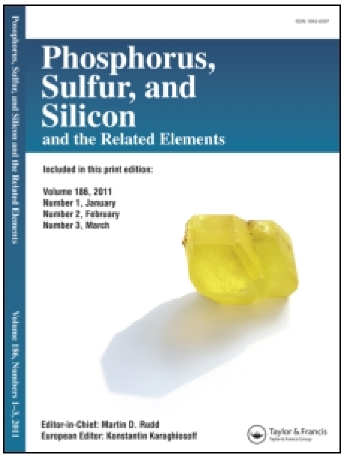

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SYNTHESIS AND REACTIONS OF 4,5-DIARYL-2-MERCAPTOIMIDAZOLES

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SYNTHESIS AND REACTIONS OF 4,5-DIARYL-2-MERCAPTOIMIDAZOLES

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4,5-Diaryl-2-mercaptoimidazoles (II) were synthesized and reacted with chloroacetic acid to form the S-carboxymethyl derivatives (III). The latter compounds were readily cyclised into the corresponding 5,6-diaryl-2,3-dihydroimidazo(2,1-b) thiazol-3-ones (IV) by the action of acetic anhydride. The 2-aryl-methylene (V) and the 2-arylhydrazono (VI) derivatives of (IV) were prepared. Compounds (IV) reacted with the aniline to give the anilide (VII) and with hydrazine hydrate to give the hydrazide (VIII), which condensed with the aromatic aldehyde to give the hydrazones (IX).

INTRODUCTION

There is an increasing interest in the chemistry of imidazothiazoles[1] and in the chemistry of hydrazones[2–5] because of their biological activities. This potentiated us to undertake the above reactions.

DISCUSSIONS

Disubstituted benzoins were prepared and fused with thiourea at 200°C to give 4,5-diaryl-2-mercaptoimidazoles (II). The ir spectra of compounds (II) show NH at 3450 cm^{-1}.

The n.m.r. Spectrum of (II$_a$) ($CDCl_3$) led to the following assignments: methoxy protons as a singlet (3H) at $\delta = 4.2$ ppm; the aromtic protons as a multiplet (9H) centred at $\delta = 7.68$ ppm; the 2NH protons as two broad singlets at $\delta = 8.95$ and 8.15 ppm, respectively.

Compounds (II) reacted with chloroacetic acid in the presence of acetic acid and the presence of fused sodium acetate to give S-carboxy-methyl derivatives (III), which were cyclised by acetic anhydride to give 4,5-diaryl-2,3-dihydroimidazo(2,1-b)thiazole-3-ones (IV). Compounds (IV) were also prepared by the reaction of (III) with thionyl chloride in the presence of benzene. The ir spectra of compounds (IV) showed the carbonyl absorption at 1725 cm^{-1}. The ^{1}H nmr of compound (IV$_b$) showed a methylene group as a singlet, (2H) at $\delta = 3.90$ ppm and the aromatic protons as a multiplet (8H) centered in the $\delta = 7.0$–7.8 ppm region.

