1,3-Dipolar Cycloaddition Reactions
of 3-Acylimino-1-methylbenzimidazolium Betaines

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3-Acylimino-1-methylbenzimidazolium betaines undergo 1,3-dipolar cycloaddition reactions with activated alkenes (methyl acrylate, acrylonitrile, and fumaronitrile) and methyl propiolate to produce 2-substituted 1-methylbenzimidazoles. The transformation involves the initial formation of a 1,3-dipolar cycloadduct followed by the N-N bond cleavage. The primary adducts can be isolated from the reaction with methyl acrylate and acrylonitrile.

The 1,3-dipolar cycloaddition reactions of heteroaromatic N-imines have been extensively studied and used to synthesize a variety of heterocycles (1). However, most of the examples are limited to the reaction of six-membered heteroaromatic N-imines. Recently, we reported the reaction of 1-alkylbenzimidazolium 3-imines (I) with acetylenic compounds to give pyrazole derivatives (III), whose formation has been believed to arise via unisolable 1,3-dipolar cycloadducts (II) (2). Since then, a paper has appeared reporting an interesting reaction of benzothiazolium N-imines (IV) and N-ethoxycarbonyliminothiazolium betaine (V) with dimethyl acetylenedicarboxylate (3). These results prompted us to investigate further the 1,3-dipolar character of 3-acylimino-1-methylbenzimidazolium betaines (VI) (4). In this paper we report the reactions of VI with several activated olefins and with methyl propiolate.
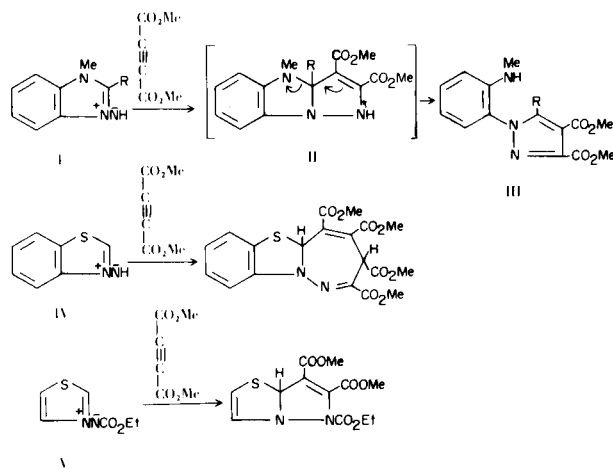
Scheme 1

In general, a solution of equimolar amounts of the betaine and the olefin in acetonitrile (5) was refluxed until the starting material disappeared (by tlc). After evaporation of the solvent the crude material was chromatographed to give 2-substituted benzimidazoles.

In this manner, 3-ethoxycarbonylimine VIa and 3-benzoylimine VIb afforded VIIIa,b and VIIIc,d when heated with methyl acrylate and acrylonitrile, respectively. It was noted that VIa (the reaction was complete after ca. 2 hours) was more reactive than VIb (the reaction was complete after ca. 9 hours). The similar difference in reactivity between VIa and VIb was also observed in the reaction with methyl propiolate as described later. This is in good agreement with that expected from the ir spectroscopic studies (4); the ir carbonyl absorption band of 3-ethoxycarbonylimine VIa appears at 1630 cm^{-1}, whereas that of 3-benzoylimine VIb is shifted to as low as 1560
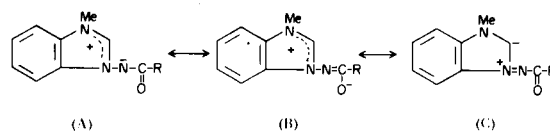

Scheme 2

cm^{-1}, suggesting that the former has more contribution from the 1,3-dipolar structures (A and/or C) than the latter.

The structures of these products were assigned on the basis of elemental analyses (Table I) and spectral data (Table II). For example, the uv spectrum (ethanol) of VIIIa closely resembles that of 1,2-dimethylbenzimidazole [λ max 247 nm sh (log ϵ 3.82), 252 (3.83), 267 sh (3.67), 275 (3.78), 282 (3.83)]. Its ir spectrum reveals the presence of NH (3440 cm^{-1}) and two carbonyl groups (1735

and 1705 cm^{-1}), and its nmr spectrum shows an NH proton at τ 4.27 (disappeared by deuterium oxide treatment), a complex multiplet (5H, -CHCH$_2$- and OCH$_2$CH$_3$) between τ 5.54 and 6.15, an N-methyl singlet at τ 6.28, a methoxyl singlet at τ 6.23, a triplet at τ 8.80 (3H, OCH$_2$CH$_3$), and a multiplet (4H) in the aromatic region between τ 2.18 and 2.85. These data are consistent with two structures VIIIa and VIIIa′, but the latter possibility was eliminated by examination of the mass spectrum which shows the fragment peaks at m/e 216 and 204 corresponding to ions a and b, respectively, presumably generated by McLafferty rearrangements.

