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# Synthesis of Substituted Indoles via Meerwein Arylation[1]

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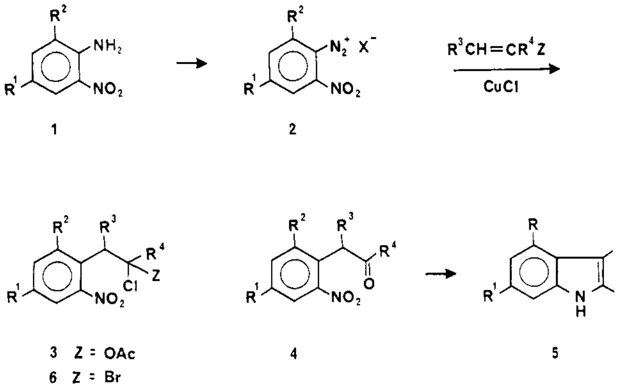
A new method for the synthesis of substituted indoles is detailed. Meerwein arylation of 4- and 6-substituted 2-nitrobenzenediazonium chlorides with vinyl acetate or vinyl bromide and subsequent reductive cyclization of the resulting adducts affords the corresponding 6- and 4-substituted ($CH_3$, $OCH_3$, Cl, Br, $CF_3$) indoles. The diazonium bisulfates of weakly basic 2-nitroanilines (4-Cl, 6-Br, 4-$CF_3$) gave higher yields of Meerwein arylation adducts than the corresponding diazonium chlorides. Coupling of 2-nitrobenzenediazonium chloride with 2-acetoxy-1-alkenes followed by reductive cyclization affords 2-alkylindoles.

The chemistry of indoles is a well-studied field, and a variety of methods for the synthesis of indoles have been developed.[3] Unfortunately, many of these methods are not regiospecific when utilized for the synthesis of certain substituted indoles and result in the formation of mixtures of isomers.[3] For example, the Fischer indole synthesis with meta-substituted phenylhydrazones gives mixtures of 4- and 6-substituted indoles.[4] Likewise, the Fischer indole synthesis with the phenylhydrazone of 2-butanone gives a mixture of 3-ethylindole and 2,3-dimethylindole.[5]

We felt that an attractive approach for the regiospecific synthesis of substituted indoles would be available by the Meerwein arylation reaction[6] of a diazonium salt **2**, derived from an appropriately substitute 2-nitroaniline **1**, with an unsaturated acceptor to give the substituted 2-nitrobenzyl carbonyl equivalent; reduction of the nitro group and subsequent cyclization and elimination should provide the substituted indole **5**.



Despite the potential utility of the Meerwein arylation reaction for the synthesis of substituted arenes, it has been utilized in only a limited number of instances for the preparation of substituted indoles. Woodward effected the Meerwein arylation of 4-methoxy-2-nitrobenzenediazonium chloride with formaldoxime to afford 2-nitroanisaldehyde; condensation with nitromethane and reductive cyclization afforded 6-methoxyindole, a necessary intermediate in the total synthesis of reserpine.[7] Meerwein arylation of 2-nitrobenzenediazonium chloride with 1,3-butadiene, followed by ozonolysis of the resulting 1-(2-nitrophenyl)-4-chloro-2-butene and reductive cyclization gave indole.[8]

We sought to develop a synthetic procedure that would regiospecifically afford a 2-nitrobenzyl carbonyl equivalent directly from the Meerwein arylation reaction, without the necessity of incorporating additional carbons or removing extraneous carbons subsequent to the Meerwein arylation. The results of these studies are detailed in this paper.

## Results and Discussion

**Meerwein Arylation Reaction.** The arylation of unsaturated compounds by diazonium salts has been investigated extensively.[6] We found that the reaction of 2-nitrobenzenediazonium chloride (**2a**) with vinyl acetate or vinyl bromide gave good yields (66–79%) of Meerwein arylation adducts. The best yields were obtained when the reaction was carried out in 65:35 (v/v) acetone–water at 0–25 °C in the presence of a catalytic amount of cupric chloride (10–20 mol %), an excess (usually 3 equiv) of the unsaturated acceptor, and added lithium chloride (2 equiv) at pH 1–2 under an oxygen-free atmosphere. In some cases, the addition of small amounts of calcium oxide to neutralize excess HCl and to maintain the pH between 1 and 2 gave higher yields of Meerwein coupling products. In contrast, when sodium acetate was added to buffer the medium, the yields of Meerwein adducts were always lowered. The highest yields of Meerwein adducts were obtained when the reaction was carried out at the minimum temperatures at which $N_2$ evolution would occur.

