An Efficient Synthesis of Acetylated Bicyclic [n.3.0] Hydroxypyrroles from Cyclic Lactams via Flash-Vacuum Pyrolysis of Meldrum's Acid Derivatives[1a]

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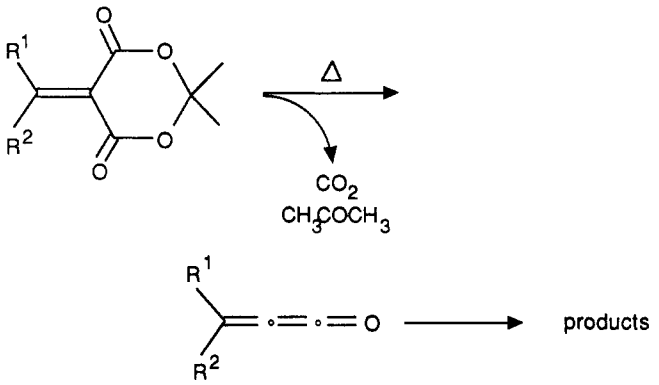
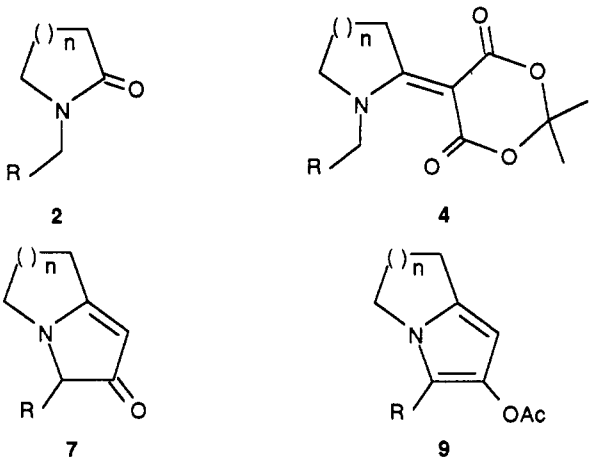
The title compounds **9** were synthesized in three steps from cyclic lactams **2**. After treatment of **2a–h** with phosgene followed by the addition of Meldrum's acid to the chloroiminium chloride intermediates **3a–h**, derivatives **4a–h** were isolated in good yields. Compounds **4a–g** were quantitatively converted to bicyclic enaminones **7a–g** by flash-vacuum pyrolysis in the temperature range 480–600 °C. In contrast, **4h** provided **8h**, the hydroxypyrrole tautomer of **7h**. The reaction takes place through the initial formation of (aminomethylene)ketenes **5a–h** followed by a 1,4-hydrogen migration from the carbon adjacent to the nitrogen atom to the central carbon of the cumulenone. The lower temperature (480 °C) needed for benzyl and *N*-carboalkoxy derivatives **4e–h** in comparison with *N*-alkyl derivatives **4a–d** (600 °C) is correlated with the gas-phase acidity of the migrating hydrogen atom. The hydroxypyrroles **8a–g**, tautomers of **7a–g** (**7** ⇄ **8**), were trapped with acetic anhydride, affording O-acetylated bicyclic [*n*.3.0] hydroxypyrroles **9a–g**.

Methyleneketenes are useful intermediates in organic chemistry that are usually generated by thermal decomposition of Meldrum's acid derivatives.[2] The nonlinear structure of the parent propadienone has been established by theoretical[3] and spectroscopic[4] studies. Moreover, it has been shown that this method is excellently suited for the production of reactive and unstable (aminomethylene)ketenes ($R^1 = NR_2$); recently, the first example of a relatively stable methyleneketene has been reported.[5]



At high temperatures, (aminomethylene)ketenes are converted into various heterocycles whose structures depend on the nature of the group attached to the nitrogen atom.[6-8]

We now describe an efficient synthesis of bicyclic enaminones **7** (tautomers of 3-hydroxypyrroles) from cyclic lactams **2** through the pyrolysis of Meldrum's acid derivatives **4**. The reaction appears quite attractive as a general



three-step route for the construction of functionalized pyrrolo fused bicyclic [*n*.3.0] systems **9** with a nitrogen atom at the ring junction. These products belong to a class of compounds known for their biological activity as anti-inflammatory and analgesic agents.[9,10]

Results and Discussion

Synthesis of 5-(Aminomethylene)-2,2-dimethyl-1,3-dioxane-4,6-diones. Enamino diesters **4a–h** were synthesized from cyclic lactams **2a–h**, which are either com-

(1) (a) Presented in part at the following Xth European Colloquium on the Heterocyclic Chemistry, Kaiserslautern, Germany, October 1984; IVth Symposium on Organic Chemistry, Aix en Provence, France, Septembre 1985. (b) Abstracted from H. Dhimane's Thesis, Reims, December 17, 1986.

