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Investigations on the Michael Reaction. V. Michael Condensation with Alkali-Metal Fluorides as Catalysts

by

A. OSTASZYŃSKI, T. URBAŃSKI and J. WIELGAT

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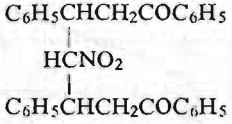
In our previous work [1] condensation of ethyl acetoacetate with various acceptors was carried out by using anhydrous commercial potassium fluoride as catalyst. At present, further attempts at Michael condensation between some donor and acceptor compounds were made in the presence of alkali-metal (other than potassium) fluorides as catalysts.

In the presence of potassium fluoride, nitromethane condensed with chalcone to give the crystalline 1.5-dibenzoyl-2,4-diphenyl-3-nitropentane (I).



$$\begin{array}{l} C_6H_5CHCH_2COC_6H_5 \\ \quad\;\;| \\ \quad\;\;HCNO_2 \\ \quad\;\;| \\ C_6H_5CHCH_2COC_6H_5 \end{array}$$

(I)

Two diastereoisomers of (I) have been isolated, m.p's. 244—245°C and 156—157°C [2].

Condensation of nitromethane with *p*-benzoquinone catalyzed by potassium fluoride, was vigorous and the reaction mixture darkened immediately. A tar was obtained, from which no crystalline product could be isolated. Modification of reaction conditions, viz., lower temperature, different solvent, and varying amounts of catalyst proved ineffective.

Attempts at condensing fluorene with chalcone, and cyclohexanone with methyl vinyl ketone, or chalcone in the presence of potassium fluoride, failed.

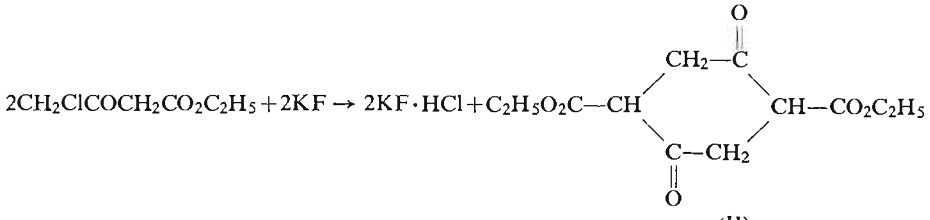
Even prolonged heating of the reaction mixture for 10, 30 or 120 hr. at 70° gave nothing but recovery of the starting materials.

Unexpectedly, the analogous reactions of ethyl α- or γ-chloroacetoacetate and ethyl γ-fluoroacetoacetate were also a failure.

Methyl vinyl ketone or ethyl fumarate added to γ-chloroacetoacetate reacted in the presence of potassium fluoride to give the crystalline product $C_{12}H_{16}O_6$, m.p. 127—128°C, in each case in the same yield.

Potassium fluoride alone (without acceptor) did also react with γ-chloroacetoactate at room temperature to afford the same product in identical yield. Ethanol did not affect the yield.

The aqueous potassium fluoride became strongly acidic and contained chloride ions. The crystalline product 2,5-dicarbethoxycyclohexane-di-1,4-one (II) was the result of the condensation of two ethyl γ-chloroacetoacetate molecules [3], during which two molecules of hydrogen chloride were split off according to the equation:



(II)

Since the γ-chlorine is very mobile, even the freshly distilled ester contains a small amount of hydrogen chloride (through hydrolysis). This combines with neutral potassium fluoride to form KF·HCl. The hydrolysis continues to proceed until an equilibrium becomes established; this, however, occurs at a *pH* too low to permit the Michael reaction.

When acid potassium fluoride was added to ethyl γ-chloroacetoacetate or ethyl γ-fluoroacetoacetate no reaction occurred.

Neutral potassium fluoride reacted exothermally with ethyl γ-fluoroacetoacetate to give the product with m.p. and IR spectrum identical with those of (II) (Fig. 1).

