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Original Scientific Paper

Syntheses of 4-Substituted-3-Methyl-2-Phenylimidazoles

M. Y. Yousif, A. M. Ismail, M. A. Metwally, and M. M. El-Kerdawy*

Department of Chemistry, Faculty of Pharmacy and Faculty of Science+, University of Mansoura, Mansoura, Egypt

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Reaction of the title compound I with aromatic aldehydes afforded α,β-unsaturated ketones II, which were allowed to react with cyanoacetamide, ethyl cyanoacetate, hydrazines. Treatment of I with hydrazines or amines gave V and VI.

Imidazole nucleus constitutes the main part in many pharmaceutical compounds possessing variable physiological activities[1-9]. Therefore, 4-acetyl--5-methyl-2-phenylimidazole (I)[10,11] was used as the key intermediate in the preparation of different substituted imidazole derivatives.

α,β-unsaturated ketones (IIa-h) were prepared by the interaction of (I) with different aromatic aldehydes in sod. ethoxide. The IR spectra of these compounds showed absorption bands at 1680—1660 cm^{-1} (C=O) and a broad one at 3250—3200 cm^{-1} (NH). The ^{1}H-NMR (DMSO-d_6) of compound IIa displayed signals at 2.2 (s, 3H, methyl aromatic), 2.55 (s, 3H, C_5—CH_3), 7.5—8.1 (m, 9H, aromatic) and a broad one at δ 13 (s, 1H, NH), in addition to the appearance of signals at 7.15 (d, 1H, CO—CH=C*H*) (J = 15 Hz) and 7.35 (d, 1H, CO—C*H*=CH) (J = 15 Hz).

Reactivity of II towards base catalyzed addition of cyanoacetamide was investigated. Thus, the treatment of compounds (IIa-h) with cyanoacetamide afforded 4-(6′-aryl-3′-cyano-2′[H]-pyridone-4′-yl)-5-methyl-2-phenylimidazoles (IIIa-h), which were also obtained by treating (II) with ethyl cyanoacetate and ammonium acetate. Compounds (IIIa-h) exhibit characteristic absorption bands at 2210 cm^{-1} for conjugated (CN), 3300 cm^{-1} (NH-ring) and 1650 cm^{-1} (C=O). ^{1}H-NMR spectra of compound IIIe showed signals at δ 2.5 (s, 3H, CH_3), 6.65 (s, 1H, pyridone C*H*), 7.5—8 (m, 9H, Ar*H*, N*H*, pyridone) and 12.5 (broad, N*H*, imidazole).

Moreover, the treatment of compounds (II) with hydrazines yielded 4-(5′-arylpyrazolin-3′-yl)-5-methyl-2-phenylimidazoles (IVa-d). The IR spectrum of IVa displayed bands at 1620 cm^{-1} (NH) and 1610 cm^{-1} (C=N). The ^{1}H-NMR spectrum of IVa displayed signals at δ 2.6 (s, 3H, —CH_3), 12.8—13 (broad, NH imidazole and pyrazole), 3.2 (broad, 2H, —CH_2), 3.81 (s, 3H, —OCH_3), and 7.1—7.9 (m, 9H, Ar—*H*). On the other hand, when hydrazines were fused with compound (I), they afforded 5-methyl-2-phenylimidazole-4-aceto-hydrazones (Va, b). The IR spectrum of Va showed bands at 1620 cm^{-1} (C=N), 1640 cm^{-1} (CH_3C=N), 3225 cm^{-1} (NH) and two sharp bands at 3300,

3320 cm^{-1} (NH_2). The ^{1}H-NMR spectrum of Vb displayed signals at δ 2.4 (s, 3H, —CH_3), 2.65 (s, 3H, —CH_3), 12.8 (s, 1H, NH-imidazole), 8.35 (s, 1H, N*H*—N=C) and 7.3—8.1 (m, 1OH, Ar*H*).

