Regioselective Fischer Indole Route to 3-Unsubstituted Indoles

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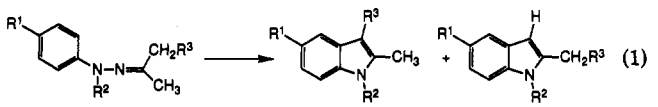
Use of Eaton's reagent ($P_2O_5/MeSO_3H$) as acid catalyst in the Fischer indole reaction using methyl ketones provides unprecedented regiocontrol to form the 3-unsubstituted indoles. In several instances where the harshness of the reagent causes decomposition and low yields, dilution in sulfolane or dichloromethane results in far less degradation and higher yields of indoles. Steric effects and the acidity of the medium are the two major factors that control the regioselectivity. The role of the P_2O_5 in the reagent mixture $P_2O_5/MeSO_3H$ is simply as a drying agent when used as catalyst for the Fischer indole reaction.

The Fischer indole reaction provides a versatile and convergent route to a wide variety of indoles. However, when the ketone component of the reaction has two enolizable sites, regiocontrol is often a problem. In 1902, Plancher and Bonavia[1] published general rules governing the direction of indolization of unsymmetrical ketone arylhydrazones, the gist of which was that hydrazones made from methyl alkyl ketones **1** give 3-substituted 2-methylindoles **2** as the major products (eq 1) and that dialkyl ketones give mixtures of products.



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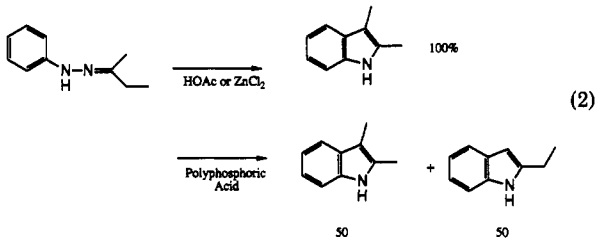
In the intervening years, many examples have supported the conclusion that methyl alkyl ketones provide the 3-substituted 2-methylindoles **2** as the sole or major product.[2] When the 3-unsubstituted isomer **3** is desired, a thioether group is often used to direct the regiochemistry in the indolization and subsequently removed.[3] Since this requires two extra steps in the overall synthetic scheme, studies have been directed at understanding how to form the 3-unsubstituted indole directly from the methyl ketone.[4-11] The consensus of these investigations was that more of the 3-unsubstituted indole **3** can be formed under very strongly acidic conditions. For example, in the indolization of the phenylhydrazone of ethyl methyl ketone, the 2,3-dimethyl isomer is formed exclusively under weak acid conditions, but the 2-ethyl isomer and the 2,3-dimethyl isomer are formed in equal amounts with use of polyphosphoric acid or 80% sulfuric acid in ethanol (eq 2).[5]



(2)

Although these results are somewhat encouraging, there exists no general method for regiospecific formation of the 3-unsubstituted indoles in high yield.

Since the 3-position is the most electrophilic center in the indole, the 3-unsubstituted indole is a valuable intermediate that can be readily elaborated. The question of direct formation of 3-unsubstituted indoles arose when we were preparing 3-acylindoles as leukotriene biosynthesis inhibitors. Since indolizations of diketones can lead to several isomers, stepwise synthesis via the 3-unsubstituted indoles as the key intermediates was the preferred route. In this paper, we describe the use of Eaton's acid, $P_2O_5/MeSO_3H$,[12] to $MeSO_3H$,[12] to prepare the 3-unsubstituted indoles from the corresponding methyl ketones in good yields. In addition, the nature of the active species in the reagent is addressed.

Results and Discussion

Determination of the Best Acid for the Fischer Indolization. While indolization of simple hydrazones (eq 2) with PPA or sulfuric acid occurs in high yield to give a mixture of both indole products, much poorer yields were obtained under these conditions with more complex hydrazones. For example, indolization of **4** using PPA at 80 °C provided the desired indole **5** in only 20% assay yield, with the major product being N–N cleavage to give the substituted aniline **7**. Likewise, in sulfuric acid/methanol mixtures, less than 10% product was formed. Using strong acid resins as Amberlyst 15 also gave poor results, with isomer ratios never above 3:1 and yields of 30–40%. The trimethylsilyl ester of PPA, usually abbreviated as PPSE, has been used successfully in indolizations as a milder catalyst.[13,14] Use of PPSE with hydrazone **4** produced a clean reaction, but the ratio of the 3-unsubstituted indole **5** to 3-substituted 2-methylindole **6** could never be improved to above a 75:25 ratio. Finally, more encouraging results were obtained with Eaton's reagent, 10% P_2O_5 in

(1) Plancher, G.; Bonavia, A. *Gazz. Chim. Ital* **1902**, *32*, 414.
(2) Robinson, B. *The Fischer Indole Synthesis*; Wiley: New York, 1982. Robinson cites several hundred examples on pp 241–250.
(3) Trofimov, F. A.; Garnova, V. I.; Grinev, A. N.; Tsyshkova, N. G. *Chem. Heterocycl. Compd.* **1979**, *15*, 63. Trofimov, F. A.; Tsyshkova, N. G.; Garnova, V. I.; Grinev, A. N. *Chem. Heterocycl. Compd.* **1975**, *11*, 1091. Trofimov, F. A.; Tsyshkova, N. G.; Grinev, A. N. USSR Patent 457,698 (*Chem. Abstr.* **1975**, *83*, 9785f).
(4) Illy, H.; Funderburk, L. *J. Org. Chem.* **1968**, *33*, 4283–4285.
(5) Palmer, M. H.; McIntyre, P. S. *J. Chem. Soc. B* **1969**, 446–449.
(6) Reed, G. W. B.; Cheng, P. T. W.; McLean, S. *Can. J. Chem.* **1982**, *60*, 419–424.
(7) Yamamoto, H.; Misaki, A.; Imanaka, M. *Chem. Pharma. Bull.* **1968**, *16*, 2313–2319.
(8) Miller, F. M.; Schinske, W. N. *J. Org. Chem.* **1978**, *43*, 3384–3388.
(9) Lyle, R. E.; Skarlos, L. *J. Chem. Soc., Chem. Commun.* **1966**, 644.
(10) Bonjoch, J.; Casamitjana, N.; Gracia, J.; Ubeda, M.-C.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 2449–2452.
(11) Bui-Hoi, N. P.; Jacquignon, P.; Perin-Roussel, O. *Bull. Soc. Chim. Fr.* **1965**, 2849.
(12) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071–4073.
(13) Yamamoto, K.; Watanabe, H. *Chem. Lett.* **1982**, 1225–1228.
(14) Bergman, J.; Pelcman, B. *J. Org. Chem.* **1989**, *54*, 824–828.

