REACTION OF 2-HALOFLUOROALKYL-CONTAINING β-KETOESTERS WITH N-DINUCLEOPHILES

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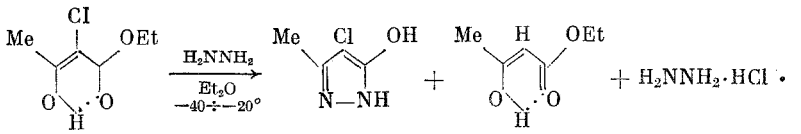
2-Chloroacetoacetic ester (Ia) with a three-fold excess of phenylhydrazine (PH) forms the phenylhydrazone which then cyclizes to 4-chloro-5-methyl-2-phenylpyrazol-3-one [1]. The chlorine atom in the latter can be displaced by a phenylhydrazyl moiety followed by degradation to 3-hydroxy-4-nitroso-5-methyl-2-phenylpyrazole [1]. The same compound is the final product of reaction of 2-bromoacetoacetic ester with PH [1]. However, there is no information on the reactions of 2-halofluoroalkyl-containing β-ketoesters (β-KE) with N-dinucleophiles.

In this work the reaction of 2-chloroacetoacetic ester (Ia), fluoroalkyl-containing 2-chloro- (Ib-d) and 2,2-dibromo-β-KE (II) with hydrazine (HY), PH, and o-phenylendiamine (PD) was studied.

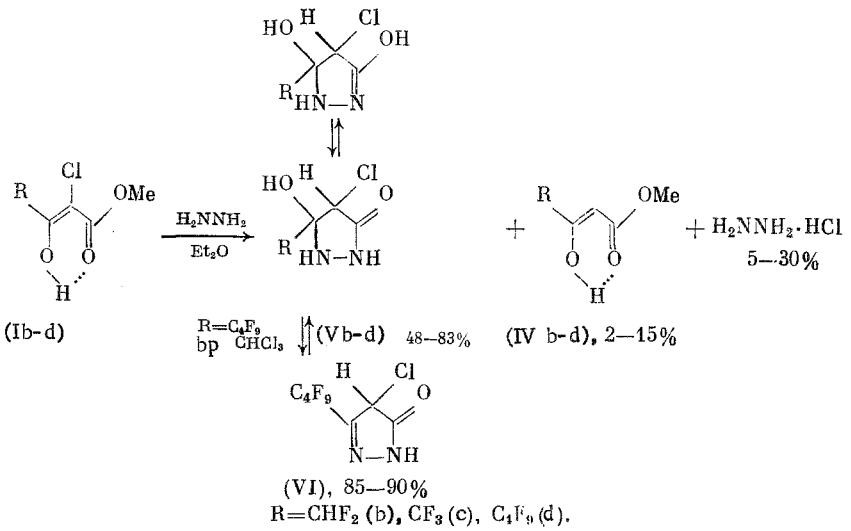
Similarly to acetoacetic ester [2], compound (Ia) in equimolar ratio with HY in ether forms 3-hydroxy-4-chloro-5-methylpyrazole (III) (Table 1). Here also the Cl is displaced by H in (Ia), since in the reaction mixture acetoacetic ester (IVa) and HY hydrochloride are found



(Ia) (III), 35% (IVa), 15% 20%

Fluoroalkyl-containing β-KE's (Ib-d) with HY give 5-hydroxy-4-chloro-5-fluoroalkylpyrazolidine-3-ones (Vb-d) (Table 1), together with dechlorinated β-KE's (IVb-d) and $N_2H_4 \cdot HCl$. With (Ia, b) it is necessary to carry out the reaction at −40 to −20°C, since at higher temperature resinification of the reaction mixture is observed, though for (Ic, d) resinification is not observed at 20-30°C.

For compounds (Vb-d) amide–imidole tautomerism is common, which is confirmed by the presence in the PMR spectra of two methine signals for the CHCl protons and in the IR spectra of C=N bands in the region of 1600-1620 cm^{-1} (Table 1).



(Ib-d)

(VI), 85—90%

R=CHF_2 (b), CF_3 (c), C_4F_9 (d).

