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Formation of Triazole and Isoxazole Derivatives from β -Substituted Pyridinium Salts¹⁾

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Treatment of 1-methyl-3-(3-phenyl-1-triazenyl)pyridinium iodide (**2a—e**) with base gave triazole derivatives (**3** and **4**) with expulsion of the pyridine ring. Similarly, the reaction of 1-methyl-3-benzoylpyridinium oxime iodide (**10a—c**) with base afforded isoxazole derivatives. A possible mechanism for the formation of these reaction products is discussed.

Keywords—triazole formation; isoxazole formation; 3-substituted pyridinium salts; additive cleavage reaction; 3-(1-phenyl-1,2,3-triazol-4-yl)acrylaldehyde; 3-(3-phenylisoxazol-4-yl)acrylaldehyde; reaction mechanism

In the previous paper,³⁾ we reported the formation of pyrazole derivatives by intramolecular additive cleavage of 1-methyl-3-phenylhydrazonomethyl pyridinium iodide with base, as outlined in Chart 1. As a continuation and extension of our studies on β -substituted pyridinium salts, our interest in the formation of heterocyclic compounds from pyridinium salts prompted us to investigate the synthesis of other heterocyclic compounds by the intramolecular cyclization of β -substituted pyridinium salts with base. The present investigation is concerned with such reactions involving the formation of substituted triazoles and isoxazoles.

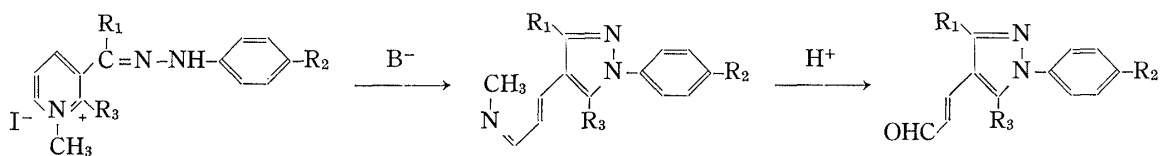


Chart 1

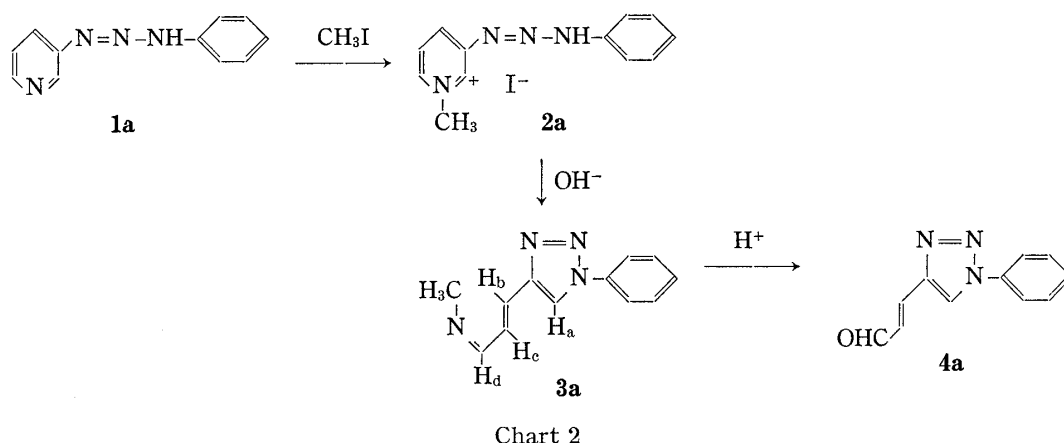
The starting material, 3-(3-phenyl-1-triazenyl)pyridine (**1a**), was synthesized by the reaction of 3-aminopyridine with diazobenzene, putting to practical use a reported method for the derivatization of 2-substituted pyridines.⁴⁾ **1a** was methylated with methyl iodide to give the quaternary pyridinium salt, 1-methyl-3-(3-phenyl-1-triazenyl)pyridinium iodide (**2a**), in 78% yield. Treatment of the pyridinium salt (**2a**) with sodium hydroxide in CH_2Cl_2 – H_2O at room temperature gave colorless needles (**3a**) of mp 148–150° in 80% yield. The structure of **3a** was determined on the basis of elemental analysis ($C_{12}H_{12}N_4$), mass (MS) (m/e 212 (M^+)), infrared (IR), and nuclear magnetic resonance (NMR) spectra, and also by comparison of some of the derivatives with authentic specimens. The IR spectrum showed the $-C=N$ -absorption band at 1670 cm^{-1} . The NMR spectrum revealed a singlet at 3.45 ppm (3H) due to the methyl group, a singlet at 8.05 ppm (1H) assignable to H_a , a doublet at 7.12 ppm (1H, $J_{bc}=14.0\text{ Hz}$) assigned to H_b , a doublet of doublets at 6.72 ppm (1H, $J_{cb}=14.0\text{ Hz}$, $J_{cd}=4.0\text{ Hz}$) due to H_c , a doublet at 7.78 ppm (1H, $J=4.0\text{ Hz}$) due to H_d and an aromatic