Reaction of **2a** with vinyl acetate gave a mixture of **3a** and 2-nitrophenylacetaldehyde (**4a**), which was formed by the hydrolysis of **3a** under the aqueous acidic condition of the reaction, in a combined, isolated yield of 79%. Since it was found that the yields of indole obtained by the reductive cyclization of **3a** and **4a** were comparable, for preparative purposes, it was convenient to reduce the mixture directly. Reaction of **2a** with vinyl bromide gave **6a** as the only Meerwein adduct in 72% yield.

Reaction of the 4-substituted 2-nitrobenzenediazonium chlorides **2b** or **2c** with vinyl acetate or vinyl bromide gave

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[2] Fellow of the Alfred P. Sloan Foundation, 1980–1984.

[3] Reviews: (a) R. K. Brown in "Indoles", Houlihan, W. J. ed., Wiley-Interscience, New York, 1972, Part 1, Chapter 2: (b) R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970, Chapter 3. For a compilation of recent references, see ref 4 in J. E. Nordlander, D. B. Catalane, K. D. Kotian, R. M. Stevens, and J. E. Haky, *J. Org. Chem.*, **46**, 778 (1981).

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[7] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

[8] (a) W. E. Noland and J. H. Sellstedt, *J. Org. Chem.*, **31**, 345 (1966); (b) R. D. Demaster, Ph.D. Dissertation, University of Minnesota, Minneapolis, MN, 1970.

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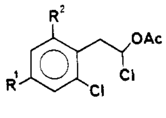
good yields (52–69%) of the corresponding Meerwein adducts. Again, mixtures of the α-chloro acetate **3** and the corresponding aldehyde **4** were obtained when vinyl acetate was used.

The 6-substituted 2-nitrobenzenediazonium chlorides **2d** or **2e** reacted with vinyl acetate to give acceptable yields of coupled products, again as a mixture of **3** and **4**. In contrast, attempts to react **2d** with vinyl bromide gave only low yields (10%) of **6d**.

The application of this strategy to 2-nitroanilines that contain an additional electron withdrawing group (4-Cl, 6-Br, 4-$CF_3$) is complicated by two factors. First, conversion of these weakly basic 2-nitroanilines to the corresponding 2-nitrobenzenediazonium chlorides requires more strongly acidic conditions; and second, when the electron-withdrawing effect of the resulting diazonium group is augmented by another electron-withdrawing group on the aromatic ring, the nitro group becomes readily susceptible to nucleophilic displacement by chloride. Thus, reaction of **2f–h** (X = Cl) with vinyl acetate or vinyl bromide afforded the desired adducts, **3f–h** and **4f–h** or **6f–h**, respectively, as well as significant amounts of undesired byproducts, **7f–h** or **8f–h** respectively, arising from nucleophilic displacement of the nitro group by chloride and subsequent Meerwein arylation. In order to circumvent these difficulties, the corresponding diazonium bisulfates **2f–h** (X = $HSO_4$) were prepared; Meerwein arylation of these salts with vinyl acetate or vinyl bromide gave the desired adducts in higher yields and greater purity than obtained from the corresponding diazonium chlorides.



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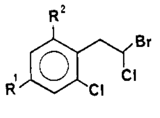

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For example, the reaction of vinyl acetate with 4-chloro-2-nitrobenzenediazonium chloride (**2f**, X = Cl) prepared by using 6.6 equiv of hydrochloric acid rather than the usual 3.0 equiv gave a mixture of **3f** and **4f** in a combined yield of 38%. When the reaction was carried out with the corresponding diazonium bisulfate **2f** (X = $HSO_4$) prepared as a solid from **1f** by using *iso*-amyl-nitrite–$H_2SO_4$, a mixture of **3f** and **4f** in a combined yield of 53% was obtained. The reaction of vinyl bromide with **2f** (X = Cl) afforded the desired adduct **6f** in 31% yield accompanied by similar amounts of the undesired byproduct **8f**, derived from nucleophilic displacement of the nitro group by chloride and subsequent Meerwein arylation. When solid 4-chloro-2-nitrobenzenediazonium bisulfate (**2f** X = $HSO_4$) was allowed to react with vinyl bromide, the yield of the desired Meerwein adduct **6f** increased slightly and the amount of the undesired product **8f** was reduced dramatically, thus facilitating product purification.

