Reactions of 1-Alkylbenzimidazolium 3-Imines with Acetylenic Compounds and Benzaldehyde

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Received September 23, 1974

1-Alkyl-3-aminobenzimidazolium salts react with dimethyl acetylenedicarboxylate or dibenzoylacetylene in the presence of base to produce unusual 1:1 adducts, 1-(2′-alkylaminophenyl)-pyrazole derivatives. Treatment of the 3-amino salts with benzaldehyde in the presence of alkali gives benzaldehyde 2-(*N*,*N*-acylalkylamino)phenylhydrazones. The same hydrazones are obtained by alkaline treatment of 1-alkyl-3-benzaliminobenzimidazolium salts, which are prepared from the 3-amino salts and benzaldehyde.

We recently reported a simple synthetic method for the preparation of *N*-imines of 1-alkylimidazoles and thiazoles (1) which involves treatment of the parent azoles with *O*-mesitylenesulfonylhydroxylamine (MSH) (2). As part of our continuing interest in the chemical properties of the heteroaromatic *N*-imines (3), we have investigated the reactions of 1-alkylbenzimidazolium 3-imines with dimethyl acetylenedicarboxylate and dibenzoylacetylene as typical examples of 1,3-dipolar cycloaddition reactions (4), and benzaldehyde. It was also of interest to compare the chemical properties of these azolium *N*-imines with those observed in their pyridine counterparts, whose chemistry have been extensively explored (5).

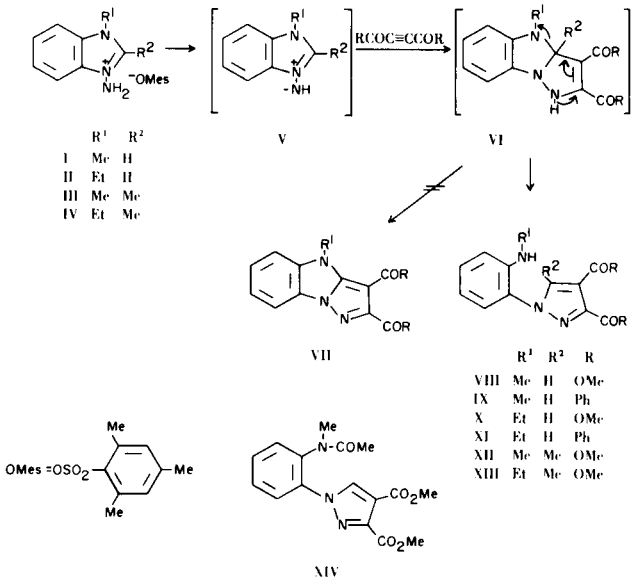
Reaction with Acetylenic Compounds.

By analogy to the behavior of pyridinium *N*-imines (6), we had expected the formation of pyrazolo[1,5-*a*]benzimidazole derivatives (VII) (7). Instead, the products isolated were the ring opened pyrazole derivatives (VIII-XIII).

In general, a solution of one mole equiv of the 1-alkyl-3-aminobenzimidazolium salt (Ia,b) and two molar equiv of the acetylenic compound in dimethylformamide in the presence of potassium carbonate were heated at 40-50° for 5 hours. After evaporation of the solvent the crude product was purified by preparative tlc and recrystallization. The use of other solvents such as ethanol or acetonitrile gave the same products but in lower yields, presumably due to low solubility of the 3-amino salts in these solvents.

In this manner both I and II afforded the pyrazoles VIII-IX and X-XI when treated with dimethyl acetylenedicarboxylate and dibenzoylacetylene, respectively. Similar treatment of III and IV with dimethyl acetylenedicarboxylate gave a complex mixture, from which products XII and XIII were isolated in low yields by preparative tlc, respectively. These reactions in the absence of potassium carbonate did not afford adducts.

