Formation of 4-arylpyridines from pyridinium salts under the action of methylammonium sulfite

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Reactions of pyridinium salts or nonquaternized pyridine with 4-methylpyridinium salts in the presence of methylammonium sulfite in aqueous methylamine afford 4-phenylpyridine in 29—57% yields. The probable mechanism of ring transformation in simplest pyridine derivatives under the action of nucleophiles is discussed.

Key words: 4-methylpyridines, pyridine, pyridinium salts, methylammonium sulfite, ring transformation, 4-arylpyridines.

Various known transformations of heterocycles involve ring opening, expansion, contraction, exchange of a heteroatom, *etc.* They are mainly initiated by nucleophilic reagents and have been studied most thoroughly for electron-deficient heterocycles containing two and more nitrogen atoms (such as pyrimidine, pyrazine, pyridazine, triazines, and their fused analogs).[1]

Pyridine is relatively resistant to ring opening, although to a lower extent than benzene.[2,3] Such a transformation was first represented by the Zincke—König reaction,[4] in which quaternized pyridine undergoes ring opening under the action of aromatic amines to give glutaconaldehyde dianils. Later, a great number of reactions of pyridine derivatives with nucleophiles causing ring opening and transformations were studied.[3,5] Mention should be given to some new rearrangements (amidine rearrangement,[6,7] enamine rearrangement of pyridine derivatives,[3,8] and an unusual conversion of nitropyridinium salts into indoles[9,10]); the latter two reactions were discovered by us.

Arylpyridines are used in the preparation of liquid crystals and as ligands and biologically active compounds.[11,12] 2-Phenylpyridine can be obtained by the reaction of phenyllithium or the Grignard reagent with pyridine or its *N*-oxide followed by oxidation or disproportionation of the resulting 1,2-dihydropyridine derivative or thermal elimination of lithium hydride (*e.g.*, see Refs. 13, 14).

4-Phenylpyridine cannot be obtained by direct phenylation of pyridine because the nucleophilic addition of corresponding organometallic reagents occurs exclusively at position 2 of the pyridine ring.[13]

Current methods for the synthesis of 4-phenylpyridine include different versions of the Suzuki reaction, free-radical arylation, and regioselective addition of the Grignard reagents, but the starting reagents for these methods are toxic or difficultly accessible.[15—18] The known commercial methods for the synthesis of 4-phenylpyridine are based on the Chichibabin reaction[19] (*e.g.,* by catalytic condensation of benzaldehyde with acetaldehyde and ammonia at 300—400 °C). However, all of the reactions yield considerable amounts of by-products (including high-boiling alkylpyridines[20,21]), which are hard to separate off.

Earlier,[3,8,22] we found that 1,2-dimethylpyridinium salts undergo recyclization into *N*-alkylanilines under the action of alkylammonium sulfite. One could assume that addition of sulfite or bisulfite ions to 1-alkylpyridinium salts would allow an intermolecular ring transformation involving another pyridinium salt containing a methyl group in position 4. Indeed, heating a mixture of 1-alkylpyridinium **1a—d** and 1-alkyl-4-methylpyridinium salts **2a—d** with methylammonium sulfite afforded 4-phenylpyridine (**3a**) in 29—57% yields (Scheme 1). A similar reaction occurs between salts **1a** and **2a** in the presence of dimethylammonium sulfite, but the yield is lower (24%).

Pyridine and 4-methylpyridine, which are formed in the side *N*-dealkylation of pyridinium salts **1a—d** and **2a—d**, can be quaternized and used in the synthesis of compound **3a**. This allows one to obtain the target product in up to 68% yield (from the pyridine bases consumed in the reaction).

The nature of the counterion was found to have a certain effect on the efficiency of the ring transformation. It turned out that the use of bromides instead of iodides somewhat increases the yield of 4-phenylpyridine (**3a**). Probably, this is due to the fact that bromides are more stable than iodides under rather drastic reaction conditions.