0022-3263/91/1956-3001$02.50/0

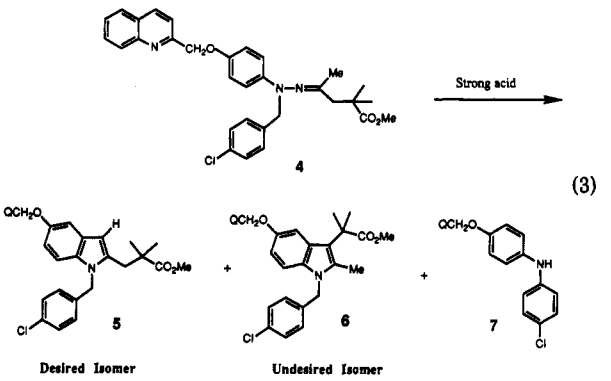
Table I. Effect of Cosolvents in Indolization of Hydrazone 4 Using $P_2O_5/MeSO_3H$

reagent/solvent	temp (°C)	isomer ratio 5:6	% yield of 5
$MeSO_3H$	23	100	40
10% $P_2O_5/MeSO_3H$ (neat)	23	100	50
10% $P_2O_5/MeSO_3H$/TMU (1:1)[a]	55	1.0	
10% $P_2O_5/MeSO_3H$/toluene (1:1)	55	50	30
10% $P_2O_5/MeSO_3H/CH_3CN$ (1:1)	55	8	65
10% $P_2O_5/MeSO_3H$/sulfolane (1:10)	55	1.5	
10% $P_2O_5/MeSO_3H$/sulfolane (1:3)	55	9	72
10% $P_2O_5/MeSO_3H$/sulfolane (1:2)	55	13	77
10% $P_2O_5/MeSO_3H$/sulfolane (1:1)	45	40	85
3% $P_2O_5/MeSO_3H/CH_2Cl_2$ (1:2)	45	100	86
$MeSO_3H$/sulfolane (1:1)	55	50	65
10% $(MeSO_2)_2O/MeSO_3H$/sulfolane	55	50	74
10% PPA/$MeSO_3H$/sulfolane (1:1)[b]	55	50	87

[a] TMU = tetramethylurea. [b] PPA = polyphosphoric acid.

$MeSO_3H$.[12] To our knowledge, this reagent has never been used to catalyze Fischer indole reactions. Using this reagent with hydrazone 4 at room temperature gave a 50% assay yield of the desired indole 5 with at least a 100:1 isomer ratio.

Use of Cosolvents with 10% P_2O_5 in $MeSO_3H$. Although the 50% yield obtained with Eaton's reagent was adequate and better than with any other acid, the 20–25% aniline 7 byproduct was still a concern. We reasoned that

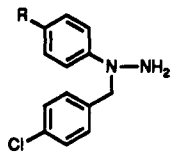
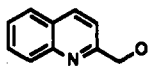
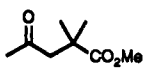
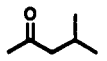
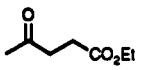
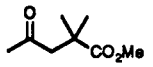
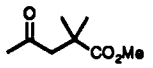
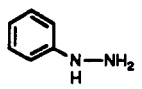
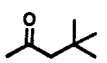
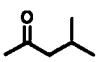
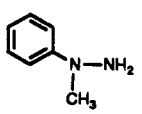
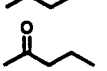
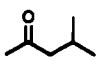


(3)

by reducing the acidity of the medium somewhat yields would improve. One way to accomplish this was to dilute the reagent with an appropriate solvent. Nonpolar solvents such as toluene and cyclohexane were not miscible with 10% P_2O_5 in $MeSO_3H$, and these two-phase systems provided no improvement over the neat reagent. Basic solvents in which the reagent was miscible such as ethers and alcohols attenuated the acidity of $MeSO_3H$ too much so that the undesired isomer 6 predominated. Therefore, a polar yet nonbasic solvent was required. The solvents that were tried included tetramethylurea, acetonitrile, sulfolane, and dichloromethane, with the latter two proving best. A survey of these two solvents at varying dilution with P_2O_5 in $MeSO_3H$ led to the optimization of the yield at 85% and isomer ratio in the 40:1–100:1 range. The results are tabulated in Table I.

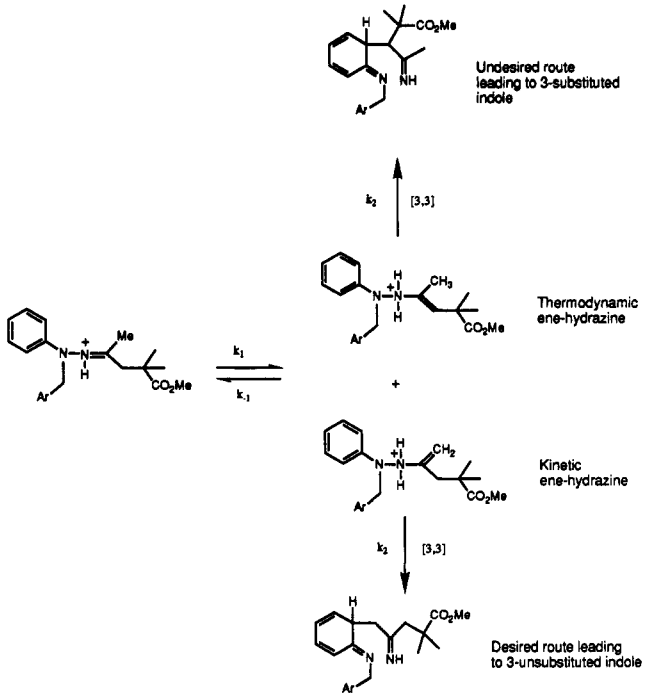
Survey of Other Indolizations Using P_2O_5 in $MeSO_3H$. Given the success in obtaining a high yield and

Table II. Yields and Isomer Ratios for Fischer Indolizations of Arylhydrazines and Methyl Ketones

hydrazine	R	methyl ketone	method[a]	isomer ratio	% total indole yield[b]	% isolated yield[c]
			A	100:1	87	81
			B	40:1	85	77
			C	100:1	50	
			A	70:1	72	68
			A	82:18	79	59
			A	86:14	76	57
	i-Pr		A	50:1	83	75
	F		A	70:1	83	79
			C	90:1	84	81
			C	85:15	86	56
			C	78:22	95	
			C	80:20	92	71
			C	90:10	85	77

[a] Key: Method A, 2 parts dichloromethane to 1 part 3% P_2O_5 in $MeSO_3H$; Method B, 1 part sulfolane to 1 part 10% P_2O_5 in $MeSO_3H$; Method C, neat 10% P_2O_5 in $MeSO_3H$. [b] Total yield of both indole isomers. [c] Isolated yield of 3-unsubstituted indole.

