Chem. Pharm. Bull. 28(4)1265—1269(1980)

Formation of Pyrazole Derivatives from β-Substituted Pyridinium Salts[1]

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(Received October 29, 1979)

Treatment of 1-methyl-3-phenylhydrazonomethyl pyridinium iodides (**2a**—**f**) with a base gave pyrazole derivatives (**3** and **4**) with expulsion of the pyridine ring. A possible mechanism for the formation of pyrazole derivatives id discussed.

Keywords——phenylhydrazone; 3-substituted pyridinium salts; additive cleavage reaction; pyrazole formation; 3-(1-phenylpyrazol-4-yl)acrylaldehyde; reaction mechanism

It is well known that the pyridine nucleus of certain pyridinium salts can be cleaved with a base, giving rise to glutacone aldehyde derivatives.[3] Earlier studies indicated that cleavage of the pyridine ring is facilitated by electron-withdrawing groups.[4] Schnekenburger and co-workers[5] reported the additive cleavage reaction of pyridinium salts having cyano groups with active methylene compounds to give the corresponding conjugated polyenes. However, Takayama and Okamoto[6] have recently reported that pyridinium salts having no electron-withdrawing group gave the corresponding polyenes upon reaction with active methylene compounds.

During the courase of our studies on β-substituted pyridinium salts, we found an intramolecular additive cleavage reaction involving pyridinium salts having no electron-withdrawing group. The present investigation was concerned with such reactions involving the formation of substituted pyrazoles.

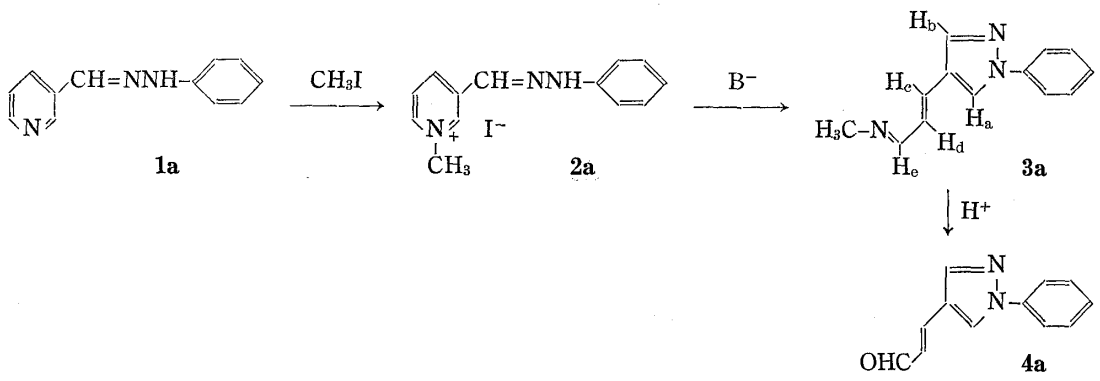


Chart 1

Nicotinaldehyde phenylhydrazone (**1a**) was methylated with methyl iodide to give the quartarnary pyridinium salt (**2a**) in quantitative yield. Treatment of the pyridinium salt (**2a**)

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) *a*) R.A. Abramovitch, "The Chemistry of Heterocyclic Compounds," John Wiley and Sons Inc., New York, Vol. 14 supplement Part 1, 1974, p.309; *b*) J. Bartos, *Ann. Pharm. Fr.*, **29**, 221 (1971); *c*) Y. Tamura, N. Tsujimoto, and Y. Hirano, *J. Pharm. Soc., Jap.*, **92**, 546 (1972).
4) A.F. Vompe and N.F. Turitsyna, *Zhur. Obsch. Khim.*, **28**, 2864 (1958).
5) J. Schnekenburger, D. Heber, and E. Brunschweigher, *Ann. Chem.*, **1976**, 1799.
6) H. Takayama and T. Okamoto, *Chem. Pharm. Bull.*, **26**, 2422 (1978).

