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SYNTHESIS OF SUBSTITUTED 2-AMINO-1-ARYL-IDENAMINOIMIDAZOLES AND 1-ARYLIDEN-AMINOIMIDAZO[1,2-*a*]IMIDAZOLES

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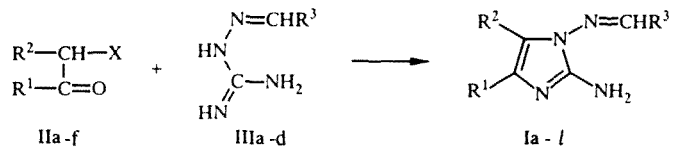
A new method is proposed for the preparation of 2-amino-1-arylidenaminoimidazoles, which react with α-haloketones to give a series of 1-arylidenamino-3-acylmethyl-2-iminoimidazolines and 1-arylidenaminoimidazo[1,2-a]imidazoles depending on the conditions.

There have been only a few reports on the preparation of 2-amino-1-arylidenaminoimidazoles (I) [1-3] and only several examples of the formation of such compounds by the reaction of aromatic α-haloketones (II) such as phenacyl bromide, its 4-methyl, 4-bromo, and 4-chloro derivatives, and desyl chloride, with acetophenone or benzaldehyde guanylhydrazones (III) [2, 3]. The reactions are carried out by heating reagents II and III taken in 1:2 molar ratio in ethanol or acetone at reflux with subsequent isolation of imidazoles I (method A).

In the present work, we examined the feasibility of expanding the applicability of this reaction. For this purpose, in addition to phenacyl bromide, 4-chlorophenacyl bromide, desyl chloride, and benzaldehyde guanylhydrazone mentioned above, we also used 2,4-dichlorophenacyl, 4-phenylphenacyl, 4-methoxyphenacyl bromides and 4-methoxybenzaldehyde, 2,4-dichlorobenzaldehyde, and 3-nitrobenzaldehyde guanylhydrazones in the condensation (see Scheme 1).



IIa-f IIIa-d Ia-*l*

Ia—*l*, IIa—e X = Br, R^2 = H, Ia,e,g,k, IIa R^1 = Ph, b,h,l, IIb R^1 = 2,4-$Cl_2C_6H_4$, Ic, IIc R^1 = 4-PhC_6H_4, Ii, IId R^1 = $MeOC_6H_4$; Ij, IIe R^1 = 4-ClC_6H_4; Id X = Cl, R^1 = R^2 = Ph; Ia—d, IIIa R^3 = Ph, Ie,f, IIIb R^3 = $MeOC_6H_4$, I g-j, IIIc R^3 = 2,4-$Cl_2C_6H_3$, I k, *l*, IIId R^3 = 3-$NO_2C_6H_4$

However, considerable tar formation was noted in the condensation of hydrazone IIIa and bromoketone IIb under the conditions described in the literature (method A) and the desired product, imidazole Ib was isolated in only 32% yield. The reactions of haloketones IIa-IIf with hydrazones IIIb-IIId carried out under these conditions were even more complex. In all cases, we obtained product mixtures, which were difficult to separate into products and yielded imidazoles Ie-Ig and Ik in low yield. Attempts to obtain pure imidazoles Ih-Ij and *Il* proved unsuccessful. Varying the reaction conditions such as the order and time of addition of reagents II and III and lowering the temperature from 80° to 20°C did not lead to the desired results.

On the other hand, we found that if NaOH is used as the condensing agent, the reaction leading to imidazoles I and IV-VI becomes the predominant pathway and does not depend on the nature of starting II and III. Better yields of imidazoles Ia-*Il* (see Table 1) are achieved at room temperature in ethanol using equimolar amounts of NaOH and reagents II and III (method B). We also note that this method permits not only the suppression of undesired side-reactions but also gives a 50% reduction in the consumption of hydrazones III.