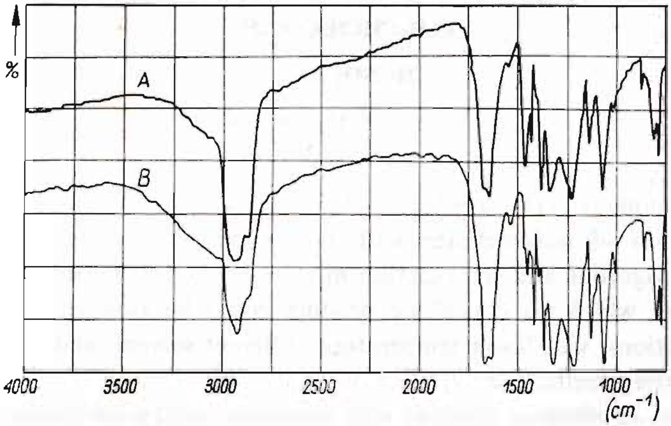
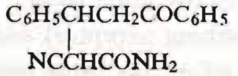


Fig. 1. IR spectra of intramolecular condensation products of ethyl γ-chloroacetoacetate (A) and γ-fluoroacetoacetate (B)

Condensation of ethyl α-chloroacetoacetate with chalcone gave a negative result. Unreacted chalcone was recovered.

In the presence of potassium fluoride, cyanoacetamide reacted with chalcone to yield a crystalline product, m.p. 152—154°C, presumably 1-benzoyl-2-phenyl-3-cyano-3-carbamidopropane (III).



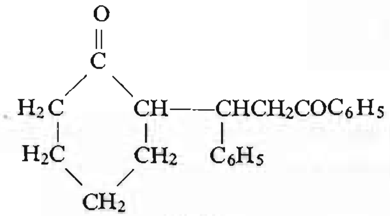
$$\begin{array}{l} C_6H_5CHCH_2COC_6H_5 \\ \quad\;\; | \\ NCCHCONH_2 \end{array}$$

(III)

The presence of the CN group was confirmed by the IR spectrum (2250 cm.$^{-1}$). Difficulties in preparing the pure substance prevented, however, precise establishment of its structure and properties. Further investigations are in progress.

For comparison of catalytic effects of other alkali-metal fluorides, including ammonium fluoride, Michael condensations were carried out in their presence.

With lithium, sodium or ammonium fluoride as catalyst ethyl acetoacetate failed to react with chalcone, even on heating the reaction mixture for several hours. Attempts at condensing ethyl acetoacetate or nitromethane with *p*-benzoquinone in the presence of lithium fluoride were also unsuccessful. On the contrary, rubidium fluoride showed a greater activity than did potassium fluoride, and, in its presence, cyclohexanone condensed with chalcone to give 2-(α-phenyl)-β-benzoylethylcyclohexanone (IV) [4].



(IV)

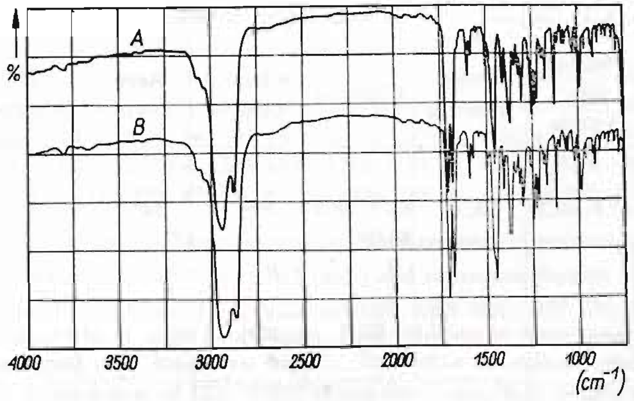


Fig. 2. IR spectra of cyclohexanone–chalcone condensation products. A – RbF as catalyst, B – $NaOC_2H_5$ as catalyst

An interesting result was obtained when ethyl acetoacetate was condensed with chalcone in the presence of rubidium fluoride. The normal condensation product, i.e. the monoderivative (VA) obtained in the presence of potassium fluoride had a m.p. of 122°C [1]. With potassium fluoride replaced by rubidium fluoride, a crystalline product (VB) with the same empirical formula, but m.p. 173—174°C, was obtained.

