A Novel Ring Transformation of Pyridinium Salts as a Route to 4-Arylpyridines

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Regiospecific phenylation of pyridine derivatives at the 4-position takes place in the reaction of 4-methylpyridinium salts **1** with other pyridinium salts **2** by intermolecular transformation of the pyridine ring in **1** and participation of the methyl group of **2**. The method developed makes it possible to carry out ring transformation not only for pyridinium salts **1** but even for pyridine itself. 4-Phenylpyridine (**3**) was produced in 29–57% yields. The new reaction proceeds in an aqueous medium on heating and on treatment with methylammonium sulfite.

Introduction

As it is an aromatic system, the pyridine ring is relatively resistant to cleavage, although to a lesser extent than benzene.[1,2] Historically, the first thoroughly studied reaction of this type was the Zincke−König reaction[3] — cleavage of the quaternized pyridine ring by aromatic amines to form glutacondialdehyde dianils. Subsequently, a large number of reactions with ring opening and ring transformation of pyridine derivatives induced by nucleophilic reagents have been discovered and studied.[2,4,5] In particular, a number of new rearrangements, some of which are general for the chemistry of heterocyclic compounds, such as the amidine rearrangement[6,7] and the enamine rearrangement[2,8] of pyridine derivatives, and the unusual ring transformation of nitropyridinium salts into indoles[9] have been described in our previous publications. The main structural factors and conditions influencing the ring transformation pathway that have been identified to date provide grounds to expect great prospects for further research along these lines.

Results and Discussion

It was found previously that 1-alkyl-2-methylpyridinium salts undergo nucleophilic recyclization into *N*-alkylanilines on treatment with alkylammonium sulfite.[2,8,10] It was assumed that the addition of sulfite or bisulfite ions to 1-alkylpyridinium salts would provide the possibility of an intermolecular ring transformation with another pyridinium salt containing the methyl group in the 4-position. Indeed, by heating a mixture of 1-alkylpyridinium salts **1a−c** (R^2 = H) and 1-alkyl-4-methylpyridinium salts **2a−c** with methylammonium sulfite, we obtained 4-phenylpyridine **3a** in yields of up to 57% (see Scheme 1).

Reactions of this type can also be induced by dimethylammonium sulfite, for example the reaction between **1a** and **2a**, although the yield of 4-phenylpyridine (**3a**) is lower (about 24%).

Pyridine and 4-methylpyridine resulting from the side *N*-dealkylation reaction of pyridinium salts **1** and **2a−c** can be used once again for the synthesis of 4-phenylpyridine (**3a**) after quaternization.

As shown previously,[10] sulfite ion, which is a soft nucleophile, appears to add preferably to the 4-position of pyridinium salts **1a−c**, giving rise to 1,4-dihydropyridines as intermediates. The violation of aromaticity of the pyridine ring promotes its opening. The glutacondialdehyde derivative thus produced condenses under the action of a base with the active methyl group of the 4-methylpyridinium salt **2a−c**. Subsequent ring-closure furnishes a benzene ring and affords, correspondingly, a quaternary 4-phenylpyridinium salt **4**. The last step is *N*-dealkylation to yield 4-phenylpyridine (**3a**).

A study of the effect of steric factors on the efficiency of formation of 4-arylpyridines **3a,b** provides evidence supporting the proposed reaction scheme. Thus, an increase in the steric bulk of the alkyl group at the nitrogen atom of the 4-methylpyridinium salt **2a−c** leads to a considerable increase in the yield of 4-phenylpyridine (**3a**; see Table 1).

Apparently, the introduction of alkyl groups (R^3) decreases the electron deficiency of the pyridine ring and creates steric hindrance to the addition of nucleophiles at the 2-position; this reduces the degree to which side reactions with pyridine ring-opening proceed. The creation of hindrance to the parallel *N*-dealkylation giving 4-methylpyridine might be yet another reason.

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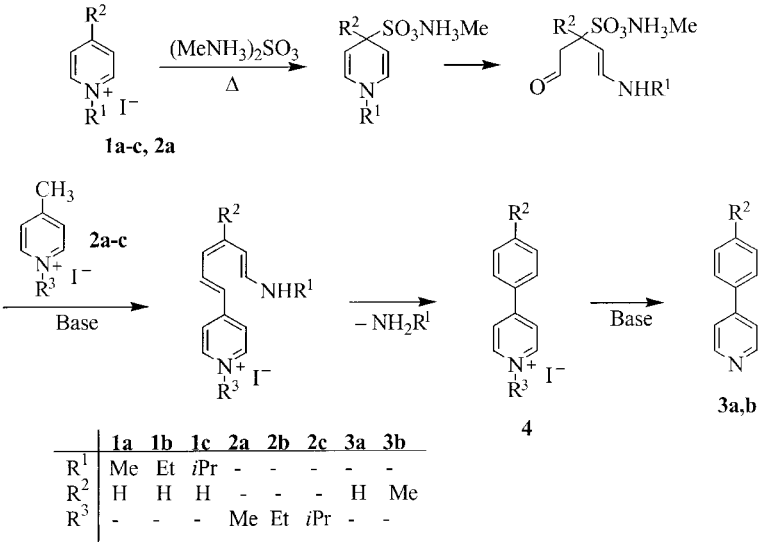


