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A New Synthetic Method of 4(1*H*)-Pyridones

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β-Diketones have been condensed with some nucleophilic reagents, such as ketones, aldehydes and esters, in the presence of alkali amide in liquid ammonia.[1,2] It has also been reported that Schiff bases have been condensed with β-diketones to give the corresponding dihydropyridiones.[3] Much like Schiff bases, nitrile is expected to condense with β-diketone to give 4(1*H*)-pyridone. Hauser and his co-workers reported[4] that acetanilide condensed with benzonitrile in the presence of two equivalents of butyllithium in *n*-hexane-tetrahydrofuran to give only ω-benzimidoylacetanilide. By the use of β-diketones instead of acetanilide in liquid ammonia, we obtained 4(1*H*)-pyridones directly. Many reports of 4(1*H*)-pyridone syntheses have appeared in the literature,[5-8] but this kind of 4(1*H*)-pyridone synthesis

1) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).

2) N. Sugiyama, M. Yamamoto, T. Takano and C. Kashima, This Bulletin, **40**, 2909 (1967).

3) N. Sugiyama, M. Yamamoto and C. Kashima, *ibid.*, **42**, 1357 (1969).

4) R. L. Gay and C. R. Hauser, *J. Am. Chem. Soc.*, **89**, 1647 (1967).

5) J. Chauvelier, *Bull. soc. chim. France*, **1954**, 734.

6) J. Chauvelier and M. Gaudemar, *Compt. rend.*, **232**, 167 (1951).

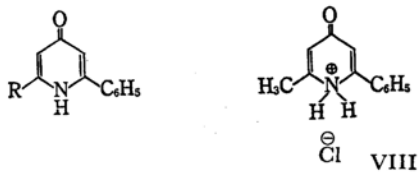
7) S. Hunig and G. Kobrich, *Ann.*, **617**, 203 (1958).

8) A. F. Thomas and A. Marxer, *Helv. Chim. Acta*, **43**, 469 (1960).

has never before been described.

Results and Discussion

In liquid ammonia, acetylacetone (I) was condensed with benzonitrile (IV) in the presence of alkali amide. When three moles of lithium amide were used, neither imino compounds nor 4(1*H*)-pyridones were obtained, but when two moles of sodium amide were used 6-methyl-2-phenyl-4(1*H*)-pyridone hydrochloride (VIII) was obtained in a 35% yield. When three moles of potassium amide were used, the yield of VIII increased to 42%. The structure of VIII was proved by a study of the spectral data and by elemental analyses. The treatment of VIII with sodium carbonate in a 90% ethanol solution gave 6-methyl-2-phenyl-4(1*H*)-pyridone (V) quantitatively; it was identified with an authentic sample.[9]



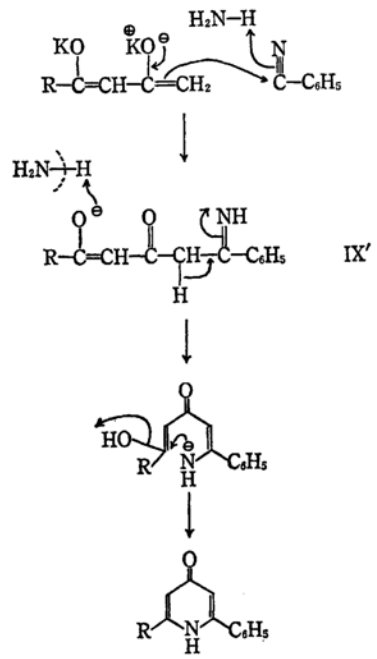
VIII

Scheme 1

In the same way, 6-phenyl-2,4-hexanedione (II) was condensed with IV. II has an activated terminal methyl group at C-1 and two activated methylene groups, at C-3 and C-5. Much as with the reaction of II with benzylidene aniline,[3] the reaction was effected to occur at the C-1 or C-5 position. However, the reaction of II occurred at C-1 and it afforded only one product, 6-phenethyl-2-phenyl-4(1*H*)-pyridone (VI).

The structure of VI was supported by the spectral data and by the elemental analyses. The infrared absorption spectrum of VI showed bands at 3260 (νNH), 1615 (conjugated ketone), 1580, 1520 (a pyridone-ring double bond), 1590, and 690 cm^{-1} (phenyl). The ultraviolet absorption spectrum showed absorption maxima at 242 and 261 mμ in an ethanol solution. The nuclear magnetic resonance spectrum in a deuterochloroform solution showed signals at τ 7.10 (singlet, 4H, phenethyl ethylene group), a doublet centered at τ 3.86 (2H, olefinic protons), a singlet at τ 2.85 (5H, aromatic protons of phenethyl group), and a multiplet centered at τ 7.32 (5H, C-2 substituted phenyl protons). These data supported the idea that the structure of VI is 6-phenethyl-2-phenyl-4(1*H*)-pyridone.

The condensation of benzoylacetone (III) with IV gave 2,6-diphenyl-4(1*H*)-pyridone (VII). The structure of VII was identified with that of an authentic sample.[10] It is considered that VII was produced *via* an intermediate imino compound (IX). However, an attempt to detect IX failed. This fact suggests that the cyclization of IX was accomplished before the neutralization.