with sodium hydroxide in CH_2Cl_2–H_2O at room temperature gave colorless needles (**3a**) in good yield. The structure of **3a** was determined on the basis of elemental analysis ($C_{13}H_{13}N_3$), mass (*m/e* 211 (M^+)), infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra, and by comparison of some of the derivatives with authentic specimens. The IR spectrum of **3a** showed a –C=N– absorption band at 1635 cm^{-1}. The NMR spectrum revealed a singlet at 3.45 ppm (3H) due to the methyl group, a doublet of doublets at 6.93 ppm (1H, J_{cd}= 14.0 Hz, J_{de}=7.0 Hz) assigned to H_d, a doublet at 7.14 ppm (1H, J_{cd}=14.0 Hz) due to H_c, a singlet at 7.99 ppm (1H) assignable to H_b, a singlet at 8.10 ppm (1H) due to H_a, a doublet at 8.11 ppm (1H, J_{de}=7.0 Hz) due to H_e and an aromatic multiplet centered at 7.12 ppm (5H). These results suggested the formation of a new heterocyclic compound with expulsion of pyridine ring, and the structure of 3a was assigned as 1-phenyl-4-(3-methyliminopropenyl)-pyrazole. The *trans* configuration was assigned for the propenyl moiety on the basis of the coupling constant (J_{cd}=14.0 Hz) in the NMR spectrum.

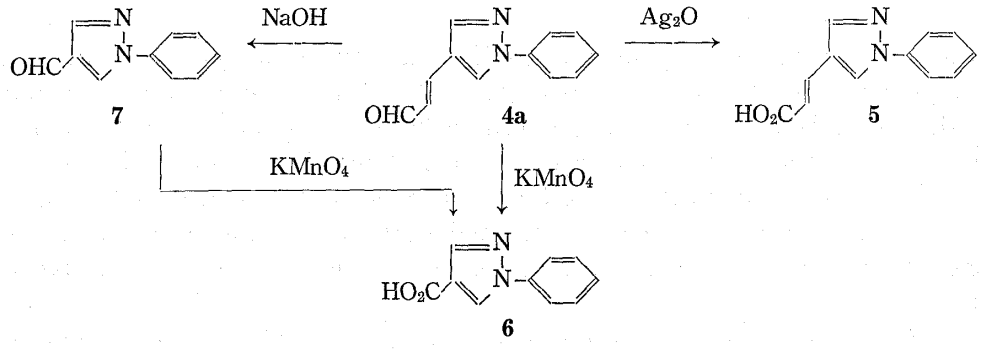


Chart 2

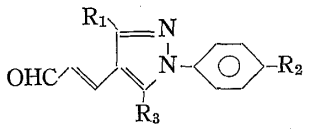
Compound **3a** was easily hydrolyzed with acid to give the corresponding aldehyde, 3-(1-phenylpyrazol-4-yl)acrylaldehyde (**4a**).[7] Although the structure of **4a** is evident from the spectral data and elemental analysis, it was confirmed unambiguously by derivatization to known compounds. Oxidation of **4a** with silver oxide afforded the corresponding carboxylic acid (**5**)[8] in 51% yield. Alternatively, potassium permanganate oxidation of **4a** gave 1-phenylpyrazole-4-carboxylic acid (6)[8] in 55% yield. Treatment of **4a** with aqueous sodium hydroxide gave 1-phenylpyrazole-4-carboxaldehyde (**7**)[8] in 26% yield. Compound **7** was further converted to the corresponding carboxylic acid (**6**) by potassium permanganate oxidation. The compounds (**5**, **6** and **7**) thus obtained were identical with authentic samples prepared by the method of Finar and Godfery.[8]

Similarly, syntheses of several other pyrazole derivatives (**3b**—**f**) bearing various substituents were attempted. In contrast to **3a**, these compounds were unstable to hydrolysis, and were thus converted to the corresponding aldehydes during the silica gel column chromatography. These compounds (**4a**—**f**) were characterized as shown in Table I. It is noteworthy that the pyrazole derivative, **4f**, was obtained even from **2f**, which was blocked at the α-position of the pyridine ring with a methyl group.

Possible mechanisms for the formation of pyrazole derivatives by the reaction of pyridinium salts with a base are shown by A and B in Chart 3. In Mechanism A, hydroxide attacks the α-carbon of the pyridine ring to afford the aldehyde (or ketone) with ring opening, the pyrazole ring is formed subsequently by condensation of the aldehyde and the nitrogen of the hydrazone. Alternatively, Mechanism B is intramolecular cyclization reaction accompanied by cleavage of the pyridine ring. The initially formed nitrogen anion (**10**) attacks the α-carbon

7) L.L. Finar and K.J. Saunder, *J. Chem. Soc.*, **1965**, 3862.
8) L.L. Finar and K.E. Godfery, *J. Chem. Soc.*, **1954**, 2293.