1) This work was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 1978.

2) Location: Hiromachi, Shinagawa-ku, Tokyo.

3) S. Tanaka, K. Wachi, and A. Terada, *Chem. Pharm. Bull.*, **28**, 1265 (1980).

4) Yu. B. Vilenskii, S.D. Zaitseva, B.M. Ivanov, V.A. Kovtun, L.I. Matusevich, V. Ya. Pochinok, I.A. Rogacheva, R.V. Timofeeva, and L.N. Fedorova, *Zh. Nauch. Prikl. Fotogr. Kinematogr.*, **12**, 121 (1967).



multiplet at 7.38—7.82 ppm (5H). In view of these results, **3a** was assigned as 1-phenyl-4-(3-methyliminopropenyl)-1,2,3-triazole. The *trans* configuration was assigned for the propenyl moiety on the basis of the coupling constant ($J_{bc}=14.0$ Hz) in the NMR spectrum. **3a** was easily hydrolyzed with acid to give the corresponding aldehyde, 3-(1-phenyl-1,2,3-triazol-4-yl)acrylaldehyde (**4a**), which was identical with an authentic sample prepared by the method of König.⁵⁾

Several triazole derivatives (**3a—d** and **4a—e**) bearing various substituents were similarly prepared, and the results are summarized in Tables I and II. In the case of the *p*-nitro-substituted compound, the initial reaction product (**3e**) could not be isolated since the methyl-imino moiety of **3e** was easily hydrolyzed during attempted purification by silica gel column chromatography.

A plausible mechanism for the formation of triazole derivatives by the reaction of pyridinium iodides with base is shown in Chart 3. As mentioned in the previous paper³⁾ in connection with the formation of pyrazole derivatives, a mechanism involving initial base-assisted pyridine ring opening would be unfavorable in this case. An intramolecular cyclization mechanism accompanied by cleavage of the pyridine nucleus would be more plausible. The initially

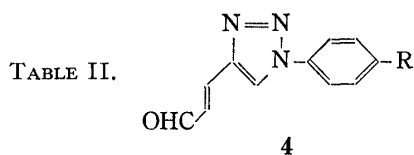
TABLE I.

3

	R	mp (°C)	Yield (%)	Formula	Analysis (%)			
					Calcd (Found)			
					C	H	N	Cl
3a	H	148—150	80	C ₁₂ H ₁₂ N ₄	67.60 (67.76)	5.70 5.40	26.40 26.25	
3b	CH ₃	182—183.5	73	C ₁₃ H ₁₄ N ₄	69.00 (69.43)	6.24 6.18	24.76 24.79	
3c	Cl	210—212	82	C ₁₂ H ₁₁ ClN ₄	58.42 (58.47)	4.49 4.45	22.71 22.33	14.37 14.45
3d	CH ₃ O	181—184	80	C ₁₃ H ₁₄ N ₄ O	64.44 (64.39)	5.82 5.63	23.13 22.98	
3e	NO ₂	—	— ^{a)}	—				

a) **3e** was isolated as the corresponding aldehyde.

