Heterocyclization reactions of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones with α-oxoketeneaminals

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During thermolysis 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones react with α-mono- and α,α-dioxoketene aminals to yield 3-acetyl-6-aryl-2-benzoylamino-4-pyridones or 6-aryl-2-methylene-4-pyrimidones, respectively. A scheme of the formation of pyrido[2,3-*d*]pyrimidines from dioxinones and 1-amino-1-benzoylamino-1-bytene-3-one has been suggested.

Key words: dioxinones, aroylketenes, ketene aminals, pyridones, pyrimidinones, pyrido-[2,3-*d*]pyrimidine-5-one.

It is known that when they are thermolyzed 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones (**1**) yield the corresponding aroylketenes,[1] which react with dinucleophilic reagents[2,3] to give the benzodiazepine,[1] 1,3-oxazine,[2] and 1,3-oxadiazole[3] derivatives.

To find new routes of using dioxinones **1** in the construction of heterocyclic systems, we have investigated their interaction with α-mono- and α,α-dioxoketene aminals, which can be easily prepared by the previously reported methods based on β-dicarbonyl compounds and cyanamides.[4–6]

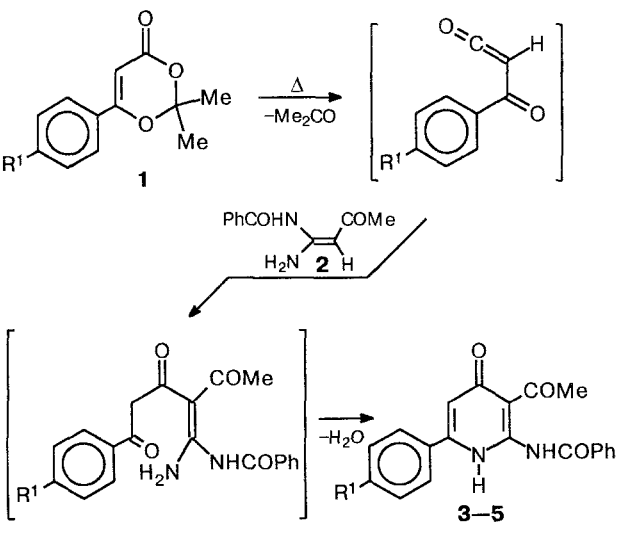
Earlier monoacylketene aminals, which contain an unsubstituted NH_2 group and can react as C,N-dinucleophiles, have been used for the synthesis of pyrimidine-4-thiones,[7] condensed 1,4-diazines and 1,2,4-triazines,[8] as well as functionalized 1,2,3-triazoles.[9]

Recently, a method of synthesizing 3-acetyl-2-amino-4-pyridone derivatives from boron chelates of diacetylketene aminals and amide acetals has been reported.[10] However, this method is only convenient in the case of pyridones containing no aryl substituents at the 6 position.

We have found that compounds **1** react with 1-amino-1-benzoylamino-1-bytene-3-one (**2**) to yield 3-acetyl-6-aryl-2-benzoylamino-4-pyridones **3—5** (Table 1, see preliminary report, Ref. 11). Thus, ketene aminal **2** also behaves as a C,N-dinucleophile in the reaction with aroylketenes generated from dioxinones **1** (Scheme 1).

Crystalline compounds **3—5** are readily soluble in $CHCl_3$ and EtOH, and poorly soluble in benzene. The spectral data are in agreement with their structure. The mass spectra of pyridinones contain intense molecular ions. The ^1H NMR spectra of compounds **3—5** in $CDCl_3$ are characterized by the presence of two signals for the NH protons, a signal for the proton bonded with the C(5) of the nitrogen-containing ring, and a singlet for the CH_3 protons of the acyl group. Comparing the ^{13}C NMR spectra of compound **3** with that of 3-acetyl-2-benzoylamino-6-methyl-4-pyridone synthesized by the method described in Ref. 10 also confirms the structure of the heterocycles obtained from **1** and **2**.

