OXIDATION OF SUBSTITUTED PYRIDINES $PyrCH_2X$ ($X=H$, COOR, COC_6H_5) WITH HYPERVALENT IODINE REAGENTS

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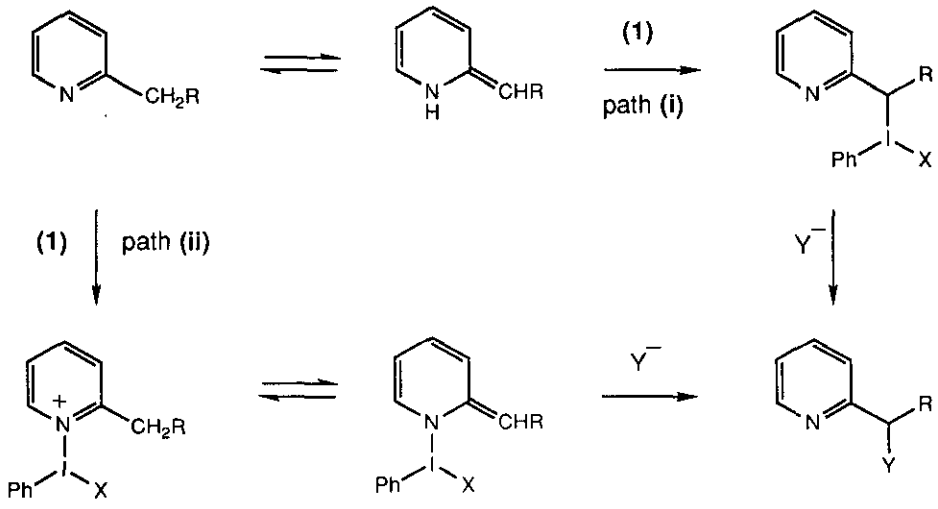
Abstract - Oxidation of a variety of pyridines, $PyrCH_2X$ ($X=H$, COOR, COC_6H_5) with hypervalent iodine reagents $PhI(X)(Y)$ ($X=OH$, $Y=OTs$; $X=Y=CH_3COO$; $X=Y=CF_3COO$) has been studied. Simple alkylpyridines are unaffected by the reagents, but 2- and 4-substituted derivatives $PyrCH_2X$ ($X=COOR$, COC_6H_5) are oxidised at the CH_2 group.

One area of hypervalent iodine chemistry that has attracted much interest in recent years has been the development of methodology using reagents of the type $PhI(X)(Y)$ ($X=OH$, $Y=OTs$; $X=Y=CH_3COO$; $X=Y=CF_3COO$) (**1**) for the oxidation of enolisable ketones and esters to α-tosyloxy, α-acetoxy and α-trifluoroacetoxy derivatives.[1-6] The ease of reaction is apparently dependent both on the nature of the hypervalent iodine reagent and on the acidity of the C-H bond which is oxidised, and in many cases it is necessary to either use base or to carry out the reaction on a preformed enolate.[5,7]

There are relatively few general procedures for the direct oxidation of alkyl substituents in π-deficient heterocycles. These substituents are, of course, weakly acidic, especially when located α- or γ- to a ring nitrogen atom, and we therefore undertook a brief investigation to determine if hypervalent iodine-based oxidation might constitute a useful and practical alternative to classical procedures such as selenium dioxide oxidation or Katada-type rearrangement of azine *N*-oxides for oxygenation of C-H bonds α- or γ- to a π-

deficient ring.[8,9] There are two obvious pathways by which such oxidations might occur (Scheme 1), similar to those proposed for the hypervalent iodine oxidation of enolisable ketones.[1,2]