Scheme I



The structures of the products were based on the elemental analyses (Table I) and spectral data (Table II). For example, the ir spectrum (potassium chloride) of VIII shows an NH absorption band at 3370 cm^{-1} and two carbonyl bands at 1740 and 1710 cm^{-1}. The nmr spectrum (deuteriochloroform) reveals a pyrazole ring proton (8) at τ 1.91 (singlet), two methoxyl singlets at τ 6.03 and 6.14, a doublet at τ 7.16 (3H, J = 5 Hz), a broad signal at τ 4.85

TABLE I

Preparation of 1-(2′-Alkylaminophenyl)pyrazoles

Compd.	M.p. °C	Recrystallized from	Yield %	Formula	Analysis Calcd. C	H	N	Found C	H	N
VIII	102-103	ether-*n*-hexane	57	$C_{14}H_{15}N_3O_4$	58.12	5.23	14.53	58.27	5.23	14.24
IX	170-171.5	benzene-*n*-hexane	70	$C_{24}H_{19}N_3O_2$	75.57	5.02	11.02	75.52	5.06	10.85
X	70-70.5	ether-*n*-hexane	33	$C_{15}H_{17}N_3O_4$	59.39	5.65	13.86	59.37	5.68	14.04
XI	112-113	benzene-*n*-hexane	53	$C_{25}H_{21}N_3O_2$	75.93	5.35	10.63	75.92	5.44	10.82
XII	116-117	ether-*n*-hexane	28	$C_{15}H_{17}N_3O_4$	59.39	5.65	13.86	59.66	5.72	13.70
XIII	104-105	ether-*n*-hexane	28	$C_{16}H_{19}N_3O_4$	60.55	6.04	13.24	60.53	6.07	13.15

TABLE II

Spectral Data of 1-(2′-Alkylaminophenyl)pyrazoles

Compd.	Ir ν max (KCl) cm^{-1}	Uv λ max (methanol) nm (log ϵ)	Nmr (Deuteriochloroform) τ R^2	R	R^1	M^+
VIII	3370 (s) 1740 (vs) 1710 (vs)	210 (4.17) 235 (4.10) 313 (3.36)	1.91 (s)	6.03 (s) 6.14 (s)	7.16 (d) J = 5 Hz	289
IX	3410 (m) 1660 (vs) 1645 (vs)	208 (4.54) 248 (4.55) 319 (3.70)	1.95 (s)	2.00-2.60 (m)	7.16 (d) J = 5 Hz	381
X	3350 (s) 1740 (vs) 1710 (vs)	208 (4.46) 236 (4.36) 315 (3.66)	1.88 (s)	6.05 (s) 6.15 (s)	6.84 (br. q) J = 7 Hz 8.80 (t) J = 7 Hz	303
XI	3380 (s) 1665 (vs) 1645 (vs)	207 (4.58) 248 (4.57) 316 (3.62)	1.89 (s)	2.00-2.65 (m)	6.83 (br. q) J = 7 Hz 8.74 (t) J = 7 Hz	395
XII	3400 (s) 1740 (vs) 1710 (vs)	208 (4.46) 235 (4.20) 305 (3.59)	7.66 (s)	6.05 (s) 6.10 (s)	7.23 (br. s)	303
XIII	3370 (s) 1745 (vs) 1710 (s)	208 (4.53) 235 (4.26) 305 (3.69)	7.65 (s)	6.04 (s) 6.11 (s)	6.87 (br. q) J = 7 Hz 8.80 (t) J = 7 Hz	317

TABLE III

Preparation of Benzaldehyde 2-(*N*,*N*-Acylalkylamino)phenylhydrazones

Compd.	M.p. °C	Recrystallized from	Yield % method (A) (a)	(B) (a)	Formula	Analysis Calcd. C	H	N	Found C	H	N
XVII	177-178 (dec)	Acetone	41	50	$C_{15}H_{15}N_3O$	71.12	5.97	16.59	71.07	5.97	16.29
XVIII	139-140	Acetone	52	69	$C_{16}H_{17}N_3O$	71.88	6.41	15.72	72.01	6.50	15.51
XIX	204-206	Acetone	41	70	$C_{16}H_{17}N_3O$	71.88	6.41	15.72	71.64	6.37	15.43
XX	174-175	Methylene chloride-petroleum ether	43	70	$C_{17}H_{19}N_3O$	72.57	6.81	14.94	72.60	6.88	14.82

(a) See Experimental.

