NEW SYNTHETIC APPROACHES TO 4(1H)-PYRIDINONE DERIVATIVES THE SYNTHESIS OF 3-ACYL-4(1H)-PYRIDINONES

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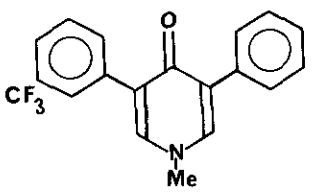
Abstract - The synthesis of 3-alkanoyl and 3-benzoylpyridin-4-ones is described from 1,3-diketones (5,11) or their equivalents. A novel C_α'-acylation of enaminones is described.

The outstanding activity of fluridone[1] (1) as a terrestrial and an aquatic herbicide has stimulated considerable work in these laboratories toward discovering alternative methods for the synthesis of 3,5-disubstituted 4(1H)-pyridinones.[2-4] As part of our continuing studies, we report in this article the synthesis of 3-acyl-5-aryl-4(1H)-pyridinones (2).



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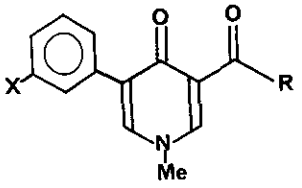

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Scheme 1

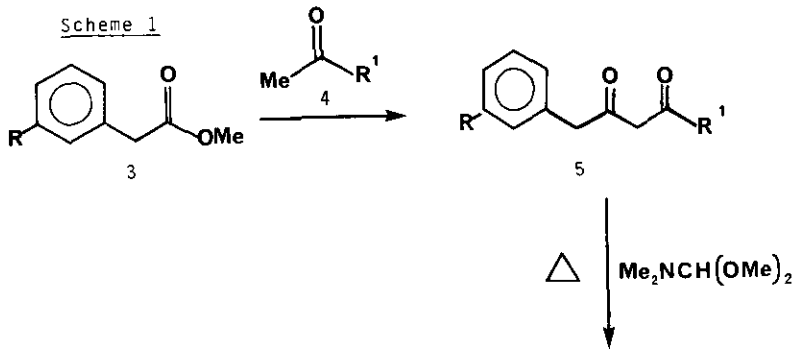

Table 1

7	R	R^1	mp°C	Percent Yield
a	CF_3	CH_3	131–132	63[8]
b	CF_3	CH_2CH_3	136–138	35
c	CF_3	n-Pr	93–94	10
d	CF_3	i-Pr	104–105	61
e	Br	CH_3	192–194	54
f	CH_3O	CH_3	147–149	42
g	Cl	CH_3	175–177	51

The facile synthesis of a pyridinone with a 3-carboethoxy function reported earlier[3], prompted us to attempt the acylation of a substituted diethylstyrylamine with diketene under analogous conditions. The presence of the required β-ketoacylstyrylamine could not be detected in the reaction mixture. This failure was attributed to the intervention of an enolate form of the dicarbonyl group in the intermediate which can readily cyclize to a pyranone derivative with elimination of diethylamine.[5] Therefore, we next attempted to construct the pyridinone ring around a preformed β-dicarbonyl system. The condensation of substituted phenylacetic acid esters with methyl alkyl ketones by Mühlemann's procedure[6], gave the required β-diketones (5) in a state of high purity. Bis-formylation with an excess of N,N-dimethylformamide dimethyl acetal at reaction temperatures below 150° followed by annelation with aqueous 40% methylamine in THF gave 3-keto-4(1H)-pyridinone derivatives (7) in yields ranging from 10 to 63% based on β-diketone (Scheme 1).

Attempts to apply Mühlemann's reaction conditions[6] to the aryl methyl ketones (8) were unsuccessful as self-condensation was more facile than the desired Claisen reaction. A convenient alternative means of effecting acylation was to convert the aryl methyl ketones into their morpholine enamines by refluxing in toluene with an excess of morpholine using p-toluenesulfonic acid as a catalyst. Rapid separation of water was monitored in a Dean Stark trap. Acylation of the enamines (9) with substituted aryl or aryloxyacetyl chlorides was uneventful and afforded E,Z-mixtures of enaminones.[9] These were usually hydrolyzed without purification to the required β-diketones (11) and an annelation sequence[3] gave the required 3-benzoyl-4(1H)-pyridinones (12) (Scheme 2).

