In summary, the earlier report on elaboration of the 2-methyloxazole, **1**, must be considered incorrect, and the surprising resistance of the 2-methyl group toward carbanion formation still stands.

Experimental Section

Reaction of 2-Methyl-4-carbethoxy-1,3-oxazole (1) with Ethyl Acetate. A flame-dried flask under a blanket of dry argon was charged with 318 mg (6.9 mmol, 1.7 equiv) of sodium hydride (50% oil dispersion) and 2 mL of dry ether (from benzophenone ketyl). A total of 0.64 mL (6.5 mmol, 1.6 equiv) of ethyl acetate (distilled) was added, followed by one drop of absolute ethanol (noted vigorous evolution of gas). Within 1 min, a solution of 650 mg (4.1 mmol) of oxazole ester **1** in 10 mL of dry ether was added dropwise with efficient stirring. After the addition was complete, a total of 9 mL of dry 1,4-dioxane (from benzophenone ketyl) was introduced into the reaction. The resulting dark solution was gently heated under reflux for 1 h. After this time, the dark solution was cooled to ambient temperature, and absolute ethanol was added (ca. 1 mL). The pH of the reaction was adjusted to 7 by addition of 30% glacial acetic acid in water (v/v). To the resulting suspension was added 10 mL of saturated aqueous sodium sulfate solution, and the solution was extracted with ether (5 × 20 mL). The combined ethereal extracts were washed with pH 7 buffered water (1 × 10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under aspirator pressure to afford 478 mg (59%) of crude product. Preparative TLC using 30% acetone in hexanes as developing solvent gave 208 mg (26%) of a colorless solid. The 60-MHz NMR spectrum ($CDCl_3$) showed it to be a mixture of β-ketoester **4a** and enol **4b**, in the ratio 4:1, based on comparative integration of the oxazole C_5 hydrogen resonances. Recrystallization of the solid from hexanes (3 times) yielded a colorless, crystalline solid: mp 79–81 °C; R_f 0.49 (silica gel, 30% acetone in hexanes); IR (KBr) 3420, 1727 (CO_2Et), 1642 (C=O), 1585, 1545 cm^{-1}; NMR ($CDCl_3$) for **4a** δ 1.25 (t, J = 7 Hz, 3 H, OCH_2CH_3), 2.48 (s, 3 H), 3.85 (s, 2 H, $COCH_2CO_2Et$), 4.13 (q, J = 7 Hz, 2 H, OCH_2CH_3), 8.11 (s, 1 H, oxazole C_5 H); for **4b** δ 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3), 2.48 (s, 3 H), 4.18 (q, J = 7 Hz, 2 H, OCH_2CH_3), 5.71 (s, 1 H, C(OH)=$CHCO_2Et$], 7.85 (s, 1 H, oxazole C_5 H), 11.98 (br, s, 1 H, OH); in CCl_4, the ratio of **4a** to **4b** was 1:2; UV (95% ethanol) λ_{max} 253 nm (log ϵ 3.74), λ_{infl} 265 nm (log ϵ 3.73); UV (0.1 N ethanolic sodium hydroxide) λ_{max} 303 nm (log ϵ 4.10).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 55.06; H, 5.62; N, 7.38.

Deuterium Exchange on 4a,b. A solution of 8 mg (0.04 mmol) of oxazoles **4** in 5 mL of D_2O/1 mL of Et_2O was stirred at ambient temperature for 72 h, after which time the ether was removed by concentration under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The 60-MHz NMR spectrum of this material in $CDCl_3$ showed deuterium incorporation in the following positions: δ 3.85 (**4a**, $COCH_2CO_2Et$), 5.71 [**4b**, C(OH)=$CHCO_2Et$], 11.98 (**4b**, OH). Integration of the spectrum showed deuterium exchange to be ca. 75% complete with no exchange of hydrogen for deuterium at δ 2.48 (2-Me).