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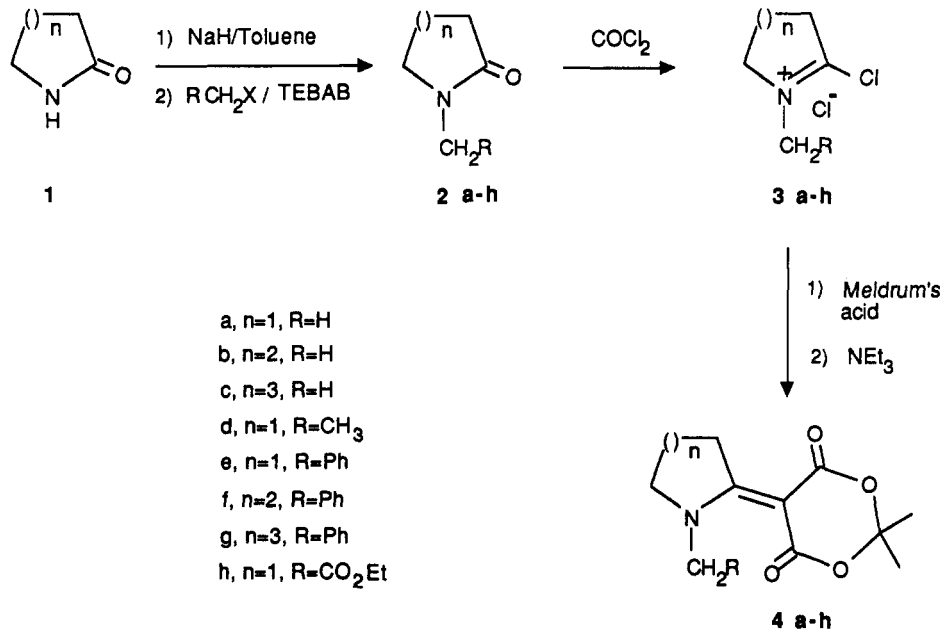
Scheme I



Scheme II

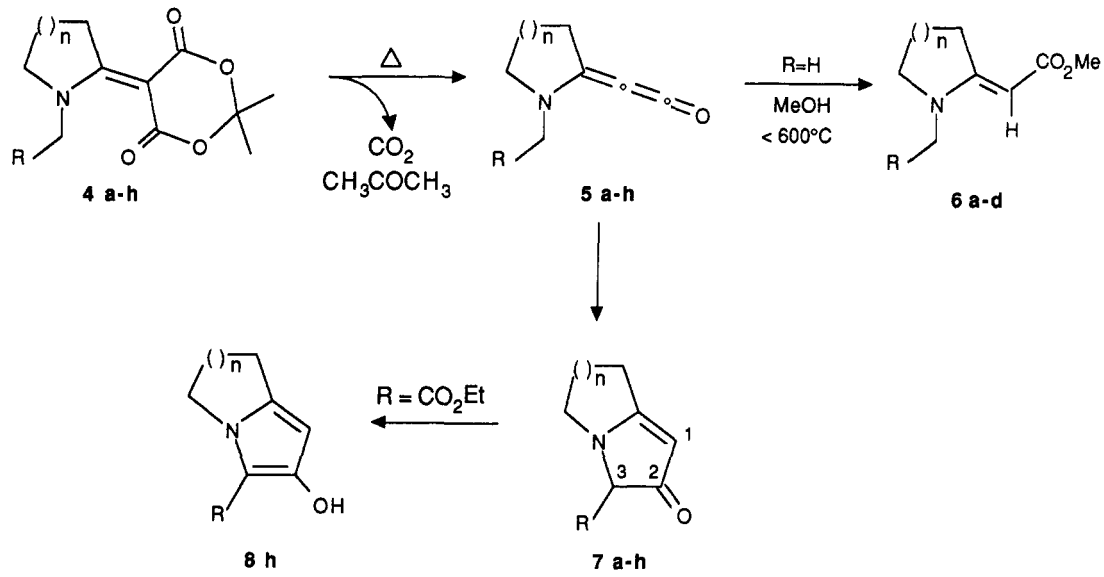


Table I. Flash Pyrolysis of Meldrum's Acid Derivative 4a

	T, °C					
	480	500	520	540	580	600
6a, %[a]	73	64	48	18	3	0
7a, %[a]	27	36	52	82	97	100

[a] Percentages determined by ^{1}H NMR.

mercial (R = H, n = 1–3; R = CH_3, Ph, n = 1) or prepared by alkylation of lactams 1 (R = Ph, n = 2,3; R = CO_2Et, n = 1). Recently, phase-transfer catalyzed N-alkylation of lactams and N-substituted carboxamides, in a two-phase system consisting of sodium hydroxide–potassium carbonate or potassium hydroxide and benzene[11,12] or THF[13] has been reported. However, for synthesis of derivatives **2f–h**, a new procedure was used (Scheme I). We found that the condensation of lactam sodium salts, prepared from lactams 1 and sodium hydride, with alkyl halides (X = Cl, **2f,g**; X = Br, **2h**) in presence of 10 mol % of tetra-*n*-butylammonium bromide (TEBAB) in toluene at room temperature proceeds smoothly to afford the corresponding N-substituted lactams **2f–h** in 75–98% yields. This method is quite general and has also been applied to the preparation of *N*-(chloroalkyl) lactams.[7b,14]

In a previous paper,[15] we have reported the conversion of lactams **2** into **4** and found that the best yields were obtained with 2-chloro iminium chlorides, which are easily

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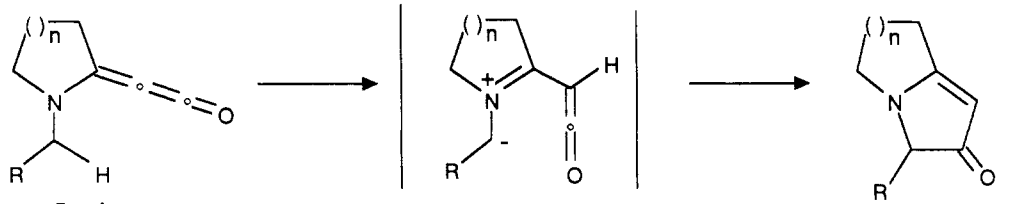
Table II. Flash-Vacuum Pyrolysis of Meldrum's Acid Derivatives 4

product	n	R	pyrolysis temperature °C	crude yield, %	yield after[a] purification, %	bp, °C/mbar (mp, °C)
7a	1	H	600	95	74	$104/6 \times 10^{-4}$
7b	2	H	600	96	76	$42/5 \times 10^{-5}$
7c	3	H	600	98	79	$98/10^{-4}$
7d	1	CH_3	600	86[b]		
7e	1	Ph	480	91[b]		
7f	2	Ph	480	96	72	[c]
7g	3	Ph	480	95[b]		
8h	1	CO_2Et	480	[d]	51	(60)

[a] Isolated product by distillation or sublimation. [b] Attempts to purify this compound have been curently unsuccessful (see text). [c] Kugelrohr distillation. [d] Not determined.

