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REACTIONS OF FLUOROALKYL-CONTAINING α-HALOGENATED β-KETOESTERS WITH AMINES

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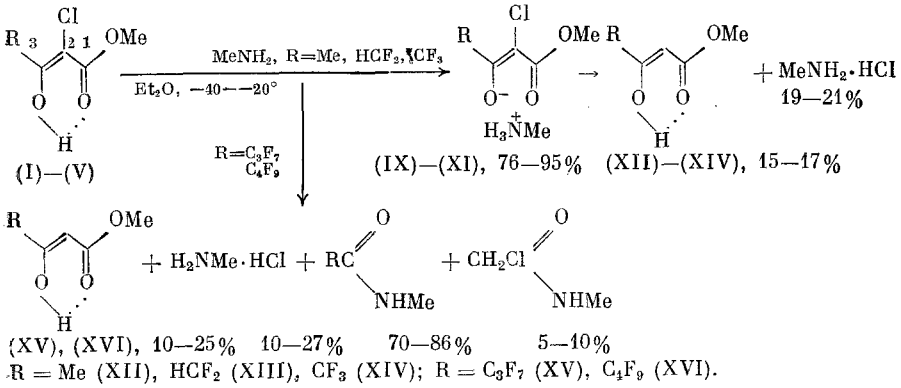
Methyl 2-chloro-4,4-difluoroacetoacetate reacts with ammonia to give methyl 2-chloro-3-amino-4,4-difluorocrotonate (65%) and difluoroacetamide (2%). When the fluoroalkyl substituent is extended and its degree of fluorination increased [CF_3, $H(CF_2)_2$, C_4F_9] only cleavage occurs and amides of fluorocarboxylic and chloroacetic acid are formed [1]. Ethyl 2,2-dibromoacetoacetate [2] and fluorine-containing 2,2-dibrominated β-ketoesters when reacting with ammonia undergo an "acidic" cleavage to give amides of dibromoacetic acid or the corresponding fluorocarboxylic acids [1]. Apart from that there is no other information about reactions of fluorine-containing α-halo-β-ketoesters with amines.

In the present work we have studied the reaction of α-chloro-β-ketoesters (I)-(V) and α,α-dibromo-β-ketoesters (VI)-(VIII) with amines (methyl-, diethyl-, and triethyl-amines) and acetamide.

Chloroketoesters (I) (R = CH_3), (II) (R = HCF_2), and (III) (R = CF_3) in equimolar ratio with methylamine in ether at −20 to −40°C form salts (IX)-(XI) (Table 1), which are gradually dechlorinated to β-ketoesters (XII)-(XIV). Chloroketoesters (IV) (R = C_3F_7) and (V) (R = C_4F_9) under these conditions give methylamides of chloroacetic and fluorocarboxylic acids together with the previously mentioned products. It is not possible to isolate salts of type (IX)-(XI), that is, increasing the length of the fluoroalkyl substituent causes stabilization of an adduct on the C^3 center, as for the reaction with ammonia [1], and there is subsequent C^2–C^3 cleavage of chloroketoesters (IV) and (V). However, when a threefold excess of methylamine is used it is possible to effect this reaction pathway also for chloroketoesters (I)-(III). It should be noted that the yield of products depends on the duration of the reaction



Changing to diethylamine and triethylamine leads not to products from C^2–C^3 cleavage but to replacement of halogen by H as a result of halophilic attack by the amine on chloroketoesters

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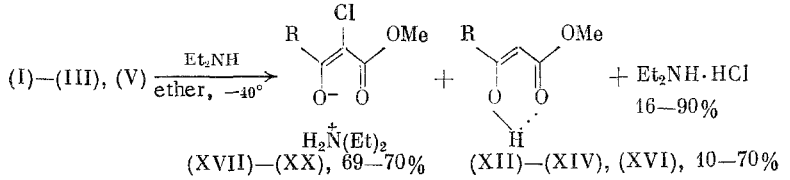
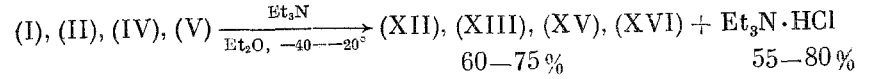
(I)-(V) to give dechlorination products (XII)-(XVI). Interpretation of the mechanism of this reaction is difficult. Thus with diethylamine, chloroketoesters (I)-(III) and (V) form salts (XVII)-(XX), which at about 20°C form a mixture of ketoesters (XII)-(XIV), (XVI), and diethylamine hydrochloride

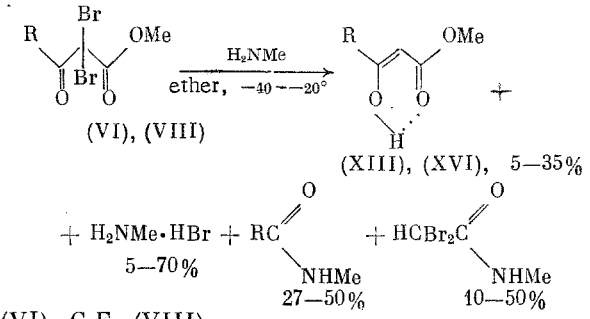


R = Me (XVII), HCF_2 (XVIII), CF_3 (XIX), C_4F_9 (XX).

