Triazolines VIII. Action of Diazoalkanes on Heterocyclic Substituted Schiff Bases (1a)

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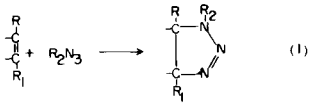
Diazoalkanes have been found to add to heterocyclic substituted Schiff bases (imines), providing a very useful route to the synthesis of the hitherto unknown heterocyclic substituted Δ^2-1,2,3-triazolines. The orientation of the addition as well as the results of synthesis accord with previously reported mechanistic considerations. The direction of dipole orientation and the structure assigned to the adducts are elucidated by nmr spectroscopy.

The 1,2,3-triazolines (Eq. 1 and 2) by virtue of their constitution, provide interesting models for studying the chemistry of the azo linkage. The various decomposition paths of the triazoline molecule provide selective synthetic procedures for azomethines, aziridines and carbonyl compounds (2). Thus the emergence of useful procedures for the synthesis of these compounds makes them increasingly available for study, both chemical and biological (3), and synthetic purposes.

Although a number of alkyl (4) and aryl (5,6) substituted triazolines as well as triazolines bearing amino (7,8), acyl, cyano (9), alkoxy (8,10) and carbalkoxy groups (9) have been synthesized, triazolines substituted with heterocyclic groups are not known. Two main approaches may be envisioned for the synthesis of heterocyclic substituted Δ^2-1,2,3-triazolines *via* 1,3-dipolar cycloaddition reactions:

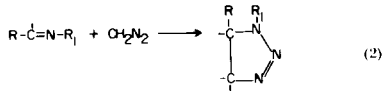
a) reaction of aryl azides with olefins bearing heterocyclic substituents or alternatively, heterocyclic azides with the more commonly available simple olefins (Equation 1).



(1)

(R and/or R_1 heteroaryl and R_2 aryl; R and/or R_1 aryl and R_2 heteroaryl).

b) action of diazoalkanes on heterocyclic substituted Schiff bases (imines) (Equation 2).

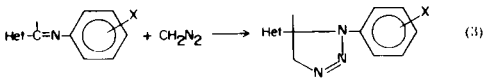


(2)

(R and/or R_1 heteroaryl)

However, in practice, approach (a) is of limited value, since triazolines derived from the action of heterocyclic azides and simple olefins are, for the most part, unstable and undergo ring opening *in situ* (11). Thus, the method more preferable for the synthesis of these compounds would be (b). Unlike olefins bearing heterocyclic groups, the heterocyclic imines can be obtained readily and in a variety, by simple reaction of the appropriate aldehydes and amines. Furthermore, unlike the azide-olefin reactions (4,9), the diazoalkane-imine additions are always performed at room temperature (5,6) which is much more suitable for the thermally labile 1,2,3-triazolines (2).

In view of these considerations, as a part of our program on 1,2,3-triazolines, we studied the action of diazomethane on heterocyclic Schiff bases (Equation 3). The mechanistic



(3)

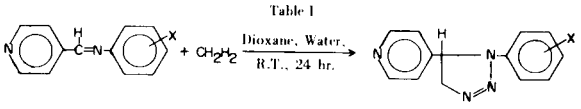
(Het = pyridyl, quinolyl, or thienyl group and X = NO_2, Cl, COOEt, CH_3 or OCH_3).

aspects of the addition of diazomethane to the carbon-nitrogen double bond have been reported earlier (5,12) and a transition state corresponding to I has been suggested.

I

Accordingly, while electron withdrawing substituents on the Schiff base nitrogen facilitated reaction, electron releasing groups had a retarding effect (Table I). The

Table I

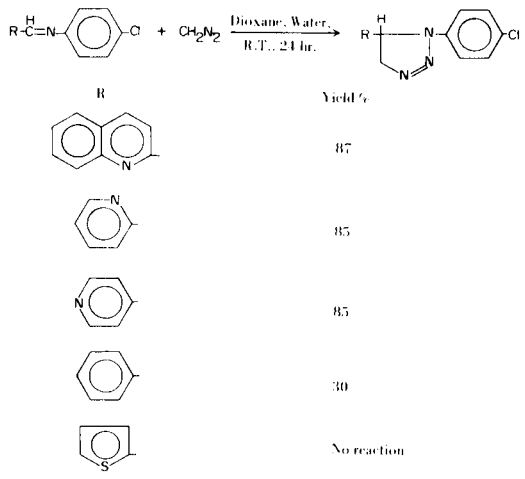


X	Yield %
m-NO_2	85 (a)
p-Cl	82
H	68 (b)
p-CH_3	66
p-OCH_3	45

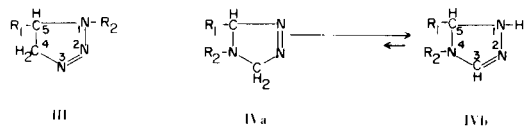
(a) In anhydrous ether, the yield was 65% of adduct. (b) The yield of adduct in anhydrous ether was 30%.

reactivity of the Schiff bases was also dependent on the heterocyclic substituent on the double bond carbon; the resonance between the substituent group and the double bond is broken as the sigma bonds are formed, but not completely. Accordingly, while a pyridyl or quinolyl group enhanced the activity by contributing to negative charge stabilization in the transition state I, a thienyl group yielded an unreactive Schiff base (13) (Table II).