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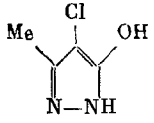
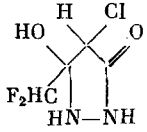
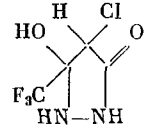
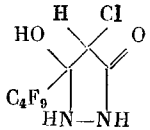
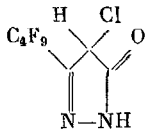
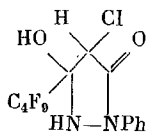
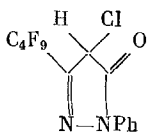
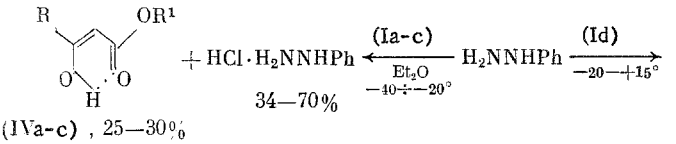
TABLE 1. Products of Reaction of β-Ketoesters with Hydrazines

Compound	Mp, °C (solvent)	Yield, %	Found/Calculated, %					Molecular formula	IR spectrum, ν, cm⁻¹				PMR spectrum (δ, ppm) (in DMSO-d_6 relative to TMS)		
			C	H	Cl	F	N		C=O	C=N	NH	OH	CH	NH, OH	CH_3; HCF_2 (J_{HCF_2}, Hz)
 (III)	203–205 (hexane)	35	36,25 36,24	3,60 3,80	26,26 26,75	–	20,60 21,14	$C_4H_5ClN_2O$	–	1620 1600 (C=C)	3200	2600	–	7,70	2,15
 (V b)	134–135 (chloroform)	45	25,82 25,75	2,59 2,70	19,58 19,01	20,15 20,37	15,13 15,02	$C_4H_5ClF_2N_2O_2$	1700	1620	3170 3220 3300	2600	4,82 4,16	6,10 6,99 9,70	6,03 (54) 6,17 (54)
 (V c)	173–175 (chloroform)	76–83	23,58 23,50	1,95 1,96	17,64 17,33	28,00 27,86	13,82 13,70	$C_4H_4ClF_3N_2O_2$	1700	1600	3170 3220 3300	2600	4,72 4,50	6,35 7,83 9,91	–
 (V d)	126–128 (ether + hexane)	57–76	23,64 23,70	1,12 1,14	10,13 10,00	48,50 48,22	7,64 7,90	$C_7H_4ClF_9N_2O_2$	1700	1620 пл	3170 3220 3300	2600	4,72 4,24	7,72 6,00	–
 (VI) *	136–138 (chloroform)	85–90	24,95 24,98	0,73 0,60	10,90 10,53	50,19 50,81	8,52 8,32	$C_7H_2ClF_9N_2O$	1700	1620	3170 3220	2600			
 (VII)	126–127 (ether-hexane)	42–67	36,14 36,25	1,67 1,87	8,53 8,23	39,98 39,70	6,31 6,51	$C_{13}H_8ClF_9N_2O_2$	1690	–	3250	2600	5,39	3,50 10,65	
 (VIII) *	131–133 (hexane)	85–90	37,63 37,84	1,37 1,47	8,79 8,59	41,06 41,44	6,83 6,79	$C_{13}H_6ClF_9N_2O$	1690	1670	–	–	–	–	–

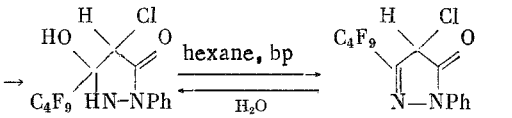
*PMR spectrum was not taken because of low solubility and high hygroscopicity.

Formation of (Vb-d) indicates that introduction into β-KE's of fluoroalkyl substituents and Cl atoms in positions 3 and 2, respectively, leads to stabilization of their HY addition products, which apparently are also the intermediates of this reaction with nonhalogenated β-KE's. Using (Vd) as an example, we established that upon boiling in chloroform elimination of a water molecule takes place, leading to 4-chloro-5-nonafluorobutylpyrazol-3-one (VI) (Table 1). The latter compound easily adds water, giving again (Vd).

Reaction of β-KE's (Ia-c) with PH in equimolar ratio does not result in addition–elimination as was observed using excess PH [1]. In this case substitution of Cl by H in position 2 of compounds (Ia-c) takes place with formation of PH hydrochloride and the corresponding 2-unsubstituted β-KE (IV)



(IVa-c), 25—30%



(VII), 42—67% (VIII), 85—90%

R = CH_3 (a), HCF_2 (b), CF_3 (c), C_4F_9 (d).

