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Contribution to the Chemistry of Indole. About the 5-(1-Indolyl)-2-pentanone System

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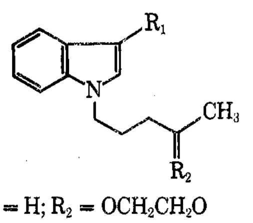
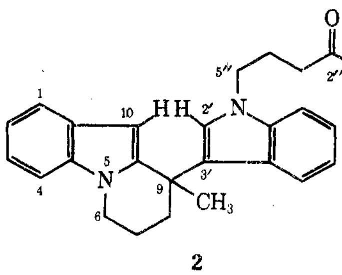
Alkylation of indole with 5-chloro-2-pentanone ethylene ketal gave **1a**. Attempts to hydrolyze the ketal gave 2 instead. The 3-substituted indoles **1b** and **1d** were hydrolyzed to the corresponding ketones **1c** and **1e**. Skatole was alkylated with the same alkylating agent to give **1f**. Hydrolysis gave the pyrido[1,2-*a*]indole 3.

The alkylation of indole[1] on nitrogen is a well-documented reaction in organic chemistry. As a model for further studies we were interested in the preparation of 5-(1-indolyl)-2-pentanone. It was our intention to obtain this compound from the corresponding ethylene ketal via mild hydrolysis in acidic medium. For this purpose indole was treated with sodium hydride in absolute DMF followed by the addition of 5-chloro-2-pentanone ethylene ketal. The product of this alkylation, 5-(1-indolyl)-2-pentanone ethylene ketal (**1a**), was obtained in 98% yield and gave ir, NMR, and mass spectral data in agreement with the expected structure **1a**.

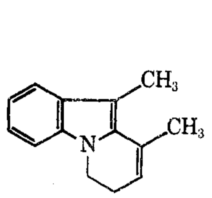
Chart I



1a, $R_1 = H$; $R_2 = OCH_2CH_2O$
b, $R_1 = COOMe$; $R_2 = OCH_2CH_2O$
c, $R_1 = COOMe$; $R_2 = O$
d, $R_1 = CH_2COOMe$; $R_2 = OCH_2CH_2O$
e, $R_1 = CH_2COOMe$; $R_2 = O$
f, $R_1 = CH_3$; $R_2 = OCH_2CH_2O$



2



3

Attempts to remove the protecting group in **1a** via hydrolysis in aqueous acetic acid did not yield the expected ketone. Instead compound **2** of the molecular composition $C_{26}H_{28}N_2O$ (*m/e* 384, M^+) was isolated in 63% yield. This formally represents a condensation between 2 mol of the product of the deketalization less 1 mol of water. One oxygen atom was retained as a saturated keto group as indicated by the presence of an ir band at 1713 cm^{-1} in the spectrum of **2** excluding the presence of an α,β-unsaturated ketone formed via an aldol condensation.

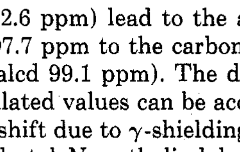
The ^1H NMR spectrum of **2** indicated ten aromatic protons and no vinylic protons, ruling out a double bond in the side chain and pointing to the structure **2**. This product was assumed to arise by intramolecular condensation of the carbonyl group liberated in the hydrolysis of **1a** at the indole 2 position followed by alkylation at C-3 of a second indole unit. Although electrophilic substitution should occur more readily in the β position of indole[1] and particularly of N-alkylated indoles, the ^1H NMR spectrum of **2** did not allow a definitive assignment of the position of the attachment of the second indole nucleus. Thus it was decided to study the ^{13}C NMR of **2** in the hope of establishing the substitution patterns of the two indole nuclei.

Discussion of the ^{13}C NMR Spectrum of 2. The fully proton decoupled spectrum of **2** gave a total of 26 peaks accounting for all the 26 carbon atoms of the product, indicating at the same time that the product on hand consisted of a single isomer.