2-Methyl-4-acetyloxazole (5). A flask under a blanket of dry argon was charged with 50 mg (0.25 mmol) of **4**, 284 mg (2.54 mmol, 10.0 equiv) of 1,4-diazabicyclo[2.2.2]octane, and 0.5 mL of xylenes. The resulting solution was gently heated under reflux by placing the flask into an oil bath maintained at 140 °C. The progress of the reaction was closely monitored by TLC (silica gel, 30% acetone in hexanes; R_f 0.49 for **4**; R_f 0.41 for **5**). After 45 min, the reaction was cooled to room temperature. The resulting semisolid was flash chromatographed using 30% acetone in hexanes as eluent to yield 20 mg (63%) of **5** as a colorless solid, which readily sublimed: mp 64–65 °C; R_f 0.41 (silica, 30% acetone–hexane); IR (KBr) 1685, 1598, 1548 cm^{-1}; NMR ($CDCl_3$) δ 2.49 (s, 6 H), 8.03 (s, 1 H); MS (70 eV), m/e 125 (M^+). This material was used directly in the next step.

2-Methyl-4-carboxyoxazole (6). The procedure of Allan and Walter[5] was employed using sodium hypobromite. The acid **6** was obtained in 59% yield, mp 182–183 °C dec (acetone), lit.[4] mp 183–184 °C dec.

Hydrolysis of 4 to 7. A total of 60 mg (0.30 mmol) of the mixture of **4a,b** and 0.5 mL (0.61 mmol, 2.0 equiv) of 5% aqueous sodium hydroxide solution were placed in a flask and stirred at ambient temperature. The progress of the reaction was monitored by TLC (30% acetone in hexanes; **4a,b** R_f 0.49). After 46 h, TLC showed no starting material. The dark solution was acidified to pH 4 by addition of 0.35 mL of 1 N sulfuric acid. The resulting solution was gently heated under reflux for 90 min. After this time, the solution was cooled to room temperature. The aqueous solution was extracted with dichloromethane (3 × 25 mL), and the combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 14 mg (40%) of *N*-acetonylacetamide (**7**): NMR ($CDCl_3$) δ 2.03 (s, 3 H), 2.20 (s, 3 H), 4.15 (d, J = 5 Hz, 2 H, CH_2COCH_3), 6.33 (br, 1 H, exchanged with D_2O, NH) [reported for *N*-acetonylacetamide:[8] NMR ($CDCl_3$) δ 2.05 (s, 3 H, CH_2COCH_3), 2.22 (s, 3 H, $NHCOCH_3$), 4.18 (d, J = 5 Hz, 2 H, CH_2COCH_3), 6.48 (br, 1 H, NH)].

Acknowledgment. The authors are grateful to the National Institutes of Health for support of this work.

Registry No. 1, 10200-43-8; **4a**, 81725-19-1; **4b**, 81725-20-4; **5**, 81740-16-1; **6**, 23012-17-1; **7**, 7737-16-8; ethyl acetate, 141-78-6.

(7) Cornforth, J. W.; Fawaz, E.; Goldsworthy, L. J.; Robinson, R. *J. Chem. Soc.* **1949**, 1549.

(8) Szmuszkovicz, J.; Baczynskyj, L.; Chidester, C. C.; Duchamp, D. J. *J. Org. Chem.* **1976**, *41*, 1743.

Reaction of Dimethyl Diazomalonate and Ethyl 2-Diazoacetoacetate with *N*-Methylpyrrole

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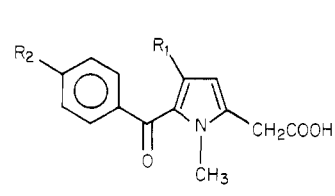
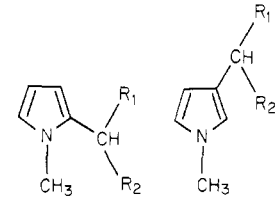
A study of the reaction of ethyl diazoacetate (EDA) with *N*-methylpyrrole and other pyrrole derivatives was conducted in our laboratory[1] as part of research directed toward improved synthetic processes for tolmetin (**1**) and zomepirac (**2**).[2] In that work we found some copper-



