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REACTION OF METHYL 3-PHENYL-3-CHLORO-2-OXOPROPIONATE WITH THIOSEMICARBAZONES

V. A. Mamedov, V. N. Valeeva, L. A. Antokhina, and I. A. Nuretdinov

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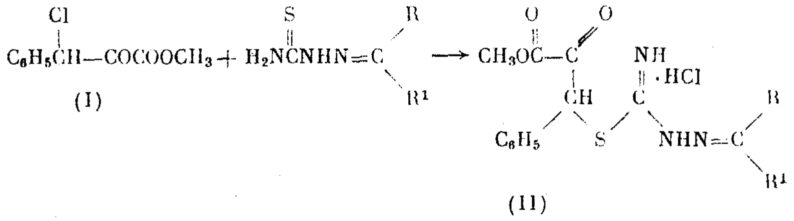
The reaction of methyl 3-phenyl-3-chloro-2-oxopropionate with thiosemicarbazones proceeds via the intermediate formation of methyl [S-(1'-alkylideneisothiosemicarbazidyl)]-3-phenyl-2-oxopropionate hydrochlorides, which then cyclize to novel 4-methoxycarbonyl-5-phenyl-2-substituted thiazoles. Hydrolysis of the intermediate products and the thiazoles obtained therefrom with simultaneous distillation of the carbonyl compound affords 2-hydrazino-4-methoxycarbonyl-5-phenylthiazole.

There have been literature reports of the synthesis of thiazoles from thioamides [1] and thiosemicarbazides [2, 3], but the use of thiosemicarbazones for this purpose has received less attention. Continuing studies of the reactions of α-chloroketones with bifunctional compounds [4, 5], we here describe the reactions of methyl-3-phenyl-3-chloro-2-oxopropionate (I) with thiosemicarbazones.

Condensation of the α-chloroketone (I) with thiosemicarbazones occurs in two stages. The first of these, formation of the intermediate methyl [S-(1'-alkylideneisothiosemicarbazidyl)]-3-phenyl-2-oxopripionate hydrochlorides (II), occurs under mild conditions, namely on mixing equimolar amounts of the reactants at ~20°C in a solvent (acetone or CCl_4).



R, R¹ = Alk, H, Ar.

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Science Center, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6, pp. 1422-1426, June, 1991. Original article submitted July 4, 1990.

TABLE 1. Yields, Properties, and Elemental Analyses of the Products

Compound	Mp, °C	Yield, %	Found/Calculated, %					Empirical-formula
			C	H	Cl	N	S	
(III) *	235	65	58,19/58,09	5,16/5,18	–	14,60/14,52	10,88/11,08	$C_{14}H_{15}N_3O_2S$
(IV)	157–159	80	52,95/53.04	5,30/5,30	10,21/10,22	12,56/12,37	9,54/9,44	$C_{15}H_{18}ClN_3O_2S$
(V) *	235	94	64,39/64,11	4,42/4,45	–	12,41/12,45	9,80/9,51	$C_{18}H_{15}N_3O_2S$
(VI)	133–135	66	55,38/55,53	5,76/5,98	9,84/9,64	11,51/11,42	8,62/8,72	$C_{17}H_{22}ClN_3O_2S$
(VII)	87–88	54	57,45/57,67	6,38/6,57	8,98/8,96	10,76/10,61	8,26/8,10	$C_{19}H_{26}ClN_3O_2S$
(VIII)	188–189	56	58,60/58,86	4.66/4,64	9,25/9,14	10,83/10,83	8,40/8,27	$C_{19}H_{18}ClN_3O_2S$
(IX)	132–133	77	58,47/58,63	6,80/6,83	8,78/8,65	10,41/10,25	8.01/7,82	$C_{20}H_{28}ClN_3O_2S$
(X) *	143–145	92	60,76/60,96	5,38/5,39	–	13,30/13,32	10,01/10.17	$C_{16}H_{17}N_3O_2S$
(XI)	148–149	84	55,64/55,84	5,46/5,47	9,41/9.69	11,48/11,49	8,90/8,77	$C_{17}H_{20}ClN_3O_2S$
(XII)	96–98	69	56,80/56,94	5,95/5,79	9.16/9,34	11,02/11,06	8,50/8,44	$C_{18}H_{22}ClN_3O_2S$
(XIII)	185	37	53,36/53,02	4,29/4,41	–	17,00/16,86	13,02/12,87	$C_{11}H_{11}N_3O_2S$
(XIV)	211–213	35	44,08/44,22	3,62/3,68	12,58/13,05	14,96/15,46	12,22/11,80	$C_{10}H_{10}ClN_3O_2S$

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*The compounds were isolated as the bases.
Compounds (VI), (VII), and (IX)-(XII) were purified by recrystallization from 2-propanol; (III), (V), (XIII), and (XIV) from ethanol; and (VIII) from a 4:1 mixture of 2-propanol and methanol.