Treatment of (Va) with *m*-chlorobenzaldehyde or pyridine-4-carboxyaldehydes yielded the corresponding mixed azines (VIIa, b). The IR spectra of these compounds showed bands at 1630 cm^{-1} (C=N) and 3220 cm^{-1} (NH).

Fusion of compound (I) with benzylamine and toluidines gave the corresponding alkylazomethines (VIa-c). The IR spectra of compounds VI showed absorption bands at 1640—1610 cm^{-1} (C=N) and a broad band at 3250—3200 cm^{-1}.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured on a Unicam sp 1000 infrared spectrophotometer (max in cm^{-1}) in KBr disc., ^{1}H-NMR spectra on a Varian EM-390 90 MHz NMR spectrometer.

α,β-Unsaturated Ketones (IIa-h)

To a solution of (I) (0.01 mol) in ethanolic sodium ethoxide (0.3 g sodium metal in 20 ml ethanol), the appropriate aldehyde (0.01 mol) was added, and the reaction mixture was heated under reflux for 2—5 hrs. After cooling, the reaction mixture was diluted with water and neutralized with hydrochloric acid. The precipitated product was filtered off, dried and crystallized from the appropriate solvent (Table I).

TABLE I

α,β-Unsaturated Ketones (IIa-h)

Compd. No.	R	Cryst. solv.	m. p. °C	Yield %	Mol. formula	Analyses/%, Calc./Found		
						C	H	N
IIa	$C_6H_4CH_3$-p	E+W	214	75	$C_{20}H_{18}N_2O$	79.4 79.2	6.0 6.0	9.3 9.7
b	$C_6H_4OCH_3$-p	E	235	80	$C_{20}H_{18}N_2O_2$	75.4 75.0	5.6 5.5	8.8 9.0
c	C_6H_4Cl-o	E+W	160	65	$C_{19}H_{15}ClN_2O$	70.7 69.9	4.7 5.2	8.7 7.9
d	C_6H_4Cl-m	E	152	80	$C_{19}H_{15}ClN_2O$	70.7 70.6	4.7 4.5	8.7 8.9
e	C_6H_4Cl-p	E+W	225	75	$C_{19}H_{15}ClN_2O$	70.7 71.2	4.7 5.2	8.7 8.4
f	$C_6H_4N(CH_3)_2$-p	E	247	65	$C_{21}H_{21}N_3O$	76.1 76.1	6.3 6.0	12.7 12.5
g	2-thiopheno	E	238	80	$C_{17}H_{14}N_2OS$	69.3 69.2	4.7 5.0	9.5 9.6
h	4-pyridino	D+E	275	75	$C_{18}H_{15}N_3O$	74.7 74.6	5.2 5.4	14.5 14.3

E = Ethanol, D = DMF and W = Water.

4-(6'-Aryl-3'-Cyano-2'[1H]-Pyridon-4'-yl)-5-Methyl-2-Phenylimidazoles (IIIa-h)

A mixture of *α,β*-unsaturated ketones (IIa-h) (0.05 mol), cyanoacetamide (0.05 mol) and a few drops of piperidine was heated under reflux on an oil bath at 140—150 °C for 6 hrs. On cooling, the reaction mixture was triturated with water, then filtered off and triturated with hot ethanol. The undissolved solid was filtered, dried and crystallized from DMF (Table II).