	1a	1b	1c	2a	2b	2c	3a	3b
R^1	Me	Et	*i*Pr	-	-	-	-	-
R^2	H	H	H	-	-	-	H	Me
R^3	-	-	-	Me	Et	*i*Pr	-	-

Scheme 1. Reagents and conditions: excess of a mixture of aq. $(MeNH_3)_2SO_3$ and $MeNH_2$, sealed tube, 230 °C, 60 h

Table 1. Effect of substituents in the pyridinium salts **1a**–**c** (R^2 = H) and **2a**–**c** on the formation of 4-phenylpyridine **3a**

	R^1		R^3	Yield [%] of **3a** [a]
1a	Me	**2a**	Me	42
1a	Me	**2b**	Et	49
1a	Me	**2c**	*i*Pr	57
1b	Et	**2a**	Me	35
1c	*i*Pr	**2a**	Me	29

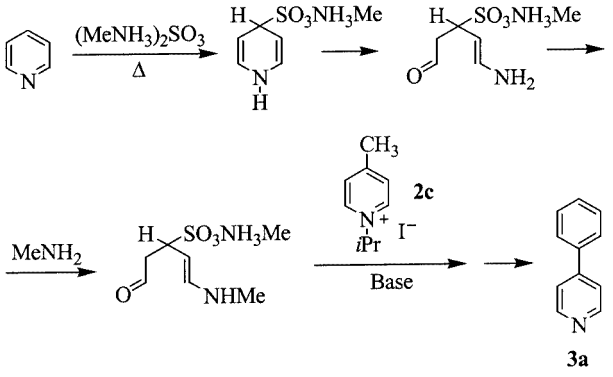
[a] Isolated yield by chromatography.

In the case of the second component **1a**–**c**, the size of the alkyl substituent at nitrogen exerts the opposite effect on the reaction efficiency. In this case, bulky substituents at the nitrogen atom appear to hamper opening of the pyridine ring considerably; this prevents ring transformation. As is to be expected in terms of the assumed reaction mechanism, the introduction of a methyl group at the 4-position of the pyridine ring brings about pronounced steric hindrance to the addition of the sulfite ion, resulting in a sharp decrease in the yield of the reaction product. Indeed, the reaction of 1,4-dimethylpyridinium iodide (**2a**) with 1-isopropyl-4-methylpyridinium iodide (**2c**) gives 4-(4-methylphenyl)pyridine (**3b**) in a yield of only 5%.

It could also be that the final step of the process is *N*-dealkylation of **4** giving rise to 4-arylpyridines **3a**,**b**. Indeed, heating 1-methyl-4-phenylpyridinium iodide (**4**; R^2 = H, R^3 = Me) in the presence of methylammonium sulfite under the above reaction conditions resulted in the quantitative formation of 4-phenylpyridine (**3a**). *N*-Alkylpyridinium salts are known to be converted into pyridine bases on treatment with liquid ammonia, aqueous solutions of ammonia, or ammonium sulfite via the exchange of the alkylamine residue with the amine group in the intermediate acyclic structure.[11–13] When the reagent used does not contain free ammonia or the ammonium cation, dealkylation can proceed without ring opening.[10,14] In this particular case, the loss of the *N*-substituent seems to proceed along the second pathway, i.e. by direct nucleophilic attack at the Me–N bond because no ammonia or (non-alkylated) ammonium ions are present in the reaction area.

The method developed makes it possible to carry out ring transformation not only for 1-alkylpyridinium salts **1a**–**c** but even for pyridine itself. Prolonged heating (120 h) of pyridine and the 4-methylpyridinium salt **2c** with an aqueous solution of methylammonium sulfite gives 4-phenylpyridine (**3a**) in a satisfactory yield (9–20%). The yield of **3a** increases substantially with an increase in the pyridine/**2c** molar ratio to 20:1.

Previously, we reported that pyridine bases undergo ring opening under the action of methylammonium sulfite yielding *N*-methylanilines.[2,8,10] The driving force of these recyclizations was the replacement of the amine residue by the methylamine residue in the intermediate acyclic structure. In our case, this intermediate appears to condense with the 4-methylpyridinium salt **2c** under the action of bases to form 4-phenylpyridine (**3a**; see Scheme 2).