The formulation of the cyclised products as (IV) is tentatively favored over the

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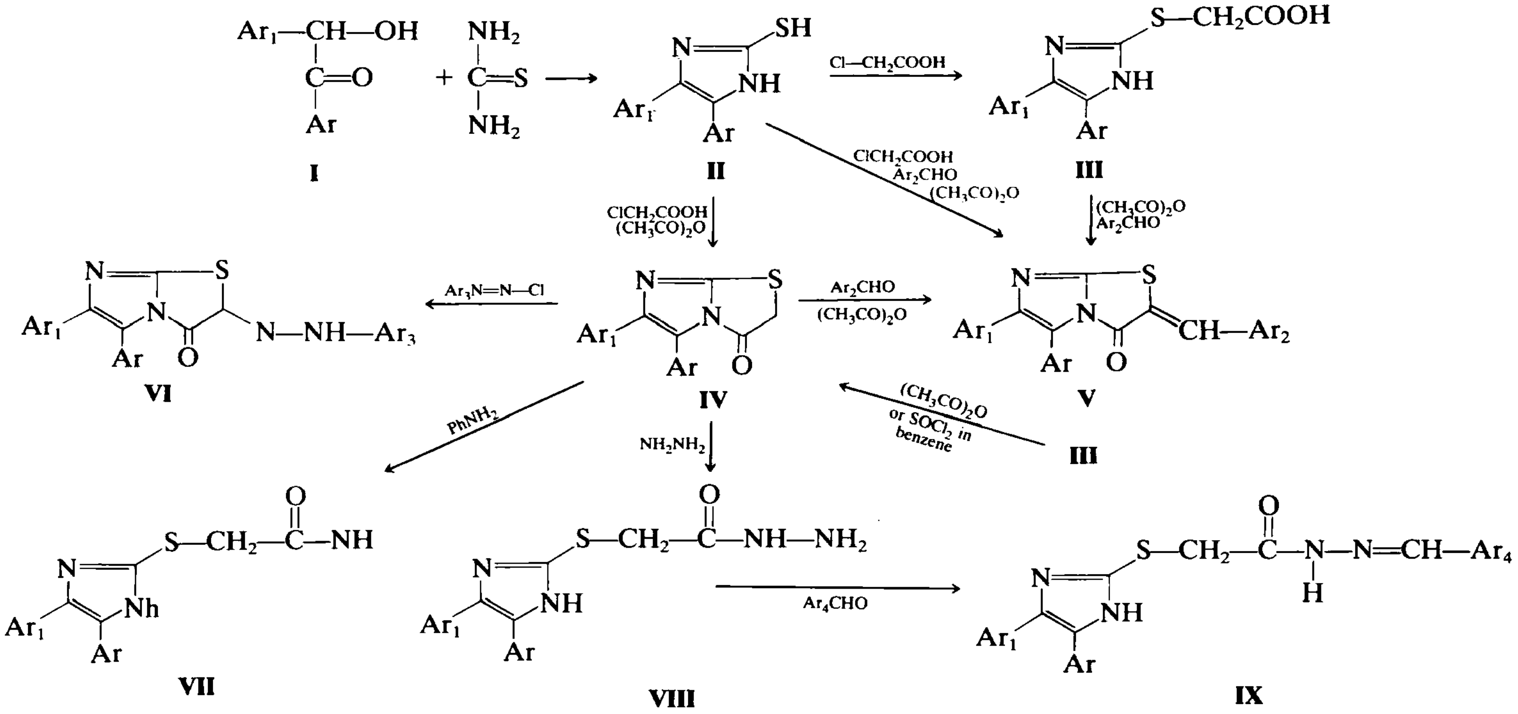
I
II
III
IV
V
VI
VII
VIII
IX
Cl—CH2COOH
ClCH2COOH Ar2CHO (CH3CO)2O
(CH3CO)2O Ar2CHO
ClCH2COOH (CH3CO)2O
Ar2CHO (CH3CO)2O
Ar3N=N—Cl
(CH3CO)2O or SOCl2 in benzene
PhNH2
NH2NH2
Ar4CHO

isomeric structures IV^{-6}. An analogous choice has been made in the case of dihydro 6-aryl-6-H-(1)benzothiepino(5,4-d)thiazolo-(3,2-a)pyrimidino-10(11H)-one-5,5-dioxides.[6]

Compounds (IV) contain an active methylene group, they condensed with aromatic aldehydes in the presence of piperidine to yield 2-arylmethylene-5,6-diaryl-2,3-dilydro imidazo (2,1b) thiazol-3-ones (V).

However, the arylmethylene derivatives (V) were prepared directly from (II) by the action of chloroacetic acid, the aromatic aldehyde and sodium acetate in the presence of acetic acid-acetic anhydride. Also, compounds (V) could be prepared from (III) by the action of the aromatic aldehyde and sodium acetate in the presence of acetic anhydride. The ir spectra of compounds (V) showed carbonyl absorption at 1700 cm^{-1}. This shift to lower frequency is due to the conjugation with the exocyclic double bond.[7]

The ^1H nmr spectrum of (V_e) in ($CDCl_3$) showed the following: a single at δ (3.9) ppm (3H) (OCH_3); a multiplet in the $\delta = 6.8$–8.2 ppm region (13H) for the aromatic protons and the benzylic proton.

Compounds (IV) coupled with aryldiazonium salts in the presence of pyridine to give 2-arylhydrazono 5,6-diaryl 2,3-dihydroimidazo(2,1-b) thiazol-3-ones (VI).