Shift theory[2] and models from the literature[2a] (the compounds **1a**, **1f**, and **3**, see below, serving as additional models) were used for the calculations. Peaks at 126.7 and 97.7 ppm (see Experimental Section) were assigned to the carbon atoms at position 2′ and 10, respectively, based upon the following arguments. The chemical shift for C_2 of an unsubstituted indole[2a] is documented to occur at 125.2 ppm. Methyl substituents in positions 1 and 3 are known to shift the absorption by +4.1 and −2.5 ppm. This is in good agreement with the observed value of 126.7 ppm (calcd

126.8 ppm) which was assigned to the **CH** at position 2′ (see Chart I for numbering) of product **2**. Similar considerations regarding the chemical shift of the C_3 of the unsubstituted indole (102.6 ppm) lead to the assignment of the observed peak at 97.7 ppm to the carbon atom in position 10 of product **2** (calcd 99.1 ppm). The difference between observed and calculated values can be accounted for by assuming an upfield shift due to γ-shielding effects.[2b] Therefore 2- and 3-*tert*-butyl-*N*-methylindoles were selected as new models based upon the known chemical shifts of *tert*-butylbenzene relative to benzene and assuming that the observed difference of 20.5 ppm is also applicable in the case of indoles.

This approximation was put to test in the case of 2-*tert*-butylindole.[3] The following values were observed.



The chemical shifts for the phenyl ring were assigned in the same relative order as those documented for indole itself. More significantly, the measured values for the C_2 and C_3 carbons of the substituted indole show similar downfield and upfield shifts relative to indole as the corresponding phenyl carbons in *tert*-butylbenzene relative to benzene.

For 1-methyl-3-*tert*-butylindole the chemical shift for the C_2 was calculated to be 126.0 ppm while for the C_3 of 1-methyl-2-*tert*-butylindole a calculated value of 98.0 ppm was obtained. This is in good agreement with the values of 126.7 and 97.7 ppm as observed for compound **2**. (See above.)

For the C_3 of 1-methyl-3-*tert*-butylindole a value of 121.8 ppm was calculated. This is in agreement with the observed peak at 122.6 ppm of **2**, which is therefore assigned to the carbon atom in position 3′. In analogy the value for the C_2 of 1-methyl-2-*tert*-butylindole was estimated to be 149.8 ppm. The observed value of 145.0 ppm for **2** was assigned to the carbon atom 9a.

Single-frequency off-resonance decoupling (sford) experiments were used to assign the number of protons attached to each carbon atom. These experiments revealed the presence of two quartets allowing peaks 23 and 24 to be assigned to the two methyl groups and a singlet at 36.7 ppm to the fully substituted carbon atom 9. In summary these studies seem to establish the presence of *one* proton in an α position and *one* proton in a β position of two different indole nuclei. If *two* protons were present each in a β position as might be concluded from the ^{1}H NMR spectrum of **2**, this should give rise to two peaks near 100 ppm (both doublets in the sford experiment) in the ^{13}C NMR spectrum of **2** in place of the peaks observed at 97.7 and 126.7 ppm and to two peaks near 145 ppm (both singlets in the sford experiment) in place of the peaks observed at 122.6 and 145.0 ppm, respectively.

The two singlets at δ 6.32 and 6.38 indicate that the C-2′ proton is shielded (approximately 0.6 ppm) by the double bond of the other indole while the C-3 proton shows relatively little shielding effect. (The shifts[4] for the α and β protons of 3-*tert*-butylindole and 2-*tert*-butylindole are δ 6.83 and 6.13, respectively.)

Alkylation of 3-Substituted Indoles. Methyl indole-3-carboxylate[5] was alkylated with 5-chloro-2-pentanone ethylene ketal to the novel 5-(3-carbomethoxy-1-indolyl)-2-pentanone ethylene ketal (**1b**) and hydrolyzed under conditions similar to those employed above to yield 1-(3-carbomethoxyindolyl)-4-pentanone (**1c**) in good yield. That the difference in stability between compound **1c** and the product of deketalization of **1a** cannot be sought in the difference of reactivity of the corresponding indole double bond alone (in the presence of the carbomethoxy group the double bond may be regarded as part of the vinylogous amide or enamino ketone[6] with reduced reactivity rather than an enamine as in the case without the carbomethoxy group) became obvious when 1-(4-dioxolanyl)pentylindole-3-acetic acid methyl ester (**1d**) was treated with 80% aqueous acetic acid. The keto ester **1e** was isolated in 95% yield.

Contrary to the observations made with indoleacetic acid, skatole formed a dihydropyrido[1,2-*a*]indole **3**. Thus when 3-methylindole was alkylated under conditions similar to those described above the expected product **1f** was isolated in good yield. Under conditions favorable for the hydrolysis of the ketal (80% aqueous acetic acid at 80°) cyclization between the carbonyl carbon and position 2 of the indole with subsequent loss of water was observed. Pure compound **3** was isolated in 58% yield. The structural assignment was based on analytical and spectral data.

