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Reactions of 1-Methyl-1H-1,2,4-triazolium 4-Imine and 4-Acylimines with Acetylenic Esters

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Reaction of 4-amino-1-methyl-1H-1,2,4-triazolium iodide with dimethyl acetylenedicarboxylate or methyl propiolate in the presence of alkali followed by heating with water gave methyl 1H-pyrazole-4-carboxylates in low yields, and reaction of 4-acylimino-1-methyl-1H-1,2,4-triazolium betaines with methyl propiolate afforded 5-substituted 1-methyl-1H-1,2,4-triazoles.

Reaction of 1-methylbenzimidazolium 3-imine (II) (generated *in situ* by base treatment of the 3-amine salt I) and 3-acylimines (V) with acetylenic esters gives a pyrazole derivative IV and 2-substituted 1-methylbenzimidazoles VII by way of a mechanism which involves intermediates III and VI, respectively.[2] On the other hand, closely related 4-amino-1-methyl-1H-1,2,4-triazolium iodide (VIII) has been reported to react with dimethyl acetylenedicarboxylate in the presence of alkali to afford a rather unusual product (IX).[3] In the light of our results on benzimidazoles we were interested in the behavior of VIII and 4-acylimino-1-methyl-1H-1,2,4-triazolium betaines (Xa—c) towards acetylenic esters.

Starting 4-amine salt VIII was synthesized from 4-amino 4H-1,2,4-triazole by using a procedure of Summers and Elguero.[3] 4-Benzoyl- (Xa), 4-acetyl- (Xb), and 4-ethoxycarbonylimines (Xc) were readily obtained by heating VIII with benzoyl chloride, acetic anhydride, and ethyl chloroformate without solvent at 50—60° followed by treatment with Amberlite IRA-410 ion-exchange resin (OH form). The 4-acylimines thus obtained have the similar general spectral features to those reported for the 3-acylimines of 1-methylbenzimidazole[4] and 4-acylimines of 1-alkyl-1H-1,2,4-triazoles.[5]

Treatment of compound VIII with dimethyl acetylenedicarboxylate in dimethylformamide in the presence of potassium hydroxide (or potassium carbonate) followed by heating in water gave low yield of dimethyl 1H-pyrazole-3,4-dicarboxylate (XIVa) accompanied by resinous material. This transformation is considered to involve initial formation of 1,3-dipolar cycloadducts (XII) between N-imine XI and the acetylene followed by ring opening to intermediate XIIIa which was hydrolyzed to XIVa. Although attempts to isolate XIIIa in pure form were unsuccessful because of the low yield and contamination of the other minor products, intermediate XIIIb could be isolated from the reaction mixture of VIII and methyl propiolate in low yield by preparative tlc. The infrared (IR) spectrum of XIIIb showed the presence of an N–H (3300 cm^{-1}), a carbonyl group (1720 cm^{-1}) and a C–N double bond (1625 cm^{-1}). Its nuclear magnetic resonance (NMR) spectrum reveals two singlets at τ 1.89 and 1.92 attributable to the pyrazole ring protons, a broad signal due to an N–H proton (disappeared by deuterium oxide treatment), and a doublet at τ 6.93 due to N-methyl protons which became

1) Location: *133–1, Yamada-kami, Suita, Osaka.*

2) *a*) Y. Tamura, H. Hayashi, J. Minamikawa, and M. Ikeda, *Chem. Ind.* (London), **1973**, 952; *b*) Y. Tamura, H. Hayashi, Y. Nishimura, and M. Ikeda, *J. Heterocyclic Chem.*, **12**, 225 (1975); *c*) Y. Tamura, H. Hayashi, and M. Ikeda, *ibid.*, **12**, 819 (1975).

3) A.J.H. Summers and J. Elguero, *Bull. Soc. Chim. France*, **1972**, 3974.

4) Y. Tamura, H. Hayashi, J. Minamikawa, and M. Ikeda, *J. Heterocyclic Chem.*, **11**, 781 (1974).

5) *a*) H.G.O. Becker, N. Sauder, and H.J. Timpe, *J. Prakt. Chem.*, **311**, 879 (1969); *b*) H.J. Timpe, *ibid.*, **315**, 775 (1973).