Scheme I



isomer ratio in the indolization shown in eq 3, a survey of other indolizations was carried out to demonstrate the generality of the method. The results are shown in Table II.

Inspection of Tables I and II shows that two major factors control the regioselectivity of the indolization.

(1) Acidity of the Medium. As described in the literature, the acidity of the medium is of prime importance in controlling the regioselectivity. Using weak acids or dilute solutions of strong acids leads to indolization from the most substituted ene–hydrazine (Scheme I), while strong acid conditions lead to indolization through the least substituted end–hydrazine to give the 3-unsubstituted indole. In the examples shown in Tables I and II, best isomer ratios were obtained in neat P_2O_5 in $MeSO_3H$. However, this medium proved to cause extensive decomposition in several cases, so the acid was diluted with either sulfolane or dichloromethane. With use of hydrazone **4** as an example, dilution of the acid in sulfolane from a 1:1 mixture to a 1:10 mixture of acid/solvent eroded the isomer ratio from 40:1 to 0.7:1. Dilution of the acid in dichloromethane did not cause as large of an effect. With hydrazone **4**, the isomer ratio dropped only from 100:1 to 30:1 as the acid was diluted from neat to 1:10 in dichloromethane. With the simple hydrazone from 2-butanone and phenylhydrazone **1h**, the ratio in neat P_2O_5 in $MeSO_3H$ was 3:1 and dropped to 1:1 in a 1:3 mixture of P_2O_5 in $MeSO_3H$ diluted in dichloromethane.

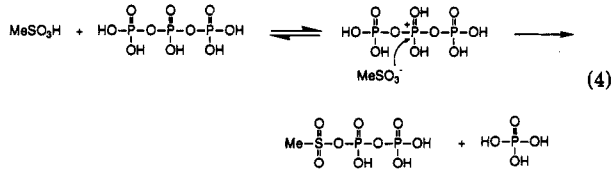
To summarize, three methods were used for indolizations. For the simple hydrazones, decomposition was not a problem, so neat P_2O_5 in $MeSO_3H$ could be used and led to the best isomer ratios. For the more complex hydrazones, dilution in dichloromethane or sulfolane reduced the amount of decomposition and still led to good isomer ratios in most cases. Of the solvents examined, dichloromethane was by far the best in that high isomer ratios were obtained with minimal degradation of the hydrazone.

(2) Steric Effects. For the N-benzylated hydrazones, isomer ratios were >50:1 for the hydrazones made from isobutyl methyl ketone **1b** and methyl 2,2-dimethyl-4-oxopentanoate **4**. However, with the hydrazones from methyl ethyl ketone **1a** and ethyl levulinate **1c**, the isomer ratio drops to 4–5 to 1. This can be rationalized from a consideration of the mechanism of the indolization, depicted in Scheme I. Each of the first two steps plays a role in the regiochemistry of the overall reaction. Formation of the most substituted ene–hydrazine in the first step followed by cyclization will lead to the undesired isomer. Although the ene–hydrazine is the most thermodynamically favored, its [3,3] rearrangement is disfavored when steric crowding becomes a factor. When steric crowding is not a factor, more of the undesired isomer is formed, as in the case of the hydrazone from methyl ethyl ketone.

The size of the substituent on nitrogen also plays a role in the regiocontrol of the indolization. The reactions of the N-benzylated hydrazones are faster and more selective than those of the unalkylated hydrazones. For example, with the hydrazone from methyl ethyl ketone using $P_2O_5/MeSO_3H$ in dichloromethane, the *N*-benzylhydrazone gives an 85:15 ratio whereas the NH hydrazone gives a 50/50 mixture under the same conditions. The N–Me hydrazones are intermediate between the *N*-benzyl- and *N*-H-hydrazones, suggesting that the larger size of the N-substituent leads to indolization from the least substituted ene–hydrazine.

Nature of the Catalytic Species in $P_2O_5/MeSO_3H$. Although $P_2O_5/MeSO_3H$ reagent has been used in hundreds of applications, the true nature of the catalytic species is not known. Eaton ruled out methanesulfonic acid and its anhydride as the catalytic species on the basis of kinetic experiments and speculated that the true catalyst was a mixed anhydride of P_2O_5 and $MeSO_3H$.[12]

An examination of the ^{13}C NMR of neat 10% $P_2O_5/MeSO_3H$ indicates the major species other than $MeSO_3H$ (δ 40.0) is methanesulfonic anhydride (δ 41.9), but 3 small resonances (δ 41.3, 41.6, 41.7) at the 0.5–1% level could be mixed anhydrides. These resonances, however, show no ^{13}C–^{31}P coupling, which may be due to the broadness of the peaks and the small size of the coupling expected over three bonds. The ^{31}P NMR spectrum (either neat or as a solution in CD_3CN) shows a group of resonances at δ −12 to −14 and −26 to −29. This spectrum is similar to that of a commercial sample of polyphosphoric acid (PPA) dissolved in sulfolane. Consequently, the species present in the 10% $P_2O_5/MeSO_3H$ solution include methanesulfonic anhydride, polyphosphoric acids, and a small amount of material that could be mixed anhydrides. In addition, in a mixture of 10% PPA in $MeSO_3H$, two of the three same small resonances are also present in the ^{13}C NMR (δ 41.3 and 41.6) as in the 10% $P_2O_5/MeSO_3H$, but they are not present in a solution of methanesulfonic anhydride and PPA in sulfolane. These experiments suggest that the peaks at δ 41.3, 41.6, and 41.7 arise from reaction of PPA with $MeSO_3H$, and are likely mixed anhydrides (eq 4).



