Reactions Catalyzed by Potassium Fluoride. III. The Knoevenagel Reaction

Leon Rand, Joseph V. Swisher, and Constance J. Cronin

Department of Chemistry, University of Detroit, Detroit, Michigan

Received March 15, 1962

The ability of potassium fluoride to serve as a basic catalyst in the Knoevenagel reaction was determined using benzaldehyde and cyclohexanone with malononitrile, ethyl cyanoacetate, and ethyl malonate. Rubidium and cesium fluorides were shown to be somewhat better than potassium fluoride in the same reactions.

Several reactions have been reported recently as being catalyzed by potassium fluoride. These reactions include the Hofmann reaction in which N-chlorobenzamide is converted into phenyl isocyanate in benzene solution,[1] adipic and 2,2,5,5-tetramethyladipic acids are cyclized to the corresponding cyclopentanones,[2] and various Knoevenagel condensations are effected.[3] Since each of these reactions is typically base-catalyzed, the potassium fluoride appears to be acting as a base, even in nonpolar media. In an effort to determine qualitatively the effectiveness of potassium fluoride as the base, the Knoevenagel reaction of benzaldehyde and cyclohexanone with various active methylene-containing compounds was studied.

In an earlier paper,[2] it was suggested that the potassium fluoride was capable of abstracting a proton from an acidic substance and subsequently giving it up to a base stronger than itself. The mechanism[4] of the Knoevenagel reaction requires the formation of the anion of the active methylene-containing compound. On the basis of measurements made by Pearson and Dillon[5] on the rate constants of ionization of pseudo acids in water (equation 1) it was expected that the Knoevenagel reaction

$$>CH_2 + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \left[>CH\right]^- + H_3O^+ \qquad (1)$$

with malononitrile ($k_a = 6.5 \times 10^{-12}$; $k_1 = 0.9$ min.$^{-1}$), ethyl cyanoacetate ($k_a < 10^{-9}$; $k_1 = 0.07$ min.$^{-1}$), and ethyl malonate ($k_a = 5 \times 10^{-14}$; $k_1 = 0.0015$ min.$^{-1}$) would serve as an indication of the degree of basicity of the potassium fluoride, assuming that little or no product results from those acids whose anion formation is not promoted by the potassium fluoride. Tables I and II summarize the results of the use of potassium fluoride in nonaqueous solvents of varying polarity. In each case, equimolar quantities of the carbonyl and methylene compounds were employed with 0.5 mole-equivalent of the potassium fluoride.[6]

The yields were determined by either the method of product isolation or by measuring the decrease in concentration of reactants by vapor phase chromatography. In some cases both methods were used. In the chromatographic determinations where the yield of product was based on the decrease in concentration of the carbonyl compound, either toluene or tetralin was used as an internal standard, the choice based on efficiency of separation of each component. The yields as determined by either method generally corresponded quite closely.

Analysis of the results shows that potassium fluoride, in less than molar-equivalent amounts, is effective as a basic catalyst with active methylene compounds. With the more easily dissociated active methylene compounds, a nonpolar solvent can be employed, but generally, a solvent with a greater polarity gives a higher yield for the same time of reaction. Thus, as would be expected, the reactions carried out in ethanol and dimethylformamide consistently showed higher yields than those carried out in benzene. One of the factors probably involved is the solubility of the potassium fluoride in the different solvents.

It was interesting to observe that in many of those reactions which occurred readily, the concentration of the active methylene compound as shown by vapor phase chromatography was several per cent lower than the concentration of the carbonyl compound, particularly during the initial hours, the reactions which went over 80% in twenty-four hours did not show any difference in concentration when determined at that time. This could be taken as evidence of the fairly rapid formation of the anion and its rather slow attack on the carbonyl group or a slow subsequent step, *i.e.* the dehydration step. Further evidence is gained from the fact that benzaldehyde reacted much more readily than cyclohexanone with the same methylene compound. We are currently working on a kinetic study of these reactions using the alkali metal fluorides.

---

[1] L. Rand and M. J. Albinak, *J. Org. Chem.*, **25**, 1837 (1960).

[2] L. Rand, W. Wagner, P. O. Warner, and L. R. Kovac, *ibid.*, **27**, 1034 (1962).

[3] (a) H. Baba, H. Midorikawa, and S. Aoyama, *J. Sci. Res. Inst.*, **52**, 99 (1958); (b) H. Igarashi, H. Midorikawa, and S. Aoyama, *ibid.*, **52**, 105 (1958); (c) A. Sakurai, H. Midorikawa, and S. Aoyama, *ibid.*, **52**, 112 (1958); (d) H. Yasuda, H. Midorikawa, and S. Aoyama, *ibid.*, **53**, 19 (1959); (e) A. Sakurai, *ibid.*, **53**, 250 (1959).

[4] S. Patai and J. Zabicky, *J. Chem. Soc.*, 2030 (1960).

[5] R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).

[6] It was found that concentrations of 0.25 to 1.0 mole-equivalent of potassium fluoride did not appreciably alter the yield of products in this series.