The reaction of 2-nitrobenzenediazonium chloride with 3 equiv of 2-acetoxy-1-propene gave a 78% yield of 1-(2-nitrophenyl)-2-propanone. Likewise, reaction of 3 equiv of **2a** with 2-acetoxy-1-pentene afforded 1-(2-nitrophenyl)-2-pentanone in 71% yield. In these cases, as well as others in which the enol acetate is derived from a ketone, it appears that the α-chloro acetate intermediate is completely hydrolyzed to the corresponding ketone under the conditions of the Meerwein arylation reaction. Reductive cyclization of these compounds afforded 2-alkylindoles.

The yields in the Meerwein arylation reaction of more substituted enol acetates were considerably lower. Thus, reaction of **2a** with 3 equiv of 3-acetoxy-2-pentene (*E*/*Z* mixture) gave 2-(2-nitrophenyl)-3-pentanone in 35% yield. Reaction of **2a** with 2-acetoxy-2-butene (*E*/*Z* mixture) or (*E*)-2-acetoxy-2-pentene gave poor yields of 3-(2-nitrophenyl)-2-butanone and 3-(2-nitrophenyl)-2-pentanone, respectively. Reductive cyclization of these compounds afforded 2,3-disubstituted indoles.

**Reductive Cyclization to Indoles.** The reductive cyclization of 2-nitrobenzylcarbonyl compounds to indoles has been carried out by using a variety of reagents,[3a,b] including $H_2/Pd$,[9] $SnCl_2$,[10] Fe/HOAc,[11] and Zn/HOAc.[12] We found that reductive cyclization of **4a–h** with 3.5 equiv of iron powder and 7 equiv of acetic acid in refluxing 80:20 (v/v) ethanol–water for 2 h gave good to excellent yields (51–90%) of the corresponding indoles. Likewise, the α-chloro acetates **3a–h** also underwent reductive cyclization to the corresponding indoles when treated with Fe/HOAc containing 1 equiv of sodium acetate to neutralize the hydrogen chloride formed during this reaction. Since the yields of indoles obtained from the α-chloro acetates **3** and the corresponding aldehydes **4** were comparable, it was convenient to carry out the reductive cyclization on the mixture obtained from the Meerwein arylation reaction. The reductive cyclization of **3a** to indole was also carried out by hydrogenation with platinum oxide catalyst at atmospheric pressure in ethanol, followed by treatment with sodium ethoxide. Likewise, the ketones **4i–m** underwent smooth reductive cyclization with Fe/HOAc.

The reductive cyclization of **6a–g** to the corresponding indoles was performed by treatment with 3.5 equiv of iron powder and 1 equiv of acetic acid in 80:20 (v/v) ethanol–water containing 2 equiv of sodium acetate. Reductive cyclization of **6c** to 6-methoxyindole in 63% yield was also effected by hydrogenation with platinum oxide catalyst, followed by treatment with triethylamine.

## Conclusion

The procedures detailed in this paper provide a convenient method for the synthesis of a variety of substituted indoles via the Meerwein arylation reaction of vinyl acetate, vinyl bromide, or 2-acetoxy-1-alkenes with aryldiazonium salts derived from 2-nitroanilines. This procedure is particularly well suited for the preparation of many 4- or 6-substituted indoles since the requisite 2-nitroanilines are readily available. It is noteworthy that these are the very isomers of substituted indoles which are difficult to obtain regiospecifically via the Fischer indole synthesis.