(4)

To address the question further, kinetic and yield experiments on the indolization of hydrazone **4** (eq 3) were run in varying media. Figure 1 shows a comparison of rates in $MeSO_3H$ containing P_2O_5 or PPA, all of which exhibited good first-order kinetics. The rates vary only slightly, even when the P_2O_5 level is varied over a 5-fold range, indicating that neither P_2O_5 nor PPA, or any species including them, is the active catalyst in this Fischer indole reaction. In-

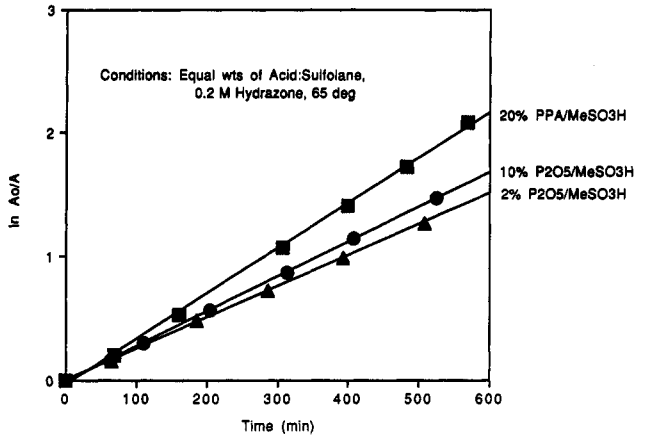


Figure 1. Kinetic plots of indolization reaction shown in eq 3 using varying amounts of P_2O_5 and PPA in $MeSO_3H$/sulfolane solutions.

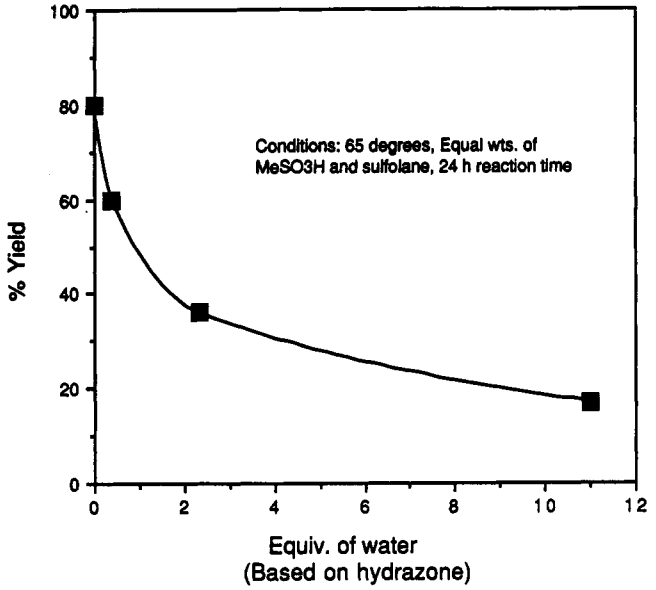


Figure 2. Plot of yield for indolization reaction shown in eq 3 vs equivalents of water added to the reaction.

deed, the reaction also proceeds at a similar rate in $MeSO_3H$ alone, although the yield of indole is ~25% lower than in the cases where PPA or P_2O_5 are present. These data indicate that PPA or P_2O_5 are necessary for high yields, but are not acting as catalytic species. Their apparent role is to keep the reaction mixture dry. Commercial $MeSO_3H$ contains ~0.2 wt % water, which corresponds to 30 mol % water based on hydrazone 4 under the normal reaction conditions. Figure 2 demonstrates the deleterious effect of water on the indolization reaction, which corroborates the hypothesis that for this Fischer indole reaction $MeSO_3H$ is the true catalytic spcies and that PPA or P_2O_5 is a drying agent.

To determine if this might be true for other reactions, the classic cyclization of phenylpropionic acid to 1-indanone was briefly examined. The results are far different than with the Fischer indole reaction. The reaction does not proceed in $MeSO_3H$ alone, and the reaction with methanesulfonic anhydride in $MeSO_3H$ is 20-fold slower than that in 10% $P_2O_5/MeSO_3H$. The reaction in 10% $P_2O_5/MeSO_3H$ is zero-order in phenylpropionic acid, but the rate is dependent on the amount of P_2O_5 used. The reaction in 10% PPA/$MeSO_3H$ is ~2-fold slower than in 10% $P_2O_5/MeSO_3H$. These data are consistent with a mixed anhydride as the catalytic species in $P_2O_5/MeSO_3H$ and PPA/$MeSO_3H$.

Summary

A regioselective route to the versatile 3-unsubstituted indoles is possible through the use of Eaton's reagent, $P_2O_5/MeSO_3H$. While suitable with some hydrazones, in many cases the neat reagent causes decomposition. However, the harshness of the reagent can be attenuated by dilution in a suitable polar, nonbasic solvent (sulfolane, dichloromethane).

Experimental Section

Preparation of Hydrazones. The hydrazones used in this study were prepared from the appropriate hydrazine and methyl ketone using acetic acid as catalyst in toluene as solvent. The hydrazones were purified either by distillation or by recrystallization from hexanes. The hydrazones having no α-substituent or a Me substituent were a mixture of geometric isomers distinguishable by ^1H NMR, while the benzyl-substituted hydrazones were generally only one geometric isomer that had the methyl group and nitrogen on the same side as determined by NOE experiments.

Prepartion of 3-Unsubstituted Indoles. Three methods were used to prepare the indoles, depending on the stability of the hydrazones in the reaction medium.

Method A. The hydrazone (1 g) was dissolved in dichloromethane (10 g), and 3% $P_2O_5/MeSO_3H$ (5 g) was added. The mixture was warmed for 1–2 days at 35–45 °C. When the reaction was judged complete, it was cooled to 0–5 °C, and then 20 mL of 2.5 N NaOH was added. The layers were separated, and the organic layer was washed with water then brine. The organic layer was concentrated, and then the indole was either chromatographed or recrystallized.

Method B. The hydrazone (1 g) was dissolved in sulfolane (6 g), and 10% $P_2O_5/MeSO_3H$ (6 g) was added. The mixture was warmed 2–5 days at 45–55 °C. When the reaction was judged complete, it was cooled to room temperature and *i*-PrOAc (15 mL) was added. The solution was cooled to 0–5 °C, and then 12.5 wt % NaOH (15 mL) was slowly added, keeping the temperature below 40 °C. The layers were separated, and the organic layer was washed with 3 × 15 mL of water, then concentrated and either recrystallized or chromatographed.

Method C. The hydrazone (1 g) was dissolved in 10% $P_2O_5/MeSO_3H$ (10 g) and stirred at ambient temperature until complete (1–2 days). Workup consisted of dilution with dichloromethane, washing with water and saturated $NaHCO_3$, and concentration.

Preparation of Indole 5. The following is a representative description of hydrazone formation followed by indole formation.