Scheme 1

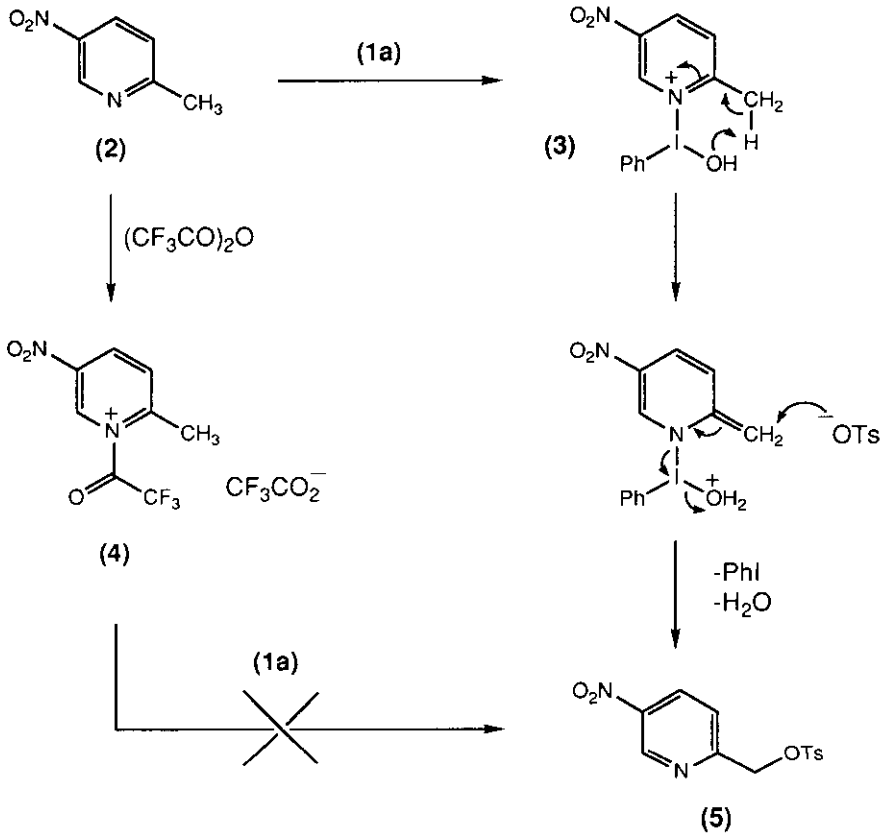


1, PhI(X)(Y); **a**, X=OH, Y=OTs; **b**, X=Y=CH_3COO, **c**, X=Y=CF_3COO

Attempts to oxidise either 2- or 4-picoline with the reagents (**1a-c**) under a variety of conditions were completely unsuccessful. The picolines were recovered unchanged when reagents (**1b**) and (**1c**) were used, even under forcing conditions, while the picolinium tosylates were formed with reagent (**1a**). As the methyl groups in 2- and 4-picoline are 10-12 pKa units less acidic than the CH groups in simple enolisable ketones, a number of substituted pyridines with increasingly acidic alkyl C-H substituents was investigated. 2- and 4-Benzylpyridine and 2-(4-nitrobenzyl)pyridine also proved inert to the action of the reagents (**1a-c**), again presumably because the acidity of the alkyl C-H groups was too low. However, treatment of 2-methyl-5-nitropyridine (**2**) with **1a** in refluxing acetonitrile gave 5-nitro-2-tosyloxymethylpyridine (**5**) in 30% yield (Scheme 2), but no reaction was observed with either **1b** or **1c**. By contrast, there was no reaction when the isomeric 4-methyl-3-nitropyridine was treated with **1a**, **1b** or **1c**. These results can be explained on the basis that reaction of **1a** with **2** proceeds by initial formation of the pyridinium salt (**3**), followed by intramolecular deprotonation of the methyl group and, finally, nucleophilic addition to the exocyclic methylene group and re-aromatisation of the ring. Some evidence in support of the mechanism summarised in Scheme 2 comes from the observation that treatment of the pyridinium salt (**4**), the methyl group of which should be

significantly more acidic than that of **2**, with **1a** did not result in any oxidation of the 2-methyl substituent. 2-Methyl-5-nitropyridine was recovered after aqueous work-up of the reaction mixture.