## Experimental Section

**General Methods.** Melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Infrared spectra were determined on a Beckman Acculab 4 spectrometer. $^1H$ NMR spectra were recorded at 60 MHz on a Varian EM-360 spectrometer with $CDCl_3$ as solvent and $Me_4Si$ as an internal standard. Flash chromatography was carried out by the method of Still.[13] The pH of solutions in the Meerwein arylation reactions was monitored with a Corning Model 7 pH meter and a Markson 7xx series polymer electrode. All chemicals were obtained from commercial sources except for the following. 6-Methoxy-2-nitroaniline was prepared by the acid-catalyzed rearrangement of *N*-nitro-*o*-anisidine.[14] 6-Bromo-2-nitroaniline was prepared by the nitration of *o*-bromoacetanilide and subsequent hydrolysis.[15] Samples of (*Z*)- and (*E*)-2-acetoxy-2-pentene

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and 2-acetoxy-1-pentene were prepared from 2-pentanone and isopropenyl acetate with *p*-toluenesulfonic acid catalysis.[16] A mixture of (*E*)- and (*Z*)-3-acetoxy-2-pentene was similarly prepared from 3-pentanone and isopropenyl acetate. A mixture of (*E*)- and (*Z*)-2-acetoxy-2-butene was prepared from 2-butanone and acetic anhydride with perchloric acid catalysis.[17]

**A. General Procedure for Meerwein Arylation of 2-Nitroaryldiazonium Chlorides with Vinyl Acetate. Preparation of 3a and 4a.** 2-Nitroaniline hydrochloride, prepared by heating a mixture of 1.38 g (10.0 mmol) of 2-nitroaniline and 2.50 mL (12 M, 30.0 mmol) of concentrated hydrochloric acid for several minutes, was cooled to −5 °C in an ice–salt bath, and a cold solution of 725 mg (10.5 mmol) of sodium nitrite in 3 mL of water was added over 15 min with stirring, while the temperature of the reaction mixture was held between −5 and 2 °C. The mixture was stirred for an additional 15 min, and 30 mg (0.50 mmol) of urea in 5 mL of cold water was added. This cold solution was added over 10 min to a stirred mixture of 2.77 mL (30.0 mmol) of vinyl acetate and 0.85 g (20.0 mmol) of lithium chloride in 50 mL of 65:35 (v/v) acetone–water in a 100-mL two-necked flask fitted with a gas bubbler that was cooled to −5 °C under an atmospheric of argon. A cold solution of 0.26 g (1.5 mmol) of cupric chloride dihydrate in 5 mL of water was then added over 10 min, and the evolution of nitrogen commenced. The temperature of the reaction mixture was held between 3 and 10 °C for 2 h and then warmed to room temperature over 2 h. After an additional 2 h, nitrogen evolution had ceased, and the acetone was evaporated. The reaction mixture was poured into 50 mL of water and extracted with dichloromethane (3 × 30 mL). The combined extracts were washed successively with water and brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent and purification by flash column chromatography on 70 g of silica gel (35% dichloromethane–hexanes eluent) gave 1.21 g (50%) of **3a** as a light yellow oil: $^1$H NMR $\delta$ 2.06 (s, 3 H, $CH_3C{=}O$), 3.70 (d, $J$ = 6 Hz, 2 H, $CH_2Ar$), 6.75 (t, $J$ = 6 Hz, 1 H, OCHCl), 7.33–8.16 (m, 4 H); IR (film) 1760 (C=O), 1530 (asym $NO_2$), 1355 (sym $NO_2$), 1210 (CO) cm$^{-1}$. Using 55:45 dichloromethane–hexanes as the eluent, 484 mg (29%) of **4a** was obtained as an oil: $^1$H NMR $\delta$ 4.18 (s, 2 H, $ArCH_2C{=}O$), 7.28–8.33 (m, 4 H), 9.92 (s, 1 H, HC=O); IR (film) 2825 (HC=O), 2740 (H-C=O), 1735 (C=O), 1535 (asym $NO_2$), 1360 (sym $NO_2$); $n^{20}_D$ 1.5672 (lit.[8] $n^{25.5}_D$ 1.5634). In most instances, it was difficult to completely separate the $\alpha$-chloro acetate and the aldehyde. Thus a mixture of these compounds was used in the reductive cyclization.

