

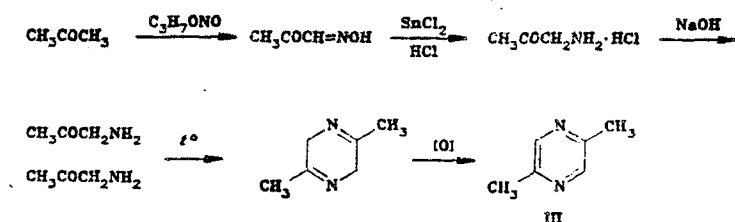
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The classical method for obtaining 2,5-dimethylpyrazine by cyclization of aminoacetone has been improved by use of ammonium persulfate in place of mercuric chloride in the stage of catalytic oxidation of 2,5-dimethyldihydropyrazine. Catalytic vapor phase oxidation of 2,5-dimethylpyrazine gave 5-methylpyrazine-2-aldehyde and pyrazine-2,5-dialdehyde.

5-Methylpyrazine-2-aldehyde (I) and pyrazine-2,5-dialdehyde (II) are starting materials for synthesis of bioactive substances, [1-3] but satisfactory methods for their preparation are not available. Thus aldehyde II (as the bisphenylhydrazone) is obtained in only 12% yield by a four-stage synthesis from 2,5-dimethylpyrazine [4].

We propose a single-stage method for synthesis of pyrazine aldehydes I and II by catalytic vapor phase oxidation of 2,5-dimethylpyrazine (III) using atmospheric oxygen with vanadium-molybdenum oxide catalysts [5]. In this connection an improvement of the literature methods for synthesis of III was needed. The most widely reported procedure is the self condensation of α -aminoacetone to 2,5-dimethyldihydropyrazine which can then be oxidized to the desired product [6], usually using mercuric chloride [7, 8] or hydrogen peroxide [9]:



With the aim of excluding toxic reagents and of increasing the yield of III we have studied the use of compounds possessing a higher oxidation potential than HgCl_2 (see Table 1).

The maximum yield of III was found when ammonium persulfate, which has the highest standard oxidation potential (+2.01 V, [10]) of all the compounds studied in the given reaction, was used as the oxidant. The yield of III (Table 1) was determined by GLC analysis of the products of oxidation of 2,5-dimethyldihydropyrazine following steam distillation.

Various solvents were checked for extraction of III from the distillate (ether, chloroform, benzene), but the best results were obtained with methylene chloride (98-99% recovery of III from the distillate).

Pyrazine III underwent oxidation by atmospheric oxygen at raised temperature in the presence of vanadium-molybdenum oxide catalysts. Optimum conditions were established using a microcatalytic reactor (volume 1 ml). The products were prepared in a flowthrough reactor (volume 25 ml). A pulsed microcatalytic method with chromatographic analysis was used to study the effects of temperature (300-450°C), contact time (0.05-0.30 sec), and atom V:Mo catalyst ratio on the oxidation of III. The procedure was analogous to that described in [11], the catalysts being vanadium and molybdenum oxides and their mixtures (Table 2). The physicochemical characteristics of the catalysts are given in [12].

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TABLE 1. Dependence of Yield of 2,5-Dimethylpyrazine (III) on Oxidant (based on Acetone oxime)

Oxidant	Yield of III, %
FeCl ₃ · 6H ₂ O	31
CuCl ₂ + KI	20
HgCl ₂	47
KMnO ₄	24
H ₂ O ₂	30
(NH ₄) ₂ S ₂ O ₈	56

TABLE 2. Catalytic Oxidation of 2,5-Dimethylpyrazine

Catalyst content (% molar)			atom ratio V:Mo	T, °C	Contact time, s	Conversion, %	Yield, % (based on III)			
V ₂ O ₅	MoO ₃	passed through					converted			
		I					II	I	II	
100	0			360	0,1	52	17	15	33	29
				400	0,1	62	8	10	13	16
				400	0,3	86	6	11	7	13
				420	0,1	75	7	9	9	12
				445	0,1	80	6	7	7	9
60	40	3:1		360	0,1	60	15	11	25	18
				300	0,1	27	11	11	41	41
33,3	66,7	1:1		335	0,1	43	25	15	48	35
				360	0,1	50	25	23	50	46
				405	0,1	75	23	21	30	28
				360	0,1	43	15	19	35	44
14	86	1:3		360	0,1	41	13	8	32	19
				8	92	1:6	400	0,1	62	10
0	100			400	0,3	81	8	7	10	8

Under the studied conditions the degree of conversion of pyrazine III amounted to 40-90%. The partial oxidation products were the pyrazine aldehydes I and II which were formed in approximately equal amounts. Their total yield reached 48 mole % (based on pyrazine III passed through) with selectivity up to 96% (based on converted pyrazine). Pyrazine-2-aldehyde was also formed in small quantities (up to 5%). The optimal conditions for formation of aldehydes I and II were a temperature of 335-360°C and contact time of 0.1 sec. Under milder conditions the conversion of III was small, and increasing the temperature and contact time led to formation of higher oxidation products (CO, CO₂, NO, NO₂). Optimal yields of aldehydes I and II were achieved using equal (ionic) quantities of V and Mo catalysts (Table 2).