Table II



Conclusive evidence on the direction of dipole orientation and the formation of a Δ^2-1,2,3-triazoline was obtained from nmr spectral studies. If the reaction involved a nucleophilic attack by the diazomethane carbon on the Schiff base carbon, it would result in the formation of a 1,5-disubstituted Δ^2-1,2,3-triazoline (III). However, if the dipole orientation was reversed, the isomeric 4,5-disubstituted 1,2,4-triazoline (IVa) which exists predominantly in the IVb form would be obtained (14).



III IVa IVb

In the case of Δ^2-1,2,3-triazolines, one would expect an ABX or ABC pattern for the three protons at positions 4 and 5, while the structure IVb should show two singlets for protons at positions 3 and 5 and one exchangeable proton at position 1. A survey of the chemical shifts for the different heterocyclic substituted triazolines (Table IV) clearly revealed an ABC pattern centered in the region 5.0-5.4 τ; there was no evidence for the formation of any 1,2,4-triazoline. The dipole orientation is therefore exclusively in agreement with structure III as depicted in Table III.

When wet, undried solutions of diazomethane were employed, an appreciable increase in yield was obtained; compare product yields in wet dioxane and anhydrous ether for compounds indicated in Table I. According to our postulates on the role of protic and dipolar aprotic solvents in 1,3-cycloaddition reactions (15,16,17), the solvent effect of water appears to result from solvation of the transition state (I) bearing a partial negative charge, through hydrogen bonding interactions. We have also discussed the extensive synthetic utility of solvent effects in 1,3-cycloadditions. And indeed, by employing a protic solvent medium (dioxane + water) in the present instance, the various heteroaryl triazoline derivatives were obtained in excellent yields in reasonably short reaction times (Table III). The method provides a convenient procedure for the synthesis of heterocyclic substituted triazolines in general.

EXPERIMENTAL

Synthesis of Heterocyclic Schiff Bases.

The Schiff bases were prepared according to known procedures (18) by heating equimolar amounts of the requisite aldehyde and amine in an appropriate solvent. The reaction of pyridine carboxaldehydes with nitroaniline and ethyl *p*-aminobenzoate required azeotropic removal of water through refluxing for 1-2 hours in benzene under a water separator. In the other cases, addition of the pyridine aldehyde (a liquid) directly to the amine resulted in an exothermic reaction and the Schiff base was obtained as a crystalline mass. The reactions involving the quinoline and thiophene aldehydes were performed in boiling ethanol. Yields and melting points are given in Table III.

Synthesis of Heterocyclic Substituted Δ^2-1,2,3-Triazolines.

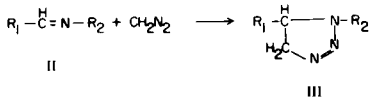
The Schiff base (0.015 mole) was added to a freshly prepared solution of diazomethane (0.05 mole) in dioxane-water mixture (75 ml.) according to procedures described earlier for aryl substituted triazolines (5,6). The reaction mixture after standing for a suitable period of time, was cooled and diluted with water to precipitate the triazoline adducts. In the majority of cases, the products thus obtained were pure and had melting points same as the analytical samples.

In the case of reactions using water-free solutions, the Schiff base (0.015 mole) was dissolved in a solution of diazomethane (0.05 mole) in ether (75 ml.) which had been previously dried over potassium hydroxide for 4 hours.

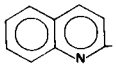
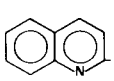
The heterocyclic substituted triazolines bearing a nitro group

Table III

Synthesis of Heterocyclic Substituted Δ^2-1,2,3-Triazolines



II III

Substituents R_1	R_2	Schiff Bases, II Yield (a) %	Schiff Bases, II M.P. (b) °C	Triazolines, III Reaction Time, Hour	Triazolines, III Yield (a) %	Triazolines, III M.P. (b) °C	Analysis (c) % C,	H,	N,
									
	X = *m*-NO_2	88	136-138	24 (d)	85	138-139	58.0	4.1	26.0
				120	71	136-138	58.0	4.2	26.0
	p-Cl	83	86-88	24	82	151-152	60.4	4.3	21.7
							60.4	4.5	21.7
	H	83	72-73	24	68	160-161	69.6	5.4	25.0
							69.5	5.4	25.1
	p-CH_3	92	100-101	92	97	157-158	71.5	5.9	23.5
				24	66	157-158	70.2	5.6	23.2
	p-OCH_3	93	98-100	24	45	143-145	66.1	5.5	22.1
							66.0	5.7	21.8
	p-COOEt	60	106-108	24	50 (e)	98-101	64.9	5.4	18.9
							65.1	5.5	18.9
		42	66-68	27	85	138	60.4	4.3	21.7
							60.5	4.4	21.7
		92	108-111	96 (d)	77	141-142	58.0	4.1	26.0
				120	74	140-141	58.1	4.3	26.1
									
