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Preparation of N-Alkyl Pyrrolidinones via Photocyclization of γ-Keto-α,β-Unsaturated Amides

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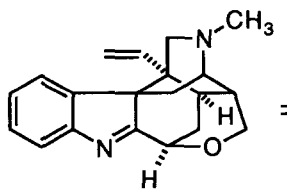
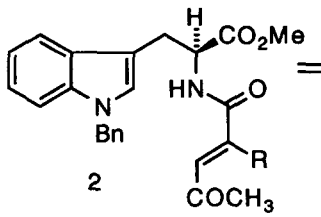
Abstract: Photolysis of γ-keto-α,β-unsaturated amides provides N-alkyl pyrrolidinones in high yield (77-100%). The procedure is applicable to a variety of amides derived from the corresponding γ-keto acid.

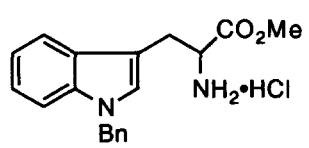
In connection with studies directed toward the synthesis of koumine **1** we explored approaches involving intramolecular [2+2] cycloaddition to the indole ring of **2**.[1-3] The required tryptophan derivative **2** was synthesized from racemic N-benzyl methyl tryptophan **3**.[4] Condensation of **3** with **4a** in the presence of bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl) provided racemic **2** in 49 % yield.[5] Compound **2** was obtained exclusively as the E isomer as evidenced by the proton proton coupling constant for the vinylic system (J = 15.5 Hz). Irradiation of a degassed solution of **2** in methanol with Pyrex filtered light failed to provide any [2+2] adduct.[6] Instead a 5-hydroxy-pyrrolin-2-one derivative was obtained as a mixture of diastereoisomers (ratio 3:1; **5**:**6**, 77 %). The observed coupling constants for the vinyl protons in **5** and **6** were consistent with a Z olefin geometry (J = 6 Hz). Interestingly, the methyl signal in isomer **5** appears at 0.41 δ compared to 1.35 δ in **6**. Examination of related systems reveals that the large difference in chemical shift for the methyl substituents may be due to the ester function in **5** (vide infra). Confirmation of structure **5** was obtained by single crystal X-ray analysis.[7] Structure **6** was assigned by comparison of the ^{1}H, ^{13}C NMR and IR data with **5**.[8,9]



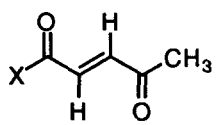
1
koumine



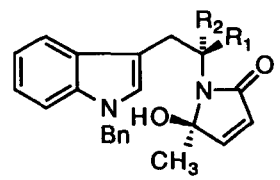
2



3



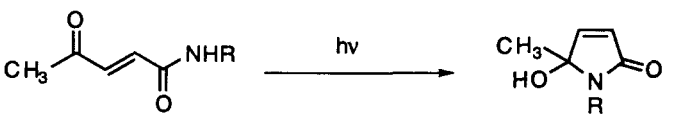
4a, X = OH
b, X = Cl



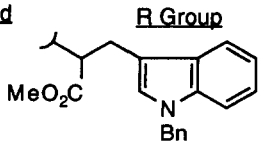
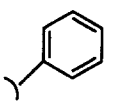
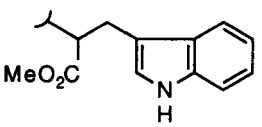
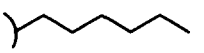
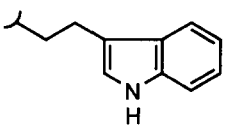
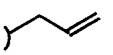
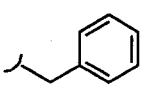
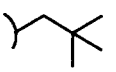
5, R_1 = CO_2Me, R_2 = H
6, R_1 = H, R_2 = CO_2Me

In order to explore the scope of the photolactamization, a series of amide derivatives **7a-f** were prepared in one step from either the γ-keto acid **4a** or the γ-keto acid chloride **4b**. The keto acid **4a** is readily available by condensation of acetone and glyoxilic acid.[10] Preparation of amide photoprecursors generally proceeded in high yield and afforded exclusively the E isomers as evidenced by ^{1}H NMR coupling constants. In every case, irradiation of a degassed solution of the amide in methanol at room temperature with Pyrex filtered light provided a high yield of the corresponding 5-hydroxy-pyrrolin-2-ones **8a-f**.[6]

Table 1



7 (2) 8 (5, 6)

Compound	R Group	% Yield 8 (5,6)	Compound	R Group	% Yield 8 (5,6)
2, 5, 6		77	7d, 8d		98
7a, 8a		80	7e, 8e		86
7b, 8b		95	7f, 8f		78
7c, 8c		100	7g		*
			7h		*

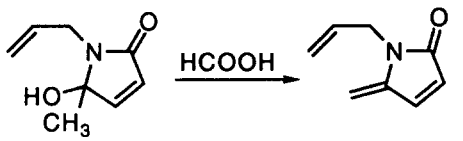
* E to Z photoisomerization

We presume the cyclization reaction proceeds via photochemical E to Z isomerization and subsequent lactam formation from the Z-β-keto amide. Consistent with this mechanism, irradiation of both **7g** and **7h** provided the corresponding Z-isomer. However neither **7g** nor **7h** was converted to cyclized product under the conditions of the photolysis. Presumably steric factors impeded lactam formation with these systems.

