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ACID-CATALYZED N-DEBENZYLATION OF BENZYLAMINOPYRIDINES

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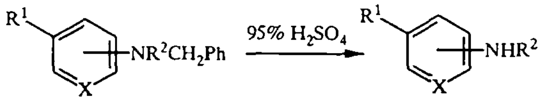
Acid-catalyzed N-debenzylation reaction of 2-benzylaminopyridine and 2-(*p*-methoxybenzylamino)pyrimidine with 10% HCl gave 2-aminopyridine and 2-aminopyrimidine in 16% and 27% yield, respectively [1]. The highest yields of the N-debenzylation reaction was observed for pyridazine derivatives, when the reaction was carried out in concentrated HBr, $HClO_4$ or H_2SO_4 [2]. Pawlowski and Gorczyca [3] used 94-98% H_2SO_4 to deprotect 8-benzylaminotheophylline and its derivatives; they obtained debenzylated 8-aminotheophyllines in very good yields.

This communication presents our results on the acid-catalyzed N-debenzylation reaction. We observed that 2-benzylaminopyridine (**1a**) was deprotected with 95% H_2SO_4 to give 2-aminopyridine (**2a**) in 85% yield. Preliminary experiments indicated that 85% H_2SO_4 is the minimal concentration ensuring the effective debenzylation of 2-benzylaminopyridine (**1a**), while the highest yields were obtained for 95% H_2SO_4. Under the same conditions 4-benzylaminopyridine (**1b**) underwent debenzylation to 4-aminopyridine (**2b**), but 3-benzylaminopyridine (**1c**) and N-benzylaniline (**1d**) did not undergo such deprotection in 95% H_2SO_4.

To check the applicability of this method to other amines, 2-benzylamino-5-benzylpyridine (**1e**) and 2-(N-benzyl-N-methyl)aminopyridine (**1f**) were chosen. For these compounds selective N-debenzylation might be expected. It was found previously [4] that 2-benzylamino-5-benzylpyridine hydrochloride underwent N-debenzylation to 2-amino-5-benzylpyridine (**2e**) in 44% yield at 250°C. We have found that **1e** and **1f** undergo N-debenzylation also in 95% H_2SO_4, yielding **2e** and 2-aminomethylpyridine (**2f**) in 80% and 73% yield, respectively (Table 1).

The experimental results indicated that N-debenzylation reaction of N-benzylaminopyridines occurred only when the benzylamino group was at the 2 or 4 position (**1a, 1b, 1e, 1f**). We expected that this method should be useful for synthesis of α- or γ-aminoderivatives of azaaromatic systems. Our preliminary results support this assumption. Debenzylation of 2,6-dibenzylaminopyridine (**1g**) led to 2,6-diaminopyridine (**2g**) and debenzylation of 2-benzylaminoquinoline (**1h**) provided 2-aminoquinoline (**2h**).

TABLE 1



1a–f 2a,b,e,f

Starting substance					Product of the reaction				
Comp.	X	R^1	R^2	Location of $-NR^2CH_2Ph$	Comp.	X	R^1	R^2	Yield, %
1a	N	H	H	2	2a	N	H	H	85
1b	N	H	H	4	2b	N	H	H	78
1c	N	H	H	3	2c	N	H	H	—
1d	CH	H	H	1	2d	CH	H	H	—
1e	N	CH_2Ph	H	2	2e	N	CH_2Ph	H	80
1f	N	H	CH_3	2	2f	N	H	CH_3	73

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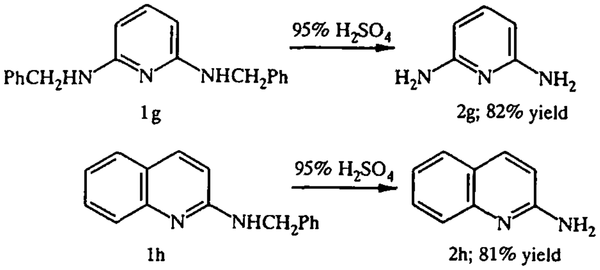

General Procedure for N-Debenzylation Reaction of Benzylaminoderivatives (1a-h) in the Presence of 95% H_2SO_4. A solution of 1 g of the respective benzylamine in 5 ml of 95% H_2SO_4 was left standing for 24 h at room temperature. The dark solution was poured into 25 ml of water, and an ice-cooled mixture was neutralized to pH 4 using 15% NaOH. The precipitate was filtered off. The pH value of the filtrate was adjusted to 10 with 15% NaOH and the solution was extracted with $CHCl_3$. The residue after evaporation of the solvent was recrystallized. Reaction yields are presented in Table 1 and in the scheme.

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