Scheme III



prepared by treatment of lactams **2** with phosgene. Thus, after addition of Meldrum's acid to activated lactams **3a–h**, compounds **4a–h** were obtained in 60–97% yields from **2a–h**. The infrared spectra of derivatives **4a–h** showed the presence of a double bond in the 1560-cm^{-1} region and of two types of carbonyl groups at 1650 and 1700 cm^{-1}, typical of Meldrum's acid and its derivatives.[16]

Pyrolysis of Meldrum's Acid Derivatives. Flash-vacuum pyrolysis of **4a** was investigated in the temperature range 410–600 °C (10^{-4}–10^{-5} Torr); the products were condensed on a liquid nitrogen cooled finger covered with methanol.[17] The decomposition of **4a** was complete at 480 °C; thus, after warming to room temperature and subsequent evaporation of acetone and methanol, a mixture of cyclic enamino ester **6a** and bicyclic enaminone **7a** was obtained (Scheme II).

Higher pyrolysis temperatures resulted in a decrease of the percentage of **6a** (see Table I), and above 600 °C only the heterocycle **7a** was isolated. On the other hand, below 480 °C, **7a** was not formed, and enamino ester **6a** and unreacted starting material **4a** were the only observed products.

When $CDCl_3$ was used instead of methanol on the cold finger, the (aminomethylene)ketene **5a** could be characterized by ^1H and ^{13}C NMR spectroscopy; moreover, it has been shown that **5a** is generated by stepwise elimination of acetone and carbon dioxide.[5]

Similarly, flash-vacuum pyrolysis of Meldrum's acid derivatives **4b–h** were carried out under the same conditions. Substituent effects on the thermolysis temperature are notable; while complete conversion of **4** into pyrrolinone **7** required 600 °C for *N*-alkyl derivatives **4a–d**, a lower temperature, 480 °C, was sufficient for derivatives **4e–h** bearing either a benzyl or a carboalkoxymethyl substituent on the nitrogen atom. Bicyclic enaminones **7a–g** have been obtained in nearly quantitative yields (Table II) as determined by ^1H NMR spectroscopy of the crude products.

Compounds **7a–g** are reasonably stable and can be stored for several weeks at 0 °C but resinify on chromatography. For analytical purposes 2-pyrolin-4-ones **7a–c** and **7f** were purified by flash distillation under high vacuum (Table II).

In agreement with previous results with monocyclic five-membered enaminones,[18–20] compounds **7a–g**, lacking polar functionalities, exist exclusively in the keto form as indicated by ^1H and ^{13}C NMR. In particular, the vinylic proton H-1 appears as a singlet around 4.95 ppm, and the proton H-3 adjacent to the nitrogen atom gives a signal in the 3.8 ppm region for **7a–d** and at a lower field (4.45 ppm) for **7e–g** as the result of the deshielding effect on the phenyl group. In the ^{13}C NMR spectrum the signals for the carbonyl group at C-2 are observed around 200 ppm. In accordance with the literature,[18] compounds **7a–g** exhibit strong carbonyl and ethylenic bands respectively at 1620–1660 and 1520–1545 cm^{-1} in the IR spectra.

In contrast with preceding results, no pyrrolinone **7h** was observed on flash-vacuum pyrolysis of **4h**. In fact, the pyrolysis product consisted exclusively of the tautomeric hydroxypyrrole **8h**; this enol form is stabilized[19] by the carboalkoxy substituent at the C-3 atom.

As regards the formation of pyrrolinones **7** from (aminomethylene) ketenes **5**, we have previously suggested[7a] that the reaction might take place through an intramolecular 1,4-hydrogen migration followed by a 6π electrocyclization of an intermediate ketenic azomethine ylide (Scheme III). Recently, it has been reported that pyrolysis of Meldrum's acid derivatives bearing a chiral carbon adjacent to the nitrogen atom give, in noncyclic systems, pyrrolinones in which partial chirality is retained.[21] These experimental results have been explained by hydrogen transfer to the in-plane p orbital at C-2 of the cumulene. On the contrary, in cyclic systems, chirality is completely lost.[21] So, it is very likely that formation of bicyclic pyrrolinones **7a–h** involves a planar dipolar intermediate.

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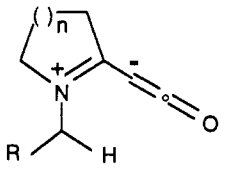
Table III. Synthesis of Bicyclo[*n*.3.0]acylated Pyrroles 9 from Derivatives 4

substituent R[a]	H	H	H	Me	Ph	Ph	Ph
n	1	2	3	1	1	2	3
acylated pyrrole	**9a**	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**
yield, %[b]	43	67	25	36	51	53	44

[a] See Scheme IV. [b] Calculated for the two steps (pyrolysis and esterification) from **4a–g**.

