HETEROGENEOUS-CATALYTIC FISCHER REACTION

IV.* CATALYTIC SYNTHESIS OF 7-AZAINDOLE AND 2-METHYL-7-AZAINDOLE IN THE PRESENCE OF γ-Al_2O_3

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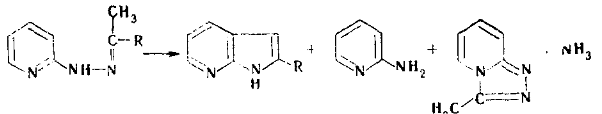
The catalytic synthesis of 7-azaindole and its 2-methyl derivative has been accomplished for the first time by cyclization of acetaldehyde and acetone 2-pyridylhydrazones in the presence of γ-Al_2O_3 and fluorinated aluminum oxide. The temperature dependence of the yields of reaction products – azaindoles and 2-aminopyridine – was studied. The cyclization of acetaldehyde 2-pyridylhydrazone proceeds under more severe conditions. The maximum yield of 7-azaindole is 15% at 450° on fluorinated aluminum oxide. The yield of 2-methyl-7-azaindole reaches 50% at 315°. Fluorinated aluminum oxide displays higher catalytic activity.

The cyclization of acetaldehyde and acetone 2-pyridylhydrazones under the conditions of the Fischer reaction with the application of acid catalysts causes considerable difficulties and does not lead to the production of 7-azaindole and its 2-methyl derivative [2, 3]. Negative results were obtained in the thermal indolyzation of acetone 2-pyridylhydrazone [4].

We first accomplished the catalytic synthesis of indole in 60% yield in the gas phase by cyclization of acetaldehyde phenylhydrazone on γ-Al_2O_3, and we determined the optimum conditions for carrying out this reaction [5-8].

In the present paper we have studied the possibility of the use of this method for the synthesis of 7-azaindole and 2-methyl-7-azaindole. It was found that the reaction with acetaldehyde (Ia) and acetone (Ib) 2-pyridylhydrazones proceeds ambiguously: 2-aminopyridine (III) and a product of cyclization at the pyridine nitrogen – 3-methyl-s-triazolo[4,3-*a*]pyridine (IV) – are formed along with the corresponding 7-azaindoles (IIa, b).



I a, ba   II a, b   III   IV

a R=H; b R=CH$_3$

The temperature dependence of the yield of products of the catalytic cyclization of the 2-pyridylhydrazones is presented in Fig. 1. Since IIa is obtained in very insignificant amounts on γ-Al_2O_3, fluorinated aluminum oxide, which is more active in the cyclization of acetaldehyde phenylhydrazone, was used to

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*See [1] for communication III.

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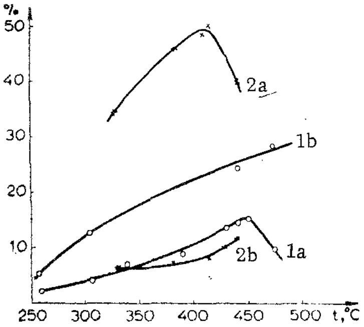

Fig. 1. Temperature dependence of the yield of products of the catalytic cyclization of Ia on fluorinated γ-Al_2O_3 (2.6% F) [1a) 7-azaindole (IIa); 1b) 2-aminopyridine (III)] and of Ib on γ-Al_2O_3 [2a) 2-methyl-7-azaindole (IIb); 2b) 2-aminopyridine (III)].

synthesize it. The amount of III increased as the temperature was raised and surpassed the yield of IIa. Cyclization of Ib to give 50% yields of IIb was accomplished in the presence of γ-Al_2O_3 (curves 2a and 2b) at 420°, and the amount of III formed was considerably lower than in the cyclization of Ia. This is explained by the lower thermal stability of the latter. The maximum yield of IIb is achieved at 315° when fluorinated aluminum oxide is used.