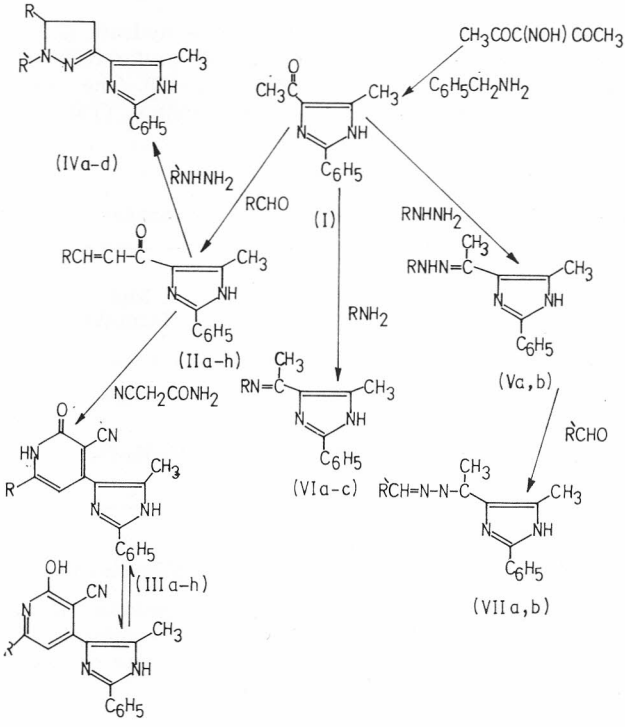
TABLE II

4-(6'-Aryl-3'-Cyano-2'[1H]-Pyridon-4'-yl)-5-Methyl-2-Phenylimidazoles (IIIa-h)

Compd. No.	R	m. p. °C	Yield %	Mol. formula	Analyses/%, calc./found		
					C	H	N
IIIa	$C_6H_4Cl_3$-*p*	> 280	60	$C_{23}H_{18}N_4O$	75.9 75.6	4.9 5.3	15.2 15.5
b	$C_6H_4OCH_3$-*p*	> 280	60	$C_{23}H_{18}N_4O_2$	72.2 72.2	4.8 4.9	14.4 14.0
c	C_6H_4Cl-*o*	> 280	45	$C_{22}H_{15}ClN_4O$	68.3 68.0	3.9 4.0	14.5 14.2
d	C_6H_4Cl-*m*	> 280	50	$C_{22}H_{15}ClN_4O$	68.3 68.2	3.9 3.8	14.5 14.3
e	C_6H_4Cl-*p*	> 280	50	$C_{22}H_{15}ClN_4O$	68.3 67.9	3.9 4.1	14.5 14.6
f	$C_6H_4N(CH_3)_2$-*p*	> 280	55	$C_{24}H_{21}N_5O$	72.9 73.0	5.3 5.3	17.7 17.5
g	2-thiopheno	> 280	65	$C_{20}H_{14}N_4OS$	67.0 66.8	3.9 4.1	15.6 15.2
h	4-pyridino	> 280	60	$C_{21}H_{15}N_5O$	71.4 71.0	4.2 4.1	19.8 20.0

4-(5'-Arylpyrazolin-3'-yl)-5-Methyl-2-Phenylimidazoles (IVa-d)

a) A mixture of (IIb) or (IIh) (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol-acetic acid mixture (30 ml) was heated under reflux for 10 hrs. After



cooling, the separated solid was filtered, dried and crystallized from aq. ethanol to give compounds (IVa, b) (c. f. Table III).

b) A mixture of (IIc) or (IIe) (0.01 mol) and phenylhydrazine (0.01 mol) in glacial acetic acid (30 ml) was heated under reflux for 10 hrs. After cooling, the separated soild product was filtered off, dried and crystallized from aq. ethanol to give compounds (IVc, d) (c. f. Table III).

TABLE III

4-(5'-Arylpyrazolin-3'-yl)-5-Methyl-2-Phenylimidazoles (IVa-d)

Compd. No.	R	R`	Yield %	m. p. °C	Mol. formula	Analyses/%, calc./found		
						C	H	N
IVa	4-pyridino	H	213	50	$C_{18}H_{17}N_5$	71.3 71.5	5.6 5.5	23.1 23.0
b	$C_6H_4OCH_3$-*p*	H	80	45	$C_{20}H_{20}N_4O$	72.3 72.0	6.0 6.1	16.9 17.0
c	C_6H_4Cl-*o*	C_6H_5	141	45	$C_{25}H_{21}ClN_4$	72.7 72.5	5.1 4.9	13.6 14.0
d	C_6H_4Cl-*p*	C_6H_5	162	45	$C_{25}H_{21}ClN_4$	72.7 72.6	5.1 5.0	13.6 13.5

