2400-3600 (br), 1710, 1220 cm^{-1}; mass spectrum, m/e 132 (M^+); $[\alpha]_D$ +27° (c 1.2, $CHCl_3$) [lit.[1] (for the optical antipode) $[\alpha]_D$ -27.2° (c 2.1, $CHCl_3$)].

Acknowledgment. We gratefully acknowledge support from the NIH and Eli Lilly and Co., as well as a Reilly Fellowship for Li Liu. Some of the 300-MHz spectra were run by Kathleen Peterson on an instrument made available by grants from NIH and the University of Notre Dame. Chemical structures were drawn by using ChemDraw by S. Rubenstein, Harvard University.

The Synthesis of Indolizines: The Reaction of α-Halo Pyridinium Salts with β-Dicarbonyl Species

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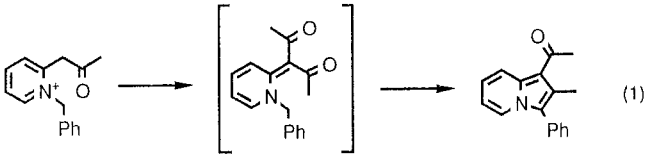
The reaction of β-keto esters and β-diketones with readily accessible 2-halo pyridinium salts in the presence of DBU serves as a rapid and convenient method for the synthesis of substituted indolizines. The use of diethyl malonate as the dicarbonyl component of the reaction enables the preparation of previously undescribed 2-hydroxyindolizines.

In the course of synthetic efforts toward the design of antiinflammatory agents, it became necessary to prepare a series of 1-carboxylic acid ester indolizines for testing. Generally, indolizines have been prepared by the reaction of pyridine salts with carboxylic acid derivatives and cyclization of the resulting quaternary salt with mild base.[1] While these methods are useful for preparing many indolizine derivatives, they are inconvenient for synthesizing indolizines that possess an ester residue at the 1-position, since the pyridine starting material is either expensive or difficult to synthesize.[2] An alternative route that utilizes acetylenes and simpler pyridinium salts is limited by the availability of the acetylenes and the constraints of their pericyclic reaction.[3]

The indolizine synthesis that has been attributed to Scholtz has been shown by Kröhnke and others to utilize the anhydro base 1 as an intermediate (eq 1).[4] Similar



(1)

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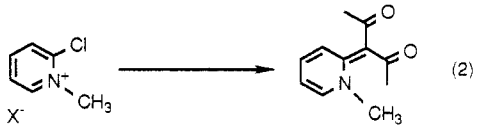
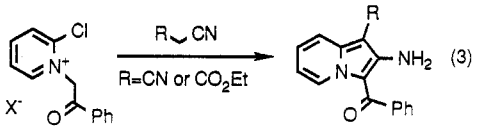
anhydro bases have been synthesized as a result of the reaction of α-halopyridinium salts with β-dicarbonyl compounds in the company of base (eq 2).[5] Although there are many examples of failure to cyclize these compounds



(2)

to indolizines, Kröhnke demonstrated that the reaction between α-chloropyridinium ylides and either malononitrile or ethyl cyanoacetate in the presence of Hunig's base (diisopropylethylamine) yielded 2-aminoindolizines **2** (eq 3).[6] We sought to broaden the scope of this reaction and utilize it in a general synthesis of indolizines.



(3)

2

Results

Halopyridinium salts **3** were prepared from 2-bromo(or 2-chloro)pyridine and an appropriate α-halo ketone or ester by heating them neat at 120 °C for 1 hour and then continuing the reaction at 80 °C for 22 h or diluting the mixture with toluene and heating at reflux for 16 h. The resulting solid was collected by filtration and recrystallized from EtOH.

Following the procedure published by Kröhnke, ethyl acetoacetate and 2-bromo 1-(2-oxopropyl)pyridinium chloride (**3**, $R_3 = CH_3$) were stirred together in *n*-propanol with $(i\text{-Pr})_2NEt$ (Hunig's base) for 24 h, but only a faint trace of nonpolar product was visible by TLC. After examining several parameters it was found that the reaction, when run in CH_3CN with DBU as base, yielded an indolizine in 44% recrystallized yield (Table I, entry 1). Further, these conditions could be applied with equal success to several other β-keto esters and pyridinium salts (Table I, entries 2-11). When the isopropyl β-keto ester **4** (R_1 = OEt, R_2 = *i*-Pr) was employed, we unexpectedly isolated the corresponding carboxylic acid in good yield (entry 5). This hydrolysis was not observed with any of the other keto esters utilized.