In the ^{1}H NMR spectrum of **1f** long-range coupling between the indole methyl group at δ 2.30 and the proton in position 2 of the indole was observed. In the spectrum of compound **3** the corresponding methyl group appeared as a sharp singlet at δ 2.42 indicating the replacement of the proton at position 2 with a carbon. The methyl group in position 9 gave rise to a broad signal at δ 2.14 which could be resolved to a quartet with the aid of the 100-MHz instrument. Decoupling experiments verified the presence of long-range coupling in **3** between the methyl group in position 9 and the vinyl proton. It also became clear that additional long-range coupling between the methyl group in position 9 and the protons in position 7 is present. Irradiation at δ 5.53 (vinyl proton) caused the multiplet at δ 2.14 to collapse to a triplet (J = 1.5 Hz).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. NMR spectra were measured on either a Varian A-60 or T-60 spectrometer and are recorded in δ values (parts per million) from Me_4Si as internal standard. The ^{13}C NMR spectra were measured on a Varian XL-100 spectrometer and are recorded in parts per million values from Me_4Si as internal standard. Ir spectra were taken on a Perkin-Elmer Model 257 or 457. Gas–liquid chromatography was carried out on a Hewlett-Packard 5750 chromatograph. Mass spectra were taken on a LKB 9000 mass spectrometer.

5-(1-Indolyl)-2-pentanone Ethylene Ketal (1a). To a mixture of 5.30 g (0.220 mol) of NaH in 50 ml of absolute DMF there was added a solution of 23.4 g (0.20 mol) of indole in 50 ml of DMF. After 2 h at room temperature 32.8 g (0.20 mol) of commercial 5-chloro-2-pentanone ethylene ketal was added slowly with an exothermic reaction taking place (~50°C). The mixture was stirred overnight at room temperature, the solvent removed in vacuo, and the residue extracted with ether and worked up in the usual way to yield 48.0 g (98%) of liquid **1a**. A sample was distilled in a Kugelrohr: bp 160° (0.2 mm); GLC 99% pure; m/e 245 (M^+); NMR ($CDCl_3$) δ 1.25 (s, 3, CH_3), 1.4–2.3 (m, 4, 2 CH_2), 3.82 (s, 4, OCH_2CH_2O), 4.03 (t, 2, J = 7.0 Hz, NCH_2), 6.43 (d, 1, J = 3 Hz, C_3H), 6.9–7.7 (m, 5, aromatic H); ir (film) 1620 cm^{-1} (weak). For ^{13}C NMR see Table I.

5-(3-Carbomethoxy-1-indolyl)-2-pentanone Ethylene Ketal (1b). From 17.5 g (0.1 mol) of methyl indole-3-carboxylate[5] and 16.5 g (0.1 mol) of 5-chloropentanone ethylene ketal in absolute DMF in the presence of 2.4 g (0.1 mol) of sodium hydride following the procedures described above there was obtained 25.0 g (83%) of **1b**: bp 160–180° (0.8 mm) (Kugelrohr); GLC one component; m/e 303 (M^+); NMR ($CDCl_3$) δ 1.27 (s, 3, CCH_3), 1.3–2.4 (m, 4, 2 CH_2), 3.9 (s) and 3.9–4.4 (m, 9, NCH_2 + OCH_3 + OCH_2CH_2O), 7.1–8.3 (m, 5, aromatic H); ir (film) 1698 cm^{-1} (ester). Anal. Calcd for $C_{17}H_{21}NO_4$ (303.4): C, 67.3; H, 7.0; N, 4.6. Found: C, 67.0; H, 6.9; N, 4.7.

5-(3-Carbomethoxy-1-indolyl)-2-pentanone (1c). Following the same procedures as described for the preparation of **2**, ketal **1b**

Table I

Peaks obsd, ppm	Rel intensity	Assignment
136.4	13	7a
129.0	36	3a
128.0	132	2
121.7 }	114	{ 5
121.2 }	147	{ 4
119.5 }	148	{ 6
109.8	52	2′
109.7	149	7
101.3	108	3
64.6	214	OCH_2
46.2	164	5′
36.2	209	3′
24.8	215	4′
23.9	101	1′

