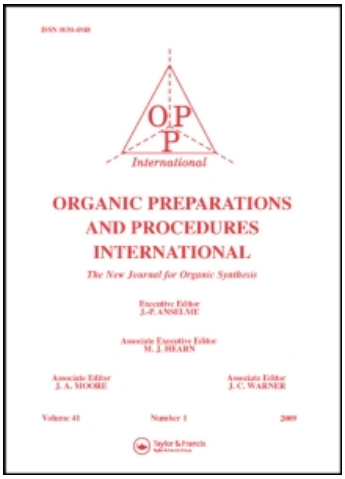

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AN IMPROVED SYNTHESIS OF 5-METHYLPYRAZINE-2-CARBOXYLIC ACID

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AN IMPROVED SYNTHESIS OF 5-METHYLPYRAZINE-2-CARBOXYLIC ACID

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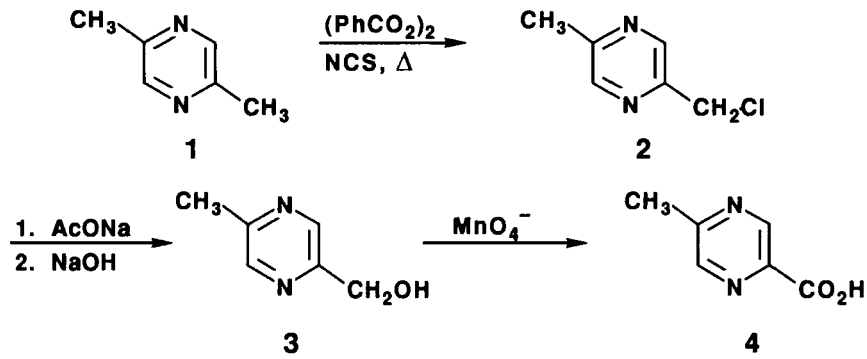
5-Methylpyrazine-2-carboxylic acid (4) is known to be an intermediate[1,2] in the synthesis of Glypizide (Minidiab). This drug is structurally related to the latest generation of sulfonylurea derivatives and is used in the treatment of insulin-independent diabetes.[3] The known route to 4 involves the oxidation of 2,5-dimethylpyrazine (1) with H_2O_2 to mono-N-oxide 5[4] which with Ac_2O, gave 2-acetoxymethyl-5-methylpyrazine (6). Hydrolysis of 6 with aqueous alkali yielded 2-hydroxymethyl-5-methylpyrazine (3).[5] Oxidation [6] of 3 with aqueous $KMnO_4$ afforded acid 4 in 18% yield from 1. Recently, the electrochemical oxidation of 1 was reported[7] to afford 4 in low yield (28%). We now report a modified procedure for the preparation of 4.

Free-radical chlorination of 1 with N-chlorosuccinimide in the presence of benzoyl peroxide as initiator[8,9] afforded 2-chloromethyl-5-methylpyrazine (2) in 80% yield. Refluxing a mixture of 2 and anhydrous NaOAc in absolute EtOH under argon gave acetoxymethyl derivative 6 (GLC yield



90%), which without isolation was treated with solid NaOH to produce alcohol 3 in yields as high as 85%. Oxidation of 3 with $KMnO_4$[6] gave (after acidification) the desired acid 4 in 47% overall yield from 1. The increased yield of 4 using the present method is due mainly to the exclusion of the low yield (33%)[5] transformation of N-oxide 5 to 6.

EXPERIMENTAL SECTION

Melting points were measured on a Boetius apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker WH-90/DS instrument using DMSO-d_6 as solvent and Me_4Si as internal standard. Mass spectra were registered on a AEI MS-50 (70 eV) apparatus. GLC analysis was carried out on a Chrom-42 instrument with a flame-ionization detector using a glass column (2.4 m x 3 mm) packed with 10% SE-30 + 2.5% Reoplex-400 on Chromosorb W-AW (60-80 mesh) at 180°. Helium (60 ml/min) was used as carrier gas. 2,5-Dimethylpyrazine, N-chlorosuccinimide and benzoyl peroxide were Fluka products.

5-Methylpyrazine-2-carboxylic acid (4).- To a solution of 2,5-dimethylpyrazine (1.08 g, 10 mmol) in CCl_4 (25 ml) were added N-chlorosuccinimide (1.33 g, 10 mmol) and benzoyl peroxide (48.4 mg, 0.2 mmol). The mixture was refluxed under an argon atmosphere, then cooled to 0° for 3-4 hrs; the succinimide was collected and washed with cold CCl_4 (60 ml). The filtrate was evaporated in vacuo to give a residue which was dissolved in absolute EtOH (20 ml). Anhydrous NaOAc (0.72 g) was added and the mixture was refluxed under argon with stirring. Finely powered NaOH (0.32 g) was added and the mixture was stirred for 10 min. After completion of the reaction (GLC control), ether (40 ml) was added; the precipitated solid was collected and washed with ether (100 ml). The combined filtrate was evaporated in vacuo, hexane (5 ml) was added and the mixture was cooled to 0° for 5-6 hrs. The solution was decanted, hexane was distilled and the residue dissolved in water. Aqueous $KMnO_4$ (1.3 g in 20.5 ml) was added dropwise for 40 min to this solution with stirring (the temperature must not exceed 25°); stirring was continued for an additional 30 min. The precipitated MnO_2 was collected and washed with hot (90°) water (70 ml). The aqueous solution was concentrated to 3-5 ml, acidified at 0-5° with conc. HCl to pH 2.0. The residue was allowed to stand

at 0° for 10-12 hrs. The precipitate was collected, washed with ice-cold water (10 ml) and dried in vacuo over P_2O_5 to give 4 (0.68 g, 47% yield from 1), mp. 165°, lit.[6] mp. 163-167°; ^1H NMR: δ 2.59 (s, 3H, CH_3), 8.68 (br s, 1H, 6-H), 9.06 (d, 1H, J = 1.8 Hz, 3-H); MS: m/z (rel. abundance, %)): 138 (M^+, 26), 120 (5), 94 (21), 93 (8), 86 (14), 66 (11), 57 (11), 44 (14), 43 (10), 42 (28), 41 (11), 39 (15), 30 (83), 29 (100). As acid 4 darkens rapidly in air, it should be kept in sealed evacuated ampoules.

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