Reductive Acylamination of Pyridine *N*-Oxide with Aminopyridines and Their *N-p*-Tolylsulfonyl Derivatives

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Abstract—Pyridine *N*-oxide reacts with 2- and 3-aminopyridines and their *N-p*-tolylsulfonyl derivatives in alkaline medium in the presence of *p*-toluenesulfonyl chloride to give *N-p*-tolylsulfonyl-2,2'- and 2,3'-dipyridylamines, respectively, as a result of reductive acylamination. In the reactions with 4-aminopyridine and 4-*p*-tolylsulfonyl-aminopyridine, their *N-p*-tolylsulfonyl- and *N,N*-bis(*p*-tolylsulfonyl) derivatives are formed, while reductive acylamination does not occur.

We previously reported [1, 2] on the reductive acylamination of pyridine *N*-oxide (**I**) with aromatic amines (aniline, *p*-methoxyaniline, and their *N-p*-tolylsulfonyl derivatives) in the presence of *p*-toluenesulfonyl chloride (**II**) and a base, which afforded *N-p*-tolylsulfonyl-substituted 2-arylaminopyridines in high yields. In continuation of these studies, in the present work we performed analogous reactions with heteroaromatic amines, 2-, 3-, and 4-aminopyridines **III–V** and their *N-p*-tolylsulfonyl derivatives **VI–VIII**. Isomeric aminopyridines, 2- and 4-aminopyridines, on the one hand, and 3-aminopyridine, on the other, exhibit qualitatively different

chemical properties [3]; therefore, reactions with these compounds could give different results.

The reactions were carried out at room temperature in a two-phase system (chloroform–water) in the presence of *p*-toluenesulfonyl chloride (**II**) and potassium or sodium hydroxide or carbonate as a base. The reaction of pyridine *N*-oxide (**I**) with 2-aminopyridine (**III**) followed the reductive acylamination pattern and led to formation of *N-p*-tolylsulfonyl-2,2'-dipyridylamine (**IX**) in 34–58% yield; in addition, 22–35% of the acylation product, 2-*p*-tolylsulfonylaminopyridine (**VI**) was isolated (Scheme 1).

Scheme 1.
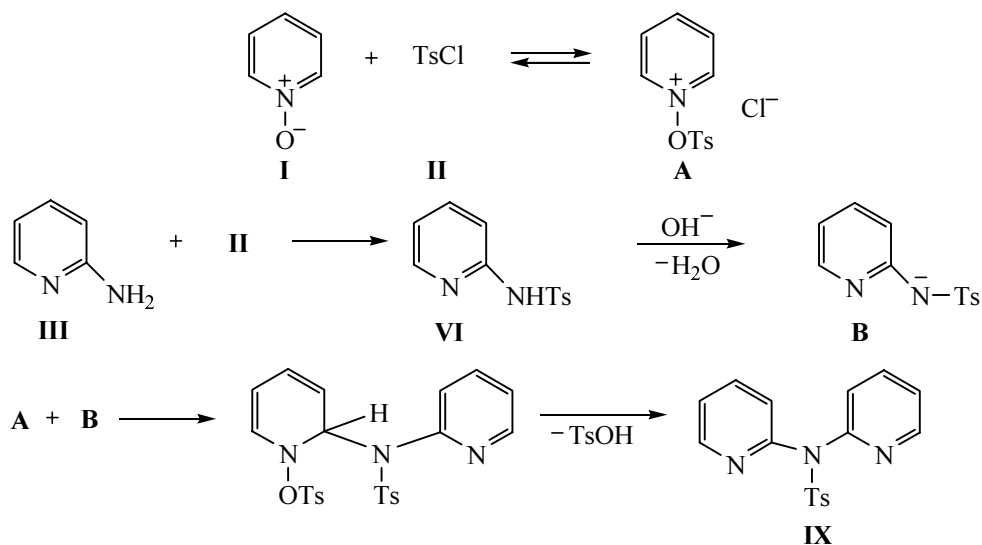
When the reaction was performed with N-p-tolyl-sulfonyl derivative **VI** as probable intermediate (instead of aminopyridine **III**), reductive acylamination of N-oxide **I** also occurred, and compound **IX** was obtained in 39% yield. These data confirm the proposed scheme of acyl-amination of aminopyridine **III**, and the above reaction may be regarded as a method of synthesis of amide **IX**. Pyridine N-oxide (**I**) reacted in a similar way with 3-amino-pyridine (**IV**) and 3-p-tolylsulfonylaminopyridine (**VII**); in both cases, the product was N-p-tolylsulfonyl-2,3'-dipyridylamine (**X**) (Scheme 2).