TABLE IV

Spectral Data of Benzaldehyde 2-(*N*,*N*-Acylalkylamino)phenylhydrazones

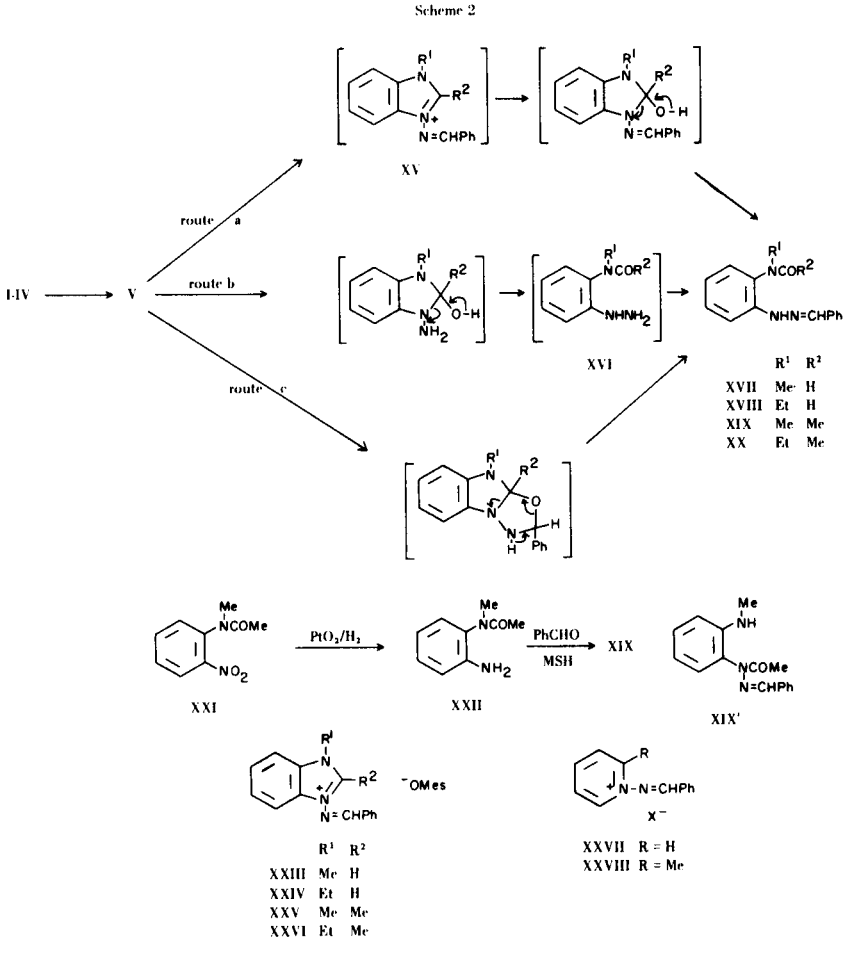
Compd.	Ir ν max (KCl) cm^{-1}	Uv λ max (Ethanol) nm (log ϵ)	Nmr (Deuteriochloroform) τ				
			R^1	–N = C*H*Ph	R^2	NH	M^+
XVII	3250 (m) 1660 (vs) 1585 (vs)	220 (4.13) 240sh (4.00) 308sh (4.02) 335 (4.18)	6.85 (s)	2.10 (s)	1.83 (s)	1.70 (br. s)	253
XVIII	3260 (m) 1660 (vs) 1590 (s)	224 (4.39) 242sh (4.27) 308sh (4.32) 335 (4.47)	6.29 (q) J = 7 Hz 8.87 (t) J = 7 Hz	2.10 (s)	1.89 (s)	1.65 (br. s)	267
XIX	3260 (m) 1640 (vs) 1590 (s)	222 (4.21) 242sh (3.97) 308sh (4.05) 335 (4.21)	6.82 (s)	2.00 (s)	8.17 (s)	1.27 (br. s)	267
XX	3230 (m) 1630 (vs) 1585 (s)	224 (4.26) 242sh (4.14) 308sh (4.23) 335 (4.40)	(a) 8.82 (t) J = 7 Hz	2.04 (s)	8.14 (s)	1.48 (br. s)	281

