[Chem. Pharm. Bull. 28(7)2083—2088(1980)]

Formation of Triazole and Isoxazole Derivatives from β-Substituted Pyridinium Salts[1]

Shigeru Tanaka, Kazuyuki Wachi, and Atsusuke Terada

Central Research Laboratories, Sankyo Co., Ltd.[2]

(Received January 31, 1980)

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 pyridinnium 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.

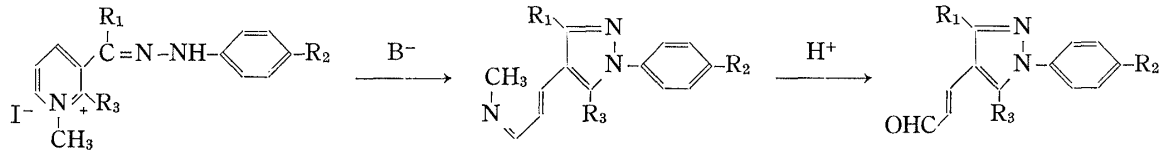


Chart 1

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 Hz) assigned to H_b, a doublet of doublets at 6.72 ppm (1H, J_{cb}=14.0 Hz, J_{cd}=4.0 Hz) due to H_c, a doublet at 7.78 ppm (1H, J=4.0 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. Kovtum, L.I. Matusevich, V. Ya. Pochinok, I.A. Rogacheva, R.V. Timofeeva, and L.N. Fedorova, *Zh. Nauch. Prikl. Fotogr. Kinematogr.*, **12**, 121 (1967).

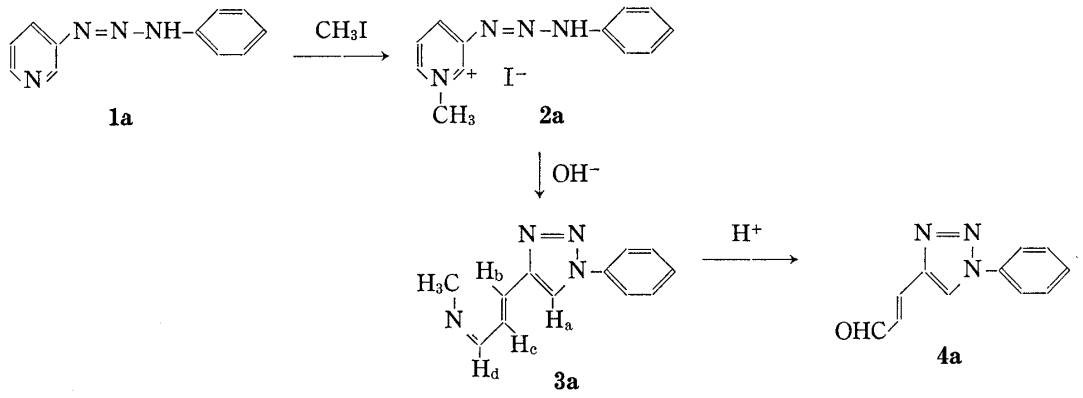


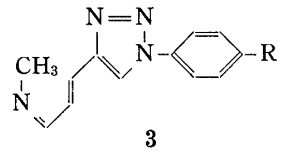
Chart 2

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 methylimino 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 paper[3] 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.



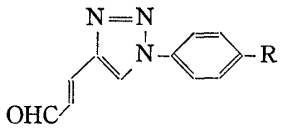
3

	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_3O	181—184	80	$C_{13}H_{14}N_4O$	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).

TABLE II.



4

	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Cl
4a	H	178.5—179.5	66	$C_{11}H_9N_3O$	66.32 (66.49	4.55 4.49	21.10 20.88)	
4b	CH_3	177 —178.5	70	$C_{12}H_{11}N_3O$	67.59 (67.86	5.20 5.05	19.71 19.41)	
4c	Cl	157 —159	80	$C_{11}H_{18}ClN_3O$	56.54 (56.45	3.43 3.73	17.98 17.79	15.17 14.97)
4d	CH_3O	170 —172	74.5	$C_{12}H_{11}N_3O_2$	62.87 (63.13	4.84 4.94	18.33 17.92)	
4e	NO_2	220 —222	70[a]	$C_{11}H_8N_4O_3$	54.10 (54.16	3.30 3.55	22.94 22.79)	

a) Yield from **2e**.