	X = *p*-Cl	87	135-137	27	87	136-137	66.1	4.2	18.2
							65.8	4.2	18.0
	m-NO_2	80	169-171	21	85	140-141	64.0	4.1	21.9
							64.0	4.2	21.9
		76	63-65	21	70 (f)	134-135	69.8	4.7	25.5
							69.9	4.8	25.4
		87	73-75	24	No Reaction		54.7	3.8	15.9
				168	23	109-111 (g)	54.9	3.8	16.2

(a) Yields reported are for pure compounds. Crystallization was effected using ethanol, ethanol-water mixture, acetone or acetone-petroleum ether mixture. (b) Melting points were determined in a Thiele's apparatus using silicone oil and are uncorrected. (c) Analyses were performed by Heterocyclic Chemical Corporation, Harrisonville, Mo. U.S.A., and by Dr. Kurt Eder, Laboratoire Microchimique, Ecole de Chimie, Geneve, Switzerland; upper analyses values are claculated, lower ones are found. (d) The nitro substituted compounds gave better yields in shorter reaction time. The reduction in yield for longer reaction periods was presumably caused by decomposition of the triazoline adduct. (e) The proximity of the m.p.'s of the Schiff base and triazoline as well as the similarity in their solubility characteristics made several crystallizations necessary to obtain a pure product which led to low yields. (f) This triazoline had a flesh pink color. (g) The triazoline underwent only slow decomposition at the m.p.

were yellow in color; other compounds were generally colorless or very pale yellowish white. They decomposed at the melting point with brisk evolution of nitrogen, a property characteristic of the triazolines in general (5). At room temperature they underwent slow decomposition upon standing for several weeks, but remained quite stable under refrigeration when protected from light and could be stored for prolonged periods without any signs of decomposition.

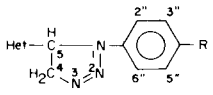
Data on yields, melting point and elemental analysis are presented in Table III.

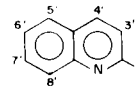
Nmr Spectra.

The nmr spectra were determined, using approximately 10% solutions of the triazolines in deuteriochloroform with TMS as the

Table IV

Proton Nmr Spectra of Heterocyclic Substituted Δ^2-1,2,3-Triazolines



Substituent Het	R	Chemical Shifts and multiplicity (a) $H_2',_6'$	$H_3',_5'$	$4CH_2,5H$	$H_2'',_6''$	$H_3'',_5''$	Others
	H	1.15 (d)	2.75 (d)	5.40 (ABC m)	Phenyl	2.75	$J_2',_3' = J_5',_6' = 5.0$ Hz
	$COOCH_2CH_3$	1.33 (d)	2.80 (d)	5.20 (ABC m)	1.95 (d)	2.75 (d)	OCH_2CH_3
							$CH_2 = 5.60$ (q)
							$CH_3 = 8.62$ (t)
							$J_{CH_2CH_3} = 7.0$ Hz
							$J_2',_3' = J_5',_6' = 5.0$ Hz
							$J_2'',_3'' = J_5'',_6'' = 8.5$ Hz
	CH_3	1.30 (d)	2.82 (d)	5.40 (ABC m)	2.85 (s)		$CH_3 = 7.72$ (s)
							$J_2',_3' = J_5',_6' = 5.0$ Hz
	Cl	1.45 (d)	2.80 (d)	5.40 (ABC m)	2.80 (m)		$J_2',_3' = J_5',_6' = 4.5$ Hz
	OCH_3	1.45 (d)	2.82 (d)	5.40 (ABC m)	2.85 (d)	3.15 (d)	$OCH_3 = 6.24$ (s)
							$J_2',_3' = J_5',_6' = 4.5$ Hz
							$J_2'',_3'' = J_5'',_6'' = 8.5$ Hz
	Cl	---	2.75 (m) overlapped with phenyl protons.	5.20 (ABC m)	2.80 (broad s)		$H_6' = 1.33$ (m) $H_4' = 2.35$ (m)
	Cl	---	---	5.0 (ABC m)	2.75 (broad s)		$H_3',_4' = 3.05$ (m) $H_5' = 2.72$ (m) overlapped with phenyl protons.
	Cl	---	---	5.0 (ABC m)	2.75 (broad s)		$H_3',_4',_5',_6',_7',_8' = 2.1$ (m)

(a) Shift values are in τ units. Multiplicity is reported as: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

internal standard, on a Varian A-60 A spectrometer (Talbe IV).

Acknowledgments.

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