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Halogenation of Pyridinols using Bis(*sym*-collidine)iodine(I) and Bis(*sym*-collidine)bromine(I) hexafluorophosphate

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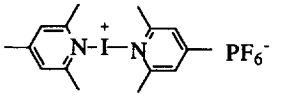
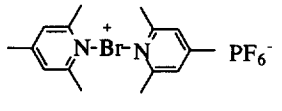
Abstract: Iodination and bromination of pyridinols was achieved by action of the title reagents in methylene chloride. © 1997 Elsevier Science Ltd.

Halopyridinols are known from a long time [1] and are well documented in the literature. Access to such compounds have been reported for the more common procedures by halogenation of the corresponding pyridinols, using bromine,[2] iodine,[3] and others reagents [4] or halogen substitutions of acid [5] and amino groups.[6] The halogenation of 2-, 3- and 4-pyridinols was found to lead to ortho and (or) para substitutions.[2,3]

We recently reported that the iodination of phenols occurred in excellent yields to iodophenols using bis(*sym*-collidine)iodine(I) hexafluorophosphate.[7] In these reactions all ortho-para free positions were substituted. We wondered if with pyridinols, the same comportment could be observed. The pyridinols used in this study were all commercially available. The halogenation reactions were carried out in methylene chloride at room temperature in the presence of bis(*sym*-collidine)iodine(I) and bis(*sym*-collidine)bromine(I) hexafluorophosphate **1** and **2**.[8] Our results are reported in the Table.



1



2

Structures of the products were easily determined from their ^{1}H NMR spectra and confirmed when possible by comparison of their melting points with those reported in the literature. Except the products reported in entries g-j, all these compounds were already known.[9]

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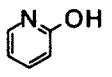
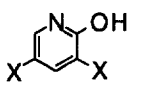
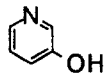
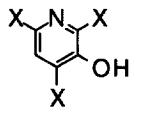
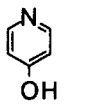
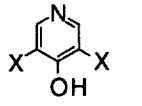
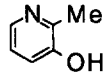
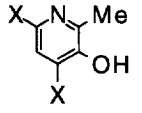
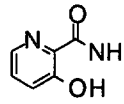
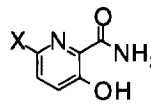
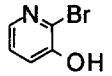
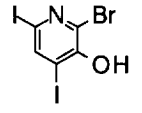
Table. Halogenation of pyridinols

Entry	Substrate	Reaction conditions (equiv. **1** or **2**; reatn time, h)	Product [a]	Isolated yield (%)	
a		(2; 2)		X = Br	90
b				X = I	78
c		(3; 2)		X = Br	95
d				X = I	89
e		(2; 2)		X = Br	79
f				X = I	95
g		(2; 2)		X = Br	86
h				X = I	72
i		(1; 48)		X = Br	70 [b]
j		(1; 72)		X = I	72 [b]
k		see text			71

[a] To simplify the Table the tautomeric pyridinones are not represented.
[b] the same result was obtained in the presence of 2 equiv. of **1** or **2**.

In the reactions examined generally no selectivity was observed. For example starting with 3-pyridinol (entries c, d) addition of one or two equivalents of reagents **1** or **2** led to a mixture of the starting material and mono-, di-, and trihalo-substituted products: only addition of a third equivalent led to the exclusive formation of the trihalopyridinols. Entry k reserves a special comment. Addition of one or two equivalents of bis(*sym*-collidine)iodine(I) hexafluorophosphate **1** to 2-bromo-3-pyridinol led to a mixture of starting pyridinol and of mono- and diiodo-substituted products. For example, after 2 h at room temperature in the presence of two equivalents of **1** we isolated a mixture of starting material (20%), 6-iodopyridinol (30%) and 4,6-diiodopyridinol (50%). The same result was obtained after 24 h. It seems that the collidine liberated during the iodination, led to the formation of pyridinolates which prevents a further reaction. We found it was possible to

obtain the formation of the diiodo product in good yield (entry k) by cooling the reaction mixture at -50°C then adding successively reagent **1** (2 equiv.) and trifluoroacetic acid (2 equiv.). It has been previously reported that only traces of this diiodopyridinol could be formed using iodine in aqueous sodium hydroxide.[2b] With reagents **1** and **2** even the unreactive 3-hydroxypicolinamide (entries i, j) led to 6-halo reaction products. In this case however, dihalogenation was never observed.