IX′

Scheme 2

We speculated that the reaction mechanism of this series is as follows: β-diketone and benzonitrile condense to give imino β-diketone (IX′) in the first step, and then IX′ is cyclized by dehydration to yield X, as is illustrated in Scheme 2.

Experimental

6-Methyl-2-phenyl-4(1*H*)-pyridone (V). *The Selection of the Reaction Conditions. A)* In a 500-m*l* three-necked flask, 300 m*l* of anhydrous liquid ammonia was placed. A small amount of potassium was then added and dissolved completely. Into the blue solution there was stirred a catalytic amount of ferric chloride, and then 5.85 g (0.15 g atom) of potassium were added in small portions. The resulting blue solution turned dark gray within 60—90 min. To this solution there was added 0.05 mol of I in 30 m*l* of anhydrous ether in small portions. After stirring for 60 min, 5.51 g (0.05 mol) of IV in 20 m*l* of anhydrous ether were added. After having been stirred for three hours at −33°C, the reaction mixture was neutralized with ammonium chloride. The liquid ammonia was evaporated rapidly on a water bath, and 100 m*l* of water was added from a dropping funnel. After 15 minutes' stirring, the ethereal layer was separated. To the alkaline aqueous layer 100 m*l* ether were added, and then the solution again extracted. To the remaining aqueous layer was added 100 m*l* of 2 N hydrochloric acid were added, after with the solution was allowed to stand at room temperature for 30 min. The resulting precipitate was recrystallized from hot water to give 4.94 g (42%)

9) S. Ruhemann, *J. Chem. Soc.*, **93**, 1281 (1908).
10) L. Neelakantan, *J. Org. Chem.*, **23**, 741 (1958).

of VIII as a white powder; mp 235—237°C, Beilstein test (+).

Found: C, 64.69; H, 5.64; N, 6.25%. Calcd for $C_{12}H_{12}NOCl$: C, 64.99; H, 5.43; N, 6.32%.

IR(KBr): 3250, 3400 (νNH), 1645, 1630 (νC=O, conjugated ketone and double bond) and 700 cm^{-1} (phenyl).

UV: λ_{max}^{EtOH} 235, 277 mμ.

B) According to the method *A*, 0.10 mol of sodium amide was used; 4.12 g (35%) of VIII was thus obtained.

C) According to the method *A*, 0.15 mol of lithium amide was used; VIII was not obtained.

To a solution of 1.0 g of VIII in 50 m*l* of 90% ethanol 5 g of anhydrous sodium carbonate was added; this mixture was then refluxed for two hours in a water bath. The resulting solution was filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from hot water to give 0.75 g (93%) of V as a white powder; mp 174—176°C (lit 177—178°C[9]).

IR(KBr): 3300, 1625, 1580, 1525 and 700 cm^{-1}.

UV: λ_{max}^{EtOH} 240 mμ (ε 24800), 262 mμ (ε 15100).

NMR(in $CDCl_3$): τ 7.64 (3H, methyl, singlet), τ 4.00 (1H, olefinic proton, doublet), τ 3.73 (1H, olefinic proton, doublet), τ 2.35—2.72 (5H, aromatic protons, multiplet) and τ 1.50—1.90 (1H, NH, broad singlet).

6-Phenethyl-2-phenyl-4(1*H*)-pyridone (VI). According to the method *A*, VI was prepared from 8.0 g (0.05 mol) of II and 0.05 mol of IV. The product was dried in the air and then recrystallized from ethanol-acetone to give 7.1 g (51%) of VI as pale yellow plates; mp 172—173°C.

Found: C, 82.53; H, 6.36; N, 5.07%. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09%.

UV: λ_{max}^{EtOH} 241 mμ (ε 37500), 261 mμ (ε 25000).

2,6-Diphenyl-4(1*H*)-pyridone (VII). According to the method *A*, VII was prepared from 8.1 g (0.05 mol) of III and 5.15 g (0.05 mol) of IV. After the solution had been stirred for three hours at −33°C, the liquid ammonia was evaporated without neutralization. To the residue a 100 m*l* portion of water was added, and then 7.5 g (0.14 mol) of ammonium chloride in 100 m*l* of water. The ethereal layer was separated. The alkaline aqueous layer was extracted with three 100 m*l* portions of chloroform. After dried over calcium chloride, the chloroform solution was evaporated; the residue was chromatographed on a silica gel column (Merck 7734, 0.05—0.2 mm) with a benzene - ethyl acetate (4 : 1 v/v) mixture. The fraction (R_f-value: 0.18*[1]) was collected and concentrated to give only VII, which was then recrystallized from benzene to yield 3.83 g (31%) as white crystals: mp 178—179°C (lit 178°C[11]). No imino compound was detected.

IR(KBr): 3250, 1615, 1517, 1535 and 690 cm^{-1}.

UV: λ_{max}^{EtOH} 249 mμ (ε 32200), 280 mμ (ε 15000).

NMR (in $CDCl_3$): τ 3.25 (2H, olefinic protons, singlet), τ 3.00—3.80 (1H, NH, broad singlet) and τ 2.10—2.68 (10H, aromatic protons, multiplet).

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*1 Thin layer chromatography: Wakogel B-500, Solvent: benzene.

11) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).