The intermediates (II) are thick, viscous liquids, only the compound with $R = R^1 = CH_3$ being obtained in the crystalline state. The occurrence in the IR spectra of carbonyl absorption at 1740 and 1770 cm^{-1}, and of a singlet signal for the methine proton of the C_6H_5–CH–S fragment in the PMR spectrum at ~5.4 ppm, are consistent with the proposed structure (II) for the intermediates. On boiling (II) in ethanol, Hansch cyclization occurs to give the final products, namely the hydrochlorides of the functionally substituted thiazoles (III)-(XII). It has been found that on boiling the thiazoles (III)-(XII) or the intermediates (II) in water with simultaneous removal by steam distillation of the carbonyl compound affords 2-hydrazino-4-methoxycarbonyl-5-phenylthiazole (XIII), which is of interest for the synthesis of novel heterocyclic compounds [6, 7]. When this reaction is carried out in the presence of hydrochloric acid, 2-hydrazino-5-phenylthiazolecarboxylic acid hydrochloride (XIV) is formed. The same compound was obtained by acid hydrolysis of the thiazole (XIII).

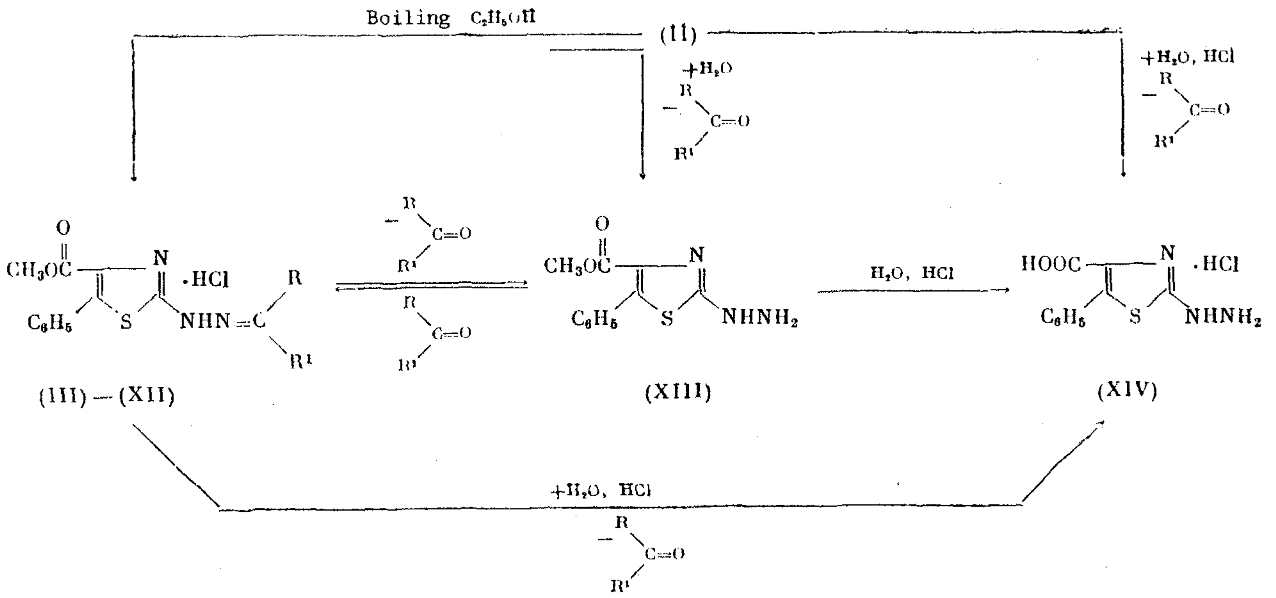
2-Hydrazino-4-methoxycarbonyl-5-phenylthiazole (XIII) reacts with carbonyl compounds to give the thiazoles (III)-(XIII) on mixing the reactants in CCl_4.