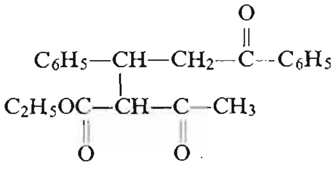
The 2,4-dinitrophenylhydrazine derivatives of compounds (VA) and (VB) have the same m.p. (175—177°), IR spectra and elemental analyses, although the spectra of the compounds VA and VB are different.

Compound VB produces a strong band at 3434 cm.$^{-1}$ also in dilute solution, assignable to O—H stretching vibrations and a few bands at 3101.5, 3077 and

3044 cm.$^{-1}$ corresponding presumably to hydrogen bonded OH groups and, in the region 1700 cm.$^{-1}$, two strong bands at 1744.5 cm.$^{-1}$ and 1712.5 cm.$^{-1}$ attributable to two ketonic C=O bonds.

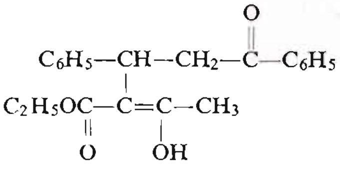
The spectrum of compound VA possesses bands neither in the 3400 nor in the 3100 cm.$^{-1}$ region. Its three strong bands at 1729, 1712 and 1681 cm.$^{-1}$ should be assigned to the C=O groups.

The compounds (VA) and (VB) differ most likely as ketonic and enolic forms, respectively.



$$\begin{array}{l} C_6H_5-CH-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-C_6H_5 \\ \qquad\qquad | \\ C_2H_5O\underset{\underset{\displaystyle O}{\|}}{C}-CH-\underset{\underset{\displaystyle O}{\|}}{C}-CH_3 \end{array}$$

(VA)



$$\begin{array}{l} C_6H_5-CH-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-C_6H_5 \\ \qquad\qquad | \\ C_2H_5O\underset{\underset{\displaystyle O}{\|}}{C}-C=\underset{\underset{\displaystyle OH}{|}}{C}-CH_3 \end{array}$$

(VB)

The latter might contain an intramolecular hydrogen bond between OH and C=O groups. Compound (VB) was also obtained by the condensation of ethyl aceto-

TABLE

Acceptor / Donor	Condensation product, yield %						
	Methyl vinyl ketone	Ethyl fumarate	Chalcone	*p*-Benzoquinone	Acrylonitrile	No acceptor	Catalyst
Ethyl acetoacetate	45.8; 60.3^b	50; 0^b	64.5; 58.4^c	39^d	52^e		KF
			63.0^a				RbF
			0	0			LiF
			0				NH_4F, NaF,
Nitromethane			52.2^f	tar			KF
				0			LiF
Cyclohexanone	0		0				KF
			35				RbF
Fluorene			0				KF
Ethyl γ-chloroacetoacetate	10^g		10^g			10^g	KF
						0	KF. HF
Ethyl γ-fluoroacetoacetate						10^g	KF
Ethyl α-chloroacetoacetate			0				KF
Cyanoacetamide			85.6				KF

a) one stereoisomer; b) at room temp.; c) less KF; d) quinhydrone; e) two adducts; f) two stereoisomers; g) intermolecular condensation; 0 denotes that no reaction took place.

acetate with chalcone in the presence of sodium ethoxide on very intensive heating. The investigations on the structure of these compounds are continued.

The results of the present and previous papers are presented in the Table.

Experimental

Condensation of nitromethane with chalcone

A mixture of nitromethane (2.0 g., 0.033 mole), chalcone (7 g., 0.033 mole) and neutral dry potassium fluoride (3.3 g., 0.05 mole) in ethanol (25 ml.) was kept 24 hr at room temperature. Subsequently, the mixture was heated 6 hr at 60°C and cooled. The resulting white precipitate was filtered, dissolved in hot acetone (400 ml.) and insoluble potassium fluoride was filtered off. After cooling of the acetone solution, white crystals of (I) separated which, upon recrystallization from toluene, had m.p. 244–245°C. (Calc. for $C_{31}H_{27}O_4N$: C, 78.0; H, 5.7; N, 2.9; found C, 78.05; H, 6.0; N, 3.1%).