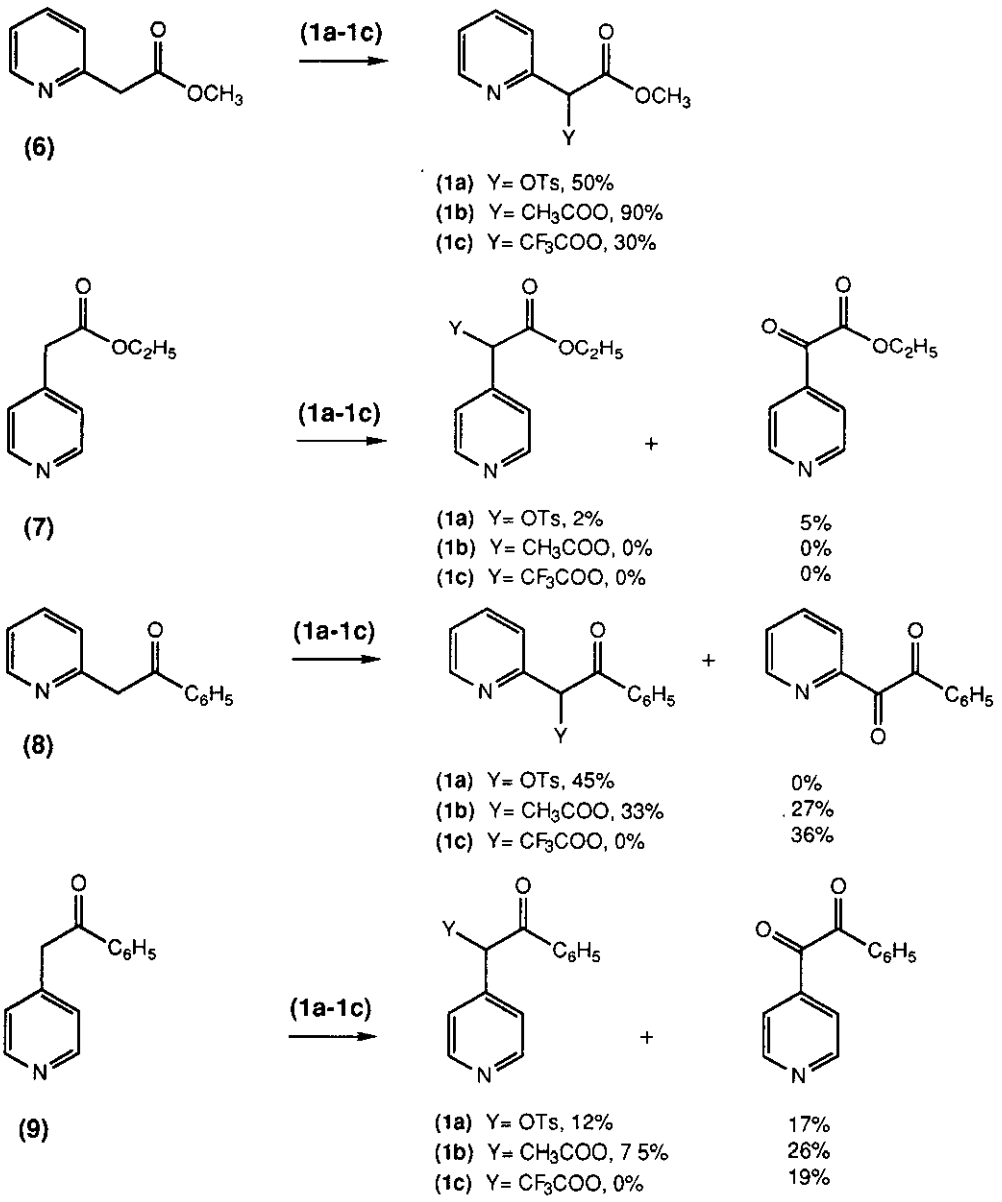
Scheme 2



A similar reactivity pattern to that described above was observed with substrates in which an electrophilic centre was placed adjacent to the alkyl substituent rather than in a ring position. Thus, while ethyl 3-pyridylacetate was unaffected by the reagents (**1a-c**), methyl 2-pyridylacetate (**6**) was oxidised by all three (Scheme 3).[10,11] When the isomeric ethyl 4-pyridylacetate (**7**) was used, a very low yield of oxidation products was obtained only with **1a**, again implying that the path (**ii**) type mechanism outlined in Schemes 1 and 2, involving a pyridinium intermediate analogous to **3**, is the major pathway. All three iodonium salts were found to be effective oxidants for 1-phenyl-2-(2-pyridyl)ethanone (**8**): with **1a**, α-tosyloxylation was observed, with **1c**, only the α-diketone was obtained, while a mixture of the oxidation products was formed

when **1b** was used. Mixtures of oxidation products were also obtained from the isomeric 1-phenyl-2-(4-pyridyl)ethanone (**9**) with reagents (**1a**) and (**1b**) whereas the diketone was obtained with **1c**.[12]

Scheme 3



Our results show that hypervalent iodine-based oxidation of alkyl-substituted pyridines is possible. However, they indicate that this is only the case for compounds in which the reactive centre is activated by a strong electron withdrawing group. We have shown that positional isomerism is of great importance; both 2- and 4- substituted pyridines undergo reaction whereas 3- substituted compounds do not. The higher yields obtained with 2- substituted pyridines suggest that the major reaction pathway involves the formation of a pyridinium intermediate such as **3**, followed by intramolecular transfer of a proton.

