NOTES

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The Claisen-Schmidt Condensation of Acetonitrile with Aromatic Carbonyl Compounds

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The reaction of acetonitrile with aromatic carbonyl compounds in ether, using sodium amide as the catalyst, are known[1] to form the derivatives of 3-hydroxypropionitrile. This paper will deal with the same reactions in acetonitrile, using sodium as the catalyst.

It has been established that methane, sodium cyanide, and diacetonitrile are formed when sodium is dissolved in acetonitrile. Diacetonitrile is the addition product of cyanomethylsodium to acetonitrile[2] and is known to add to the aromatic carbonyl compounds.[3] Therefore, if some aromatic carbonyl compounds are added to a solution prepared by dissolving sodium in acetonitrile, the following reactions are expected to occur: the addition reactions of cyanomethylsodium to the carbonyl compounds (addition a), the addition reaction of cyanomethylsodium to acetonitrile (addition b), the addition reaction of diacetonitrile to the carbonyl compound, and the reaction of the carbonyl compound with the carbonyl compound (reaction c). These reactions might be competing reactions. If the addition a is faster than the addition b or the reaction c, the adducts of cyanomethylsodium to the carbonyl compounds must be formed. The reactions of benzaldehyde, acetophenone, or benzophenone with cyanomethylsodium in acetonitrile have been attempted in order to clarify this possibility.

When benzaldehyde or acetophenone was added to a solution which has been prepared by dissolving sodium in acetonitrile (solution I), 3-hydroxy-3-phenylpropionitrile or 3-hydroxy-3-phenylpropionitrile was isolated from the reaction products. This fact suggests that cyanomethylsodium in acetonitrile dose not react with acetonitrile as rapidly as anticipated.

When benzaldehyde is stirred into solution I

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[1] a) H. Lettré, G. Meiners and H. Wickmann, *Naturwissenschaften*, **33**, 158 (1946). b) While the present authors were preparing the manuscript of this paper, E. M. Kaiser *et al.* reported that 3-hydroxy-3,3-diphenylpropionitrile can be formed by the reaction of acetonitrile with benzophenone in the presence of *n*-butyl lithium. They obtained *β*-phenylcinnamonitrile, not as the reaction product, but only through the dehydration of 3-hydroxy-3,3-diphenylpropionitrile with mineral acid; *J. Org. Chem.*, **33**, 3402 (1968).

[2] R. Holtzwart, *J. prakt. Chem.*, [2] **39**, 230.

[3] E. Mohr, *ibid.*, [2] **56**, 125.

at room temperature, benzyl alcohol, 3-hydroxy-3-phenylpropionitrile, and a small amount of cinnamonitrile are formed. Although benzoic acid was not isolated, benzyl alcohol might be formed by the Cannizzaro reaction of benzaldehyde and cinnamonitrile might be formed by the Claisen-Schmidt condensation of acetonitrile with benzaldehyde.

In the case of acetophenone, 3-hydroxypropionitrile was isolated from the product when the reaction was carried out at room temperature, while β-methylcinnamonitrile, the product of the Claisen-Schmidt condensation of acetonitrile with acetophenone, was formed when the reaction mixture was refluxed for 3 hr.

When a solution of benzophenone in the solution I was stirred for 17 hr at room temperature, the product isolated was not the derivative of hydroxypropionitrile but β-phenylcinnamonitrile, the product of the Claisen-Schmidt condensation of acetonitrile with benzophenone. The yield of β-phenylcinnamonitrile increased markedly when the reaction mixture was heated under reflux for 9 hr.[4]

The formation of the derivatives of dicyanovinylidene by the reaction of malonitrile with ketones are well known,[5] but the formation of the derivatives of cinnamonitrile by the one-step reaction with aromatic carbonyl compounds has not been found. This reaction will serve as a convenient method for preparing β-phenylcinnamonitrile.

Experimental

All the mps are corrected, while the bps are not corrected. The NMR spectra were taken on a JNM-3H-60 (60 Mc) NMR Spectrometer, with tetramethylsilane as the internal standard. The chemical shifts (ppm) were followed by splitting patterns (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and relative strengths. The IR spectra were recorded on a Hitachi EPI-G2-type Grating Infrared Spectrophotometer. The molecular weight was determined on a vapor-pressure osmometer in a benzene solution.

