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CYCLIZATION OF S-BLOCKED ISOTHIOSEMICARBAZONES. I. A NEW ROUTE TO 2-MERCAPTOIMIDAZOLE DERIVATIVES AND 4(5)-SUBSTITUTED IMIDAZOLES

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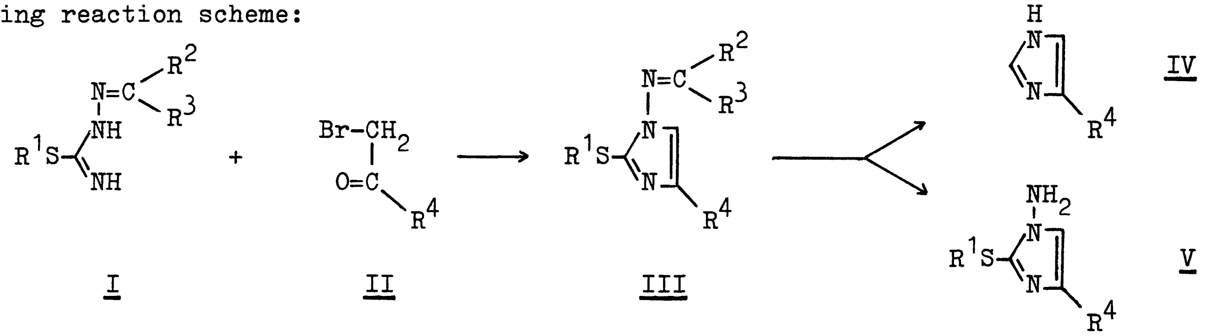
Condensation of an aromatic aldehyde or ketone S-methyl-, allyl-, or benzylisothiosemicarbazone with acetonyl or a phenacyl bromide yielded 1-arylideneamino-2-methylthio-, allylthio-, or benzylthio-4-aryl- or methyl-imidazoles in moderate yields. Treatment of these imidazoles with zinc/acetic acid in the presence of acetic anhydride afforded 1-acetyl-4-substituted imidazoles. Hydrolysis of the arylideneamino linkage succeeded only with the α-methyl-p-methoxybenzylideneamino compound.

Condensation of certain thiosemicarbazones of aromatic and heteroaromatic aldehydes with α-haloketones leads to the formation of a thiazole derivative owing to the preferential attack of the more nucleophilic mercapto group on the halogen-bearing carbon of the haloketone.$^{1)}$ This paper describes the cyclization of an isothiosemicarbazone, which has been blocked at the mercapto group by a methyl, allyl, or benzyl group, with acetonyl or a phenacyl bromide to an imidazole derivative, as well as reductive and hydrolytic cleavage of the cyclized products, as represented in the following reaction scheme:



where Ia (R^1, R^2, and R^3 given) CH_3, H, C_6H_5; Ib CH_3, H, p-CH_3O-C_6H_4; Ic CH_3, H, 3,4-$(CH_3O)_2C_6H_3$; Id CH_3, CH_3, p-CH_3O-C_6H_4; Ie $C_6H_5CH_2$, H, C_6H_5; If $C_6H_5CH_2$, H, p-CH_3O-C_6H_4; Ig CH_2=$CHCH_2$, H, p-CH_3O-C_6H_4: IIa (R^4 given) C_6H_5, IIb p-Cl-C_6H_4, IIc p-CH_3O-C_6H_4, IId p-O_2N-C_6H_4, IIe CH_3.

