyl)indole Monohydrogen Fumarate (**20**).

Lactam **17** (2.9 g, 8.4 mmoles) in 25 ml of tetrahydrofuran was added slowly to a mixture of 1.0 g (26 mmoles) of lithium aluminum hydride in 25 ml of tetrahydrofuran and the resulting solution was heated under reflux for 2 hours. Water (1 ml), 1 ml of 15% sodium hydroxide and 3 ml of water were added sequentially and the suspension was filtered. Evaporation of the filtrate afforded 1.6 g (83%) of the free base of **20** as a thick oil. This was dissolved in methanol and treated with 0.79 g (6.8 mmoles) of fumaric acid. Addition of ether precipitated the monohydrogen fumarate salt, mp 58-60°; nmr (deuteriodimethylsulfoxide): δ 1.11 (t, 3H, J = 7 Hz), 2.41 (dd, 1H, J = 11, 11 Hz), 2.52 (dd, 1H, J = 11, 2 Hz), 2.65 (q, 2H, J = 7 Hz), 3.08 (broad d, 1H, J = 11 Hz), 3.21 (broad d, 1H, J = 11 Hz), 3.86 (ddd, 1H, J = 11, 11, 2 Hz), 4.08 (dd, 1H, J = 11, 2 Hz), 4.98 (dd, 1H, J = 11, 2 Hz), 6.56 (broad s, 1H, C-3H), 6.62 (s, 2H, fumaric acid), 7.02 (d, 1H, J = 7.5 Hz), 7.06 (dd, 1H, J = 7.5, 7.5 Hz), 7.32 (broad s, 1H C-2H), 7.34 (d, 1H, J = 7.5 Hz), 9.50 (broad, 2H, exchangeable), 11.30 (s, 1H, exchangeable).

Anal. Calcd. for $C_{18}H_{22}N_2O_5 \cdot 0.9\ H_2O$: C, 59.63; H, 6.61; N, 7.72. Found: C, 59.84; H, 6.50; N, 7.34.

4-(4-*n*-Propyl-2-morpholinyl)indole Monohydrogen Fumarate (**21**).

This material was prepared analogously to **20** without isolation of intermediates with the exception of lactam **18** that was purified by chromatography. The overall yield from **8** was 61%, mp 72-74°; nmr (deuteriodimethylsulfoxide): δ 0.88 (t, 3H, J = 7 Hz), 1.55 (m, 2H), 2.36 (dd, 1H, J = 11, 11 Hz), 2.40-2.60 (m, 3H), 3.02 (broad d, 1H, J = 11 Hz), 3.15 (broad d, 1H, J = 11 Hz), 3.85 (dd, 1H, J = 11, 11 Hz), 4.05 (d, 1H, J = 11 Hz), 4.96 (d, 1H, J = 11 Hz), 6.55 (broad s, 1H), 6.63 (s, 2H, fumaric acid), 7.00 (d, 1H, J = 7.5 Hz), 7.06 (dd, 1H, J = 7.5 Hz), 7.31 (d, 1H, J = 2 Hz), 7.38 (d, 1H, J = 7.5 Hz), 10.5 (broad, 2H, exchangeable), 11.16 (s, 1H, exchangeable).

Anal. Calcd. for $C_{19}H_{24}N_2O_5 \cdot 0.75\ H_2O$: C, 61.03; H, 6.71; N, 7.77. Found: C, 61.31; H, 6.75; N, 7.42.

Acknowledgement.

We wish to thank Mr. D. Repke and Dr. J. Muchowski for useful suggestions in regard to this work.

REFERENCES AND NOTES

[1] Contribution No. 645 from the Institute of Organic Chemistry.

[2] P. S. Anderson, J. J. Baldwin, D. E. McClure, G. F. Lundell and J. H. Jones, *J. Org. Chem.*, **47**, 2184 (1982).

[3] L. Nedelec, D. Frechet, C. Dumont, G. Plassard, and M. L. Brown, European Patent Application 34-546 (34-989) (1981); *Chem. Abstr.*, **96**, 6573t (1982).

[4] P. S. Anderson, J. J. Baldwin, D. E. McClure, G. F. Lundell, J. H. Jones, W. C. Randall, G. E. Martin, M. Williams, J. M. Hirshfield, B. V. Clineschmidt, P. K. Lumma and D. C. Remy, *J. Med. Chem.*, **26**, 363 (1983).

[5] J. R. Boissier, L. Nedelec and C. Oberlander, Abstracts of Papers, Symposium on Dopamine Receptor Agonists, Stockholm, Sweden, April 20-23, 1982.

[6] J. Guillame, L. Nedelec and C. Damont, French Patent 2,501,208; *Chem. Abstr.*, **98**, 72119s (1983).

[7] W. Leimgruber and A. D. Batcho, Abstracts of Papers, Third International Congress of Heterocyclic Chemistry, Tohoku University, Sendai, Japan, Aug. 1971; A. D. Batcho and W. Leimgruber, U.S. Patent 3,976,639 (1976); *Chem. Abstr.*, **75**, 63605v (1971).

[8] A synthesis of 4-carbomethoxyindole utilizing similar conditions (benzene as solvent) has been reported: A. P. Kozikowski, H. Ishida and Y. Y. Chen, *J. Org. Chem.*, **45**, 3350 (1980).

[9] G. S. Ponticello and J. J. Baldwin, *ibid.*, **44**, 4003 (1979).

[10] F. C. Uhle, *J. Am. Chem. Soc.*, **71**, 761 (1949).

[11] M. Somei and M. Natsume, *Tetrahedron Letters*, 2451 (1973).