This 1,4-hydrogen shift is favored by the high degree of negative charge at C-2 due to the important contribution of the canonical form A as suggested by NMR spectroscopy.[5] Moreover, the lowering by 120 °C of the temperature needed for the complete conversion of **4e–h** into **7e–h** when R is either a phenyl or an ester group might well be correlated with an increase of the gas phase acidities of C–H bonds due to these substituents.[22] In contrast with **5a–d**, (aminomethylene)ketenes **5e–h** could not be trapped with methanol. For example, flash-vacuum pyrolysis of **4e** at 460 °C gave pyrrolinone **7e** (86%) and recovered starting material (14%); similar results were obtained with **5h** (460 °C; **8h**/**4h** = 95/5). It appears that the free energy of activation for the second step (formation of **7e,h** from **5e,h**) is lower than the first one (formation of **5e,h** from **4e,h**) and, in this context, (aminomethylene)ketenes can be considered as short-lived intermediates.

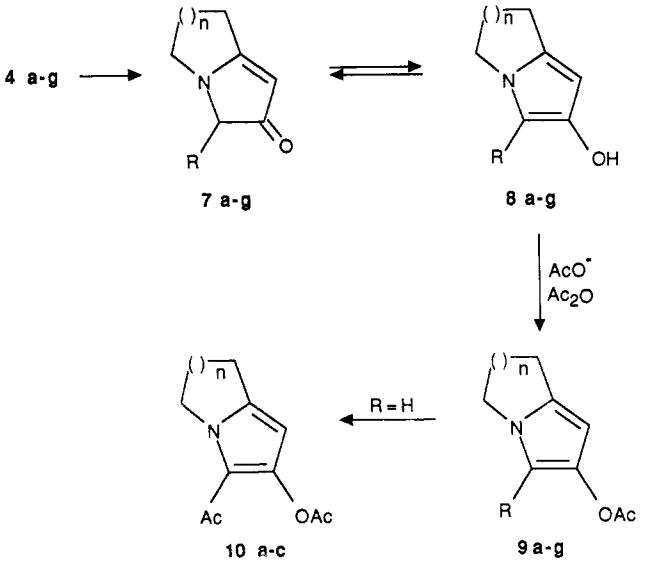


A

Esterification of Hydroxypyrroles 8a–g. It has been reported that pyrrolin-3-ones exist exclusively in the keto form in nonpolar solvents,[18] while in polar solvents the enol form is predominant.[23] Moreover, these compounds react with acetic anhydride to give O-acetylated pyrroles.[24] Thus, when crude products **7a–g** obtained by pyrolysis of **4a–g** were heated in acetic anhydride in the presence of a catalytic amount of sodium acetate for 15 min, bicyclic [*n*.3.0] acylated pyrroles **9a–g** were formed (Scheme IV). These substituted pyrroles **9a–g** are much more stable than pyrrolin-3-ones **7a–g** and could be isolated by flash chromatography (Table III). The H-1 proton gives a signal in the 5.70 ppm region and a strong absorption is observed at 1750 cm^{-1} in the IR spectra. Prolonged heating with an excess of acetic anhydride resulted in C-acylation in the 3-position of compounds **9a–c** (R = H; 140 °C, 1 h; **10a**/**9a** = 1/5; **10b**/**9b** = 1/5; **10c**/**9c** = 2/3).

In summary, the flash-vacuum pyrolysis of Meldrum's acid derivatives provides a facile synthetic access to acetylated bicyclic [*n*.3.0] hydroxypyrroles from cyclic lactams.

Scheme IV



Experimental Section

^1H NMR spectra were recorded on a Bruker WP 80 CW spectrometer with Me_4Si as an internal standard, ^{13}C NMR spectra on a Bruker WP 60 spectrometer operating at 18.05 MHz. IR spectra were measured with either a Philips Model SP 2000 or Model SP 300 spectrometer. Melting points were determined in open capillaries with a Büchi apparatus and are uncorrected.

Preparation of *N*-Alkyl Lactams 2. General Procedure. To a suspension of sodium hydride (0.1 mol) in dry toluene (350 mL) was added a toluene solution (50 mL) containing the lactam (0.1 mol). The mixture was stirred at reflux for 1 h and cooled, and 3.22 g of tetra-*n*-butylammonium bromide (0.01 mol) and the alkyl halide (0.12 mol) were added at room temperature. Vigourous stirring was maintained for 16 h. The reaction mixture was evaporated in vacuo, and the residue was poured in ether (100 mL).

After filtration, the solvent was evaporated and the alkyl lactam was distillated under reduced pressure. 1-Benzyl-2-piperidinone (**2f**) (*n* = 2): 96% yield; bp 106 °C (10^{-2} Torr) [lit.[25] bp 156 °C (4 Torr)]. *N*-Benzyl-ε-caprolactam (**2g**) (*n* = 3): 83% yield; bp 110 °C (10^{-2} Torr) [lit.[12] bp 145–149 °C (1 Torr)]. 1-(Carbethoxymethyl)-2-pyrrolinone (**2h**) (*n* = 1): 75% yield; bp 70 °C (10^{-2} Torr) [lit.[26] 136–139 °C (3 Torr)].

Synthesis of β-Enamino Diesters 4a–h. General Procedure. A 20% solution of phosgene in toluene (500 mL per mol of **2**) was added dropwise to a stirred solution of the *N*-alkyl lactam **2** (1.0 equiv) in chloroform (400 mL per 1 mol of **2**) at 0 °C, and stirring was continued for 5 h at 0 °C. Then, Meldrum acid (1.0 equiv) was adddded, followed by the slow addition of a solution of triethylamine (280 mL per mol of **2**) in chloroform (300 mL per mol of triethylamine). The mixture was stirred at room temperature overnight. The organic layer was separated, washed with water (3 × 50 mL), dried with sodium sulfate, and concentrated in vacuo. The solid residue was triturated with ether or ethyl acetate and recrystallized from ethanol.