(a) Signals due to $>NCH_2CH_3$ group appeared as part of an ABX_3 system with the AB portion centered at τ 6.27 with $J_{AB} = 21$ Hz and $J_{AX} = J_{BX} = 7$ Hz.

and a multiplet (4H) in the aromatic region between τ 3.9 and 2.7. After treatment with deuterium oxide, the signal at τ 4.85 disappeared and the doublet at τ 7.16 became a singlet, suggesting the presence of an $NHCH_3$ grouping. Acetylation of VIII with acetic anhydride gave *N*-acetate (XIV).

As previously suggested (1a), a possible mechanism for the formation of compounds (VIII-XIII) involves an initial formation of the 3-imines (V) which undergo a 1,3-dipolar cycloaddition reaction with acetylenic compounds followed by ring opening reaction of a primary adduct VI to the final products. Apparently, the driving force for the

Scheme 2



ring opening reaction is derived from the relief of the strain in the [6.5.5] fused ring system.

Reaction with Benzaldehyde.

Treatment of I-IV with benzaldehyde in methanol in the presence of 5% potassium hydroxide with ice-cooling for 5 minutes gave single products XVII-XX, respectively. The structures of these products were established by analytical and spectral data (Tables III and IV) and an independent synthesis of XIX.

For example, the ir spectrum (potassium chloride) of XIX shows an NH absorption band at 3260 cm^{-1} and a carbonyl band at 1640 cm^{-1}. The nmr spectrum (deuteriochloroform) shows an *N*-methyl singlet at τ 6.82, an acetyl methyl singlet at τ 8.17, a singlet at τ 2.00 (1H), a broad singlet at τ 1.27, and a multiplet for the remaining hydrogens between τ 3.20 and 2.25. These data are consistent with two structures XIX and XIX'. Final confirmation of the structure was given by an independent synthesis, which involves treatment of a solution of two molar equiv of 2-amino-*N*-methylacetanilide (XXII) and one mole equiv of benzaldehyde with one mole equiv of MSH for 30 minutes at room temperature to give XIX in 94% yield (9).

One of the mechanistic rationalizations for the formation of XVII-XX from I-IV involves condensation of the initially generated 3-imines (V) with benzaldehyde to give XV. This step is then followed by an attack of hydroxide ion to the 2-position and base-catalyzed ring opening to afford XVII-XX (route a). The passage of XV to XVII-XX was substantiated by the following experiment.

When an ethanolic solution of 3-amino salts (I-IV) with benzaldehyde was heated at reflux for 2-5 hours, nearly quantitative yields of 1-alkyl-3-benzaliminobenzimidazolium salts (XXIII-XXVI) were obtained, whose structures were confirmed by elemental analyses and spectral data (Tables V and VI). For example, the ir spectrum (potassium chloride) of XXV shows an absorption band due to C=C and/or C=N at 1620 and 1595 cm^{-1}, and the nmr spectrum (in dimethylsulfoxide-d_6) shows a singlet at τ 0.61 (1H, methine proton), an *N*-methyl singlet at τ 5.95, a methyl singlet at τ 7.08, and a multiplet in the aromatic region between τ 2.40 and 1.70, and signals due to mesitylene ring. Treatment of XXIII-XXVI under similar reaction conditions used for the transformation of I-IV to XVII-XX gave the same hydrazone derivatives (XVII-XX) in good yields.