The physicochemical data of the compounds obtained together with their spectral data (IR, PMR) are given in Tables 1 and 2, respectively.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument, as a vaseline mull, and PMR spectra on a Varian T-60, operating frequency 60 MHz, internal standard TMS. The PMR spectrum of (XIII) was obtained on a Bruker WM-250.

The starting thiosemicarbazones were obtained by boiling equimolar amounts of the reactants in a Dean and Stark apparatus.



$R = R^1 = CH_3$ (III); $R = CH_3$, $R^1 = C_2H_5$ (IV); $R = H$, $R^1 = C_6H_5$ (V); $R = CH_3$, $R^1 = C_4H_9$-*n* (IV); $R = C_2H_5$, $R^1 = C_4H_9$-*i* (VII); $R = CH_3$, $R' = C_6H_5$ (VIII); $R = R' = C_4H_9$-*i* (IX); $R—R^1 = (CH_2)_4$ (X); $R—R^1 = (CH_2)_5$ (XI); $R—R^1 = (CH_2)_2-\underset{\overset{|}{CH_3}}{C}-(CH_2)_2$ (XII).

TABLE 2. Spectral Features of Products Obtained

Compound	IR spectrum (ν, cm⁻¹) (vaseline mull)	PMR spectrum (δ, ppm) (solvent)
(III)	1570, 1680, 1720, 3245	1,95 s $\left(6H,\ \begin{matrix}CH_3 \\ CH_3\end{matrix}\!\!>\!C\right)$, 3,36 br.s (1H, NH–N=), 3,63 s (3H, CH_3O), 7,35 s (5H, C_6H_5); $(CD_3)_2SO$
(IV)	1635, 1720, 3245, 3435	1,00 t (3H, $\underline{CH_3}-CH_2$), 2,00 s (3H, $CH_3-C=N$), 2,23 q (2H, $CH_3-\underline{CH_2}$), 3,63 s (3H, CH_3O), 7,20 s (5H, C_6H_5); CF_3COOH
(V)	1715, 3215	3,63 s (3H, CH_3O), 7,10–7,66 m (10H, $2C_6H_5$, 7,90 s (1H, CH=N); $(CD_3)_2SO$
(VI)	1635, 1720, 3240, 3430	0,73 t (3H, $\underline{CH_3}CH_2CH_2$), 1,00–1,56 m (4H, $CH_3\overline{CH_2CH_2}CH_2$), 1,90 s (3H, $\underline{CH_3}-C=N$), 2,06–2,50 m (2H, $-\overline{CH_2}-C=N$), 3,63 s (3H, $\underline{CH_3}O$), 7,23 s (5H, C_6H_5); CF_3COOH
(VII)	1635, 1720, 3215, 3415	0,46–1,23 m (10H, $\underline{CH_3}-CH_2$, $\overline{(CH_3)_2CH}CH_2$), 1,96–2,46 m (4H, $CH_3-\underline{CH_2}$, $(CH_3)_2CH-\underline{CH_2}$), 3,63 s (3H, CH_3O), 7,20 s (5H, C_6H_5); CF_3COOH
(VIII)	1720, 3215, 3440	2,20 s (3H, CH_3), 3,63 s (3H, CH_3O), 6,09–7,60 m (10H, $2C_6H_5$); $(CD_3)_2SO$
(IX)	1720, 3245, 3430	0,73 d (0,83 d (12H, $2(\underline{CH_3})_2CH$), 1,73–2,33 m (6H, $2(CH_3)_2CH-CH_2$), 3,63 s (3H, CH_3O), 7,13 s (5H, C_6H_5); CF_3COOH
(X)	1720, 3260	1,76 br.s (4H, $-\overline{CH_2CH_2}-$), 2,40 br.s (4H, $(CH_2)_2C=N$), 3,63 s (3H, CH_3O), 7,26 s (5H, C_6H_5); CF_3COOH
(XI)	1715, 3240, 3430	1,60 br.s (6H, $-CH_2CH_2CH_2-$), 2,16–2,56 s (4H, $(CH_2)_2C=N$), 3,63 s (3H, CH_3O), 7,20 s (5H, C_6H_5), CF_3COOH
(XII)	1625, 1719, 3390	1,16 d (3H, CH_3- in cyclohexyl fragment), 1,40–2,73 m (9H, cyclohexyl fragment), 3,64 s (3H, CH_3O), 7,13 s (5H, C_6H_5), CF_3COOH
(XIII)	1650, 1720, 3150, 3200, 3340	3,67 s (3H, CH_3O), 5,10 br.s (2H, NH_2), 7,42 s (5H, C_6H_5), 8,90 s (1H, NH), $(CD_3)_2SO$
(XIV)	1720, 2400, 3000	7,03 s (5H, C_6H_5), 9,80 br.s (4H, $NHNH_2\cdot HCl$), $(CD_3)_2SO$

