New Routes to the *v*-Triazolo[1,5-*a*]pyridine and Pyrazolo[1,5-*a*]pyridine Ring Systems

Yasumitsu Tamura, Joong-Hyup Kim, Yasuyoshi Miki, Hironori Hayashi, and Masazumi Ikeda

Faculty of Pharmaceutical Sciences, Osaka University, 133-1, Yamada-kami, Suita, Osaka, Japan

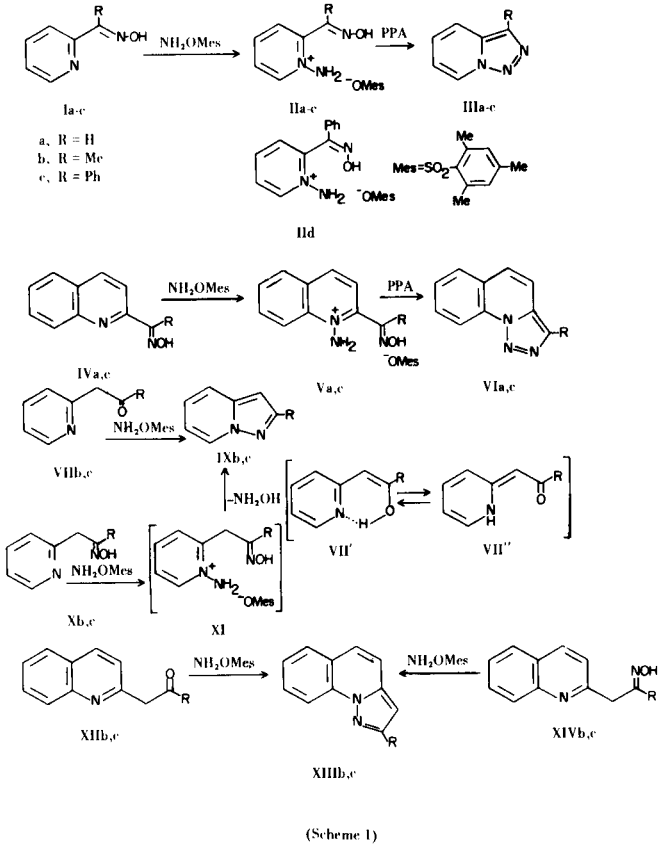
Received December 24, 1974

New routes to the *v*-triazolo[1,5-*a*]pyridine and pyrazolo[1,5-*a*]pyridine ring systems are described. Treatment of the *N*-amine salts of 2-picolinealdehyde oxime or 2-pyridyl ketone oximes with polyphosphoric acid gave *v*-triazolo[1,5-*a*]pyridines in fair yields. Treatment of 2-picolyl ketones or their oximes with *O*-mesitylenesulfonylhydroxylamine produced directly pyrazolo-[1,5-*a*]pyridines. These reactions were extended to the quinoline cases.

A variety of bridgehead nitrogen heteroaromatic compounds have been prepared from *N*-amine salts of heteroaromatic amines. These include, for examples, pyrazolo-[1,5-*a*]pyridines and pyrazolo[1,5-*x*]diazines (*x* = *a*,*b*,*c*) (1), *s*-triazolo[1,5-*a*]pyridines and *s*-triazolo[1,5-*x*]diazines (*x* = *a*,*b*,*c*) (2), pyrazolo[5,1-*b*]thiazoles (3), imidazo[1,2-*b*]-pyrazoles (3), thiazolo[3,2-*b*]-*s*-triazoles (4) and 2*H*-pyrido[1,2-*b*]-*as*-triazines (5). Because the *N*-amine salts are now readily available by the reaction of the parent heterocycles with *O*-mesitylenesulfonylhydroxylamine (MSH) (6), it appeared to be worthwhile to investigate further application of the *N*-amine salts to the syntheses of bridgehead nitrogen heterocycles. We now wish to report new synthetic routes to *v*-triazolo[1,5-*a*]pyridines (III) and pyrazolo[1,5-*a*]pyridines (IX) and their benzo derivatives VI and XIII by intramolecular cyclization of 2-substituted *N*-aminopyridinium and *N*-aminoquinolinium salts.

