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Solvent and Substituent Effects on the Conversion of 4-Methoxypyridines to N-Methyl-4-Pyridones

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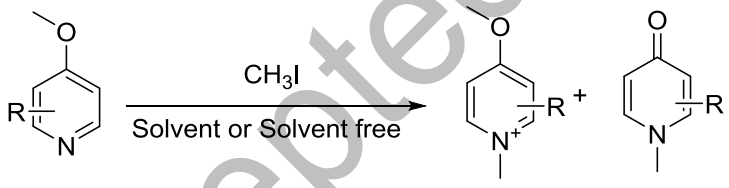
Abstract

In the reaction of 4-methoxypyridine derivatives with alkyl iodides in the presence or absence of solvent, not only the pyridinium ions but also the related 1-methylpyridones are produced. The presence of solvent favours the formation of the 1-methylpyridone. Electron withdrawing groups on the pyridine ring also favours this conversion. A possible mechanism is presented.

Graphical Abstract



KEYWORDS: substituent effect; rearrangement; solvent effect; pyridine

INTRODUCTION

Aromatic heterocycles have many key roles in metabolism and other cellular processes. A large number of aromatic *N*-heterocycles are used as structural components of pharmaceuticals and agrochemicals, due to their biological activity. Among these

compounds, pyridine derivatives are found as compounds of herbicides, insecticides, vitamins, pharmaceuticals and adhesives.[1]

The compound 4-hydroxypyridine has an interesting chemical structure due to the presence of two tautomers, 4-hydroxypyridine and pyridine-4-one.[2] The hydroxy-tautomer is detected in significant amounts in nonpolar solvents such as in petroleum ether or in the gas phase[3]; in contrast, the more polar pyridone tautomer is favoured in polar solvents such as *N*-methylpyrrolidinone[4]. The polar nature results from the charge-separation in the pyridine form[5].

Hydroxypyridine has two different reactive nucleophilic centers and the alkylation of such compound can occur on either the phenolic oxygen or the pyridine nitrogen. The favoured route depends on the alkylating agent and the reaction conditions. *N*-alkylation, as well as *O*-alkylation can be afforded during the alkylation in normal case.[4,6] Generally, *O*-alkylation occurs in non-polar solvents and *N*-alkylation proceeds in polar solvents. *O*-alkylation predominates for reactions with silyl chloride[7], whereas *N*-alkylation occurs exclusively when 4-hydroxypyridine reacts with 1,2-dibromo-4,5-dimethylbenzene[8]. The 4-pyridone can also be converted from its corresponding 4-pyridyl ether with base in a polar solvent.[4]

Hydroxypyridinium is an important intermediate which is not synthesized from hydroxypyridine via direct alkylation due to the mixture of tautomers present. Generally, an *O*-protecting group is induced via the Mitsunobu reaction which yields the

corresponding *O*-alkylated product in preference to *N*-alkylation[9]. The *O*-protecting group was then deprotected to afford the hydroxypyridinium analogues[9,10].

N-methylated derivatives of 4-pyridone have found application as useful functional intermediates in the production of pharmaceuticals, veterinary drugs, pesticides and liquid crystal materials.[11] One of the 4-pyridone derivatives, 1,2-dimethylpyridin-4-one is currently used to treat iron overload in β-thalassemia patients.[12]

Recently, we reported that the presence of fluorine on the 3- position of 4-pyridyl ethers strongly influenced its reaction with methyl iodide. The predicted 1-methylpyridinium salts were not formed and instead the 1-methylpyridone was obtained.[13] Here we would like to report the effects of solvent and substituents at the 2- or 3-position of 4-methoxypyridine on its reaction with alkyl iodides.

In order to obtain 2- or 3-substituted 4-methoxypyridines (**1)** as starting materials, the commercially available 4-hydroxypyridine analogues were first treated with $POCl_3$ to afford 4-chloropyridine derivatives[14], followed by methoxylation with NaOMe to obtain 4-methoxypyridine analogues.[15] The 2- or 3-substituted 4-methoxypyridines were then treated with methyl iodide in the presence or absence of solvent, the corresponding 1-methylpyridinium ions and/or 1-methylpyridones were afforded (Scheme 1).