A similar route is also typical for the reaction of chloroketoesters (I), (II), (IV), and (V) with Et_3N. However, in contrast to the above it is not possible to isolate salts of type (IX)-(XI) and (XVII)-(XX) because of their instability.



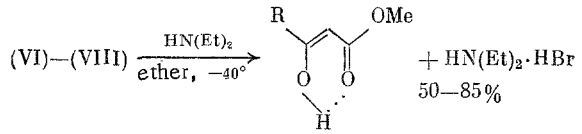
For bromoketoesters (VI)-(VIII) dehalogenation is partially effected even in the case of $MeNH_2$, regardless of the length and degree of fluorination of R, and occurs as the only route for Et_2NH. Thus, reactions of bromoketoesters (VI) (R = HCF_2) and (VIII) (R = C_4F_9) with $MeNH_2$ give the following mixtures of products.



R = HCF_2 (VI), C_4F_9 (VIII).

Conversion of (VI)-(VIII) as in the case of chloroketoesters is determined by the time of reaction.

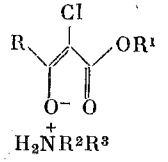
Bromoketoesters (VI)-(VIII) react with Et_2NH to give β-ketoesters (XIII), (XIV), and (XVI), which do not contain bromine



The absence of products from "acidic" cleavage of chloroketoesters and bromoketoesters reacting with Et_2NH is evidently due to steric hindrance from the latter.

It should be noted that when chloroketoesters and bromoketoesters react with NH_3 we did not isolate any ketoesters not containing a halogen in the 2-position as was found in reactions with $MeNH_2$. Evidently the existence of an additional reaction route is due to the presence of an alkyl group on the N atom. The determining influence of this factor is borne out, in our opinion, by the fact that chloroketoesters (I)-(V) and bromoketoesters (VI)-(VIII) do not react with acetamide in the temperature range −40°C to +20°C. Only in boiling chloroform is there formation of ketoesters (XIII) and (XIV) and bromo- and dibromoacetamide. However, in this case the bromoketoesters act as brominating agents towards the methyl group of acetamide, which is in agreement with previously obtained information on the bromination of acetone when treated with bromoketoesters [3]

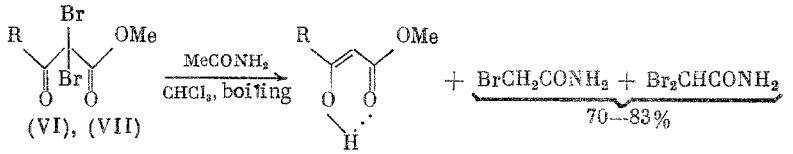
TABLE 1. Salts of α-Chloro-β-Ketoesters with Methylamine and Diethylamine



Compound	R	R^1	R^2	R^3	mp, °C	Yield, %	Found/Calculated, %					Empirical formula	IR spectrum, cm^{-1}			PMR spectrum (δ, ppm from TMS in DMSO-d_6)						
							C	H	N	F	Cl		C=O	C=C	NH	OR^1		$H_2NR^2R^3$			R	
																OCH_2	CH_3	CH_2	CH_3	NH	CH_3	HCF_2 (J, Hz)
(IX)	Me	Et	H	Me	*	95	42,66 / 42,97	6,81 / 7,21	7,01 / 7,16		18,45 / 18,12	$C_7H_{14}ClNO_3$	*			4,05	1,17	–	2,40	5,40	2,20	–
(X)	HCF_2	Me	H	Me	124–125	82	33,34 / 33,12	4,88 / 4,63	6,26 / 6,44	17,30 / 17,46	16,01 / 16,29	$C_6H_{10}ClF_2NO_3$	1640	1620	1520 2100 2500 3300	–	3,50	–	2,27	3,80	–	6,95 (56,25)
(XI)	CF_3	Me	H	Me	84–86	76	30,67 / 30,59	3,82 / 3,85	5,97 / 5,95	24,20 / 24,19	15,22 / 15,05	$C_6H_9ClF_3NO_3$	1670	1620	1520 2100 2500 3200	–	3,57	–	2,41	7,00	–	–
(XVII)	Me	Et	Et	Et	*	96	50,34 / 50,52	7,97 / 8,48	6,03 / 5,89	–	–	$C_{10}H_{20}ClNO_3$	†			4,05	1,16	2,90	1,17	5,50	2,20	–
(XVIII)	HCF_2	Me	Et	Et	123–125	76	41,66 / 41,64	6,39 / 6,21	5,39 / 5,39	14,83 / 14,63	13,37 / 13,65	$C_9H_{16}ClF_2NO_3$	1670	1620	1540 2500	–	3,56	3,00	1,20	3,80	–	7,10 (58,00)
(XIX)	CF_3	Me	Et	Et	70–72	70	39,09 / 38,93	5,61 / 5,44	5,03 / 5,04	20,80 / 20,53	12,38 / 12,77	$C_9H_{15}ClF_3NO_3$	1680	1610	1590 1540 2500	–	3,51	2,90	1,20	6,70	–	–
(XX)	C_4F_9	Me	Et	Et	53–55	69	33,84 / 33,70	3,48 / 3,54	3,15 / 3,27	39,99 / 39,98	8,78 / 8,29	$C_{12}H_{15}ClF_9NO_3$	1680	1610	1590 1510 2500	–	3,54	2,90	1,20	8,50	–	–