The ir spectra of compounds (VI) showed NH at 3225 cm^{-1} and carbonyl absorption at 1715 cm^{-1} which appears at lower frequency due to the conjugation with the exocyclic double bond. This compound can exist only in the hydrazo form.[7]

The thiazolone ring of (IV) has been cleaved by aniline to yield 2(4,5-diarylimidazol-2-ylthio) acetanilide (VII). The ir spectra of compounds (VII) lack the band characteristic for $c = 0$ frequency. Instead, a broad band exists around 3440 cm^{-1} which indicates hydrogen bonding with the carbonyl oxygen. Also 4,5-diaryl-imidazol-2-ylthioacetylhydrazides (VIII) have been prepared by the condensation of hydrazine hydrate with compounds (IV) in the presence of ethanol. Compounds (VIII) readily condensed with aromatic aldehydes to yield the corresponding hydrazones. The ir spectrum of compounds (VIII) showed the ($c = 0$) absorption at 1675 cm^{-1} and the (NH) absorption at 3200 cm^{-1}.

EXPERIMENTAL

Preparation of 4,5 diaryl-2-mercaptoimidazoles ($II_{a,b}$). Compounds II_a and II_b were prepared according to Hammam[8,9] in almost pure state and satisfactory yield (c.f. Table I).

(4-methoxyphenyl-5-phenyl-2-imidazolythio)acetic acid (III_a). A mixture of 4-methoxyphenyl-2-mercaptoimidazole II_a (0.01 mol), monochloroacetic acid (0.01 mol), fused sodium acetate (1.5 g), and glacial acetic acid (20 ml) was refluxed for 3 hours, then allowed to cool. The crystals, which separated, were filtered, washed with hot water, and crystallised from the proper solvent (c.f. Table II).

(4,5-Di-o-chlorophenyl-2-imidazolythio)acetic acid (III_b). A mixture of 4,5-di-*o*-chlorophenyl-2-mercaptoimidazolo II_b (0.01 mol) monochloroacetic acid (0.01 mol), fused sodium acetate (1.5 g), and glacial acetic acid (20 ml) was refluxed for 3 hours, then allowed to cool. The crystals, which separated were filtered, washed with hot water, and crystallised from the proper solvent (c.f. Table II).

Action of thionyl chloride on compounds (III_a, III_b). Thionyl chloride (10 ml) was added to compounds III_a or III_b (1 g). The reaction mixture was warmed on water bath for one hour, after

TABLE I

4,5-Diaryl-2-mercaptoimidazoles (II)

Comp. No.	M.P. C° solvent	Yield %	Ar_1/Ar	Formula (M.W.)	Analysis calcd/found				
					C	H	N	S	Cl
II_a	225 EtOH	83	p-$C_6H_4OCH_3$ C_6H_5	$C_{16}H_{14}N_2OS$ (282)	68.08 67.85	4.96 7.07	9.92 10.12	11.34 10.36	
II_b	200 EtOH	80	o-C_6H_4Cl o-C_6H_4Cl	$C_{15}H_{10}N_2SCl_2$ (320)	56.25 57.00	3.12 3.41	8.75 9.12	10.0 9.80	21.87 21.23

cooling the reaction mixture was poured into light petroleum and the precipitate was filtered and crystallised from the proper solvent. Melting points and mixed melting points were identical with compounds (IV) obtained by the action of acetic anhydride and chloroacetic acid on compounds (II).

5,6-Diaryl-2,3-dihydroimidazo(2,1-b)thiazol-3-one ($IV_{a,b}$). (4,5-Diaryl-2-imidazolythio)acetic acid (10 g) was refluxed in 20 ml acetic anhydride for 1 hour, then poured into water. The solid product which separated was filtered, washed with water, and recrystallised from the proper solvent (c.f. Table III).

2-Arylidene-5,6-diaryl-2,3-dihydroimidazo(2,1-b)thiazol-3-one (V).

Method (*A*)

A mixture of (0.01 mol) of compound (IV), (0.01 mol) of the aromatic aldehyde and (1 g) of sodium acetate in 10 ml of acetic anhydride was refluxed for 1 hr, then poured into cold water. The precipitate was filtered and crystallised from the proper solvent. (c.f. Table IV).