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TABLE 1. Physical Indices of Products I, IV-VI, and VIII-XI

Compound	mp, °C*	Chemical formula	Found, % / calculated, %				Yield, %†
			C	H	Cl (or Br)	N	
Ia	213 (dec.) ‡	$C_{16}H_{14}N_4$	—	—	—	—	76 (78)
Ib	210...212	$C_{16}H_{12}Cl_2N_4$	57,84 / 58,02	3,81 / 3,65	21,75 / 21,41	17,16 / 16,92	65 (32)
Ic	213...214	$C_{22}H_{18}N_4$	78,36 / 78,08	5,18 / 5,36	—	16,80 / 16,56	62 (47)
Id	201...203 ‡	$C_{22}H_{18}N_4$	—	—	—	—	49 (42)
Ie	197...198	$C_{17}H_{16}N_4O$	68,66 / 69,85	5,70 / 5,52	—	19,30 / 19,16	56 (25)
If	200...201	$C_{23}H_{20}N_4O$	75,27 / 74,98	5,18 / 5,47	—	15,03 / 15,21	41 (36)
Ig	221...222	$C_{16}H_{12}Cl_2N_4$	57,80 / 58,02	3,48 / 3,65	21,80 / 21,46	17,15 / 16,92	73 (38)
Ih	142...143	$C_{16}H_{10}Cl_4N_4$	48,30 / 48,03	2,35 / 2,52	35,81 / 35,45	17,81 / 14,00	45
Ii	220 (dec.)	$C_{17}H_{14}Cl_2N_4O$	56,31 / 56,53	4,12 / 3,91	20,01 / 19,63	15,74 / 15,51	46
Ij	212...213	$C_{16}H_{11}Cl_3N_4$	53,01 / 52,75	3,31 / 3,05	28,54 / 28,82	14,30 / 15,39	49
Ik	236...238	$C_{16}H_{13}N_5O_2$	62,30 / 62,52	4,43 / 4,27	—	22,98 / 22,80	54 (28)
Il	184...186	$C_{16}H_{11}Cl_2N_5O_2$	51,03 / 51,20	3,17 / 2,96	19,06 / 18,65	18,44 / 18,67	48
Va	233...235	$C_{24}H_{20}N_4O \cdot HBr$	62,27 / 62,48	4,76 / 4,59	17,83 / 17,32	12,35 / 12,14	80
Vb	230...231	$C_{24}H_{18}Cl_2N_4O \cdot HBr$	54,17 / 54,36	3,84 / 3,61	—	10,39 / 10,57	67
Vc	245...247	$C_{25}H_{22}N_4O_2 \cdot HBr$	61,39 / 61,11	4,95 / 4,72	16,47 / 16,26	11,30 / 11,40	73
Vd	238...240	$C_{24}H_{19}ClN_4O \cdot HBr$	57,92 / 58,14	4,21 / 4,07	—	11,19 / 11,30	68
Ve	248...250	$C_{24}H_{19}FN_4O \cdot HBr$	60,35 / 60,14	4,12 / 4,21	—	11,80 / 11,69	72
VIa	219...221	$C_{24}H_{18}N_4 \cdot HBr$	65,29 / 65,02	4,21 / 4,32	18,30 / 18,02	12,78 / 12,64	76 (90)
VIb	238...239	$C_{24}H_{16}Cl_2N_4 \cdot HBr$	56,03 / 56,28	3,47 / 3,35	—	11,18 / 10,94	68 (80)
VIc	233...234	$C_{22}H_{22}N_4$	77,35 / 77,16	6,38 / 6,48	—	16,51 / 16,36	57
VId	233...235	$C_{30}H_{22}N_4 \cdot HBr$	69,51 / 69,37	4,31 / 4,46	15,50 / 15,38	10,62 / 10,79	76
VIe	225...227	$C_{36}H_{26}N_4 \cdot HBr$	72,35 / 72,61	4,79 / 4,57	13,25 / 13,42	9,60 / 9,41	96
VIf	248...250	$C_{30}H_{20}Cl_2N_4 \cdot HBr$	61,48 / 61,25	3,78 / 3,60	—	9,45 / 9,52	66
VIg	229...230	$C_{30}H_{22}N_4 \cdot HBr$	69,58 / 69,37	4,60 / 4,46	15,18 / 15,38	10,94 / 10,79	54
VIh	245...246	$C_{35}H_{30}Cl_2N_4 \cdot HBr$	63,60 / 63,84	4,87 / 4,75	—	8,42 / 8,51	71
VIi	225	$C_{31}H_{24}N_4O$	79,23 / 79,46	5,35 / 5,16	—	12,18 / 11,96	64
VIj	209...211	$C_{24}H_{16}Cl_2N_4$	67,08 / 66,83	3,56 / 3,74	16,75 / 16,44	12,75 / 12,99	79
VIk	235	$C_{24}H_{15}Cl_2N_4$	70,16 / 66,99	3,44 / 3,51	16,32 / 16,48	13,21 / 13,02	68

*Recrystallization solvents: Ia from 2:1 dioxane—water, Ib, Ic, and If from acetone, Id from benzene, Ie, Ih, and Ii from dioxane, and Ig, Ij, and Ik from methanol, Il from ethanol.

