

OXIDATION OF SUBSTITUTED PYRIDINES PyrCHRSiMe_3 ($\text{R} = \text{H}, \text{Me}, \text{Ph}$) AND SUBSTITUTED QUINOLINES $\text{QnCH}_2\text{SiMe}_3$ WITH HYPERVALENT IODINE REAGENTS

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Abstract - Oxidation of a variety of substituted pyridines, PyrCHRSiMe_3 ($\text{R} = \text{H}, \text{Me}, \text{Ph}$) and quinolines, $\text{QnCH}_2\text{SiMe}_3$ with hypervalent iodine reagents PIDA, $(\text{PhI}(\text{OCOCH}_3)_2)$ and PIFA, $(\text{PhI}(\text{OCOCF}_3)_2)$ has been studied. Oxy-desilylation with PIDA/TBAF gives low to moderate yields of PyrCHROR^1 and QnCH_2OR^1 ($\text{R}^1 = \text{H}, \text{Ac}$), while good yields of PyrCHROH and QnCH_2OH are obtained when PIFA is used.

Recently we reported the use of the hypervalent iodine compounds $\text{PhI}(\text{OH})(\text{OTs})$, $\text{PhI}(\text{OCOCH}_3)_2$ and $\text{PhI}(\text{OCOCF}_3)_2$ for the direct oxidation of 2- and 4- alkyl-substituted pyridines in which the alkyl $\alpha\text{-CH}$ bond is activated by a strong electron-withdrawing group.¹ The ease of reaction was found to be dependent on both the reactivity of the hypervalent iodine reagent and the acidity of the C-H bond which was oxidised. Simple 2- and 4- alkylpyridines did not undergo this direct hypervalent iodine oxidation, presumably because of the low acidity of the $\alpha\text{-CH}$ bonds.

There is much literature precedent for the successful use of pre-formed ester and ketone enolates in hypervalent iodine-mediated oxidations.²⁻⁵ Once the enolate is formed the acidity of the precursor ceases to be a controlling factor in the hypervalent iodine oxidation. We have examined the reactivity of alkylpyridine equivalents of pre-formed enolates towards hypervalent iodine oxidation, and now summarise our results.

Reaction of 2-picolylolithium with PIDA resulted in formation of 1,2-bis-(2-pyridyl)ethane in 46% yield, possibly *via* an oxidative radical coupling process, together with much tarry material. Reaction of the isomeric 4-picolylolithium with PIDA resulted only in tar formation. We decided, therefore, to investigate the reactivity towards both PIDA and PIFA of the masked alkylpyridyl and methylquinolyl carbanions, PyrCHRSiMe_3 ($\text{R}=\text{H, Me, Ph}$) and $\text{QnCH}_2\text{SiMe}_3$.⁶

Attempts to oxidise 2-(trimethylsilyl)methylpyridine (**1**) with PIDA proved unsuccessful. 2-Picoline was the only product obtained, even after prolonged reaction at high temperatures. However, reaction of **1** with PIDA in the presence of TBAF ($n\text{-Bu}_4\text{NF}$) at ambient temperature resulted in the slow formation of 2-acetoxymethylpyridine in 20% yield; protodesilylation to give 2-picoline accounted for the majority of the starting organosilane (**1**). Treatment of **1** with PIFA alone, however, resulted in the rapid formation at room temperature of 2-trifluoroacetoxymethylpyridine in quantitative yield (determined by ^1H nmr). The corresponding alcohol, 2-hydroxymethylpyridine, was isolated in 60% yield after acid/base work-up. This pattern of reactivity was repeated for a number of related pyridines and quinolines (Tables 1 and 2).

Three pathways by which the transformations may occur are shown in the Scheme, which highlight the difference in reactivity of the more electrophilic PIFA compared to PIDA. The low yield of 3-acetoxymethylpyridine obtained by reaction of 3-(trimethylsilyl)methylpyridine (**2**) with PIDA and TBAF in THF, (for which only the central pathway shown in the Scheme is operative), was attributed to rapid quenching of the highly reactive 3-picolyl anion by water present in the TBAF solution. Lack of reaction between compound (**2**) and PIFA provides further evidence for the mechanism outlined in the Scheme. Complexation of **2** with PIFA presumably gives a pyridinium salt in which the C-Si bond is insufficiently polarised to allow facile nucleophilic displacement of the silyl group. Addition of TBAF to this mixture had no effect. As the literature suggests, much more forcing conditions are required to affect this transformation.⁸