TABLE V

Preparation of 1-Alkyl-3-benzaliminobenzimidazolium Salts

Compd.	M.p. °C	Yield %	Formula	Analysis Calcd. C	H	N	Found C	H	N
XXIII	202-204	96	$C_{24}H_{25}N_3O_3S$	66.19	5.79	9.65	66.20	5.80	9.66
XXIV	225-226	95	$C_{25}H_{27}N_3O_3S$	66.80	6.05	9.35	66.77	6.11	9.26
XXV	205-207	95	$C_{25}H_{27}N_3O_3S$	66.80	6.05	9.35	66.43	6.12	9.32
XXVI	163-164	96	$C_{26}H_{29}N_3O_3S$	67.37	6.31	9.07	67.04	6.60	9.27

TABLE VI

Spectral Data of 1-Alkyl-3-benzaliminobenzimidazolium Salts

Compd.	Ir ν max (KCl) cm^{-1}	Uv λ max (Ethanol) nm	Nmr (DMSO-d_6) R^1	R^2	$-N=CH$Ph
XXIII	1610 (m) 1595 (s) 1550 (s) 1460 (s)	270 (4.12) 276sh (4.11) 301 (4.16)	5.83 (s)	−0.50 (s)	0.60 (s)
XXIV	1610 (m) 1595 (s) 1540 (vs) 1460 (s)	270 (4.23) 277sh (4.21) 303 (4.29)	5.41 (q) J = 7 Hz 8.40 (t) J = 7 Hz	−0.50 (s)	0.60 (s)
XXV	1620 (s) 1595 (s) 1560 (s) 1460 (vs)	270 (4.34) 276sh (4.25) 300 (4.21)	5.95 (s)	7.08 (s)	0.61 (s)
XXVI	1620 (m) 1600 (s) 1560 (s) 1460 (vs)	270 (4.30) 276sh (4.22) 300 (4.15)	5.42 (q) J = 7 Hz 8.59 (t) J = 7 Hz	7.08 (s)	0.63 (s)

This does not eliminate, however two other possiblilties that the 3-imines (V) undergo a base-induced ring-opening reaction to hydrazines (XVI) followed by condensation with benzaldehyde (route b), and that V undergoes a 1,3-dipolar cycloaddition reaction with benzaldehyde followed by ring-opening (route c). In the latter mechanism the oxygen atom of the acyl group of XVII-XX must be derived from that of benzaldehyde.

These results are in contrast to the behavior of benzalimines XXVII and XXVIII derived from an *N*-aminopyridinium salt and an *N*-amino-2-methylpyridinium salt which have been shown to give benzaldehyde and benzonitrile, respectively, by alkaline treatment (10, 11).

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with an Hitachi EPI G-2 spectrophotometer, uv spectra on an Hitachi 124 spectrophotometer, and, unless otherwise stated, nmr spectra on an Hitachi R-20A spectrometer (tetramethylsilane as internal standard). Mass spectra were obtained with an Hitachi RMU-6D instrument with a direct inlet system operating at 70 ev. Preparative tlc was carried out on Merck Alumina PF_{254}.

General Procedure for 1-(2′-Alkylaminophenyl)pyrazoles (VIII-XIII).

A mixture of the 1-alkyl-3-aminobenzimidazolium salt (I-IV) (1b) (1 mmole), potassium carbonate (138 mg.), and dimethyl acetylenedicarboxylate or dibenzoylacetylene (1.5-2.0 mmoles) in dimethylformamide (7.0 ml.) was stirred at 40-50° for 5 hours. The solvent was removed *in vacuo*, and the residue was extracted with chloroform. The dried extract was concentrated. The residue was purified by preparative tlc using benzene:chloroform (3:1) as solvent, and recrystallization. The results are summarized in Tables I and II.

Dimethyl 1-(2′-*N*,*N*-Acetylmethylaminophenyl)pyrazole-3,4-dicarboxylate (XIV).