It was anticipated that the most direct route to *v*-triazolo[1,5-*a*]pyridines (III) would be from the *N*-amine salts (II). In fact, when the *N*-amine salts IIa-c readily prepared by the reaction of oximes Ia-c with MSH (7) were heated in polyphosphoric acid (PPA) at 70-110°, *v*-triazolo[1,5-*a*]-pyridines (IIIa-c) were obtained in 63-76% yields. This reaction proceeded when the E-form of the oxime (IIc) was used, while the Z-form (IId) gave only an intractable mixture, suggesting that the reaction proceeds in a concerted manner. This reaction could be successfully applied to the syntheses of *v*-triazolo[1,5-*a*]quinolines (VIa,c). Thus the starting *N*-amine salts Va and Vc could be obtained by treatment of IVa and IVc (a mixture of E and Z forms) with MSH in 65 and 59% yields, respectively. Heating Va and Vc in PPA at 80-100° gave VIa and VIc in 72 and 75% yields, respectively.

Entry into the pyrazolo[1,5-*a*]pyridines (IX) was first obtained when 1-(2-pyridyl)-2-propanone (VIIb) and 2-(2-pyridyl)acetophenone (VIIc) were allowed to react with an equimolar amount of MSH in chloroform or methanol at room temperature. Analyses of the reaction mixtures



(Scheme 1)

by tlc indicated the presence of IX and the starting ketones. The isolated yields of IXb and IXc were 34-35% and the unchanged ketones were recovered in 15-40% yields. Similar results were obtained with quinoline derivatives XIIb and XIIc, in which the yields of the desired pyrazolo-[1,5-*a*]quinolines XIIIb and XIIIc were only 10%. One possible explanation for the low yields may be related to the fact that these ketones exist predominantly in enol (VII') and enamine forms (VII'') rather than keto form (VII) (8). More suitable starting materials would be the corresponding oximes X and XIV. In fact, it was found that X and XIV reacted readily with an equimolar quantity of MSH to give directly IX and XIII in 33-80% yields. The formation of IX from X may involve the initial formation of *N*-amine salt (XI) which undergoes cyclization with elimination of hydroxylamine. In fact, hydroxylamine mesitylenesulfonate was isolated from the reaction mixture of X and MSH in high yields. However, attempted isolation of XI proved unsuccessful.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on an Hitachi EPI G-2 spectrophotometer, uv spectra on an Hitachi 124 spectrophotometer, nmr spectra on an Hitachi R-20A spectrometer and mass spectra on an Hitachi RMU-6D mass spectrometer operating at 70 ev. Preparative thin layer chromatography was carried out on Merck Alumina PF_{254}.

Material.

2-Picolinealdehyde oxime (Ia) was obtained commercially. The following compounds were prepared following procedures reported in the literature. Unless otherwise specified, the configuration of the oximes is uncertain: Methyl 2-pyridyl ketone oximes (Ib), m.p. 121.5-122° (9), (*E*)-phenyl 2-pyridyl ketone oxime (Ic), m.p. 153-154° (10), (*Z*)-phenyl 2-pyridyl ketone oxime (Id), m.p. 161-165° (10), quinaldaldehyde oxime (IVa), m.p. 190-191° (11), phenyl 2-quinolyl ketone oxime (IVc), m.p. 145-152° (probably a mixture of E and Z forms) (12), 1-(2-pyridyl)-2-propanone (VIIb) (13), 2-(2-pyridyl)acetophenone (VIIc) (14), 1-(2-pyridyl)-2-propanone oxime (Xb), oil (a mixture of E and Z forms in a ratio of 2:1 or 1:2 by nmr) (13), 2-(2-pyridyl)acetophenone oxime (Xc), m.p. 115-117° (12), 1-(2-quinolyl)-2-propanone (XIIb) (15), 2-(2-quinolyl)acetophenone (XIIc) (12), 2-(2-quinolyl)acetophenone oxime (XIVc), m.p. 179-181° (12).

1-(2-Quinolyl)-2-propanone Oxime (XIVb).

