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Aromatic nucleophilic substitution with 4-hydroxypyridine

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Abstract

The compound 4-hydroxypyridine is reacted with aromatic substrates that have a leaving group (usually halogen) and that is activated by an electron-withdrawing group or a heterocycle. Only *N*-aryl-4(1*H*)-pyridones are produced in this efficient aromatic nucleophilic substitution reaction. Some mechanistic aspects of the reaction have also been examined.

Keywords: 4-hydroxypyridine; aromatic nucleophilic substitution; pyridone.

The compound 4-hydroxypyridine has especially interesting chemistry due to the presence of two different reactive nucleophilic centers. In simple alkylation chemistry either the phenolic oxygen or the pyridine nitrogen may react depending on the specific alkylating agent and conditions. For example, phase transfer alkylation with simple alkyl bromides produces a mixture of *O*- and *N*-alkylation[1] while the *N*-alkylation occurs exclusively when α,α′-dibromo-*o*-xylene reacts with 4-hydroxypyridine.[2] Reactions with silyl chlorides and their analogues produce only *O*-alkylation[3] and these intermediates are useful for subsequent *N*-alkylation.[4] Conjugate additions also appear to go primarily on nitrogen.[5] Acylation with carbamoyl chloride produces the corresponding amides and esters depending on different conditions[6,7] while, when reacted with carboxylic acids, only esters are produced.[8]

Numerous aromatic nucleophilic substitution (S_NAr type) reactions with phenols are known and so it is very surprising that the use of 4-hydroxypyridine as a partner in the aromatic nucleophilic substitution reaction has been thus far only intermittent at best. The few documented examples of aromatic nucleophilic substitution with 4-hydroxypyridine indicate that reaction occurs only at nitrogen. For example, reaction with 2,4-dinitrochlorobenzene gives 1-(2,4-dinitrophenyl)-4(1*H*)-pyridone[9] and 4-chloronitrobenzene gives 1-(4-nitrophenyl)-4(1*H*)-pyridone.[10] More recently, a critical pharmaceutical intermediate was prepared by reaction of 4-hydroxypyridine with a derivative of 4-fluoroacetophenone.[11]

Now we report here that 4-hydroxypyridine is a very reactive partner with many other aromatic substrates. Conventional aromatic nucleophilic substitution reactions occur between an aromatic substrate with a leaving group (usually halogen) which is activated by an electron-withdrawing group. Recently, the scope of aromatic nucleophilic substitution chemistry has been broadened significantly by polymer

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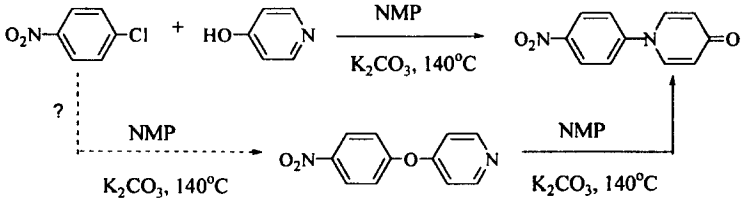
chemists who have introduced other unconventional activating groups including heterocyclic rings that have also been exploited here.[12]

Generally, the reactions we have examined are performed using an excess of 4-hydroxypyridine and potassium carbonate in *N*-methylpyrrolidinone (NMP) or water as solvent. The choice of solvent is dictated by the reactivity of the substrate, its melting point and the relative ease of isolation of the polar product from a dipolar aprotic solvent and water mixture versus isolation from pure water. If the melting point of the substrate is higher than 100°C or the reaction temperature higher than 100°C, then the reaction could only be reliably carried out in NMP (we have only run these reactions at atmospheric pressure). If the solubility of the product is very good both in NMP and water, then the reaction can only be carried in water and the yield is sometimes diminished due to complications in isolation of the polar product. The reactions are heated at such a temperature to complete the reaction in a convenient time and the conditions are not individually optimized. Many substrates have been examined and the results are summarized in Table 1.

When there is an efficient electron-withdrawing group on the benzene ring, the reaction temperature is relatively low and the reaction time is short as in entries 1–3, 10, 19 and 21–23. In entries 12, 13 and 20, when the electron-withdrawing group is weaker, the reaction temperature is higher. It is remarkable that the 4-alkylfluorobenzene (entry 7) reacts to give the pyridone product (albeit at high temperature and in modest yield). However, the 4-alkoxyfluorobenzene (entry 11) does not react productively even at 220°C for many hours. In our experiments with pseudohalogen substrates (triflate and tosylate) the desired pyridone is obtained in poor yield or not at all. For example, in entries 14 and 15, no pyridone is obtained, however, 4-phenylphenol is recovered. The pseudohalogen substrates are not reactive for attack at C but do react at S.[15]

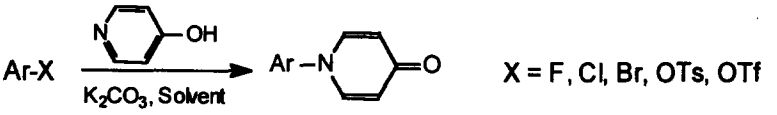
The ^{1}H NMR spectrum of selected pyridones (entries 1, 6, 9 and 12) show an unexpected singlet at about 2 ppm with an integration of 2H. This peak can be removed simply by shaking the solution with excess deuterium oxide. Thermal gravimetric analysis (TGA) shows a weight loss comparable to 1 molecule of water below 100°C. In many cases this water of hydration cannot be removed until the pyridone is heated above 100°C for overnight.