Scheme 3
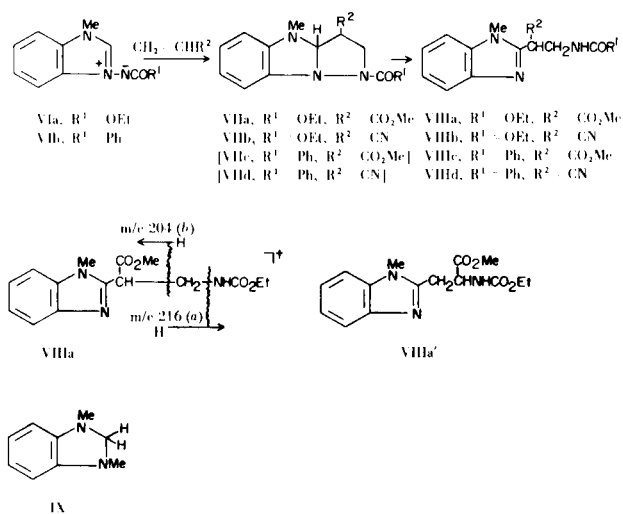
This transformation is considered to involve initial formation of 1,3-dipolar cycloadducts (VII) followed by the N-N bond cleavage. The intermediates VII were, in fact, isolated from shorter periods of the reaction with methyl acrylate and acrylonitrile at lower temperature. When a chloroformic solution of VIa and methyl acrylate was heated at 40-50° for 30 minutes and the reaction was

monitored by tlc, the formation of a new product VIIa was seen along with the formation of ring opened product VIIIa and unchanged starting material. The products could be separated by preparative tlc. The new product VIIa was found to be a mixture of two possible diastereomers. Its nmr spectrum exhibits two distinct N-methyl signals in a ratio of ca. 1:1, which have chemical shifts (τ 7.13 and 7.21) in the region observed for the N-methyl group (τ 7.34) of 1,3-dimethylbenzimidazoline (IX) (6) (the N-methyl signal of 1-methylbenzimidazole appears at τ 6.19). That VIIa is actually the intermediate of the reaction (VIa → VIIIa) was demonstrated by the following experiment; after a deuteriochloroformic solution of VIIa was allowed to stand at 35° for ca. 180 hours in an nmr tube, it was completely converted into VIIIa. Similar results were obtained with the reaction of VIa with acrylonitrile. The adduct VIIb was less stable than VIIa and was converted into VIIIb after standing at 35° for 30 hours.

In contrast to the reaction of VI with methyl acrylate and acrylonitrile, reaction of VIb with fumaronitrile afforded XI. The elemental analysis and mass spectrometry indicated that hydrogen cyanide molecule is lost from an expected 1:1 adduct (XII). Its ir spectrum reveals the presence of a CN group (2210 cm^{-1}) and a carbonyl group (1690 cm^{-1}). The nmr spectrum consists of a broad doublet at τ -4.15 (1H, J = 11 Hz, NH), a doublet at τ 1.67 (1H, J = 11 Hz, olefinic proton), a singlet at τ 5.92 (3H, NCH$_3$), and a multiplet at τ 1.80-2.80 (9H, aromatic protons). The large vicinal coupling constant for an NH and an olefinic proton was confirmed by deuterium exchange and spin-decoupling experiments. Of two possible structures XI and XI′, these data established the structure XI except for the stereochemistry about the C-C double bond. It is not clear, however, when the molecule of HCN is lost.

Reaction of VI with methyl propiolate proceeded faster than with olefins. 3-Ethoxycarbonylimine VIa reacted with methyl propiolate at room temperature and the reaction was complete after 1 hour. The nmr spectrum of

TABLE I

Preparation of Methyl 3-Acylamino-2-[2-(1-methylbenzimidazolyl)]propionates
and 3-Acylamino-2-[2-(1-methylbenzimidazolyl)]propionitriles

				Analysis					
				Calcd.			Found		
Compound	M.p. °C	Yield (%)	Formula	C	H	N	C	H	N
VIIIa	oil	72	C$_{15}$H$_{19}$N$_3$O$_4$	59.00	6.27	13.76		(a)	
VIIIb	115-116	80	C$_{14}$H$_{16}$N$_4$O$_2$	61.75	5.92	20.58	61.63	6.07	20.46
VIIIc	147-148	55	C$_{19}$H$_{19}$N$_3$O$_3$	67.64	5.68	12.46	67.42	5.79	12.24
VIIId	169-170	62	C$_{18}$H$_{16}$N$_4$O	71.03	5.30	18.41	70.81	5.40	18.25

(a) The picrate: m.p. 156-158° (from ethanol-ether); Anal. Calcd. for C$_{21}$H$_{22}$N$_6$O$_{11}$: C, 47.19; H, 4.15; N, 15.73. Found: C, 47.33; H, 4.24; N, 15.68.