5-(1-Methyl-2-pyrrolidinylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4a): 97% yield: mp 151 °C; IR ($CHCl_3$) 3000, 1705, 1660, 1570, 1440, 1405, 1390, 1375, 1325, 1290, 1270, 1190, 1045; ^1H NMR ($CDCl_3$) δ 1.68 (s, 6 H), 1.9–2.4 (m, 2 H), 3.18 (s, 3 H), 3.25–3.60 (m, 2 H), 3.60–3.95 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 177.4 (s), 162.7 (s), 102.0 (s), 80.3 (s), 59.0 (t), 40.4 (q), 38.0 (t), 26.3 (q), 19.7 (t); mass spectrum, *m*/*e* (relative intensity) 225 (M^+, 34), 168 (61), 167 (94), 124 (29), 123 (100), 95 (86). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.29; H, 6.48; N, 5.91.

5-(1-Methyl-2-piperidylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4b): 55% yield; mp 157 °C; IR ($CHCl_3$) 3000, 1690, 1640, 1570, 1430, 1400, 1390, 1370, 1340, 1290, 1270, 1190, 1050;

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^{1}H NMR ($CDCl_3$) δ 1.68 (s, 6 H), 1.7–2.0 (m, 4 H), 3.30 (s, 3 H), 3.2–3.3 (m, 4 H); mass spectrum, *m/e* (relative intensity) 239 (M^+, 26), 182 (35), 181 (77), 138 (22), 137 (100), 136 (26), 109 (24), 108 (80), 81 (44), 80 (18). Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.10; H, 7.03; N, 6.13.

5-(1-Methyl-2-hexahydroazepinylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4c): 66% yield; mp 131 °C; IR ($CHCl_3$) 1700, 1650, 1580; ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 6 H), 1.89 (m, 6 H), 1.89 (m, 6 H), 3.16 (m, 2 H), 3.30 (s, 3 H), 3.79 (m, 2 H). Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.50; H, 7.43; N, 5.60.

5-(1-Ethyl-2-pyrrolidinylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4d): 70% yield; mp 145 °C; IR ($CHCl_3$) 3000, 1705, 1655, 1560, 1435, 1390, 1375, 1325, 1290, 1265, 1180, 1050, 920; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H, *J* = 7 Hz), 1.73 (s, 6 H), 2.11 (m, 2 H), 3.38–3.91 (m, 6 H); mass spectrum, *m/e* (relative intensity) 239 (M^+, 29), 182 (43), 181 (95), 138 (14), 137 (57), 109 (46), 108 (100), 80 (17). Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.12; H, 7.22; N, 5.93.

5-(1-Benzyl-2-pyrrolidinylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4e): 69% yield; mp 155 °C; IR ($CHCl_3$) 3000, 1705, 1660, 1550, 1440, 1390, 1375, 1325, 1290, 1270; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 6 H), 2.12 (m, 2 H), 3.55 (t, 2 H, *J* = 7 Hz), 3.72 (t, 2 H, *J* = 7 Hz), 4.85 (s, 2 H), 7.30 (m, 5 H); mass spectrum, *m/e* (relative intensity) 301 (M^+, 19), 244 (25), 243 (100), 225 (11), 214 (34), 199 (35), 198 (13), 171 (22), 170 (42). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.83; H, 6.45; N, 4.73.

5-(1-Benzyl-2-piperidylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4f): 60% yield; mp 164 °C; IR ($CHCl_3$) 3000, 1690, 1550, 1420, 1390, 1370, 1330, 1290, 1265; ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 6 H), 1.74 (m, 4 H), 3.40 (m, 4 H), 4.76 (s, 2 H), 7.24 (m, 5 H); mass spectrum, *m/e* (relative intensity) 315 (M^+, 17), 258 (18), 257 (52), 228 (15), 214 (18), 213 (100), 212 (20), 185 (21), 184 (77). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.19; H, 6.54; N, 4.67.

5-(1-Benzyl-2-hexahydroazepinylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4g): 69% yield; mp 198 °C; IR ($CHCl_3$) 3000, 1690, 1640, 1550, 1440, 1410, 1390, 1370, 1340, 1315, 1290, 1270; ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 12 H), 3.25 (m, 2 H), 3.63 (m, 2 H), 4.76 (s, 2 H), 7.38 (m, 5 H); mass spectrum, *m/e* (relative intensity) 329 (M^+, 19), 272 (20), 271 (58), 253 (33), 228 (19), 227 (100), 226 (17), 199 (19), 198 (71). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.02; H, 6.93; N, 4.45.

5-[1-(Carbethoxymethyl)-2-pyrrolidinylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (4h): 30% yield; mp 133 °C; IR ($CHCl_3$) 3000, 1740, 1710, 1670, 1540, 1440, 1420, 1390, 1375, 1325, 1290, 1270; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3 H, *J* = 7 Hz), 1.68 (s, 6 H), 2.16 (m, 2 H), 3.55 (t, 2 H, *J* = 7 Hz), 3.9 (t, 2 H, *J* = 7 Hz), 4.25 (q, 2 H, *J* = 7 Hz), 4.38 (s, 2 H). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.70; H, 6.74; N, 4.75.