Compound (Id) with PH gives 5-hydroxy-4-chloro-2-phenyl-5-nonafluorobutylpyrazolidin-3-one (VII) which upon boiling in hexane dehydrates to pyrazolone (VIII) (Table 1). The latter is easily rehydrated to (VII). In the PMR spectrum of (VII) unlike (Vb-d) one CHCl signal is present (Table 1). This indicates it exists in only one tautomeric form (with the phenyl substituent most likely in position 2 of the pyrazolidine ring, since in this case enolization is not possible).

With PD in equimolar ratio at 25°C, (Ia) forms azomethine (IX) (Table 2), β-KE's (Ib, c) form benzodiazepinones (Xb, c) similarly to fluorinated β-KE's not containing chlorine [2], and (Id) gives 2-nonafluorobutylbenzimidazole (XI) (Table 2). In all cases PD hydrochloride and the corresponding unchlorinated β-KE (IV) are present in the reaction mixture.

In the PMR spectrum of azomethine (IX) there are two signals for the CH_3 group in the β-position, the CHCl signal, two sets of EtO signals, and also signals of the NH and NH_2 groups (Table 2). In the IR spectrum of (IX), C=N and C=O bands are observed. This indicates the presence of amine–imine tautomerism in (IX)

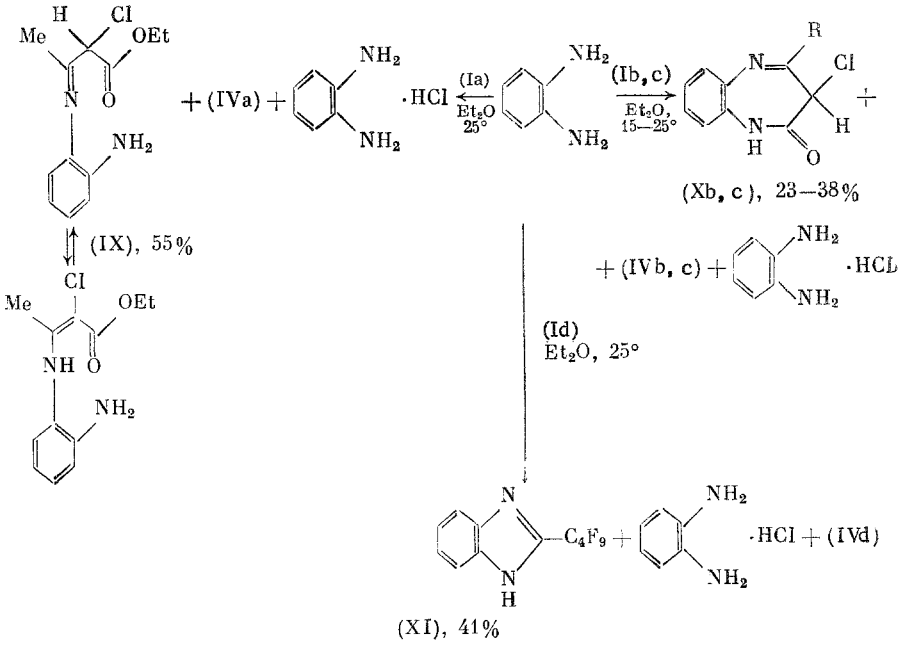
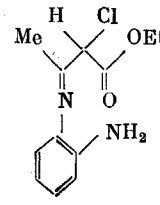
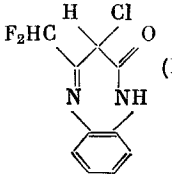
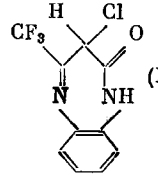
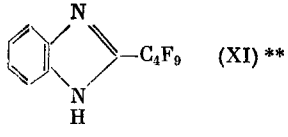
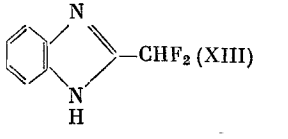