REFERENCES

1. R.M.Moriarty, H.Hu, and S.C.Gupta, *Tetrahedron Lett.*, 1981, **22**, 1283.
2. E.I.Koser, A.E.Relenyi, A.N.Kalos, L.Rebrovic, and R.H.Wettach, *J.Org.Chem.*, 1982, **47**, 2487.
3. R.M.Moriarty, M.P.Duncan, and O.Prakash, *J Chem.Soc., Perkin Trans. I*, 1987, 1781.
4. R.M.Moriarty, O.Prakash, M.P.Duncan, and R.K.Vaid, *J.Org.Chem.*, 1987, **52**, 150.
5. R.M.Moriarty, R.Penmasta, A.K.Awashti, W.R.Epa, and I.Prakash, *J.Org.Chem*, 1989, **54**, 1101.
6. R.M.Moriarty, B.A.Bergland, and R.Penmasta, *Tetrahedron Lett.*, 1992, **33**, 6065.
7. R.M.Moriarty and H.Hu, *Tetrahedron Lett.*, 1981, **22**, 2747.
8. C.A.Buehler, J.O.Harris, and W.F.Arendale, *J.Am.Chem.Soc.*, 1950, **72**, 4953.
9. A.R.Katritzky and J.M.Lagowski, *"Chemistry of the Heterocyclic N-Oxides"* , Academic Press, New York, 1971, p.352.
10. Typical Experimental Procedure: To a stirred solution of methyl 2-pyridylacetate (0.4 g, 2.6 mmol) in dichloromethane (10 ml) at ambient temperature under nitrogen was added diacetoxyiodobenzene (0.84 g, 2.6 mmol). The pale yellow solution was stirred at ambient temperature for 48 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel to give 0.49 g (90%) of product.
11. All yields refer to isolated products, the structures of which were confirmed by spectroscopic analysis.
12. All pyridines were commercially available, with the exceptions of 2-methyl-5-nitropyridine (**2**),[13] 1-phenyl-2-(2-pyridyl)ethanone (**8**),[14] and 1-phenyl-2-(4-pyridyl)ethanone (**9**).[14]
13. W.Gruber and K.Schlogl, *Monatsh.Chem.*, 1949, **80**, 499.
14. J.Wolfe, D.Portlock, and D.Feuerbach, *J Org.Chem.*, 1974, **39**, 2006.

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