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The Reaction of Ethyl Acetoacetate with Benzonitrile in Liquid Ammonia

Noboru Sugiyama, Makoto Yamamoto, Susumu Kobayashi, and Choji Kashima
Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo

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It is well known that β-diketones[1,2] and β-keto-esters[3,4] condense with an electrophile in the presence of bases in liquid ammonia.

In a previous paper,[5] we reported that acetylacetone condensed with benzonitrile in the presence of alkali amide in liquid ammonia to give 4(1*H*)-pyridone. As one of our series of studies of the syntheses of heterocycles, the present paper will describe the reaction of ethyl acetoacetate (**1**) with benzonitrile (**2**) in liquid ammonia.

If the reaction of **1** with **2** proceeds as the reaction of acetylacetone with **2**, the reaction product may be expected to be 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyridine (**4**). However, the reaction of **1** with an equimolar amount of **2** in the presence of twice as many moles of sodium amide in liquid ammonia resulted in the formation of 10% of ethyl 5-amino-3-oxo-5-phenyl-4-pentenoate (**3**), 5.0% of **4**, and 33% of 4-oxo-6-methyl-2-phenyl-1,4-dihydropyrimidine (**5**). The structures of **3**, **4**, and **5** were supported by the spectral data. Compounds **4** and **5** were identified by a direct comparison with authentic samples.[6,7] Since **3** was converted to **4** in liquid ammonia or in ether in the presence of sodium amide, **3** is considered to be an intermediate of the formation of **4** from **1** and **2**. Compound **4** was also formed by heating **3** over 150°C.

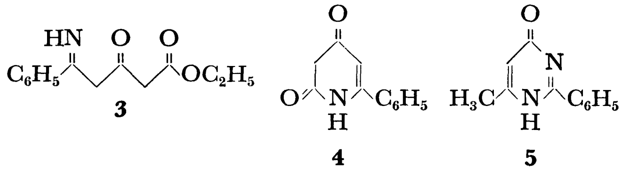

Fig. 1

When the reaction was carried out with a molar ratio of **1**, **2**, and sodium amide of 1 : 1 : 3, the yields of the reaction procduts, based on **1**, were 52.5% of **5** and 20% of **3**, plus a trace of **4**.

It has been reported that **2** is converted into benzamidine[8] in the presence of the amide ion, and that benzamidine and **1** condense to a pyrimidine derivative in the presence of sodium ethoxide in ethanol.[7] This fact suggests that the amide anion attacks the compound **2** to give benzamidine in liquid ammonia, and that benzamidine then condenses with **1** to yield **5**.

The condensation reaction at the terminal methyl group is considered to be initiated by the formation of a dianion by the abstraction of two protons from the methyl and methylene groups of β-diketone. The methyl proton of **1** is less acidic than that of acetylacetone or benzoylacetone.[4] When sodium amide was reacted on **1**, the monoanion of **1** is predominant, this monoanion reacts with **2** to give **5** (Scheme 1). When potassium amide is used instead of sodium amide, the

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[3] N. Sugiyama, M. Yamamoto, T. Takano, and C. Kashima, *ibid.*, **40**, 2909 (1967).

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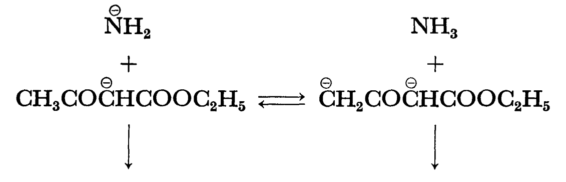
[6] F. Arndt B. Eistert, H. Schloz, and E. Aron, *Ber.*, **69**, 2373 (1936).

[7] A. Sitte and H. Paul, *Chem. Ber.*, **102**, 615 (1969).

[8] E. F. Cornell, *J. Amer. Chem. Soc.*, **59**, 3311 (1928).



$$\begin{array}{ccc} \overset{\ominus}{N}H_2 & & NH_3 \\ + & & + \\ CH_3CO\overset{\ominus}{C}HCOOC_2H_5 & \rightleftharpoons & \overset{\ominus}{C}H_2CO\overset{\ominus}{C}HCOOC_2H_5 \\ \downarrow & & \downarrow \\ \mathbf{5} & & \mathbf{3} \end{array}$$

Scheme 1

dianion of **1** is predominant because the ability of dianion formation of potassium amide is a little higher than that of sodium amide in liquid ammonia.[5,9] The dianion reacted with **2** to give **3**. Actually, the yield of **3** increased to 43%, as is listed in Table 1.

Table 1. The products of the reaction of **1** with **2**

Amide	n[a]	Reaction time (hr)	Product (%) **3**	**4**	**5**
$NaNH_2$	2	2.5	10	5.0	33
$NaNH_2$	3	2.5	20	trace	53
KNH_2	2	2.5	43	trace	3.8
KNH_2	2	5.0	32	15	3.7

a) Molar ratio, **1**:**2**: amide = 1 : 1 : n

The extension of the reaction time leads to an increase in the yield of **4**. This fact suggests that the initially-formed **3** has been converted to **4** by the residual amide ion in liquid ammonia.