5-Methyl-2-Phenylimidazole-4-Acetohydrazones (Va, b)

A mixture of (I) (0.01 mol) and excess hydrazine hydrate (0.1 mol) or phenylhydrazine (0.03 mol) was fused on an oil-bath at 150° under reflux for 4 hrs. After cooling the content was washed with pet. ether (60—80). The obtained solid product was filtered off, dried and crystallized from ethanol, (Table IV).

TABLE IV

5-Methyl-2-Phenylimidazole-4-acetohydrazones (Va, b)

Compd. No.	R	m. p. °C	Yield %	Mol. formula	Analyses/%, calc./found		
					C	H	N
Va	H	> 280	70	$C_{12}H_{14}N_4$	67.0 66.5	6.6 6.5	26.1 25.7
b	C_6H_5	160	40	$C_{18}H_{18}N_4$	74.5 74.2	6.2 6.0	19.3 19.5

4-(α-Methyl-N-Aralkylazomethin)-5-Methyl-2-Phenylimidazoles (VIa-c)

A mixture of I (0.01 mol) and benzylamine, *o*-toluidine or *m*-toluidine (0.05 mol) was fused in an oil-bath at 150 °C for 5 hrs. After cooling the residue was triturated with pet. ether (60—80), then filtered off, dried and recrystallized from aq. ethanol to give compounds (VIa-c) (c. f., Table V).

TABLE V

4-(α-Methyl-N-Aralkylazomethin)-5-Methyl-2-Phenylimidazoles (VIa-c)

Compd. No.	R	m. p. °C	Yield %	Mol. formula	Analyses/% calc./found		
					C	H	N
VIa	$-CH_2C_2H_5$	115	75	$C_{19}H_{19}N_3$	78.9 79.0	6.6 6.4	14.5 14.2
b	$-C_6H_4CH_3$-*o*	> 280	60	$C_{19}C_{19}N_3$	78.9 78.6	6.6 6.5	14.5 14.4
c	$-C_6H_4CH_3$-*m*	210	45	$C_{19}H_{19}N_3$	78.9 79.2	6.6 6.3	14.5 14.5

Preparation of Mixed Azines (VIIa, b)

To a solution of Va (0.01 mol) in glacial acetic acid (30 ml), pyridine-4-carboxyaldehyde or *m*-chlorobenzaldehyde (0.01 mol) was added and the reaction mixture was heated under reflux for 6 hrs. After cooling, a sufficient amount of water was added. The solid product that separated was filtered off, dried and recrystallized from the appropriate solvent, (Table VI).

TABLE VI

Compd. No.	R'	Cryst. solv.	m. p. °C	Yield %	Mol. formula	Analyses/%, calc./found		
						C	H	N
VIIa	4-pyridino	ethanol	105	65	$C_{18}H_{17}N_5$	71.3 70.9	5.6 5.3	23.1 23.4
b	C_6H_4Cl-*m*	benzene	90	70	$C_{19}H_{17}ClN_4$	67.8 68.0	5.1 5.0	16.6 16.5

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SAŽETAK

Sinteza 4-supstituiranih-3-metil-2-fenilinidazola

M. Y. Yousif, A. M. Ismail, M. A. Metwally i M. M. El-Kerdawy

Reakcijom naslovnog spoja s aromatskim aldehidima pripravljeni su α,β-nezasićeni alkil-imidazolil-4-ketoni. Njihovom kondenzacijom s cijanoacetamidom, etilcijanoacetatom i hidrazinom pripravljeni su 4-pirazolil-4-pirimidonil-imidazoli, te hidrazo- i amino-derivati spoja I (spojevi V i VI))