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Pyridine Hydrochloride: a New Reagent for the Synthesis of o-Chloro Hydroxy Derivatives in Pyridine and Quinoline Series.

Florence Mongin, Olivier Mongin, François Trécourt, Alain Godard and Guy Quéguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique de l'IRCOF, associé au CNRS
Institut National des Sciences Appliquées de Rouen BP 08 76131 Mont-Saint-Aignan (France)

Abstract: Pyridine hydrochloride has been widely used in the cleavage of ethers. It is shown herein that this reagent is also efficient for the synthesis of chloro compounds starting from the corresponding bromo derivatives in π-deficient series such as pyridine and quinoline. Thus, for example, 7-bromo-8-hydroxyquinoline was almost quantitatively converted into 7-chloro-8-hydroxyquinoline. The scope of the reaction has been studied.

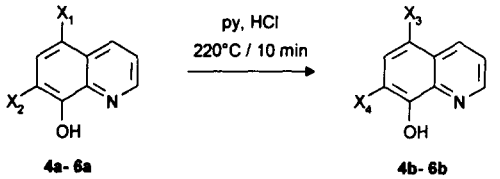
Pyridine hydrochloride (py,HCl)[1] has been extensively used for ether cleavages,[2] cyclization[3] and dehydration reactions.[4] We herein describe a new application of py,HCl as a chlorinating reagent in hydroxyquinoline and pyridine series. During the course of an ether cleavage with py,HCl we observed the replacement of a bromine atom by chlorine. This observation led us to study and test this unusual reaction for the synthesis of chlorohydroxy derivatives in quinoline and pyridine series starting from the corresponding bromo derivatives. 8-Hydroxyquinoline (oxine) and its halo derivatives at the phenyl ring have found extensive applications as analytical reagents, metal extracting agents and corrosion inhibitors because of their ability to form complexes with many metal ions.[5] They are also used as insecticides,[6] bactericides,[7] fungicides,[8] anti malarial agents[9] and more recently as anti tumoral agents.[10]

In pyridine series, direct bromination of 2-hydroxypyridine is regioselective at C-3[11] whereas chlorination is not. However, heating 3-bromo-2-hydroxypyridine (**1**) in py,HCl at its boiling temperature led to the corresponding 3-chloropyridine **2** in good yield (Scheme 1).

Scheme 1

In quinoline series, direct bromination at the phenyl ring is regioselective at C-7,[12] whereas direct chlorination is not. Heating 7-bromo-8-hydroxyquinoline (**3a**) in py,HCl quantitatively afforded 7-chloro-8-hydroxyquinoline **3b** (Scheme 1).[13] Note that direct displacement of Br by Cl had already been observed for **3b** (HCl under pressure at 160-180°C) but the yield is not mentioned.[14]

Under the same conditions, 5-bromo-8-hydroxyquinoline (**4a**), 5,7-dibromo-8-hydroxyquinoline (**5a**) and 7-bromo-8-hydroxy-5-methylquinoline (**6a**)[15] led to the corresponding chloro compounds **4b-6b** in good to excellent yields (Scheme 2, Table 1).



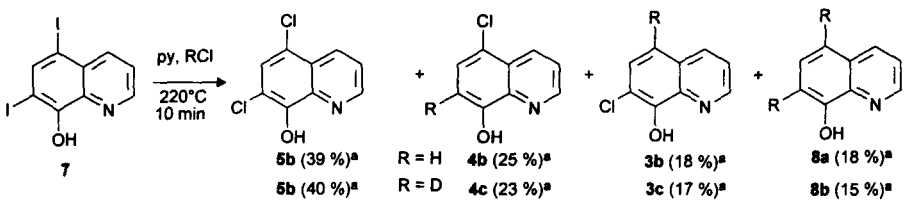
Scheme 2

Table 1: Pyridine hydrochloride Reaction on Various 8-Hydroxyquinoline Derivatives

Starting material	X_1	X_2	Product	X_3	X_4	Yield %
4a	Br	H	**4b**	Cl	H	93
5a	Br	Br	**5b**	Cl	Cl	90
6a	CH_3	Br	**6b**	CH_3	Cl	99

This reaction was also tested on iodo quinolines since it is known that their reactivity is different from bromoquinolines. In the case of 5,7-diiodo-8-hydroxyquinoline (**7**), a mixture of 5,7-dichloro-8-hydroxyquinoline (**5b**), monochloro-8-hydroxyquinolines **3b-4b** and 8-hydroxyquinoline (**8a**) was obtained. As expected 5,7-dichloro-8-hydroxypyridine (**5b**) was the major product; however, formation of dehalogenated compounds were also observed in significant ratio.

Moreover, when the reaction was carried out with deuterated pyridine hydrochloride (py,DCl) instead of py,HCl, compound **5b** and deuterated quinolines **3c**, **4c** and **8b** were obtained in a similar ratio; the deuterium incorporation taking place at each chlorine atom position (Scheme 3).



[a] Yields determined by ^{1}H NMR analysis of the crude product.

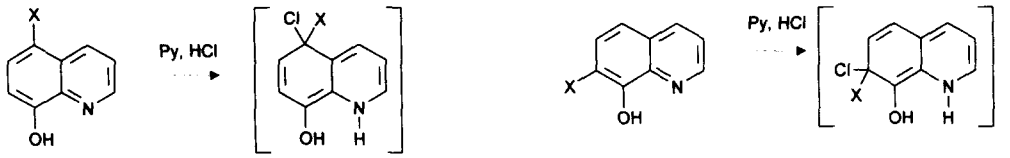
Scheme 3

It is to be noted that under the same conditions, 2- and 4-bromophenols gave a complex mixture of chloro and bromophenols.[16] Intracyclic nitrogen atom seems to take a significant part in the 2-hydroxypyridine and 8-hydroxyquinoline series.

