DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

CATALYTIC SYNTHESIS OF PYRAZINAMIDE FROM 2,5-DIMETHYLPYRAZINE

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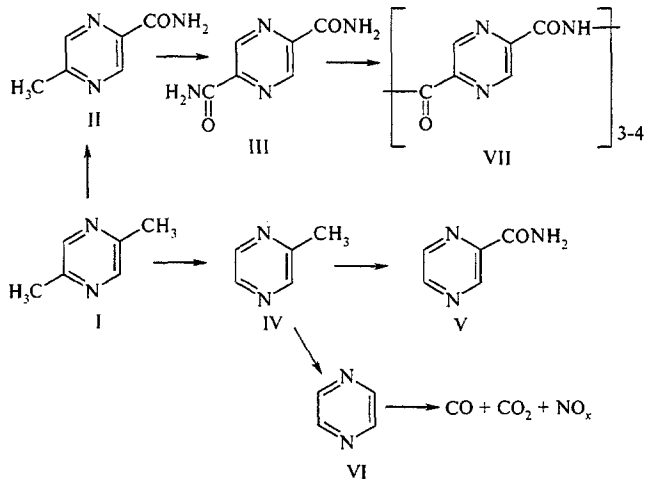
Compounds of the pyrazine series, including pyrazinecarboxylic acid amides, are widely used in the production of various drugs. One of the well known compounds in this series is 2-pyrazinecarboxylic acid amide, known as the antituberculous drug pyrazinamide. We have established that this drug can be synthesized with a high yield by oxidative ammonolysis of 2-methylpyrazine [1]. It was found that the process, proceeding in an aqueous ammonia solution, involves oxidation of the methyl group to nitrile, followed by its conversion into amide in the course of high-temperature hydrolysis. By the same token, during oxidative ammonolysis of 2,5-dimethylpyrazine (I) on a molybdenum – cerium – titanium mixed oxide catalyst, the initial compound converted sequentially into 5-methylpyrazine-2-carboxamide (II) and 2,5-pyrazinedicarboxamide (III) [2].

Below we present the results of investigation of the oxidative ammonolysis of compound I in the presence of three samples of catalysts representing a molybdenum – antimony – titanium mixed oxide system. The samples had the same molar ratio $MoO_3/Sb_2O_3 = 1 : 0.5$ and a variable relative content of TiO_2: 0.25, 0.50, and 0.75 mole TiO_2 per mole MoO_3.

Selection of this catalyst system was based on the known facts evidencing that the presence of antimony oxides markedly facilitates the oxidative ammonolysis of organic compounds [3, 4]. Antimony oxides favor the activation of oxygen supplied from the gas phase to the contact zone [5] and, under certain conditions, may generate or regenerate active centers on the surface of MoO_3, acting by a mechanism of the "remote control" type [6].

The results obtained in our experiments indicate that the oxidative ammonolysis of compound I involves both the formation of partial oxidation products and products of more profound transformations.

The oxidative ammonolysis of 2,5-dimethylpyrazine (I) with the formation of amides II and III is accompanied by the demethylation of compound I with the formation of 2-methylpyrazine (IV) and pyrazine (VI). Compound IV converts into the target 2-pyrazinecarboxylic acid amide (V). Also observed, albeit in trace amounts, was 2,5-pyrazine polyamide (VII). All the above substances were isolated from the reaction mixture and identified.



Qualitative composition of the products of oxidative ammonolysis of compound I was the same for all the three catalysts. However, the quantitative ratio of the products was markedly different, depending on the content of titanium dioxide in the sample and on the temperature (Table 1).

The first catalyst sample had the oxide component ratio $MoO_3/Sb_2O_3/TiO_2 = 1 : 0.5 : 0.25$. Study of the oxidative ammonolysis of compound I on this catalyst showed that the

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degree of conversion increased from 25 to 100% when the process temperature rose from 320 to 420°C. The main reaction product was pyrazinamide (V), the yield of which also increased in the temperature range studied to reach 76% at 420°C. Analysis of the reaction mixture revealed, besides amide V, the presence of pyrazines II, III, IV, and VI. The maximum yield of diamide III did not exceed 5 – 6%, being virtually independent of the temperature. Approximately the same pattern was observed for compound II. The yield of IV increased from 10 to 28% when the temperature rose from 320 to 380°C, but then dropped sharply to 2 – 3% as the temperature approached 420°C. The yield of compound VI permanently increased with the temperature to reach 10% at 400 – 420°C. These data indicate that the process on this catalyst sample involves a considerable contribution of oxidative demethylation, similarly to that observed previously for the oxidative ammonolysis of 2-methyl-5-ethylpyridine on a V–Ti–O catalyst system [7].