TABLE I

CONDENSATION REACTIONS BETWEEN BENZALDEHYDE AND ACTIVE METHYLENES CATALYZED BY POTASSIUM FLUORIDE

Active methylene	Solvent	Temp., °C.	Time, hr.	Yield of product, %	
				VPC	Isolated
Malononitrile	Abs. ethanol	25	1		93
	Benzene	25	1		84
	DMF	25	1		100
Ethyl cyanoacetate	Abs. ethanol	25	1	100	100
	Benzene	60	6	94	90.5
	DMF	25	6	89	89
		60	6	100	100
Ethyl malonate	Abs. ethanol	60	6	<1	0
			24	14	0
			1 week		4
	Benzene	60	6	0	
			24	0	0
	DMF	60	6	0	0
			24	0	

TABLE II

CONDENSATION REACTION BETWEEN CYCLOHEXANONE AND ACTIVE METHYLENES CATALYZED BY POTASSIUM FLUORIDE

Active methylene	Solvent	Temp., °C.	Time, hr.	Yield of product, %	
				VPC	Isolated
Malononitrile	Abs. ethanol	60	6		Tar
	Benzene	60	6		75
	DMF	60	6		Tar
Ethyl cyanoacetate	Abs. ethanol	60	6	77	
			24	78	71
	Benzene	60	6	0	
			24	9	11
	DMF	25	18		20
		60	6	73	
			24	75	65
Ethyl malonate	DMF	60	6	0	
			24	0	0

The condensation of cyclohexanone and ethyl cyanoacetate in ethanol was run, using each of the alkali metal fluorides in 0.25 mole-equivalent amounts as the catalyst. The results, shown in Table III, are based on the decrease in the concentration of the cyclohexanone, and were determined after ninety minutes at 60° by vapor phase chromatography.

TABLE III

REACTION OF CYCLOHEXANONE AND ETHYL CYANOACETATE IN ETHANOL WITH ALKALI FLUORIDE

Fluoride	% yield
LiF	0
NaF	<5
KF	52
RbF	77
CsF	71

Since the fluoride is the most basic of the halides,[7] and since there is a decrease in the electronegativity of the alkali metals from lithium to cesium,[8] the basicity of the fluoride in the salts would tend to become greater in the same order. This increase in basicity can thus account for the increase in yield of product in the Knoevenagel reaction as shown above. The effect of solubility, however, cannot be ruled out entirely since the yields of product are in essentially the same order as the solubilities (Table IV) of the salts in alcohol. Although much less soluble than in water,[9] the order of the solubilities is the same as for alcohol. A comparison of the effect of sodium fluoride *vs.* rubidium fluoride in which their concentrations were equimolar but low enough for them both to be completely in solution would allow the basicities to be evaluated. The results of this experiment showed that the rubidium fluoride was the more active catalyst. It also showed that although equimolar amounts of the catalyst are not necessary there is a practical lower limit to the concentration that can be used.

TABLE IV

SOLUBILITIES OF THE ALKALI METAL FLUORIDES (moles/100 ml. of ethanol at 27°)

Fluoride	Solubility
LiF	<0.01
NaF	< .01
KF	.06
RbF	.16
CsF	.25

Experimental

Materials.—Sodium and potassium fluorides were obtained from Baker and Adamson, lithium fluoride from

---

[7] E. S. Gould, "Inorganic Reactions and Structure," Holt, Rinehart and Winston, New York, N. Y., 1962, p. 217.

[8] L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p. 93.

[9] N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. 1, Oxford University Press, London, 1950, p. 93.

J. T. Baker Chemical Co., and cesium and rubidium fluorides from American Potash and Chemical Corp. The benzaldehyde, cyclohexanone, and nitromethane were distilled before use. Absolute ethanol, dry benzene, and dimethylformamide were used as solvents.

Condensation of Benzaldehyde and Cyclohexanone with Active Methylene Compounds.—In a typical reaction, 0.1 mole of the carbonyl compound, 0.1 mole of the active methylene, 0.025 mole of potassium fluoride, and 50 ml. of solvent were mixed and maintained at 25 or 60° during the course of the reaction. The reaction mixture was then poured into cold water and extracted with ether. The ether was removed under reduced pressure, and the product was recrystallized from ethanol or distilled. The products obtained were ethyl benzylidenecyanoacetate, m.p. 49–51° (lit.,[3a] m.p. 50–51°) benzylidenemalononitrile, m.p. 83–84° (lit.,[10] m.p. 83.5–84°), cyclohexylidenemalononitrile, b.p. 138–140°/10 mm., $n^{25}\text{D}$ 1.5104 (lit.,[11] b.p. 137–138°/10 mm., $n^{25}\text{D}$ 1.5110), and ethyl cyclohexylidenecyanoacetate, b.p. 159–165°/15 mm., $n^{25}\text{D}$ 1.4963 (lit.,[12] b.p. 150–151°/9 mm., $n^{25}\text{D}$ 1.4950). The per cent yields of products isolated are listed in Tables I and II. Those reactions that were analyzed by vapor phase chromatography contained 0.19 mole of the carbonyl compound, 0.19 mole of the active methylene, 0.095 mole of potassium fluoride, 10 ml. of solvent, and the internal standard, tetralin or toluene. The components of the reaction mixture were separated on a 6-ft. "Tide" column, using a Barber-Colman chromatograph, Model 23C. Amounts of starting materials remaining were determined at 0, 6, and 24 hr.