1, R_1 = H; R_2 = CH_3
2, R_1 = CH_3; R_2 = Cl



3 **4**

a, R_1 = H; R_2 = $CO_2C_2H_5$
b, R_1 = R_2 = CO_2CH_3
c, R_1 = H; R_2 = CO_2CH_3
d, R_1 = $C(O)CH_3$; R_2 = $CO_2C_2H_5$

(1) (a) Maryanoff, B. E. *J. Org. Chem.* **1979**, *44*, 4410; Maryanoff, B. E. *J. Heterocycl. Chem.* **1977**, *14*, 177. (b) We wish to correct two errors in the *J. Org. Chem.* paper: on p 4417, dimethyl sulfate should read diethyl sulfate; on p 4416, the EM-360 NMR instrument should be attributed to Varian (not Perkin-Elmer).

(2) Tolmetin is an important nonsteroidal antiinflammatory agent for the treatment of arthritis, and its sodium salt is sold by McNeil Pharmaceutical under the registered tradename Tolectin. Zomepirac is a potent nonnarcotic analgesic, and its sodium salt is sold by McNeil Pharmaceutical under the registered tradename Zomax.

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Table I. Reaction of *N*-Methylpyrrole with Dimethyl Diazomalonate

entry no.	metal catalyst	mol % catalyst	bath temp, °C	total yield,[a] %	3b/4b ratio[b]	yield of 3b,[c] %
1	Cu bronze	10.0	110	~30[d]	6.5	~25[d]
2	$Cu(acac)_2$	1.0	80	65	9.0	58
3	$Cu(hfacac)_2$	1.0	70	83	7.3	73
4	$Cu(CSAL)_2$	1.0	100	69	5.4	58
5	$Cu(IPSAL)_2$	1.0	90	76	12.0	70
6	$Cu(OTf)_2$[e]	1.0	70	70	5.0	58
7	$Rh_2(OAc)_4$	0.5	70	92	9.8	83

[a] Yields (based on the limiting reagent DMDM) for product (**3b** and **4b**) isolated by distillation (Kugelrohr). EDA reaction yield of **3a** and **4a**: 40, 36, 57, 60, 50, 61, minor (top to bottom). [b] Ratios are from GLC analyses (**3b** eluted first), assuming no difference in detector response between the isomers; this was supported by nearly identical ratios from ^1H NMR spectra. EDA reaction **3a**/**4a** ratio: 5.4, 11.5, 3.8, 4.0, 17.0, 1.4, not measurable (top to bottom). [c] EDA reaction yield of **3a**: 34, 33, 45, 48, 47, 36, minor (top to bottom). [d] Copper bronze was a poor catalyst for this reaction. Much unreacted DMDM and a little **3c** were present in the reaction product. The yield had to be corrected for the presence of these impurities, thus it is an estimate. [e] OTf = trifluoromethanesulfonate.

(II)-promoting agents ("catalysts"), which increased yields of key synthetic intermediate **3a** and minimized production of undesired byproduct **4a**, relative to copper(0) and copper(I) catalysts. With such information in hand, we explored the reaction of dimethyl diazomalonate (DMDM)[3] and ethyl 2-diazoacetoacetate (EDAA) with *N*-methylpyrrole. Malonate adduct **3b** would be readily convertible to desired pyrrolylacetate **3c** via decarbomethoxylation,[4] and acetoacetate adduct **3d** would be convertible to **3c** by deacetylation.

Results and Discussion

The reaction of *N*-methylpyrrole with DMDM was conducted using six copper-promoting agents and rhodium(II) acetate dimer (Table I). The copper agents are representative of the reactivity range discussed in our EDA study,[1] and $Cu(acac)_2$, $Cu(CSAL)_2$, $Cu(IPSAL)_2$, and $Cu(hfacac)_2$ are preferred agents for the reaction of *N*-methylpyrrole with EDA (giving high yields and/or minimal β-substitution).[1,5] In every reaction, both α- and β-pyrrolylmalonates (**3b** and **4b**) were produced, with the α-isomer **3b** predominating.[6] The α/β ratios ranged from 12.0 for $Cu(IPSAL)_2$ to 5.0 for $Cu(OTf)_2$. In the EDA reaction, these two "catalysts" also marked termini of the range of regioselectivity, with α/β ratios of 16.9 and 1.4, respectively.[1] The trend of regioselectivity for the DMDM reactions parallels that for the EDA reactions, but the range of the DMDM isomer ratios is compressed. This compression is more pronounced at the lower (less selective) end of the regiochemical scale with $Cu(OTf)_2$ and $Cu(hfacac)_2$ (see Table I).