As the content of TiO_2 in the molybdenum – antimony catalyst increases, the ratio of components in the reaction mixture exhibits significant variation. The $MoO_3/Sb_2O_3/TiO_2 = 1 : 0.5 : 0.5$ catalyst sample shows a decrease in dealkylating ability, which is manifested by an increase in the yield of disubstituted products and a decrease in the contribution of the demethylation process.

TABLE 1. Yields of the Products of Oxidative Ammonolysis of 2,5-Dimethylpyrazine (I) Depending on the Reaction Temperature and the TiO_2 Content in the Catalyst

Molar ratio $MoO_3/Sb_2O_3/TiO_2$	T, C°	Yield, %					
		I	II	III	IV	V*	VI
1 : 0.50 : 0.25	320	75	2	3	10	7	1
	340	68	3	5	14	7	3
	360	47	3	5	20	11	5
	380	32	3	5	28	21	5
	400	21	3	5	15	33	10
	420	2	2	6	2	76	10
1 : 0.50 : 0.50	320	60	–	3	14	19	3
	340	40	3	4	15	23	4
	360	32	3	5	20	33	5
	380	24	5	7	15	44	4
	400	12	6	10	10	55	2
	420	4	8	12	–	65	–
	440	–	8	12	–	68	–
1 : 0.50 : 0.75	320	58	6	10	3	3	2
	340	41	10	17	2	5	2
	360	32	16	25	2	5	2
	380	20	27	34	1	5	2
	400	4	32	51	1	5	2
	420	–	20	59	–	5	1
	440	–	–	86	–	5	–

Notes: molar ratio of reagents $I/O_2/NH_3/H_2O = 1 : 10 : 15 : 75$.
* Pyrazinamide.

For the $MoO_3/Sb_2O_3/TiO_2 = 1 : 0.5 : 0.75$ sample, the main products are compounds II and III, the yields of which increase with the temperature in the interval 320 – 400°C to reach 32 and 51%, respectively. As the temperature grows further to 440°C, monoamide II intensively converts into diamide III and the yield of the latter product approaches 90%. The proportion of the products of complete or partial demethylation on this catalyst does not exceed 3 – 5%, being virtually independent of the reaction temperature.

Thus, by controlling the composition of the Mo–Sb–Ti oxide mixed catalyst through variation of the TiO_2 content, the process of oxidative ammonolysis of compound I on this system can be directed toward predominant formation of amides III or 'V, with the main product yield reaching 80% (Table 1).

It should be noted that diamide III exhibits bacteriostatic activity *in vitro* with respect to mycobacteria of the Academia human tuberculosis type [8]. The antituberculous activity of this compound was also confirmed by experiments *in vivo*.

EXPERIMENTAL CHEMICAL PART

The molybdenum – antimony – titanium catalysts were prepared by mixing the corresponding oxides, followed by fusing the mixture at 900°C in a muffle furnace. Upon cooling, the fused mass was crushed and a 3.0 – 3.5 mm fraction was separated for experiments.

The initial compound I was synthesized from 1-amino-2-propanol as described in [9].

Oxidative ammonolysis of 2,5-dimethylpyrazine (I). The reaction was conducted in a quartz reactor of the flow type having a diameter of 20 mm and a volume of 25 cm^3. The process temperature was varied in the range 320 – 440°C. The molar ratio of components $I/NH_3/O_2/H_2O$ was controlled within the limits 1:(10 – 20):(10 – 15):(75 – 80). A mixture of compound I with an aqueous ammonia solution was supplied at a rate of 800 – 960 liter/h per liter catalyst, and air was supplied at 325 – 475 liter/h per liter catalyst. The contact time in this flow regime is about 0.6 – 0.9 sec.

The reaction products condensed in the collecting system were extracted with methylene chloride. The extract was dried and the solvent distilled off, after which the product mixture was dissolved in water and purified from gummy impurities by chromatography on a column filled with activated charcoal of BAU grade. The products were analyzed and identified by methods of IR spectroscopy (UR-20 spectrophotometer, Germany), high-performance liquid chromatography (HPC chromatograph, Czech Republic) in a column filled with Separon SGC and eluted with a methanol – water system (7 : 3), and ebulliography (EP-76 ebullioscope, Russia).

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