Unlike 2- and 3-aminopyridines, 4-aminopyridine (**V**) and its N-p-tolylsulfonyl derivative **VIII** underwent acylation to give 4-bis(p-tolylsulfonyl)aminopyridine (**XI**). The most probable reason is the higher basicity of amine **V** ($pK_a = 9.1$) relative to 2- and 3-aminopyridines (**III**, $pK_a = 7.2$; **IV**, $pK_a = 6.6$ [3]). Another factor responsible for the lack of substitution and the occurrence of repeated acylation of isomer **V** is strong delocalization of the negative charge on the exocyclic nitrogen atom in intermediate **C**, which is typical of para-substituted arenes (hetarenes), and hence sharp reduction of its nucleophilicity.

C
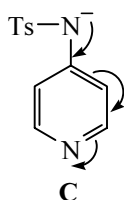
The structure of compounds **IX** and **X** was proved by their acid hydrolysis to 2,2'- and 2,3'-dipyridylamines **XII** and **XIII**, respectively (Scheme 3).

The described reactions attract interest from the viewpoint of synthesis of sulfonamides, dihetarylamines, and also amines themselves, which are potential physiologically active compounds.

EXPERIMENTAL

The progress of reactions and the purity of products were monitored by paper chromatography (no. 2, fast) using the system 1-butanol–hydrochloric acid–water (50:7:14, by volume); the chromatograms were developed with Dragendorff's spray reagent [4].

Acylamination of pyridine N-oxide (I) with 2-aminopyridine (III). A solution of 10 mmol of pyridine N-oxide (**I**), 10 mmol of 2-aminopyridine (**III**), and 20 mmol of p-toluenesulfonyl chloride (**II**) in 22 ml of chloroform was mixed with 10 ml of a 10% aqueous solution of potassium carbonate, and the mixture was stirred for 2 h at 20°C. The aqueous phase was separated

Scheme 2.
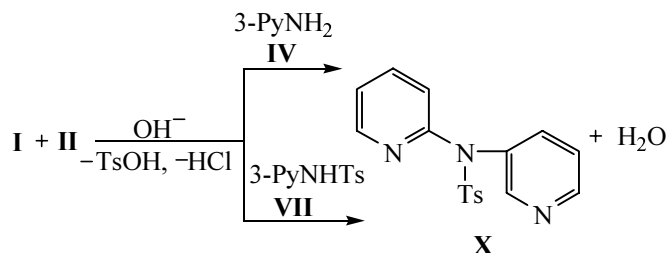
Scheme 3.
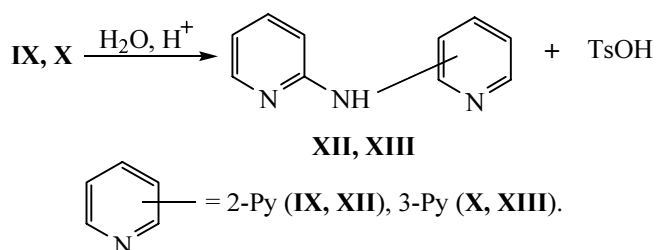
and extracted with several portions of chloroform, the extracts were combined with the organic phase, dried over sodium sulfate, and evaporated, and the residue was washed with diethyl ether and hot ethanol to obtain 1.6 g (62%) of amide **VI**, mp 210–211°C (from ethanol); published data [5]: mp 213–214°C. The solvent was distilled off to isolate 0.58 g (17%) of compound **IX**, mp 150–151°C (from acetonitrile), R_f 0.9. Found, %: C 62.7; H 4.4; N 12.86. $C_{17}H_{15}N_3O_2S$. Calculated, %: C 62.8; H 4.6; N 12.92.

The acid solution was made alkaline by adding potassium carbonate to pH 8–9 and extracted with diethyl ether, and the extract was evaporated to isolate 0.11 g (11%) of unreacted amine **III**, mp 55–56°C.

When potassium hydroxide was used as a base, the yields of products **IX** and **VI** were 60 and 31%, respectively.

Acyalmination of pyridine N-oxide (I) with N-(2-pyridyl)-p-toluenesulfonamide (VI). A solution of 2 mmol of pyridine N-oxide (**I**), 2 mmol of amide **VI**, and 4 mmol of p-toluenesulfonyl chloride (**II**) in 12 ml of chloroform was mixed with 6 ml of a 10% aqueous solution of potassium carbonate, and the mixture was stirred for 2 h at 20°C and treated as described above. We isolated 0.35 g (70%) of unchanged amide **VI** with mp 210–211°C (from ethanol) and 0.11 g (17%) of compound **IX** with mp 150–151°C (R_f 0.9).