1-(4-Chlorobenzyl)-1-[4-(2-quinolylmethoxy)phenyl]hydrazine (10.11 g, 25.4 mmol), methyl 2,2-dimethyl-4-oxopentanoate (4.50 g, 28.5 mmol), 4-Å sieves (7.0 g), and toluene (100 mL) were combined. The mixture was cooled to 0 °C, and acetic acid (2.91 g, 48.5 mmol) was added. The reaction was stirred for 6 h at 0 °C and 15 h at 21 °C. At this point, HPLC analysis indicated 0.8% unreacted hydrazine and 92 area % hydrazone 4.

The reaction mixture was filtered, and the cake of sieves was washed with 2 × 10 mL of toluene. The filtrate was rotary evaporated to an oil, and then 2 × 30 mL toluene was added and the mixture concentrated after each addition. The toluene flush azeotropically removes acetic acid, which interferes with the next step.

To the crude hydrazone 4 was added anhydrous sulfolane (80 g, water content 70 mg/L) and 1:10 $P_2O_5/MeSO_3H$ solution (80 g).[15] The mixture was stirred in the dark for 3 days at 45 °C, 1 day at 55 °C, and 1 day at 60 °C. HPLC analysis at the end of the reaction showed the following mol % products, on the basis of hydrazine: unreacted hydrazone 4, 1.8%; aniline 7, 5.5%; indole 6, 2.3%; indole 5, 77%. The step yields were 91% for hydrazone formation and 85% for indolization.

The reaction was worked up by cooliing to room temperature and adding isopropyl acetate (150 mL). With ice cooling, 12.5% NaOH (200 mL) was added over a 30-min period, while the

(15) A 1:10 $P_2O_5/MeSO_3H$ solution was prepared by adding 8 g of P_2O_5 to 80 g of $MeSO_3H$ and stirring 6 h to dissolve. The mixture was filtered under nitrogen to remove undissolved fine particles.

temperature was kept below 40 °C. Another 10 mL of 50% NaOH was added to bring the pH to 10. The two-phase mixture was stirred 10 min, during which time the mixture turned from greenish black to reddish brown. The layers were separated, and the organic layer was washed with 3 × 200 mL of water to remove sulfolane. The organic layer was filtered through silica to remove color and then was rotary evaporated to an oil. Methanol (100 mL) was added and the mixture was warmed to 60 °C to dissolve the oil. When the mixture was cooled, thick crystallization occurred. The mixture was stirred 3 h at ambient temperature and 1 h at 5 °C, and then filtered and washed with 5 × 20 mL of ice-cold methanol. After the mixture was dried under vacuum at 50 °C, 9.15 g of indole **5** was obtained (69% yield from hydrazine) as a tan solid having a purity of 98 wt %. The major impurity was aniline **7** (1.3%). HPLC assay for components of reaction mixture: Zorbax 25-cm RX column; detection at 220 nm; eluent consisting of 70% acetonitrile/30% 0.1% aqueous phosphoric acid; flow, 1.5 mL/min. Retention times: hydrazine, 1.6 min; aniline **7**, 2.5 min; indole isomer **6**, 6.2 min; indole product **5**, 6.8 min; hydrazone **4**, 8.8 min.

Characterization of hydrazone 4: white crystals; mp 68–69 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 6 H, CMe_2), 1.65 (s, 3 H, N=CMe), 2.52 (s, 2 H, CH_2C), 3.58 (s, 3 H, CO_2Me), 4.39 (s, 2 H, CH_2N), 5.36 (s, 2 H, CH_2O), 6.8–7.0 (m, 4 H, O-bearing aromatic), 7.24 (s, 4 H, Cl-bearing aromatic), 7.5–8.2 (m, 6 H, quinoline H); ^{13}C NMR ($CDCl_3$) δ 20.0 (q), 26.3 (2, q), 41.4 (s), 49.0 (t), 52.1 (t), 62.5 (q), 72.6 (t), 116.2 (d), 120.4 (d), 120.7 (d), 127.5 (d), 128.5 (s), 128.86 (d), 128.91 (d), 129.8 (d), 130.7 (d), 131.2 (d), 132.8 (s), 137.8 (d), 139.0 (s), 146.1 (s), 148.5 (s), 154.3 (s), 159.2 (s), 168.7 (s), 178.5 (s).

Characterization of indole 5: white needles; mp 105.5–106 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6 H, CMe_2), 2.92 (s, 2 H, CH_2C), 3.66 (s, 3 H, CO_2Me), 5.30 (s, 2 H, CH_2N), 5.43 (s, 2 H, CH_2O), 6.22 (s, 1 H, H-3), 6.8–8.3 (m, 13 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 25.5 (q), 36.4 (t), 43.2 (s), 46.0 (t), 52.0 (q), 72.0 (t), 102.0 (d), 103.7 (d), 110.3 (d), 111.7 (d), 119.3 (d), 126.3 (d), 127.2 (d), 127.6 (s), 127.7 (d), 128.5 (s), 128.92 (d), 128.94 (d), 129.7 (d), 132.2 (s), 133.0 (s), 136.4 (s), 136.9 (d), 137.5 (s), 147.6 (s), 153.1 (s), 158.9 (s), 177.7 (s). Anal. Calcd for $C_{31}H_{29}ClN_2O_3$: C, 72.58; H, 5.70; N, 5.46; Cl, 6.91. Found: C, 72.57; H, 5.76; N, 5.45; Cl, 7.00.

Characterization of Hydrazones. 1a: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2$, R^3 = Me; 85:15 ratio of geometric isomers, mp 97–101 °C; ^{1}H NMR of major isomer ($CDCl_3$) δ 1.09 (t, 3 H, CH_3CH_2), 1.73 (s, 3 H, CH_3), 2.28 (q, 2 H, CH_2CH_3), 4.42 (s, 2 H, CH_2N), 5.37 (s, 2 H, CH_2O), 6.8–7.0 (m, 4 H, O-bearing aromatic), 7.25 (s, 4 H, Cl-bearing aromatic), 7.5–8.2 (m, 6 H, quinoline protons).

1b: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2$, R^3 = *i*-Pr; ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 6 H, *J* = 7.4 hz, $CHMe_2$), 1.73 (s, 3 H, N=CMe), 1.92 (m, 1 H, $CHMe_2$), 2.16 (d, 2 H, *J* = 7.4 Hz, N=CCH_2), 4.43 (s, 2 H, CH_2N), 5.34 (s, 2 H, CH_2O), 6.86–6.95 (m, 4 H, N,O-bearing aromatic H), 7.26 (s, 4 H, Cl-bearing aromatic H), 7.5–8.2 (m, 6 H, quinoline H).

