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IODOPYRIDINES FROM BROMO- AND CHLOROPYRIDINES

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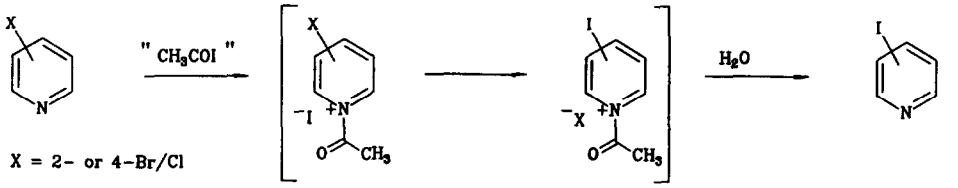
Abstract: *Bromo- and chloropyridines may be converted to the corresponding iodopyridines by treatment with sodium iodide and acetyl chloride in acetonitrile.*

Iodopyridines are useful intermediates for the synthesis of complex pyridine derivatives.[1] Although a number of methods have been used for the synthesis of iodopyridines,[2] routes which proceed from the corresponding chloro- or bromopyridines are particularly attractive. Two methods for accomplishing the bromide/chloride to iodide transformation have been recently been described: a stannylation-iododestannylation procedure[3], and a procedure in which a chloropyridine is refluxed with NaI in concentrated hydriodic acid.[4] Though less versatile, the latter procedure has the virtues of low cost and simplicity.

We recently had need of 2,4-diiodopyridine. A single attempt on our part at applying the NaI/HI protocol to 2,4-dichloropyridine[5] was a complete failure. The mechanistic basis for the NaI/HI procedure undoubtedly lies with the activation of the pyridine ring towards nucleophilic aromatic substitution by protonation of the pyridine nitrogen.[6] We reasoned that it might be possible to activate the pyridine nitrogen in a milder fashion through acylation, rather than protonation. The activated intermediate in this case is simply that which is invoked to explain the nucleophilic catalysis of acylations by pyridines.[7]



Indeed, treatment of 2,4-dichloropyridine with three equivalents of anhydrous sodium iodide and two equivalents of acetyl chloride in refluxing acetonitrile for 24 hours led to the formation of 2,4-diiodopyridine in 35% yield. The results of the application of this procedure to a number of other halopyridines are given in the following Table. A number of features of this reaction warrant comment.

i) Although the halogen-iodide exchange is an equilibrium reaction, it is not necessary to use a large excess of sodium iodide; the equilibrium is driven to the iodide by precipitation of sodium chloride.[8]

ii) Several substrates fail to react. In the case of 2,6-dichloropyridine (entry 3) we assume that the flanking chlorines sterically hinder the formation of the activated acylated pyridinium intermediate.[9] We speculate that the failure of the two methyl nicotinate derivatives to react (entries 5 and 6) may be a result of a decrease of the nucleophilicity of the pyridine nitrogen to the extent that little or none of the acylated pyridinium species is formed, although some type of selective destruction of the product iodide may also be possible.

iii) 2-Bromopyridine reacted much more rapidly than 2-chloropyridine (entries 1 and 2). Encouraged by this increased reactivity, we examined the reaction of ethyl 6-bromonicotinate (entry 7). However, none of the desired iodide was formed. In addition to recovered starting material, a small amount of ethyl nicotinate was detected by GC-MS; this type of reduction has been observed for some electron poor substrates subjected to the NaI/HI procedure.[4]

Reaction of Halopyridines with AcCl/NaI

Entry	Substrate	Reflux Time (Hr.)	Yield of Iodide Product[10]
1	2-chloropyridine	24	55%
2	2-bromopyridine	3	64
3	2,4-dichloropyridine	24	35
4	2,6-dichloropyridine	48	0
5	methyl 2-chloronicotinate	45	0
6	methyl 6-chloronicotinate	72	0*
7	ethyl 6-bromonicotinate	24	0#
8	2-chloroquinoline	25	64

*Traces of the iodide product were visible by GC-MS at 3 hours; on prolonged reflux this disappeared. #Starting material and ethyl nicotinate was recovered; see text.

Although the method described here lacks the general versatility of the stannylation-iododestannylation procedure of Yamamoto,[3] it represents a simple, low cost method for the conversion of suitable bromo- and chloropyridines into the corresponding iodides. In some instances it is complimentary to the NaI/HI procedure described by Newkome.[1a,4]

Typical procedure: 2-chloropyridine (0.228 g, 2 mmol), dry sodium iodide (0.459 g, 3.1 mmol), and freshly distilled acetyl chloride (0.30 mL, 4.2 mmol) in 2.25 mL dry acetonitrile were refluxed under nitrogen for 24 hours.[11] Aqueous 10%K_2CO_3/5% $NaHSO_3$ was added and the mixture extracted three times with chloroform. After drying (Na_2SO_4) and evaporation of the chloroform, flash chromatography (50% ethyl acetate/petroleum ether) yielded 2-iodopyridine (0.234 g, 55%). The melting point of the picrate was 122-123 °C (lit.[12] 119-120 °C).

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9. The same explanation has been advanced to explain the lack of activity of 2-methylpyridine as an acylation catalyst; Butler, A. R. and Gold, V., *J. Chem. Soc.*, **1961**, 4362.
10. All products had spectral data (^1H NMR, ^{13}C NMR, IR, MS) consistent with the assigned structures.
11. The reactions are best followed by GC of a worked-up aliquot, as the starting material and products are generally not separated by silica gel TLC. In some instances, the reaction appears to stop after 5-6 hours; addition of a further equivalent of AcCl and NaI usually drives the reaction to completion.
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