†The yields of Ia-Il obtained by method A and of VIa and VIb from imidazolines Va and Vb are given in parentheses.

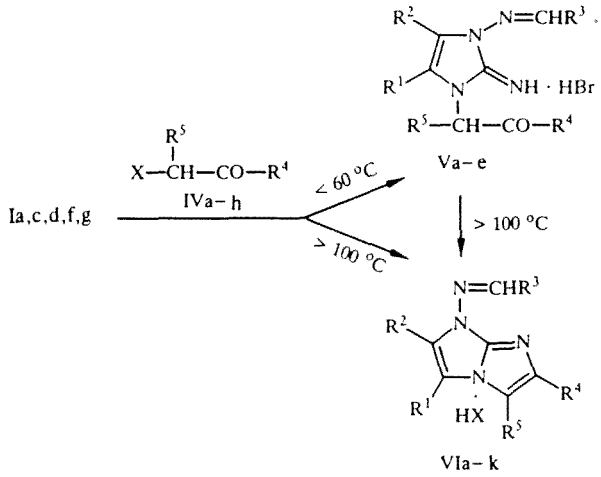
‡The melting point corresponds to the literature value [2].

The structure of the resultant imidazoles Ia-Il was supported by elemental analysis and, for several of these compounds, by PMR spectroscopy (see Table 1 and Experimental). The melting points and R_f data for imidazoles Ia and Id were in complete accord with the literature data. Furthermore, imidazoles If and Ik were converted by hydrazinolysis into the corresponding 1,2-diaminoimidazoles described by Hetzheim et al. [1, 2].

The reaction of heterocycles containing the $H_2N—C=N$ fragment with α-haloketones leads to condensed imidazoheterocyclic systems [4-6]. However, with the exception of a single example [7], there have been no reports of the participation of 2-amino-1-arylidenaminoimidazoles in such reactions. Hence, we studied the reaction of imidazoles Ia-Ij with α-haloketones (IV).

On boiling imidazoles Ia, c, d, f, g with α-haloketones IVa-g in acetone, as in reaction of 1-methyl-2-aminoimidazole with α-bromoketones [5], we obtained hydrobromides of the corresponding 1-arylidenamino-3-acylmethyl-2-imino-4-phenylimidazolines Va-e (see Table 1). In the case of imidazolines Va, b we found that boiling them in ethanol leads to cleavage of a water molecule with formation of hydrobromides of the corresponding 1-arylidenaminoimidazo[1,2-a]imidazoles VIa, b.

The most complete heterocyclization of imidazolines Va and Vb occurs when they are heated in reflux in solvents such as dioxane or DMF, which permit raising the reaction temperature to ≥ 100°C. 1-Arylidenaminoimidazoles may also undergo cyclocondensation with α-haloketones under these conditions. Thus, the corresponding imidazo[1,2-*a*]imidazoles IVa-VIk were synthesized in one step from imidazoles Ia, Ic, Id, If, and Ig (see Table 1 and Experimental section).



IVa—f, Va—e X = Br, $R^1 = R^3$ = Ph, $R^2 = R^5$ = H, a R^4 = Ph, b R^4 = 2,4-$Cl_2C_6H_3$, e R^4 = $MeOC_6H_4$, d R^4 = 4-ClC_6H_4, e R^4 = 4-FC_6H_4, f R^4 = 4-PhC_6H_4; IVg X = Cl, R^4 = *t*-Bu, R^5 = H; IVh X = Br, R^4 = 2,4-$Cl_2C_6H_3$, R^5 = *n*-C_5H_{11}; IVa—g $R^2 = R^5$ = H, R^3 = Ph, a $R^1 = R^4$ = Ph, b R^1 = Ph, R^4 = 2,4-$Cl_2C_6H_3$, c R^1 = Ph, R^4 = *t*-Bu, d R^1 = 4-PhC_6H_4, R^4 = Ph, e $R^1 = R^4$ = 4-PhC_6H_4, f R^1 = 4-PhC_6H_4, R^4 = 2,4-$Cl_2C_6H_3$, g $R^1 = R^4$ = Ph; VIh R^1 = 4-PhC_6H_4, R^2 = H, R^3 = Ph, R^4 = 2,4-$Cl_2C_6H_3$, R^5 = *n*-C_5H_{11}; VI i $R^1 = R^2 = R^4$ = Ph, R^3 = 4-$MeOC_6H_4$, R^5 = H; VI j,k R^1 = Ph, $R^2 = R^5$ = H, R^3 = 2,4-$Cl_2C_6H_3$, j R^4 = Ph, k R^4 = 4-ClC_6H_4