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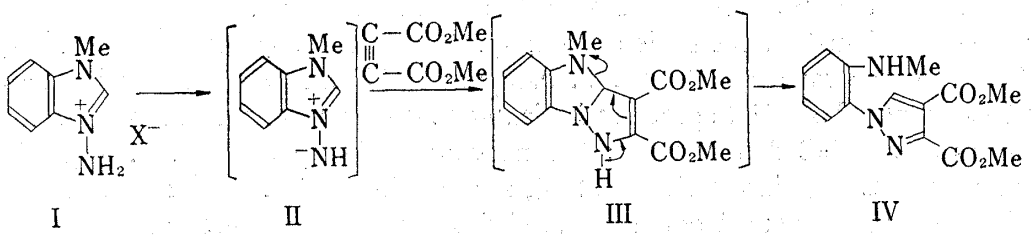

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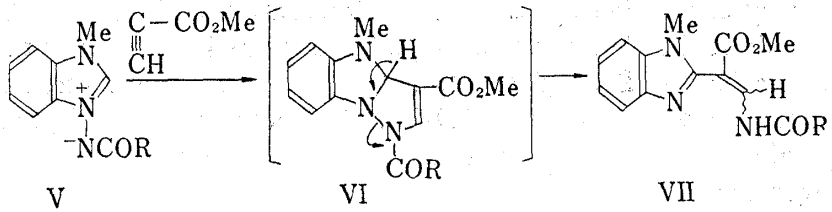

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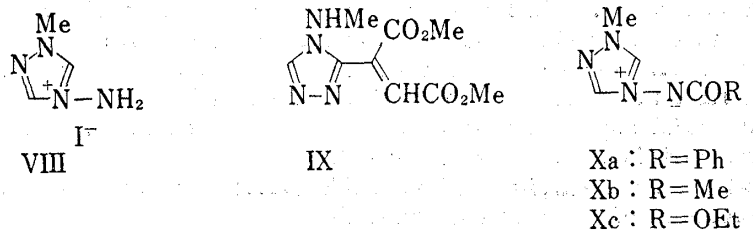
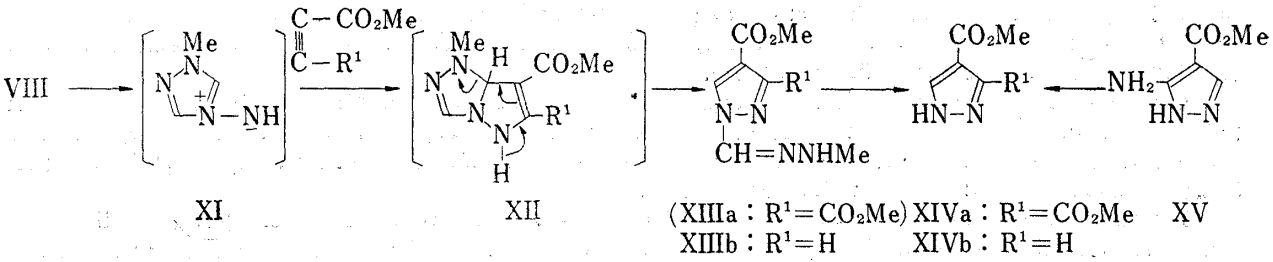


VIII IX Xa : R=Ph
Xb : R=Me
Xc : R=OEt

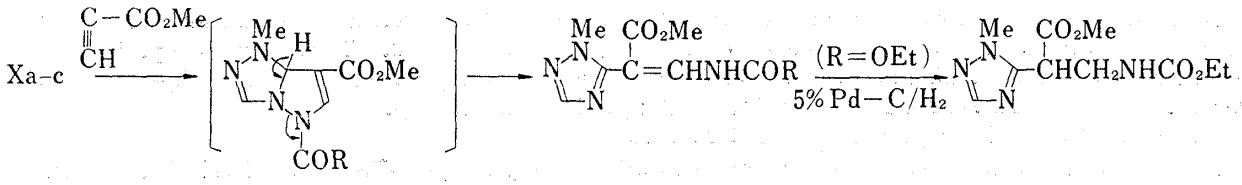
Chart 1

a singlet after deuterium oxide treatment. The rest of the NMR spectrum contains a singlet at τ 2.93 (methine proton) and a singlet at τ 6.13 (O-methyl). Heating of XIIIb in water gave XIVb in high yield. Compound IX reported by Summers and Elguero[3] has not as yet been isolated.

