HOMOLYTIC ACETYLATION OF 2,5-DIMETHYLPYRAZINE

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2,5-Dimethylpyrazine prepared by the method described in the literature was acetylated by means of acetaldehyde, *tert*-butylhydroperoxide and ferrous sulfate. 2,5-Diacetyl-3,6-dimethylpyrazine and 2-acetyl-3,5,6-trimethylpyrazine were obtained. The structure of the products was confirmed by NMR and mass spectral data, and the compounds were screened for biological activity using 20 different screens. No interesting biological activity was found.

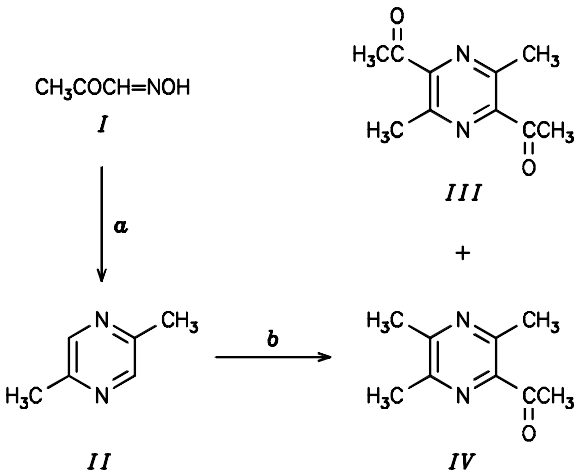
The inductive effect of the ring nitrogen atoms and the resonance structures cause a positive charge on the ring carbon atoms, and thus pyrazine does not undergo direct substitution by electrophilic reagents. Various ring substituted pyrazine derivatives can, however, be obtained by homolytic substitution reactions[1–7]. Homolytic acylation of pyrazine has been studied by Caronna et al.[5]. Acyl radicals were generated from an aldehyde using redox system *tert*-butylhydroperoxide/ferrous sulfate. The reaction was carried out in water containing acetic and sulfuric acids, and the corresponding diacyl derivative was formed as the main product. Houminer and co-workers[1] used a slightly modified procedure eliminating acetic acid from the reaction mixture, and obtained the monoacyl pyrazine as the major product. In addition, small amounts of the corresponding diacyl and alkylated products were also detected. Acyl radicals can also be generated by Ag-catalyzed decarboxylation of α-keto acids by persulfate[6,7]. In this paper, we report on the results of homolytic acetylation of 2,5-dimethylpyrazine, which to our knowledge has not been studied so far.

A modification of Charrier's method[8,9] was used to prepare the starting material 2-oxopropanal-1-oxime (*I*). 2,5-Dimethylpyrazine (*II*) was obtained according to Kastron et al.[10] and acetylated using the procedure described by Houminer and co-workers[1,2]. An equivalent amount of 80% *tert*-butylhydroperoxide in di-*tert*-butylhydroperoxide was used. The addition of *tert*-butylhydroperoxide and ferrous sulfate to the reaction mixture required 75 min instead of 15 min as mentioned in the literature[1,2]. The reaction

mixture contained unreacted 2,5-dimethylpyrazine and three new products. Two of them reacted positively with 2,4-dinitrophenylhydrazine. These two compounds were separated by means of column chromatography and identified as 2,5-diacetyl-3,6-dimethylpyrazine (*III*) and 2-acetyl-3,5,6-trimethylpyrazine (*IV*, Scheme 1).

Both substances were described in the literature previously. Compound *III* was isolated during studies aimed at the synthesis of pyrroles[11–13] and guanidino-β-diketones[14]. Condensation of the pyrazine ring from aliphatic precursors was used in these studies. Compound *IV* was prepared by the Grignard reaction between 3,5,6-trimethyl-2-pyrazinecarbonitrile and methylmagnesium bromide[15]. NMR spectroscopy and mass spectrometric data of these compounds have not been reported previously.

The ^{1}H NMR spectra of compounds *III* and *IV* show absence of signals between δ 6–10 ppm indicating substitution on carbons 2 and 5 of both compounds. The symmetry of structure *III* is reinforced by the observation of only half the number of expected proton and carbon signals in the ^{1}H and ^{13}C NMR spectra, respectively. The assignment of ^{1}H and ^{13}C absorptions was assisted by the use of 2D H,C-COSY spectra, and also from comparison of the reported[16] ^{13}C NMR chemical shifts of pyrazine and methylpyrazine. The ^{1}H NMR spectrum of *IV* showed the presence of four methyl signals (δ 2.69, 2.74, 2.56 and 2.57 ppm). From the 2D H,C-COSY spectrum only one of these (δ 2.69 ppm) corresponds to that for an acetyl methyl group. Hence, the second group substituted

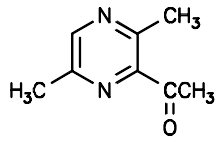


a) 1. $SnCl_2$, HCl; 2. NaOH, Δ; 3. [O]; *b*) CH_3CHO, 80% *tert*-butylhydroperoxide, $FeSO_4$, H_2SO_4

SCHEME 1

onto the pyrazine ring must be methyl. Further confirmation was obtained from MS analysis which gave a molecular ion of 164.0989 (M^+).