The structure of imidazolines V and imidazo[1,2-*a*]imidazoles VI were indicated by elemental analysis and IR spectroscopy. The IR spectra of imidazolines V show bands at 1640-1670, 1680-1710, and 3160-3280 cm^{-1}, indicating the presence of azomethine, carbonyl, and imine groups, respectively. The IR spectra of VI lack bands characteristic for the CO and NH groups, indicating closure of the second imidazole ring.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for KBr pellets. The PMR spectra were taken on a Bruker AS-80 spectrometer at 80 MHz in DMSO-d_6 with TMS as the internal standard. The chemical shifts are given on the δ scale. The melting points were found on a Boetius heating block and were uncorrected. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using 10:1 chloroform—2-propanol as the eluent. The yields, melting points, and elemental analysis data are given in Table 1.

Benzaldehyde Guanylhydrazone (IIIa). A sample of 3 ml water, 2.2 g (0.02 mole) benzaldehyde, and 6 ml 20% hydrochloric acid were added to 2.70 g (0.02 mole) aminoguanidine carbonate. After completion of the liberation of carbon dioxide, the mixture was heated to reflux and then cooled. A sample of 3.5 ml 40% aqueous potassium hydroxide was added and the mixture was heated at reflux for an additional 5 min. The reaction mixture was cooled. The precipitate formed was filtered off, washed with water until the wash water was at pH 7, dried, and recrystallized from ethanol to give 2.5 g (79%) hydrazone IIIa, mp 177°C (178°C [8]).

Hydrazones IIIb-IIId were synthesized analogously from the corresponding aldehydes.

4-Methoxybenzaldehyde guanylhydrazone (IIIb) was obtained in 70% yield, mp 185°C. PMR spectrum: 3.77 (3H, s, CH_3O), 5.48-5.69 (4H, br.s, NH_2, NH, C=NH), 6.84-7.67 (4H, m, H_{arom}), 7.98 ppm (1H, s, N=CH). Found: C, 56.48; H, 6.17; N, 29.03%. Calculated for $C_9H_{12}N_4O$: C, 56.23; H, 6.29; N, 29.15.

2,4-Dichlorobenzaldehyde guanylhydrazone (IIIc) was obtained in 74% yield, mp 210°C. PMR spectrum: 5.57-5.81 (4H, br.s, NH_2NH, C=NH), 6.11-7.52 (3H, m, H_{arom}), 8.13 ppm (1H, s, N=CH). Found: C, 41.35; H, 3.60; Cl, 30.94, N, 24.41%. Calculated for $C_8H_8Cl_2N_4$: C, 41.58; H, 3.49; Cl, 30.69; N, 24.25%.

3-Nitrobenzaldehyde guanylhydrazone (IIId) was obtained in 85% yield, mp 205°C. PMR spectrum: 5.67-5.83 (4H, br.s, NH_2, NH, C=NH), 6.14-8.03 (4H, m, H_{arom}), 8.12 ppm (1H, s, N=CN). Found: C, 46.20; H, 4.54; N, 33.95%. Calculated for $C_8H_9N_5O$: C, 46.37; H, 4.38; N, 33.80%.

2-Amino-1-arylidenaminoimidazoles (Ia-Il) (general procedure). A. A solution of 0.01 mole α-haloketone II and 0.02 mole hydrazone III in 10 ml ethanol or acetone was heated at reflux for 1.5-3 h. The reaction mixture was cooled. The precipitate formed was filtered off, washed with hot water, dried, and recrystallized. Ethanol was used for imidazoles Ia-Id and acetone for imidazoles Ie and If. In the case of imidazoles Ig and Ik, the reaction was carried out in acetone at room temperature for 10-12 h.