**B. General Procedure for Meerwein Arylation with Substituted Vinyl Acetates. 1-(2-Nitrophenyl)-2-propanone (4i)** was prepared by the reaction of 3.34 mL (30.0 mmol) of 2-acetoxypropene with 2-nitrobenzenediazonium chloride, obtained from 1.38 g (10.0 mmol) of 2-nitroaniline, buffered with 0.23 g (4.0 mmol) of calcium oxide, using 0.26 g (1.5 mmol) of cupric chloride dihydrate as the catalyst and 0.85 g (20.0 mmol) of added lithium chloride in 60 mL of 65:35 acetone–water by the general procedure outlined above. Extraction with dichloromethane and purification by flash column chromatography on 70 g of silica gel (55:45 dichloromethane–hexanes as the eluent) gave 1.40 g (78%) of **4i** as an oil, which was crystallized from ethanol–water to give a sample with mp 27–28 °C (lit.[18a] mp 26–27 °C); $^1$H NMR $\delta$ 2.27 (s, 3 H, $CH_3C{=}O$), 4.13 (s, 2 H, $ArCH_2C{=}O$), 7.13–8.20 (m, 4 H); IR (film) 1715 (C=O), 1525 (asym $NO_2$), 1350 (sym $NO_2$) cm$^{-1}$.

**C. General Procedure for Meerwein Arylation of 2-Nitroaryldiazonium Chlorides with Vinyl Bromide. Preparation of 6a.** The procedure detailed above was utilized, except vinyl bromide (30.0 mmol) was used instead of vinyl acetate. Extractive workup with diethyl ether and purification by flash column chromatography of 50 g of silica gel (25:75 dichloromethane–hexanes eluent) gave 2.21 g of a light yellow solid, which was recrystallized from 95:5 ethanol–water to afford 1.91 g (72%) of **6a**: mp 64–65 °C; $^1$H NMR $\delta$ 3.93 (dd, $J$ = 6.5, 13 Hz, 2 H, $CH_2Ar$), 6.17 (t, $J$ = 6.5 Hz, 1 H, BrCHCl), 7.45–8.30 (m, 4 H).

Table I. Yields for Meerwein Arylation of Vinyl Acetates and Reductive Cyclization to Indoles[a, b]

| entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ | yield, % 3 + 4 | yield, % 5[e] |
|---|---|---|---|---|---|---|
| a | H | H | H | H | 79 | 90, 80[f] |
| b | Me | H | H | H | 69 | 79 |
| c | MeO | H | H | H | 66 | 83 |
| d | H | Me | H | H | 41[c] | 76 |
| e | H | MeO | H | H | 43 | 73 |
| f | Cl | H | H | H | 53[d] | 74 |
| g | $CF_3$ | H | H | H | 32[d] | 72 |
| h | H | Br | H | H | 49[d] | 51 |
| i | H | H | H | Me | 78[c] | 68 |
| j | H | H | H | *n*-Pr | 71[c] | 66 |
| k | H | H | Me | Me | 13 | 62 |
| l | H | H | Me | Et | 35[c] | 53 |
| m | H | H | Et | Me | 14 | 52 |

[a] All indoles are known compounds. [b] Meerwein arylation with diazonium chloride, unless otherwise noted. [c] Calcium oxide added to maintain pH 1–2. [d] Meerwein arylation with diazonium bisulfate. [e] Reductive cyclization with Fe/HOAc, unless otherwise noted. [f] Reductive cyclization with $H_2/PtO_2$.

**D. General Procedure for Meerwein Arylation of 2-Nitroanilines Containing Electron-Withdrawing Substituents. Preparation of 3f and 4f.** A suspension of 4-chloro-2-nitroaniline bisulfate, prepared by the addition of 1.40 mL (36 N, 25.2 mmol) of sulfuric acid to 865 mg (5.00 mmol) of 4-chloro-2-nitroaniline in 10 mL of absolute ethanol, was cooled to 0 °C and diazotized by the addition of 0.75 mL (5.50 mmol) of isoamyl nitrite with strirring over 5 min. The solution was stirred for 1 h at 0 °C, and 10 mL of anhydrous diethyl ether was added and the mixture stored at −15 °C. The mixture was filtered, and the solid was washed with fresh ether to yield 1.12 g of the colorless salt, which was combined with a second crop (0.14 g) of crystals for a total of 1.26 g (90%) of 4-chloro-2-nitrobenzenediazonium bisulfate: mp 94–98 °C dec. This compound was used immediately in the next step.