A solution of VIII (58 mg.) in acetic anhydride (0.3 ml.) was heated at 90-95° for 30 minutes. The excess acetic anhydride was evaporated *in vacuo*. The residue was recrystallized from benzene-*n*-hexane, m.p. 96-97.5°, yield, 49 mg. (73%); ir (potassium chloride): cm^{-1} 1750 (vs), 1720 (vs) and 1665 (vs); uv λ max (methanol): 207 nm (log ε 4.43), 230 sh (4.23) and 248 sh (4.03); nmr (deuteriochloroform, at 130°) (12): τ 2.01 (1H, s, pyrazole H), 6.05 (3H, s, OMe), 6.17 (3H, s, OMe), 6.92 (3H, s, NMe), 8.16 (3H, s, COMe), and 2.30-2.78 (4H, m, aromatic H). At 35°, signals at τ 2.01, 6.92, and 8.16 split, presumably due to a restricted rotation about the amide bond (13). The mass spectrum shows the molecular ion at m/e 331 (Calcd. 331).

Anal. Calcd. for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 58.17; H, 5.20; N, 12.79.

General Procedure for Benzaldehyde 2-(*N*,*N*-Acylalkylamino)-phenylhydrazones (XVII-XX).

(A) From the 1-Alkyl-3-aminobenzimidazlium Salt (I-IV).

To a stirring solution of the 1-alkyl-3-aminobenzimidazolium salt (I-IV) (1 mmole) in methanol (10 ml.) was added a 5% potassium hydroxide solution (1.2 ml.) and a solution of benzaldehyde (1.1 mmole) in methanol (2 ml.) with ice-cooling. After the reaction mixture was stirred at 0° for 5 minutes, the solvent was removed *in vacuo*, and the residue was extracted with chloroform. The dried extract was concentrated. The residual solid was purified by recrystallization. The results are summarized in Tables III and IV.

(B) From the 1-Alkyl-3-benzaliminobenzimidazolium Salt (XXIII-XXVI).

To a stirring solution of the 1-alkyl-3-benzaliminobenzimidazolium salt (XXIII-XXVI) (1 mmole) in methanol (10 ml.) was added a 5% potassium hydroxide solution (1.2 ml.) with ice-cooling. After the reaction mixture was stirred at 0° for 10 minutes, the solvent was removed *in vacuo*, and the residue was extracted with chloroform. The dried extract was concentrated. The residual solid was purified by recrystallization. The results are summarized in Tables III and IV.

General Proceudre for 1-Alkyl-3-benzaliminobenzimidazolium Salts (XXIII-XXVI).

A solution of the 1-alkyl-3-aminobenzimidazolium salt (I-IV) (1 mmole) and benzaldehyde (1.2 mmoles) in ethanol (5 ml.) was refluxed for 2-5 hours. The solvent was removed. After addition of ether, the precipitated crystals were collected and recrystallized from ethanol-ether. The results are summarized in Tables V and VI.

2-Amino-*N*-methylacetanilide (XXII).

2-Nitro-*N*-methylacetanilide (XXI) (14) (1.15 g.) was hydrogenated over platinum oxide (18 mg.) in ethanol (10 ml.) at room temperature (1 hour). After the catalyst was removed by filtration, the solvent was evaporated. The residual solid was recrystallized from 30% aqueous ethanol, m.p. 145° [lit. (15) m.p. 151-152°], yield, 490 mg. (96%).

Benzaldehyde 2-(*N*,*N*-Acetylmethylamino)phenylhydrazone (XIX) from XXII.

To a mixture of XXII (164 mg.) and benzaldehyde (53 mg.) in ethanol (5 ml.) was added MSH (107 mg.). After the reaction mixture was stirred at room temperature for 30 minutes, water (5 ml.) was added. The precipitated crystals were collected and recrystallized from acetone to give crystals, m.p. 202-204°, yield, 112 mg. (94%), which were identified with XIX by mixed melting point determination and ir spectral comparison.

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