5) W. König, M. Coenen, W. Lorenz, F. Bahr, and A. Bassl, *J. Pract. Chem.*, **30**, 96 (1965).



	R	mp (°C)	Yield (%)	Formula	Analysis (%)			
					Calcd (Found)			
					C	H	N	Cl
4a	H	178.5—179.5	66	C ₁₁ H ₉ N ₃ O	66.32 (66.49)	4.55 (4.49)	21.10 (20.88)	
4b	CH ₃	177 —178.5	70	C ₁₂ H ₁₁ N ₃ O	67.59 (67.86)	5.20 (5.05)	19.71 (19.41)	
4c	Cl	157 —159	80	C ₁₁ H ₁₈ ClN ₃ O	56.54 (56.45)	3.43 (3.73)	17.98 (17.79)	15.17 (14.97)
4d	CH ₃ O	170 —172	74.5	C ₁₂ H ₁₁ N ₃ O ₂	62.87 (63.13)	4.84 (4.94)	18.33 (17.92)	
4e	NO ₂	220 —222	70 ^{a)}	C ₁₁ H ₈ N ₄ O ₃	54.10 (54.16)	3.30 (3.55)	22.94 (22.79)	

a) Yield from 2e.

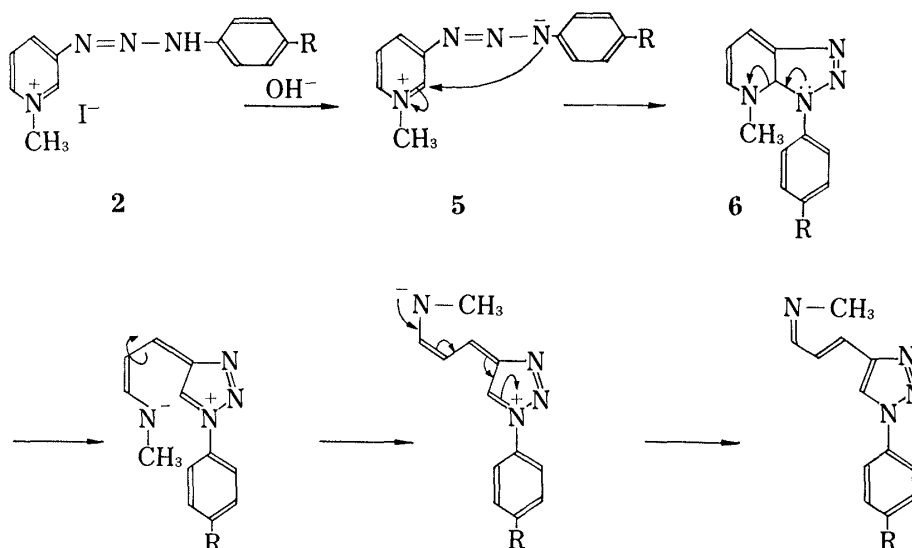


Chart 3

formed nitrogen anion (5) could attack the α -carbon of the pyridine ring to afford the bicyclic intermediate (6), followed by ring opening of the pyridine nucleus to give the zwitterion 7. This intermediate, having the *cisoid* configuration, could undergo conversion to the *transoid* configuration, followed by bond isomerization to give the product.