Flash Pyrolyses of Derivatives 4a–h. General Procedure. The pyrolysis apparatus consisted of a 60 × 3 cm quartz tube (heated by an electric Hermann-Moritz oven) leading directly to a liquid nitrogen cooled finger[17] connected to the pumping system ($p = 10^{-5}$ Torr). The quartz tube had an opening behind the furnace to allow the methanol to be initially condensed on the cold finger surface. The derivatives **4a–h** (2.5 mmol) were sublimed (90–160 °C) during 4–6 h through the quartz tube heated in the temperature range 450–650 °C. The emergent vapors were collected on the cold finger, and after warming the collected vapors to room temperature, a dilute solution of pyrolyzate was obtained. The excess of MeOH was removed, and spectral analyses were realized before and after purification. Lower yields of bicyclic enaminones **7** were obtained when chloroform or acetone was used instead of methanol.

6-Oxo-2,3,5,6-tetrahydroxy-1*H*-pyrrolizine (7a): 74% yield; oil; 104 °C (6×10^{-4} Torr); IR ($CHCl_3$) 3020, 1645, 1545; ^{1}H NMR ($CDCl_3$) δ 2.26 (m, 2 H), 2.77 (m, 2 H), 3.40 (t, 2 H, *J* = 7 Hz), 3.67 (m, 2 H), 4.93 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 201.0 (s), 185 (s), 92.8 (d), 56.6 (t), 49.5 (t), 27.3 (t), 23.2 (t); mass spectrum, *m/e* (relative intensity) 123 (M^+, 100), 122 (15), 97 (13), 96 (15), 95 (39), 94 (25), 68 (11), 67 (58). Anal. Calcd (CI high resolution mass spectrum) for C_7H_9NO 123.0683, found 123.0683.

2-Oxo-2,3,5,6,7,8-hexahydroindolizine (7b): 76% yield; oil; 69 °C (2×10^{-4} Torr); IR ($CDCl_3$) 3010, 1620, 1520; ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 4 H), 2.64 (m, 2 H), 3.31 (t, 2 H, *J* = 5.5 Hz), 3.73 (m, 2 H), 4.9 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.1 (s), 177.7 (s), 97.6 (d), 60.1 (t), 45.5 (t), 25.3 (t), 22.9 (t), 19.6 (t); mass spectrum, *m/e* (relative intensity) 137 (M^+, 100), 109 (25), 108 (55), 81 (31).

2-Oxo-2,3,6,7,8,9-hexahydro-5*H*-pyrrolo[1,2-*a*]azepine (7c): 79% yield; oil; 98 °C (10^{-4} Torr); IR ($CHCl_3$) 3020, 1650, 1530; ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 6 H), 2.52 (m, 2 H), 3.37 (m, 2 H), 3.82 (s, 2 H), 4.95 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 198.0 (s), 182.7 (s), 99.7 (d), 62.2 (t), 48.6 (t), 30.3 (t), 29.9 (t), 28.2 (t), 25.6 (t); mass spectrum, *m/e* (relative intensity) 151 (M^+, 100), 123 (32), 122 (42), 95 (47).

5-Methyl-6-oxo-2,3,5,6-tetrahydro-1*H*-pyrrolizine (7d): 86% in crude product; brown oil; IR ($CDCl_3$) 3010, 1650, 1540; ^{1}H NMR ($CDCl_3$) δ 1.37 (d, 3 H, *J* = 7 Hz), 2.21–2.48 (m, 2 H), 2.76–2.91 (m, 2 H), 3.17–3.81 (m, 3 H), 4.92 (s, 1 H); ^{13}C NMR δ 204.0 (s), 182.9 (s), 90.9 (d), 61.7 (d), 46.3 (t), 27.3 (t), 23.2 (t), 14.4 (q); mass spectrum, *m/e* (relative intensity) 137 (M^+, 76), 136 (17), 109 (35), 108 (100), 81 (32).

6-Oxo-5-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolizine (7e): 91% in crude product; IR ($CHCl_3$) 3000, 1660, 1540; ^{1}H NMR ($CDCl_3$) δ 2.50 (m, 2 H), 2.80 (m, 2 H), 3.29 (m, 2 H), 4.47 (m, 1 H), 4.96 (s, 1 H), 7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 201.6 (s), 184.6 (s), 134.5 (s), 128.8 (d), 127.9 (d), 127.2 (d), 90.6 (d), 70.0 (d), 46.6 (t) 27.4 (t), 23.2 (t); mass spectrum, *m/e* (relative intensity) 199 (M^+, 100), 198 (42), 182 (9), 171 (10), 170 (43).

2-Oxo-3-phenyl-2,3,5,6,7,8-hexahydroindolizine (7f): 72% yield; IR ($CHCl_3$) 3020, 1650, 1520, 1450; ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 2 H), 2.65 (m, 2 H), 3.07 (m, 2 H), 4.37 (s, 1 H), 4.89 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 198.2 (s), 177.8 (s), 134.5 (s), 128.9 (d), 128.1 (d), 127.6 (d), 95.5 (d), 73.1 (d), 43.6 (t), 25.4 (t), 22.9 (t), 19.6 (t); mass spectrum, *m/e* (relative intensity) 213 (M^+, 100), 212 (26), 196 (13), 185 (20), 184 (72).

3-Phenyl-2-oxo-2,3,6,7,8,9-hexahydro-5*H*-pyrrolo[1,2-*a*]-azepine (7g): 95% yield in crude product; IR ($CHCl_3$) 3010, 1650, 1600, 1520, 1440, 1140; ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 6 H), 2.66 (m, 2 H), 3.30 (m, 2 H), 4.45 (s, 1 H), 4.99 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 199.1 (s), 183.2 (s), 134.6 (s), 128.8 (d), 128.1 (d), 127.8 (d), 97.1 (d), 75.0 (d), 47.0 (t), 30.2 (t), 28.3 (t), 25.6 (t); mass spectrum, *m/e* (relative intensity) 227 (100), 226 (29), 210 (16), 199 (10), 198 (38), 150 (15).