Scheme 1



R^1 = H (**3**), Me (**4**), Cl (**5**)

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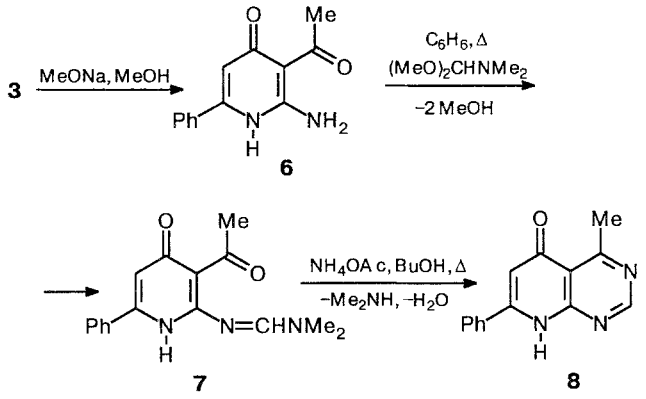
Pyridones **3—5** containing the benzoylamino group are easily debenzoylated to form compounds with an unsubstituted NH_2 group in the *ortho*-position to the acetyl group. The latter can be used for the annelation of a second nitrogen-containing ring to the pyridine ring. For example, pyridone **6** obtained from compound **3**, when boiled with dimethylformamide dimethylacetal in benzene, forms amidine **7**, which undergoes cyclization to the corresponding pyrido[2,3-*d*]pyrimidine-5-one (**8**) when treated with ammonium acetate in boiling butanol (Scheme 2).

Scheme 2



The spectral data (IR, NMR, and spectrometry) confirm the structure of bicyclic compound **8** (see Experimental).

The α,α-dioxiketene aminals (**9**, **10**) unsubstituted at the nitrogen atom behave as N,N-dinucleophiles in the reactions with dioxinones **1**, which lead to the formation of 4-pyrimidinone derivatives **11—16** (see preliminary report 12, Scheme 3). The reaction occurs when equimolar amounts of the reagents are heated without a solvent at 150—155 °C for 10—15 minutes.

The formation of compounds **11—16** is probably caused by the introduction of one of the aminogroups of ketene aminal **9** or **10** to the C=C bond, which occurs during the reaction of aroylketene, and by the sequential cyclization of the α-aroylacetamide derivatives.

The spectral characteristics of 4-pyrimidinones **11—16** are given in Table 2. Their IR spectra (a suspension in vaseline oil) exhibit νCO bands at 1710—1690 cm^{-1} and 1625—1600 cm^{-1} (**11—13**) or 1660—1630 cm^{-1} (**14—16**) together with the νNH bands at 3100—2900 cm^{-1}.

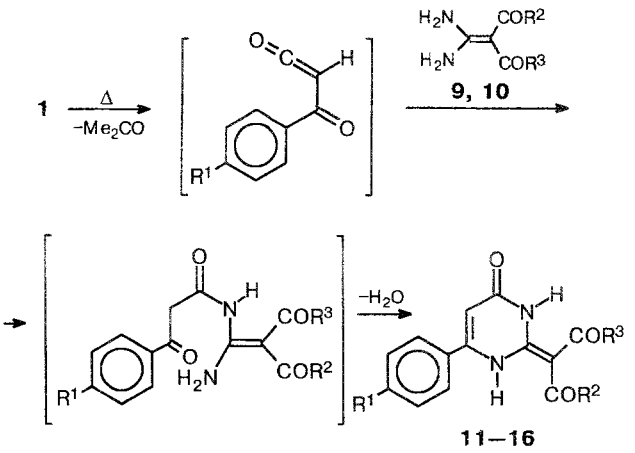
The ^1H NMR spectra of compounds **11—13** in $CDCl_3$ are characterized by the presence of singlets for the NH protons at 14.90—15.07 and 13.10—13.16 ppm and a signal for the proton bonded to the C(5) of the pyrimidinone system at 6.38—6.40 ppm.

In the ^1H NMR spectra of 4-pyrimidinones **11—16** in $CDCl_3$, four singlets for the NH group protons are observed at 12.52—16.48 ppm, which supports the conclusion about the *E,Z*-isomerism of this compounds. However, the spectrum recorded in DMSO-d_6 shows only one set of signals, which attests that the barrier to rotation around the C=C bond is not high.