The DMDM reactions, compared to the corresponding EDA reactions, generally gave higher yields of monosubstitution products (total yield of **3b** and **4b**), as well as higher yields of desired isomer **3b** (Table I). Interestingly, in the EDA reaction $Rh_2(OAc)_4$ did not work at all.[1a] Reaction temperatures for the DMDM reactions had to be elevated, relative to the corresponding EDA reactions, to cause nitrogen evolution and, thus, adduct formation. The increased stability of DMDM to the catalysts (compared with EDA) is reflected in the poor results obtained for the copper bronze reaction.

The reaction of diazomalonic esters with aromatic compounds has received little attention,[3] compared to the interest devoted to diazoacetic esters.[1,3,8] From a small number of studies, diazomalonic esters appear to react less readily with benzenoid compounds.[3] When our work with DMDM was in progress, the first reactions of DMDM with π-excessive five-membered-ring heterocycles were reported by Gillespie, Porter, and co-workers.[9a] They found that thiophene reacts with DMDM under Rh(II) catalysis to give a thiophenium ylide, which thermally rearranges to dimethylthiophene-2-malonate.[9a] In further work, 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide (**5**) was used as a chemical equivalent of biscarbomethoxycarbene [$:C(CO_2CH_3)_2$, **6**];[9b] it reacted with electron-rich benzenes and π-excessive heterocycles, in the presence of $Cu(acac)_2$, to give high yields of substitution products. In this manner, pyrrole afforded dimethyl pyrrole-2-malonate in 73% yield, with only α-substitution being reported.[9b]

Our study reveals that DMDM itself is certainly a very effective source of **6** (in the form of a reactive carbenoid) for substitution (C-alkylation) of the pyrrole nucleus. Better yields of **3b** were realized in the reaction of *N*-methylpyrrole with DMDM, than the corresponding yields of **3a** in the EDA reaction, because of (1) higher yields of total adducts (**3b** and **4b**) and (2) high regiochemical preference for **3b**. Best results, for yield and purity, were obtained with $Rh_2(OAc)_4$, $Cu(hfacac)_2$, and $Cu(IPSAL)_2$ as promoting agents. The $Rh_2(OAc)_4$ result is particularly remarkable in that this catalyst was useless for the reaction of EDA with *N*-methylpyrrole. With the proper choice of promoting agent, DMDM should have general usefulness for selective 2-position functionalization of pyrroles.

Given the favorable results in the DMDM reaction, ethyl 2-diazoacetoacetate (EDAA) was also examined. The reaction of EDA with *N*-methylpyrrole using $Cu(hfacac)_2$, $Cu(IPSAL)_2$, and $Rh_2(OAc)_4$ afforded reasonable isolated

(3) For a review on diazomalonic esters, see (a) Peace, B. W.; Wulfman, D. S. *Synthesis* **1973**, 137. Also (b) Wulfman, D. S.; Linstrumelle, G.; Cooper, C. F. In "The Chemistry of Diazonium and Diazo Groups"; S. Patai, Ed.; Wiley: Chichester, U.K., 1978; pp 821–976. Wulfman, D. S.; Poling, B. In "Reactive Intermediates"; R. A. Abramovitch, Ed.; Plenum Press: London, 1980; Vol. 1, pp 321–512.

(4) (a) Krapcho, A. P.; Jahngen, Jr., E. G. E.; Lovey, A. J.; Short, F. W. *Tetrahedron Lett.* **1974**, 1091. Liotta, C. L.; Cook, F. L. *Ibid.* **1974**, 1095. Ho, T. L. *Synth. Commun.* **1979**, *9*, 609. For a review, see McMurry, J. *Org. React.* **1976**, *24*, 187. (b) Decarbomethoxylation of **3b** and **4b** is described under Experimental Section.