Treatment of XIIb (1.1 g.) with hydroxylamine hydrochloride (2.1 g.) and potassium acetate (2.5 g.) in 50% methanol (30 ml.) gave XIVb, m.p. 141-142° (ethanol); yield, 1.1 g.; nmr (dimethylsulfoxide-d_6): τ -0.60 (s, 1H, OH), 1.63-2.67 (m, 6H, aromatic protons), 6.18 (s, 2H, CH_2), 8.20 (s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.18; H, 6.09; N, 13.85.

General Procedure for *N*-Amination.

Using the same procedure as that described in a preceding paper (7), the following *N*-amine salts were prepared from the corresponding pyridine (I) and quinoline derivatives (IV). Compound IIa was obtained in 75% yield, m.p. 179-180° (methanol-ether).

Anal. Calcd. for $C_{15}H_{19}N_3O_4S$: C, 53.40; H, 5.68; N, 12.46. Found: C, 53.60; H, 5.79; N, 12.22.

Compound IIb was obtained in 77% yield, m.p. 153-155° (methanol-ether).

Anal. Calcd. for $C_{16}H_{21}N_3O_4S$: C, 54.69; H, 6.02; N, 11.96. Found: C, 54.83; H, 6.10; N, 11.68.

Compounds IIc and IId were obtained in 75 and 71% yields, respectively, in an amorphous form and used for the next reaction after washing with ether.

Compound Va was obtained in 65% yield, m.p. 231° dec. (ethanol).

Anal. Calcd. for $C_{19}H_{21}N_3O_4S$: C, 58.91; H, 5.46; N, 10.85. Found: C, 58.82; H, 5.52; N, 10.86.

Compound Vc was obtained in 59% yield as hygroscopic crystals, m.p. 110-115° (methanol-ether).

v-Triazolo[1,5-*a*]pyridines (IIIa-c) and *v*-Triazolo[1,5-*a*]quinolines (VIa,c).

A mixture of II or V (1 mmole) and PPA (1 g.) was heated at 80-110° for 2-3 hours. After cooling, the reaction mixture was poured into ice-water, made alkaline with sodium hydroxide and extracted with chloroform. The dried extract was concentrated to give the desired products (III or VI) in 63-76% yields. Compound IIIa was obtained in 64% yield, m.p. 34° [lit. (16) m.p. 34-35°].

Compound IIIb was obtained in 63% yield, m.p. 84-85° [lit. (17) m.p. 84-85°].

Compound IIIc was obtained in 76% yield, m.p. 114-115° [lit. (16) m.p. 113-115°].

Compound VIa was obtained in 72% yield, m.p. 80-82° [lit. (18) m.p. 81.5-82°].

Compound VIc was obtained in 75% yield, m.p. 149-150° (chloroform-petroleum ether); mass spectrum m/e 245 (M^+).

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.51; H, 4.61; N, 17.18.

Pyrazolo[1,5-*a*]pyridines (IX) and Pyrazolo[1,5-*a*]quinolines (XIII).

(A)

To a solution of the ketone (VII or XII) (1 mmole) in chloroform (3 ml.) (in the case of VIIc, methanol was used) was added a solution of MSH (1 mmole) in chloroform (3 ml.) under ice cooling and the reaction mixture was allowed to stand at room temperature for 15 minutes. After the solvent was removed, the residue was submitted to tlc (alumina, benzene) to give the desired product (IX or XIII) and the unchanged ketone. Compound IXb was obtained in 35% yield, characterized as picrate, m.p. 146-148° [lit. (13, 19), m.p. 135°], accompanied by unchanged ketone VIIa (15%).

Compound IXc was obtained in 34% yield, m.p. 111-112° [lit. (17) m.p. 109°], accompanied by unchanged ketone VIIc (40%).

Compound XIIIb was obtained in 10% yield, m.p. 56-58° (petroleum ether) (20); mass spectrum m/e 182 (M^+), accompanied by unchanged ketone XIIb (13%).

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.38. Found: C, 79.03; H, 5.56; N, 15.05.

