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Project 4-08-03-002

AD-B969 511

INTERIM REPORT

PREPARATION OF 4-BENZYLPYRIDINE

by

F. W. Hoffmann
Walter Gall

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INTERIM REPORT

This is an unedited report. It is issued to transmit urgently needed data to authorized personnel as rapidly as possible. Its conclusions are tentative and are subject to revision.

CRLIR 1
Project 4-08-03-002

PREPARATION OF 4-BENZYLPYRIDINE

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CRLIR 1
Project: 4-08-03-002

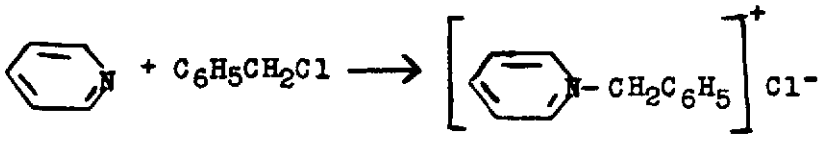
PREPARATION OF 4-BENZYLPYRIDINE.

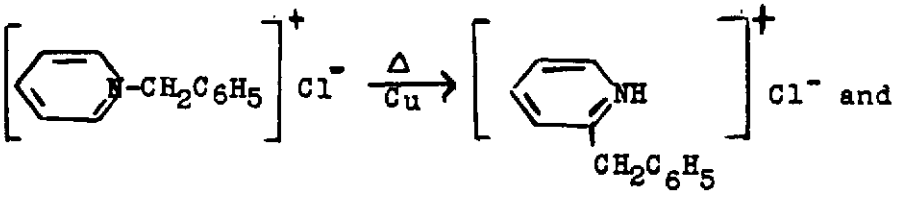
I. OBJECT.

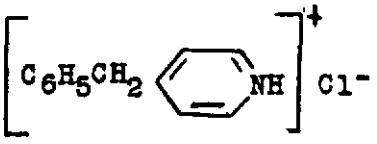
The work reported herein was done under Project 4-08-03-002, Methods for Analysis of CW Agents, in order to provide an improved method for the synthesis of 4-benzylpyridine, an intermediate in the preparation of DB3 (4-(p-nitrobenzyl) pyridine).

II. HISTORICAL.

The present procedure for the production of DB3 involves a four-step process starting from pyridine and benzylchloride. The individual steps of this process are illustrated by the following sequence of equations:

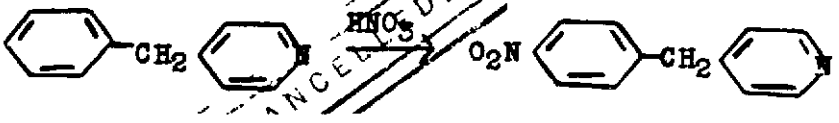
a. 

b. 



c. $\left[C_6H_5CH_2C_5H_4NH\right]^+Cl^- \xrightarrow{NaOH} C_6H_5CH_2C_5H_4N$

mixture of 2- and 4-benzyl derivative.

d. 

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The overall yield of 4-benzylpyridine by this procedure is only about 8% (based on pyridine) due to the poor yield obtained in the Ladenburg rearrangement (step b.) of the benzylpyridinium chloride. The benzyl group migrates in this reaction in preference to the 2-position of the pyridine ring, and the mixture of 2- and 4-benzylpyridine obtained in step c. has to be separated by fractional distillation. The subsequent nitration of the 4-isomer affords the desired DB3 in about 50% yield based on 4-benzylpyridine, or in an overall yield of approximately 4% based on pyridine.

The well-known reactivity of the methyl groups in α- and γ-picoline suggests the use of the commercially available γ-picoline (4-methylpyridine) as starting material for the synthesis of 4-benzylpyridine avoiding thus the undesired formation of the α-isomer.

One of several possible approaches to the synthesis of 4-benzylpyridine from γ-picoline, based on the arylation of α-picoline with bromobenzene in liquid ammonia via α-picolyl potassium (Dirstine and Bergstrom, J. Org. Chem. 11, 55-59 (1946)) appeared to be promising and was investigated, therefore, in some detail.

III. EXPERIMENTAL.

The γ-picoline used throughout this investigation was procured from Reilly Tar & Chemical Corporation.

A. Reaction of p-Picolyl Potassium and Chlorobenzene.

To 500 cc. of liquid ammonia condensed in a 1 liter 3-neck flask fitted with stirrer and air cooled condenser was added 0.1 g. of ferric oxide and 6 g. (0.15 atom) of metallic potassium, and the mixture stirred at the boiling point of the ammonia until the blue color of the dissolved potassium disappeared. To the grayish-white solution was then added slowly 14 g. (0.15 mol.) of γ-picoline, followed by 28 g. (0.25 mol.) of chlorobenzene. The resulting reaction mixture had assumed a deep purple color. A solution of potassium amide, prepared in the same manner as above in separate equipment from 6 g. of potassium and 250 cc. of liquid ammonia, was then forced through a glass tube into the purple reaction mixture and the contents of the flask stirred for 1 hour at the boiling point of the ammonia. Subsequent addition of 32 g. of solid ammonium chloride to the well stirred mixture caused decolorization. The excess ammonia was then allowed to evaporate, 100 cc. of water added to the residue to dissolve the inorganic salt, and the mixture ex-