Next, we investigated the synthesis of isoxazole derivatives by means of the aforementioned reaction. The starting material, 1-methyl-3-benzoylpyridinium oxime iodide (10a),⁶⁾ was synthesized by methylation of 3-benzoylpyridine oxime (9a).^{6,7)} The pyridinium salt (10a) showed two singlets, due to the hydroxy proton of the oxime, at 12.30 and 12.46 ppm in the NMR spectrum, indicative of a 1:1 mixture of *syn*- and *anti*-forms. Treatment of the pyridinium salt (10a) with sodium hydroxide in CH₂Cl₂-H₂O at room temperature, followed by silica gel column chromatography, gave 3-(3-phenylisoxazol-4-yl)acrylaldehyde (12a) in 10% yield. The product, 12a, might be obtained by hydrolysis of the methylimino compound

6) R.J. Kitz, S. Ginsburg, and I.B. Wilson, *Biochem. Pharmacol.*, **14**, 1471 (1965).

7) B. Jeiteles, *Monatshefte für Chemie*, **17**, 518 (1896).

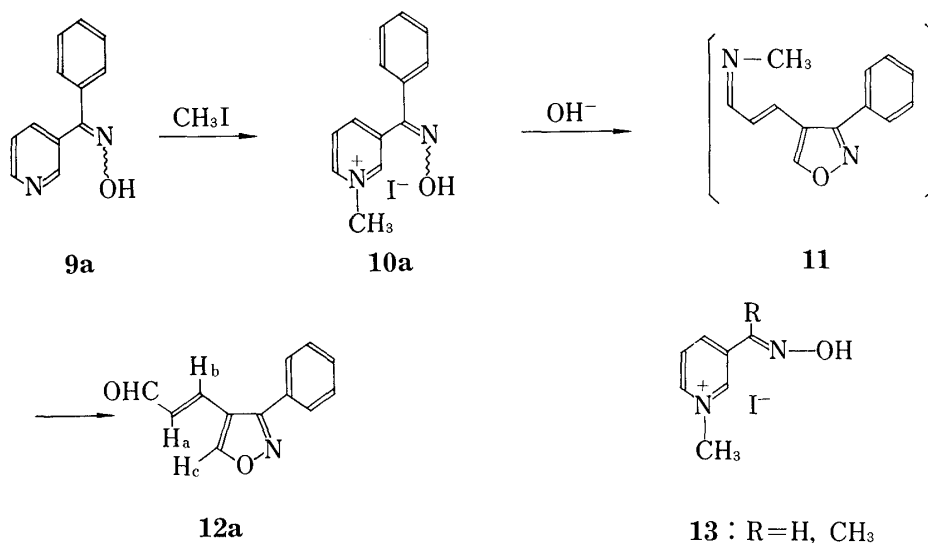
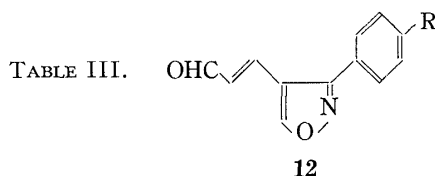


Chart 4



	R	mp (°C)	Yield (%)	Formula	Analysis (%)			
					Calcd	Found		
					C	H	N	Cl
12a	H	64—65	10 ^{a)} (25) ^{b)}	C ₁₂ H ₉ NO ₂	72.35 (72.57)	4.55 4.57	7.03 7.13	
12b	Cl	120—122	5.7 ^{a)}	C ₁₂ H ₈ ClNO ₂	61.68 (61.51)	3.45 3.38	5.99 6.12	15.17 15.01
12c	CH ₃ O	114—115	13 ^{a)}	C ₁₃ H ₁₁ NO ₃	68.11 (68.23)	4.83 5.08	6.11 5.98	

^{a)} From a mixture of *anti*- and *syn*-forms.

^{b)} From the *anti*-form.