(5) Abbreviations: acac = acetylacetonate; CSAL = 5-chlorosalicylaldehydate; IPSAL = *N*-isopropylsalicylaldiminate; hfacac = hexafluoroacetylacetonate.

(6) Small amounts (2–5%) of pyrrolylacetates **3c** and **4c** were also present, from minor decarbomethoxylation (GLC/MS; GLC coinjection of authentic **3c**[7]).

(7) Orth, W.; Rappen, L.; Busse, G., U.S. Patent 3 544 589, 1970.

(8) Dave, V.; Warnhoff, E. W. *Org. React.* **1970**, *18*, 270. Marchand, A. P.; Brockway, N. M. *Chem. Rev.* **1974**, *74*, 431.

(9) (a) Gillespie, R. J.; Murray-Rust, J.; Murray-Rust, P.; Porter, A. E. A. *J. Chem. Soc., Chem. Commun.* **1978**, 83. Gillespie, R. J.; Porter, A. E. A.; Willmott, W. E. *Ibid.* **1978**, 85. Gillespie, R. J.; Porter, A. E. A., *J. Chem. Soc., Perkin Trans. 1* **1979**, 2624. (b) Cuffe, J.; Gillespie, R. J.; Porter, A. E. A. *J. Chem. Soc., Chem. Commun.* **1978**, 641. Gillespie, R. J.; Porter, A. E. A. *Ibid.* **1979**, 50.

(10) Compound **3c** was also confirmed by GLC coinjection of authentic material.[7]

yields (68, 62, and 72%) of monoadduct, which consisted solely of α-isomer **3d** (^{1}H and ^{13}C NMR). Because of its high regioselectivity, EDAA should be very useful for α-substitution of pyrroles.

Experimental Section

General Procedures. Infrared (IR) spectra were recorded on Perkin-Elmer 727B or 283 spectrophotometers. Proton NMR spectra were determined on a Varian EM-360 (60 MHz) or Perkin-Elmer R32 (90 MHz) instrument using $CDCl_3$ as solvent and Me_4Si as an internal reference (20 mg of compound in 0.3 mL of solvent).[1b] Carbon-13 NMR spectra were obtained on a JEOL FX60Q spectrometer (15.00 MHz) in $CDCl_3$ with Me_4Si as an internal reference (150 mg of compound in 2 mL of solvent). Both proton noise-decoupled and off-resonance decoupled ^{13}C NMR spectra were recorded; only noise-decoupled data are presented. GLC analyses were performed on a Perkin-Elmer 3920B instrument with a flame-ionization detector, equipped with a Hewlett-Packard 3352B data system and 18652A A/D converter; a 6 ft × $^1/_8$ in. glass 1.35% OV-17 on Chromosorb W AW/DMS (100–120 mesh) column was employed. GLC–mass spectra (electron impact) were obtained on a Hitachi Perkin-Elmer RMU-6E instrument at an ionizing voltage of 70 eV. GLC/MS exact mass measurements were performed on a VG Micromass 7035 spectrometer at 70 eV. All reactions with diazo compounds were conducted under a dry nitrogen atmosphere.