We examined the consequences of changing bases and solvents in the reaction; the results are displayed in Table II. Numerous organic (Et_3N, Hunig's base, DaBCO, and pyridine) and inorganic (K_2CO_3, NaOH, and NaOMe)

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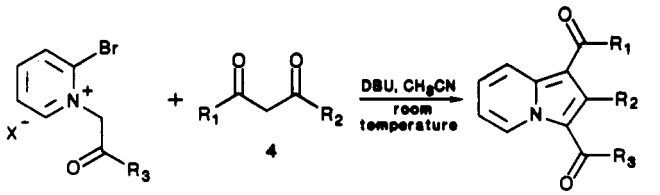
Table I



entry	R_1	R_2	R_3	yield,[a] %	mp, °C
1	OC_2H_5	CH_3	CH_3	44	96–97.5[b]
2	OC_2H_5	C_6H_5	CH_3	63	100–101
3	OC_2H_5	3-$(CH_3O)C_6H_4$	CH_3	44	85–87
4	OC_2H_5	3,4-$(CH_3)_2C_6H_3$	CH_3	46	89–90
5	OC_2H_5	$(CH_3)_2CH$	CH_3	23[c]	158–160
6	OC_2H_5	CH_3	$(CH_3)_2CH$	36	65.5–66.5
7	OC_2H_5	C_6H_5	$(CH_3)_2CH$	33	126–127
8	OC_2H_5	3-$(CH_3O)C_6H_4$	$(CH_3)_2CH$	30	90.5–92
9	OC_2H_5	3,4-$(CH_3)_2C_6H_3$	$(CH_3)_2CH$	30	105–107
10	OC_2H_5	CH_3	C_6H_5	53	93–94
11	OC_2H_5	C_6H_5	C_6H_5	47	116.5–118
12	CH_3	CH_3	OC_2H_5	13	84
13	CH_3	CH_3	$(CH_3)_2CH$	24	115–117
14	$(CH_3)_2CH$	$(CH_3)_2CH$	CH_3	36	94–95
15	$(CH_3)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	35	73.5–75
16	C_6H_5/CH_3	CH_3/C_6H_5	C_6H_5	41[d]	
17		$CH_2C(CH_3)_2CH_2$	OC_2H_5	11[e]	163–164.5[f]
18	OC_2H_5	OH	CH_3	40	136–137
19	OC_2H_5	OH	$(CH_3)_2CH$	41	116.5–117.5
20	OC_2H_5	OH	C_6H_5	49	144–146

[a] Isolated yield. Satisfactory analytical data (±0.4% for C, H, N) were obtained for all new compounds listed in the table. [b] Lit.[8] mp 99–100 °C. [c] Isolated as the carboxylic acid. [d] Reaction run in DMF at 60 °C. Isolated as a mixture of isomers (4.3:1). See Experimental Section for details. [e] Reaction run in THF with triethylamine and DBU as bases. [f] Lit.[9] mp 168–169 °C.

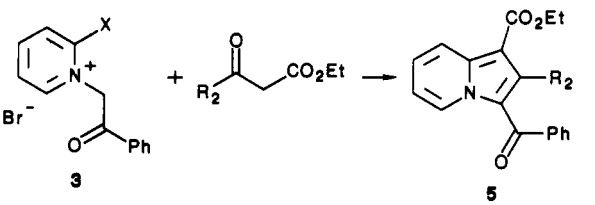
bases were examined and found to be inferior to DBU in effecting the transformation of ethyl acetoacetate and pyridinium salt **3** ($R_3 = CH_3$) into an indolizine. In most cases we failed to observe any reaction; however, with Et_3N and Hunig's base the reaction rate was found to be slower, such that even upon extended stirring the isolated yield was not as great as with DBU. Both polar and nonpolar solvents were found to be less efficient than CH_3CN. However, we found no difference either in rate or in yield by changing the halogen substituent on the pyridine ring from Br to Cl.