TABLE II

Spectral Data of Methyl 3-Acylamino-2-[2-(1-methylbenzimidazolyl)]propionates and 3-Acylamino-2-[2-(1-methylbenzimidazolyl)]propionitriles

| Compound	Ir ν max (chloroform) cm⁻¹	Uv λ max (ethanol) nm (log ε)	Nmr (deuteriochloroform) τ NH	CH-CH₂	NMe	Mass m/e (relative intensity %)
VIIIa	3440 (m) 1735 (vs) 1705 (vs)	249sh (3.86) 254 (3.89) 267 (3.82) 276 (3.89) 284 (3.89)	4.27 (br.t)	5.54-6.15 (m)	6.28 (s)	305 (27) 217 (20) 216 (29) 204 (51) 184 (29) 172 (100)
VIIIb	3440 (m) 2240 (w) 1710 (vs)	249sh (3.87) 254 (3.88) 267 (3.79) 276 (3.87) 284 (3.86)	3.90 (br.t)	5.32-6.10 (m)	6.18 (s)	272 (16) 184 (23) 183 (92) 182 (49) 172 (26) 171 (100) 170 (17)
VIIIc	3440 (m) 1735 (vs) 1650 (vs)	225sh (4.26) 247sh (4.05) 255sh (4.00) 269 (3.88) 276 (3.95) 284 (3.92)	(a)	5.39-5.88 (m)	6.28 (s)	337 (12) 217 (18) 216 (36) 205 (14) 204 (22) 185 (14) 184 (60) 173 (34) 172 (64) (b)
VIIId	3440 (m) 2240 (w) 1655 (vs)	224sh (4.22) 245sh (4.10) 253sh (4.04) 267 (3.90) 276 (3.95) 284 (3.92)	(a)	5.13-5.90 (m)	6.12 (s)	304 (7) 183 (100) 182 (87) 171 (15)

(a) The integral showed the presence of a diffused NH signal between τ -1.0 and -3.0. (b) The base peak is m/e 105.
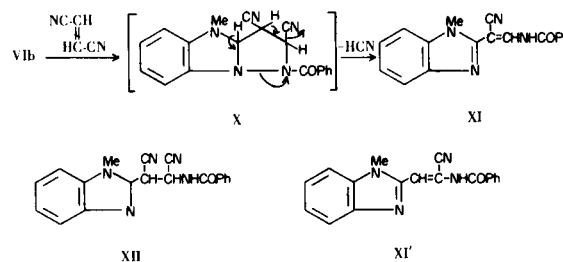
Scheme 4

Scheme 5

the product XIVa indicates that it is a mixture of cis and trans isomers about C-C double bond. Thus it shows two broad singlets (7:3) at τ 1.63 and 2.20 (1H, olefinic proton), two methoxyl singlets (7:3) at τ 6.19 and 6.27 (3H), two N-methyl singlets (7:3) at τ 6.38 and 6.39 (3H), a broad quartet at τ 5.75 (2H, OCH₂CH₃), and two triplets (7:3) at τ 8.69 and 8.70 (3H, OCH₂CH₃). The remaining signals consists of a broad signal at τ 0.05 (1H, NH) and a multiplet for the aromatic protons at τ 2.07-2.87 (4H). The isomers could not be separated by the conventional means. For example, the nmr spectrum of the base XIVa recovered after repeated recrystallizations of its hydrochloride showed it to be a mixture of essentially the same ratio as before the treatment. Final confirmation of structure XIVa was given by conversion by catalytic hydrogenation to VIIIa.

Less reactive 3-benzoylimine VIb did not react with methyl propiolate at room temperature but it gave an adduct XIVb by refluxing in acetonitrile for 2 hours. The adduct was again shown to be a mixture of two isomers (7). The nmr spectrum of the crude material exhibited two singlets due to N-methyl group at τ 6.28 and 6.30 in a ratio of ca. 2.5:1. After two recrystallizations from 2-propanol the ratio was changed to 5:1, but further recrystallization did not alter this ratio appreciably.