In conclusion, we reported in this paper a new and efficient method for the halogenation of pyridinols. However the high electrophilicity of these reagents does not allow in general selective mono reactions when poly halogenations were possible.

Procedure for the iodination of 2-pyridinol (entry b): to a solution of 2-pyridinol (0.192 g, 2 mmol) in methylene chloride (40 mL) was added bis(*sym*-collidine)iodine(I) hexafluorophosphate **1** (2.05 g, 4 mmol). After stirring the reaction mixture 2 h at room temperature, the heterogeneous mixture was concentrated under vacuum to ~ 5 mL and 3,5-diiodo-2-pyridinol was isolated by filtration. Similar procedures were used with the substrates reported in the entries e, f, j.

Procedure for the iodination of 3-pyridinol (entry d): after reaction conducted as reported above the homogenous mixture was concentrated to ~ 5 mL and ether (20 mL) was added, leading to the precipitation of a white solid (collidinium hexafluorophosphate). This solid was filtrated off and the filtrate concentrated under vacuum. The residue was then purified by liquid chromatography over silica gel (ethyl acetate-hexane) to give triiodo-3-pyridinol. Similar procedures were used with the substrates reported in the entries a, c, g-i.

Preparation of 2-bromo-4,6-diiodo-3-pyridinol (entry k): a solution of 2-bromo-3-pyridinol (0.176 g, 1 mmol) in methylene chloride (20 mL) was cooled at -50°C and bis(*sym*-collidine)iodine(I) hexafluorophosphate **1** (1.028 g, 2 mmol) was added, followed by trifluoroacetic acid (0.154 mL, 2 mmol). After 10 minutes at this temperature the cooling bath was removed and the mixture stirred during 3 hours. The mixture was concentrated under vacuum to ~ 5 mL and ether (20 mL) was added. The solid formed was filtered off and the filtrate concentrated under vacuum. The residue was then purified by liquid chromatography over silica gel (ethyl acetate-hexane) to give 0.3 g of 2-bromo-4,6-diiodo-3-pyridinol.

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7. Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* **1995**, *36*, 8217-8221.
8. Reagent **1** was prepared as previously reported: Simonot, B.; Rousseau, G. *J. Org. Chem.* **1993**, *58*, 4-5. Reagent **2** was obtained using the same procedure.
9. 4,6-Dibromo-2-methyl-3-pyridinol: ^{1}H NMR ($CDCl_3$) δ 12.1 (bs, 1H), 7.46 (s, 1H), 2.54 (s, 3H); mp: 106°C. 4,6-Diiodo-2-methyl-3-pyridinol: ^{1}H NMR ($CDCl_3$) δ 12.0 (bs, 1H), 7.83 (s, 1H), 2.51 (s, 3H); mp: 146°C. 6-Bromo-3-hydroxypicolinamide: ^{1}H NMR ($CDCl_3$) δ 12.0 (s, 1H), 7.60 (bs, 1H), 7.50 (d, J = 6.5 Hz, 1H), 7.21 (d, J = 6.5 Hz, 1H), 5.65 (bs, 1H); mp: 215°C (sublimation). 6-Iodo-3-hydroxypicolinamide: ^{1}H NMR ($CDCl_3$) δ 12.0 (bs, 1H), 8.05 (d, J = 9.5 Hz, 1H), 7.95 (bs, 1H), 7.32 (d, J = 9.5 Hz, 1H), 6.0 (bs, 1H); mp: 243°C (sublimation).

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