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tracted with 100 cc. of benzene. The two layers were filtered to remove some flocculent material, the benzene layer was separated, extracted with 100 cc. of 8N HCl, the HCl extract made alkaline with strong NaOH, the oily layer taken up in benzene, washed with water, dried with solid NaOH, and the benzene removed by distillation. The brown oily residue was distilled twice at atmospheric pressure to give 3.5 g. (13.7%) of 4-benzylpyridine, as a pale-yellow oil, boiling at 260-288° (mostly at 280-282°) and 0.5 g. of a reddish liquid, b.p. 290-325°, from which almost colorless crystals, m.p. 105-107°, separated on standing for several days. This solid material is presumably 4-benzhydryl pyridine $(C_6H_5)_2CHC_5H_4N$.

B. Reaction of γ-Picolylsodium and Chlorobenzene.

To 600 cc. of liquid ammonia was added with stirring 0.3 g. of ferric ammonium nitrate and 2-3 g. of metallic sodium of a total of 11.5 g. (0.5 atom) to be added. After the liquid had assumed the blue sodium color, the remainder of the sodium was added. The mixture was stirred until decolorization occurred and then 23.2 g. (0.25 mol.) of γ-picoline added slowly, followed after 20 minutes by 28.1 g. (0.25 mol.) of chlorobenzene. After stirring for two hours the run was worked up as described in the foregoing section when using p-picolyl potassium. The yield was 10.4 g. (24.5%) of 4-benzylpyridine, b.p. 278-285° (mostly 281-282°).

C. Reaction of γ-Picolylsodium and Bromobenzene.

A run employing 0.25 mol. of bromobenzene instead of chlorobenzene was carried out under exactly the same conditions as described for experiment B, and yielded 23% of 4-benzylpyridine.

D. Reaction of γ-Picoline, Sodamide, and Chlorobenzene.

To 500 cc. of liquid ammonia was added 39 g. (1 mol.) of powdered, technical grade sodamide and then 46.5 g. (0.5 mol.) of γ-picoline in one portion. The mixture was stirred for 40 minutes at the boiling point of the ammonia during which period a red-brown color developed. Chlorobenzene (56 g., 0.5 mol.) was then added rapidly to the vigorously stirred mixture which assumed a black-brown color. After a stirring period of 45 minutes without external cooling, the mixture was decolorized with solid ammonium chloride and worked up as in the previous runs to yield 23.5 g. (25%) of 4-benzylpyridine.

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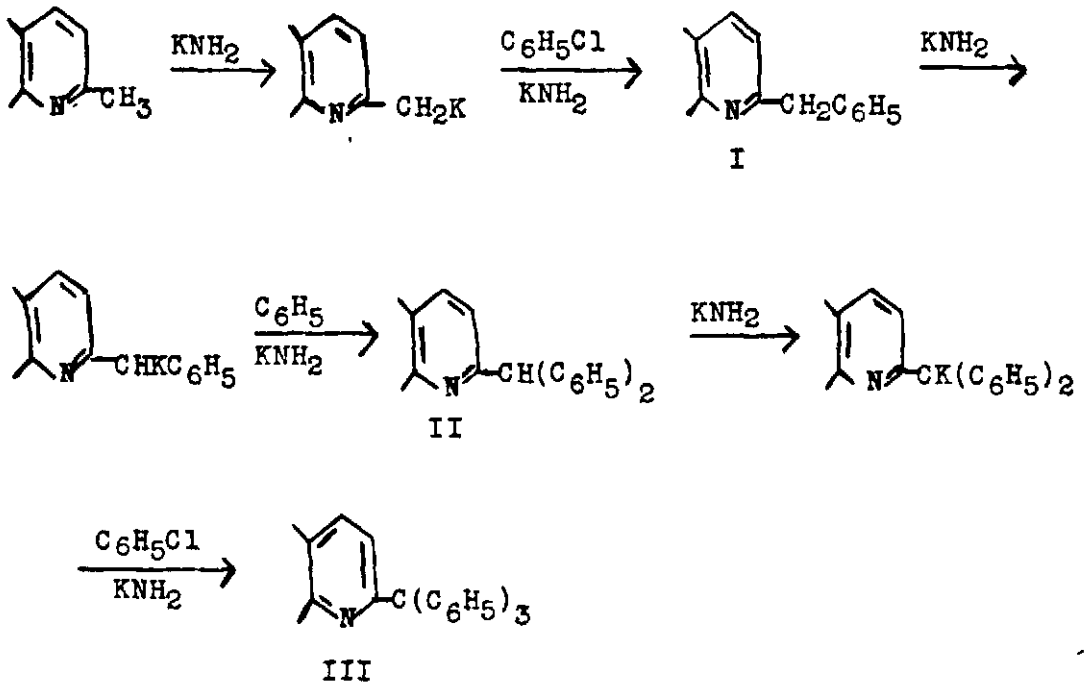
IV. DISCUSSION.