To a stirred mixture of 0.62 mL (6.75 mmol) of vinyl acetate, 60 mg (0.35 mmol) of cupric chloride dihydrate, and 191 mg (4.50 mmol) of lithium chloride in 22 mL of 65:32 acetone–water containing 1.00 mmol of hydrochloric acid at −5 °C under an atmosphere of argon was added 630 mg (2.24 mmol) of solid 4-chloro-2-nitrobenzenediazonium sulfate. The temperature of the reaction mixture was held between 3 and 10 °C for 2 h and warmed to room temperature over 2 h. After an additional 2 h, the reaction mixture was extracted with dichloromethane, the extracts were dried with $MgSO_4$, the solvents were evaporated, and the residue was purified by flash column chromatography on 30 g of silica gel (30; dichloromethane–hexanes) to give 188 mg (27%) of **3f** as an oil: $^1$H NMR $\delta$ 2.10 (s, 3 H, $CH_3C{=}O$), 3.70 (d, $J$ = 6 Hz, 2 H, $CH_2Ar$), 6.72 (t, $J$ = 6 Hz, 1 H, OCHCl), 7.33–8.20 (m, 3 H). Using 55:45 dichloromethane–hexanes as the eluent afforded 130 mg (26%) of **4f** as an oil: $^1$H NMR $\delta$ 4.17 (s, 2 H, $ArCH_2C{=}O$), 7.30–8.35 (m, 3 H), 9.93 (s, 1 H, HC=O).

Again, mixtures of the $\alpha$-chloro acetates and the corresponding aldehydes were used in most instances in the reductive cyclization. Meerwein arylation of the aryldiazonim sulfates with vinyl bromide was carried out as described above, substituting vinyl bromide for vinyl acetate.

**E. General Procedure for Reductive Cyclization Using Iron/Acetic Acid.** In a 250-mL one-necked flask, fitted with a reflux condenser, were placed 1.22 g (5.00 mmol) of 1-acetoxy-1-chloro-2-(2-nitrophenyl)ethane (**3a**), 0.98 g (17.5 mmol) of iron powder (200 mesh), 2.10 g (35.0 mmol) of acetic acid, 0.68 g (5.0 mmol) of sodium acetate dihydrate, and 100 mL of 80:20 (v/v) ethanol–water. The mixture was heated to reflux with stirring for 2 h under an atmosphere of argon. The reaction mixture was cooled, the ethanol was evaporated, and the residue was extracted with dichloromethane (3 × 30 mL). The combined

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[15] (a) H. Franzen and E. Engel, *J. Prakt. Chem.* **102(2]**, 178 (1951); (b) C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 3092 (1929).

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[18] "Dictionary of Organic Compounds", 4th ed., J. R. A. Pollock and R. Stevens, Eds., Oxford University Press, New York, 1965: (a) Vol. 4, p 2481; (b) Vol. 3, p 1846; (c) Vol. 4, p 2231; (d) Vol. 5, p 2795; (e) Vol. 2, p 1184; (f) Vol. 3, p 1396.

Table II. Yields for Meerwein Arylation of Vinyl Bromide and Reductive Cyclization to Indoles[a,b]

| | | | | | yield, % | |
|---|---|---|---|---|---|---|
| entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ | 6 | 5[e] |
| a | H | H | H | H | 72 | 85 |
| b | Me | H | H | H | 52 | 70 |
| c | MeO | H | H | H | 65 | 71, 63[f] |
| d | H | Me | H | H | [c] | 7[g] |
| f | Cl | H | H | H | 34[d] | 70 |
| g | $CF_3$ | H | H | H | [c,d] | 14[g] |

[a] All indoles are known compounds. [b] Meerwein arylation with diazonium chloride, unless otherwise noted. [c] Intermediate not isolated. [d] Meerwein arylation with diazonium bisulfate. [e] Reductive cyclization with Fe/HOAc, unless otherwise noted. [f] Reductive cyclization with $H_2/PtO_2$. [g] Overall yield from corresponding substituted nitroaniline.

extracts were washed successively with water and brine and dried over potassium carbonate. Evaporation of the solvent and purification by flash column chromatography on 50 g of silica gel (50:50 dichloromethane–hexanes eluent) gave 0.53 g (90%) of indole (**5a**): mp 52–53 °C (lit.[18b] mp 52 °C); $^1$H NMR was in agreement with reported spectra.