Although the possible intermediates XIII could not be isolated, by analogy to the reaction of VI with olefins they were assumed to be involved in this reaction.
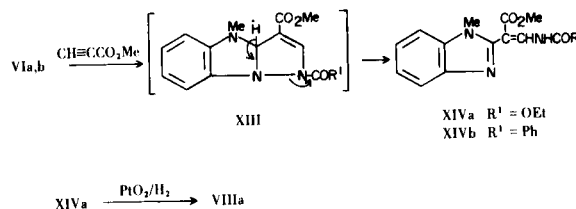
The behavior of VI towards olefins and an alkyne is related to those observed for 1-methylbenzimidazole 3-oxide (8), but is in contrast to the behavior of N-acylimino-pyridinium betaine (1f) which reacted with dimethyl acetylenedicarboxylate to give dimethyl pyrazolo[1,5-a]-pyridine-2,3-dicarboxylate. Apparently the driving force

for the facile transformation of the primary cycloadducts VII, X, and XIII into the ring opened products is derived from the relief of the ring strain of the 5-5 ring system and from aromatic stabilization.

EXPERIMENTAL

All melting points are uncorrected. Their spectra were recorded on an Hitachi EPI-G2 spectrophotometer, uv spectra on an Hitachi 124 spectrophotometer, and 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 70eV. Preparative tlc was carried out on Merck Alumina PF_{254}.

General Procedure for Methyl 3-Acylamino-2-[2-(1-methylbenzimidazolyl)]propionates (VIIIa,c) and 3-Acylamino-2-[2-(1-methylbenzimidazolyl)]propionitriles (VIIIb,d).

A solution of a betaine VI (0.5 mmole) and methyl acrylate or acrylonitrile (0.5 mmole) in acetonitrile (7 ml.) was refluxed until the starting material disappeared on tlc (ca. 2 hours for VIa and ca. 9 hours for VIb). The solvent was removed and the residue was purified by preparative tlc using chloroform as solvent. Crystalline compounds were recrystallized from chloroform-petroleum ether (b.p. 30-60°). The results are summarized in Tables I and II.

3-Benzamido-2-[2-(1-methylbenzimidazolyl)]acrylonitrile (XI).

A solution of VIb (126 mg.) and fumaronitrile (39 mg.) in acetonitrile (7 ml.) was refluxed for 7 hours. Work up as described above gave colorless needles of XI, m.p. 196-197° (from ethanol), yield, 60 mg. (40%); ir (chloroform): cm^{-1} 2210 (m), 1690 (s), and 1605 (vs); uv λ max (ethanol): 240 nm (log ε 4.06), 270 (4.14), and 344 (4.19); nmr (deuteriochloroform): τ -4.15 (1H, br.d, J = 11 Hz, NH, disappeared by deuterium oxide treatment), 1.67 (1H, d, J = 11 Hz, olefinic H, became a singlet after deuterium oxide treatment), 1.80-2.80 (9H, m, aromatic H), and 5.92 (3H, s, NCH_3). The mass spectrum shows the molecular ion at m/e 302 (Calcd. 302).

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.48; H, 4.71; N, 18.67.

1-Ethoxycarbonyl-3-methoxycarbonyl-4-methyl-1,2,3,4-tetrahydro-4H-pyrazolo[1,5-a]benzimidazole (VIIa).

A solution of VIa (110 mg.) and methyl acrylate (43 mg.) in chloroform (4 ml.) was heated at 40-50° for 30 minutes and the solvent was removed. Tlc analysis of the reaction mixture showed the presence of a new product in addition to VIIIa and the starting material. The products were separated by preparative tlc using chloroform as solvent. The major product VIIa (an oil) gave the following spectral data, ir (chloroform): cm^{-1} 1730 (vs) and 1700 (vs); uv λ max (ethanol): 258 sh nm, 265, 273, 279, and 304; nmr (deuteriochloroform): τ 2.90-3.55 (4H, m, aromatic H), 4.79-4.90 (1H, m, ring H), 5.55-5.95 (3H, m, OCH_2CH_3 and ring H), 6.24 (3H, s, OCH_3), 6.55-6.82 (2H, m, ring H), 7.13, 7.21 (3H, 1:1, s, NCH_3), and 8.62 (3H, t, J = 7 Hz, OCH_2CH_3).

1-Ethoxycarbonyl-3-cyano-4-methyl-1,2,3,4-tetrahydro-4H-pyrazolo[1,5-a]benzimidazole (VIIb).