The phenylation of methyl groups in 2-position to heterocyclic N with chlorobenzene has been investigated by Bergstrom and co-workers (J. Org. Chem. 1, 179 (1939); 11, 55 (1946)) and found to be catalyzed by potassium amide. In all instances, the phenylation was found to proceed beyond the monosubstitution stage, and di- and triphenylated products were obtained as well. The following sequence of equations will serve to illustrate the general course of the reaction:



The potassium derivatives of the methyl-substituted N heterocyclics do not react with halobenzenes in the absence of excess potassium amide. To effect the phenylation reaction one equivalent of potassium amide is required. However, the role of the amide is two fold; it not only catalyzes the phenylation, but also reacts with the monophenylated product (I) to form its potassium derivative which in turn is further phenylated to yield the diphenyl derivative (II). This contains still a replaceable methyl H atom and undergoes phenylation to a triphenyl derivative (III). As a result of this amide-catalyzed sequence of reactions a mixture of substitution products of the type I, II, and III is obtained with I as the main reaction product.

The application of Bergstrom's phenylation reaction to γ-picoline (see experiment A) afforded the desired monophenylated derivative, the 4-benzylpyridine, in about 14% yield together with a small quantity of 4-benzhydrylpyridine. Throughout the investigation reported herein no effort was made to isolate the di- and possibly trisubstituted picoline derivatives, but only the 4-benzylpyridine was separated by distillation from the crude reaction product as described in the experimental section.

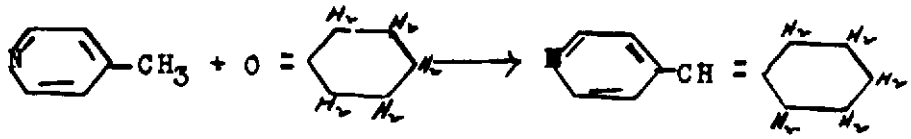
It was found that the technique used by Bergstrom can be simplified considerably by adding the amount of alkali amide required to effect the condensation reaction together with that necessary to form the picolyl alkali derivative, instead of adding an alkali amide suspension in liquid ammonia to a mixture of the picolyl alkali derivative and chlorobenzene in ammonia. It was shown that the phenylation of γ-picolyl with chlorobenzene proceeds also via the sodium derivative and is equally well catalyzed by sodamide. A further simplification of the method consists in the use of technical sodamide for the formation of the picolyl sodium derivative and its successful condensation with chlorobenzene, instead of forming it by reaction of metallic sodium and ammonia with the latter serving also as reaction medium (see experiment B). A yield of 25% of 4-benzylpyridine was thus obtained from γ-picoline, sodamide, and chlorobenzene (see experiment D). No improvement over this yield could be obtained by substituting bromobenzene for the chlorine derivative, as might be expected (see experiment C).

An attempt to cut down the formation of higher phenylated picolines by reducing the amount of sodamide necessary to catalyze the condensation from 1 to 0.3 equivalent resulted in a decrease of the 4-benzylpyridine yield from 25 to 13%.

Several attempts to carry out the phenylation of γ-picoline with sodamide and chlorobenzene in dry benzene at reflux temperature were unsuccessful. Picoline reacts with technical sodamide in refluxing benzene to form the violet picolyl sodium derivative. By refluxing the mixture with chlorobenzene for 24 hours only tarry, undistillable material was formed, whereas after a reflux period of 8 hours most of the picoline was recovered unreacted. In the latter run only a minute amount of the tarry product was formed.

Several other approaches to the synthesis of 4-benzylpyridine have been undertaken during this investigation. It is known that γ-picoline undergoes condensation of its reactive methyl group with aldehyde carbonyl groups.

Based on this reactivity of the methyl group, which is not shown by aromatic methyl substituents, an attempt was made to condense γ-picoline with cyclohexanone according to the following reaction:



A condensation product of this type might possibly be dehydrogenated to 4-benzylpyridine. However, all attempts to effect the condensation of picoline and cyclohexanone in the presence of catalyst, such as $NaOCH_3$, $ZnCl_2$, Al_2O_3, $AlCl_3$, in sealed tubes at elevated temperature or by condensation of the reactants in acetic anhydride in the presence of pyridine at reflux temperature, were unsuccessful and the starting materials were recovered.

Another attempt to synthesize 4-benzylpyridine by sodium catalyzed addition of γ-picoline to cyclohexene, according to:

and subsequent dehydrogenation was also unsuccessful, since the desired addition reaction could not be effected; unreacted cyclohexene was recovered.

V. SUMMARY.

An improved method for the synthesis of 4-benzylpyridine in 25% yield from γ-picoline, technical sodamide, and chlorobenzene in liquid ammonia as reaction medium is described.

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PREPARATION OF 4-BENZYLPYRIDINE.

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