TABLE I. 3-(1-Phenylpyrazol-4-yl)acrylaldehyde Derivatives (**4**)



4	R_1	R_2	R_3	Method	mp (°C)	Yield (%)[a]	Formula	Analysis (%) Calcd (Found) C	H	N
a	H	H	H	A B	86 — 87.5	70 43	$C_{12}H_{10}N_2O$	72.71 (72.78	5.09 4.92	14.13 14.00)
b	H	Cl	H	A C	129 —131	85 60	$C_{12}H_9ClN_2O$	61.94 (61.79	3.89 3.91	12.03 11.93)
c	H	CH_3O	H	A	113 —115	69	$C_{13}H_{12}N_2O_2$	68.41 (68.03	5.30 5.21	12.27 12.13)
d	CH_3	H	H	A	107.5—109	20	$C_{13}H_{12}N_2O$	73.56 (73.40	5.70 5.59	13.20 12.90)
e	C_6H_5	H	H	A	165 —166	75	$C_{18}H_{14}N_2O$	78.81 (78.68	5.14 4.99	10.21 10.22)
f	H	H	CH_3	A	85 — 86	15	$C_{13}H_{12}N_2O$	73.56 (73.51	5.70 5.56	13.20 13.21)

Method A: $NaOH/CH_2Cl_2$–H_2O
B: NaH/DMF
C: NaOEt/EtOH
a) Yield from **2**.

