STUDIES ON THE IMIDAZOLE SERIES

XLVI. Alkyl-, Aryl-, and Acyl-Substituted Imidazo[2,1-b]thiazoles*

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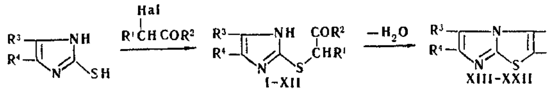
The reaction of 2-mercaptoimidazole and its 4(5)-aryl- and 4,5-diaryl-substituted derivatives with α-halogenoketones has yielded a number of alkyl-, acyl-, and aryl-substituted imidazo[2,1-b]thiazoles.

3-Alkyl-, 3-aryl-, 2,3-diaryl-, 3,5,6-triaryl-, 3-alkyl-5,6-diaryl-, 2-acyl-3-alkyl-, and 2-acyl-3-alkyl-5,6-diarylimidazo[2,1-b]thiazoles have not been described in the literature. In preceding investigations [2-4] we have studied the reaction of 2-mercaptoimidazole and 2-mercapto-4,5-diphenylimidazole with α-halogenoketones of the aliphatic and aliphatic-aromatic series, and also the reactions of 2-mercapto-4(5)-phenyl- and 2-mercapto-4(5)-(p-nitrophenyl)imidazoles with p-bromo- and p-nitrophenyl bromides. The performance of these reactions in ethanol in the presence of sodium ethoxide leads to the 2-(acylalkylthio)imidazoles I-XII. In the IR spectra of these compounds, unlike the IR spectra of the 2-(formylalkylthio)imidazoles [1, 5] and the 2-(acylmethylthio)imidazolines [6], which exist in the solid state as the tautomeric forms, 3-hydroxyimidazo[2,1-b]thiazoles and 3-hydroxy-5,6-dihydroimidazo[2,1-b]thiazoles, respectively, there are four bands of the stretching vibrations of the CO group in the 1675-1730 cm^{-1} region, which shows their structure as imidazol-2-ylthiomethyl ketones.

When 2-mercaptoimidazole and 2-mercapto-4,5-diphenylimidazole are boiled with chloroacetone and with 3-chloropentane-2,4-dione in ethanol or butanol in the absence of alkali, imidazo[2,1-b]thiazole derivatives (XIII, XVII, XXI, XXII) are formed. The reaction of 2-mercaptoimidazole with aliphatic-aromatic halogenoketones (phenacyl bromide and desyl chloride) under similar conditions stops at the stage of the 2-(phenacylthio)- and 2-(desylthio)imidazoles (I, IV).

The 2-(acylmethylthio)imidazoles having residues of aliphatic ketones, such as IX, readily split out a molecule of water on being boiled in ethanol or butanol in the presence of HCl, being converted into derivatives of imidazo[2,1-b]thiazole (XXI). The imidazol-2-ylthioketones containing residues of aliphatic-aromatic ketones undergo no change under these conditions. They cyclize to form aryl-substituted imidazo[2,1-b]thiazoles only under the action of strong water-abstracting agents such as phosphorus oxychloride. In this way compounds I-IV, VI, and VII yielded XIV-XVI and XVIII-XX (Table 1).



R¹ = H, Ac; R² = Alk, Ar; R³ = H, Ar; R⁴ = H, Ar

EXPERIMENTAL

2-(Acylalkylthio)imidazoles (I-XII, table). A) To a solution of sodium ethoxide prepared from 0.01 g-atom of metallic sodium and 15-60 ml of absolute ethanol was added 0.01 mole of 2-mercaptoimidazole [7], 2-mercapto-4(5)-phenylimidazole [8], 2-mercapto-4(5)-(p-nitrophenyl)imidazole [8], or 2-mercapto-4,5-diphenylimidazole [9] and 0.01-0.0105 mole of an α-halogenoketone (chloroacetone, 3-chloropentane-2,4-dione, desyl chloride; and in all the other examples the corresponding bromoketones). The mixture was stirred at 60-65°C for 1-2 hr and was then boiled for 5-10 min (until the solution was neutral) and cooled, and the precipitate was filtered off and washed with water. The evaporation of the ethanolic mother solution to small volume gave an additional amount of product. Compounds I-V were isolated after dilution of the reaction mixture with water.