*Decomposes on melting.

†IR spectra not studied because of low stability of salts (IX), (XVII).



(VI), (VII)

(XIII), (XIV), 80—85%

R = HCF_2 (VI), CF_3 (VII).

It may be concluded from the results of this work and also the data of [1, 2] that important factors influencing the direction of the reaction of chloroketoesters and bromoketoesters with amines are the steric hindrance of the reacting amines, the electron-seeking nature of the substituent at the γ-position of the β-ketoester, and the degree of halogenation of its α-position. Thus, increasing the degree of fluorination of the γ-substituent and its length as well as the degree of halogenation of the α-position promote an "acidic" C^2–C^3 cleavage of chloroketoesters and bromoketoesters, while the presence of alkyl groups on the N atom of the reacting amine gives rise to a new reaction pathway – dehalogenation from the 2-position of the β-ketoester.

EXPERIMENTAL

PMR spectra were recorded on a Tesla BS-567 A (100 MHz) spectrometer relative to TMS in DMSO-d_6 and $CDCl_3$. IR spectra were obtained on a UR-20 instrument in a mull from petrolatum oil. GLC analysis was carried out on a LKhM-72 chromatograph, with a katharometer detector, helium carrier gas, steel column 1 mm × 3 mm, 5% SE-30 on Chromaton N-AW-DMCS, column temperature 150-200°C.

Fluorine-containing β-ketoesters (XII)-(XVI) and their α-halogen derivatives (I)-(VIII) were obtained according to [4].

Identification of β-ketoesters (XII)-(XVI), methylamides of dibromoacetic, chloroacetic, and fluorocarboxylic acids as well as bromo- and dibromoacetamide was carried out by comparison with known samples using IR, PMR, and GLC analysis (apart from amides of dibromo- and bromoacetic acid).

Amine salts were identified by comparison with known samples according to their IR spectra and from the absence of melting point depression for a sample of the mixture.

Reaction of α-Halogenated β-Ketoesters with Amines. 0.01 mole of α-halo-β-ketoester in 20 ml of anhydrous ether was added to a flask cooled to −40°C and an equimolar quantity or threefold excess of amine was added with agitation during 1 h. In the case of acetamide the reaction was carried out in chloroform with subsequent boiling (4 h).

Isolation and purification of the reaction products was conducted in the following manner: a) On reaction of chloroketoesters and bromoketoesters with methyl- and diethylamine, the precipitate of salts (IX)-(XII) and (XVII)-(XX) was filtered off and washed with chilled ether or chloroform (see Table 1); b) dehalogenated β-ketoesters (XII)-(XVI) were analyzed in the reaction mixture as indicated above: c) methylamides of fluorocarboxylic and dibromoacetic acids were isolated by sublimation from the residue obtained after distilling off the solvent. Chloroacetic acid methylamide, methyl- and diethylamine hydrobromides, and methyl-, diethyl-, and triethylamine hydrochlorides were isolated by reprecipitation with hexane from a solution of unsublimable residue in chloroform. Their identification was carried out as indicated above; d) in the reaction with acetamide the precipitates of bromo- and dibromoacetamide after washing with ether were determined as indicated above.

CONCLUSIONS

1. In the reactions of α-chloro- and α,α-dibromo-β-ketoesters with aliphatic amines, increasing the degree of fluorination of the γ-substituent and its length as well as the degree of halogenation of the α-position promotes their "acidic" cleavage, while increasing the steric hindrance of the amine leads to suppression of this reaction.

2. When α-chloro- and α,α-dibromo-β-ketoesters react with aliphatic amines a new reaction pathway is effected – dehalogenation from the α-position of the β-ketoesters.

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