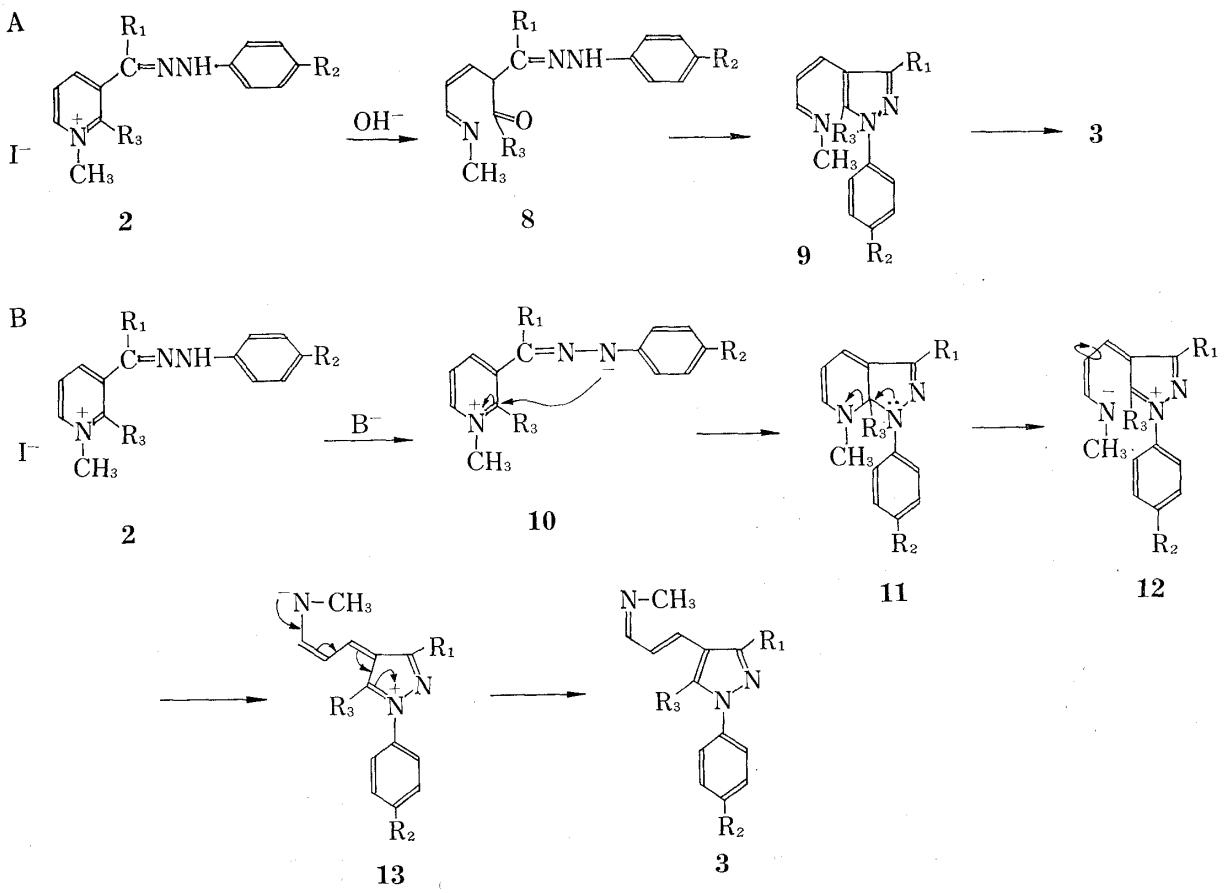


Chart 3

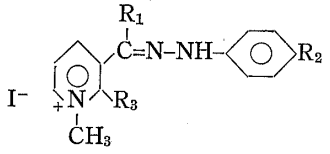
of the pyridine ring to afford the bicyclic intermediate (**11**), followed by ring opening of the pyridine nucleus to give the zwitterion **12**. This intermediate, having the *cisoid* configuration, undergoes conversion to the *transoid* configuration, followed by bond isomerization to give the product. In order to investigate the applicability of these mechanisms, the pyridinium salt (**2a**) was subjected to reaction with NaH in DMF followed by silica gel chromatography. This afforded **4a** in 43% yield. In addition, **4b** was obtained after silica gel chromatography of the product from the reaction of **2b** with NaOEt in EtOH. These results support Mechanism B as the route of formation of the pyrazoles.

Experimental

Melting points were determined with a Büchi 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. Proton NMR spectra were measured with a Varian T-60 or HA-100 machine.

General Procedure for the Preparation of 1-Methyl-3-phenylhydrazonomethylpyridinium Iodide (2a—f) ——A solution of nicotinealdehyde phenylhydrazone (0.1 mol) and methyl iodide (0.15 mol) in acetone (300 ml) was heated under reflux for 2 hr. After cooling, the resulting crystalline substance was collected by filtration and recrystallized from EtOH. Yields, melting points and analytical data for these pyridinium salts are recorded in Table II.

Table II. 1-methyl-3-phenylhydrazonomethylpyridinium Iodide Derivatives (**2**)



2	R_1	R_2	R_3	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	I
a	H	H	H	210—211.5	95	$C_{13}H_{14}IN_3$	46.03 (46.11	4.16 4.08	12.38 12.35	37.41 37.55)
b	H	Cl	H	251—253	89	$C_{13}H_{13}ClIN_3$	41.79 (41.64	3.50 3.58	11.24 11.19	33.96 33.72)
c	H	CH_3O	H	233—235	74	$C_{14}H_{16}IN_3O$	45.54 (45.72	4.36 4.43	11.38 11.32	34.37 34.56)
d	CH_3	H	H	237—240	93	$C_{14}H_{16}IN_3$	47.60 (47.52	4.56 4.58	11.89 11.89	35.92 35.89)
e	C_6H_5	H	H	184—187	98	$C_{19}H_{18}IN_3$	54.95 (54.66	4.36 4.38	10.11 9.77	30.59 30.52)
f	H	H	CH_3	264—264.5	58	$C_{14}H_{16}IN_3$	47.60 (47.49	4.56 4.57	11.89 11.60	35.92 36.12)

1-Phenyl-4-(3-methyliminopropenyl)pyrazole (3a)——A suspension of 1.7 g of **2a** in CH_2Cl_2 (100 ml) and H_2O (90 ml) was treated with 2.5% of aqueous sodium hydroxide solution (10 ml) at 8—10°. The reaction mixture was stirred for 20 hr at room temperature. The organic layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give a solid. Recrystallization from C_6H_6–hexane gave 0.5 g of **3a**, mp 87—89°. *Anal.* Calcd for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89, Found: C, 73.68; H, 6.22; N, 19.90.

Hydrolysis of 1-Phenyl-4-(3-methyliminopropenyl)pyrazole (3a)——A solution of **3a** (0.8 g) in EtOH (10 ml) was treated with 5% HCl (10 ml) at room temperature. The reaction mixture was stirred for 1 hr then extracted with AcOEt, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give a solid. Recrystallization from C_6H_6–hexane gave 0.5 g of **4a** as colorless needles, mp 86—87.5°. *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13, Found: C, 72.78; H, 4.92; N, 14.00.

General Procedure for the Preparation of 3-(1-Phenylpyrazol-4-yl)-acrylaldehyde Derivatives (4) Method A ——A suspension of **2** (0.015 mol) in CH_2Cl_2 (150 ml) and H_2O (135 ml) was treated with a 10% aqueous solution (10 ml) of NaOH at 8—10°. The reaction mixture was stirred for 20 hr at room temperature. The

organic layer was separated, washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel and eluted with C_6H_6–AcOEt (10: 1) to give a solid. Recrystallization from C_6H_6–hexane gave **4**. The results are summarized in Table I.