We were then led to examine the behavior of 4-acylimines (X) towards acetylenic esters for comparison. Under the similar reaction conditions used for the benzimidazole system,



XI XII (XIIIa : R^1=CO_2Me) XIVa : R^1=CO_2Me XV
XIIIb : R^1=H XIVb : R^1=H



XVI XVIIa : R =Ph
XVIIb : R =Me
XVIIc : R =OEt
XVIII

Chart 2

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compounds X with methyl propiolate gave 5-substituted triazole derivatives XVII, whose structures were assigned on the basis of their spectral data. For example, the IR spectrum of XVIIc shows two carbonyl absorption bands at 1745 and 1705 cm^{-1} and a C=C double bond at 1630 cm^{-1}. Its NMR spectrum indicates that it is an about 1:1 mixture of *cis* and *trans* isomers about C=C double bond: the relevant peaks appear at τ 1.65 (d, J=12 Hz, olefinic proton), τ 2.04 (triazole ring proton), and τ 6.185 and 6.190 (1:1, N-methyl). The large vicinal coupling constant between the olefinic proton and N–H proton was confirmed by deuterium exchange experiment, indicating the presence of a =CH–NH– grouping. The isomers could not be separated by conventional means. Further confirmation of the assigned structure was given by conversion by catalytic hydrogenation of XVIIc to XVIII. In the NMR spectrum of XVIII, the olefinic proton signal disappeared and instead three methylene protons appeared at τ 5.60—6.20, and the N-methyl signal became a singlet.

In conclusion, the behavior of 1-methyl-1H-1,2,4-triazolium 4-imine (XI) and 4-acylimines (X) towards acetylenic esters was found to be closely analogous to those of previously reported benzimidazole congeners.[2)]

Experimental

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27G spectrophotometer, ultraviolet (UV) spectra on a Hitachi EPS-3T spectrophotometer, and IR spectra on a Hitachi EPS-3T spectrophotometer, and NMR spectra on a Hitachi R-20A spectrometer (tetramethylsilane as internal standard). Low and high resolution mass spectra were obtained with a Hitachi RMU-6M and JEOL-JMS-OISG instrument with a direct inlet system operating at 50 and 75 eV, respectively. Preparative thin layer chromatography (TLC) was carried out on Merck Alumina PF_{254}.

Material——4-Amino-1-methyl-1H-1,2,4-triazolium iodide (VIII) was synthesized from 4-amino-4H-1,2,4-triazole by using a procedure of Summers and Elguero.[3)]

General Procedure for 4-Acylimino-1-methyl-1H-1,2,4-triazolium Betaines (Xa—c)——A mixture of VIII (1 mmole) and an acylating agent (benzoyl chloride, acetic anhydride, or ethyl chloroformate) (1 ml) was heated at 50—60° for 4—5 hr, until all the crystals of VIII dissolved. The excess reagent was evaporated *in vacuo*. The residue was dissolved in MeOH and the solution was passed through a column of Amberlite IRA-410 ion exchange resin (OH form). The methanolic elute was concentrated to give white crystals, which were purified by recrystallization from acetone–ether.

Compound Xa was obtained in 60% yield, mp 192—194°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1565 (C=O); UV $\lambda_{max}^{CHCl_3}$ nm: 280 (log ε 4.05) and 289 (4.06). NMR ($CDCl_3$) τ: −0.93 (1H, s, H-5) and 1.44 (1H, s, H-3). Mass Spectrum *m/e* (relative intensity): 202 (50, M^+), 201 (48), 147 (36), 125 (100), 119 (15), 105 (8), 83 (17), 77 (15), and 56(6). *Anal.* Calcd. for $C_{10}H_{10}ON_4$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.22; H, 4.93; N, 27.88.

Compound Xb was obtained in 55% yield, mp 214—215° (dec.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1580 (C=O); UV $\lambda_{max}^{CHCl_3}$ nm: 267 (log ε 3.77). NMR ($CDCl_3$)[6)] τ: −0.62 (1H, s, H-5) and 1.62 (1H, s, H-3). Mass Spectrum *m/e* (relative intensity): 140 (100, M^+), 125 (87), 83 (70), and 56 (60). *Anal.* Calcd. for $C_5H_8ON_4$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.82; H, 5.62; N, 39.49.