TABLE 2. Products of Reaction of β-Ketoesters with o-Phenylenediamine

Compound	Mp, °C (solvent)	Yield, %	Found/Calculated, %					Molecular formula	IR spectrum, ν, cm⁻¹			PMR spectrum (in acetone-d_6 relative to TMS) (δ, ppm)					
			C	H	Cl	F	N		C=O	C=N (conj.)	NH	CH	CH_3	OC_2H_5	NH, OH	HCF_2, (J_{HCF_2}, Hz)	Ph
 (IX)*	60–61 (hexane)	55	56,15 / 56,58	6,11 / 5,94	14,28 / 13,92	–	11,21 / 11,00	$C_{12}H_{15}ClN_2O_2$	1620	1630	3200 3360 3460	5,18	2,08 2,29	1,34 CH_3 1,36 CH_3 4.28 CH_2 4,26 CH_2	3,80 NH_2 11,04 NH	–	6,80
 (Xb)	170–172 (chloroform)	38	49,10 / 49,10	2,68 / 2,88	15,00 / 14,49	15,47 / 15,53	11,47 / 11,45	$C_{10}H_7ClF_2N_2O$	1690	1650	3200	5,10	–	–	2,80	6,30 (53,4)	7,10
 (Xc)	159–161 (hexane)	16–23	45,71 / 45,73	2,03 / 2,30	13,81 / 13,50	22,19 / 21,70	10,61 / 10,67	$C_{10}H_6ClF_3N_2O$	1690	1660	3200	5,32	–	–	2,80	–	7,30
 (XI)**	178–179 (chloroform)	41	39,55 / 39,30	1,27 / 1,50	–	51,10 / 50,86	8,14 / 8,33	$C_{11}H_5F_9N_2$	–	1670	3100	–	–	–	3,50	–	7,60
 (XIII)	146–148 (benzene)	30	57,28 / 57,14	4,05 / 3,60	–	22,00 / 22,60	16,53 / 16,66	$C_8H_6F_2N_2$	–	1680	3100	–	–	–	2,80	7,10 (53,7)	7,50

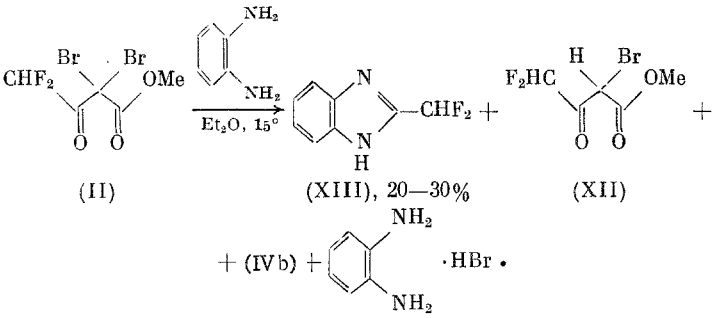
*PMR spectrum in $CDCl_3$.

**PMR spectrum in dimethylsulfoxide-d_6.

Thus, in the reaction with PD substitution of Cl in position 2 of β-KE's (Ia-d) takes place as in the reactions with HY. Closure to a benzodiazepine ring for (Ib, c) becomes possible as a result of the higher electrophilicity of carbon of the complexed ester group compared to (Ia) because of the presence of electron-withdrawing fluoroalkyl substituents. Formation of benzimidazole (XI) can be explained by "acidic" disintegration of β-KE (Id) under the action of PD followed by cyclization to benzimidazole. This agrees with earlier obtained data which indicate that with increase of the fluoroalkyl substituent length the susceptibility of 2-halo-substituted fluorine-containing β-KE's to "acidic" disintegration increases [3].

The reaction of (II) with HY and PH in ether at −40 to −20°C leads to difficultly identifiable mixtures in which by GLC the presence of compounds (XII) and (IVb) and hydrobromides of HY or PH can be detected. Thus, one of the reaction paths in this case is substitution of the Br in position 2 of (II).

Compound (II) also reacts with PD by another path and, together with substitution of Br, formation of (XIII) is observed (in the reaction products are found PD hydrobromide and 4,4-difluoro-2-bromo- and 4,4-difluoroacetoacetic esters)(Table 2).



Compound (XIII) is obtained, apparently as the result of "acidic" disintegration of (II) under the action of PD followed by cyclization, which indicates the high susceptibility of 2,2-dibromo substituted β-KE's to this type of transformation as compared to (I) which undergoes this reaction only for R = C_4F_9.