The absence of 2-acetyl-3,6-dimethylpyrazine (*V*) in the reaction mixture obtained under the conditions described in the present paper is rather surprising. It may be possible to obtain this compound by homolytic acetylation using α-keto acid as a source of the acyl radical[6,7].



V

The compounds obtained are pyrazine analogues of ring substituted acetophenone. As some acetophenone derivatives show antirheumatic[17] and antiasthmatic[18] activity, both the isolated products were screened against a variety of different therapeutic targets. The final assay concentrations ranged from 2–40 μg/ml. None of the compounds exhibited any activity.

EXPERIMENTAL

The analytical TLC was carried out on silica gel plates Silufol UV 254 (Kavalier, Votice) using petroleum ether–ethyl acetate mixture 80 : 20 (v/v) as eluent. Silpearl (Kavalier, Votice) was used for flash column chromatography. Melting points were determined with Boetius apparatus and are uncorrected. Elemental analyses were performed with CHN analyzer (Laboratory Instruments, Prague). Infrared spectra were measured in KBr pellets with Perkin–Elmer 577 IR Spectrophotometer; wavenumbers are given in cm^{-1}. ^1H and ^{13}C NMR spectra (δ, ppm) were recorded at room temperature in $CDCl_3$ in 5 mm tubes with a JEOL GSX-270 (^1H, ^{13}C) FT spectrometer at 270.16 (^1H) and 67.97 (^{13}C) MHz, using the deuterium signal of the solvent as the lock and Me_4Si as internal standard. The parameters were: spectral width 3 kHz (^1H) and 18 kHz (^{13}C), pulse width 3 μs (^1H) and 4.2 μs (^{13}C) (ca 40 and 45° flip angle, respectively), acquisition time 5.46 or 0.90 s, number of scans 16 (^1H) and 600 (^{13}C) and computer memory 32 K. Mass spectra were measured on a JEOL JMS-DX303 mass spectrometer.

Homolytic Acetylation of 2,5-Dimethylpyrazine

To a stirred mixture of 2,5-dimethylpyrazine (7.4 g, 0.07 mol) and freshly distilled acetaldehyde (18.5 g, 0.42 mol) in 35 ml 3.4 M sulfuric acid at 5 °C, 80% *tert*-butylhydroperoxide (33.1 g, 0.294 mol) and a solution of ferrous sulfate heptahydrate (116.9 g, 0.42 mol) in 350 ml water were added concurrently over 75 min. The resulting mixture was stirred for an additional 1 h. During this time the temperature increased to 15 °C. A saturated solution of sodium sulfite was added until a test with starch-iodide paper was negative. The mixture was then continually extracted with dichloromethane. The organic extract was washed with water, dried (anhydrous Na_2SO_4) and evaporated under reduced pressure. From the residue, two compounds were isolated by means of repeated column chromatography on silica gel using petroleum ether–ethyl acetate mixture 80 : 20 (v/v) as the eluent.

2,5-Diacetyl-3,6-dimethylpyrazine (III). Crystallization from ethanol, sublimation at 60–70 °C/1.73 kPa afforded yellow needles, R_F 0.82, yield 1 g (7.6%), m.p. 98.5–99.5 °C (refs[13,14] 97–98 °C or refs[11,12] 101 °C). For $C_{10}H_{12}N_2O_2$ (192.2) calculated: 62.49% C, 6.29% H, 14.57% N; found: 62.05% C, 5.92% H, 14.97% N. IR spectrum: 3 015, 2 945 (CH aliph.); 1 690 (CO); 1 420, 1 390, 1 365, 1 265, 1 200, 1 125, 970. ^{1}H NMR spectrum: 2.72 s, 6 H ($OCCH_3$); 2.80 s, 6 H (CH_3). ^{13}C NMR spectrum: 27.7 ($OC\mathbf{C}H_3$), 201.7 ($O\mathbf{C}CH_3$), 22.9 (CH_3), 146.6 (C-2 and C-5), 149.9 (C-3 and C-6). Mass spectrum, *m/z* (%): 192.9854 (M^+, $C_{10}H_{12}N_2O_2$, 100), 149.97290(40).

2-Acetyl-3,5,6-trimethylpyrazine (IV). Sublimation at 45–55 °C/1.73 kPa gave cream coloured leaflets, R_F 0.43, yield 1 g (8.9%), m.p. 57–60 °C (ref.[15] 61–62 °C). IR spectrum: 2 990, 2 950 (CH-aliph.); 1 685 (CO); 1 535, 1 417, 1 365, 1 305, 1 250, 1 200, 1 180, 1 120, 970. ^{1}H NMR spectrum: 2.69 s, 3 H ($OCCH_3$); 2.74 s, 3 H (3-CH_3); 2.56 and 2.57 s, 2 × 3 H (5- and 6-CH_3). ^{13}C NMR spectrum: 27.8 ($OC\mathbf{C}H_3$), 201.7 ($O\mathbf{C}CH_3$), 23.0 (3-CH_3), 21.5 and 22.2 (5- and 6-CH_3), 143.5 (C-2), 148.4 (C-3), 154.4 (C-5), 150.4 (C-6). Mass spectrum, *m/z* (%): 164.0989 (M^+, $C_9H_{12}N_2O$, 100), 121.0873 (96).

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