General Results of *N*-Methylpyrrole and DMDM. *N*-Methylpyrrole (1.21 g, 15 mmol; commercial material from Aldrich Chemical Co. was distilled from CaH_2 and stored at −20 °C) and metal-promoting agents (Table I) were placed in a flask and heated at 70 °C in an oil bath with stirring. Two drops of dimethyl diazomalonate[11] solution (0.93 g in 200 μL of CH_2Cl_2,[12] 5 mmol) were added. If nitrogen evolution began within 0–2 min, the remainder of the DMDM solution was added drop by drop over about 5 min at 70 °C. Otherwise, the temperature was slowly increased (110 °C maximum) until nitrogen evolution was initiated and then the remainder of the DMDM was added drop by drop at the initiation temperature. After 50–60 min of additional heating, the reaction was concentrated, and the residue was distilled on a Kugelrohr apparatus (ca. 90 °C at 0.1 torr) to give a pale yellow liquid. Specific experimental results are collected in Table I. In some of the reactions (entries 1–5) small amounts (1–3%) of **3c** were detected by GLC (confirmed by coinjection of authentic **3c**[7] and GLC/MS), in addition to the malonate adducts. Malonates **3b** and **4b** were first identified by GLC/MS. The isomers showed virtually identical mass spectra with major peaks at m/z 211 ($M^{+\cdot}$), 179 (M − CH_3O, H), 152 (M − $COOCH_3$, base peak), 125, 121 (M − $COOCH_3$, OCH_3), 108, 94, 93 (M − $2COOCH_3$), 92, 65, 44, 42, 39; exact mass, m/z 211.0835 (found for $C_{10}H_{13}NO_4$, 211.0840), 121.0478 (found for C_7H_9NO, 121.0503). Spectral data for a mixture of **3b** and **4b** in an 8:1 GLC ratio: IR (neat) ν_{max} 2960, 1743 (C=O), 1496, 1438, 1300, 1244, 1152, 1027, 718 cm^{-1}; ^{1}H NMR δ 3.55 (s, 3, NCH_3), 3.74 (s, 6, OCH_3), 4.73 (s, 1, CH), 6.0–6.25 (m, 1.90, β pyrrole H), 6.5–6.7 (m, 1.12, α pyrrole H); the ^{1}H NMR β-proton/α-proton integral ratio of 1.70 (= 1.90/1.12) corresponds to the GLC α/β isomer ratio of 8.0:1 [β/α proton ratio = (mole fraction of α isomer + 1)/(mole fraction of β isomer + 1) = 1.889/1.111 = 1.70]; ^{13}C NMR for **3b**, δ 34.2 (NCH_3), 50.2 (CH), 52.9 (OCH_3), 107.3 (C_3), 109.9 (C_4), 123.0 (C_2), 123.8 (C_5), 167.8 (CO); for **4b**, δ 36.2 (NCH_3), 50.7 (CH), 52.6 (OCH_3), 108.8 (C_4), 114.4 (C_3), 121.1 (C_2), 122.0 (C_5), 169.3 (CO). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found (mixture of **3b** and **4b**): C, 56.82; H, 6.25; N, 6.60.

Conversion of 3b and 4b to 3c and 4c.[4a] A mixture of **3b** and **4b** from the $Cu(acac)_2$ reaction (148 mg, 0.7 mmol, **3b**/**4b** = 7.3:1) was combined with LiCl (60 mg, 0.4 mmol), 13 μL of water, and 1 mL of dimethylformamide. The mixture was heated at reflux for 1 h, cooled, diluted with brine, and extracted with CCl_4. The organic extract was dried (Na_2SO_4) and concentrated. Distillation by Kugelrohr gave 50 mg (47%) of colorless oil, almost entirely composed of **3c** and **4c** in a 6.5:1 ratio (GLC/MS).[11]