As shown by us earlier,[22] a sulfite ion as a soft nucleophile seems to add predominantly at position 4 of salts **1a—d**, which affords an intermediate 1,4-dihydropyridine derivative. The disturbance of the aromaticity of the pyridine ring facilitates its opening. The resulting glutacon-

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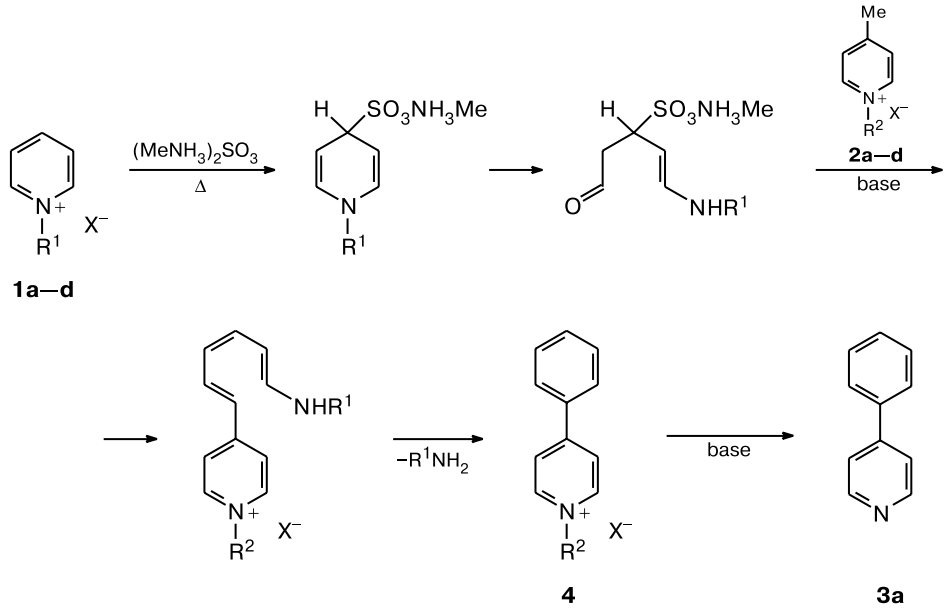
Scheme 1



1, 2: R^1, R^2 = Me (**a**), Et (**b**, **c**), Pr^i (**d**); X = I (**a**, **b**, **d**), Br (**c**)
4: R^2 = Me, X = I

aldehyde derivative undergoes condensation with a reactive methyl group of 4-methylpyridinium salt **2a—d** under the action of a base. Subsequent ring closure gives quaternary 4-phenylpyridinium salt **4**, which is converted to 4-phenylpyridine (**3a**) as a result of *N*-dealkylation.

The data obtained in the study of the effect of steric factors on the efficiency of the formation of 4-arylpyridines confirm the proposed reaction scheme. A bulkier alkyl group bound to the nitrogen atom in 4-methylpyridinium salts **2a—d** favors an increase in the yield of 4-phenylpyridine (**3a**) (Table 1). Apparently, the presence of the alkyl group at the nitrogen atom in salts **2a—d** reduces the electron deficiency of the pyridine ring and presents steric hindrances to addition of nucleophiles at position 2; this in turn reduces the probability of the side opening of the pyridine ring and prevents competitive *N*-dealkylation yielding 4-methylpyridine.

Table 1. Effects of the substituents and counterions in pyridinium salts **1a—d** and **2a—d** on the yield of 4-phenylpyridine (**3a**)

Compound	R^1	X	Compound	R^2	X	Yield of **3a** (%)
1a	Me	I	**2a**	Me	I	42
1a	Me	I	**2b**	Et	I	49
1a	Me	I	**2c**	Et	Br	53
1a	Me	I	**2d**	Pr^i	I	57
1b	Et	I	**2a**	Me	I	35
1c	Et	Br	**2a**	Me	I	37
1d	Pr^i	I	**2a**	Me	I	29

In contrast, a bulkier alkyl substituent bound to the nitrogen atom in salts **1a—d** seems to considerably hinder the opening of the pyridine ring.