Table 1. Yields and characteristics of 3-acetyl-6-aryl-2-benzoylamino-4-pyridones (**3—5**), 6-aryl-2-dibenzoylmethylene-4-pyrimidinones (**11—13**), and 6-aryl-2-ethoxycarbonyl(acetyl)methylene-4-pyrimidinones (**14—16**)

Compound	Yield (%)	M.p./°C	Found / Calculated (%) C	H	N	Molecular formula
3	52	246—247	75.96 / 76.13	4.38 / 4.60	6.82 / 7.10	$C_{25}H_{18}N_2O_3$
4	51	234—235	76.19 / 76.46	4.78 / 4.94	6.71 / 6.86	$C_{26}H_{20}N_2O_3$
5	84	230—231	69.84 / 70.14	3.75 / 3.99	6.33 / 6.53	$C_{25}H_{17}ClN_2O_3$
11	75	155—156	63.75 / 63.99	5.09 / 5.37	9.12 / 9.33	$C_{16}H_{16}N_2O_4$
12	79	171—172	64.73 / 64.96	5.58 / 5.77	8.67 / 8.91	$C_{17}H_{18}N_2O_4$
13	86	201—202	57.23 / 57.41	4.26 / 4.52	8.13 / 8.37	$C_{16}H_{15}ClN_2O_4$
14	93	262—263	72.05 / 72.28	4.63 / 4.85	8.27 / 8.43	$C_{20}H_{16}N_2O_4$
15	64	225—226	72.56 / 72.82	4.97 / 5.24	7.84 / 8.09	$C_{21}H_{18}N_2O_3$
16	82	242—243	65.26 / 65.49	4.01 / 4.12	7.42 / 7.64	$C_{20}H_{15}ClN_2O_3$

Scheme 3



R^1 = H (**11**, **14**), Me (**12**, **15**), Cl (**13—16**);
R^2 = R^3 = Ph (**9**, **11—13**); R^2 = Me, R^3 = OEt (**10**, **14—16**).

Table 2. IR (ν/cm^{-1}) and ^{1}H NMR ($CDCl_3$, δ) spectral data of compounds **3—5** and **11—16**

Compound	IR spectrum		^{1}H NMR				
	NH	CO	NH, s	Ph, m	CH, s	CH_2, q	Me
3	3150—3080	1650, 1630, 1590	14.75, 13.40	7.80—7.20	6.70	—	2.89 s
4	3150—3050	1680, 1630, 1600	14.73, 13.25	7.80—7.20	6.65	—	2.80 s
5	3150—3050	1670, 1640, 1600	14.50, 13.10	7.80—7.20	6.60	—	2.85 s
11	3100—3000	1690, 1620, 1610	13.16, 14.95	7.80—7.10	6.40		
12	3100—3000	1700, 1620, 1610	14.90, 13.10	7.70, 7.40—7.10	6.38	—	2.45 s
13	3100—2800	1705, 1625, 1600	15.07, 13.13	7.75, 7.39—7.10	6.38		
14	3100—2900	1710, 1660, 1630	16.48, 14.70, 13.90, 12.80	7.70—7.57	6.30, 6.20	4.35	2.55 s, 1.40 t
15	3100—2900	1710, 1660, 1640	16.38, 14.63, 13.88, 12.79	7.60—7.32	6.30, 6.20	4.35	2.45 s, 2.30 s, 1.30 t
16	3100—2900	1700, 1650, 1630	14.40, 14.00, 12.80, 12.52	7.70—7.50	6.30, 6.20	4.40, 4.30	2.58 s, 2.52 s, 1.42 t, 1.35 t

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument, and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. The IR spectra were registered on a Specord M-80 instrument. The mass spectra were obtained on a MAT-311A spectrometer (70 eV).

3-Acetyl-6-aryl-2-benzoylamino-4-pyridones (3—5). A mixture of 1.7 mmol of dioxinone **1** and 1.7 mmol of ketene aminal **2** was heated for 20 min at 145—150 °C. After cooling, the reaction mixture was treated with toluene to obtain the crystalline pyridones **3—5**. The yields, melting points, and elemental analysis data of these compounds are given in Table 1; IR and ^{1}H NMR spectra are given in Table 2.

^{1}H NMR spectrum of pyridone **3** ($CDCl_3$), δ: 204.15 (CO), 178.85 (C(4)), 170.02 (CON), 152.56 (C(2)), 143.74 (C(6)), 134.02, 132.13, 131.69, 131.03, 129.67, 127.98, 125.57 (2 Ph), 116.16 (C(5)), 106.88 (C(3)), 33.26 (Me).