1c: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2Cl$, R^3 = CH_2CO_2Et; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.71 (s, 3 H, CH_3C=N), 2.56–2.60 (m, 4 H, CH_2CH_2), 4.11 (q, 2 H, *J* = 7.0 Hz, CH_2CH_3), 4.40 (s, 2 H, CH_2Ar), 5.33 (s, 2 H, CH_2O), 6.81 (d, 2 H, aromatic ortho to O), 6.90 (d, 2 H, aromatic ortho to N), 7.23 (s, 4 H, Cl-bearing aromatic), 7.5–8.2 (m, 6 H, quinoline H).

1d: R^1 = *i*-Pr, R^2 = 4-$ClC_6H_4CH_2$, R^3 = $C(Me)_2CO_2Me$; off-white powder; mp 43–44 °C; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 6 H, CMe_2), 1.16 (d, 6 H, $CHMe_2$), 1.65 (s, 3 H, CH_3C=N), 2.53 (s, 2 H, CH_2C), 2.77 (m, 2 H, $CHMe_2$), 3.53 (s, 3 H, CO_2Me), 4.43 (s, 2 H, CH_2N), 6.77 (d, 2 H), 7.06 (d, 2 H), 7.24 (m, 4 H, H on Cl-bearing aromatic); ^{13}C NMR ($CDCl_3$) δ 20.0 (q), 24.7 (q), 26.4 (q), 34.6 (d), 41.9 (s), 49.2 (t), 52.5 (q), 62.9 (t), 119.2 (d), 127.9 (d), 129.2 (d), 131.1 (d), 133.5 (s), 139.3 (s), 143.1 (s), 149.9 (s), 170.2 (s), 179.9 (s). Anal. Calcd for $C_{24}H_{31}ClN_2O_2$: C, 69.47; H, 7.53; N, 6.75; Cl, 8.54. Found: C, 69.60; H, 7.65; N, 6.74; Cl, 8.64.

1e: R^1 = F, R^2 = 4-$ClC_6H_4CH_2$, R^3 = $C(Me)_2CO_2Me$; off-white powder; mp 61–62 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 6 H, CMe_2), 1.68 (s, 3 H, CH_3C=N), 2.55 (s, 2 H, CH_2C), 3.58 (s, 3 H, CO_2Me), 4.43 (s, 2 H, CH_2N), 6.88 (m, 4 H, aromatic), 7.25 (s, 4 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 19.7 (q), 25.9 (q), 40.8 (s), 48.6 (t), 51.7 (q), 62.5 (t), 115.5 (d, J_{CF} = 22 Hz), 119.8 (d, J_{CF} = 7.5 Hz), 128.3 (d), 129.8 (d), 132.6 (s), 137.2 (s), 147.2 (s, J_{CF} = 2 Hz), 157.9 (s, J_{CF} = 240 Hz), 168.0 (s), 177.9 (s). Anal. Calcd for $C_{21}H_{24}FClN_2O_2$: C, 64.53; H, 6.19; N, 7.17; Cl, 9.07. Found: C, 64.84; H, 6.45; N, 7.15; Cl, 9.18.

1f: R^1 = H, R^2 = H, R^3 = *t*-Bu; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9 H, CMe_3), 1.92 (s, 3 H, CH_3C=N), 2.23 (s, 2 H, CH_2), 6.8–7.3 (m, 5 H, aromatic).

1g: R^1 = H, R^2 = H, R^3 = *i*-Pr; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, 6 H, $CHMe_2$), 1.87 (s, 3 H, CH_3C=N), 2.02 (m, 1 H, $CHMe_2$), 2.22 (d, 2 H, CH_2), 6.87 (m, 2 H), 7.09 (m, 2 H), 7.28 (m, 1 H).

1h: R^1 = H, R^2 = H, R^3 = Me; distilled at 108–110 °C (1 mm); 83:17 ratio of geometric isomers; ^{1}H NMR of major isomer ($CDCl_3$) δ 1.18 (t, 3 H, CH_2CH_3), 1.88 (s, 3 H, CH_3C=N), 2.35 (q, 2 H, CH_2CH_3), 6.8–7.3 (m, 5 H, aromatic).

1i: R^1 = H, R^2 = Me, R^3 = Et; distilled at 105 °C (1 mm); 80:20 ratio of geometric isomers; ^{1}H NMR of major isomer ($CDCl_3$) δ 1.03 (t, 3 H, $CH_2CH_2CH_3$), 1.70 (m, 2 H, $CH_2CH_2CH_3$), 1.97 (s, 3 H, CH_3C=N), 2.40 (t, 2 H, $CH_2CH_2CH_3$), 3.01 (s, 3 H, NMe), 6.87 (m, 3 H), 7.27 (m, 2 H).

1j: R^1 = H, R^2 = Me, R^3 = *i*-Pr; distilled at 93–95 °C (1 mm); 83:17 ratio of geometric isomers; ^{1}H NMR of major isomer ($CDCl_3$) δ 1.05 (d, 6 H, $CHMe_2$), 1.97 (s, 3 H, CH_3C=N), 2.10 (m, 1 H, $CHMe_2$), 2.31 (d, 2 H, CH_2), 3.03 (s, 3 H, NMe), 6.8–7.3 (m, 5 H, aromatic).

Characterization of Indole Products. 3a: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2$, R^3 = Me; mp 153–154 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3 H, *J* = 7.5 Hz, CH_3CH_2), 2.63 (q, 2 H, *J* = 7.5 Hz, CH_3CH_2), 5.24 (s, 2 H, CH_2N), 5.44 (s, 2 H, CH_2O), 6.26 (s, 1 H, H-3), 6.8–8.2 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 12.6 (q), 20.0 (t), 45.8 (t), 72.0 (t), 103.8 (d), 106.0 (d), 109.7 (d), 111.1 (d), 119.2 (d), 126.3 (d), 127.2 (d), 127.5 (s), 127.7 (d), 128.5 (s), 128.84 (d), 128.87 (d), 129.6 (d), 132.5 (s), 133.0 (s), 136.4 (s), 136.8 (d), 143.5 (s), 147.6 (s), 153.0 (s), 158.9 (s). Anal. Calcd for $C_{27}H_{23}ClN_2O$: C, 75.96; H, 5.43; N, 6.56; Cl, 8.30. Found: C, 75.73; H, 5.54; N, 6.61; Cl, 8.24.