General Reaction of *N*-Methylpyrrole and EDAA. *N*-Methylpyrrole (1.21 g, 15 mmol) was reacted with ethyl 2-diazoacetoacetate[13] (0.905 g, 5 mmol) according to the DMDM procedure, using $Cu(hfacac)_2$ (28 mg, 0.05 mmol), $Cu(IPSAL)_2$ (30 mg, 0.05 mmol), or $Rh_2(OAc)_4$ (11 mg, 0.025 mmol) (at 75, 90, and 70 °C, respectively). GLC analyses of the yellow, oily distillates were erratic, probably due to thermal decomposition; GLC/MS was thus precluded. Spectral data were collected on the $Cu(hfacac)_2$ reaction product: direct-inlet MS showed major peaks at m/z 209 ($M^{+\cdot}$), 167, 166 (M − $COCH_3$), 163 (M − OC_2H_5), 138, 121 (M − CH_3, $COOC_2H_5$; base peak), 94, 93; IR (neat) ν_{max} 2988, 1721, 1646, 1616, 1334, 1253, 1228, 1090, 709 cm^{-1}; ^{1}H NMR δ 1.21 (t, 3, OCH_2CH_3), 1.86 (s, 2.53, enol CH_3C=), 2.18 (s, 0.50, keto CH_3CO), 3.38 (s, 2.40, enol NCH_3), 3.52 (s, 0.65, keto NCH_3), 4.24 (q, 2, OCH_2), 4.68 (s, 0.26, keto CH), 5.85–6.15 (m, 1.87, β pyrrole H), 6.6–6.7 (m, 0.94, α pyrrole H), 13.23 (s, 0.78, enol OH); the ^{1}H NMR β-proton/α-proton integral ratio of 1.99 indicates that virtually no β isomer, **4d**, is present (limit of detection is ca. 5%),[14] and ^{1}H NMR indicates an ca. 4:1 enol/keto ratio; ^{13}C NMR δ 14.1 (keto CH_2CH_3), 14.4 (enol CH_2CH_3), 19.9 (=CCH_3), 28.5 ($COCH_3$), 33.7 (NCH_3), 58.6 (keto CH), 60.7 (enol OCH_2), 61.8 (keto OCH_2), 95.0 (=COH), 107.0 (enol C_3), 107.7 (keto C_3), 109.9 (keto C_4), 110.1 (enol C_4), 121.7 (enol C_5), 123.9 (keto C_5), 126.3 (enol C_2), keto C_2 not observed, 172.9/177.7 ($CO_2C_2H_5$, 2:1 intensity ratio, *E* and *Z* enol double bond isomers), $C(O)CH_3$ was not observed. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.09; H, 7.27; N, 6.70. ^{1}H NMR spectra for the products from the $Cu(IPSAL)_2$ and $Rh_2(OAc)_4$ reactions were virtually identical with spectra for the $Cu(hfacac)_2$ reaction product.

Acknowledgment. We thank Martin Mutter and Roberta Acchione for NMR spectral data, Joan Rogers for IR data, and James Kalbron and Dr. Sai Chang for MS data. Samuel Nortey is acknowledged for the preparation of EDAA.

Registry No. 3a, 49669-45-6; **3b**, 81643-08-5; **3c**, 51856-79-2; **3d**, 81643-09-6; **4a**, 62822-16-6; **4b**, 81643-10-9; **4c**, 81643-11-0; *N*-methylpyrrole, 96-54-8; DMDM, 6773-29-1; EDAA, 2009-97-4.

(11) Peace, B. W.; Carman, F. C.; Wulfman, D. S. *Synthesis* **1971**, 658.
(12) The small amount of CH_2Cl_2 was used to facilitate slow addition of the DMDM. The DMDM may be added undiluted or dissolved in a small amount (200 μL) of *N*-methylpyrrole, which is already present in excess. (The excess *N*-methylpyrrole serves as a solvent and minimizes formation of bisadducts.)
(13) Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Prep. Proced.* **1969**, 99.
(14) ^{1}H NMR spectra of the products from each of the catalysts tested were identical, indicating a regioselectivity for **3d** of ≥95%.

Mono- and Bisdiazotization of Proflavine

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In the course of developing photoaffinity probes of biologically active compounds, we undertook the synthesis of the monoazido analogue, **4**, of proflavine (**1**) by selective diazotization and appropriate substitution of the diazonium salt. An early claim[1] to the preparation of the monodiazonium salt **2** and its subsequent reduction in ethanol to yield 3-aminoacridine (**6**) has been disputed.[2] Other workers have prepared the monodiazonium salt by first monoacetylation and then diazotization.[3] We report that the major product from the diazotization of proflavine

(1) Grandmougin, E., Smirous, K. *Chem. Ber.* **1913**, *46*, 3425.
(2) Sherlin, S. M.; Gras, G. J.; Jakukowitsch, A. S.; Warobjowa, E. I.; Ssergyev, A. P. *Justus Leibigs Ann. Chem.* **1935**, *516*, 218.
(3) Martin, R. F.; Tong, J. H. *Aus. J. Chem.* **1969**, *22*, 487.

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