B) A solution of 0.03 mole of 2-mercaptoimidazole and 0.03 mole of phenacyl bromide in 30 ml of ethanol was boiled for 1 hr, poured into water, and neutralized with sodium bicarbonate, and the precipitate was filtered off. Yield of I, 5.95 g (91%). Compound IV was obtained similarly, yield 89%.

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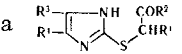
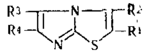
*For part XLV, see [1].

Table 1. 2-(Acylalkylthio)imidazolines[a]  I-XII and Imidazo[2,1-b]thiazole Derivatives[a]  XIII-XXII

Compound	R^1	R^2	R^3	R^4	Mp, °C	Empirical formula	Found, %					Calculated, %					Yield, %
							C	H	halogen	N	S	C	H	halogen	N	S	
I	H	C_6H_5	H	H	162—163,5	$C_{11}H_{10}N_2OS$	60,32	4.95	—	13,03	14,46	60,53	4.62	—	12.83	14.69	96
II	H	C_6H_4Br-*p*	H	H	121—122	$C_{11}H_9BrN_2OS$ [b]	44,40	2.84	27.29	9.31	10.24	44.46	3.05	26.89	9.43	10.79	88
III	H	$C_6H_4NO_2$-*p*	H	H	157—158	$C_{11}H_9N_3O_3S$	50.33	3.50	—	15,09	11.98	50.18	3.45	—	15,96	12.18	99
IV	C_6H_5	C_6H_5	H	H	168—170	$C_{17}H_{14}N_2OS$	69,17	4.60	—	9.54	11,07	69.36	4.79	—	9.52	10.89	86
V	H	C_6H_4Br-*p*	H	C_6H_5	152—153	$C_{17}H_{13}BrN_2OS$ [c]	54.99	3.52	21,13	7.42	8.50	54.70	3,51	21,41	7,50	8,59	83
VI	H	C_6H_5	H	$C_6H_4NO_2$-*p*	174—175	$C_{17}H_{13}N_3O_3S$	59.89	3.90	—	12,18	9,61	60.16	3,86	—	12.38	9,45	80
VII	H	C_6H_4Br-*p*	H	$C_6H_4NO_2$-*p*	177—179	$C_{17}H_{12}BrN_3O_3S$	49.02	3,05	19.10	10.26	7.32	48.81	2,89	19.10	10.05	7.66	86
VIII	C_6H_5	C_6H_5	H	$C_6H_4NO_2$-*p*	128—130	$C_{23}H_{17}N_3O_3S$	66.24	4.48	—	10.10	7.24	66,49	4.10	—	10,11	7,72	99
IX	H	CH_3	C_6H_5	C_6H_5	147—148,5	$C_{18}H_{16}N_2OS$ [d]	70,53	5.35	—	9.15	10.51	70.10	5.23	—	9.09	10.40	92
X	H	C_6H_5	C_6H_5	C_6H_5	180—181	$C_{23}H_{18}N_2OS$	74.60	5.00	—	7.12	8.87	74.57	4.90	—	7.56	8.66	84
XI	H	C_6H_4Br-*p*	C_6H_5	C_6H_5	185—186	$C_{23}H_{17}BrN_2OS$	61,60	4,07	18.23	6.15	6.94	61,47	3.81	17,78	6.23	7.14	97
XII	H	$C_6H_4NO_2$-*p*	C_6H_5	C_6H_5	186—188	$C_{23}H_{17}N_3O_3S$	66,42	4.29	—	10.22	7,91	66,49	4.12	—	10.11	7.72	80
XIIIa	H	CH_3	H	H	134—135	$C_6H_6N_2S \cdot H_2SO_4$ [e]	30,35	3,66	—	11.47	27.05	30,50	3.41	—	11.86	27.14	73
XIVa	H	C_6H_5	H	H	221—223	$C_{11}H_8N_2S \cdot H_2SO_4$ [f]	44,63	3,24	—	9.28	21.34	44,28	3.38	—	9,39	21.49	96
XV	H	C_6H_4Br-*p*	H	H	125,5—127	$C_{11}H_7BrN_2S$	47,30	2.56	28,70	10.04	11,68	47.32	2.53	28.63	10,04	11.49	75
XVI	H	$C_6H_4NO_2$-*p*	H	H	214—215	$C_{11}H_7N_3O_2S$	54.17	3,09	—	16,56	12,74	53,87	2,88	—	17.13	13,07	88
XVIIa	CH_3CO	CH_3	H	H	>240decomp.	$C_8H_8N_2OS \cdot HCl$ [g]	43,99	4.22	16.22	13,09	15.21	44.34	4,19	16.36	12.93	14.80	55
XVIII	C_6H_5	C_6H_5	H	H	153—154	$C_{17}H_{12}N_2S \cdot {}^1/_2H_2O$	71,82	4.30	—	9.29	11,04	71.54	4.59	—	9.81	11.23	82
XIX	H	C_6H_5	H	$C_6H_4NO_2$-*p*	204—206	$C_{17}H_{11}N_3O_2S$	63,94	3,42	—	13,13	10 03	63.54	3.45	—	13.08	9.98	99
XX	H	C_6H_4Br-*p*	H	$C_6H_4NO_2$-*p*	261—262	$C_{17}H_{10}BrN_3O_2S$	51,60	2,62	—	9.78	7,88	51,01	2,52	—	10.50	8.01	97
XXIa	H	CH_3	C_6H_5	C_6H_5	243—245	$C_{18}H_{14}N_2S \cdot HCl$	66.54	4,57	11.00	8.61	9.88	66.14	4.63	10.85	8.57	9.81	68
XXII	CH_3CO	CH_3	C_6H_5	C_6H_5	190—191	$C_{20}H_{16}N_2OS$	72.69	4,96	—	8.35	9.44	72,26	4.85	—	8.43	9.65	52