Scheme 2

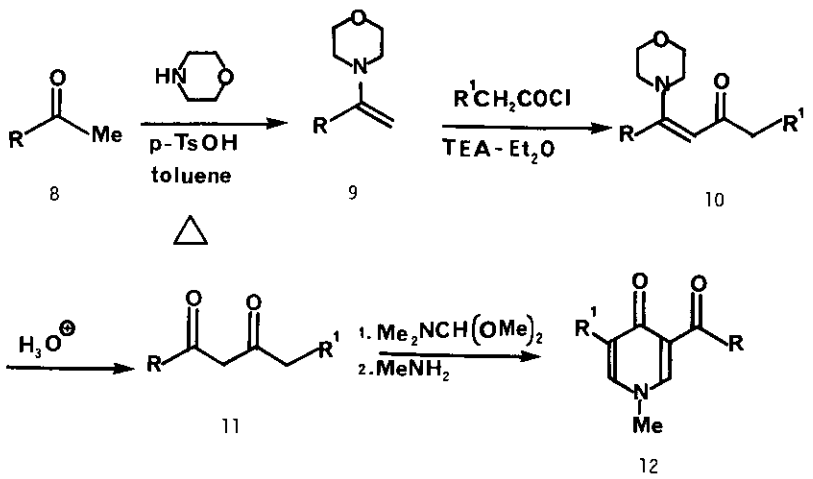

Table 2

12	R	R^1	mp°C	Percent Yield
a	m-CF_3-Ph-	m-CF_3Ph-	115-116	27
b	Ph-	m-CF_3-Ph-	140-141	22
c	m-CF_3-Ph-	PhO-	170-172	56

In the instance of pyridinones (2) with certain substituents (R=1,1-dimethylethyl, 1,1-dimethylpropyl or methoxymethyl), both of the preceding routes failed to afford product in amounts required for biological evaluation, though trace amounts were present. This recalcitrance could be due to steric hindrance posed by the t-alkyl groups in the condensation steps (Mühlemann procedure) and by the resistance of t-alkyl methyl ketones toward enamine formation.[10]

We therefore developed a new approach to the required pyridinones, using as the key step a hitherto unreported enaminone acylation reaction. While the alkylation of related enaminones has been recently reported by others[11,12] at the α'-position, no reports of α'-acylation appear in the literature.[13] Thus, treatment of enaminone (15)[14] with LDA in THF at -80°C gave the anion (13), which was smoothly acylated with the required t-alkanoyl chloride or the alkoxyacetyl chloride, respectively, to give α'-acylated enaminones, which could be cyclized to the required pyridinones in the usual manner.[2] The overall synthetic route is shown in Scheme 3.

Scheme 3

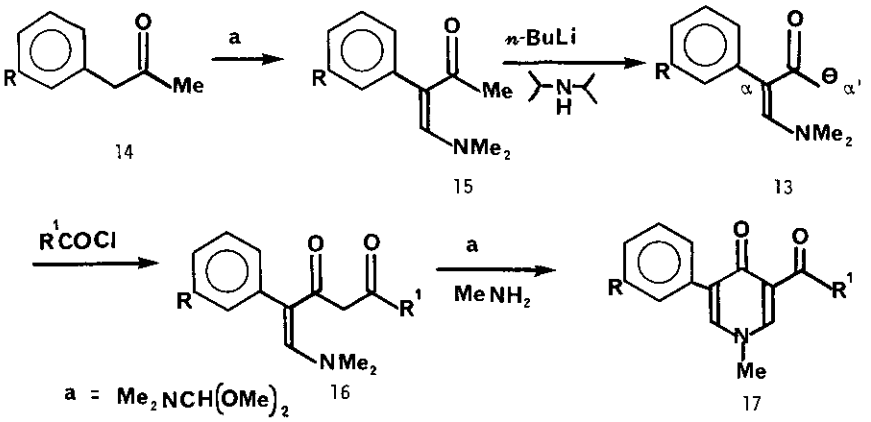

Table 3

17	R	R^1	mp°C	Percent Yield
a	CF_3	Me_3C	80–88	19
b	CF_3	$MeCH_2C(Me)_2$	108–110	10
c	CF_3	$MeOCH_2$	140 d	21

In summary, we have extended our pyridine ring synthesis to give us 3-acyl- and 3-benzoyl-4(1H)-pyridinones either from β-diketone precursors or via unprecedented α'-acylation of enaminones. The versatility of these routes enables one to prepare pyridine rings with a plethora of different substituent groups in the 3 and 5-positions.[15]