Table II

Peaks obsd, ppm	Rel intensity	Assignment
136.8	9	7a
129.2	25	3a
125.7	93	2
121.6 }	97	{ 5
119.3 }	76	{ 4
118.8 }	97	{ 6
110.3 }	22	{ 3
109.9 }	50	{ 2′
109.5	110	7
64.7	214	OCH_2
46.0	130	5′
36.4	121	3′
25.0	125	4′
23.9	80	1′
9.6	46	C_3CH_3

gave **1c** in yield of 93%: bp 180–200° (0.5 mm) (Kugelrohr); GLC one component; *m/e* 259 (M^+); NMR ($CDCl_3$) δ 2.05 (s) and 1.7–2.5 (m, 7, CCH_3 + $CH_2CH_2C{=}O$), 3.90 (s, 3, OCH_3), 4.08 (t, 2, J = 6.5 Hz, NCH_2), 7.0–8.3 (m, 5, aromatic H); ir (film) 1715 (ketone), 1698 cm^{-1} (ester). Anal. Calcd for $C_{15}H_{17}NO_3$ (259.3): C, 69.5; H, 6.6; N, 5.4. Found: C, 69.4; H, 6.7; N, 5.4.

1-[3-(2-Methyl-2-dioxolanyl)propyl]indole-3-acetic Acid Methyl Ester (1d). Starting with 18.9 g (0.1 mol) of 3-indoleacetic acid methyl ester[7] and 16.5 g (0.1 mol) of 5-chloropentanone ethylene ketal in DMF in the presence of 2.9 g (0.1 mol) of NaH following the procedures described for the preparation of **1a** there was obtained after distillation 25.0 g (79%) of **1d**: bp 200° (0.7 mm) (Kugelrohr); GLC one component; *m/e* 317 (M^+); NMR ($CDCl_3$) δ 1.26 (s, 3, CCH_3), 1.3–2.1 (m, 4, 2 CH_2), 3.67 (s, 3, OCH_3), 3.75 (s, 2, CH_2COOMe), 3.85 (s, 4, OCH_2CH_2O), 4.03 (t, 2, J = 6.5 Hz, NCH_2), 6.9–7.7 (m, 5, aromatic H); ir (film) 1740 cm^{-1} (ester). Anal. Calcd for $C_{18}H_{23}NO_4$ (317.4): C, 68.1; H, 7.3; N, 4.4. Found: C, 68.4; H, 7.3; N, 4.7.

1-(4-Oxo-1-pentyl)indole-3-acetic Acid Methyl Ester (1e). Compound **1d** was hydrolyzed under the same conditions described for the preparation of **1c** to give **1e** in 95% yield: bp 200° (0.8 mm) (Kugelrohr); GLC one component; *m/e* 273 (M^+); NMR ($CDCl_3$) δ 2.03 (s, 3, $CH_3C{=}O$), 1.6–2.5 (m, 4, 2 CH_2), 3.68 (s, 3, OCH_3), 3.75 (s, 2, CH_2COOMe), 4.08 (t, 2, J = 6.5 Hz, NCH_2), 6.9–7.7 (m, 5, aromatic H); ir (film) 1745 (ester), 1720 cm^{-1} ($C{=}O$). Anal. Calcd for $C_{16}H_{19}NO_3$ (273.32): C, 70.3; H, 7.0, N, 5.1. Found: C, 70.4; H, 6.9; N, 5.3.

5-(3-Methyl-1-indolyl)-2-pentanone Ethylene Ketal (1f). Starting with 20.0 g (0.15 mol) of 3-methylindole and 26.3 g (0.16 mol) of 5-chloropentanone ethylene ketal in 200 ml of absolute DMF in the presence of 3.85 g (0.16 mol) of NaH following the procedures described for the preparation of **1a** there was obtained after distillation 31.1 g (80%) of **1f**: bp 140–160° (0.05 mm) (Kugelrohr); *m/e* 259 (M^+); NMR ($CDCl_3$) δ 1.27 (s, 3, $OCCH_3$), 1.4–2.2 (m, 4, 2 CH_2), 2.30 (d, 3, J = 1.0 Hz, indole CH_3), 3.85 (s, 4, OCH_2CH_2O), 4.00 (t, 2, J = 6.5 Hz, NCH_2), 6.80 (d, 1, J = 1.0 Hz, indole C_2 H), 6.9–7.6 (m, 4, aromatic); ir (CH_2Cl_2) 1620 cm^{-1} (weak). Anal. Calcd for $C_{16}H_{21}NO_2$ (259.3): C, 74.1; H, 8.2; N, 5.4. Found: C, 74.1; H, 8.4; N, 5.4. For ^{13}C NMR see Table II.