Treatment of 4-(trimethylsilyl)methylpyridine (**3**) with PIFA resulted in tar formation. Presumably in this case the silicon group is lost very rapidly from the intermediate pyridinium salt to give a highly reactive pyridine methide. In attempts to slow the rate of desilylation, more bulky silicon groups were employed; however, there was no reaction when 4-(triethylsilyl)methyl-, 4-(triisopropylsilyl)methyl-

Table 1 Reaction of substituted pyridines PyrCHRSiMe₃ (R=H, Me, Ph) and substituted quinolines QnCH₂SiMe₃ with PIDA/TBAF (PhI(OCOCH₃)₂)^{9,11}

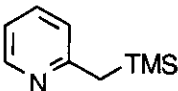
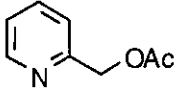
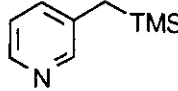
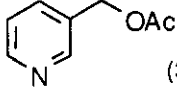
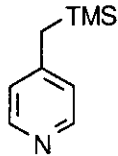
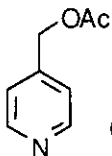
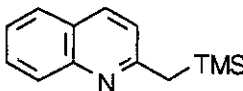
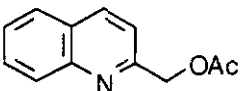
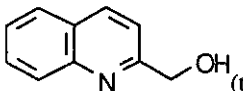
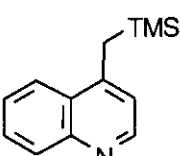
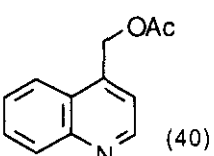
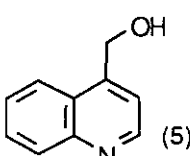