EXPERIMENTAL SECTION

1-(m-Trifluoromethylphenyl)-pentan-2,4-dione (5a):

To a stirred suspension of 40 g (1 mol) of sodium amide in 400 ml of anhydrous ether under N_2 at 30°C was added a mixture of 116 g (0.5 mol) of ethyl m-trifluoromethylphenylacetate and 40 g (0.68 mol) of acetone, dropwise over 1 hour. Vigorous reflux and evolution of ammonia occurred during addition. After addition, the reaction mixture was stirred for 4 hours and then cautiously poured in one batch into 1.5 L of ice water with stirring. One liter of ether was added and the unreacted components were extracted into the organic phase. The clear aqueous extract was acidified to pH 5.0 with 2N HCl and then to pH 7.5 with sodium bicarbonate solution. Three extractions with 500 ml portions of ether gave an amber solution which was dried ($MgSO_4$) and

evaporated in vacuo to give 55 g (45%) of the crude diketone. Fractional distillation gave 22 g (16 rec.) of pure title compound, bp 109-110°C/0.4 mm. Subsequent runs on larger scales gave distilled yields ranging from 30 to 40 . NMR ($CDCl_3$) δ ppm: 2.01 (s, 3H,-CH_3); 3.63 (s, 2H, -CH_2-); 5.45 (s, 1H, =CH-, enol); 7.2-7.6 (m, 4H, aromatic). Anal. Calcd for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54; F, 23.34. Found C, 58.78; H, 4.48; F, 23.30.

3-Acetyl-1-methyl-5-(α,α,α-trifluoro-m-tolyl)-4(1H)-pryidinone (7a):

To 100 g of diketone (5a) was added 400 ml of N,N-dimethylformamide dimethyl acetal and the mixture was stirred for 14 hours at reflux temperature. The excess acetal was recovered by distillation in vacuo. The viscous brown oil remaining was dissolved in 1 L of THF and treated with 100 ml of 40% aqueous methylamine solution. After stirring for 3 days the reaction mixture was stripped and taken up in $CHCl_3$, washed with 1N HCl then saturated aqueous NaCl solution, dried ($MgSO_4$) and stripped. Stirring under 500 ml of diisopropyl ether gave 76 g (63%) of the title compound as a white crystalline solid. NMR ($CDCl_3$) δ ppm: 2.73 (s, 3H, $COCH_3$); 3.80 (s, 3H, N-CH_3); 7.4 (d, J=2.75 Hz, 5H pyridinone); 8.17,(d, J=2.75 Hz, H_2 pyridinone); 7.6-7.8 (m, J=4 Hz, aromatic). Anal. Calcd. for $C_{15}H_{12}F_3NO_2$: C, 61.02; H, 4.07; N, 4.75. Found: C, 60.72; H, 4.30; N, 4.87.

1-Methyl-3-pivaloyl-5-(α,α,α-trifluoro-m-tolyl)-4(1H)-pyridinone (17a):

To a solution of 3.9 g of diisopropylamine in 175 ml of anhydrous (Linde 4A) THF was added at -60°C a solution of 16 ml of 2.4M n-BuLi in hexane, dropwise over 15 minutes. After stirring for 40 minutes a solution of 10.0 g of enaminone (15a) in 50 ml of THF and 25 ml of HMPTA was added dropwise over 30 minutes. The mixture was stirred for 1 hour to generate the enaminone anion and at -60°C was added dropwise a solution of 4.7 g of pivaloyl chloride in 25 ml of THF. The solution was stirred to room temperature overnight. After quenching the reaction with KH_2PO_4 the reaction mixture was partitioned between ether and water.

