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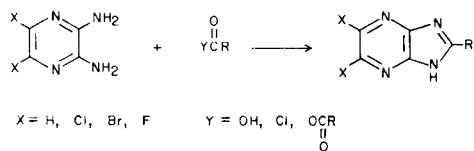
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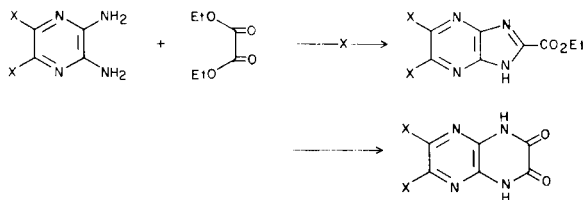
Methods for the preparations of 1*H*-imidazo[4,5-*b*]pyrazine-2-carboxylic acid and derivatives are reported.

J. Heterocyclic Chem., **17**, 381 (1980).

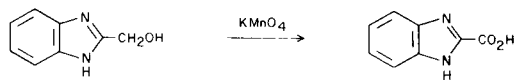
In Part I of this series, we reported the preparation of 2-alkyl-1*H*-imidazo[4,5-*b*]pyrazines by condensing diaminopyrazines with acids, acid chlorides or acid anhydrides.



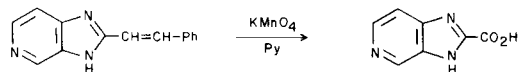
Where R is carboxylic acid or derivative thereof, the formation of a pyrazino[2,3-*b*]pyrazine ring resulted (2). We are not aware of any 1*H*-imidazo[4,5-*b*]pyrazine-



-2-carboxylic acid or derivatives thereof in the literature. Benzimidazole-2-carboxylic acid was prepared by permanganate oxidation of the corresponding 2-hydroxymethyl compound (3a,b).

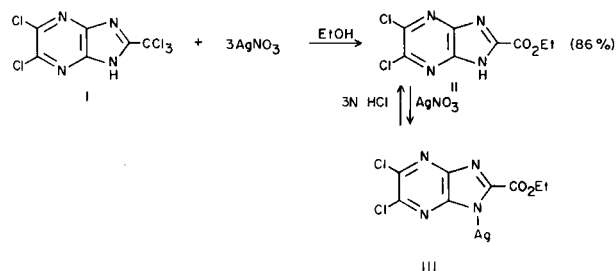


1(or 3)*H*-Imidazo[4,5-*c*]pyridine-2-carboxylic acid was obtained by permanganate oxidation in pyridine of the 2-styryl compound (4).

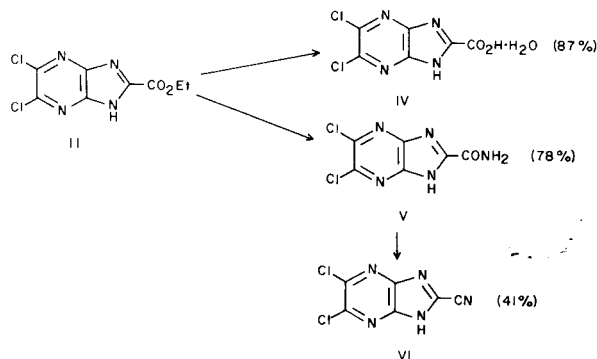


2-Trichloromethyl-1*H*-imidazo[4,5-*b*]pyrazine, I, was on hand from earlier work. Attempted acid or base hydrolysis failed to convert the trichloromethyl group to the corresponding carboxylic acid. Silver nitrate in ethanol did give the ethyl ester, II, in good yield (86%). Care had to be taken to keep the ratio of silver nitrate to trichloromethyl compound to slightly less than three. An

excess of silver nitrate converted the product to a solid silver compound, III, which was insoluble in alcohol. It was reconverted to the desired compound by 3*N* hydrochloric acid.



The ester was converted to the acid (IV), amide (V) and nitrile (VI) by normal procedure.



As the methyl group can be chlorinated to the trichloromethyl group with ease this procedure offers an alternate way to carboxylates as opposed to direct oxidations.

EXPERIMENTAL

Ethyl 5,6-Dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-carboxylate (II).

In a flask protected from light were mixed 50.9 g. (0.17 mole) of 5,6-dichloro-2-trichloromethyl-1*H*-imidazo[4,5-*b*]pyrazine (I), 85 g. (0.5 mole) of silver nitrate and 500 ml. of absolute ethanol. The whole was heated to reflux for 10 hours while being stirred with a mechanical stirrer. At the end of the reaction period, the mixture was allowed to cool to 70° and filtered. The filtrate was poured into 1.5 kg. of ice, stirred well and filtered. The solid,

after drying in a vacuum oven at 55°, weighed 37.5 g. (86%), m.p. 171-172°; ir: 1745 cm⁻¹ (CO₂Et).

Anal. Calcd. for C₈H₆Cl₂N₄O₂: C, 36.8; H, 2.3; N, 21.5. Found: C, 36.7; H, 2.1; N, 21.4.

5,6-Dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-carboxylic Acid (IV).

In 80 ml. of water was dissolved 2.4 g. (60 meq.) of sodium hydroxide. To this caustic solution was added 5.7 g. (22 mmoles) of ester II, and the reaction mixture warmed on a steam bath. After the ester dissolved, the solution was filtered and the filtrate acidified with acetic acid. The solid collected showed an ir spectrum typical of a carboxylic acid salt. (1625 and 1650 cm⁻¹). The solid was stirred in 3*N* hydrochloric acid and filtered to give 4.8 g. (87%) of the carboxylic acid monohydrate, m.p. 223-224°.

Anal. Calcd. for C₆H₂Cl₂N₄O₂·H₂O: C, 28.7; H, 1.6; N, 22.3. Found: C, 28.7; H, 1.9; N, 22.2.

5,6-Dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-carboxamide (V).

A mixture of 13.0 g. (0.05 mole) of ester II and 300 ml. of concentrated ammonium hydroxide was stirred at room temperature overnight. The solid was collected by filtration, washed with 3*N* acetic acid and water and dried to give 9.1 g. (78%) of the amide, m.p. 333-335°; ir: 1690 cm⁻¹ (CONH₂).

Anal. Calcd. for C₆H₃Cl₂N₅O: C, 31.1; H, 1.3; N, 30.2.

Found: C, 31.1; H, 1.6; N, 29.6.

5,6-Dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-carbonitrile (VI).

To 100 ml. of phosphorus oxychloride was slowly added 5.8 g. (0.025 mole) of amide V. The whole was heated gently until all the solid dissolved, and then heated to reflux for 2 hours. The excess of phosphorus oxychloride was removed under reduced pressure and the residue was washed with dichloromethane. Recrystallization from ethanol yielded 2.2 g. (41%) of nitrile, m.p. 238°; (DTA) ir: 2250 cm⁻¹ (CN).

Anal. Calcd. for C₆HCl₂N₅: C, 33.7; H, 0.5; N, 32.7. Found: C, 33.7; H, 0.8; N, 32.3.

REFERENCES AND NOTES

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- (5) This work was partially supported by the National Cancer Institute under contract No. N01-CM-12313.