The mildness of the conditions and the potential generality of the reaction prompted us to examine the reaction of pyridinium salts with other active methylene species. We first undertook the preparation of 1,3-diacylindolizines.

Acetylacetone and **3** (R = OEt) were stirred together for 30 min at 22 °C to prepare an indolizine (Table I, entry 12) in moderate yield, and other symmetrical β-diketones behaved similarly. Of theoretical interest is the reaction between pyridinium salts and an unsymmetrical diketone, which should lead to a mixture of two products. When the salt **3** (R = Ph) and benzoylacetone were subjected to the standard reaction conditions, we were surprised to discover that the reaction had barely progressed even after 18 h. However, when the reaction was run in DMF at 60 °C for 45 min, we were able to isolate a 4.3:1 mixture of indolizines as identified by NMR (Table I, entry 16). We were unable to separate these two products.

Extension of this reaction to cyclic diketones proved formidable, where even upon warming the conversion was very poor. In this case the solution proved to be a return to a milder base. A mixture of dimedone and pyridinium salt **3** (R = OEt) in THF was treated with Et_3N and DBU for 48 h, from which we were able to isolate the pyridoisoindole **5** (R_1, $R_2 = CH_2C(CH_3)_2CH_2$, R_3 = OEt) in 11% yield. Unfortunately, these conditions were unsuccessful for reactions with other cyclic diketones, such as 1,3-indandione and 1,3-cyclohexanedione.

Table II



R_2	X	base[a]	solv	time, h	yield,[b] %
CH_3	Br	DBU	CH_3CN	0.5	53
CH_3	Br	DBU	DMF	2	37
CH_3	Br	DBU	THF	1	34
CH_3	Br	HB	*n*-PrOH	72	14
CH_3	Br	HB	CH_3CN	72	7
CH_3	Br	TEA	CH_3CN	72	8
CH_3	Br	TEA	THF	72	15
CH_3	Br	NaOMe	MeOH	24	0
Ph	Br	DBU	CH_3CN	0.5	47
Ph	Cl	DBU	CH_3CN	0.5	46
Ph	H	DBU	CH_3CN	72	0

[a] HB = Hunig's base, TEA = triethylamine. [b] Isolated yields.

The synthesis of 2-hydroxyindolizine 1-esters has been accomplished by the reaction of ethyl 2-pyridyl acetate with α-halomalonic esters, but there are no literature references to indolizines which contain the 3-acyl-2-hydroxy substitution pattern.[2b] Stirring diethyl malonate and the pyridinium salt **3** ($R = CH_3$) together in CH_3CN with DBU for 70 h yielded 3-acetyl-2-hydroxyindolizine 1-ester in 40% yield (Table 1, entry 18). Although the reaction is slower than those previously observed, it worked

as efficiently as reactions involving β-keto esters as shown.

The pyridinium ylide is attacked at the α-carbon atom by the dicarbonyl anion, and the resulting elimination of HBr yields an anhydro base, which is similar to that observed by earlier workers. The pyridine ylide now adds to the adjacent carbonyl to give upon elimination of water the indolizine ring system.

In summary, the reaction of 2-halo-1-(β-keto)pyridinium salts and β-keto esters in the presence of DBU serves as a convenient method for synthesizing indolizine 1-esters. The reaction conditions are quite mild, and the starting materials are readily available. These conditions can be employed for the synthesis of 1,3-diacylindolizines by using β-diketones. Reactions with malonic esters result in an expedient synthesis of 2-hydroxyindolizine 1-esters.