Summing up the obtained results for the reaction of fluoroalkyl-containing β-KE's with HO- and HS-nucleophiles [4], NH_3 [5], aliphatic amines, and acetamide [3], and in this work with HN-dinucleophiles, one can assume that in the first stage of the reaction of 2-halo substituted β-KE's with the studied nucleophiles, adducts (B type; scheme) at the β-carbon atom are formed. This is in accord with the discovery of these adducts in the solution of a reaction with HO- and HS-nucleophiles [4]. In the case of HN-nucleophiles similar intermediates (B) cannot be observed because of their small lifetime on the NMR time scale. However, their existence is confirmed by formation of all the product types (C-G) obtained by us. The further course of the reaction is determined by the structure of both the fluorine-containing β-KE and the nucleophile.

A competing path in the reaction with nucleophiles is substitution of halogen atoms by H in position 2 of β-KE's (A → H → I).

EXPERIMENTAL

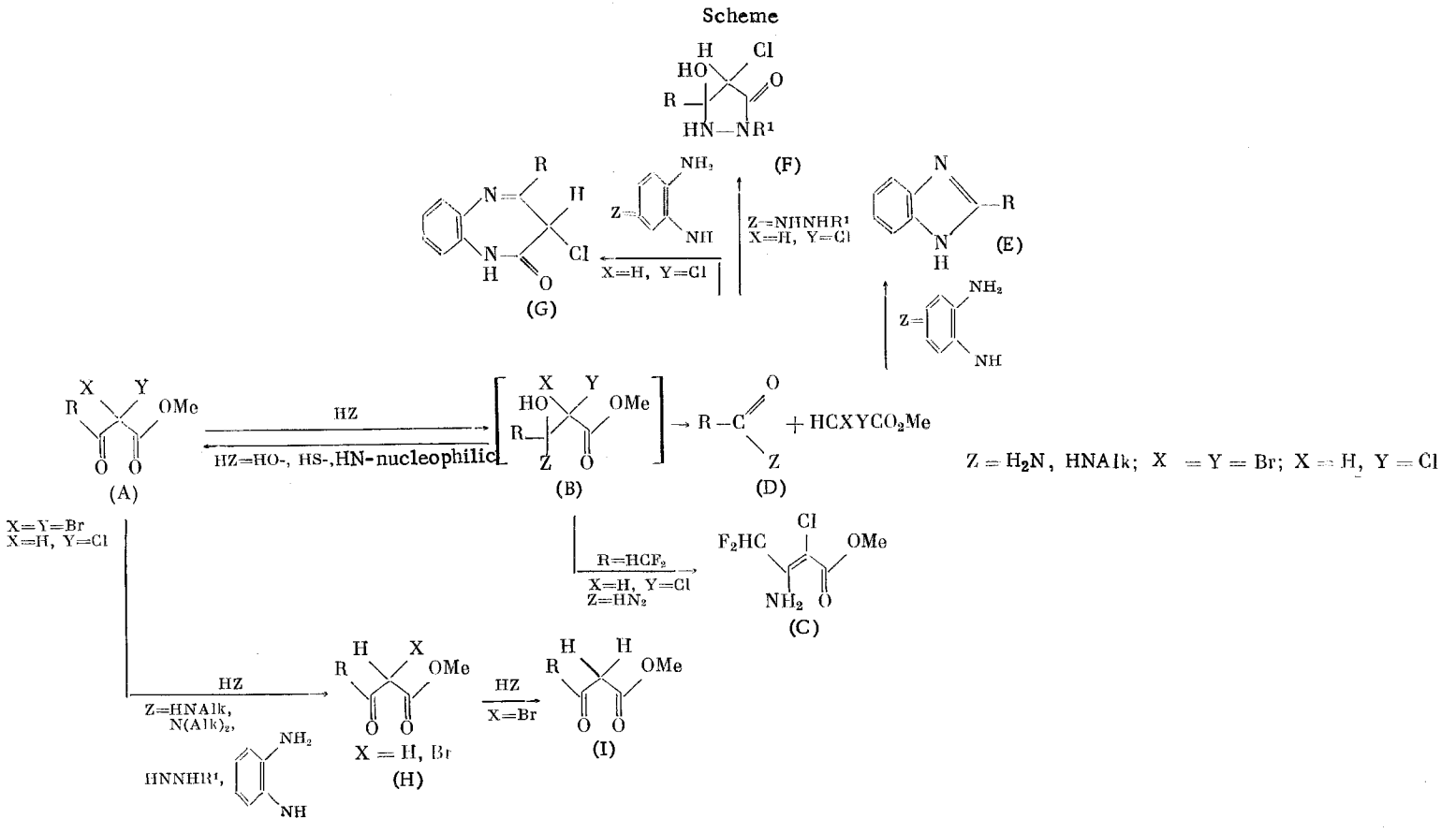
IR spectra were obtained on an IR-75 spectrometer in Nujol mulls and PMR spectra on a Tesla BS-567A spectrometer (100 MHz) relative to TMS. GLC analysis was realized on a LKhM-8MD chromatograph with catharometer detector, helium carrier gas, and column with ℓ = 2 m, d = 4 mm, 5% SE-30 Silicon on N-AW-DMCS chromaton.