This is a simple and convenient method for the synthesis of a compound of the **4** type, because the only method for synthesizing **4** previously reported (F. Arndt *et al.*[6]) is very complicated.

Experimental

Ethyl 5-amino-3-oxo-5-phenyl-4-pentenoate (3). To a solution of 0.1 mol of sodium amide in about 300 m*l* of liquid ammonia in a three-necked flask, we added, drop by drop, 0.05 mol (6.5 g) of **2** in 30 m*l* of anhydrous ether. After this mixture had been stirred for 1 hr, 0.05 mol (5.2 g) of **1** in 30 m*l* of anhydrous ether was added. The dark gray color of the solution soon turned to a brownish green. After being stirred for an additional 2.5 hr, the reaction mixture was neutralized with solid ammonium chloride. The liquid ammonia was evaporated rapidly in a water bath, and 100 m*l* of ether was added. The resulting ethereal suspension was shaken with 2N hydrochloric acid to dissolve the inorganic salts. The acidic aqueous layer was separated and again extracted with fresh ether. The two ether layers were combined and dried over anhydrous sodium sulfate, and the ether was evaporated under reduced pressure. The residue was chromatographed on a silica-gel (Merk 7734, 0.05—0.2 mm) column with a benzene-ethyl acetate (4: 1 v/v) mixture. A fraction which showed a brown color in a ferric chroride test was collected and evaporated to afford **3** (1.17 g, 10%) as an orange oil.

Found: C, 66.50; H, 6.63; N, 5.99%. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01%. IR(liquid film): 3400 (νNH), 1730 (νC=O, ester carbonyl), 1610 (νC=N) and 695 cm^{-1} (phenyl). UV: λ_{max}^{EtOH} 242 (ε 9390) and 328 nm (ε 17000). NMR(in CCl_4): δ 1.21 (t, 3H, methyl protons), 3.20 (s, 2H, C-2 methylene protons), 4.05 (q, methylene protons of the ester group), 5.32 (s, 1H, C-4 enolic olefin proton), 6.37 (broad, 1H, non-hydrogen bonded NH), 7.40 (m, 5H, aromatic protons), and 9.80 (braod, 1H, hydrogen bonded NH).

The compound **3** was not distilled because of its easy conversion by heat. By heating at 150—170°C for 30 min, about 46% of the **3** was converted into **4**.

After the compound **3** was obtained, **5** was eluted with benzene-ethyl acetate (2: 1 v/v) from the same column. Yield, 0.48 g (5.2%).

2,4-Dioxo-6-phenyl-1,2,3,4-tetrahydropyridine (4). After adjusting the pH to 4—5, the aqueous layer was allowed to stand at room temperature for two hours. The resulting precipitate was collected and then treated with hot acetone. The acetone-insoluble solid was collected and recrystallized from hot pyridine to give **4** as a white solid; 0.47 g (5.0%); mp 312—314°C (lit, 315—318°C[6]). IR(KBr): 3100 (νNH), 1645 (νC=O, conjugated ketone) and 695 cm^{-1} (phenyl). UV: λ_{max}^{EtOH} 308 nm (ε 10300).

4-Oxo-6-methyl-2-phenyl-1,4-dihydropyridine (5). When the hot acetone solution obtained above was cooled, compound **5** was separated as colorless needles. Yield, 2.58 g (28%); mp 215—216°C (lit, 218—221°C[7]).

Found: C, 71.15; H, 5.43; N, 14.92%. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05%. IR(KBr): 3175 (νNH), 1670 (νC=O, conjugated ketone) and 690 cm^{-1} (phenyl). UV: λ_{max}^{EtOH} 240 (ε 17300) and 293 nm (ε 11200). NMR(in $CDCl_4$): δ 2.38 (s, 3H, methyl protons), 6.28 (s, 1H, olefin proton), 7.52 (m, 3H, aromatic protons), and 8.20 (m, 2H, aromatic protons).

The Condensation Reactions of 1 with 2 under Various Conditions. The condensation reactions of **1** with **2** were carried out by using potassium amide, instead of sodium amide, and were also carried out by changing the molar ratio of amide to **1** and to **2** and/or by changing the reaction time. The results are listed in Table 1.

The Cyclization of 3 to 4. *a*) A solution of 122 mg of **3** in 5 m*l* of anhydrous ether was added to 50 m*l* of liquid ammonia containing 35 mg of sodium amide. The mixture was stirred for two hours and then neutralized with 60 mg of solid ammonium chrolide. After the evaporation of the ammonia, the residue was acidified with 30 m*l* of dilute hydrochloric acid; the resulting white precipitate was collected by filtration. Yield, 74 mg (76%). This compound was identified by comparing its spectral data with those of an authentic sample of 2-phenyl-4,6-dihydroxypyridine.

b) To 80 m*l* of anhydrous ether there were added 30 mg of sodium amide and 100 mg of **3** in 20 m*l* of anyhdrous ether. The solution was then stirred at room temperature for two hours. The **4** was identified by comparison with an authentic sample by means of thin-layer chromatography.

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[9] Unpublished data by M. Yamamoto *et al.*