Method (*B*)

A mixture of (0.01 mol) of compound (II), (0.01 mol) of chloroacetic acid, (0.01) mol of the appropriate aldehyde and 2 g of fused sodium acetate in 20 ml acetic acid and 14 ml acetic anhydride was refluxed for 2 hr, allowed to cool, then poured into cold water. The product was filtered and crystallised from the proper solvent (see Table IV).

2-(Arylhydrazino) 5,6-diaryl-2,3-dihydroimidazo(2-1-b)thiazol-3-one (VI). The aromatic amines (0.01 mol) was dissolved in 3 ml of concentrated hydrochloric acid and 2 ml of water, cooled to 0° and treated with (0.7 g) of sodium nitrite in (5 ml) of water. This diazotised amine was added gradually while stirring to a cooled solution of (0.01 mol) of compounds IV in 30 ml pyridine. The reaction mixture was refrigerated for $\frac{1}{2}$ hour. The product was filtered, washed with water and crystallised from the proper solvent (c.f. Table V).

4,5-Diaryl-(2-imidazolythio)acetanilide (VII_a). 5,6-Diaryl-2,3-dihydro-imidazo(2,1b)thiazol-3-one (IV_a) (0.005 mol) and (0.006 mol) of the amine were refluxed in 15 ml of ethanol for 2 hr. The reaction mixture was allowed to cool, then poured into water. The solid product formed was collected, washed with a little ethanol and crystallised from the proper solvent, (c.f. Table VI).

TABLE II

(4,5-Diaryl-2-imidazolythio)acetic acid (III)

Comp. No.	M.P. C° solvent	Yield %	Ar_1/Ar	Formula (M.W.)	Analysis calcd/found				
					C	H	N	S	Cl
III_a	120 EtOH	70	p-$C_6H_4OCH_3$ C_6H_5	$C_{18}H_{16}N_2O_3S$ (340)	63.52	4.70	8.23	9.41	
III_b	110 aqEtOH	73	o-C_6H_4Cl o-C_6H_4Cl	$C_{17}H_{19}N_2O_2SCl_2$ (378)	53.96 54.11	3.11 3.41	7.40 8.00	8.46 9.11	18.51 18.90

TABLE III

4,5-Diaryl-2,3-dihydro-imidazo(2,1-b)thiazol-3-ones (IV)

Comp. No.	M.P. C° solvent	Yield %	Ar_1/Ar	Formula (M.W.)	Analysis calcd/found				
					C	H	N	S	Cl
IV_a	125 EtOH	80	p-$C_6H_4OCH_3$ C_6H_5	$C_{18}H_{14}N_2O_2S$ (322)	67.08 66.70	4.34 4.10	8.69 9.12	0.93 8.90	
IV_b	80 EtOH	75	o-C_6H_4Cl o-C_6H_4Cl	$C_{17}H_{10}N_2OSCl_2$ (360)	56.66 56.13	2.77 3.01	7.77 8.12	8.88 9.01	19.44 18.01

TABLE IV

2-Arylidene-5,6-diaryl-2,3-dihydroimidazo(2,1-b)thiazol-3-one (V)

Comp. No.	M.P. C° solvent	Yield %	Ar_1/Ar	Ar_2	Formula (M.W.)	Analysis calcd/found				
						C	H	N	S	Cl
V_a	230 aq AcOH	70	p-$C_6H_4OCH_3$ C_6H_5	p-$C_6H_4OCH_3$	$C_{26}H_{20}O_3N_2S$ (440)	70.90 69.06	4.54 5.07	6.36 7.00	7.27 7.48	
V_b	245 AcOH	75	p-$C_6H_4OCH_3$ C_6H_5	p-C_6H_4Cl	$C_{25}H_{17}O_2N_2SCl$ (444.5)	67.49 67.31	3.82 3.11	6.26 6.22	7.19 7.48	
V_c	190 aq AcOH	79	o-C_6H_4Cl o-C_6H_4Cl	C_6H_5	$C_{24}H_{14}N_2OSCl_2$ (448)	64.28 64.61	3.12 3.22	6.25 6.41	7.14 8.01	
V_d	200 Benzene-Pet eth	80	o-C_6H_4Cl o-C_6H_4Cl	o-C_6H_4Cl	$C_{24}H_{13}ON_2SCl_3$ (483.5)	59.56 59.12	2.68 3.31	5.79 6.21	6.61 6.23	
V_e	215 Benzene-Pet eth	75	o-C_6H_4Cl o-C_6H_4Cl	p-$C_6H_4OCH_3$	$C_{25}H_{17}N_2O_2Scl_2$ (478)	62.76 63.41	3.55 3.22	5.85 6.12	6.69 7.21	