(**11a**). The structural assignment of **12a** was based on the elemental analysis (C₁₂H₉NO₂) and MS spectrum (*m/e* 199 (M⁺)). The IR spectrum showed the existence of an aldehyde group (1960 cm⁻¹). The NMR spectrum revealed a doublet of doublets at 6.55 ppm (1H, *J*=16.0 Hz, *J*=8.0 Hz) due to H_a, a doublet at 7.37 ppm (1H, *J*=16.0 Hz) assignable to H_b, a singlet at 8.97 ppm (1H) assigned to H_c, a doublet at 9.75 ppm (1H, *J*=8.0 Hz) for the aldehyde proton and a singlet at 7.63 ppm (5H) due to the aromatic protons. The *trans* configuration for the acrylaldehyde moiety is evident from its coupling constant (*J*=16.0 Hz). Considering the reaction mechanism postulated for the formation of analogous products, the *anti*-form⁸⁾ of **10a** might be favorable for intramolecular cyclization rather than the *syn*-form. Subsequently, the pure *anti*-isomer of **10a** was synthesized by the method of Kitz and co-workers.⁶⁾ Reaction of *anti*-10a with base as before gave **12a** in 25% yield. In contrast, the pure *syn*-isomer⁶⁾ when treated similarly did not give **12a**. The *p*-chloro- and *p*-methoxy substituted derivatives (**12b** and **c**) were similarly prepared using a mixture of *syn*- and *anti*-forms (**10b** and **c**), because our attempts to separate mixtures of *syn*- and *anti*-forms of these

8) With respect to the pyridine ring and the lone pair of ketoxime nitrogen.

compounds (**9b** and **c**, or **10b** and **c**) have so far been unsuccessful. The results are summarized in Table III.

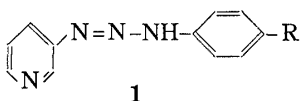
Attempted preparation of isoxazoles by the reaction of pyridinium salts (**13**, R=H, CH₃) with base was not successful. We attribute this to the known tendency⁹⁾ of these compounds to exist exclusively as the *syn*-isomers.

Experimental

Melting points were determined with a Buchi melting point apparatus and are uncorrected. IR spectra were determined on a Hitachi EPI-G3 grating IR spectrometer and mass spectra were recorded on a JEOL JMS-01S spectrometer. NMR spectra were measured with a Varian T-60 or HA-100 machine.

General Procedure for the Preparation of 3-(3-Phenyl-1-triazenyl)pyridine (1a—e)—An aqueous solution (20 ml) of sodium nitrate (0.12 mol) was added dropwise to a mixture of hydrochloric acid (30 ml) and substituted aniline (0.11 mol) with stirring at 10–15°. The reaction mixture was stirred at this temperature for 1.5 hr. The aqueous solution of diazonium compound thus obtained was added dropwise to a mixture of 3-aminopyridine (0.1 mol), sodium acetate (1.0 mol), H₂O (50 ml) and EtOH (100 ml) at –3––2°. After

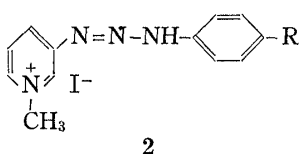
TABLE IV.



1

	R	mp (°C)	Yield (%)	Formula	Analysis (%)			
					Calcd	Found		
					C	H	N	Cl
1a	H	149–150	62	C ₁₁ H ₁₀ N ₄	66.49 (66.65)	5.04 5.09	28.53 28.29	
1b	CH ₃	135–137	56	C ₁₂ H ₁₂ N ₄	67.90 (68.16)	5.70 5.69	26.40 26.45	
1c	Cl	163–165	77	C ₁₁ H ₉ ClN ₄	56.78 (56.68)	3.89 3.87	24.07 24.07	15.23 15.27
1d	CH ₃ O	132–134	23	C ₁₂ H ₁₂ N ₄ O	63.14 (63.20)	5.30 5.26	24.55 24.51	
1e	NO ₂	224–225 (dec.)	81	C ₁₁ H ₉ N ₅ O ₂	54.32 (54.53)	3.73 3.65	28.80 28.58	

TABLE V.



