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A Novel Method for the Synthesis of 1-Phenyl-2,3-dihydro-4-pyridones

Noboru SUGIYAMA, Makoto YAMAMOTO and Choji KASHIMA

Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo

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The condensation of β-diketones, benzoylacetone (II), acetylacetone (III), or 6-phenyl-2,4-hexanedione (IV) with benzylidenaniline (I), in the presence of three moles of potassium amide in liquid ammonia, was found to give a dihydropyridone or an aminodiketone. Thus, the condensation of II with I afforded aminodiketone, 1-anilino-1,5-diphenyl-3,5-pentanedione (V), which cyclized to 2,3-dihydro-1,2,6-triphenyl-4-pyridone (IX) upon being treated with sulfuric acid. The condensation of III with I gave 2,3-dihydro-1,2-diphenyl-6-methyl-4-pyridone (X) without any treatment with sulfuric acid. IV and I gave 2,3-dihydro-1,2-diphenyl-6-phenethyl-4-pyridone (XI) as the main product, with 3-benzyl-2,3-dihydro-1,2-diphenyl-6-methyl-4-pyridone (XII) as a by-product.

The condensation of β-diketones with ketones or aldehydes in the presence of alkali amide in liquid ammonia has previously been reported.[1,2] It appeared of interest to investigate whether the reaction could be extended to the condensation of β-diketones with Schiff bases. Thus, the reaction of β-diketones, *e. g.*, benzoylacetone (II), acetylacetone (III), or 6-phenyl-2,4-hexanedione (IV), with benzylidenaniline (I), a Schiff base, was carried out in the presence of three moles of potassium amide in liquid ammonia. It was proved that a dihydropyridone or an aminodiketone was produced by this reaction. A few reports of dihydropyridone synthesis have appeared in the literature;[3,4] in these syntheses dihydropyridones have been prepared by the partial reduction of the corresponding pyridones. In our method, however, dihydropyridones are directly prepared from β-diketones and a Schiff base.

Results and Discussion

A β-diketone was condensed one molar equivalent of a Schiff base in the presence of three molar equivalents of potassium amide in liquid ammonia. The condensation of II with I gave 1-anilino-1,5-diphenyl-3,5-pentanedione (V). The structure of V was proved by its IR, UV, and NMR spectra and by the results of elemental analysis.

The treatment of V with sulfuric acid gave 2,3-dihydro-1,2,6-triphenyl-4-pyridone (IX), whose structure was supported by its IR, UV, and NMR spectra as well as by the results of elemental analysis. The NMR spectrum of IX showed a multiplet at τ 6.37—7.35, a triplet centered at τ 4.70 and a singlet at τ 4.42; these can be assigned to C-3 methylene, C-2 methine, and olefinic protons of the 2,3-dihydro-4-pyridone nucleus respectively. The UV maxima at 249 and 353 mμ remained unchanged in either an acidic and an alkaline solution. These facts favor the dihydropyridone structure of IX. The reaction course from V to IX is a cyclization by dehydration and seems analogous to that from an aminodiketone to a 4-pyridone.[5]

III and I were treated under the conditions similar to those described above. In this case, the expected aminodiketone (VI) was not detected, but 2,3-dihydro-1,2-diphenyl-6-methyl-4-pyridone (X) was obtained. The structure of X was supported by the spectral data and by the results of elemental analysis.

It is suggested that VI is the intermediate in the synthesis of X, as V is the intermeidate in the synthesis of IX, and that the intermediate VI is cyclized during the neutralization with ammonium chloride. Thus, the detection of VI was examined before the neutralization. However, X was the only product obtained, and no aminodiketone was detected. These facts indicate that the cyclization

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

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

[3] J. Hebky and J. Kejha, *Chem. Listy.*, **50**, 834 (1956).

[4] E. Winterfeldt, *Chem. Ber.*, **97**, 2463 (1964).

[5] S. Boatman, R. E. Smith, G. F. Morris, W. G. Kofron and C. R. Hauser, *J. Org. Chem.*, **32**, 3817 (1967).

of VI was already accomplished before the neutralization.

The reaction of IV and I was also carried out. Compound IV has a terminal methyl group (C-1 position) and a C-5 methylene group, which can be activated by the vicinal carbonyl group. The treatment of IV and I by the general procedure gave 2,3-dihydro-1,2-diphenyl-6-phenethyl-4-pyridone (XI) and its isomer, 3-benzyl-2,3-dihydro-1,2-diphenyl-6-methyl-4-pyridone (XII), in a molar ratio of 4:1. The structures of XI and XII were supported by the spectral data and by the results of elemental analysis. For the formation of XI and XII, it is also supposed that the VII and VIII intermediates must be formed first. Thus, it is reasonable to suppose that the reaction proceeds not only at the terminal methyl group, but also at the C-5 methylene group of IV. The yield of XI and XII supports the idea that, in IV, the terminal methyl is more reactive than the C-5 methylene group. This might be in agreement with the fact that IV and methyl iodide in the presence of sodium amide in liquid ammonia gave the corresponding methylation products at C-1 and C-5 positions in a ratio of 89:11.[6)]

Furthermore, we attempted to perform experiments on the condensation of a β-diketone III with aliphatic Schiff bases, benzylidenemethylamine, and ethylidenaniline. However, neither the corresponding dihydropyridone nor the aminodiketone was obtained, probably because these Schiff bases are unstable under the conditions of the general procedure.