The acetonitrile was dried over phosphorus pentoxide and was distilled before use. The benzaldehyde and acetophenone were distilled before use, while the benzophenone was used without purification.

The solution I was prepared by dissolving 4.6 g (0.2 g atom) of sodium in 150 m*l* of acetonitrile. The flask which contained the solution I was flushed with nitrogen, and the aromatic carbonyl compounds were added from a dropping funnel (benzaldehyde or acetophenone) or directly (benzophenone).

Reaction of Acetonitrile with Benzaldehyde. A mixture of 21.1 g (0.2 mol) of benzaldehyde in solution I was stirred for 5 hr at room temperature. The reaction mixture was then neutralized, and the precipitates were removed by filtration. The filtrate was dried over anhydrous magnesium sulfate, concentrated, and distilled *in vacuo* to give the following fractions: *fraction 1*, 1.5 g (7%) of benzyl alcohol (I); bp 61—67°C/1.5 mmHg; $n_D^{13.6}$ 1.5396 (lit[6] n_D^{20} 1.5403); IR (neat) 3300, 1370, 1010 cm^{-1} (OH); NMR ($CDCl_3$) τ 2.9 (s, 5), 5.6 (s, 2), 5.9 (s, 1); *fraction 2*, 2.0 g of a mixture of I, 3-hydroxy-3-phenylpropionitrile (II), and cinnamonitrile (III); bp 67—129°C/0.002 mmHg; NMR ($CDCl_3$) τ 2.9 (I+II), 4.2, 4.5 (III), 5.3 (II), 5.6 (I+II), 7.5 (II); *fraction 3*, 5.2 g (18%) of II; bp 127—131°C/0.002 mmHg; $n_D^{13.0}$ 1.5447; IR (neat) 3400, 1320, 1050 cm^{-1} (OH), 2230 cm^{-1} (CN); NMR ($CDCl_3$) τ 2.8 (s, 5), 5.3 (t, 1, *J*=6 cps, –C**H**(OH)–), 5.5 (s, 1, O**H**), 7.6 (d, 2, *J*=6 cps, –C**H**$_2$–); mol wt, Found: 146, Calcd for C_9H_9NO: 147; and *a residue*, 13.1 g of unknown compound.

When an ethanol solution of the fraction 3 was treated with hydrogen peroxide under alkaline conditions, white crystals were obtained; 3-hydroxy-3-phenylpropionamide, mp 124°C; Found: C, 65.71; H, 6.68; N, 8.90%; Calcd for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48%.

The presence of I and II in the fraction 2 was confirmed by a study of NMR spectrum. Besides the resonance signals of I and II, there were other signals at τ 4.2 and 4.5. These signals were presumed to be signals of *cis*- and *trans*-III, because the following fraction was isolated from the reaction product which was obtained under similar reaction conditions: bp 81—84°C/4 mmHg; IR (neat) 2200 cm^{-1} (CN), 960 cm^{-1} (C=C); NMR ($CDCl_3$) τ 2.3—2.8 (m, 6), 4.3—4.9 (q, 1). When an ethanol solution of the fraction was treated with hydrogen peroxide under alkaline conditions, white crystals were formed; cinnamamide, mp 145—147°C; Found: C, 74.00; H, 6.16; N, 9.51%; Calcd for C_9H_9ON: C, 73.49; H, 6.16; N, 9.52%.

Reaction of Acetonitrile with Acetophenone. *1) Reaction at Room Temperature* A mixture of 24.0 g (0.2 mol) of acetophenone and solution I was allowed to stand at room temperature. The reaction product was then worked up to give the following fractions: *fraction 1*, 10.2 g (44%) of acetophenone; bp below 66°C/2 mmHg; $n_D^{13.3}$ 1.5342 (lit[6] n_D^{20} 1.5337); The IR was identical with that of acetophenone except for the weak absorption at 2180 cm^{-1} (perhaps from an impurity); *fraction 2*, 1.9 g of an unknown compound; bp 66—120°C/2 mmHg; *fraction 3*, 3.9 g of crude 3-hydroxy-3-methyl-3-phenylpropionitrile (VI); bp 120—129°C/2 mmHg; IR (neat) 3450, 1380, 1020 cm^{-1} (OH), 2185 cm^{-1} (CN), 1740 cm^{-1} (perhaps from an impurity); NMR ($CDCl_3$) τ 2.6 (m, 5), 6.5 (s, 1, –O**H**), 7.3 (s, 2, –C**H**$_2$–),

