THE CONDENSATION OF METHYL TRIFLUOROPYRUVATE WITH CARBONYL COMPOUNDS

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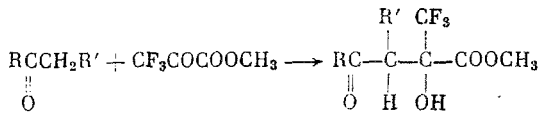
Methyl pyruvate in the absence of catalyst forms stable aldol condensation products with carbonyl compounds in high yield. This reaction is facilitated by a high enol form content in the carbonyl compound. The erythro-threo selectivity of this reaction was evaluated and high steric specificity in the case of cyclopentanone and cyclohexanone was demonstrated.

Polyfluoroketones form stable aldol condensation products with ketones upon heating in the absence of solvent [1]. In the present communication, we examine the analogous reactions of methyl pyruvate.*

Methyl pyruvate (I) was found to undergo uncatalyzed condensation with β-diketones, esters of β-oxocarboxylic acids, and aliphatic and aryl aliphatic ketones, which are capable of enolization.



(I) (II)—(VIII)

R = CH_3, R′ = $COCH_3$ (II); R = Ph, R′ = $COCH_3$ (III); R = CH_3, R′ = $COOC_2H_5$ (IV); R = Ph, R′ = H (V); R = CH_3, R′ = H (VI); R, R′ = $-(CH_2)_3-$ (VII); R, R′ = $-(CH_2)_4-$ (VIII).

The reaction conditions are a function of the content of the enol form in the carbonyl compound. At 20-25°C, acetylacetone, benzoylacetone, and ethyl acetoacetate form (II)-(IV), respectively, in 90-95% yield 3 h after mixing with ester (I) without solvent. Under these conditions, acetophenone, acetone, cyclopentanone, and cyclohexanone are converted to condensation products (V)-(VIII), respectively, in 60-80% yield after seven days. Heating ester (I) with the corresponding ketone at 100°C leads to the formation of (V)-(VIII) in 80-90% yield.

^1H and ^{13}C NMR spectroscopy indicated that (II)-(VIII) exist in the keto form in light of the finding of a methyl carbon signal in the ^{13}C NMR spectrum, magnetic nonequivalence of the CH_2 groups in the PMR spectra of (V) and (VI), and the methine proton signal in the PMR spectra of (VII) and (VIII). This conclusion is in accord with the data of Ioffe et al. [3], who mentioned that esters of β-oxocarboxylic acids and β-diketones, which have bulky substituents at the α position, exist in the ketone form.

The erythro-threo selectivity in the formation of aldols (III), (IV), (VII), and (VIII) was evaluated using the ^1H and ^{19}F NMR spectra. The isomer ratio was found from the ratio of the integral intensities of the methyl group signals (for (III) and (IV)), methine proton signals (for (VII) and (VIII)) in the PMR spectra and of the CF_3 signals in the ^{19}F NMR spectra. The assignments in the NMR spectra were carried out after completion of the reaction and prior to purification of the product. At 25°C, (III) was obtained as a 2.3:1 mixture of isomers, while (IV) was obtained as a 1.6:1 mixture. The ratio of the forms was 1.8:1 in the case of (VII) obtained at 25°C, but raising the reaction temperature to 100°C led to a sharp increase in this ratio to 8.7:1. An increase in the reaction temperature in the preparation of (VII) also led to a change in the isomer ratio from 1.6:1 to 4.4:1. The isomer, whose methine proton signal is at lower field, predominates in both (VII) and (VIII). Crystallization of (VII) and (VIII) from hexane gave the predominant isomers in pure form. A study of the geometry of these isomers is underway.

*The work of Saloutin et al. [2], who described the reaction of methyl pyruvate with acetone, appeared after the completion of this study.

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TABLE 1. Properties of (II)-(VIII)

Compound	Yield, %		Mp, °C	Found/Calculated, %			Chemical formula
	method A	method B		C	H	F	
(II)	92	–	48–50	42,10 / 42,19	3,90 / 4,30	22.24 / 22.26	$C_9H_{11}F_3O_5$
(III)	90	–	67–69 *	52,53 / 52,83	3,78 / 4,09	18,25 / 17,92	$C_{14}H_{13}F_3O_5$
(IV)	95	–	51–53 *	41,48 / 41,96	4,55 / 4,54	19,73 / 19,93	$C_{10}H_{13}F_3O_6$
(V)	75	85	85–87	52,02 / 52,17	3,65 / 3,99	21,08 / 20,65	$C_{12}H_{11}F_3O_4$
(VI)	60	80	61–63	39,08 / 39,25	3,94 / 4,20	26,80 / 26,63	$C_7H_9F_3O_4$
(VII)	80	90	59–60 **	45,09 / 45,00	4,25 / 4,58	23,59 / 23,75	$C_9H_{11}F_3O_4$
(VIII)	80	88	57–59 **	47,27 / 47,24	5,34 / 5,12	22,48 / 22,44	$C_{10}H_{13}F_3O_4$

*Melting point of isomer mixture.
**Melting point of isomer mixture obtained according to general method B.