The condensation was brought about by heating the isothiosemicarbazone (I) with the α-haloketone (II) either in a molar ratio of 2:1 in ethanolic solution (Method A) or in an equimolar proportion in N,N-dimethylformamide (Method B) at 70-75°C for 2-3 hours. Thus, when two moles of anisaldehyde S-methylisothiosemicarbazone (Ib) were allowed to react with one mole of phenacyl bromide (IIa) by heating them together in ethanolic solution at 75°C for 2 hours, 1-p-methoxybenzylideneamino-2-methylthio-4-phenylimidazole (IIIba) crystallized out as pale yellow needles with mp 166-166.5°C in 52% yield. The compounds IIIbe, IIIda, and IIIfe were isolated by means of column chromatography on silica gel using benzene containing 3% v/v of ethanol as an eluant. In Method B, the desired products were isolated by diluting the reaction mixture with water and purified by recrystallization of the precipitated crude products from ethanol or a pyridine/ethanol mixture. Although extensive efforts to improve the yield in the cyclization are not yet made, a preliminary work suggested

Table 1.

Compound[*1]	Appearance	Mp, °C[*2]	%Yield		PMR($CDCl_3$, δ ppm[*3])			
			A	B	SCH_3	SCH_2	H-5	CH=N
IIIaa	pale yellow needles	140-141	49	40	2.73	--	*7	8.24
IIIab	yellow needles	177	47	17	2.92[*5]	--	*7	8.76
IIIac	yellow lustrous plates	145-145.5	29	14	2.89[*5]	--	7.97	8.74
IIIad	bright orange needles	225-226	37	23	2.98[*5]	--	8.40	8.84
IIIba	pale yellow needles	168.5-169	52	49	2.73	--	*7	8.20
IIIbb	yellow-brown needles	179-179.5	45	20	2.93[*5]	--	8.05	8.69
IIIbc	pale yellow needles	156.5-157	29	12	2.74	--	7.62	8.20
IIIbd	brown needles	211-212	53	10	2.93[*5]	--	8.32	8.76
IIIbe	pale yellow prisms	112-113	39	-	2.71	--	7.16	8.13
IIIca	pale yellow needles	182-183	47	-	2.94[*5]	--	8.05	8.72
IIIda	pale yellow plates	137-138	62	-	2.67	--	*7	--
IIIea	light brown needles	127.5-128	30	-	--	4.65	*7	8.26
IIIfa	yellow prisms	136-137	35	9[*4]	--	4.53	*7	8.12
IIIfe	yellow fine prisms	120.5-121.5	6.5	-	--	4.44	*7	8.05
IIIga	pale yellow plates	110-111	16	-	--	3.95[*6]	*7	8.15

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*1 The product obtained from the reaction between Ia and IIb, for example, was reported as IIIab. *2 All the melting points are uncorrected. *3 TMS was used as an internal standard. *4 Obtained as HBr salt. *5 Measured in CF_3CO_2D because of poor solubility in $CDCl_3$. *6 Appeared as a doublet, J=7.0 Hz. *7 The signal was obscured by aromatic proton peaks.

that acetonitrile could be substituted for ethanol in Method A with significantly good results. Attempts to cyclize S-methylisothiosemicarbazones of acetone, acetophenone, and p-nitrobenzaldehyde were unsuccessful. The products III were summarized in Table 1.

The structures of III were confirmed by a study of their IR, PMR, and mass spectra and by the results of elemental analyses. As shown in the equation above, condensation should occur so as to keep R^4 group away from the bulky arylideneamino group at 1-position because of the steric repulsion between these groups, as well as because the N^4 atom in I may possibly be less nucleophilic than the N^2 atom by analogy with benzalaminoguanidine$^{2)}$ and therefore undergo condensation with the halogen-bearing carbon much slower than the latter. In fact, none of isomers substituted at 5-position have been detected in the reaction mixture. In mass spectrometry, the compounds arbitrarily selected, IIIba, IIIbb, IIIbd, IIIbe, IIIfa, and IIIfe, showed peaks corresponding to the ions R^4-CN^+ in relatively large abundance (9-30%) and no peaks at m/e values corresponding to fragments formed by the loss of HCN molecule from the molecular ion. A prominent peak was observed in each spectrum at a mass corresponding to the loss of p-methoxybenzylideneamino moiety from the molecular ion, while the moiety appeared as an intens peak of m/e 134. In the products having a benzylthio group the most abundant fragment ion was tropylium ion, m/e 91. Each compound showed a prominent peak in agreement with the respective molecular weight.