For the aldehyde preparation a catalyst was prepared by application of the active phase of the determined composition onto corundum (an inert carrier with a small specific surface area of less than 0.1 m²/g). The following results were obtained under optimal conditions (see experimental): 56% conversion of starting pyrazine; 21 and 10% yields respectively of aldehydes I and II.

EXPERIMENTAL

GLC analysis was carried out on a Chrom-4 instrument with flame ionization detector using a glass column (2.4 m × 3 mm) filled with 10% silicone elastomer E-301 and 2.5% Reoplex-400 on chromosorb W-AW (60-80 mesh). The carrier gas was helium or air (60 ml/min) and the operating temperature 120-150°C. PMR Spectra were taken on a Bruker WH-90/DS (90 MHz) instrument and mass spectra on a Kratos MS-25 (70 eV) chromatography-mass spectrometer and on an MS-50 (70 eV) mass spectrometer.

2,5-Dimethylpyrazine. Acetone oxime (17.4 g, 0.2 mole) was added in small portions to a mixture of stannous chloride (90 g, 0.4 mole) and conc. HCl (130 ml). The reaction flask was cooled with iced water, and water (200 ml), NaOH (25%, 380 ml), and ammonium persulfate (64 g, 0.28 mole) were added in turn. After standing for 2 h it was steam distilled to give 250 ml of distillate which was extracted with methylene chloride (4 × 150 ml). The extracts were dried (anhydrous sodium sulfate) and evaporated in vacuo. Distillation at normal pressure gave a fraction boiling at 153-156°C (lit. bp 153.5-155°C [8]). Yield 6.65 g (56%). PMR Spectrum (CDCl₃, TMS): 2.50 (s, 6H, CH₃), 8.25 ppm (s, 2H, ring protons). Mass spectrum, m/z (peak intensity, %): 108 (M⁺, 60), 81 (12), 42 (100), 41 (27).

5-Methylpyrazine-2-aldehyde and Pyrazine-2,5-dialdehyde. A flowthrough catalytic reactor was charged with 15 ml of catalyst consisting of a mixture of V₂O₅ and MoO₃ (V:Mo = 1:1) loaded at 10% level on corundum granules of diameter ~5 mm. A stream of air (40 liter/h) was passed through, the catalyst heated to 360°C and a 5% aqueous solution of pyrazine III was introduced (72 ml/h) with a peristaltic pump. (The reaction mixture was diluted with water to suppress heating of the catalyst due to the exothermic reaction.) At the reactor exit the organic reaction products and water were condensed in an ice-cooled trap. The experiment was continued for 6 h and 380 ml of catalyzate was collected. The organic materials were extracted with ether with GLC monitoring of the completeness of the extraction. The extracts were dried (anhydrous magnesium sulfate), the ether removed, and the residue vacuum distilled. The first fraction (10 g, bp 20-25°C, 1 mm Hg) was pyrazine III which was returned to the oxidation process. The second fraction (4.5 g, bp 38-40°C, 1 mm) was aldehyde I (mp 10-15°C, n_D²⁰ 1.536). PMR Spectrum (CDCl₃, TMS): 2.69 (s, 3H, CH₃), 8.60 (s, 1H, ring proton), 9.04 (s, 1H, ring proton), 10.11 ppm (s, 1H, CHO). Mass spectrum (peak intensity, %): 122 (M⁺, 100), 94 (66), 93 (33), 67 (43), 66 (41), 53 (40), 52 (33), 42 (47), 40 (42).

Recrystallization of the residue from dioxane gave aldehyde II (2 g, mp 96-98°C, mp of bisphenylhydrazone 265°C, lit. mp 266°C [4]). PMR Spectrum (DMSO-d₆): 9.25 (s, 2H, ring protons), 10.53 ppm (s, 2H, CHO). Mass spectrum, m/z (peak intensity, %): 136(M⁺, 96), 108 (67), 80 (13), 79 (23), 54 (13), 53 (75), 52 (100).

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