The acetone filtrate was concentrated and cooled to crystallize the second stereoisomer of (I) 3.7 g. m.p. 156–157°C (from ethanol. ($C_{31}H_{27}O_4N$ requires: C, 77.97, H, 5.7, N, 2.93; found: C, 77.6, H, 5.85, N, 2.93%).

Condensation of cyclohexanone with chalcone in the presence of rubidium fluoride

Rubidium carbonate prepared by the method of Suhrmann and Clusius [7] was converted by hydrofluoric acid into rubidium fluoride. A mixture of cyclohexanone (1.8 g., 0.018 mole), chalcone (3.6 g., 0.017 mole), rubidium fluoride (1.8 g., 0.017 mole), and absolute ethanol (5 ml.) was refluxed 10 hr. at 60–65°C with stirring and cooled. Some water was added to dissolve RbF and the mixture was filtered. The precipitated 2-(α-phenyl)-β-benzoyl-ethylcyclohexanone (IV) (1.9 g., 35%) was recrystallized from ethanol, m.p. 148.5–149.5°C.

The same product was obtained by condensation of cyclohexanone with chalcone according to Allen and Sallans [5]. The m.p. of the mixed compounds was 148.5–149.5°C, and their IR spectra were identical (Fig. 2): 3056 vw, 3033vw, 1743 vs, 1679 vs, 1603, 1580, 1540 vw, 1500, 1453 s. 1410, 1368, 1342, 1320, 1307, 1262 vw, 1248, 1233, 1219, 1191, 1174, 1125, 1106, 1075, 1063, 1023 w, 1005 w, 988, 962, 924 vw, 915, 889, 856 vw, 837 vw, 809, 783 vw, 757 and 750 cm.$^{-1}$.

Condensation of ethyl γ-chloroacetoacetate in the presence of potassium fluoride

(1) When γ-chloroacetoacetate (5. g., 0.033 mole) and potassium fluoride (1.6 g. 0.033 mole) were mixed together, an immediate exothermic reaction took place and the solution darkened. The mixture was kept 10 hr at room temperature. After addition of some water, an oily layer separated which was dried over anhydrous $MgSO_4$. The white crystalline condensation product (II) [3] (0.5 g., 10%) had a m.p. of 127–128°C (Calc. for $C_{12}H_{16}O_6$ C, 56.28; H, 6.25; found C, 56.75; H, 6.56%) and an IR spectrum: 1660, 1637 s, 1545 w, 1458, 1429, 1377, 1334, 1225, 1137, 1119, 1070, 1019 vw, 868 w, 806 and 788 cm.$^{-1}$.

(2) The mixture of γ-chloroacetoacetate and vinyl ketone or chalcone made to react with potassium fluoride added in the equimolar amount, yielded the same product (0.5 g.)(II).

Condensation of ethyl γ-fluoroacetoacetate in the presence of potassium fluoride

When potassium fluodrie (0.65 g., 0.013 mole) was added to γ-fluoroacetoacetate (2 g., 0.013 mole) an exothermic reaction took place. Ethanol (5 ml.) was added and the solution was kept 24 hr at room temperature. Potassium fluoride was filtered off, and from the filtrate, crystals (100 mg., m.p. 126–127°C) were obtained. The product was identical with (II). The m.p. of the mixture did not show any depression.

Condensation of cyanoacetamide with chalcone

A mixture of cyanoacetamide (4.2 g., 0.05 mole), chalcone (10.4 g., 0.05 mole) and potassium fluoride (1 g., 0.03 mole) in ethanol (15 ml.) was heated 2 hr. at 60–65°C. Water was added to dissolve the fluoride. Extraction with ether afforded the product (III) (12.5 g., 85.5%), $C_{18}H_{16}N_2O_2$,