When potassium hydroxide was used as a base, the yield of **IX** was 39%.

Acylamination of pyridine N-oxide (I) with 3-aminopyridine (IV). A solution of 10 mmol of N-oxide

I hydrochloride, 10 mmol of amine **IV**, and 20 mmol of *p*-toluenesulfonyl chloride (**II**) in 40 ml of chloroform was mixed with 60 ml of a 10% aqueous solution of potassium carbonate, and the mixture was stirred for 2 h at 20°C. The aqueous phase was separated and acidified with concentrated hydrochloric acid, and the precipitate was filtered off. We thus isolated 0.65 g (26%) of amide **VII**, mp 187–188°C (from ethanol); published data [6]: mp 190–191°C. The organic phase was dried over sodium sulfate and evaporated, and the residue was washed with diethyl ether and ethanol to isolate 0.92 g (38%) of compound **X** with mp 83–85°C (from ethanol), R_f 0.6. Found, %: N 12.83. $C_{17}H_{25}N_3O_2S$. Calculated, %: N 12.92.

When an equivalent amount of potassium hydroxide was used as a base, the yields of products **VII** and **X** were 48 and 33%, respectively, and with the use of sodium hydroxide, 36 and 46%, respectively.

Acylamination of pyridine *N*-oxide (I) with *N*-(3-pyridyl)-*p*-toluenesulfonamide (VII). A solution of 5 mmol of pyridine *N*-oxide hydrochloride, 5 mmol of amide **VII**, and 10 mmol of *p*-toluenesulfonyl chloride (**II**) in 40 ml of chloroform was mixed with 50 ml of a 10% aqueous solution of sodium hydroxide. The mixture was then treated as described in the preceding experiment to isolate 0.9 g (70%) of unchanged amide **VII** with mp 188–190°C and 0.45 g (28%) of compound **X** with mp 83–85°C, R_f 0.6. Found, %: N 12.80. $C_{17}H_{25}N_3O_2S$. Calculated, %: N 12.92.

Acylation of 4-aminopyridine (V) under acylamination conditions. A solution of 10 mmol of pyridine *N*-oxide hydrochloride, 10 mmol of amine **V,** and 20 mmol of *p*-toluenesulfonyl chloride (**II**) in 80 ml of chloroform was mixed with 40 ml of a 10% aqueous solution of sodium hydroxide, and the mixture was stirred for 2 h at 20°C. The aqueous phase was separated and acidified with concentrated hydrochloric acid, and the precipitate of amide **VIII** was filtered off. Yield 1.6 g (60%), mp 280°C (sublimes) [7]. No depression of the melting point was observed on mixing with an authentic sample of *N*-(4-pyridyl)-*p*-tolenesulfonamide.

The organic phase was dried over sodium sulfate and evaporated, the semicrystalline residue was treated with hot ethanol, the solution was cooled, and the precipitate was filtered off to obtain 1.2 g (27%) of imide **XI** with mp 204–205°C [8], R_f 0.7.

Acylation of amide VIII under acylamination conditions. A mixture of 5 mmol of pyridine *N*-oxide hydrochloride, 5 mmol of amide **VIII** [8], and 5 mmol of *p*-toluenesulfonyl chloride (**II**) in 40 ml of chloroform was mixed with 50 ml of a 10% aqueous solution of sodium hydroxide, and the mixture was stirred for 2 h at 20°C. The aqueous phase was separated and acidified with concentrated hydrochloric acid, and the precipitate was filtered off and repeatedly washed with a solution of sodium carbonate and with water. Yield of **XI** 1 g (80%), mp 204–205°C (from ethanol) [8], R_f 0.7.

Hydrolysis of amides IX and X. A solution of 4 mmol of amide **IX** or **X** in 20 ml of concentrated hydrochloric acid was heated for 12 h at the boiling point. The mixture was evaporated to dryness, the residue was washed with diethyl ether, and the solvent was distilled off to leave *p*-toluenesulfonic acid. Yield 66 and 80% from amides **IX** and **X**, respectively, mp 90–92°C; published data [9]: mp 92°C. The material insoluble in diethyl ether was dissolved in a minimal amount of water, the solution was made alkaline by adding potassium carbonate and was extracted with chloroform, and the solvent was removed from the extract to isolate amine **XII** {yield 68%, mp 94–95°C (from benzene); published data [7]: mp 95°C} or **XIII** {yield 70%, mp 143–144°C (from hexane); published data [10]: mp 143.8–144°C)}.

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