The other indoles in Table I were obtained similarly either from the separated α-chloro acetates, the corresponding aldehydes, or mixtures of these compounds. Likewise, reductive cyclization of the dihalides **6** under the same conditions, but using 2 equiv of sodium acetate dihydrate gave the results indicated in Table II.

**F. Reductive Cyclization by Catalytic Hydrogenation. 1. Preparation of Indole.** A solution of 0.49 g (2.0 mmol) of 1-acetoxy-1-chloro-2-(2-nitrophenyl)ethane (**3a**) in 40 mL of absolute ethanol containing 30 mg of platinum oxide was hydrogenated at 1 atm of pressure and room temperature. After stirring for 30 min, the theoretical amount (136 mL) of hydrogen had been taken up. The reaction mixture was purged with argon, 0.14 g (2.1 mmol) of sodium ethoxide was added, and the mixture was stirred at room temperature for 1 h. Evaporation of the ethanol, extraction with dichloromethane, and flash column chromatography on 20 g of silica gel (50:50 dichloromethane–hexanes eluent) gave 188 mg (80%) of indole (**5a**): mp 52–53 °C. (lit.[18b] mp 52 °C).

**2. Preparation of 6-Methoxyindole.** The reductive cyclization was carried out as described above starting with 0.59 g (2.0 mmol) of **4c**, except that after the hydrogen uptake was complete triethylamine (6.0 mmol) was added and the reaction mixture was heated at reflux for 6 h. Evaporation of ethanol, extraction with dichloromethane, and purification by flash chromatography on 20 g of silica gel (50:50 dichloromethane–hexanes) and crystallization from petroleum ether gave 186 mg (63%) of 6-methoxyindole: mp 91–92 °C (lit.[7] mp 91–92 °C); $^1$H NMR δ 3.80 (s, 3 H, $CH_3$) 6.40–6.57 (m, 1 H), 6.70–7.70 (m, 4 H), 7.98 (br s, 1 H, NH).

**Data for Indoles Prepared by Reductive Cyclization.** All of the indoles prepared by the above procedures had melting points and/or boiling points in agreement with literature values and exhibited $^1$H NMR spectra consistent with the assigned structures. 6-Methylindole (**5b**): mp 28–29 °C (lit.[9] mp 29–30.5 °C); $^1$H NMR δ 2.35 (s, 3 H, $CH_3$), 6.20–6.32 (m, 1 H), 6.62–7.50 (m, 4 H), 8.10 (br s, 1 H, NH). 4-Methoxyindole (**5e**): mp 68–69 °C from petroleum ether (lit.[19] mp 69.5–70.5 °C); $^1$H NMR δ 3.95 (s, 3 H, $CH_3O$); 6.42–7.20 (m, 5 H), 8.15 (br s, 1 H, NH). 4-Methylindole (**5d**): bp 110 °C (1 mm) [lit.[20] bp 110 °C (1 mm)]; $^1$H NMR δ 2.50 (s, 3 H, $CH_3$), 6.33–6.50 (m, 1 H), 6.73–7.15 (m, 4 H), 8.00 (br s, 1 H, NH). 6-Chloroindole (**5f**): mp 88–89 °C from petroleum ether (lit.[19] mp 88.5–89 °C); $^1$H NMR δ 6.35–6.50 (m, 1 H), 6.90–7.60 (m, 4 H), 8.15 (br s, 1 H, NH). 6-Trifluoromethylindole (**5g**): mp 107–108 °C from petroleum ether (lit.[21] mp 109–110 °C); $^1$H NMR δ 6.52–6.68 (m, 1 H), 7.22–7.84 (m, 4 H), 8.30 (br s, 1 H, NH). 4-Bromoindole (**5h**): bp 96 °C (1 mm) [lit.[19] bp 115–118 °C (3 mm)]; $^1$H NMR δ 6.57–6.73 (m, 1 H), 6.90–7.48 (m, 4 H), 8.20 (br s, 1 H, NH). 2-Methylindole (**5i**); mp 59–60 °C from ethanol–water (lit.[18c] mp 61 °C); $^1$H NMR δ 2.28 (s, 3 H, $CH_3$), 6.03–6.23 (br s, 1 H), 6.85–7.55 (m, 5 H). 2-*n*-Propylindole (**5j**): mp 33–34 °C from ethanol–water (lit.[18d] mp 33–34 °C); $^1$H NMR δ 0.88 (t, $J$ = 7 Hz, 3 H, $CH_3$), 1.22–1.85 (m, 2 H, $CH_2$), 2.45 (t, $J$ = 7 Hz, 2 H, $CH_2$-2-indolyl), 6.10–6.27 (br s, 1 H), 6.90–7.70 (m, 5 H). 2,3-Dimethylindole (**5k**): mp 105–107 °C from petroleum ether (lit.[18e] mp 107–109 °C); $^1$H NMR δ 2.15 (s) and 2.22 (s) (total 6H, $CH_3$), 6.82–7.60 (m, 5 H). 2-Ethyl-3-methylindole (**5l**): mp 65–66 °C from ethanol–water (lit.[18f] mp 66 °C); $^1$H NMR δ 1.22 (t, $J$ = 7 Hz, 3 H, $CH_3$), 2.18 (s, 3 H, $CH_3$-3-indolyl), 2.66 (q, $J$ = 7 Hz, 2 H, $CH_2$), 6.83–7.60 (m, 4 H), 7.90 (br s, 1 H, NH). 3-Ethyl-2-methylindole (**5m**): mp 44–45 °C from ethanol–water (lit.[18f] mp 44–45 °C); $^1$H NMR δ 1.21 (t, $J$ = 7 Hz, 3 H, $CH_3$), 2.22 (s, 3 H, $CH_3$-2-indolyl), 2.66 (q, $J$ = 7 Hz, 2 H, $CH_2$-3-indolyl), 6.80–7.70 (m, 5 H).