Using a similar procedure described above, compound VIa provided an oily mixture of VIIb and VIIIb. The former compound gave the following spectral data, ir (chloroform): cm^{-1} 2250 (w) and 1720 (vs); uv λ max (ethanol): 256 nm, 275 sh, 284, and 304; nmr (deuteriochloroform): τ 2.60-3.55 (4H, m, aromatic H), 4.79-

4.94 (1H, m, ring H), 5.45-5.98 (3H, m, OCH_2CH_3 and ring H), 6.34-6.84 (2H, m, ring H), 7.02, 7.10 (3H, 3:2, s, NCH_3), and 8.63 (3H, t, J = 7 Hz, OCH_2CH_3).

Transformation of VII into VIII.

Compound VII (ca. 0.1 mmole) was dissolved in deuteriochloroform (0.4 ml.) in an nmr tube and the reaction was monitored by nmr spectroscopy. Compound VIIa was completely converted into VIIIa after 180 hours and VIIb was converted into VIIIb after 30 hours. The identification of VIIIa and VIIIb was made by tlc, nmr, ir and uv spectra.

Methyl 3-Ethoxycarbonylamino-2-[2-(1-methylbenzimidazolyl)]-acrylate (XIVa).

A solution of VIa (150 mg.) and methyl propiolate (58 mg.) in acetonitrile (7 ml.) was stirred at room temperature for 1 hour. The solvent was removed and the residue was submitted to preparative tlc using chloroform as solvent to give an oil of XIVa, yield, 150 mg. (70%), ir (chloroform): cm^{-1} 3330 (w), 1745 (vs), 1700 (vs), and 1625 (vs); uv λ max (ethanol): 256 nm (log ε 4.34), 278 (4.16), and 286 (4.17); nmr (deuteriochloroform): τ 0.05 (1H, br, NH), 1.63, 2.20 (1H, 7:3, br.s, olefinic H), 2.07-2.87 (4H, m, aromatic H), 5.75 (2H, br.q, OCH_2CH_3), 6.19, 6.27 (3H, d, 7:3, OCH_3), 6.38, 6.39 (3H, 7:3, s, NCH_3), and 8.69, 8.70 (3H, 3:7, t, OCH_2CH_3). The mass spectrum shows the molecular ion at m/e 303 (Calcd. 303).

The hydrochloride, m.p. 162-164° (from ethanol-ether); nmr d_6-dimethylsulfoxide): τ -1.05 (1H, br.d, J = 12 Hz, NH, exchanged with deuterium oxide), 1.61 (1H, d, J = 12 Hz, olefinic H, became a singlet after deuterium oxide treatment), 1.90-2.45 (4H, m, aromatic H), 5.77 (2H, q, J = 7 Hz, OCH_2CH_3), 6.15 (3H, s, OCH_3), 6.27 (3H, s, NCH_3), and 8.75 (3H, t, J = 7 Hz, OCH_2CH_3).

Anal. Calcd. for $C_{15}H_{18}ClN_3O_4$: C, 53.02; H, 5.34; N, 12.37. Found: C, 52.74; H, 5.56; N, 12.16.

Catalytic Hydrogenation of XIVa.

Compound XIVa (100 mg.) was hydrogenated over platinum oxide (15 mg.) in ethanol (10 ml.) at room temperature and atmospheric pressure. After 10 hours, the catalyst was filtered and the filtrate was concentrated. The residue was purified by tlc using chloroform as solvent to give a colorless oil (64 mg.) which was identified as VIIIa by ir, nmr, and uv spectra.

Methyl 3-Benzamido-2-[2-(1-methylbenzimidazolyl)]acrylate (XIVb).

A solution of VIb (125 mg.) and methyl propiolate (42 mg.) in acetonitrile (7 ml.) was refluxed for 2 hours. The solvent was evaporated and the residue was purified by tlc followed by two recrystallizations from 2-propanol, m.p. 178-181°, yield, 90 mg. (54%), ir (chloroform): cm^{-1} 1705 (vs), 1695 (vs), and 1610 (vs); uv λ max (ethanol): 244 nm (log ε 4.27), 270 (4.32), and 310 (4.27); nmr (deuteriochloroform): τ -2.20 (1H, br, NH, disappeared by deuterium oxide treatment), 1.21 (1H, d, J = 11 Hz, olefinic H, became a singlet after deuterium oxide treatment), 1.87-2.76 (9H, m, aromatic H), 6.09, 6.18 (3H, 5:1, s, OCH_3), and 6.28, 6.30 (3H, 5:1, s, NCH_3). The mass spectrum shows the molecular ion at m/e 335 (Calcd. 335).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.96; H, 5.25; N, 12.55.

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