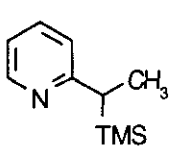
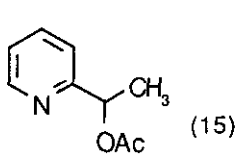
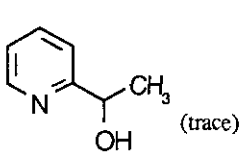
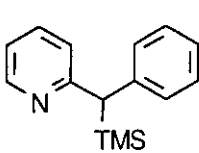
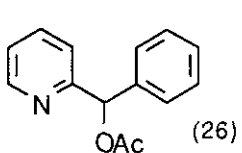
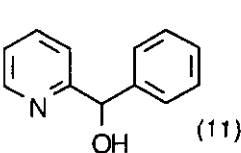
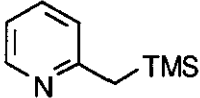
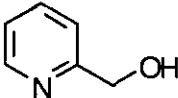
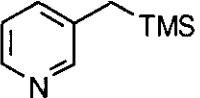
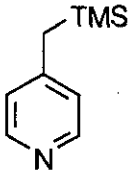
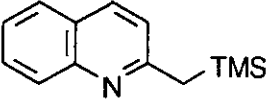
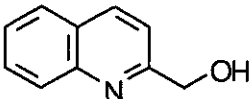
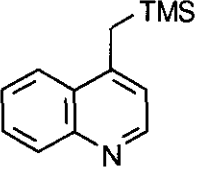
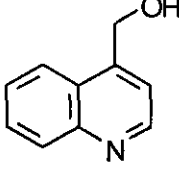
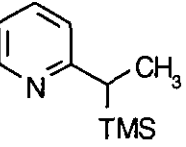
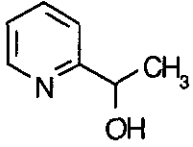
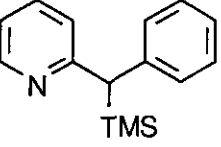
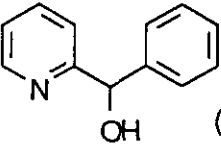
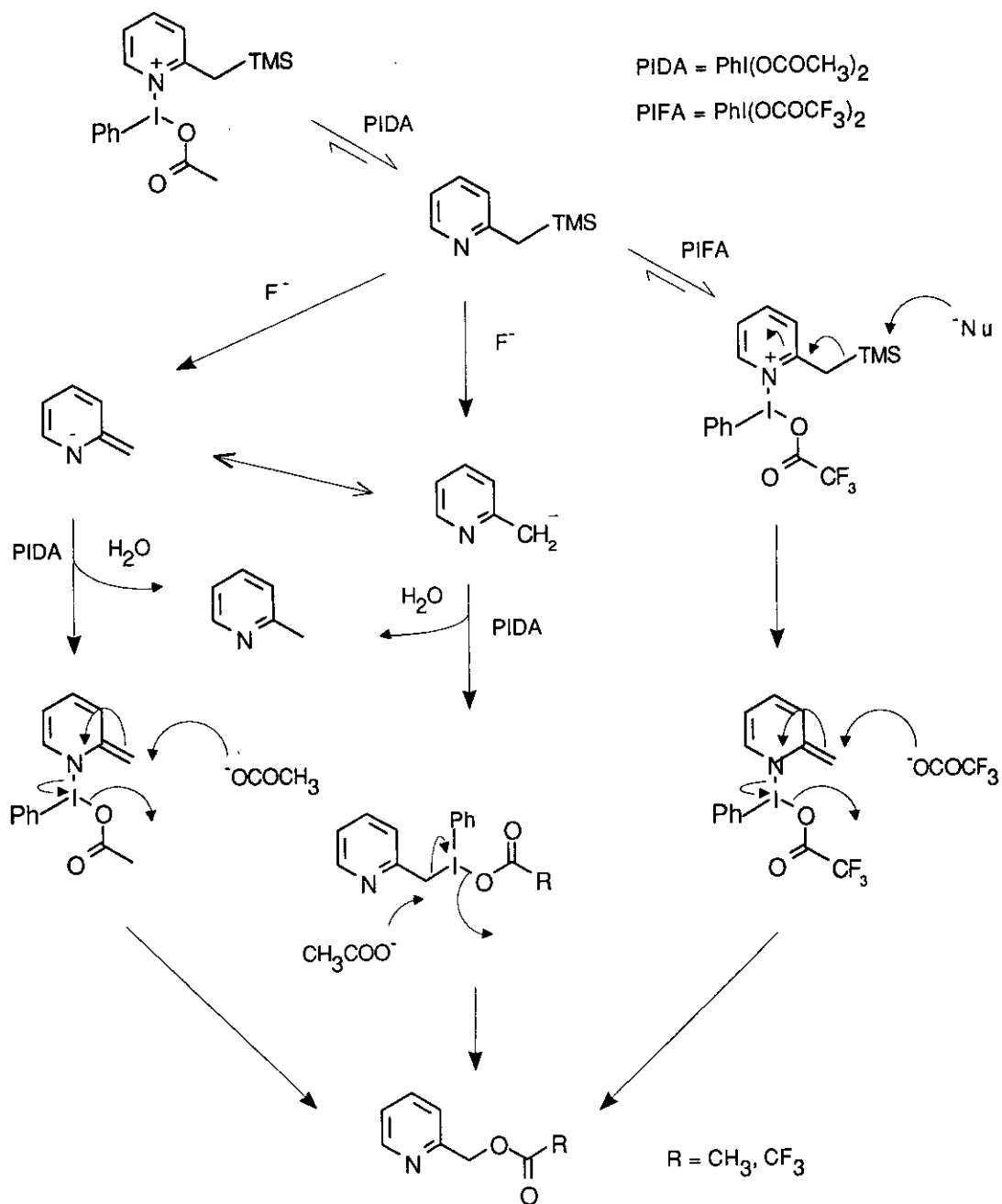
Compound Number and Structure	Products (Yield %)
(1) 	 (20)
(2) 	 (3)
(3) 	 (48)
(4) 	 (52) +  (trace)
(5) 	 (40) +  (5)
(6) 	 (15) +  (trace)
(7) 	 (26) +  (11)

Table 2 Reaction of substituted pyridines PyrCHRSiMe₃ (R=H, Me, Ph) and substituted quinolines QnCH₂SiMe₃ with PIFA (PhI(OCOCF₃)₂).^{10,11}