3-Acetyl-2-amino-6-phenyl-4-pyridone (6). A mixture of 0.33 g (1 mmol) of pyridone **3** and 1 mmol of MeONa in 10 mL of MeOH was boiled for 1 h, cooled to 20 °C, and acidified with 0.5 mL of AcOH. The precipitate was filtered off, washed with 30 mL of water and 10 mL of ether, and dried to obtain 0.20 g (87 %) of pyridone **6**, m.p. 249—251 °C (from MeCN). Found (%): C, 67.87; H, 5.24; N, 12.38. $C_{13}H_{12}N_2O_2$. Calculated (%): C, 68.41; H, 5.30; N, 12.27. IR (KBr), ν/cm^{-1}: 3305, 3170 (NH), 1652 (CO), 1640 (CO), 1578, 1510. ^{1}H NMR (DMSO-d_6), δ: 2.50 (s, 3 H, Me), 6.10 (s, 1 H, H(5)), 7.45—7.58 (m, 3 H, Ph), 7.67—7.80 (m, 2 H, Ph), 8.10 (br.s, 2 H, NH_2), 10.55 (br.s, 1 H, NH). Mass spectrum, *m/z* (I_{rel}(%)): 228 $[M]^+$ (100), 231 $[M-Me]^+$ (90).

4-Methyl-7-phenyl-8*H*-pyrido[2,3-*d*]pyrimidine-5-one (8). A mixture of 0.23 g (1 mmol) of pyridone **6** and 0.27 mL (2 mmol) of dimethylformamide dimethylacetal in 15 mL of benzene was boiled for 2 h. The solvent was removed *in vacuo*, and the residue was chromatographed on a column with SiO_2 (eluent was $CHCl_3$). 0.15 g (53 %) of amidine **7** was obtained. ^{1}H NMR ($CDCl_3$), δ: 2.91 (s, 3 H, Me), 3.13 and 3.18 (two s, 6 H, $N(Me)_2$), 6.93 (s, 1 H, H(5)), 7.40—7.50 (m, 3 H, Ph), 8.0 (m, 2 H, Ph), 8.67 (s, 1 H, CH=), 13.60 (br.s, 1 H, NH).

0.82 g (10.6 mmol) of $AcONH_4$ was added to amidine **7** (0.53 mmol) in 10 mL of butanol. The mixture was boiled for 3 h and stored for 12 h at ~20 °C. The precipitate was filtered off and washed with hexane to obtain 0.074 g (59 %) of compound **8**, m.p. 295—297 °C (from MeCN). Found (%): C, 71.09; H, 4.67; N, 17.84. $C_{14}H_{11}N_3O$. Calculated (%): C, 70.87; H, 4.67; N, 17.71. IR (KBr), ν/cm^{-1}: 3300—2800 (NH, CH), 1635 (CO), 1580, 1550. ^{1}H NMR (DMSO-d_6), δ: 2.93 (s, 3 H, Me), 6.46 (s, 1 H, H(6)), 7.49—7.60 (m, 3 H, Ph), 7.77—7.87 (m, 2 H, Ph), 8.92 (s, 1 H, H(2)), 12.43 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 24.81 (q, Me, ^1J = 129.0 Hz), 112.39 (d, C(6), ^1J = 165.68 Hz), 114.38 (q, C(4a), ^3J = 5.4 Hz), 127.39, 128.67, 130.58, 132.67 (Ph), 150.34 (s, C(7)), 156.09 (d, C(8a), ^2J = 11.0 Hz), 157.81 (d, C(2), ^1J = 202.5 Hz), 170.13 (q, C(4), ^2J = 6.5 Hz), 178.22 (s, C(5)). Mass spectrum, *m/z* (I_{rel}(%)): 237 $[M]^+$ (100), 209 $[M-CO]^+$ (62).

6-Aryl-2-dibenzoylmethylene-4-pyrimidinones (11—13) and 6-aryl-2-ethoxycarbonyl(acetyl)methylene-4-pyrimidinones (14—16). A mixture of 3.4 mmol of dioxine **1** and 3.4 mmol of ketene aminal **9** or **10** was heated for 10 min at 145—150 °C until the gas liberation stopped. The reaction mixture was cooled and treated with toluene to obtain compounds **11—13** or **14—16**. The yields, melting points, and elemental analysis data of compounds **11—16** are given in Table 1, and the IR and ^{1}H NMR spectra are given in Table 2.

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