The reaction mechanism is certainly complex. However some observations can be made. The replacement of a bromine or a iodine atom either by chlorine, hydrogen or deuterium occurs regiospecifically. When bromo derivatives were used as starting material, the replacement of bromine atoms by chlorine atoms was only observed. However in the case of iodoquinolines, there is a significant formation of dehalogenated compounds.

An aromatic electrophilic substitution by H^+ or D^+ could be suggested to explain the formation of dehalogenated compounds since py,HCl had been previously described as a dehalogenating agent in the phenol series by Royer.[17]

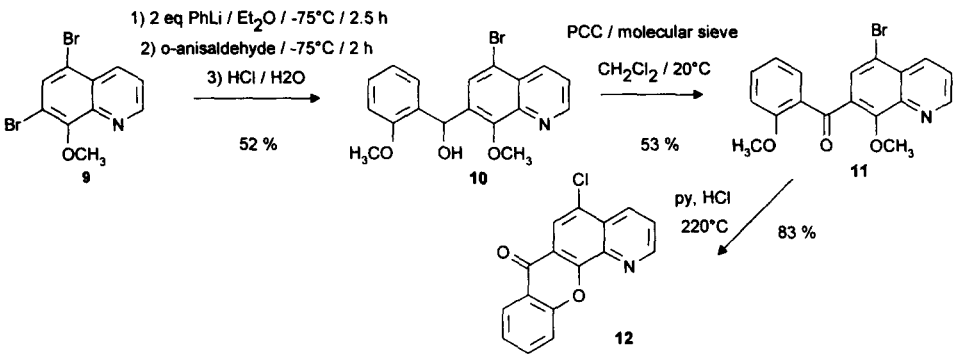
A nucleophilic substitution by the Cl^- species of py,HCl could also be suggested since the reaction occurs very favorably at C-5 or/and C-7 of 8-hydroxyquinolines. In this very protic medium, an intermediate Mesenheimer complex could be stabilised (Scheme 4).



Scheme 4

Application to the Synthesis of a Chloropyridoxanthone. Xanthone derivatives have potential pharmaceutical properties.[18] Taking advantage of the previously described replacement of a bromine atom by a chlorine, a chloro pyridoxanthone could be obtained.

From 5,7-dibromo-8-methoxyquinoline (**9**), a regioselective bromine-lithium exchange[19] with phenyllithium[20] in diethylether, followed by reaction of the lithio derivative with *o*-anisaldehyde, led to alcohol **10**.[21] Oxidation of **10** was achieved by pyridinium chlorochromate[22] (PCC) in the presence of molecular sieves in dichloromethane at room temperature to give the ketone **11**.[23] Cyclisation of **11** with py,HCl gave 5-chloro-pyrido[3,2-c]xanthone **12**.[24] The replacement of the bromine atom by a chlorine was confirmed by mass spectrum analysis (Scheme 5).



Scheme 5

Reactions using pyridine hydrochloride; General Procedure: A mixture of pyridine (10 mL) and conc. HCl (10.2 mL) was heated to 220°C for 5 min. The hot pyridine hydrochloride thus obtained was added to the required 8-hydroxyquinoline derivative (or 3-bromo-2-hydroxypyridine) (1.33 mmol). The mixture was refluxed (220°C) for 10 min and poured onto ice (10 g). Neutralisation with $NaHCO_3$ (12 g), extraction by EtOAc (4 x 30 mL), drying (Na_2SO_4, 10 g) and removal of solvent afforded a crude product which was filtered over silica gel (10 g, eluent: EtOAc).

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13. Compound **3b** mp 152°C; ^{1}H NMR (DMSO-d_6 at 200 MHz): δ 7.42 (d, 1H, H_5, J = 8.9) 7.54 (d, 1H, H_6, J = 8.9), 7.57 (dd, 1H, H_3, J = 8.4-4.2), 8.36 (dd, 1H, H_4, J = 8.4-1.6), 8.88 (dd, 1H, H_2, J = 4.2-1.6), 9.50 (s, 1H, OH).

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21. Compound **10** mp 150°C; ^{1}H NMR (DMSO-d_6 at 200 MHz): δ 3.8 (s, 1H, OH), 3.83 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 6.60 (s, 1H, CHOH), 6.94 (m, 2H, Ph), 7.28 (m, 2H, Ph), 7.48 (dd, 1H, H_3, J = 8.6-4.2) 7.94 (s, 1H, H_6), 8.47 (dd, 1H, H_4, J = 8.6-1.6), 8.91 (dd, 1H, H_2, J = 4.2-1.6).

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23. Compound **11** mp 133°C; ^{1}H NMR (DMSO-d_6 at 200 MHz): δ 3.59 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.96 (m, 2H), 7.55 (m, 3H), 7.94 (s, 1H, H_6), 8.49 (m, 1H, H_4), 8.94 (m, 1H, H_2).

24. 5-Chloro-pyrido[3,2-c]xanthone **12** mp 261°C; ^{1}H NMR (DMSO-d_6 at 200 MHz): δ 7.49 (m, 1H, Ph), 7.8 (m, 3H, H_3 and Ph), 8.4 (m, 2H, H_6 and Ph), 8.69 (dd, 1H, H_4, J = 8.5-1.5), 9.19 (dd, 1H, H_2, J = 4.5-1.5). MS (CI): *m/z* (%) = 282/284 (M^+ + 1).

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