Compound Number and Structure	Products (Yield %)
(1) 	 (60)
(2) 	No Reaction
(3) 	Tar Formation
(4) 	 (80)
(5) 	 (47)
(6) 	 (66)
(7) 	 (63)

Scheme



and 4-(tert-butyldimethylsilyl)methylpyridines were treated with PIFA, whereas both 4-(isopropyldimethylsilyl)methylpyridine (slowly) and 4-(ethyldimethylsilyl)methylpyridine (rapidly) gave mixtures containing trace amounts of desired product and 4-picoline along with intractable tars. To a much lesser extent, tar formation was also observed in the reaction of 4-(trimethylsilyl)methylquinoline (5) with PIFA, along with the desired alcohol in 48% yield. A comparable yield of the acetoxymethyl compound, together with some alcohol, was obtained on reaction of 5 with PIDA. Both 2-acetoxymethylquinoline and 2-hydroxymethylquinoline were obtained in good yield from reactions of 2-(trimethylsilyl)methylquinoline (4) with PIDA/TBAF and PIFA respectively. Compound (6), 2-(1-trimethylsilyl)ethylpyridine, gave a mixture of the ester and alcohol in low yield on treatment with PIDA/TBAF along with a good yield of the alcohol when reacted with PIFA, as did compound (7), 2-(1-trimethylsilyl-1-phenyl)methylpyridine.

In conclusion, our results demonstrate the hypervalent iodine oxidation of (pyridylalkyl)trimethylsilanes and (quinolylmethyl)trimethylsilanes to the corresponding alcohols and esters. They confirm that both the position of the substituent group and the nature of the hypervalent iodine reagent are of great importance: a variety of 2- substituted pyridines undergo smooth reaction with PIFA, whereas 2-, 3- and 4-substituted pyridines undergo reaction with PIDA to varying degrees. This oxidation, which takes place under exceptionally mild conditions when compared to classical procedures such as selenium dioxide oxidation or Katada-type rearrangements, has the potential to be a general procedure for the oxidation of suitably substituted pyridines and quinolines, especially the 2- and 4- substituted derivatives.

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6. General procedure for the preparation of compounds (1), (3), (4), (6) and (7): A solution of n-butyllithium in hexane (2.5 M, 1 eq.) was added to a stirred solution of the alkyl heterocycle in THF at -70°C under N₂. The solution of the anion thus generated was stirred at -70°C for 1 h and then quenched with trimethylchlorosilane (1 eq.) The mixture was concentrated to give an oily solid which was treated with n-hexane. Lithium chloride was removed by filtration and the crude product obtained after removal of the solvent was purified by vacuum distillation. Using the same general procedure, compound (5) was prepared with 1.0 M lithium hexamethyldisilazane in THF in place of 2.5 M butyllithium in hexane. Compound (2) was prepared according to the literature.⁷
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8. K.Tamao, N.Ishida, and M.Kumada, *J. Org. Chem.*, 1983, **48**, 2120.
9. Typical procedure: PIDA (1.5 g, 4.6 mmol) and then TBAF (1.0 M solution in THF, 5 ml, 5 mmol) were added to a stirred solution of 2-(trimethylsilyl)methylquinoline (4) (0.5 g, 2.3 mmol) in dichloromethane (10 ml) at ambient temperature under N₂. The resultant mixture was stirred at ambient temperature for 20 h. Solvent was removed under reduced pressure and the residue treated with ether (15 ml) and 10% HCl (aq.) (10 ml). The aqueous phase was basified to pH 8-9 with 2 M sodium hydroxide solution and the resulting mixture was extracted with dichloromethane (20 ml x 3). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate as eluant to give 0.24 g (52%) of pure product.
10. Typical procedure: PIFA (1 g, 2.3 mmol) was added to a stirred solution of 4 (0.5 g, 2.3 mmol) in dichloromethane (10 ml) at ambient temperature under N₂, and the resultant mixture was stirred at ambient temperature for 1 h. Solvent was removed under reduced pressure and the residue was partitioned between ether (15 ml) and 10% HCl (aq.) (15 ml). The aqueous phase was basified to pH 8-9 with 2 M sodium hydroxide solution and the resulting solution was extracted into

dichloromethane (20 ml x 3). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure to give 0.3 g (82%) of product.

11. All yields refer to isolated products, the structures of which were confirmed by spectroscopic analysis.

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