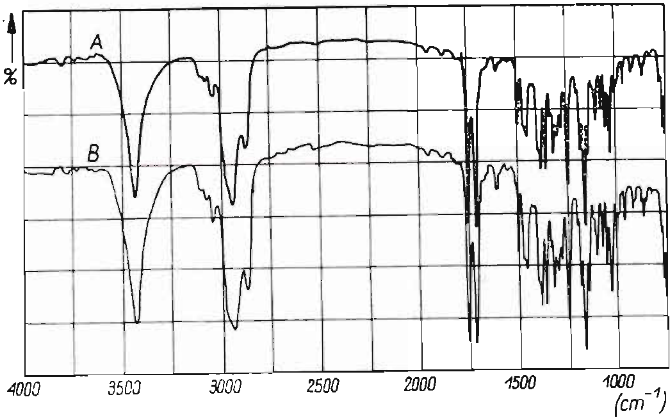


Fig. 3. Spectra of chalcone–ethyl acetoacetate condensation products (m.p. 174–177°C). A – RbF as catalyst, B – $NaOC_2H_5$ as catalyst

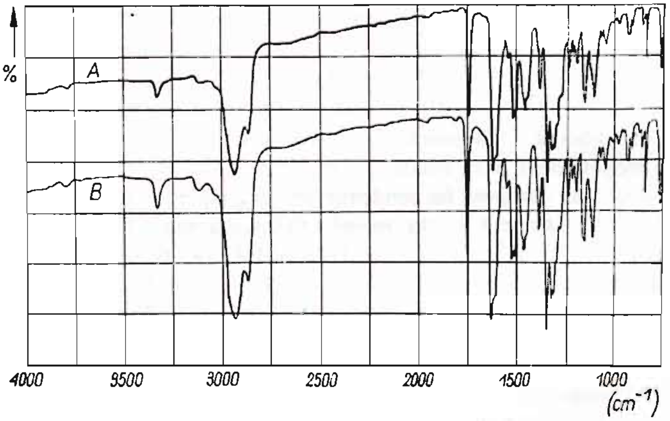


Fig. 4. IR spectra of both DNP derivatives of chalcone–ethylacetoacetate condensation products

m.p. 152–154°C ($C_{18}H_{16}N_2O_2$ requires C, 73.95; H, 5.52; N 9.58; Found: C, 75.59; H, 5.70; N, 9.99%). For verification of the structure of compound (III) cyanoacetamide was condensed with chalcone according to Kohler and Souther [6]. The product obtained had a m.p. of 180–181°C (Calc. for $C_{18}H_{16}N_2O_2$ C, 73.95; H, 5.52; N, 9.58; found: C, 74.19; H, 6.26; N, 8,86%) and no band in the region 2250 cm.$^{-1}$.

Condensation of ethyl acetoacetate with chalcone in the presence of rubidium fluoride

A mixture of ethyl acetoacetate (1.2 g., 0.0094 mole), chalcone 1.9 g., 0.0094 mole), rubidium fluoride (1 g., 0.0094 mole) and absolute ethanol (5 ml.) was refluxed 2 hr. at 60–65°C and cooled. The resulting precipitate was filtered, washed with water (to remove RbF) and cold ether, and recrystallized from ethanol to give the product (VB) (2.2 g., 63%, m.p. 174–176°C) ($C_{21}H_{22}O_4$ requires: C, 74.53; H, 6.55; found: C, 74.92; H, 6.24%). The IR spectrum was: 3434 vs, 3101 vw, 3078 w, 3045 w, 1948 w, 1872 w, 1787 w, 1747 vs, 1713 vs, 1665 vw, 1064 w, 1538 vw, 1498, 1450, 1420 vw, 1382 s, 1354 s, 1332 w, 1316, 1292, 1280, 1240 s, 1203 w, 1184, 1165 vs, 1141, 1118 vw, 1099, 1070, 1047, 1026, 1000, 960, 920 w, 910 vw, 725 vw, 860, 846 vw, 815 vw, 773, 762 and 750 cm.$^{-1}$.