**Registry No.** **1a**·HCl, 15873-52-6; **1b**, 89-62-3; **1c**, 96-96-8; **1d**, 570-24-1; **1e**, 16554-45-3; **1f**, 89-63-4; **1g**, 400-98-6; **1h**, 59255-95-7; **2f** (X = $HSO_4$), 13617-62-4; **2g** (X = $HSO_4$), 85355-31-3; **2h** (X = $HSO_4$), 85355-33-5; **3a**, 67098-21-9; **3b**, 85355-34-6; **3c**, 85355-35-7; **3d**, 85355-36-8; **3e**, 85355-37-9; **3f**, 85355-38-0; **3g**, 85355-39-1; **3h**, 85355-40-4; **3i**, 85355-41-5; **3j**, 85355-42-6; **3k**, 85355-43-7; **3l**, 85355-44-8; **3m**, 85355-45-9; **4a**, 1969-73-9; **4b**, 85355-46-0; **4c**, 69111-92-8; **4d**, 85355-47-1; **4e**, 85355-48-2; **4f**, 69111-49-5; **4g**, 85355-49-3; **4h**, 85355-50-6; **4i**, 1969-72-8; **4j**, 85355-51-7; **4k**, 85355-52-8; **4l**, 85355-53-9; **4m**, 85355-54-0; **5a**, 120-72-9; **5b**, 3420-02-8; **5c**, 3189-13-7; **5d**, 16096-32-5; **5e**, 4837-90-5; **5f**, 17422-33-2; **5g**, 13544-43-9; **5h**, 52488-36-5; **5i**, 95-20-5; **5j**, 13228-41-6; **5k**, 91-55-4; **5l**, 19013-49-1; **5m**, 35246-18-5; **6a**, 85355-55-1; **6b**, 85355-56-2; **6c**, 85355-57-3; **6f**, 85355-58-4; **6g**, 85355-59-5; **7f**, 85355-60-8; **7g**, 85355-61-9; **7h**, 85355-62-0; **8f**, 85355-63-1; **8g**, 85355-64-2; **8h**, 85355-65-3; vinyl acetate, 108-05-4; 2-acetoxypropene, 108-22-5; vinyl bromide, 593-60-2; 3-acetoxy-2-pentene, 13893-75-9; 2-acetoxy-2-butene, 6203-88-9; (*E*)-2-acetoxy-2-pentene, 24471-78-1.

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