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[a] For analysis, the substances were purified by crystallization: I, IV, IX, XV, and XVIII from 50% ethanol; II and XIII from 30% ethanol; III, V, XIVa, XVIIa, XXIa, and XXII from ethanol; VI and VIII-XII from butanol; VII from dichloroethane; XIX from ethanol-dichloroethane (1 : 2); XX from dichloroethane-dioxane (2 : 1); XIV from butanol-dimethylformamide (10 : 1); and XIII by precipitation with ether from ethanol. The bases XIII, XIV, XVII, and XXI are oily liquids. [b] Picrate with mp 172-173°C (from 30% ethanol). [c] Picrate with mp 167-169°C (from ethanol). [d] Picrate with mp 173-175°C (from 30% ethanol). [e] Picrate of the base XIII with mp 179-181°C (from ethanol). [f] Picrate of the base XIV with mp 161-164°C (from ethanol). [g] Values of ν_{CO} in the IR spectrum (UR-10, in paraffin oil), cm^{-1}: I) 1681; II) 1680; IV) 1678; V) 1675; VI) 1676; VII 1692; VIII) 1678; IX) 1728; X) 1689; XI) 1680; XII) 1689; XIIIa) 1648.

Imidazo[2,1-b]thiazole derivatives (XIII-XXII). A) A solution of 0.02 mole of a 2-mercaptoimidazole derivative and 0.021 mole of an α-chloroketone in 10-50 ml of butanol was boiled for 2-3 hr and cooled, and the precipitate of the hydrochloride (XIIIa, XVIIa, XXIa, XXIIa) was filtered off and washed with ether. Evaporation of the mother liquor yielded additional amounts of these substances. The decomposition of the hydrochlorides with sodium bicarbonate in aqueous solution yielded the bases XIII, XVII, XXI, and XXII. The base XVII was also obtained by performing the reaction in ethanol (boiling for 3 hr).

B) To 0.01 mole of IX in 20 ml of butanol was added 5 ml of 10% ethanolic hydrogen chloride, the mixture was boiled for 3 hr and cooled, and the precipitate was filtered off and washed with ether. The yield of XXIa was 2.56 g (78.5%).

C) A mixture of 0.005 mole of a 2-(acylalkylthio)imidazole (I-IV, VI, VII) and 10-15 ml of $POCl_3$ was boiled for 7 hr (in the preparation of XIV, XVIII, and XIX), 14 hr (XVI), or 17 hr (XV, XX) and then the $POCl_3$ was distilled off in vacuum, the residue was treated with 10-20 ml of cold water and made alkaline with sodium carbonate or ammonia, and the precipitate was filtered off and washed with water. After the neutralization of the solution, XIV and XVIII were extracted with chloroform.

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