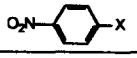
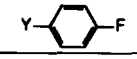
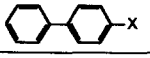
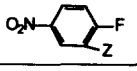
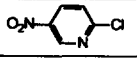
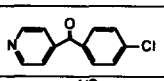
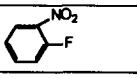
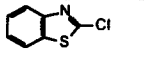
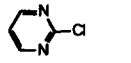


As mentioned before, alkylation and acylation of the 4-hydroxypyridine can occur either on N or O depending on the different reagents and conditions. However, we have found that the aromatic nucleophilic substitution with 4-hydroxypyridine appears to produce only *N*-substitution under our reaction conditions. In order to clarify the mechanism of this reaction, we independently synthesized the 4-nitrophenyl-4-pyridyl ether (which would be the *O*-substitution product) by an alternative known procedure.[16] We have found that treatment of this pyridyl ether under the reaction conditions used for aromatic nucleophilic substitution results in a complete rearrangement (by TLC) to the pyridone isomer (isolated and compared to authentic material). Hence, even if the ether product is formed to any extent during the reaction it is ultimately completely converted to the pyridone.

These pyridones are very interesting compounds in their own right as liquid crystals[17] and also serve as useful intermediates for other derivatives with useful physical properties such as the methylenedihydropyridine liquid crystals.[18,19] Since these pyridones are very polar and have complexing capability by

Table 1
Nucleophilic substitution reactions with 4-hydroxypyridine



Entry	Structure	Rxn (°C)[a]	Rxn (min)	Solvent	Yield (%)	Ratio[f]	m.p.[e] (°C)
							
1	X = F	110	90	NMP	100	1:1	202[c]
2	X = Cl	150	30	NMP	92	1:2	198[c]
3	X = Br	150	40	NMP	74	1:2	201[c]
4	X = OTf	180	60	NMP	0	1:2	none
5	X = OTs	170	90	NMP	12	1:2	201[c]
							
6	Y = SO_2CH_3	100	90	H_2O	82	1:2	221
7	Y = C_5H_{11}	220	1440	NMP	41	1:2	liquid
8	Y = CHO	100	120	H_2O	34	1:2	219
9	Y = COOEt	140	180	NMP	86	1:1.5	176[d]
10	Y = CN	150	40	NMP	79	1:2	195
11	Y = OC_8H_{17}	220	300	NMP	0	1:2	none
12	Y = 	180	120	NMP	87	1:2	141
							
13	X = F	180	360	NMP	95	1:2	187
14	X = OTf	180	60	NMP	0[b]	1:2	none
15	X = OTs	180	270	NMP	0[b]	1:2	none
							
16	Z = CH_3	100	105	H_2O	95	1:2	213
17	Z = NH_2	140	1h	NMP	73	1:2	289
18	Z = F	100	90	H_2O	66	1:2	170
19		100	5	H_2O	77	1:2	226
20		180	120	NMP	90	1:2	116
21		100	75	H_2O	89	1:2	93
22		100	30	NMP	75	1:2	188
23		90	30	H_2O	80	1:2	192

[a]: for NMP as the solvent, oil bath temperature in °C; for water as solvent, water boiling temperature.
[b]: 4-phenylphenol was recovered. [c]: lit. m.p.: 202°C.[13] [d]: lit. m.p.: 178-179°C.[14]
[e]: m.p. direct from H_2O; these products are often associated with H_2O or solvent.
[f]: substrate : 4-hydroxypyridine.

hydrogen bonding they may also prove useful for the preparation of materials with bulk supramolecular structure.

General procedure for reactions in H_2O (preparation for entry 6): A mixture of 4-fluorophenyl methyl sulfone (1.74 g, 10 mmol), 4-hydroxypyridine (1.90 g, 20 mmol), K_2CO_3 (2.76 g, 20 mmol) and water (12 mL) was heated to reflux for 4 h. The product precipitated after cooling and was then filtered off and dried under vacuum to give 2.04 g (82%) of a white solid. Mp 221°C; TGA showed 5.3% weight loss below 100°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 6.54 (d, *J*=7.8 Hz, 2H), 7.59 (d, *J*=8.7 Hz, 2H), 7.65 (d, *J*=7.8 Hz, 2H), 8.14 (d, *J*=8.4 Hz, 2H).

General procedure for reactions in NMP (preparation for entry 3): A mixture of 1-bromo-4-nitrobenzene (1.01 g, 5 mmol), 4-hydroxypyridine (0.95 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol) and NMP (6 mL) was heated at 150°C (oil bath temperature) for 40 min. Water was added to precipitate the product. The solid was filtered off, washed by water and dried under vacuum to give 0.805 g (74%) of a yellow solid. Mp 201°C; TGA showed 7.3% weight loss below 100°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (d, *J*=7.8 Hz, 2H), 7.57 (d, *J*=9.0 Hz, 2H), 7.67 (d, *J*=7.8 Hz, 2H), 8.43 (d, *J*=9.0 Hz, 2H).

Procedure for the rearrangement of 4-nitrophenyl-4-pyridyl ether: A mixture of 4-nitrophenyl-4-pyridyl ether (0.61 g, 2.8 mmol), K_2CO_3 (0.78 g, 5.6 mmol) and NMP (5 mL) was heated at 140°C (oil bath temperature) for 2 h. TLC showed the disappearance of the ether and clean conversion to the pyridone. Water was added to precipitate the product and the solid was filtered off, washed by water and dried under vacuum to give 0.38 g (62%) of the pyridone as a light yellow solid. Mp 201°C. This rearrangement product is identical with that obtained from the aromatic nucleophilic substitution reaction.

Acknowledgements

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