3b: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2$, R^3 = *i*-Pr; mp 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 6 H, *J* = 6.5 Hz, $CHMe_2$), 1.89 (m, 1 H, $CHMe_2$), 2.50 (d, 2 H, *J* = 7.0 Hz, CH_2CH), 5.24 (s, 2 H, CH_2N), 5.43 (s, 2 H, CH_2O), 6.25 (s, 1 H, H-3), 6.9–8.2 (m, 13 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 22.7 (q), 28.1 (d), 36.1 (t), 46.0 (t), 71.9 (t), 100.7 (d), 103.7 (d), 110.0 (d), 111.1 (d), 119.3 (d), 126.3 (d), 127.2 (d), 127.6 (s), 127.7 (d), 128.6 (s), 128.90 (d), 128.93 (d), 129.6 (d), 132.4 (s), 133.0 (s), 136.5 (s), 136.9 (d), 140.9 (s), 147.6 (s), 153.0 (s), 159.0 (s). Anal. Calcd for $C_{29}H_{27}ClN_2O$: C, 76.56; H, 5.98; N, 6.15; Cl, 7.79. Found: C, 76.50; H, 5.90; N, 6.00; Cl, 7.65.

3c: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2$, R^3 = CH_2CO_2Et; mp 88–89 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 2.69 (t, 2 H, *J* = 7.5 Hz, CH_2CH_2), 2.96 (t, 2 H, *J* = 7.5 Hz, CH_2CH_2), 4.14 (q, 2 H, *J* = 7.0 Hz, CH_2CH_3), 5.26 (s, 2 H, CH_2N), 5.43 (s, 2 H, CH_2O), 6.25 (s, 1 H, H-3), 6.8–8.2 (m, 13 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 22.0 (t), 32.8 (t), 45.9 (t), 60.7 (t), 71.9 (t), 99.4 (d), 103.9 (d), 110.0 (d), 111.7 (d), 119.2 (d), 126.4 (d), 127.3 (d), 127.6 (s), 127.7 (d), 128.4 (s), 128.93 (d), 128.98 (d), 129.7 (d), 132.6 (s), 133.2 (s), 136.2 (s), 136.9 (d), 139.9 (s), 147.6 (s), 153.1 (s), 158.8 (s), 172.5 (s). Anal. Calcd for $C_{30}H_{27}ClN_2O_3$: C, 72.21; H, 5.45; N, 5.61; Cl, 7.10. Found: C, 72.10; H, 5.40; N, 5.55; Cl, 7.00.

3d: R^1 = *i*-Pr, R^2 = 4-$ClC_6H_4CH_2$, R^3 = $C(Me)_2CO_2Me$; white crystalline solid; mp 75–76 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 6 H, CMe_2), 1.33 (s, 6 H, $CHMe_2$), 2.98 (s, 2 H, CH_2C), 3.03 (m, 1 H, $CHMe_2$), 3.70 (s, 3 H, CO_2Me), 5.34 (s, 2 H, CH_2N), 6.32 (s, 1 H, H-3), 6.86 (d, 2 H), 7.06 (q, 2 H), 7.24 (d, 2 H), 7.46 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.7 (q), 25.5 (q), 34.1 (d), 36.4 (t), 43.2 (s), 45.9 (t), 52.0 (q), 101.9 (d), 109.3 (d), 117.1 (d), 120.5 (d), 127.3 (d), 128.2 (s), 128.9 (d), 133.0 (s), 135.4 (s), 136.6 (s), 136.8 (s), 140.5 (s), 177.8 (s). Anal. Calcd for $C_{24}H_{28}ClNO_2$: C, 72.44; H, 7.09; N, 3.52; Cl, 8.91. Found: C, 72.67; H, 7.18; N, 3.52; Cl, 8.80.

3e: R^1 = F, R^2 = 4-$ClC_6H_4CH_2$, R^3 = $C(Me)_2CO_2Me$; oil; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3 H, CMe_2), 2.98 (s, 2 H, CH_2C), 3.70 (s, 3 H, CO_2Me), 5.34 (s, 2 H, CH_2N), 6.33 (s, 1 H, H-3), 6.85 (m, 3 H), 7.04 (m, 1 H), 7.23 (m, 3 H); ^{13}C NMR ($CDCL_3$) δ 25.5 (q), 36.5 (t), 43.2 (s), 46.0 (t), 52.1 (q), 102.1 (d, J_{CF} = 4.3 Hz), 105.0 (d, J_{CF} = 23.6 Hz), 109.5 (d, J_{CF} = 26.2 Hz), 110.1 (d, J_{CF} = 9.9 Hz), 127.1 (d), 128.4 (s, J_{CF} = 10.1 Hz), 129.0 (d), 133.2 (s, J_{CF} = 6.3 Hz), 136.1 (s), 138.6 (s), 158.1 (s, J_{CF} = 235 Hz), 177.6 (s).

Anal. Calcd for $C_{21}H_{21}FClNO_2$: C, 67.47; H, 5.66 N, 3.75; Cl, 9.48. Found: C, 67.38; H, 5.73; N, 3.72; Cl, 9.40.

3f: R^1 = H, R^2 = H, R^3 = *t*-Bu; mp 104-105 °C (lit.[16] mp 102-104 °C); ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 9 H, CMe_3), 2.63 (s, 2 H, CH_2), 6.25 (d, J = 2.1 Hz, 1 H, H-3), 7.1-7.6 (m, 4 H, aromatic), 7.8 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 29.7, 31.9, 43.0, 101.9, 110.4, 119.6, 119.8, 121.0, 128.9, 135.7, 137.6.

3g: R^1 = H, R^2 = H, R^3 = *i*-Pr; mp 42-43 °C (lit.[17] mp 42.5 °C); ^{1}H NMR ($CDCl_3$) δ 1.01 (d, 6 H, Me_2CH), 2.01 (m, 1 H, $CHMe_2$), 2.64 (d, 2 H, CH_2), 6.28 (s, 1 H, H-3), 7.12 (m, 2 H), 7.32 (m, 1 H), 7.57 (d, 1 H), 7.83 (br s, 1 H, NH).