5-Carbethoxy-6-hydroxy-2,3-dihydro-1*H*-pyrrolizine (8h): 51% yield; beige solid; mp 60 °C; IR ($CHCl_3$) 3500, 3350, 2990, 1690, 1640, 1560; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H, *J* = 7 Hz), 2.40 (m, 2 H), 2.82 (t, 2 H, *J* = 7 Hz), 4.07 (t, 2 H, *J* = 7 Hz), 4.32 (q, 2 H, *J* = 7 Hz), 5.53 (s, 1 H), 8.95 (m, OH); ^{13}C NMR ($CDCl_3$) δ 162.8 (s), 158.6 (s), 142.2 (s), 102.6 (s), 89.5 (d), 59.5 (t), 48.2 (t), 25.5 (t), 25.4 (t), 14.6 (q); mass spectrum, *m/e* (relative intensity) 195 (M^+, 47), 150 (19), 149 (100), 121 (18), 93 (96). Anal. Calcd for $C_{10}H_{13}NO_3$ C, 61.52; H, 6.71; N, 7.17. Found: C, 61.60; H, 6.70; N, 7.20.

O-Acylation of 2-Pyrrolin-4-ones 7a–g. The O-acylation reaction was carried out by treatment of the crude pyrolysis product with 4 equiv of acetic anhydride and 0.01 equiv of sodium acetate. The mixture was stirred for 15 min at 90 °C, and the resulting mixture was diluted with 30 mL of dichloromethane and 10 mL of water. The organic layers were dried over anhydrous magnesium sulfate and concentrated. The crude acetates **9** were purified by flash chromatography or by sublimation. When R = H, prolonged heating (1 h) resulted in a mixture of O-acylation and C-acylation products **9a–c** and **10a–c**.

6-Acetoxy-2,3-dihydro-1*H*-pyrrolizine (9a): flash chromatography using 80:20 petroleum ether–ethyl acetate; mp 31 °C; 43% yield from **4a**; IR ($CHCl_3$) 3000, 2945, 1750, 1635, 1555, 1430, 1365, 1225, 1015, 910; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 2.41 (m, 2 H), 2.85 (m, 2 H), 3.94 (t, 2 H, *J* = 7 Hz), 5.70 (d, 1 H, *J* = 1.6 Hz), 6.62 (d, 1 H, *J* = 1.6 Hz); mass spectrum, *m/e* (relative intensity) 165 (28), 137 (11), 136 (9), 124 (10), 123 (100), 122 (68), 106 (17). Anal. Cacld for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.47. Found: C, 65.53; H, 6.71; N, 8.42.

6-Acetoxy-5-acetyl-2,3-dihydro-1*H*-pyrrolizine (10a): ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.35 (s, 3 H), 282 (m, 2 H), 4.32 (m, 2 H), 5.88 (s, 1 H).

2-Acetoxy-5,6,7,8-tetrahydroindolizine (9b): flash chromatography using 70:30 petroleum ether–ethyl acetate; 67% yield from **4b**; IR ($CHCl_3$) 3000, 2940, 1740, 1700, 1560, 1360, 1220; ^{1}H

NMR ($CDCl_3$) δ 1.84 (m, 4 H), 2.19 (s, 3 H), 2.57 (m, 2 H), 3.84 (t, 2 H, J = 7 Hz), 5.66 (d, 1 H, J = 2 Hz), 6.48 (d, 1 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 137.5 (s), 126.9 (s), 107.8 (d), 97.1 (d), 45.3 (t), 23.7 (t), 21.2 (t), 20.9 (q); mass spectrum, m/e (relative intensity) 179 (36), 138 (10), 137 (100), 136 (47), 120 (30), 109 (14).

2-Acetoxy-3-acetyl-5,6,7,8-tetrahydroindolizine (10b): ^1H NMR ($CDCl_3$) δ 1.84 (m, 4 H), 2.27 (s, 3 H), 2.60 (m, 2 H), 4.25 (m, 2 H), 5.77 (s, 1 H).

2-Acetoxy-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine (9c): sublimation; mp 65 °C; 25% yield from **4c**; IR ($CHCl_3$) 3010, 2930, 1740, 1560, 1460, 1425, 1350, 1235, 1010; ^1H NMR ($CDCl_3$) δ 1.73 (m, 6 H), 2.19 (s, 3 H), 2.60 (m, 2 H), 3.77 (m, 2 H), 5.73 (d, 1 H, J = 2 Hz), 6.54 (d, 1 H, J = 2 Hz); mass spectrum, m/e (relative intensity) 193 (39), 152 (10), 151 (100), 150 (37), 134 (46), 123 (10). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.08; H, 7.91; N, 7.12.

2-Acetoxy-3-acetyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]-azepine (10c): ^1H NMR ($CDCl_3$) δ 1.73 (m, 6 H), 2.28 (s, 3 H), 2.36 (s, 3 H), 2.62 (m, 2 H), 4.55 (m, 2 H), 5.88 (s, 1 H).

6-Acetoxy-5-methyl-2,3-dihydro-1*H*-pyrrolizine (9d): flash chromatography using 70:30 ether–petroleum ether; mp 72 °C; 36% yield from **4d**; IR ($CHCl_3$) 3030, 1750, 1590, 1360, 1240; ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H), 2.25 (s, 3 H), 2.43 (m, 2 H), 2.86 (t, 2 H, J = 7 Hz), 3.83 (t, 2 H, J = 7 Hz), 5.66 (s, 1 H); mass spectrum, m/e (relative intensity) 179 (30), 138 (10), 137 (100), 136 (98), 120 (11). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.05; H, 7.44; N, 7.85.