The ether layer was separated, dried ($MgSO_4$) and stripped to give crude enaminodione (16a). Chromatography over silica gel (Woelm, activity 1) using gradient elution with EtOAc/CH_2Cl_2 gave 3.6 g of the enamindione (16a). NMR ($CDCl_3$) δ ppm: 1.03 (s, 9H, t-Butyl); 2.78 (s, 6H, NMe_2); 5.03 (s, 1H, =CH- enol); 7.53 (m, 4H, aromatic); 7.76 (s, 1H, =CH-N). The enaminodione was dissolved in 17 ml of N,N-dimethylformamide dimethyl acetal and was refluxed in an oil bath at 100°C overnight under nitrogen. The reaction mixture was stripped dry, and the remaining oil was dissolved in 120 ml of THF and treated with 15.0 ml of 40% aqueous methylamine solution. The reaction was over in 50 minutes and was stripped to a brown oil. Chromatography over silica gel

(Woelm, activity 1) using EtOAc/CH_2Cl_2 gave 0.63 g (17% based on enaminodione) of the required pyridinone, mp 86–88°C (hexane). NMR ($CDCl_3$) δ ppm, 1.25 (s, 9H, t-Butyl); 3.81 (s, 3H, N-CH_3); 7.6–8.3 (m, 6H, pyridinone protons + aromatic). Anal. Calcd. for $C_{18}H_{18}F_3NO_2$: C, 64.09; H, 5.38; N, 4.15. Found: C, 63.99; H, 5.16; N, 4.12.

1-Phenoxy-4-(α,α,α-trifluoro-m-tolyl)-butan-2,4-dione (11c):

To 38.0 g of 1-morpholino-m-(trifluoromethyl)styrene[15] dissolved in 400 ml of anhydrous ether was added 7.9 g of pyridine, and at 0–5°C was added a solution of 17 g (0.1 mol) of phenoxyacetyl chloride in 200 ml of anhydrous ether dropwise over 3 hours. The solution was stirred to room temperature overnight, filtered and stripped. The resulting semi-solid was dissolved in 1 L of benzene and to it was added 480 ml of 10% hydrochloric acid aqueous solution, and the mixture was stirred under reflux for 2 hours.

The benzene solution was separated and washed with sodium bicarbonate solution and saturated sodium chloride solution, and dried ($MgSO_4$). Removal of benzene in vacuo, gave an amber oil which was made analytically pure by column chromatography (Woelm silica gel activity 1, toluene as eluting solvent) and afforded 11.5 g (24%) of compound. Anal. Calcd. for $C_{18}H_{15}F_3O_3$: C, 63.35; H, 4.04. Found: C, 63.13; H, 4.17.

1-Methyl-3-phenoxy-5-(m-Trifluoromethyl)-phenyl-4(1H)-pyridinone (12b):

To 1.3 g of the phenoxydiketone (11b) in 30 ml of dry toluene was added 4.0 ml of N,N-dimethylformamide dimethyl acetal. The mixture was heated under reflux for 18 hours and evaporated to dryness in vacuo. The oily residue was dissolved in 200 ml of THF and 15.0 ml of 40% aqueous methylamine solution was added. The reaction was monitored by tlc until homogeneous, then stripped dry and the resulting semi-solid mass triturated under diisopropyl ether. A crystalline solid, mp 170–172°C, was obtained, in 0.85 g (56%) yield. NMR ($CDCl_3$) δ ppm: 3.65 (s, 3H, N-CH_3); 7.0–8.3 (m, 11 H, pyridinone and aromatic). Anal. Calcd. for $C_{20}H_{14}F_3NO_3$: C, 64.35; H, 3.78; N, 3.75. Found: C, 64.33; H, 4.00; N, 3.55.

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14) The enaminone (15) is obtained in quantitative yield by refluxing equivalent amount of m-trifluoromethylphenylacetone and N,N-dimethylformamide dimethylacetal for 12 hrs, when the product separates out as a solid in a state of analytical purity.

15) We thank Mr. Paul L. Unger and his co-workers for the ir and nmr spectra, and Dr. G. Maciak for the microanalyses.

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