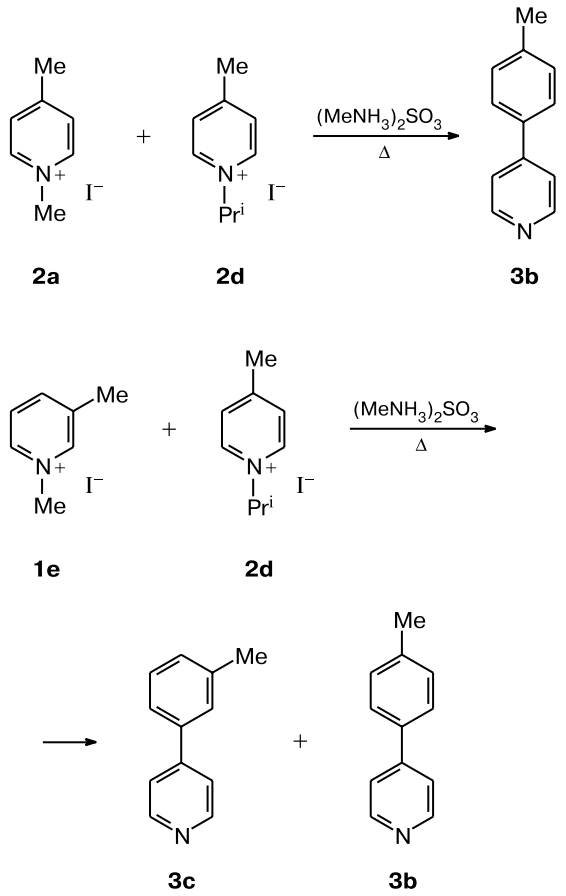
According to the proposed reaction mechanism, a methyl group in position 4 of the pyridine ring presents considerable steric hindrances to addition of a sulfite ion, which sharply reduces the yield of the reaction product (Scheme 2). For instance, the reaction of 1,4-dimethylpyridinium iodide (**2a**) with 1-isopropyl-4-methylpyridinium iodide (**2d**) gives 4-(4-methylphenyl)pyridine (**3b**) only in 5% yield.

The reaction of 1,3-dimethylpyridinium iodide (**1e**) with 1-isopropyl-4-methylpyridinium iodide (**2d**) affords a 3 : 1 mixture of 4-(3-methylphenyl)pyridine (**3c**) and 4-(4-methylphenyl)pyridine (**3b**) in a total yield of 8% (see Scheme 2); *i.e.*, the methyl group in position 3 of salt **1e** also prevents the addition of a sulfite ion at position 4. The competitive formation of 4-(4-methylphenyl)pyridine (**3b**) can be explained by self-condensation of salt **2d**, which proceeds as in the preceding example.

A further increase in the number of methyl groups in positions 3—5 makes the pyridinium ring unable to addition and opening under the action of nucleophiles, which prevents its transformation.

The final step of the process could be assumed to be *N*-dealkylation of an intermediate compound of type **4** to give 4-arylpyridines **3a—c**. Indeed, heating of 1-methyl-4-phenylpyridinium iodide (**4**) in the presence of methylammonium sulfite afforded 4-phenylpyridine (**3a**) in 93% yield. It is known that *N*-alkylpyridinium salts under the

Scheme 2



action of liquid ammonia, aqueous ammonia, or ammonium sulfite are converted into pyridine bases because of exchange of the alkylamine residue for an amine in an acyclic intermediate.[23—25] In the absence of ammonia or an ammonium salt, dealkylation can proceed without ring opening.[22,26] In the case under consideration, the reaction sphere contains no ammonia or ammonium ions (nonalkylated) and the *N*-substituent is probably eliminated as a result of the direct attack of a nucleophile on the Me—N bond.