2

	R	mp (°C)	Yield (%)	Formula	Analysis (%)			
					Calcd	Found		
					C	H	N	I
2a	H	143–145 (dec.)	78	C ₁₂ H ₁₃ IN ₄	42.37 (42.14)	3.45 3.89	16.47 16.12	37.30 37.36
2b	CH ₃	151–153	57	C ₁₃ H ₁₅ IN ₄	44.08 (44.20)	4.26 4.29	15.81 15.64	35.82 35.65
2c	Cl	188–190 (dec.)	93	C ₁₂ H ₁₂ ClN ₄	38.47 (38.61)	3.22 3.24	14.95 15.07	33.87 33.76
2d	CH ₃ O	164–165	79	C ₁₃ H ₁₅ IN ₄ O	42.17 (42.42)	4.08 4.10	15.13 15.18	34.28 34.13
2e	NO ₂	219–221 (dec.)	53	C ₁₂ H ₁₂ IN ₅ O ₂	37.42 (37.11)	3.14 3.18	18.18 18.50	32.94 32.74

9) J.M. Lehn and D. Crepau, *Organic Magnetic Resonance*, **7**, 524 (1975).

stirring for 3 hr at room temperature, the resulting precipitate was collected by filtration, washed with H_2O , and recrystallized from EtOH. Yields, melting points and analytical data are recorded in Table IV.

General Procedure for the Preparation of 1-Methyl-3-(3-phenyl-1-triazenyl)pyridinium Iodide (2a—e)—A solution of 1 (0.05 mol) and methyl iodide (0.2 mol) in 200 ml of EtOH was heated under reflux for 3 hr. After cooling, the resulting precipitate was collected by filtration, washed with EtOH and recrystallized from EtOH. The results are summarized in Table V.

General Procedure for the Preparation of 1-(4-Substituted phenyl)-4-(3-methyliminopropenyl)-1,2,3-triazoles (3a—d)—An aqueous solution (25 ml) of NaOH (0.1 mol) was added dropwise to a suspension of 2 (0.03 mol) in H_2O (200 ml)– CH_2Cl_2 (200 ml) at 10 – 12° , and the mixture was stirred at room temperature for 24 hr. The organic layer was separated, washed with H_2O and dried over Na_2SO_4 . After removal of CH_2Cl_2 by evaporation, the residual solid was recrystallized from C_6H_6 . The results are summarized in Table I.

General Procedure for the Preparation of 3-[1-(4-Substituted phenyl)-1,2,3-triazol-4-yl]acrylaldehyde (4a—d)—A solution of 3 in C_6H_6 was absorbed on silica gel and eluted with C_6H_6 –AcOEt (5: 1). After removal of the organic solvent, the resulting solid was recrystallized from C_6H_6 . The results are summarized in Table II.

3-[1-(4-Nitrophenyl)-1,2,3-triazol-4-yl]acrylaldehyde (4e)—An aqueous solution (10 ml) of NaOH (2.0 g) was added dropwise to a suspension of 3.8 g of 2e in H_2O (90 ml)– CH_2Cl_2 (90 ml) at 10 – 12° with stirring. The reaction mixture was stirred for 24 hr at room temperature. The CH_2Cl_2 layer was separated, washed with H_2O , dried over Na_2SO_4 and concentrated. The residual semi solid was chromatographed on silica gel and eluted with C_6H_6 –AcOEt (2: 1). The crystalline substance was recrystallized from C_6H_6 to give 4e (1.7 g). Yield, melting point and analytical data are recorded in Table II.

General Procedure for the Preparation of 3-[3-(4-Substituted phenyl)-isoxazol-4-yl]acrylaldehyde (12a—c)—A suspension of 10 (0.01 mol), synthesized by the method of Kitz and coworkers,⁹ in CH_2Cl_2 (50 ml)– H_2O (60 ml) was treated dropwise with an aqueous solution (10 ml) of NaOH (0.05 mol) at 5 – 7° . The reaction mixture was stirred at room temperature for 24 hr. The CH_2Cl_2 layer was separated, washed with H_2O and dried over Na_2SO_4 . After evaporation to dryness, the residue was chromatographed on silica gel. The crystalline material obtained from the fraction eluted with C_6H_6 –AcOEt (20: 1) was recrystallized from C_6H_6 –hexane. The results are summarized in Table III.