Experimental Section

General Methods. Mass spectra, infrared spectra, and combustion analysis were obtained by the physical and analytical chemistry department of The Upjohn Company. ^{1}H NMR spectra were obtained at 90 MHz on a Varian EM 390 in $CDCl_3$ solutions containing tetramethylsilane as an internal standard. Melting points were measured on a Thomas/Hoover apparatus and are uncorrected. Thin-layer chromatography was conducted on Merck glass plates precoated with silica gel F-254. The TLC plates were visualized with UV light or iodine. Column chromatography was conducted at medium pressure utilizing silica gel (E. Merck, 230–400 mesh). All solvents were reagent grade distilled in glass (Burdick and Jackson). The β-dicarbonyl species were either obtained commercially or prepared according to known methods.[7]

General Procedure for the Synthesis of Pyridine Salts: 2-Bromo-1-(3-methyl-2-oxobutyl)pyridinium Bromide (3, R_3 = $CH(CH_3)_2$). 1-Bromo-3-methylbutan-2-one (7.69 g, 46.6 mmol) and 2-bromopyridine (7.27 g 46.6 mmol) were heated on a steam bath for 1 h and then at 80 °C for 22 h. The resulting solid was dissolved in hot EtOH, decolorized with Darco, filtered, and then precipitated with ether: 7.22 g (22.4 mmol, 48%); mp 158–159 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.2 (d, J = 7 Hz, 6 H), 3.0 (m, 1 H), 6.3 (s, 2 H), 8.4 (m, 1 H), 8.8 (d, J = 5 Hz, 2 H), 9.5 (d, J = 6 Hz, 1 H). Anal. Calcd for $C_{10}H_{13}Br_2NO$: C, 37.18; H, 4.06; N, 4.34. Found: C, 36.81; H, 4.00; N, 4.33.

General Procedure for the Synthesis of Indolizines: 3-Acetyl-2-methylindolizine-1-carboxylic Acid Ethyl Ester (5, R_1 = OEt, R_2 = R_3 = Me). The pyridinium salt **3** (R_3 = CH_3) (4.0 g, 16.0 mmol) and ethyl acetoacetate (3.06 ml, 3.12 g, 16.0 mmol) in CH_3CN (25 mL) were treated with DBU (7.2 mL, 48.0 mmol) and stirred at 22 °C for 4 h. The reaction was diluted with ethyl acetate (50 mL), washed with 1 N HCl (3 × 10 mL), H_2O (10 mL), and saturated NaCl (10 mL), dried with $MgSO_4$, and then concentrated to a brown syrup, which solidified upon standing. This was recrystallized from *i*-PrOH (charcoal) to yield pale yellow needles: 1.70 g (7.0 mmol, 44%); mp 96–97.5 °C (lit. mp 99–100 °C);[8] IR 1681, 1629, 1621, 1504, 1397, 1237, 1196, 1095, 789 cm^{-1}; ^{1}H NMR δ 1.44 (t, J = 7 Hz, 3 H), 2.62 (s, 3 H), 2.9 (s, 3 H), 4.4 (q, J = 7 Hz, 2 H), 6.92 (dt, J_t = 7.5 Hz, J_d = 2 Hz, 1 H), 7.3 (dt, J_t = 9 Hz, J_d = 2 Hz, 1 H), 8.3 (dd, J_1 = 9 Hz, J_2 = 1 Hz, 1 H), 10.0 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1 H); mass spectrum, m/e 245 (M^+), 230, 200. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56, H, 6.16; N, 5.71. Found: C, 68.72; H, 6.16; N, 5.72.

1,3-Dibenzoyl-2-methylindolizine (5, R_1 = R_3 = C_6H_5, R_2 = CH_3) and 1-Acetyl-3-benzoyl-2-phenylindolizine (5, R_1 = CH_3, R_2 = R_3 = C_6H_5). The pyridinium salt **3** (R_3 = C_6H_5) (3.51 g, 10 mmol) and benzoyl acetone (1.62 g, 10 mmol) in DMF (10 mL) were treated with DBU (6.0 mL, 40 mmol) and heated to 55–60 °C for 45 min. After cooling to 22 °C, the reaction was diluted with H_2O and extracted with CH_2Cl_2 (3 × 25 mL), and then the organics were washed with H_2O (2 × 25 mL), dried with $MgSO_4$, and stripped. An analytical mixture of the isomers was obtained by chromatography with CH_2Cl_2 and then a second time with EtOAc/hexane (3:2) and recrystallization once from EtOH and then from MeOH/H_2O: 1.39 g (4.10 mmol, 41%); mp, softened at 140 °C and then slowly melted as temperature was increased to 170 °C. ^{1}H NMR analysis of **5** showed this to be a 4.3:1 mixture of isomers. Major isomers **5**, R_1 = R_3 = C_6H_5, R_2 = CH_3: ^{1}H NMR δ 1.9 (s, 3 H), 7.6–7.0 (m, 12 H), 8.65 (d, J = 9 Hz, 1 H), 9.65 (d, J = 7 Hz, 1 H). Minor isomer **5**, R_1 = CH_3, R_2 = R_3 = C_6H_5: ^{1}H NMR δ 2.0 (s, 3 H), 7.6–7.0 (m, 12 H), 8.65 (d, J = 9 Hz, 1 H), 9.55 (d, J = 7 Hz, 1 H); mass spectrum, m/e 339 (M^+). Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.29; H, 5.18; N, 4.07.