The method developed by us allows one to effect the ring transformation not only in 1-alkylpyridinium salts **1a—d** but also in pyridine itself. Prolonged heating of pyridine and 4-methylpyridinium salt **2d** with aqueous methylammonium sulfite gives 4-phenylpyridine (**3a**) in up to 20% yield (Table 2). With an excess of salt **2d**, 4-(4-methylphenyl)pyridine (**3b**) was formed, along with 4-phenylpyridine (**3a**), as a result of self-condensation of salt **2d** (^{1}H NMR data). The yield of 4-phenylpyridine (**3a**) and its purity were significantly increased when the molar ratio of pyridine to salt **2d** was 20 : 1. In this case, 4-(4-methylphenyl)pyridine (**3b**) was not detected by the ^{1}H NMR method. Taking into account that a significant portion of pyridine is recovered, one can conclude that

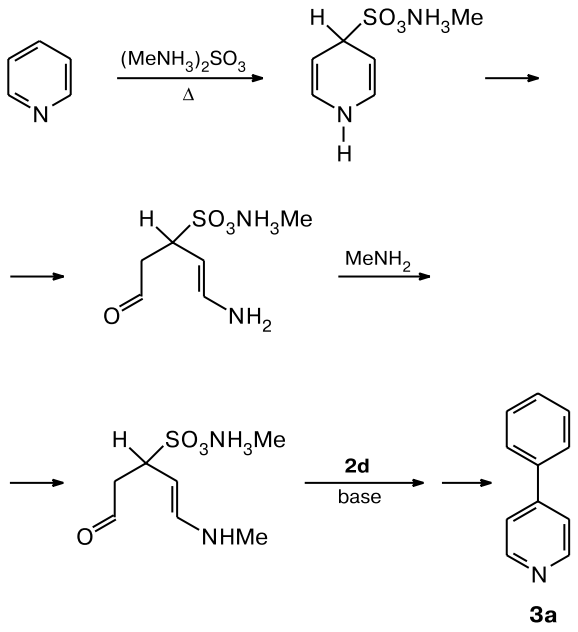
Table 2. Effects of the molar ratio of pyridine to 1-isopropyl-4-methylpyridinium iodide (**2d**) and the reaction duration on the yield of 4-phenylpyridine (**3a**)

Pyridine : salt **2d**	Time/h	Yield of **3a** (%)
1 : 2	120	3
1 : 1	120	7
2 : 1	120	13
20 : 1	60	20

the yield of 4-phenylpyridine (**3a**) from the consumed pyridine can be substantially higher.

Previously,[3,8,22] we found that pyridine bases can undergo ring opening under the action of methylammonium sulfite to give *N*-methylanilines. The driving force of these recyclization processes is an exchange of the amine residue for a methylamine one in an acyclic intermediate. Here, this intermediate seems to undergo condensation with 4-methylpyridinium salt **2d** under the action of bases to give 4-phenylpyridine (**3a**) (Scheme 3).

Scheme 3



Thus, we discovered a novel reaction of simplest pyridine derivatives, which can be important for the chemistry of pyridine. The reaction occurs between pyridinium salts in the presence of alkylammonium sulfite. At the same time, we found a simple and convenient route to high-purity 4-phenylpyridine obtained in good yields from substances available from by-product coke industry.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer in $CDCl_3$ and DMSO-d_6 with Me_4Si as the internal

standard. Chemical shifts were measured to within 0.01 ppm, spin-spin coupling constants were measured to within 0.01 Hz. Mass spectra were recorded on a Finnigan MAT 8430 instrument (ionizing voltage 70 eV, direct inlet probe). The course of the reaction was monitored by TLC on DC-Alufolien Kieselgel 60 F_{254} plates (Merck). Column chromatography was carried out on Kieselgel 60 silica gel (0.063—0.100 mm; Merck). Pyridinium salts **1a—e** were prepared according to a common procedure.[27] 1-Ethyl-4-methylpyridinium iodide **2b** and 1-methyl-4-phenylpyridinium iodide (**4**) were synthesized according to the known procedures.[28,29]

1-Isopropyl-4-methylpyridinium iodide (2d). 4-Methylpyridine (5 mL, 50 mmol) was added to isopropyl iodide (15 mL, 150 mmol). The reaction mixture was left for a month. The precipitate that formed was washed with hexane and dried *in vacuo*. The yield of **2d** was 8.2 g (60%), m.p. 130—132 °C. ^{1}H NMR (DMSO-d_6), δ: 1.59 (d, 6 H, 2 Me, J = 6.71 Hz); 2.62 (s, 3 H, Me); 4.94—5.02 (m, 1 H, CH); 8.00 (d, 2 H, H(2), H(6), J = 6.27 Hz); 9.02—9.08 (m, 2 H, H(3), H(5)). Found (%): C, 41.01; H, 5.44; N, 5.28. $C_9H_{14}IN$. Calculated (%): C, 41.08; H, 5.36; N, 5.32.