6-Acetoxy-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (9e): flash chromatography using 55:45 petroleum ether–ethyl acetate; mp 93 °C; 51% yield from **4e**; IR ($CHCl_3$) 3000, 1760, 1600, 1580, 1565, 1510, 1360, 1300; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.17–2.65 (m, 2 H), 2.92 (t, 2 H, J = 7 Hz), 4.06 (t, 2 H, J = 7 Hz), 5.87 (s, 1 H), 7.36 (m, 5 H); mass spectrum, m/e (relative intensity) 241 (18), 200 (17), 199 (100), 198 (47), 182 (8). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.24; H, 6.16; N, 5.91. Found: C, 74.66; H, 6.26; N, 5.80.

2-Acetoxy-3-phenyl-5,6,7,8-tetrahydroindolizine (9f): flash chromatography using 75:25 petroleum ether–ethyl acetate; mp 105 °C; 53% yield from **4f**; IR ($CHCl_3$) 3010, 2960, 1755, 1610, 1585, 1510, 1415, 1370, 1350, 1230; ^1H NMR ($CDCl_3$) δ 1.86 (m, 4 H), 2.10 (s, 3 H), 2.82 (m, 2 H), 3.80 (m, 2 H), 5.84 (s, 1 H), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) 170.0 (s), 134.4 (s), 130.6 (s), 129.6 (d), 128.4 (d), 127.5 (s), 126.9 (d), 120.6 (s), 98.8 (d), 44.4 (t), 23.7 (t), 23.5 (t), 20.9 (t), 20.7 (q); mass spectrum, m/e (relative intensity) 255 (19), 214 (18), 213 (100), 212 (28), 196 (10). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48. Found: C, 75.15; H, 6.64; N, 5.41.

2-Acetoxy-3-phenyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine (9g): flash chromatography using 75:25 petroleum ether–ethyl acetate; mp 104 °C; 44% yield from **4g**; IR ($CHCl_3$) 3000, 2940, 1750, 1610, 1585, 1470, 1360, 1225; ^1H NMR ($CDCl_3$) δ 1.66 (m, 6 H), 2.01 (s, 3 H), 2.65 (m, 2 H), 3.73 (m, 2 H), 5.77 (s, 1 H), 7.20 (m, 5 H); mass spectrum, m/e (relative intensity) 269 (20), 228 (16), 227 (100), 226 (22), 210 (10), 196 (10). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.11; N, 5.20. Found: C, 75.91; H, 7.07; N, 5.37.

Registry No. **1a**, 616-45-5; **1b**, 675-20-7; **1c**, 105-60-2; **2a**, 872-50-4; **2b**, 931-20-4; **2c**, 2556-73-2; **2d**, 2687-91-4; **2e**, 5291-77-0; **2f**, 4783-65-7; **2g**, 33241-96-2; **2h**, 61516-73-2; **4a**, 86208-87-9; **4b**, 86208-88-0; **4c**, 86208-89-1; **4d**, 115860-49-6; **4e**, 115860-50-9; **4f**, 115860-51-0; **4g**, 115860-52-1; **4h**, 115860-53-2; **6a**, 78167-68-7; **7a**, 97181-96-9; **7b**, 97202-63-6; **7c**, 97202-64-7; **7d**, 115860-54-3; **7e**, 115860-55-4; **7f**, 115860-56-5; **7g**, 115860-57-6; **8h**, 115860-58-7; **9a**, 115860-59-8; **9b**, 115860-61-2; **9c**, 115860-63-4; **9d**, 115860-65-6; **9e**, 115860-66-7; **9f**, 115860-67-8; **9g**, 115860-68-9; **10a**, 115860-60-1; **10b**, 115860-62-3; **10c**, 115860-64-5.

Synthesis of 2-Substituted Imidazoles and Benzimidazoles and of 3-Substituted Pyrazoles by Lithiation of *N*-(Dialkylamino)methyl Heterocycles[1]

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The lithiation of *N*-(dialkylamino)methyl (aminal) derivatives of imidazole, benzimidazole, and pyrazole (themselves readily available from the parent heterocycles, formaldehyde, and a secondary amine) occurs smoothly at the 2-, 2-, and 5-positions, respectively, upon treatment with *n*-butyllithium in ether or tetrahydrofuran. Reaction with electrophiles, and subsequent facile acid-catalyzed hydrolysis of the protecting group, provides 2-substituted imidazoles, 2-substituted benzimidazoles, and 3(5)-substituted pyrazoles in good overall yields.

Introduction

The lithiation of heterocyclic compounds containing an NH group normally leads only to the *N*-lithio derivative[3] but, when the nitrogen is substituted, C-lithiation can occur. If the N-substituent can be later removed, it serves as a protecting group for the NH. Thus the lithiation of, for example, imidazoles[4-5] occurs readily when the ring *N*-hydrogen atom is replaced. Many groups have been used for protection of imidazole in this way (cf. discussion in ref 5):

(a) The imidazole nitrogen is efficiently protected by an alkyl group,[3] but such compounds cannot be deprotected under normal conditions.

(b) Benzylic N-protection of imidazole[6] is unsatisfactory since competitive lithiation[5] at the benzylic methylene group is usually observed.

(c) *tert*-Butyl has also been used[5] for the protection of imidazole nitrogen, unfortunately, it was rather difficult to introduce and to remove.

(d) 1-(Triphenylmethyl)imidazole[7] has only a slight solubility in diethyl ether,[5] and thus the deprotonation step

(1) A paper in a series entitled "Heterocyclic Carbanions". For the previous paper, see: ref 18. Also see: ref 16 and 17.
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