Effect of Catalyst Concentration.—In order to determine if the amount of catalyst had any effect on the results of these condensation reactions, the reaction of 10.6 g. (0.1 mole) of benzaldehyde and 11.3 g. (0.1 mole) or ethyl cyanoacetate in 50 ml. of ethanol was catalyzed by 0.025 mole, 0.050 mole, and 0.1 mole of potassium fluoride, respectively. An essentially quantitative yield of the ethyl benzylidenecyanoacetate was obtained from each reaction after 6 hr. at 60°. When potassium fluoride was omitted, no product could be isolated.

Comparison of Alkali Fluoride Catalysts.—Lithium fluoride, sodium fluoride, potassium fluoride, rubidium fluoride, and cesium fluoride in amounts of 0.0024 mole, were each used to catalyze the reaction between 0.93 g. (0.0095 mole) of cyclohexanone and 1.08 g. (0.0095 mole) of ethyl cyanoacetate in 10 ml. of ethanol at 60°. Tetralin (0.93 g.) was used as an internal standard. The decrease in the concentration of the starting materials was determined by vapor phase chromatography. The results after 90-min. reaction time are shown in Table III.

This reaction was repeated using ten times the quantities of all materials except the catalyst. In the two runs 0.01 g. (0.0024 mole) of sodium fluoride and 0.025 g. (0.0024 mole) of rubidium fluoride were employed. These amounts of catalysts were completely dissolved. The results, determined as above, showed that after 72 hr. the reaction catalyzed by rubidium fluoride had progressed about four times as much as the one catalyzed by sodium fluoride or to about 40% completion.

Solubility of Alkali Fluorides in Ethanol.—The solubilities were determined by adding absolute alcohol from a buret to samples of lithium fluoride (0.25 g.) sodium fluoride (0.50 g.) potassium fluoride (1.00 g.), rubidium fluoride (5.00 g.), and cesium fluoride (10.00 g.) at 27° until solution was complete. The final additions of alcohol were made over several hours and the mixtures were stirred rapidly to hasten solution. The results are summarized in Table IV.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society and to the University Research Council for support of this research.

---

(10) B. B. Corson and R. W. Stoughton, *J. Am. Chem. Soc.*, **50**, 2825 (1928).

(11) A. C. Cope and K. E. Hoyle, *ibid.*, **63**, 733 (1941).

(12) A. C. Cope, *ibid.*, **59**, 2327 (1937).

Pyrimidines. II. Chlorinated Pyrimidines Derived from Orotic Acid

HERMAN GERSHON[1a]

Pfister Chemical Works, Inc., Ridgefield, New Jersey

Received April 5, 1962

The preparation of 2,6-dichloro-4-pyrimidinecarboxylic acid, 2,5,6-trichloro-4-pyrimidinecarboxylic acid, their methyl esters, and intermediates is described. It was also found that the chlorine atoms in the 2- and 6-positions could undergo solvolysis in the presence of methyl alcohol to yield hydroxyl groups, hydrolysis of 2,6-dichloropyrimidine-4-carboxylic acid in boiling water produced uracil instead of the expected orotic acid, and treatment of 5-chloroörotic acid with phosphorus oxychloride and phosphorus pentachloride followed by reduced pressure distillation produced 2,4,5,6-tetrachloropyrimidine.

In the course of our studies on chlorinated pyrimidines, it became desirable to prepare both 2,6-di- and 2,5,6-trichloro-4-pyrimidinecarboxylic acids.

At the time that this program was initiated, the literature[1b,2] on 2,6-dichloro-4-pyrimidinecarboxylic acid was questionable. Recently, Daves,[3] *et al.*, reported the correct structure of the compound and also attempted to explain the results reported earlier.[1,2]

Scheme I summarizes the reaction sequences that were undertaken and the results that were observed, which in a number of cases, were unexpected.

Starting with orotic acid[4] (I), orotyl chloride (II) was produced by refluxing with excess thionyl chloride in the presence of a catalytic quantity of pyridine. Without isolating the acid chloride, methyl alcohol was added both to decompose any

---

(1a) Present address: Boyce Thompson Institute for Plant Research, Yonkers, New York.

(1b) G. Biscaro and E. Belloni, *Ann. Soc. Chim. Milano*, **11**, 71 (1905).

(2) M. Bachstez, *Ber.*, **63A**, 1000 (1930).

(3) G. D. Daves, Jr., F. Baiocchi, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 2755 (1961).

(4) Orotic acid monohydrate was employed and offered no disadvantages over the anhydrous acid under the conditions of these reactions.