Table III

Peaks obsd, ppm	Rel intensity	Sford	Assignment
207	31	s	2″
145.0	44	s	9a
137.1	24	s	
135.9	19	s	
128.0	33	s	
126.7	181	d	2′
125.3	29	s	
122.6	34	s	3′
121.0	158		
120.7	172		
120.2	197		
119.9	166		
119.4	199		
118.4	170		
109.5	190	d	
108.9	129	d	
97.7	203	d	10
44.5 }	157	t	{ 5″
42.0 }	190	t	{ 6
39.6	205	t	3″
36.7	74	s	9
34.8	191	t	8
29.4 }	72	q	{ 11
29.0 }	148	q	{ 1″
23.7	149	t	7
19.6	197	t	4″

Table IV

Peaks obsd, ppm	Rel intensity	Assignment
136.4	7	4a
132.6	8	9a
129.9	14	9
129.3	18	10a
122.4	109	8
121.2 }	115	{ 2
119.1 }	159	{ 3
119.0 }	152	{ 1
108.6	120	4
107.7	10	10
39.7	217	6
24.3	199	7
21.1	159	C_9CH_3
10.1	53	$C_{10}CH_3$

5-[3-(6,7,8,9-Tetrahydro-9-methylpyrido[1,2-*a*]indol-9-yl)]-1-indolyl-2-pentanone (2). A solution of 20.0 g (0.082 mol) of ketal **1a** in 65 ml of acetic acid and 15 ml of water was heated to reflux for 2 h. A liquid which separated from the cold solution crystallized after the addition of ether. There was obtained 9.8 g (63%) of **2**, mp 123–124°. The product was recrystallized from CH_2Cl_2–ether: mp 126–127°; *m/e* 384 (M^+); NMR ($CDCl_3$) δ 1.93 and 2.01 (2 s), 1.7–2.8 (m, total 14 H, 2 CH_3 + 4 CH_2), 3.7–4.4 (m, 4, 2 NCH_2), 6.32 (s, 1), 6.38 (s, 1), 6.9–7.7 (m, 8, 2 C_6H_4); ir (CH_2Cl_2) 1713 cm^{-1} ($C{=}O$). Anal. Calcd for $C_{26}H_{28}N_2O$ (384.5): C, 81.2; H, 7.3; N, 7.3. Found: C, 81.0; H, 7.6; N, 7.3. For ^{13}C NMR see Table III.

6,7-Dihydro-9,10-dimethylpyrido[1,2-*a*]indole (3). A solution of 5.2 g (0.02 mol) of **1f** in 20 ml of 80% aqueous acetic acid was warmed to 80°C for 1 h. Addition of water gave a solid which was filtered off and recrystallized from ethanol–water to give 2.3 g (58%) of pure **3**: mp 60–61°; *m/e* 197 (M^+); NMR ($CDCl_3$) δ 2.14 (q, 3, J = 1.5 Hz, C_9 CH_3), 2.42 (s, 3, C_{10} CH_3), 2.0–2.7 (m, 2, NCH_2CH_2), 3.82 (t, 2, J = 6.5 Hz, NCH_2), 5.53 (m, 1, vinyl H), 6.9–7.6 (m, 4, C_6H_4); ir (CH_2Cl_2) 1610 cm^{-1} (weak). Anal. Calcd for $C_{14}H_{15}N$ (197.3): C, 85.2, H, 7.7; N, 7.1. Found: C, 85.0; H, 7.7; N, 7.0. For ^{13}C NMR see Table IV.

Acknowledgment. The author would like to thank Dr. W. J. Houlihan for his interest and support, Dr. Renate Coombs for supplying the mass spectral data, and Dr. S. Barcza and his staff for recording the spectra and for helpful discussion in evaluating the data.

Registry No.—**1a**, 57512-87-5; **1b**, 57512-88-6; **1c**, 57512-89-7; **1d**, 57512-90-0; **1e**, 57512-91-1; **1f**, 57512-92-2; **2**, 57512-93-3; **3**, 57512-94-4; indole, 120-72-9; 5-chloro-2-pentanone ethylene ketal, 5978-08-5; methyl indole-3-carboxylate, 942-24-5; 3-indoleacetic acid methyl ester, 1912-33-0; 3-methylindole, 83-34-1.