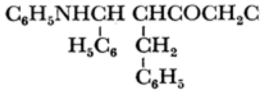
$RCOCH_2COCH_3$

$RCOCH_2COCH_2\underset{C_6H_5}{CH}NHC_6H_5$

II: $R=C_6H_5$ V: $R=C_6H_5$

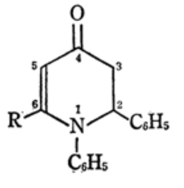
III: $R=CH_3$ VI: $R=CH_3$

IV: $R=C_6H_5CH_2CH_2$ VII: $R=C_6H_5CH_2CH_2$



$C_6H_5NH\underset{H_5C_6}{CH}\,\underset{\underset{C_6H_5}{CH_2}}{CH}COCH_2COCH_3$

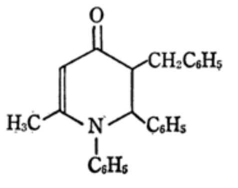
VIII



IX: $R=C_6H_5$

X: $R=CH_3$

XI: $R=C_6H_5CH_2CH_2$



XII

Experimental

General Procedure. In a 500-m*l* three-necked flask, 300 m*l* of anhydrous liquid ammonia were placed. A small amount of potassium was then added and dissolved completely. Into the blue solution there were stirred a catalytic amount of ferric chloride and then 5.85 g (0.15 mol) of potassium in small portions. The resulting blue solution turned dark gray within 90 min. To this solution there was added, in small protions, 0.05 mol of β-diketone in 30 m*l* of anhydrous ether. After stirring for 45—60 min, 0.05 mol of a Schiff base in 30 m*l* of anhydrous ether was added to the solution. After stirring for an additional hour, the reaction mixture was neutralized with ammonium chloride. The liquid ammonia was evaporated rapidly on a water bath, and 100—150 m*l* of ether were added from a dropping funnel. The ethereal layer was separated and reserved. To the remaining layer there were added 150 m*l* of dilute hydrochloric acid, and this solution was extracted with chloroform. After drying over anhydrous sodium sulfate, the ether and the chloroform were evaporated. Both residues gave a crude condensation product.

1-Anilino-1,5-diphenyl-3,5-pentanedione (V). According to the general procedure, V was prepared from 8.1 g (0.05 mol) of II and 9.05 g (0.05 mol) of I. The crude product was recrystallized from a benzene - *n*-hexane (1:1 v/v) mixture to give 7.3 g (43%) of V as colorless plates, mp 116—118°C.

Found: C, 80.05; H, 6.05; N, 4.10%. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08%.

IR (KBr): 3370 (νNH), 1600 (νC=O), 1570 (νC=C, enol) and 700 cm^{-1} (phenyl).

UV: λ_{max}^{EtOH} 249 mμ (ε 19000) and 311 mμ (ε 17200).

$\lambda_{max}^{HCl\text{-}EtOH}$ 319 mμ (ε 16600).

$\lambda_{max}^{NaOH\text{-}EtOH}$ 247 mμ (ε 22000) and 332 mμ (ε 17800).

NMR (CCl_4): τ 7.10 (doublet, 2H, $COC\underline{H}_2$–CH), τ 5.14 (triplet, 1H, CH_2–C$\underline{H}$–Ph), τ 3.92 (singlet, 1H, Ph–C=C$\underline{H}$–CO), and τ 2.08—3.50 (multiplet, 15H, phenyl).

2,3-Dihydro-1,2,6-triphenyl-4-pyridone (IX). To 2.0 g of V, 15 m*l* of concentrated sulfuric acid were added, and then the mixture was allowed to stand at room temperature for two hours. About 100 g of crushed ice were then added to the reaction mixture, and the solution was neutralized with a cold concentrated potassium hydroxide solution. This solution was extracted with chloroform, and the chloroform layer was washed with water and dried over anhydrous sodium sulfate. The solution was evaporated, and the residue was chromatographed on a silica-gel (Merck 7734) column with a benzene - ethyl acetate (2:1 v/v) mixture. The fraction, which showed a violet color in a ferric chloride test, was collected and concentrated to give crude IX, which was then recrystallized from ether to yield 0.12 g (6.3%) of IX as yellow plates; mp 149—151°C.

Found: C, 84.82; H, 5.97; N, 4.34%. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30%.

IR (KBr): 1645 (νC=O) and 1550 cm^{-1} (νC=C).

UV: λ_{max}^{EtOH} 249 mμ (ε 16300) and 353 mμ (ε 21500).