TABLE 2. IR Spectra (ν, cm^{-1}) and ^{13}C NMR Spectra in $CDCl_3$ (δ, ppm, $^1J_{C-F}$ = 285 Hz) of (II)-(VIII)

Compound	IR spectrum	^{13}C NMR spectrum			
		OCH_3	CF_3	$CH(CH_2)$	other carbon atoms
(II)	1700, 1730, 1755 (C=O), 3470 (OH)	60,49	123,39 q	53,50	200,52; 200,08; 167,90 (C=O); 30,56; 29,48 (CH_3)
(III)	1710, 1755, 1765 (C=O), 3465 (OH)	63,93	119,81 q	54,21	199,90; 194,10; 167,1 (C=O); 134,70; 128,99 (Ph); 30,28 (CH_3)
(IV)	1715, 1745, 1765 (C=O), 3465 (OH)	59,80	122,47 q	54,38	200,99; 167,93; 165,8 (C=O); 62,57 (CH_2); 13,69 (CH_3)
(V)	1685, 1750 (C=O), 3480 (OH)	52,24	121,37 q	38,87	193,08; 167,54 (C=O); 133,94; 132,17; 126,9; 126,27 (Ph)
(VI)	1715, 1770 (C=O), 3400 (OH)	54,03	122,90 q	44,83	203,51; 169,10 (C=O); 30,30 (CH_3)
(VII)	1740, 1760 (C=O), 3400 (OH)	52,51	124,79 q	55,15	170,83 (C=O); 38,69; 25,30; 21,31 ($-(CH_2)_3-$)
(VIII)	1710, 1765 (C=O), 3390 (OH)	52,94	122,76 q	53,43	208,25; 169,46 (C=O) 41,48; 26,48; 26,13; 23,91 ($-(CH_2)_4-$)

We should note that the methine proton signal of both forms of (VIII) is a doublet of doublets with J = 6.0 and 12.4 Hz. This finding indicates fixation of the ring in (VIII) in a conformation with equatorial orientation of the α-carbomethoxy-α-hydroxytrifluoroethyl group. Such an effect has been noted for the product of the reaction of hexafluoroacetone and 4-tert-butylcyclohexanone [4].

Condensation products (II)-(VIII) are stable upon heating and do not tend to undergo spontaneous dehydration. These products are white crystalline compounds. The structures of (II)-(VIII) were demonstrated by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and elemental analysis.

TABLE 3. ^1H and ^{19}F NMR Spectra (δ, ppm, J, Hz) of (II)-(VIII)

Compound	Solvent	^1H		^{19}F
		OCH_3	other protons	
(II)	CCl_4	3,85 s	4,33 s (1H, CH); 2,31 s (3H, CH_3); 2,18 s (3H, CH_3); 4,50 br.s (1H, OH)	
(IIIa)	DMSO-d_6	3.64 s	8,06–7,43 (5H, Ph); 7,30 s (1H, OH); 5,30 s (1H, CH); 2,17 s (3H, CH_3)	–3,68 s
(IIIb)	DMSO-d_6	3.74 s	8.06–7,43 (5H, Ph); 7,14 s (1H, OH); 5,95 s (1H, CH); 2,06 s (3H, CH_3)	–4,24 s
(IVa)	DMSO-d_6	3,86 s	7,74 s (1H, OH); 4,23 q (2H, OCH_2); 4,15 s (1H, CH) 2,30 s (H, CH_3); 1,26 t (3H, CH_3)	–3,80 s
(IVb)	DMSO-d_6	3,80 s	7,15 s (1H, OH); 4,30 s (1H, CH); 4,26 q (2H, OCH_2); 2,20 s (3H, CH_3); 1,30 t (3H, CH_3)	–3,70 s
(V)	CCl_4	3,97 s	7,80–7.44 (5H, Ph); 4,11 br.s (1H, OH); 3.77and 3.65 (2H, CH_2,AB system ma, J_{H-H}=17,6)	1,2 s
(VI)	$CDCl_3$	3.86 s	3,23 and 3,11 (2H, CH_2, AB system J_{H-H}=17,6) 2,18 s (3H, CH_3)	
(VIIa)	$CDCl_3$	3.88 s	2,95 d.d (1H, CH, J=8,5 and 11.0); 2.37-1,64 (6H, $-CH_2CH_2CH_2-$)	–1.51 s
(VIIb)	$CDCl_3$	3.77 s	2,60 d.d (1H, CH, J=8,5 and 11,0); 2,37–1,64 (H, $-CH_2CH_2CH_2-$)	–1.36 s
(VIIIa)	$CDCl_3$	3,76 s	3,26 d.d (1H, CH, J=6.0 and 12.4); 2.47 1,56 (8H, $-CH_2CH_2CH_2CH_2-$)	–3,27 s
(VIIIb)	$CDCl_3$	3.99 s	3.03 d.d (1H, CH, J=6.0 and 12.4); 2.47 1,56 (8H, $-CH_2CH_2CH_2CH_2-$)	–2,81 s

EXPERIMENTAL

The NMR spectra were taken on a Bruker WP-200-SV spectrometer at 200.13 MHz for the PMR spectra, 188.31 MHz for the ^{19}F NMR spectra, and 50.31 MHz for the ^{13}C NMR spectra, The chemical shifts are given relative to TMS as an internal standard for the ^1H and ^{13}C NMR spectra and CF_3CO_2H as an external standard. The IR spectra were taken on a UR-20 spectrometer.

