Synthesis of 2-Arylpyrido[3,4-*b*]pyrazine Derivatives Through Condensation of 3,4-Diaminopyridine with β-Keto Sulfoxides

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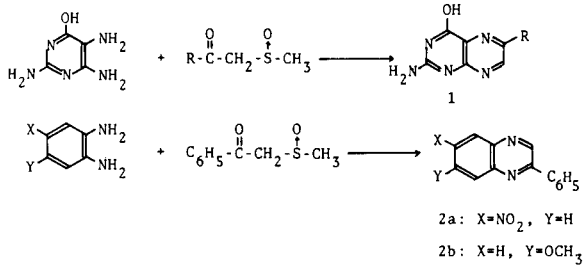
The reaction between 3,4-diaminopyridine and α-methylsulfinylacetophenone in benzene containing acetic acid under reflux gave 2-phenylpyrido[3,4-*b*]pyrazine. In this way, 2-(4-methoxyphenyl)pyrido[3,4-*b*]-pyrazine and 2-(3,4-dimethoxyphenyl)pyrido[3,4-*b*]pyrazine were obtained by condensation of 3,4-diamino-pyridine with the corresponding α-methylsulfinylacetophenones.

J. Heterocyclic Chem., **20**, 769 (1983).

An acid-catalyzed condensation of diamino compounds with β-keto sulfoxides served a positionally selective synthesis of poly-substituted condensed pyrazine derivatives as exemplified in the synthesis of pteridines (**1**) (1) and quinoxalines (**2**) (2). In the synthesis of quinoxalines, the more basic amino group preferably reacted with the α-carbon of the sulfinyl group. We have extensively studied an acid-catalyzed condensation of 3,4-diaminopyridine with β-keto sulfoxides in the expection that 2-substituted pyrido[3,4-*b*]pyrazine derivatives might form with a positional selectivity, since the amino group at the 3-position should be more basic than another amino group. The results of our studies are described in this paper.

Scheme 1

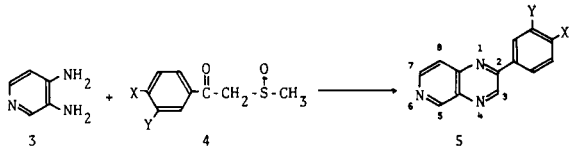


2a: X=NO_2, Y=H

2b: X=H, Y=OCH_3

A mixture of 3,4-diaminopyridine (**3**) and an equimolar amount of α-methylsulfinylacetophenone (**4a**) (3) in benzene was heated in the presence of acetic acid and allowed exclusive formation of 2-phenylpyrido[3,4-*b*]pyrazine (**15a**) (4) in 65% yield, mp 124-126°. The structure of the product was determined by direct comparison (5) with the spectral data of the authentic sample of **5a** (5) donated from Professor E. Hayashi. In a similar manner, 2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine (**5b**) and 2-(3,4-dimethoxyphenyl)pyrido[3,4-*b*]pyrazine (**5c**) were prepared by condensation of **3** with the corresponding α-methylsulfinylacetophenones (**4b**) and (**4c**) (3), respectively. Thus, positionally selective synthesis of 2-substituted pyrido[3,4-*b*]-pyrazines was achieved, as expected, by an acid-catalyzed condensation of 3,4-diaminopyridine with β-keto sulfoxides.

Scheme 2



a: X=Y=H; b: X=OCH_3, Y=H; c: X=Y=OCH_3

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H nmr spectra were recorded with a Varian T-60 instrument at 60 MHz. Mass spectra were obtained with a Hitachi RMU-7L spectrometer.

General Procedure for the Synthesis of 2-Arylpyrido[3,4-*b*]pyrazines.

A mixture of 2.18 g (20 mmoles) of 3,4-diaminopyridine and 20 mmoles of α-methylsulfinylacetophenone in a mixture of 50 ml of benzene and 1 ml of acetic acid under reflux for 2 hours. After removal of the solvent, the remaining residue was made basic with 28% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated. The resulting residue was chromatographed on silica gel (20 g) by using chloroform as an eluent. Removal of the solvent (200-250 ml) afforded the corresponding 2-arylpyrido[3,4-*b*]pyrazines in a nearly pure state.

2-Phenylpyrido[3,4-*b*]pyrazine (**5a**).

This compound was synthesized in 65% yield (2.69 g), mp 125-126° (methanol), which was identical with the authentic specimen, donated from Professor E. Hayashi, in all respects; m/e 207 (M^+); ^{1}H nmr (deuteriochloroform): δ 7.48-7.66 ppm (3H, m), 8.12-8.30 (2H, m), 7.88 (1H, d, J = 6 Hz), 8.77 (1H, d, J = 6 Hz), 9.34 (1H, s), 9.47 (1H, s).

Anal. Calcd. for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 75.32; H, 4.35; N, 20.34.

2-(4-Methoxyphenyl)pyrido[3,4-*b*]pyrazine (**5b**).

This compound was obtained in 60% yield (2.84 g), mp 140-142° (methanol); m/e 237 (M^+); ^{1}H nmr (deuteriochloroform): δ 3.90 ppm (3H, s), 7.02 (2H, d, J = 8 Hz), 7.83 (1H, d, J = 6 Hz), 8.17 (2H, d, J = 8 Hz), 8.78 (1H, d, J = 6 Hz), 9.30 (1H, s), 9.40 (1H, s).

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.81; H, 4.42; N, 17.92.

2-(3,4-Dimethoxyphenyl)pyrido[3,4-*b*]pyrazine (**5c**).

This compound was obtained in 58% yield (3.10 g), mp 122-124° (methanol); m/e 267 (M^+); ^{1}H nmr (deuteriochloroform): δ 3.96 ppm (3H, s), 4.03 (3H, s), 6.87 (1H, d, J = 9 Hz), 7.23 (1H, s), 7.75 (1H, d, J = 9 Hz), 7.73 (1H, d, J = 6 Hz), 8.73 (1H, d, J = 6 Hz), 9.32 (1H, s), 9.42 (1H, s).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.76; N, 15.72. Found: C, 67.48; H, 4.76; N, 15.69.

Acknowledgement.

We are grateful to Professor Eisaku Hayashi, Shizuoka College of Pharmacy, for donating of the authentic sample and spectral data of 2-phenylpyrido[3,4-*b*]pyrazine.

REFERENCES AND NOTES

(1) A. Rosowsky and K. K. N. Chen, *J. Org. Chem.*, **38**, 2073 (1973).

(2) S. Kano, S. Shibuya, and Y. Yuasa, *J. Heterocyclic Chem.*, **17**, 1559 (1980).

(3) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965); **4b** and **4c** were also prepared by this method and used without purification.

(4) C. Iijima, K. Honda, and E. Hayashi, Abstract of 102th Annual Meeting of Pharmaceutical Society of Japan, April 3, 1982, Osaka, Japan, p 442.

(5) The authentic sample of **5a** was kindly donated from Professor E. Hayashi, and spectral data were taken under the same conditions as our sample for their comparison.