Two methods were used to separate and isolate the products from the catalyzates obtained in the cyclization of Ia, b – partition chromatography on aluminum oxide and preparative gas-liquid chromatography. The first method was used to isolate IIb in yields up to 35% (from the results of the analysis, the maximum yield is 50%). Since the cyclization of Ia proceeds with considerably greater difficulty, and the maximum yield of IIa, according to analysis, is 15%, it could not be isolated by partition chromatography on aluminum oxide. In this connection, a preparative method involving the use of GLC (see the Experimental section) was developed to isolate IIa from the products of the cyclization of Ia.

EXPERIMENTAL

The catalytic experiments were carried out in a vertical apparatus of the flow type at atmospheric pressure with automatic feeding of the benzene solution of the appropriate hydrazone in a stream of helium.

The catalysts used were aluminum oxide prepared by the Angarsk Petrochemical Combine and fluorinated aluminum oxide containing 2.6% fluorine.* Prior to the experiments the catalysts were activated in a stream of dry air for 6 h at 600° (for γ-Al_2O_3) and at 500° (for the fluorinated sample). Compounds Ia, b were first purified by recrystallization from hexane. The purity of the starting materials was checked by chromatography.

Benzene solutions (7%) of Ia (mp 69-71°) or Ib (mp 72-73°) were passed at a rate of 0.3 ml/min through a layer of heated catalyst (g 1.2 g, V 2 ml, particle diameter 0.2 mm). The helium flow rate was 60 ml/min. The reaction was studied over a broad temperature range from 250 to 500°.

Analysis of the Catalyzates. The catalyzates were analyzed by GLC with a Tswett-3 chromatograph with a column 2 m long and 3 mm in diameter packed with Porovina. The liquid phase was polyethylene glycol adipate (4 wt. %), the column temperature was 160°, the carrier gas was helium, and the flow rate was 46 ml/min.

Isolation of the Reaction Products. Two methods were used to isolate the products. In the first case, the catalyzate was evaporated, and the mixture of products was subjected to chromatographic separation with a column filled with aluminum oxide (the separation was monitored by paper chromatography). The starting hydrazone was eluted with petroleum ether, a mixture of IIb and III was then eluted with petroleum ether–ether (1:1), after which chloroform eluted IV. The different basicities of IIb and III were used to separate these compounds: III was extracted from a mixture of IIb and III in an organic solvent (ether or benzene) with an aqueous buffer solution with pH 6.09.

Thus the following substances were isolated by partition chromatography on aluminum oxide from the catalyzates obtained in the cyclization of Ib in the presence of γ-aluminum oxide at 420°.

2-Methyl-7-azaindole (IIb). This compound had mp 132-133° (from heptane). Found: C 72.56; H 5.96; N 21.43%. $C_8H_8N_2$. Calculated: C 72.70; H 6.07; N 21.20%.

2-Aminopyridine (III). This compound had mp 56°.

3-Methyl-s-triazolo-[4,3-*a*]pyridine (IV). This compound had mp 131-132° (from ethyl acetate). Found: C 63.00, H 5.15; N 31.33%. $C_7H_7N_3$. Calculated: C 63.14; H 5.30; N 31.56%. The trihydrate of IV [9] had mp 58-59° (from benzene).

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*We take this opportunity to thank T. V. Antipina for supplying us with the fluorinated aluminum oxide for the study.

For the preparative separation of the products of the catalytic cyclization of Ia, the catalyzates obtained from several experiments were evaporated, and the mixture was fed in 0.2 ml portions with a syringe into the preparative column of a Khrom-31 chromatograph. The column (2.5 m long and 6 mm in diameter) was packed with polyethylene glycol (8 wt. %) on Cellite C-22 (60-80 mesh). The column was thermostatted at 135°, and the carrier gas (helium) flow rate was 86 ml/min. The purity of the individual fractions was monitored by chromatography on an analytical column, as previously described. Thus 7-azaindole (IIa) with mp 104-106° was isolated from the catalyzate obtained in the cyclization of Ia. The IR spectrum of the IIa that we obtained completely coincided with the spectrum of an authentic sample of this compound that was synthesized via the method in [10].

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