Compound Xc was obtained in 50% yield, mp 154—155°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1625 (C=O). UV $\lambda_{max}^{CHCl_3}$ nm: 265 (log ε 3.75). NMR ($CDCl_3$) τ: −0.22 (1H, s, H-5) and 1.52 (1H, s, H-3). Mass Spectrum *m/e* (relative intensity): 170 (24, M^+), 125 (100), 98 (60), 83 (96), and 56 (60). *Anal.* Calcd. for $C_6H_{10}O_2N_4$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.47; H, 5.82; N, 32.81.

Dimethyl 1H-Pyrazole-3,4-dicarboxylate (XIVa)——To a stirred solution of VIII (4.2 g) in dimethylformamide (10 ml) was added K_2CO_3 (2.66 g) and then dimethyl acetylenedicarboxylate (3.3 g) under ice-cooling. After the reaction mixture was stirred at room temperature for 5 hr, the solvent was removed *in vacuo* and the residue was extracted with ether. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated. The residue was then heated with 30% aqueous EtOH (3 ml) under reflux for 30 min and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC using alumina and $CHCl_3$ as solvent followed by recrystallization from $CHCl_3$–hexane to give white crystals of XIVa, mp 138—140° (lit.[7)] 141°); yield, 120 mg (3.4%).

Use of KOH instead of K_2CO_3 gave a similar result.

Methyl 1-Methylhydrazonoformyl-1H-pyrazole-4-carboxylate (XIIIb)——To a stirred solution of VIII (1.2 g) in dimethylformamide (5 ml) was added K_2CO_3 (0.73 g) and then methyl propiolate (0.67 g) under

6) Taken with a JEOL-PS-100 spectrometer.
7) J. Bastide and J. Lematre, *Bull. Soc. Chim. France*, **1971**, 1336.

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ice-cooling. After the reaction mixture was stirred at room temperature for 10 hr, the solvent was removed *in vacuo* and residue was extracted with ether. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC using alumina and benzene as solvent to give XIIIb as low melting crystals, yield, 48 mg (5%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 1720 (C=O), and 1625 (C=N). NMR ($CDCl_3$) τ: 1.25 (1H, br, NH, disappeared by D_2O treatment), 1.89 and 1.92 (2H, 2×s, two pyrazole ring H), 2.93 (1H, s, methine H), 6.13 (3H, s, OCH_3), and 6.93 (3H, d, $J=4$ Hz, NCH_3, became a singlet after D_2O treatment).

Methyl 1H-Pyrazole-4-carboxylate (XIVb)——(A) From XIIIb: A solution of XIIb (40 mg) in 30% aqueous EtOH (1.5 ml) was heated under reflux for 1.5 hr and then extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC using alumina and $CHCl_3$ as solvent followed by recrystallization from $CHCl_3$–pet. ether to give white crystals of XIVb, mp 134—135°, yield, 25 mg (90%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH) and 1715 (C=O). NMR ($CDCl_3$) τ: 1.93 (2H, s, pyrazole ring H) (lit.[8] τ 1.90) and 6.15 (3H, s, OCH_3). The mass spectrum shows the molecular ion at *m/e* 126 (Calcd. 126). *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.58; H, 4.88; N, 22.50.

This compound was identical with an authentic sample prepared from methyl 5-amino-1H-pyrazole-4-carboxylate (XV) in all respects.

(B) From Methyl 5-Amino-1H-pyrazole-4-carboxylate (XV): To an ice-cooled solution of XV (700 mg)[9] in 95% EtOH (10 ml) and concentrated H_2SO_4 (1 ml) was slowly added with stirring a solution of $NaNO_2$ (400 mg) in minimum quantity of H_2O. The reaction mixture was stirred below 10° for 1 hr and the EtOH was distilled off. The residue was made alkaline with 10% aqueous ammonia and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC using alumina and $CHCl_3$ as solvent followed by recrystallization from $CHCl_3$–pet. ether to give white crystals of XIVb, mp 135—136°, yield, 300 mg (48%).