The reaction of ester (I) with carbonyl compounds (general procedure). A. A sample of 7.8 g (0.05 mole) ester (I) was added with stirring to 0.05 mole carbonyl compound, maintaining the temperature at 20-25°C. The mixture was maintained under these conditions for 3 h in the preparation of (II)-(IV) or seven days in the case of (V)-(VIII). The product was separated by crystallization from hexane.

B. A mixture of 0.05 mole carbonyl compound and 7.8 g (0.05 mole) ester (I) was heated for 3 h in a glass ampule at 100°C. The product was separated by crystallization from hexane.

A fivefold excess of acetone was used in carrying out the reaction of ester (I) with acetone both by procedures A and B.

The reaction conditions, yields, and elemental analysis results of the methyl esters of 2-hydroxy-2-trifluoromethyl-substituted 4-oxo-3-acetylpentanoic (II), 3-benzoyl-4-oxopentanoic (mixture of isomers (IIIa) and (IIIb)), 3-acetylsuccinic (mixture of isomers (IVa) and (IVb)), 4-oxo-4-phenylbutanoic (V), and 4-oxopentanoic acids (VI), as well as the methyl esters of 2-hydroxy-2-(cyclopentanon-2-yl)- (mixture of isomers (VIIa) and (VIIb)) and 2-hydroxy-2-(cyclohexanon-2-yl)trifluoropropionic acids (mixture of isomers (VIIIa) and (VIIIb)) are given in Tables 1-3.

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THE C-ALKYLATION OF SOME HETEROAROMATIC COMPOUNDS BY THE TRIFLUOROACETYLIMINE OF METHYL TRIFLUOROPYRUVATE

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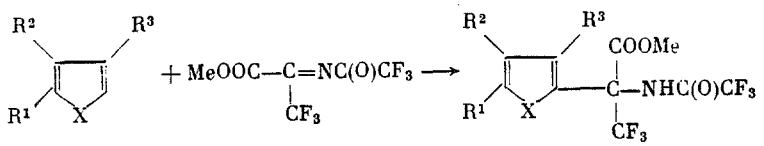
The trifluoroacetylimine of methyl trifluoropyruvate regiospecifically C-alkylates furan, N-methylpyrrole, and thiophenes at the free C^2 position, indoles at the C^3 position, and 1-phenyl-3-methyl-5-pyrazolone at the C^4 position. The alkylation products were converted to trifluoromethylated amino acids and their ester and amine derivatives.

The C-alkylation of indoles and thiophene by the benzenesulfonylimine of methyl trifluoropyruvate was described in our previous work [1]. Details are given below for the reactions of the trifluoroacetylimine of methyl trifluoropyruvate (I) with some five-membered heterocyclic compounds.

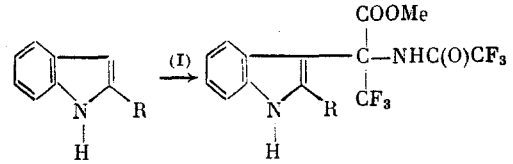
Thiophene derivatives are selectively alkylated by imine (I) in CCl_4 at reflux at the free C^2 position to give thiophenes (II)-(VI) in preparative yields. Furan and N-methylpyrrole undergo this reaction in chloroform from −50 to +20°C to give the C^2-alkylation products (VII) and (VIII).



(I) (II)—(VIII)

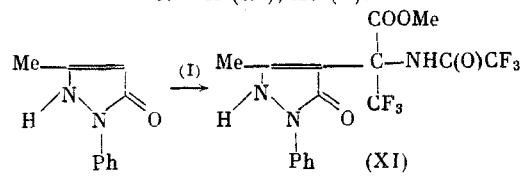
X = S, $R^1 = R^3 = H$, R^2 = *p*-Tol(II); X = S, R^1 = Ph, $R^2 = H$, R^3 = = Me(III); X = S, $R^1 = R^2$ = Ph, R^3 = Me(IV); X = S, R^1 = Me, R^2 = = H, R^3 = Ph(V); X = S, $R^1 = H$, R^2 = Ph, R^3 = Me(VI); X = O, $R^1 = R^2 = R^3 = H$(VII); X = N — Me, $R^1 = R^2 = R^3 = H$(VIII).

Indole, 2-methylindole, and 1-phenyl-3-methyl-5-pyrazolone react with (I) in chloroform at 20°C to give C^3-alkylated indoles (IX) and (X) and C^4-alkylated pyrazolone (XI).



(IX), (X)

R = H (IX), Me (X).



(XI)

The structure of indole (IX) was confirmed by the following transformations. The alkaline hydrolysis of (IX) gives acid (XII), which decarboxylates upon sublimation in vacuum to give

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