NMR (CCl_4): τ 6.37—7.35 (multiplet, 2H, C-3 methylene), τ 4.70 (triplet, 1H, C-2 methine), τ 4.42 (singlet, 1H, olefinic proton), and τ 2.40—3.20 (multiplet, 15H, phenyl).

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6) K. G. Hampton, T. M. Harris and C. R. Hauser, *J. Org. Chem.*, **31**, 663 (1966).

2,3-Dihydro-1,2-diphenyl-6-methyl-4-pyridone(X). X was synthesized from 5.0 g (0.05 ml) of III and 9.05 g (0.05 mol) of I by the general procedure. The residue was chromatographed on a silica-gel (Merck 7734) column with a benzene-ethyl acetate (4 : 1 v/v) mixture. The fraction, which showed a brownish violet color in a ferric chloride test, was collected and evaporated to afford crude X, which was then recrystallized from carbon tetrachloride to give 6.5 g (50%) of colorless needles; mp 84—85°C.

Found: C, 81.94; 81,98; H, 6.53, 6.54; N, 5.26%. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32%.
IR (KBr): 1645 (νC=O) and 1560 cm^{-1} (νC=C).
UV: λ_{max}^{EtOH} 240 mμ (ε 2180) and 327 mμ (ε 10400).
$\lambda_{max}^{HCl-EtOH}$ 242 mμ (ε 1640) and 325 mμ (ε 8100).
NMR (CCl_4): τ 8.20 (singlet, 3H, CH_3–C=), τ 6.88—7.62 (ABX-type, 2H, $COCH_2$–CH), τ 5.10 (triplet, 1H, CH–Ph), τ 4.96 (singlet, 1H, olefinic proton), and τ 2.85—2.92 (multiplet, 10H, phenyl).

In order to examine for the presence of the intermediate of VI, the whole procedure was modified as follows. Two grams of V (0.02 mol) were allowed to react with 3.6 g (0.02 mol) of I, and then the liquid ammonia was evaporated without neutralization. To the residue 50 g of crushed ice and 50 g of water were added. After stirring for 10 min, the reaction mixture was extracted with chloroform. The aqueous layer was neutralized with dilute hydrochloric acid, and then again extracted with chloroform. From both solutions, only X was detected, not VI.

2,3-Dihydro-1,2-diphenyl-6-phenethyl-4-pyridone (XI). By the general procedure, XI was prepared from 9.5 g of IV and 9.05 g of I. The residue was chromatographed on a silica-gel (Merck 7729) column with a benzene-ethyl acetate (4 : 1 v/v) mixture; a fraction which showed a violet color in a ferric chloride test was collected. After the evaporation of the solvent, the residue was recrystallized from benzene-*n*-hexane (1:1 v/v) to afford 3.5 g (20%) of XI as colorless plates; mp 99—100°C.

Found: C, 84.79; H, 6.62; N, 4.10%. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96%.
IR (KBr): 1635 (νC=O), 1550 (νC=C) and 705 cm^{-1} (phenyl).
UV: λ_{max}^{EtOH} 238 mμ (ε 4500) and 330 mμ (ε 17500).
$\lambda_{max}^{HCl-EtOH}$ 236 mμ (ε 5200) and 326 mμ (ε 13200).
NMR (CCl_4): τ 7.72—7.10 (multiplet, 4H, Ph–CH_2–CH_2–). τ 7.28 (multiplet, 2H, C-3 methylene), τ 5.10 (triplet, 1H, C-2 methine), τ 4.66 (singlet, 1H, C=CH), and τ 2.60—3.10 (multiplet, 15H, phenyl).

3-Benzyl-2,3-dihydro-1,2-diphenyl-6-methyl-4-pyridone (XII). As in the preceding fractionating chromatography for XI, a fraction which showed a light brown color with ferric chloride was collected, concentrated, and recrystallized from benzene to yield 0.9 g (5.0%) of XII as yellow plates; mp 179—180°C.

Found: C, 84.99; H, 6.71; N, 4.09%. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96%.
IR (KBr): 1623 (νC=O), 1555 (νC=C) and 700 cm^{-1} (phenyl).
UV: λ_{max}^{EtOH} 240 mμ (ε 4580) and 333 mμ (ε 16900).
$\lambda_{max}^{HCl-EtOH}$ 245 mμ (ε 3620) and 331 mμ (ε 13400).
NMR ($CDCl_3$): τ 7.98 (singlet, 3H, CH_3–C=C), τ 6.62—7.23 (multiplet, 4H, C-3 methylene and Ph–CH_2–), τ 5.45 (singlet, 1H, C-2 methine), τ 4.78 (singlet, 1H, CH=C), and τ 2.60—3.10 (multiplet, 15H, phenyl).

Reaction of III with Aliphatic Schiff Bases. By the general procedure, 2.0 g (0.02 mol) of III were condensed with 2.38 g (0.02 mol) of benzylidenemethylamine or with 2.38 g (0.02 mol) of ethylideneaniline. In these reactions, neither the corresponding dihydropyridones nor the corresponding aminodiketones were detected by thin-layer chromatography.