Scheme 2. Reagents and conditions: excess of a mixture of aq. $(MeNH_3)_2SO_3$ and $MeNH_2$, sealed tube, 230 °C, 120 h

Arylpyridines are an important class of heterocyclic compounds encountered in a number of fields, including liquid crystals, ligands, and molecules of pharmacological interest.[15,16] The main approaches to the synthesis of 4-phenylpyridine proposed to date include various modifications of the Suzuki reaction, free-radical arylation and regioselective addition of Grignard reagents, i.e. they are fairly expensive or require initial compounds that are often difficult to prepare.[17−20] The known industrial methods for the preparation of 4-phenylpyridine are based on catalytic condensation of benzaldehyde with acetaldehyde and ammonia at 300−400 °C. However, this reaction always yields considerable amounts of by-products that are difficult to separate (in particular, high-boiling alkylpyridines).[21,22]

Conclusion

We have found a new reaction of pyridine derivatives which could be of high value in pyridine chemistry. This process is based on the interaction of pyridinium salts with one another in the presence of alkylammonium sulfite. Simultaneously, we found a simple and convenient method for the synthesis of 4-phenylpyridine, formed with high purity and in high yields from readily available substances (products and wastes of the coke industry).

Experimental Section

General Remarks: Unless stated otherwise, reagents and solvents were obtained from commercial sources and used as received. The pyridinium salts **1a**−**c** were prepared according to a known procedure.[23] 1-Ethyl-4-methylpyridinium iodide (**2b**) was also synthesised according to a known procedure.[24] TLC was performed with Merck Kieselgel 60 F_{254} plates, with viewing under ultraviolet light (254 nm). Column chromatography was performed with Merck Kieselgel 60 (0.063−0.100 mm). Melting points were determined with a MEL-Temp II apparatus in a capillary and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker DRX-500 (500 MHz) spectrometer as solutions in $CDCl_3$ or [D_6]DMSO; δ values are reported in ppm downfield from tetramethylsilane; *J* values are in Hz. Mass spectra were measured at an ionizing voltage of 70 eV by electron impact with a Finnigan MAT 8430 instrument. Elemental analysis was performed at the microanalytical laboratory of the A. N. Nesmeyanov Institute of Organoelement Compounds in Moscow, Russia.

1-Isopropyl-4-methylpyridinium iodide (2c): 4-Methylpyridine (5 mL, 50 mmol) was added to isopropyl iodide (15 mL, 150 mmol). The reaction mixture was plugged with a stopper and left for one month. The precipitate was then washed with hexane and dried under vacuum. Yield: 8.2 g (60%). M.p. 130−132 °C. ^{1}H NMR ([D_6]DMSO, 30 °C): δ = 1.59 (d, *J* = 6.71 Hz, 6 H, 2 CH_3), 2.62 (s, 3 H, CH_3), 4.94−5.02 (m, 1 H, CH), 8.00 (d, *J* = 6.27 Hz, 2 H, C(2)-H, C(6)-H), 9.02−9.08 [m, 2 H, C(3)-H, C(5)-H] ppm. $C_9H_{14}IN$ (263.12): calcd. C 41.08, H 5.36, N 5.32; found C 41.01, H 5.44, N 5.28.

4-Phenylpyridine (3a): A 40% aqueous solution of CH_3NH_2 (5 mL), a 68% solution of $CH_3NH_3HSO_3$ (4 mL), and water (3 mL) were added to a mixture of 1-alkylpyridinium salt **1a**−**c** (3 mmol) and 1-alkyl-4-methylpyridinium salt **2a**−**c** (3 mmol) dissolved in water (2 mL). The mixture was heated in a sealed tube in a metal autoclave on a Wood-alloy bath at 230 °C for 60 h. After opening the tube, the contents were diluted with water and extracted with benzene. The extract was dried with Na_2SO_4 and concentrated. The resulting 4-phenylpyridine (**3a**) was separated from pyridine and 4-methylpyridine by column chromatography on silica gel using benzene and a benzene/ethyl acetate mixture (2:1) as eluents. Yield: 135−265 mg (29−57%). M.p. 72−74 °C (ref.[25] 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) ppm.

4-(4-Methylphenyl)pyridine (3b): The procedure for the reaction of salt **2a** with salt **2c** to give 4-(4-methylphenyl)pyridine (**3b**) was similar to that described above. Yield: 25 mg (5%). M.p. 88−89 °C (ref.[26] 89.5−90.5 °C). ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3 H), 7.30 (d, 2 H), 7.50 (m, 2 H), 7.55 (d, 2 H), 8.64 (d, 2 H) ppm. MS (EI, 70 eV): *m/z* = 169 (100) [M^+], 168 (86), 167 (45), 166 (11), 142 (22), 141 (29), 139 (14), 115 (29), 91 (32), 51 (13).

General Procedure for the Reaction of Pyridine and Pyridinium Salt 2c: The general procedure for the reaction of pyridine with salt **2c** was similar to that described above. Mixtures of pyridine and 1-isopropyl-4-methylpyridinium iodide (**2c**) in various molar ratios were heated for the same or longer periods of time. 4-Phenylpyridine (**3a**) was isolated as described above. Yield: 42−93 mg (9−20%).

Acknowledgments

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