β-KE's (I), (II), and (XII) were obtained by the method of [6].

Determination of β-KE's (IV) and (XII) in the reaction mass was carried out by comparison with known samples by GLC. The salts of HY, PH, and PD after their isolation were determined by comparison with known samples by IR, TLC, and by mixed melting points.

Reactions of β-KE's with Hydrazines. To a solution of 30 mmoles of (I) in 50 ml of absolute ether an equimolar amount of HY (PH) was added dropwise with cooling to −40 to −20°C (for HY and R = CF_3 and C_4H_9 the reaction proceeds also at 20-30°C) and to −40 to −15°C (PH),

Scheme


(F)
(G)
(E)
(A)
(B)
(D)
(C)
(H)
(I)
HZ
HZ=HO-, HS-,HN-nucleophilic
X=H, Y=Cl
Z=NHNHR¹
X=H, Y=Cl
X=Y=Br
X=H, Y=Cl
R=HCF₂
X=H, Y=Cl
Z=HN₂
Z=HNAlk,
N(Alk)₂,
HNNHR¹,
X = H, Br
X=Br
+ HCXYCO₂Me
Z = H₂N, HNAlk; X = Y = Br; X = H, Y = Cl

with stirring for 4 h. The precipitate was filtered and recrystallized. Compounds (III) and (Vb-c) and PH hydrochloride (hydrobromide) were obtained. For R = C_4H_9 the solvent was distilled off and the residue reprecipitated from ether by hexane. There were obtained pyrazolidones (Vd) and (VII), from which by boiling in chloroform or hexane (VI) and (VIII) were isolated. Reaction of (Id) with PH proceeds also without solvent. In this case the yield of (VII) is the largest. The yields and constants are shown in Table 1.

Reaction of β-KE's with o-Phenylenediamine. To a solution of 30 mmoles of (I) in 50 ml of absolute ether an equimolar amount of PD in 100 ml ether was added dropwise both with cooling with cold water and at ∿20°C and stirred for 4 h. PD hydrochloride (hydrobromide) was filtered off and solvent was distilled off under vacuum. The residue was recrystallized, washed with water in order to remove the remaining amount of PD, and dried under vacuum. The following pure compounds were obtained: (IX), (Xb, c), (XI), and (XIII). The yields and constants are shown in Table 2.

CONCLUSIONS

During the reaction of hydrazines and o-phenylenediamine with 2-halosubstituted β-keto-esters, including fluoroalkyl substituted, two reaction paths are realized: substitution of the halogen atoms in position 2 by hydrogen and condensation with formation of various compounds depending on the structure of the starting β-ketoester and dinucleophile.

LITERATURE CITED

1. R. Schönbrodt, Liebigs. Ann. Chem., 253, 168 (1889).
2. K. I. Pashkevich and V. I. Saloutin, Usp. Khim., 54, 1997 (1985).
3. Z. É. Skyrabina, V. I. Saloutin, and K. I. Pashkevich, Izv. Akad. Nauk SSSR, Ser. Khim., 1560 (1987).
4. Z. É. Skyrabina, V. I. Saloutin, K. I. Pashkevich, et al., Izv. Akad. Nauk SSSR, Ser. Khim., 2046 (1986).
5. K. I. Pashkevich, Z. É. Skryabina, and V. I. Saloutin, Izv. Akad. Nauk SSSR, Ser. Khim., 1190 (1985).
6. V. I. Saloutin, Z. É. Skryabina, M. N. Rudaya, and K. I. Pashkevich, Izv. Akad. Nauk SSSR, Ser. Khim., 1106 (1984).