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4) According to Holtzwart,[2] half of the sodium used was consumed in the formation of cyanomethylsodium by the following equation:

$$2CH_3CN + 2Na = CH_4 + NaCN + CH_2NaCN.$$

When a mixture of benzophenone (0.1 mol) and cyanomethylsodium in acetonitrile (0.2 g atom of Na in 150 m*l* of acetonitrile) was refluxed for 9 hr, the yield of β-phenylcinnamonitrile reached 88% (based on benzophenone). This suggested that 88% of the cyanomethylsodium formed was trapped by benzophenone and not by acetonitrile.

5) T. Metler, A. Uchida and S. I. Miller, *Tetrahedron*, **24**, 4290 (1968).

6) W. Foerst, "Ullmanns Enzyklopädie der technischen Chemie," 9. Band, Urban & Schwarzenberg, München-Berlin (1957), p. 559.

8.3 (s, 3, $-CH_3$) and small signals at τ 7.5 and 8.1 (perhaps from impurities), and *fraction 4*, 8.3 g (26%) of VI; bp 110—125°C/0.005 mmHg; mp 61—63°C (benzene); Found: C, 74.49; H, 7.65; N, 8.82%; mol wt, 157; Calcd for $C_{10}H_{11}ON$: C, 74.51; H, 6.88; N, 8.69%; mol wt, 161 ; (KBr Disk) 3430, 1378, 1028 cm^{-1} (OH), 2250 cm^{-1} (CN); NMR ($CDCl_3$) τ 2.7 (m, 5), 7.1 (s, 2, $-CH_2-$), 8.3 (s, 3, $-CH_3$).

2) Reaction under Reflux. A mixture of 24.0 g (0.2 mol) of acetophenone and solution I was refluxed for 3 hr. The reaction product was worked up to give the following fractions: *fraction 1*, 4.2 g (*ca.* 18%) of crude acetophenone; bp 61—91°C/3 mmHg; *fraction 2*, 7.0 g (25%) of β-methylcinnamonitrile (VII); bp 91—93 C/3 mmHg; $n_D^{12.0}$ 1.5836; IR (neat) 2210 cm^{-1} (CN), 830 cm^{-1} (C=C); NMR (neat) 2.7 (s, 5), 4.5, 4.6 (both q, total 1, J=*ca.* 1.5 cps, $-CH_3$); *fraction 3*, 0.8 g of a mixture of VI and VII; bp 140—170°C/0.001 mmHg; NMR (neat) τ 2.6 (m), 7.3 (s), 8.3 (s) which were the signals of VI and 2.7 (m), 4.5 (q), 7.7 (d) which were the signals of VII, and *a residue*, 15.5 g of an unknown compound.

Reaction of Acetonitrile with Benzophenone. A mixture of 18.2 g (0.1 mol) of benzophenone and solution I was refluxed for 9 hr. The reaction product was worked up to give the following fractions: *fraction 1*, 1.3 g of an unknown compound; bp below 160°C/1.5 mmHg; *fraction 2*, 18.1 g (88%) of β-phenylcinnamonitrile; bp 160—200°C/1.5 mmHg; mp 47—48°C (benzene-ethanol); Found: C, 88.28; H, 5.18; N, 6.79%; mol wt, 198; Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82%; mol wt, 205; NMR ($CDCl_3$) τ 2.7 (d, 10), 4.3 (s, 1, $-CH=C=$); IR (KBr Disk) 2200 cm^{-1} (CN), 840 cm^{-1} (C=C), and *a residue*, 3.0 g of an unknown compound.

When a mixture of 18.2 g of benzophenone and cyanomethylsodium (0.1 g atom of sodium in 100 m*l* of acetonitrile) was stirred for 17 hr at room temperature, 71% of benzophenone was recovered and 9% of the β-phenylcinnamonitrile was obtained. When the same reactants were refluxed for 6 hr, 35% of the benzophenone was recovered and 37% of the β-phenylcinnamonitrile was obtained.