Method B 3-(1-Phenylpyrazol-4-yl)acrylaldehyde (4a)——A solution of 1-methyl-3-phenylhydrazonomethylpyridinium iodide (**2a**) (3.4 g) in 100 ml of DMF was reacted with 0.96 g of NaH (50% oily mixture) at −3——2° under N_2 atmosphere. The temperature was gradually raised to room temperature. After stirring for 4 hr, the reaction mixture was poured onto ice-water and extracted with AcOEt. The extracts were washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was chromatographed on silica gel and eluted with C_6H_6–AcOEt (10: 1) to give a solid. Recrystallization from C_6H_6–hexane gave 0.85 g of **4a**, which was identical with the sample prepared by Method A.

Method C 3-[1-(4-Chlorophenyl)pyrazol-4-yl]acrylaldehyde (4b)——A suspension of **2b** (3.7 g) in 100 ml of EtOH was reacted with an ethanol solution (50 ml) of sodium ethoxide (prepared from 1.0 g of Na and 50 ml of EtOH) at 5—10°. The reaction mixture was stirred for 20 hr at room temperature, then poured into ice-water, extracted with AcOEt, washed with H_2O and dried over Na_2SO_4. After removal of AcOEt by evaporation, the residue was chromatographed on silica gel. The crystalline substance obtained from the C_6H_6–AcOEt (10: 1) eluate was recrystallized from C_6H_6–hexane to give 1.4 g of **4b**, which was identical with the sample prepared by Method A.

3-(1-Phenylpyrazol-4-yl)acrylic Acid (5)——A solution of **4a** (1.0 g) in 200 ml of EtOH was treated with an aqueous solution (7 ml) of silver nitrate (1.85 g) and then an aqueous solution (44 ml) of 0.5 N sodium hydroxide at room temperature with vigorous stirring. The reaction mixture was stirred overnight at room temperature. Insoluble inorganic material was filtered off and washed with EtOH. The filtrate was concentrated under reduced pressure and the residue was dissolved in 20 ml of H_2O then acidified with conc. HCl. The resulting precipitate was collected by filtration and washed with H_2O. Recrystallization from EtOH gave 0.55 g of **5** as colorless needles, mp 188—190°. *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08, Found: C, 67.30; H, 4.91; N, 13.08. NMR (DMSO-d_6) δ: 6.52 (1H, d, J=16 Hz), 7.33—8.10 (5H, m), 7.73 (1H, d, J=16 Hz), 8.27 (1H, s), 9.00 (1H, s), 11.95 (1H, broad s).

1-Phenylpyrazole-4-carboxylic Acid (6), from 4a——A suspension of **4a** (2.0 g) in 100 ml of H_2O was treated under reflux with an aqueous solution (200 ml) of potassium permanganate (9.0 g). After refluxing for 2 hr, 15 ml of EtOH was added to the reaction mixture. Insoluble manganese dioxide was filtered off and washed with hot H_2O. The filtrate was concentrated to 100 ml and then acidified with conc. HCl. The resulting crystalline substance was collected by filtration and washed with H_2O. Recrystallization from EtOH gave 1.0 g of **6** as a colorless powder, mp 222.5—224°. *Anal.* Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89, Found: C, 63.56; H, 4.16; N, 14.68. NMR (DMSO-d_6) δ: 7.40—8.10 (5H, m), 8.35 (1H, s), 9.05 (1H, s), 11.20 (1H, s).

1-Phenylpyrazole-4-carboxyaldehyde (7)——A mixture of **4a** (3.4 g), NaOH (1.0 g), EtOH (60 ml) and H_2O (200 ml) was refluxed for 24 hr. After cooling, the reaction mixture was extracted with AcOEt, washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel and eluted with C_6H_6–AcOEt (50: 1) to give a solid. Recrystallization from C_6H_6–hexane gave 0.93 g of **7** as colorless prisms, mp 85—86°. *Anal.* Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27, Found: C, 69.92; H, 4.47; N, 16.12. NMR ($CDCl_3$) δ: 7.42—8.03 (5H, m), 8.30 (1H, s), 8.57 (1H, s), 10.07 (1H, s).

1-Phenylpyrazole-4-carboxylic Acid (6), from 7——A suspension of **7** (2.3 g) in 100 ml of H_2O was treated under reflux with an aqueous solution (200 ml) of $KMnO_4$ (9.0 g) and refluxed for 2 hr. EtOH (20 ml) added to the reaction mixture and insoluble manganese dioxide was filtered off and washed with hot H_2O. The filtrate was concentrated to 100 ml. The residual solution was acidified with conc. HCl. The resulting crystalline substance was collected by filtration and recrystallized from EtOH to give 1.3 g of **6**, mp 222.5—224°, which showed no depression of mp on admixture with the product obtained by the oxidation of **4a**. In addition, the IR spectrum was superimposable on that of the product obtained from **4a**.