Condensation of ethyl acetoacetate with chalcone in the presence of sodium ethoxide

A mixture of ethyl acetoacetate (1.9 g., 0.0094 mole), chalcone (1.2 g., 0.0095 mole), absolute ethanol (3 ml.) and a few drops of alcoholic sodium ethoxide was quickly brought to boiling. The mixture was kept 24 hr at room temperature and, a white solid precipitated which was filtered, washed with water and cold ether. The product (VB) (2.5 g., 71.5% yield) had m.p. 174–177°C (Calc. for $C_{21}H_{22}O_4$ C, 74.53; H, 6.55; found C, 74.15; H, 6.78%). The m.p. of the mixture of this compound with that obtained in the condensation with rubidium fluoride did not show any depression, and their IR spectra were identical (Fig. 3). The reaction of both these compounds (VA, m.p. 122°C; VB, 174–176°C) with 2,4-dinitrophenylhydrazine (DNP) gave the derivatives: (a) m.p. 175–177°C and (b) 176–178°C. The m.p. of the mixture of both these compounds did not show any depression and their IR spectra (Fig. 4) were identical. ($C_{27}H_{26}O_7N_4$ requires: N, 10,85; found (a): N, 11.23; (b) N, 11,29%).

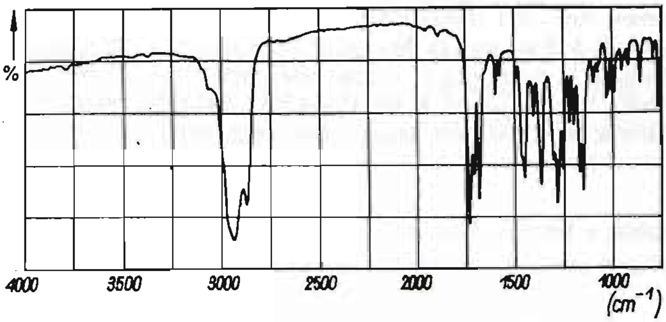


Fig. 5. IR spectrum of chalcone–ethylacetoacetate condensation product, m.p. 122°C (KF – catalyst)

The IR spectrum of DNP shows the following bands: 3323, 1736, 1608 vs, 1540, 1512, 1500, 1450, 1438, 1377, 1335 vs, 1311, 1299, 1285, 1266, 1226, 1200, 1182, 1151, 1144, 1104, 1056, 1035 vw, 1000 vw, 969, 927, 905 vw, 865 vw, 851, 837, 759 and 750 cm.$^{-1}$.

The spectrum (Fig. 5) of the ethyl acetoacetate and chalcone condensation product, (VA) m.p. 122°C, has the following bands: 3061 vw, 1899 vw, 1729 vs, 1712, 1681 s, 1599, 1580 w, 1561 vw, 1448, 1403, 1363, 1304, 1283 s, 1252, 1224, 1201, 1170, 1151 s, 1099 w, 1079 vw, 1068 vw, 1030, 1007, 993, 948 w, 934 vw, 915 w, 856, 790, 764 and 750 cm.$^{-1}$.

Conclusions *)

1. Potassium fluoride has proved to be an active catalyst for the Michael condensation of ethyl acetoacetate, nitromethane and acetamide with such acceptors as methyl vinyl ketone, ethyl fumarate, chalcone, and acrylonitrile.

2. With potassium fluoride replaced by sodium, lithium or ammonium fluoride the reaction failed to proceed.

3. Rubidium fluoride is a more active catalyst than is potassium fluoride, as observed in the condensation of cyclohexane with chalcone.

4. In the reaction of ethyl acetoacetate with chalcone in the presence of rubidium fluoride, the second stereoisomer of the normal condensation product was obtained.

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*) Concerning previous and present work.

5. By the reaction of ethyl acetoacetate with p-benzoquinone in the presence of potassium fluoride, quinhydrone was obtained.

6. If potassium fluoride is added to ethyl γ-chloro- or γ-fluoroacetoacetate, autocondensation takes place with the formation of 2,5 carbethoxy cyclohexane-di-1.4-one.

INSTITUTE OF ORGANIC SYNTHESIS, POLISH ACADEMY OF SCIENCES
(ZAKŁAD SYNTEZY ORGANICZNEJ, PAN)

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