4-Phenylpyridine (3a). ***A.*** A 68% solution of $MeNH_3HSO_3$ (4 mL), aqueous 40% $MeNH_2$ (5 mL) and water (3 mL) were added to a 1-alkylpyridinium salt **1a—d** (3 mmol) and a 1-alkyl-4-methylpyridinium salt **2a—d** (3 mmol) dissolved in 2 mL of water. The reaction mixture was heated in a sealed tube placed in a metal autoclave on a Wood´s alloy bath at 230 °C for 60 h. After the tube was opened, the contents was diluted with water and extracted with benzene. The extract was dried with Na_2SO_4 and concentrated. The resulting 4-phenylpyridine was separated from pyridine and 4-methylpyridine by column chromatography on SiO_2 with benzene and then benzene—ethyl acetate (2 : 1) as eluents. M.p. 72—74 °C (*cf.* Ref. 13: m.p. 74 °C). ^{1}H NMR ($CDCl_3$), δ: 7.45 (m, 1 H); 7.49—7.52 (m, 4 H); 7.65 and 8.67 (both m, 2 H each). Pyridine and 4-methylpyridine were converted into hydrochlorides, and their ratio in the mixture was determined by ^{1}H NMR spectroscopy.

B. A 68% solution of $MeNH_3HSO_3$ (4 mL), aqueous 40% $MeNH_2$ (5 mL), and water (3 mL) were added to iodide **4** (197 mg, 1 mmol) dissolved in 2 mL of water. The reaction was carried out as described above. The yield was 144 mg (93%), m.p. 72—74 °C (*cf.* Ref. 13: m.p. 74 °C). ^{1}H NMR ($CDCl_3$), δ: 7.45 (m, 1 H); 7.49—7.52 (m, 4 H); 7.65 (m, 2 H); 8.67 (m, 2 H).

4-(4-Methylphenyl)pyridine (3b) was obtained by analogy with **3a** (procedure ***A***) from 1,4-dimethylpyridinium iodide (**2a**) and 1-isopropyl-4-methylpyridinium iodide (**2d**). The yield was 5%, m.p. 88—89 °C (*cf.* Ref. 30: m.p. 89.5—90.5 °C). ^{1}H NMR ($CDCl_3$), δ: 2.42 (s, 3 H, Me), 7.30 (d, 2 H, H(3´), H(5´)); 7.50 (m, 2 H, H(3), H(5)); 7.55 (d, 2 H, H(2´), H(6´)); 8.64 (d, 2 H, H(2), H(6)). MS (m/z, I_{rel} (%)): 169 (100) [M^+], 168 (86), 167 (45), 166 (11), 142 (22), 141 (29), 139 (14), 115 (29), 91 (32), 51 (13).

4-(3-Methylphenyl)pyridine (3c) was obtained by analogy with **3a** (procedure ***A***) from 1,3-dimethylpyridinium iodide (**1e**) and 1-isopropyl-4-methylpyridinium iodide (**2d**). The total yield of a mixture of **3c** and **3b** (3 : 1) was 8%. ^{1}H NMR ($CDCl_3$), δ: 2.45 (s, 3 H, Me); 7.27 (m, 1 H, H(4´)); 7.39 (m, 1 H, H(5´)); 7.45 (d, 1 H, H(6´)); 7.46 (s, 1 H, H(2´)); 7.51 (m, 2 H, H(3), H(5)); 8.66 (m, 2 H, H(2), H(6)). Chemical shifts of the signals for isomer **3b** are identical with those presented above.

Reaction of pyridine with salt 2d (general procedure). The reaction was carried out by analogy with procedure ***A*** by heating a mixture of pyridine and 1-isopropyl-4-methylpyridinium iodide (**2d**) (see Table 2). 4-Phenylpyridine (**3a**) was also isolated according to procedure ***A***.

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