7,8,9,10-Tetrahydro-8,8-dimethyl-10-oxopyrido[2,1-*a*]isoindole-6-carboxylic Acid Ethyl Ester (5, R_1, R_2 = $CH_2C(CH_3)_2CH_2$, R_3 = OC_2H_5). The pyridinium salt **3** (R_3 = OC_2H_5) (2.0 g, 6.2 mmol) and dimedone (0.86 g, 6.2 mmol) in THF (6 mL) were treated with Et_3N (3.47 mL, 24.8 mmol) and stirred at 22 °C for 24 h. Then DBU (3.7 mL, 24.8 mmol) was added and the solution stirred another 24 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 × 25 mL), and the extracts were dried with $MgSO_4$ and stripped. Chromatography (hexane/EtOAc, 1:1) and recrystallization from EtOH yielded pure product: 189 mg (0.66 mmol, 11%); mp 163–164.5 °C [lit. mp 168–169 °C (light petroleum ether)];[9] IR 1677, 1651, 1512, 1500, 1415, 1406, 1202, 767 cm^{-1}; ^{1}H NMR δ 1.0 (s, 6 H), 1.45 (t, J = 7 Hz, 3 H), 2.45 (s, 2 H), 3.10 (s, 2 H), 4.4 (q, J = 7 Hz, 2 H), 7.0 (t, J = 7 Hz, 1 H), 7.35 (t, J = 9 Hz, 1 H), 8.4 (d, J = 9 Hz, 1 H), 9.6 (d, J = 7 Hz, 1 H); mass spectrum; m/e 285 (M^+), 157. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.17; N, 4.91. Found: C, 71.39; H, 6.73; N, 4.82.

General Procedure for the Synthesis of 2-Hydroxyindolizines: 3-Benzoyl-2-hydroxyindolizine-1-carboxylic Acid Ethyl Ester (5, R_1 = OC_2H_5, R_2 = OH, R_3 = C_6H_5). The pyridinium salt **3** (R_3 = C_6H_5) (5.26 g, 15.0 mmol) and diethyl malonate (2.3 mL, 15.0 mmol) in CH_3CN (15 mL) were treated with DBU (9.0 mL, 60 mmol) and then stirred at 22 °C for 72 h. The reaction was quenched with excess 1 N HCl, and then the resulting dark precipitate was filtered and washed with H_2O. Recrystallization from CH_3CN afforded the desired product as pale orange crystals: 2.26 g (7.3 mmol, 49%); mp 144–146 °C; IR 3247 (brd), 1657, 1594, 1550, 1487, 1473, 1444, 1225, 634 cm^{-1}; ^{1}H NMR δ 1.45 (t, J = 7 Hz, 3 H), 4.40 (q, J = 7 Hz, 2 H), 6.95 (dt, J_t = 7 Hz, J_d = 1 Hz, 1 H), 7.41 (m, 4 H), 7.85 (m, 2 H), 7.95 (d, J = 8 Hz, 1 H), 9.90 (d, J = 7 Hz, 1 H), 10.1 (s, 1 H, OH); mass spectrum, m/e 309 (M^+), 263, 262, 130. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.67; H, 5.13; N, 4.52.

Acknowledgment. We are grateful to Dr. H. W. Smith for helpful discussions. The support of the Physical and Analytical Chemistry Unit of The Upjohn Company is also appreciated.

Supplementary Material Available: Full characterization data for all new compounds (6 pages). Ordering information is given on any current masthead page.

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