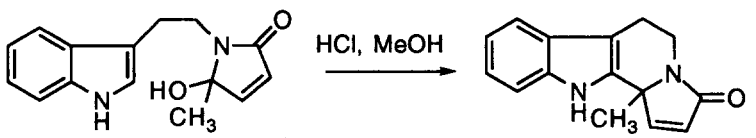
The methyl absorption for **5** occurs at unusually high field (0.41 δ) in the ^{1}H NMR spectrum. Tryptophan derivative **8a**, which lacks the N-benzyl group, provides similar data for the two diastereoisomers with methyl absorptions occurring at 0.46 δ and 1.37 δ. The single methyl absorption for tryptamine derivative

8b however occurs at 1.47 δ. Thus the unusually high chemical shift for the methyl substituents in **5** and one isomer of **8a** can be attributed to shielding by the ester function.

The α-hydroxy pyrrolinones are potentially useful synthetic intermediates. Thus treatment of **8f** with formic acid at 0 °C for 1 h gave the methylene lactam **9**. In similar fashion, treatment of **8b** with dilute HCl in methanol at 60 °C for 30 min provided the β–carboline **10**.[11] Related β–carboline systems have been prepared and tested for activity as hypotensive agents.[12] These have also served as intermediates in synthetic approaches to a number of alkaloid systems including vinblastine,[13] 1-methoxycanthin-6-one,[14] eburnamonine, quebrachamine and vincadine.[15] Finally β–carbolines derived from tryptophan have been isolated from the fruits of the plant Clerodendron trichotomum Thunb.[16]



8f 9



8b 10

In summary, photolysis of readily available γ-keto-α,β-unsaturated amide systems provides efficient access to N-alkyl-5-methyl-5-hydroxy-2- pyrrolidinones.

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6. Photochemical experiments were conducted using a 450-watt Canrad-Hanovia medium pressure quartz mercury-vapor lamp. The lamp was placed in a water-cooled Pyrex immersion well. Reaction solutions were saturated with argon prior to irradiation.
7. Single crystal X-ray analyses were determined by Jon Bordner and Debra Decosta at Pfizer Central Research. A representative crystal was surveyed and a 1 Å data set (maximum sin θ/λ=0.5) was collected on a Nicolet R3m/μ diffractometer.
8. All products gave spectral data (^{1}H NMR, IR, MS) which were consistent with the assigned structures. Satisfactory combustion analyses or high resolution mass spec data were obtained for all new products.
9. Compounds **5** and **6** gave the following physical and spectral data:

   Compound 5: mp 134-135°C; IR (film) 3430, 1735, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.41 (s, 3 H), 2.82 (s, 1 H), 3.62 (dd, 1 H, J = 4.3 and 14.5 Hz), 3.84 (s, 3 H), 3.91 (dd, 1 H, J = 11.6 and 14.5 Hz), 4.27 (dd, 1 H, J = 4.3 and 11.6 Hz), 5.22 (s, 2 H), 5.99 (d, 1H, J = 6.0 Hz), 6.76 (d, 1 H, J = 6.0 Hz), 6.97 (s, 1 H), 7.06-7.63 (m, 9 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.0 (CH_3), 24.1 (CH_2), 49.8 (CH_2), 53.0 (CH), 55.1 (CH_3), 90.0 (C), 109.7 (CH), 111.4 (C), 118.6 (CH), 119.3 (CH), 121.7 (CH), 125.9 (CH), 126.8 (CH, 2 C), 127.3 (CH), 127.6 (C), 128.0 (CH), 128.6 (CH, 2 C), 136.3 (C), 137.5 (C), 151.1 (CH), 170.2 (C=O), 172.4 (C=O); GC/MS (EI, 70 eV) m/e 387 (M^+) 291, 221, 91; UV (MeOH) λ_{max} (ε) 276 (5900), 226 (29000), 207 (27000) nm; Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.21; H, 5.98. Found: C, 71.11; H, 5.97.

   Compound 6: mp: 132-135°C; IR (film) 3400, 2930, 1740, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (s, 3 H), 2.05 (s, 1 H), 3.58 (dd, 1H, J = 4.9 and 14.5 Hz), 3.79 (s, 3 H), 4.35 (dd, 1 H, J = 4.9 and 10.9 Hz), 5.17 (d, 1 H, J = 15.8 Hz), 5.28 (d, 1 H, J = 15.8 Hz), 5.96 (d, 1 H, J = 5.9 Hz), 6.65 (d, 1 H, J = 5.9 Hz), 6.98 (s, 1 H), 7.03-7.63 (m, 10 H); ^{13}C NMR ($CDCl_3$; 50.3 MHz) δ 22.3 (CH_3), 24.4 (CH_2), 49.9 (CH_2), 52.6 (CH), 54.6 (CH_3), 89.6 (C), 110.0 (CH), 111.7 (C), 119.0 (CH), 119.7 (CH), 122.3 (CH), 125.9 (CH), 126.8 (CH, 2 C), 127.3 (C), 127.4 (CH), 127.7 (CH), 128.8 (CH, 2 C), 136.3 (C), 137.4 (C), 150.8 (CH), 168.8 (C=O), 171.1 (C=O); UV (MeOH) λ_{max} (ε) 224 (11000) nm; HRMS calcd for $C_{24}H_{24}N_2O_4$ 404.1736, found 404.1719.
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