B. A solution of 0.8 g (0.02 mole) NaOH in 15 ml ethanol was added dropwise over about 0.5 h to a stirred solution of 0.02 mole α-haloketone II and 0.02 mole hydrazone III in 30 ml ethanol. The reaction mixture warmed to 40-45°C and a precipitate formed. The mixture was left at room temperature for 10-12 h. The precipitate was filtered off, washed with hot water, dried, and crystallized.

2-Amino-1-benzylidenamino-4-phenylimidazole (Ia). PMR spectrum: 6.21 (2H, s, NH_2), 7.18-7.96 (10H, m, H_{arom}), 8.02 (1H, s, =CH), 8.58 ppm (1H, s, C=CH).

2-Amino-1-(3-nitrobenzylidene-4-phenylimidazole (Ik). PMR spectrum: 6.44 (2H, s, NH_2), 7.28-8.27 (10H, m, H_{arom}), 8.42 ppm (1H, s, C=CH).

2-Amino-1-(3-nitrobenzylidene)-4-(2,4-dichlorophenyl)imidazole (Il). PMR spectrum: 6.40 (2H, s, NH_2), 7.54-8.21 (7H, m, H_{arom}), 8.29 (1H, s, N=CH), 8.34 ppm (1H, s, C=CH).

Hydrobromide Salts of 1-Arylidenamino-3-acylmethyl-2-imino-4-phenylimidazolines (Va-Ve) (general procedure). A solution of the corresponding haloketone IV in 5 ml acetone was added with stirring to a solution of 0.01 mole imidazole Ia in 10 ml acetone. The reaction mixture was heated at reflux for 8 h and cooled. The hydrobromide salt precipitate was filtered off, thoroughly washed with acetone, and dried.

Hydrobromide Salt of 1-Benzylidenamino-2-imino-4-phenyl-3-phenacylimidazole (Va). IR spectrum: 1665 (N=CN), 1690 (C=O), 3260 cm^{-1} (C=NH). PMR spectrum: 5.75 (2H, s, CH_2), 7.05-7.51 (15H, m, H_{arom}), 7.60-8.09 ppm (3H, m, C=CH, N=CH, C=NH).

Imidazo[1,2-*a*]imidazoles (VIa-VIk). A. From imidazoles Ia-Ij. A mixture of 0.005 mole imidazole Ia-Ij and 0.005 mole α-haloketone IV in 30-40 ml dioxane, DMF, or 1:1 DMF—dioxane was heated at reflux for 6-8 h and then cooled. The precipitate was filtered off, washed with acetone, and dried. Dioxane was used as the solvent to obtain imidazo[1,2-*a*]imidazoles VIa, VIb, and VId-VIh, DMF was used for VIj, and 1:1 DMF—dioxane was used for VIc, VIi, and VIk.

B. From imidazolines Va and Vb. A solution of 3.7 g (0.008 mole) imidazoline V in 40 ml dioxane was heated at reflux for 6 h and cooled. The precipitate was filtered off, washed with acetone, and dried to give imidazo[1,2-*a*]imidazole VIa. Analogously, imidazo[1,2-*a*]imidazoline VIb was obtained from imidazoline VIIb.

Hydrobromide Salt of 1-Benzylidenamino-3,6-diphenylimidazo[1,2-*a*]imidazole (VIa). IR spectrum: 1660 cm^{-1} (N=CH). PMR spectrum: 7.46-7.88 (15H, m, H_{arom}), 7.88-8.44 ppm (3H, m, C=CH, N=CH).

Hydrobromide Salt of 1-Benzylidenamino-3,6-di[(4-phenyl)phenyl]imidazo[1,2-*a*]imidazole (VIe). IR spectrum 1670 cm^{-1} (N=CH). PMR spectrum: 7.48-7.86 (23H, m, H_{arom}), 7.95-8.12 ppm (3H, m, C=CH), N=CH) [sic].

1,2-Diamino-4-phenylimidazole. A mixture of 2.9 g (0.01 mole) imidazole Ik, 3 ml hydrazine hydrate, and 10 ml ethyleneglycol was maintained at 160-170°C for 6 h, cooled, and poured into water. The precipitate formed was filtered off, washed with water, and crystallized from ethanol to give 1.13 g (75%) 1,2-diamino-4-phenylimidazole, mp 241-243°C (dec.) (mp 242-243°C [1, 2]). Analogously, imidazole If gave 1,2-diamino-4,5-diphenylimidazole in 70% yield, mp 226-228°C [2].

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