3h: R^1 = H, R^2 = H, R^3 = Me; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3 H, CH_2CH_3), 2.82 (q, 2 H, CH_2CH_3), 6.28 (s, 1 H, H-3), 7.1-7.6 (m, 4 H, aromatic), 7.85 (br s, 1 H, NH). NMR matches that reported previously.[7]

3i: R^1 = H, R^2 = Me, R^3 = Et; mp 41.5-42.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3 H, CH_3CH_2), 1.81 (m, 2 H, $CH_2CH_2CH_3$), 2.77 (t, 2 H, $CH_2CH_2CH_3$), 3.71 (s, 3 H, NMe), 6.31 (s, 1 H, 3-H), 7.20 (m, 3 H), 7.59 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.9, 28.9, 29.4, 98.7, 108.7, 119.2, 119.7, 120.5, 127.9, 137.5, 142.0.

3j: R^1 = H, R^2 = Me, R^3 = *i*-Pr; ^{1}H NMR ($CDCl_3$) δ 1.11 (d, 6 H, J = 6.5 Hz, Me_2CH), 2.10 (m, 1 H, $CHMe_2$), 2.72 (d, 2 H, J = 7.2 Hz, CH_2), 3.74 (s, 3 H, NMe), 6.37 (s, 1 H, H-3), 7.16-7.39 (m, 3 H, aromatic), 7.68 (d, 1 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 22.7 (q), 28.4 (d), 29.6 (q), 36.2 (t), 100.0 (d), 108.9 (d), 119.3 (d), 119.8 (d), 120.5 (d), 128.0 (s), 137.4 (s), 140.4 (s).

2a: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2$, R^3 = Me; ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 5.22 (s, 2 H, CH_2N), 5.46 (s, 2 H, CH_2O), 6.8-8.2 (m, 13 H, aromatic).

2c: R^1 = 2-quinolylmethoxy, R^2 = 4-$ClC_6H_4CH_2$, R^3 = CH_2CO_2Et; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 2.32 (s, 3 H, CH_3C), 3.69 (s, 2 H, CH_2COOR), 4.11 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 5.23 (s, 2 H, CH_2N), 5.47 (s, 2 H, CH_2O), 6.8-8.3 (m, 13 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 10.4 (q), 14.2 (q), 30.6 (t), 46.0 (t), 60.7 (t), 71.8 (t), 102.2 (d), 104.7 (s), 109.7 (d), 111.2 (d), 119.2 (d), 126.3 (d), 127.3 (d), 127.5 (s), 127.6 (d), 128.3 (s), 128.85 (d), 128.87 (d), 129.6 (d), 131.7 (s), 133.0 (s), 135.0 (s), 136.3 (s), 136.8 (d), 147.5 (s), 153.0 (s), 158.7 (s), 171.8 (s).

2e: R^1 = F, R^2 = 4-$ClC_6H_4CH_2$, R^3 = $C(Me)_2CO_2Me$; mp 116-117 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 6 H, CMe_2), 2.28 (s, 3 H, 2-Me), 3.70 (s, 3 H, CO_2Me), 5.24 (s, 2 H, CH_2N), 6.85 (m, 3 H), 7.06 (dd, 1 H), 7.26 (m, 2 H), 7.39 (q, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.7 (q), 27.5 (q), 43.8 (s), 45.8 (t), 52.3 (q), 105.2 (d, J_{CF} = 24.7 Hz), 108.9 d, J_{CF} = 26.3 Hz), 109.6 (d, J_{CF} = 19.8 Hz), 127.1 (d), 129.0 (d), 132.9 (s), 133.2 (s), 133.8 (s), 136.0 (s), 157.7 (s, J_{CF} = 233 Hz), 178.5 (s). Anal. Calcd for $C_{21}H_{21}FClNO_2$: C, 67.47; H, 5.66; N, 3.75; Cl, 9.48. Found: C, 67.43; H, 5.70; N, 3.71; Cl, 9.45.

2i: R^1 = H, R^2 = Me, R^3 = Et; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H, CH_2CH_3), 2.45 (s, 3 H, CH_3C), 2.87 (q, 2 H, CH_2CH_3), 3.71 (s, 3 H, NCH_3), 7.28 (m, 3 H), 7.64 (d, 1 H).

Supplementary Material Available: NMR spectra for compounds **4**, **1a-c**, **1f-j**, **3i**, **3j**, **2a**, **2c** and **2i** (19 pages). Ordering information is given on any current masthead page.

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Aprotic Nitration ($NO_2^+BF_4^-$) of 2-Halo- and 2,6-Dihalopyridines and Transfer-Nitration Chemistry of Their *N*-Nitropyridinium Cations

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$NO_2^+BF_4^-$ nitration of 2,6-dibromo-1 and 2,6-dichloropyridine **2** in CH_3CN results in predominant C-nitration, whereas in CH_2Cl_2, N-nitration is predominant. With 2,6-difluoropyridine **3** only C-nitration was observed. Dehalogenation of the C-nitrated **1** and **2** affords 3-nitropyridine (3-NP) in moderate but greatly improved yields over conventional protic nitration of pyridine. Despite favorable presence of steric inhibition to resonance and the $-I$ effect of halogens, N-nitrated pyridinium salts **1b** and **2b** do not transfer-nitrate to aromatics even under forcing conditions. The lack of transfer-nitration reactivity is not due to in situ rearrangement of the nitro onium to nitrito onium ions. A mechanism involving neighboring group participation by the 2,6-halogens is proposed. The monohalo-*N*-nitropyridinium cations transfer-nitrate toluene and benzene. Transfer-nitration selectivity of the 2-bromo-*N*-nitro- and 2-chloro-*N*-nitropyridinium cations are comparable (K_T/K_B = 41-44), but the 2-fluoro-*N*-nitro cation is much less selective (more reactive) (K_T/K_B = 15.4), indicative of a stronger $-I$ effect, weakening the N^+-N^+ bond.

Introduction

C-Nitrated pyridines and their derivatives are important intermediates in syntheses of heterocyclic compounds and in dyes and pharmaceutical products.[1] Whereas 4-nitropyridine (4-NP) is obtained in high yields (90%) by nitration of the *N*-oxide and subsequent reduction, 3-nitropyridine (3-NP) was obtained only in low yields (5%) under forcing condition (HNO_3/H_2SO_4; 370 °C).[2]

An indirect route to 3-NP involving selective oxidation of 3-aminopyridine is available, but electrophilic nitration in reasonable yields was not achieved. Although application of 2,6-di-*tert*-butyl blocking groups leads to exclusive C-nitration, deblocking (transalkylation) proved impossible even in superacids, as facile N-protonation prevents the formation of a high-energy ipso protonated dication intermediate.[3]

We report herein our aprotic nitration studies utilizing dihalo blocking groups. Our rational was that (a) presence of bulky halogens should reduce N-nitration both sterically and inductively; (b) C-nitration at position 3 should be

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