RESULTS AND DISCUSSION

When 4-methoxypyridine was treated with methyl iodide in the absence of any solvent for 12h, only the expected 4-methoxy-1-methylpyridin-1-ium salt was formed (Entry 1, Table 1). However, in the presence of acetone, a different reaction was observed. TLC showed that apart from the main spot (4-methoxy-1-methylpyridin-1-ium), another spot above the main spot was observed. NMR and MS data demonstrated that the methyl group of 4-methoxypyridine disappeared and the product 1-methylpyridin-4-one was obtained (Entry 2). Similar phenomena were observed for the reaction in the presence of other solvents such as toluene, acetonitrile, methanol and THF. The ratio of the products **2** and **3** is around 1:1 (see for example Entries 3-6). Prolonging the reaction time does not change the product ratio. Surprisingly, when solvent DMF was used, only product **3** was observed (Entry 7). However, when 4-methoxypyridine was treated with dimethyl sulphate or bromoethane instead of methyl iodide in the presence or absence of any solvent, the reaction failed and only the starting material was observed as assessed by TLC (Entry 8). Similarly, when an electron donating group such as methyl or methoxy was substituted at the 3-position of the pyridine ring, only pyridinium **2** was afforded in the absence of any solvent, whereas a mixture of **2** and **3** was obtained in the presence of acetone (Entries 9-12). When the position 3 of pyridine was substituted by an electron withdrawing group such as NO_2, the 1-methylpyridinium derivative was not formed either in the presence or absence of acetone. Instead, the 1-methylpyridin-4-one derivative was obtained (Entries 13-14). Similarly, when the adjacent position of 4-methoxypyridine was substituted by another electron withdrawing atom such as Br, the same phenomena were observed, that is, only the 1-methylpyridin-4-one derivative was afforded (Entries 15-18). In contrast to the 3-substituted 4-methoxypyridines, the 2-

substituted analogues reacted with methyl iodide to afford product in a slightly different way. All the selected 2-substituted 4-methoxypyridines reacted with methyl iodide in the absence of solvent to afford the 1-methylpyridinium derivative, regardless of the presence of an electron donating or an electron withdrawing group at position 2 (**1g, 1h, 1i**). In the presence of acetone, although the main product was the 1-methylpyridinium derivative, trace amount of the 1-methylpyridone was also detected (Entry 20). By changing the electron donating group methyl to electron withdrawing group Cl or COOH at position 2, the yield of the corresponding 1-methylpyridone was increased (Entry 22, Entry 24). However, the presence of electron withdrawing groups on position 2 of pyridine inactivated the lone pair of electrons on N and therefore the reaction required in harsher conditions.

In addition, when 3,5-dibromo-4-methoxypyridine (**1f**) was treated with ethyl iodide instead of methyl iodide in the presence or absence of acetone, besides the expected product 3,5-dibromo-1-ethylpyridin-4(1H)-one **(4f),** a small amount of 3,5-dibromo-1-methylpyridin-4(1H)-one **(3f)** was also obtained (**4f**:**3f** = 3:1) (Scheme 2). This phenomenon indicated that EtI reacted with **1f** to produce traces of MeI. MeI is more susceptible than EtI to be attacked by the lone pair of electrons on N of the pyridine. Similarly, a mixture of 3,5-dibromo-1-isopropylpyridin-4(1H)-one **(5f)** and 3,5-dibromo-1-methylpyridin-4(1H)-one **(3f)** (1:1) were afforded when **1f** was treated with isopropyl iodide. The higher proportion of **3f** in this reaction compared to that of the reaction with EtI results from the steric effect of the isopropyl group.

A possible mechanism for this conversion may involve a rearrangement of methyl from 4-methoxy to N. Theoretically the lone pair of electrons on N atom attacks the electrophilic methyl iodide to form 1-methylpyridinium. The resulting intermediate 1-methylpyridinium could be attacked by the iodide ion. The presence of an electron withdrawing group at position 3 drives this reaction, favouring 1-methylpyridone derivatives. In contrast to the presence of 3- electron withdrawing groups, electron withdrawing groups at C-2 of pyridine inactivates the lone pair of electrons on N and reduces the methylation at N. The presence of solvent facilitates the rearrangement.

EXPERIMENTAL SECTION

General Procedure For Methylation Of Compounds In Solvent-Free System

To a round bottle flask containing 1 (2 mmol) was added methyl iodide (10 mmol; 5 equiv.) and the mixture was stirred at room temperature or refluxed overnight. The reaction was monitored by TLC. After completion, the resulting precipitate was separated by filtration and purified by recrystallization.

General Procedure For Methylation Of Compounds In The Presence Of Solvent

Methyl iodide (4 mmol; 2 equiv.) was added to a solution of 1 (2 mmol) in various solvents (15 ml) and the mixture was refluxed overnight. The reaction was monitored by TLC. After completion, the solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc: MeOH, 20:1→5:1) to obtain the products.

Characterization Data For Selected Compounds

1,3-Dimethyl-4-Pyridone (3b)

White needles, m.p. 110 °C-112 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 – 7.66 (m, 1H), 7.64 (dd, *J* = 7.4, 2.2 Hz, 1H), 6.13 (dt, *J* = 7.1, 1.7 Hz, 1H), 3.64 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.63, 141.51, 139.85, 126.04, 114.98, 43.34, 14.02. HRMS (ESI): m/z calcd for $(C_7H_{10}NO)^+$: 124.0684; found: 124.0689.

2-Chloro-4-Methoxy-1-Methylpyridinium Iodide (2h)

Pale yellow needles, m.p. 115 °C -117 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.95 (dd, *J* = 7.2, 2.9 Hz, 1H), 8.02 (d, *J* = 2.9 Hz, 1H), 7.65 (dd, *J* = 7.2, 1H), 4.15 (s, 3H), 4.11 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.65, 148.92, 148.07, 114.66, 112.95, 59.19, 45.89, 40.42. HRMS (ESI): m/z calcd for $(C_7H_9{}^{35}ClNO)^+$: 158.0367; found: 158.0370.