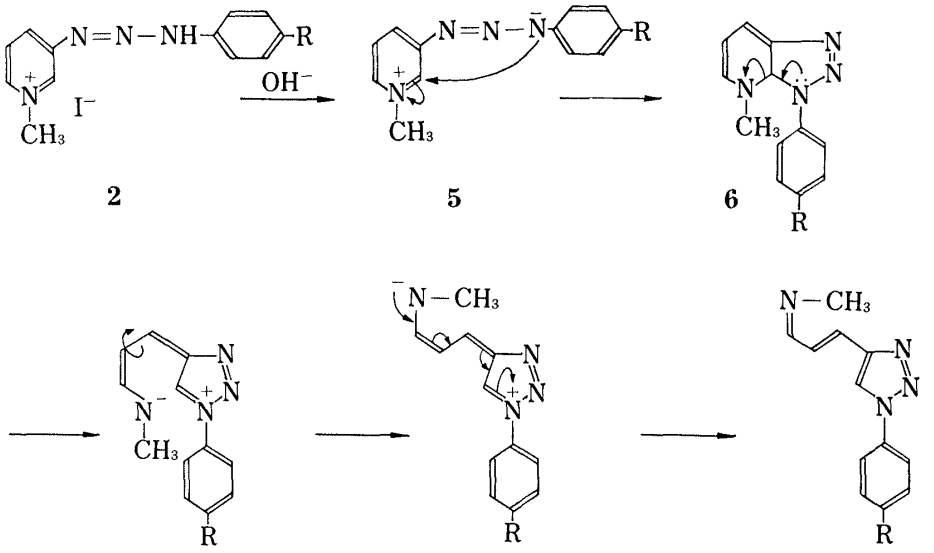
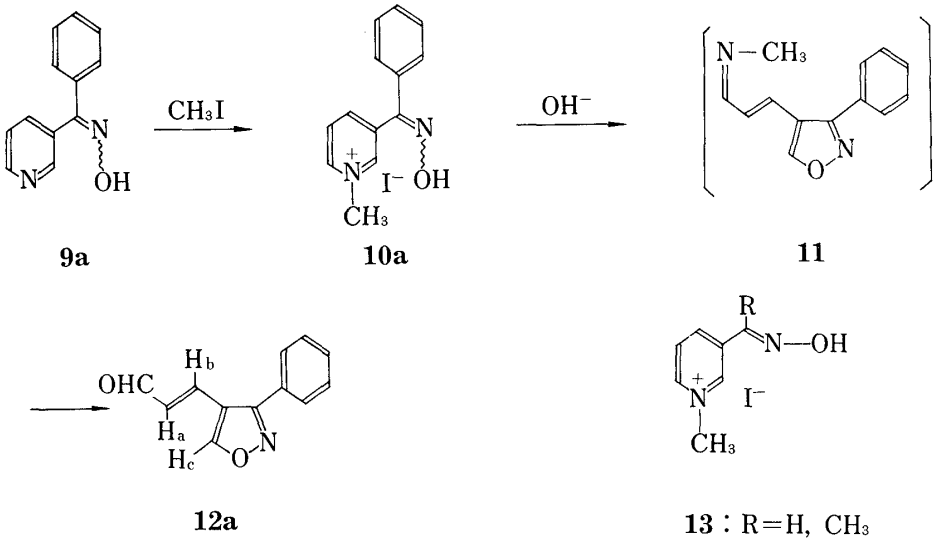


Chart 3

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 CH_2Cl_2–H_2O 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).



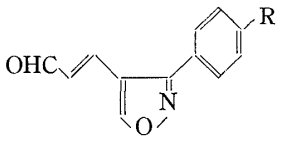
9a **10a** **11**

12a

13 : R=H, CH_3

Chart 4

TABLE III.



12

	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Cl
12a	H	64—65	10[a] (25)[b]	$C_{12}H_9NO_2$	72.35 (72.57	4.55 4.57	7.03 7.13)	
12b	Cl	120—122	5.7[a]	$C_{12}H_8ClNO_2$	61.68 (61.51	3.45 3.38	5.99 6.12	15.17 15.01)
12c	CH_3O	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 ($C_{12}H_9NO_2$) 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*-form[8] 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*-isomer[6] 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.

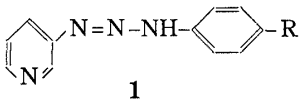
Attempted preparation of isoxazoles by the reaction of pyridinium salts (**13**, R=H, CH_3) with base was not successful. We attribute this to the known tendency[9] of these compounds to exist exclusively as the *syn*-isomers.

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), H_2O (50 ml) and EtOH (100 ml) at −3——2°. After

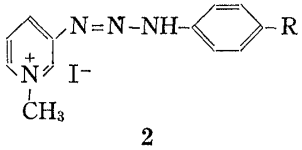
Table IV.



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	5.04	28.53	
					(66.65	5.09	28.29)	
1b	CH_3	135—137	56	$C_{12}H_{12}N_4$	67.90	5.70	26.40	
					(68.16	5.69	26.45)	
1c	Cl	163—165	77	$C_{11}H_9ClN_4$	56.78	3.89	24.07	15.23
					(56.68	3.87	24.07	15.27)
1d	CH_3O	132—134	23	$C_{12}H_{12}N_4O$	63.14	5.30	24.55	
					(63.20	5.26	24.51)	
1e	NO_2	224—225 (dec.)	81	$C_{11}H_9N_5O_2$	54.32	3.73	28.80	
					(54.53	3.65	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	3.45	16.47	37.30
					(42.14	3.89	16.12	37.36)
2b	CH_3	151—153	57	$C_{13}H_{15}IN_4$	44.08	4.26	15.81	35.82
					(44.20	4.29	15.64	35.65)
2c	Cl	188—190 (dec.)	93	$C_{12}H_{12}ClN_4$	38.47	3.22	14.95	33.87
					(38.61	3.24	15.07	33.76)
2d	CH_3O	164—165	79	$C_{13}H_{15}IN_4O$	42.17	4.08	15.13	34.28
					(42.42	4.10	15.18	34.13)
2e	NO_2	219—221 (dec.)	53	$C_{12}H_{12}IN_5O_2$	37.42	3.14	18.18	32.94
					(37.11	3.18	18.50	32.74)

9) J.M. Lehn and D. Crepaux, *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,[6] 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.