All the compounds III gave appropriate PMR data in accord with the structures assigned among which the chemical shift values of predominant importance were included in Table 1. The chemical shifts observed in deuteriotrifluoroacetic acid are invariably at significantly lower fields than that obtained in deuteriochloroform and this tendency is notable in the H-5 and arylidene protons. Unsubstituted phenyl proton signals generally appeared as a complex multiplet in deuteriochloroform whereas they are very simplified in deuteriotrifluoroacetic acid so that peak assignment of H-5 is greatly facilitated.

A weak band in the range of 3140-3110 cm^{-1} was invariably observed in the infrared spectra (KBr) of all the products III, as well as the hydrogenolytic and hydrolytic derivatives IV and V, and was assigned to the νC-H at 5-position of the imidazole ring. The compounds containing p-$CH_3OC_6H_4$ grouping showed a characteristic band in the 2830-2820 cm^{-1} region due to the νC-H of O-methyl group,$^{3)}$ and also showed a very strong band at 1260-1250 cm^{-1}(ν_{as}C-O-C) and a strong band at 850-830 cm^{-1} (δCH).

Reductive cleavage occurred when IIIba was stirred with acetic acid and zinc dust in the presence of acetic anhydride at room temperature giving 1-acetyl-4-phenylimidazole (38%), 4(5)-phenylimidazole (IVa: $R^4=C_6H_5$) which was isolated as a picrate (19%), and N-acetyl-p-methoxybenzylamine (VI). These products had melting points substantially identical with those described in the literature.[4-6] The picrate was treated with aqueous ammonia to give the free imidazole (IVa). Similarly, IIIab and IIIac gave 1-acetyl-4-p-chlorophenylimidazole (PMR in DMSO-d_6: δ 8.18 ppm, d, H-5; 8.42, d, H-2, $J_{2,5}$=1.4 Hz. IR: νC=O 1720 cm^{-1}) and 1-acetyl-4-p-methoxyphenylimidazole (8.05 ppm, d, H-5; 8.45, d, H-2, $J_{2,5}$=1.4 Hz. IR: νC=O 1730 cm^{-1}) in 82 and 78% yields, respectively. Hydrolysis of these 1-acetyl compounds by a hydrochloric acid/ethanol mixture afforded the corresponding deacetylated products in more than 80% yields. Both 4(5)-p-chlorophenylimidazole (IVb: R^4=p-ClC_6H_4) and 4(5)-p-methoxyphenylimidazole (IVc: R^4=p-$CH_3OC_6H_4$) are known compounds and showed the same melting points as those reported by Norris[7] and Weidenhagen,[5] respectively. IIIad gave 1-acetyl-4-p-acetamidophenylimidazole as a result of simultaneous reduction of the nitro group. IIIbe yielded 4(5)-methylimidazole (IVd: $R^4=CH_3$) and no 1-acetyl compound was isolated. Treatment of IIIfa under the same conditions as above yielded 1-acetyl-2-benzylthio-4-phenylimidazole along with IVa, but prolonged stirring resulted in complete removal of the benzylthio group. Similarly, IIIga gave 1-acetyl-4-phenylimidazole, IVa, and VI with removal of the allylthio group. This reduction process provides not only a clear evidence for the structure of III but also a new route to 4(5)-substituted imidazoles. Hydrolysis of the 1-arylideneamino to amino group was possible only with the compound IIIda, which yields a new compound 1-amino-2-methylthio-4-phenylimidazole (V: $R^1=CH_3$, $R^4=C_6H_5$). PMR($CDCl_3$, δ ppm): 2.66 SCH_3, 4.56 NH (disappeared on addition of deuterium oxide).

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