Methyl [S-(1-isopropylideneisothiosemicarbazidyl)]-3-phenyl-2-oxopropionate Hydrochloride (II), R = R^1 = CH_3. To a suspension of 4 g of acetone thiosemicarbazone in 150 ml of acetone was added at 18-20°C 9.8 g of methyl 3-phenyl-3-chloro-2-oxopropionate. The crystals which separated were filtered off and washed on the filter with ether to give 7.9 g (57%) of product, mp 135-136°C. IR spectrum (ν, cm^{-1}): 1580, 1645 (C=N), 1740, 1770 (C=O), 2700 ($\gt\overset{+}{N}-$), 3140 (N–H). PMR spectrum [δ, ppm, $(CD_3)_2SO$]: 2.00 d (6H, $(\underline{CH_3})_2C=N$), 3.10-3.46 m (1H, N–$\underline{NH}$–), 3.63 s (3H, CH_3O), 5.43 s (1H, S–$\underline{CH}$–), 7.23 s (5H, C_6H_5). Found, %: C 47.78; H 5.21; Cl 10.12; N 12.43; S 9.71. $C_{14}H_{18}ClNO_3S$. Calculated, %: C 47.72; H 5.24; N 12.22; S 9.33.

The remaining compounds (II) were obtained similarly, and used without further purification in the subsequent reactions.

2-Isopropylidenehydrazo-4-methoxycarbonyl-5-phenylthiazole Hydrochloride (III). One gram of methyl [S-(1'-isopropylidenethiosemicarbazidyl)]-3-phenyl-2-oxopropionate hydrochloride was dissolved in a small amount of ethanol, and the mixture kept at ~20°C for 48 h. The solid which had separated (0.56 g, 65%) (III) was filtered off. Mp 235°C (from ethanol).

2-(2-Butylidene-2-hydrazino)-4-methoxycarbonyl-5-phenylthiazole Hydrochloride (IV). To a suspension of 7.3 g of ethyl methyl ketone thiosemicarbazone in 150 ml of acetone was added at 20°C 9.8 g of methyl 3-phenyl-3-chloro-2-oxopropionate, and the mixture stirred for 3 h at ~20°C. The solvent was then removed under reduced pressure, and the residue treated with 50 ml of ethanol and boiled for 10 min. Following removal of the solvent under reduced pressure, the residue was treated with ether, and the crystalline solid filtered off to give 13.5 g (80%) of (IV), mp 157-159°C (from 2-propanol).

Compounds (V)-(XII) were obtained similarly.

2-Hydrazino-4-methoxycarbonyl-5-phenylthiazole (XIII). In a distillation flask were placed 3.6 g of (III), 30 ml of methanol, and 20 ml of water. The mixture was boiled for 30 min with simultaneous removal of acetone in steam. The hot mixture was filtered through filter paper, and the crystals which separated were isolated by filtration to give 1.08 g of (XIII), mp 185°C (from ethanol).

In a similar way, (XIII) was obtained from methyl [S-(1-isopropylidenethiosemicarbazidyl)]-3-phenyl-2-oxopropionate hydrochloride (II).

2-Hydrazino-5-phenylthiazolecarboxylic Acid Hydrochloride (XIV). In a distillation flask were placed 10 g of (II) and 200 ml of 1 N hydrochloric acid, and the mixture boiled with simultaneous removal of acetone and methanol in water vapor, until all the (II) had dissolved. Removal of the solvent under reduced pressure gave 2.76 g (35%) of product, mp 211-213°C.

Under similar conditions, (XIV) was obtained from isopropylidenehydrazono-4-methoxycarbonyl-5-phenylthiazole (III) in 40% yield.

Acid Hydrolysis of 2-Hydrazino-4-methoxycarbonyl-5-phenylthiazole. (By a modification of the method reported in [8].) Two grams of (XIII) were boiled in a round-bottomed flask with 30 ml of concentrated hydrochloric acid and 50 ml of water for 5 h. The solid which separated was filtered off and dried in vacuo to give 2 g (73%) of (XIV), mp 210-212°C.

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