TABLE V

2-(Arylhydrazino)-5,6-diaryl-2,3-dihydro-imidazo(2-1-h)thiazol-3-ones (VI)

Comp. No.	M.P. C° solvent	Yield %	Ar_1/Ar	Ar_3	Formula (M.W.)	Analysis calcd/found			
						C	H	N	S
VI_a	165 aq AcOH	70	$C_6H_4OCH_3$ C_6H_4	C_6H_5	$C_{24}H_{18}O_2N_4S$ (426)	67.60 68.10	4.22 4.00	13.14 12.80	7.51 7.11
VI_b	230 Benzene-Pet eth	75	p-$C_6H_4OCH_3$ C_6H_5	p-$C_6H_4CH_3$	$C_{25}H_{20}O_2N_4S$ (440)	68.18 67.40	4.54 4.12	12.72 11.91	13.75 13.12

TABLE VI

(4,5-Diaryl-2-imidazolythio)acetanilide (VII_a)

Comp. No.	M.P. C° solvent	Yield %	Ar_1/Ar	Formula (M.W.)	Analysis calcd/found			
					C	H	N	S
VII_a	80 EtOH	70	$C_6H_4OCH_3$ C_6H_4	$C_{24}H_{20}N_3O_2D$ (414)	69.56 69.12	4.83 4.31	10.14 9.80	7.72 8.21

TABLE VII

(4-Methoxyphenyl-5-phenyl-2-imidazolythio)acetyl hydrazide ($VIII_a$)

Comp. No.	M.P. C° solvent	Yield %	Ar_1/Ar	Formula (M.W.)	Analysis calcd/found			
					C	H	N	S
$VIII_a$	100 aq EtOH	75	$\frac{C_6H_4OCH_3}{C_6H_4}$	$C_{18}H_{18}N_4O_2S$ (354)	61.10 61.34	5.08 5.32	15.81 16.12	9.03 8.90

TABLE VIII

Aldehyde-hydrazones (IX)

Comp. No.	M.P. C° solvent	Yield %	Ar_1/Ar	Ar_4	Formula (M.W.)	Analysis calcd/found				
						C	H	N	S	Cl
IX_a	120 aq EtOH	80	$\frac{p\text{-}C_6H_4OCH_3}{C_6H_5}$	C_6H_5	$C_{25}H_{22}N_4O_2S$ (442)	67.87 67.12	4.97 4.22	12.66 12.10	7.23 7.42	
IX_b	135 EtOH	85	$\frac{p\text{-}C_6H_4OCH_3}{C_6H_5}$	$p\text{-}C_6H_4OCH_3$	$C_{26}H_{23}N_4O_3S$ (472)	66.24 66.41	4.88 5.10	11.88 11.23	6.79 7.23	
IX_c	200 aq EtOH	70	$\frac{p\text{-}C_6H_4OCH_3}{C_6H_5}$	$p\text{-}C_6H_4Cl$	$C_{25}H_{20}N_4O_2SCl$ (476.5)	63.09 63.01	4.10 4.21	11.77 11.0	6.72 5.91	7.46 6.91

(4-Methoxyphenyl-5-phenyl-2-imidazolythio)acetyl hydrazide ($VIII_a$). To a mixture of compound $(IV)_a$ (0.005 mol and 0.006 mol) of hydrazine hydrate was added 15 ml of ethanol, the mixture was refluxed for 2 hrs. The reaction mixture allowed to cool, then poured into water. The solid product formed was collected, washed with a little ethanol and crystallised from the proper solvent, (c.f. Table VII).

Aldehyde-hydrazones (IX). A mixture of 1.5 g of compound ($VIII_a$) and the equivalent amount of the aromatic aldehyde in (50 ml) of ethanol was refluxed for 3 hr, allowed to cool and the crystals that separated were filtered and recrystallised from the proper solvent, (c.f. Table VIII).

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