4-Methoxy-1,2-Dimethylpyridinium Iodide (2g)

White needles, m.p. 168 °C -169 °C (lit.[16] 168 °C). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.76 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 3.0 Hz, 1H), 7.48 (dd, *J* = 7.2, 3.0 Hz, 1H), 4.06 (s, 6H), 2.69 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 170.46, 157.31, 147.78, 113.90, 111.82, 58.28, 44.02, 20.36. HRMS (ESI): m/z calcd for $(C_8H_{12}NO)^+$: 138.0913; found: 138.0917.

CONCLUSIONS

In conclusion, we have discovered a different route for the preparation of 1-substituted pyridine-4-ones from 4-methoxypyridines at mild conditions. The presence of solvents

favoured the formation of the 1-methylpyridones, whereas the absence of solvents favoured the formation of the pyridinium salts. The presence of an electron withdrawing group on pyridine ring can lead to the conversion easily, and significantly for such group at 3-position of the pyridine ring.

ACKNOWLEDGMENTS

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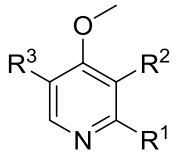
Table 1. Methylation of 4-methoxypyridines with methyl iodide in presence or absence of solvent



Entry	Substrate	R^1	R^2	R^3	Solvent	Product (yield)	
						2	**3**
1	**1a**	H	H	H	-	92%	-
2					acetone	69%	22%
3					toluene	57%	33%
4					acetonitrile	41%	47%
5					methanol	49%	36%
6					THF	44%	39%
7					DMF	-	87%
[a]8					-	-	-
9	**1b**	H	CH_3	H	-	87%	-
10					acetone	36%	53%
11	**1c**	CH_3	OCH_3	H	-	85%[b]	-
12					acetone	34%	57%
13	**1d**	H	NO_2	H	-	-	85%
14					acetone	-	95%
15	**1e**	CH_3	OCH_3	Br	-	-	71%
16					acetone	-	73%

17	**1f**	H	Br	Br	-	-	84%
18					acetone	-	91%
19	**1g**	CH_3	H	H	-	86%	-
20					acetone	80%	trace
21	**1h**	Cl	H	H	-	71%	-
22					acetone	42%	37%
23	**1i**	COOH	H	H	-	74%	-
24					acetone	47%	32%[d]

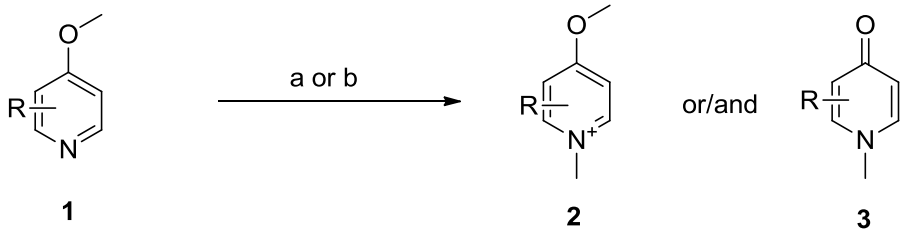
[a]Dimethyl sulphate or bromoethane was used instead of methyl iodide.

[b]4-Hydroxy-1-methylpyridinium was produced instead of 4-methoxy-1-methylpyridinium. The reason for the removal of methyl at 4-OH is not clear.

[c]Longer reaction time for this methylation is required.

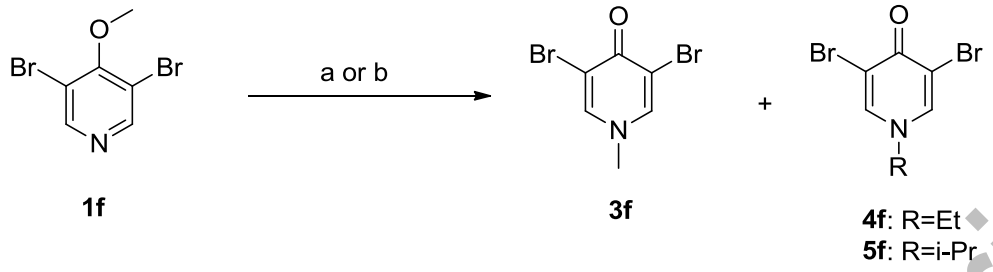
[d]Carboxyl group on C-2 was esterified by MeI. This phenomenon does not occur in the corresponding pyrdinium product.

Scheme 1 Synthesis of pyridinium or/and pyridinone. (a) MeI, r.t. or reflux, 12h. (b) MeI in organic solvent, reflux 12h.



1 **2** **3**

Scheme 2 The generation of a mixture of N-alkyl pyridinones. (a) EtI only or EtI in acetone, reflux, 24h; (b) i-PrI only or i-PrI in acetone, reflux, 48h.



1f **3f** **4f**: R=Et **5f**: R=i-Pr