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Preparation and Reactions of β-Chloro-α,β-Unsaturated Ketones[1]

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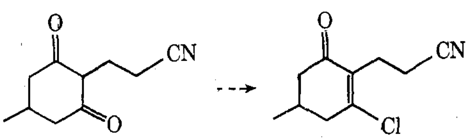
β-Chloro-α,β-unsaturated ketones are conveniently prepared by treating β-diketones or β-keto aldehydes with oxalyl chloride in an inert solvent such as benzene or chloroform. Symmetrical cyclic β-diketones and β-keto aldehydes afford a single β-chloroenone in good yield. Unsymmetrical cyclic β-diketones yield a mixture of isomeric β-chloroenones. Acyclic β-diketones yield a mixture of *E* and *Z* β-chloroenones. β-Keto esters do not afford β-chloro-α,β-unsaturated esters by this procedure; the only product produced is the enol chlorooxalate. The product β-chloroenones are smoothly dehalogenated by silver–zinc couple in methanol and readily couple with lithium dialkylcuprates. In contrast to β-alkoxy-α,β-unsaturated ketones, β-chloroenones do not undergo regiospecific base-catalyzed alkylation.

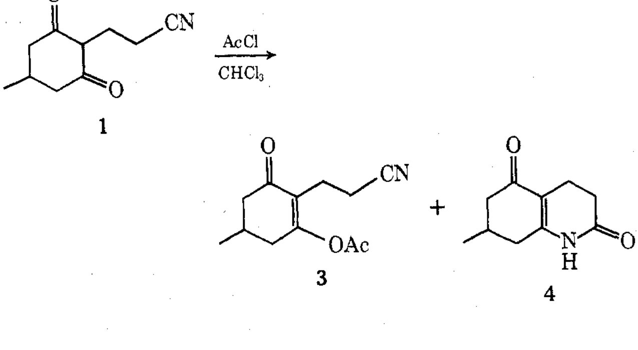
Preparation of β-Chloroenones. β-Chloro-α,β-unsaturated ketones have been prepared from β-diketones by reaction with phosphorus trichloride,[2-4] phosgene,[5] acetyl chloride,[6] thionyl chloride,[3] and phosphorus oxychloride.[2,7] Reported yields for this conversion are generally in the range 50–70%.[8]

In connection with a projected synthesis, we had occasion to prepare β-chloroenone 2 from cyanodione 1. How-



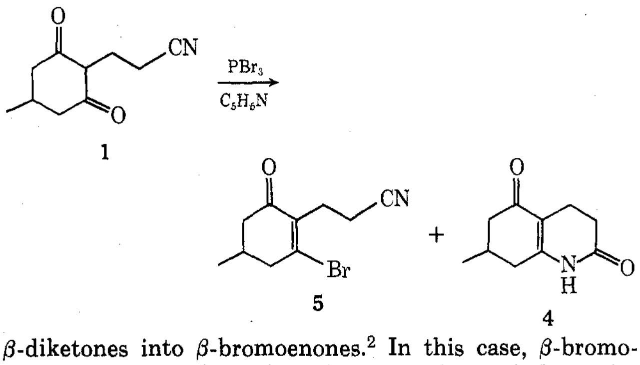
1 2

ever, the presence of the nitrile function caused serious complications when we attempted to use standard methodology for this conversion. For example, treatment of 1 with acetyl chloride in chloroform[6] gives no β-chloroenone 2. The only products obtained are acetate 3 (49–61%) and lactam 4 (29–39%).[9] Phosphorus trichloride does afford β-chloroenone 2 in 40–50% yield, but it is contaminated by substantial amounts of lactam 4.



1 3 4

Similar difficulties were encountered when we attempted to transform dione 1 into β-bromoenone 5 using phosphorus tribromide in pyridine, a reagent often used to convert

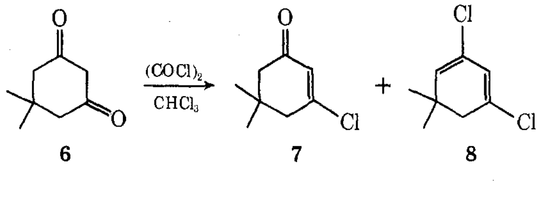


1 5 4

β-diketones into β-bromoenones.[2] In this case, β-bromoenone may be isolated in only 20% yield, and the major product appears to be lactam 4 (isolated in 20% yield).

These difficulties led us to explore alternate methods for accomplishing the conversion of β-diketones to β-haloenones. In this paper, we report a successful solution to this problem, using a method which appears to be generally applicable and which, in many cases, gives higher yields than do the standard methods.[2-6]

Dimedone (6) reacts with oxalyl chloride (2.5 equiv) in refluxing chloroform to afford β-chloroenone 7 in 91% yield. The only side-product is a small amount of dichlorodiene 8 (ca. 2%), and the amount of this material may be suppressed by minimizing the reaction time. Application of



6 7 8