General Procedure for Methyl 3-Acetylamino-2-[5-(1-methyl-1H-1,2,4-triazolyl)]acrylates (XVIIa—c)——A solution of X (1 mmole) and methyl propiolate (1 mmole) in acetonitrile (5 ml) was stirred at room temperature until the starting material disappeared on TLC (*ca.* 5 hr for Xb and Xc, and overnight for Xa). The solvent was removed and the residue was purified by preparative TLC using alumina and $CHCl_3$ as solvent followed by recrystallization from isopropanol.

Compound XVIIa was obtained in 70% yield, mp 180—184.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O), 1705 (C=O), and 1620 (C=C). UV λ_{max}^{EtOH} nm: 240 (log ε 3.98) and 300 (4.27). NMR ($CDCl_3$) τ: −1.80——1.25 (1H, br, NH, disappeared by D_2O treatment), 1.32 (1H, d, $J=12$ Hz, olefinic H, became a singlet after D_2O treatment), 2.0 (1H, s, triazole ring H), 2.05—2.56 (5H, m, aromatic H), 6.12 (3H, s, OCH_3), and 6.135, 6.14 (3H, 1:1, s, NCH_3). The mass spectrum shows the molecular ion at *m/e* 286 (Calcd. 286). *Anal.* Calcd. for $C_{14}H_{14}O_3N_4$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.56; H, 5.14; N, 19.20.

Compound XVIIb was obtained in 59% yield, mp 156—159.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O), 1710 (C=O), and 1620 (C=C). UV λ_{max}^{EtOH} nm: 274 (log ε 4.25). NMR ($CDCl_3$) τ: −0.5—0.05 (1H, br, NH, disappeared by D_2O treatment), 1.56 (1H, d, $J=12$ Hz, olefinic H, became a singlet after D_2O treatment), 2.13 (1H, s, triazole ring H), 6.17 (3H, s, OCH_3), 6.195, 6.20 (3H, 1:1, s, NCH_3), and 7.82 (3H, s, $COCH_3$). The mass spectrum shows the molecular ion at *m/e* 224 (Calcd. 224). *Anal.* Calcd. for $C_9H_{12}O_3N_4$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.55; H, 5.57; N, 25.17.

Compound XVIIc was obtained in 64% yield, mp 120—124°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745 (C=O), 1705 (C=O), and 1630 (C=C). UV λ_{max}^{EtOH} nm: 268 (log ε 4.25). NMR ($CDCl_3$) τ: 0.2—0.8 (1H, br, NH, disappeared by D_2O treatment), 1.65 (1H, d, $J=12$ Hz, olefinic H, became a singlet after D_2O treatment), 2.04 (1H, s, triazole ring H), 5.72 (2H, q, $J=11$ Hz, $\underline{CH_2}CH_3$), 6.16 (3H, s, OCH_3), 6.185, 6.19 (3H, 1:1, s, NCH_3), and 8.68 (3H, t, $J=11$ Hz, $CH_2\underline{CH_3}$). The mass spectrum shows the molecular ion at *m/e* 254 (Calcd. 254). *Anal.* Calcd. for $C_{10}H_{14}O_4N_4$: C, 47.24; H, 5.55; N, 22.04. Found: C, 47.04; H, 5.59; N, 21.83.

Catalytic Hydrogenation of XVIIc——Compound XVIIc (50 mg) was hydrogenated over 5% Pd-C (5 mg) in EtOH (10 ml) at room temperature and atmospheric pressure. After 4 hr, the catalyst was filtered off and the filtrate was concentrated. The residue was purified by TLC using alumina and $CHCl_3$ as solvent to give a colorless oil of XVIII, yield, 45 mg (90%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1740 (C=O), and 1705 (C=O). NMR ($CDCl_3$) τ: 2.18 (1H, s, triazole ring H) 4.20 (1H, br. t, NH, disappeared by D_2O treatment), 5.60—6.20 (5H, m, $=\underline{CHCH_2}-$ and $O\underline{CH_2}CH_3$), 6.10 (3H, s, OCH_3), 6.28 (3H, s, NCH_3), and 8.78 (3H, t, $J=7$ Hz, $OCH_2\text{-}\underline{CH_3}$). The mass spectrum shows the molecular ion at *m/e* 256.1223 (Calcd. for $C_{10}H_{16}O_4N_4$: 256.1172).

8) G. Guillerm, A. L'Honor, L. Veniard, G. Pourcelot, and J. Benaim, *Bull. Soc. Chim. France*, **1973**, 2739.
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