Compound XIIIc was obtained in 10% yield, m.p. 87-88° (petroleum ether); mass spectrum m/e 244 (M^+), accompanied by unchanged ketone XIIc (10%).

Anal. Calcd. for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.56; H, 5.01; N, 11.45.

(B)

To a solution of the oxime (X or XIV) (1 mmole) in chloroform

(3 ml.) was added a solution of MSH (1 mmole) in chloroform (3 ml.). The reaction mixture was allowed to stand at room temperature for 15 minutes. Ether was added and the precipitated crystals of hydroxylamine were removed. The filtrate was concentrated to give the product (IX or XIII). Compound IXb was obtained in 35% yield, m.p. of the picrate, 146-148°.

Compound IXc was obtained in 80% yield, m.p. 111-112°.

Compound XIIIb was obtained in 33% yield, m.p. 56-58°.

Compound XIIIc was obtained in 61% yield, m.p. 87-88°.

Hydroxylamine mesitylenesulfonate was obtained in 83% yield from the reaction of Xb and MSH, m.p. 181-182° (methanol-ether). This compound was identical with an authentic sample prepared from hydroxylamine and mesitylenesulfonic acid by ir and m.p.

Anal. Calcd. for $C_9H_{15}NO_4S$: C, 46.35; H, 6.48; N, 6.01. Found: C, 46.49; H, 6.45; N, 6.06.

REFERENCES

(1a) For examples, R. Huisgen, R. Grasher, and R. Krischke, *Tetrahedron Letters*, 387 (1962); (b) K. T. Potts, U. P. Singh, and J. Bhattacharyya, *J. Org. Chem.*, **33**, 3766 (1968); (c) Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *J. Chem. Soc. Perkin I*, 2580 (1973); (d) S. Suzue, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull. (Tokyo)*, **21**, 2146 (1973); (e) K. Kasuga, M. Hirobe, and T. Okamoto, *ibid.*, **22**, 1814 (1974).

(2a) K. T. Potts, H. R. Burton, and J. Bhattacharyya, *J. Org. Chem.*, **31**, 260 (1966); (b) T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *Chem. Pharm. Bull. (Tokyo)*, **14**, 506 (1966); (c) Y. Tamura, J.-H. Kim, and M. Ikeda, *J. Heterocyclic Chem.*, **12**, 107 (1975).

(3) H. Koga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull. (Tokyo)*, **22**, 482 (1974).

(4) Y. Tamura, H. Hayashi, E. Saeki, J.-H. Kim, and M, Ikeda, *J. Heterocyclic Chem.*, **11**, 459 (1974).

(5) A. Kakehi and S. Ito, *J. Org. Chem.*, **39**, 1542 (1974).

(6) Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.*, **38**, 1239 (1973).

(7) Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 4133 (1972).

(8) M. Yamazaki, K. Noda, and M. Hamana, *Chem. Pharm. Bull. (Tokyo)*, **18**, 908 (1970).

(9) C, Engler and P. Rosumoff, *Ber.*, **24**, 2527 (1891).

(10) T. Kato, Y. Goto, and T. Chiba, *J. Pharm. Soc. Japan*, **86**, 1022 (1966).

(11) C. E. Kwartler and H. G. Lindwall, *J. Am. Chem. Soc.*, **59**, 524 (1937).

(12) T. Nakashima, *J. Pharm. Soc. Japan*, **77**, 1298 (1957).

(13a) J. P. Wibaut and J. I. deJong, *Rec. Trav. Chim.*, **68**, 485 (1949); (b) Y. Tamura, A. Yamakami, and M. Ikeda, *J. Pharm. Soc. Japan*, **91**, 1154 (1971).

(14) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

(15) N. N. Goldberg and R. Levine, *ibid.*, **74**, 5217 (1952).

(16) J. H. Boyer, R. Borgers, and L. T. Wolford, *ibid.*, **79**, 678 (1957).

(17) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957).

(18) R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).

(19) The m.p. of the picrate reported in ref. (13b) should be revised to m.p. 146-148°.

(20) J. Elguero, R. Jacquier, and G. Tarrago, *Bull. Soc. Chim. France*, 2876 (1969). The m.p. was not reported.