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Pseudo Vilsmeier Reagents
A New Protocol for Regiospecific C-C Bond Formation in Pyridines

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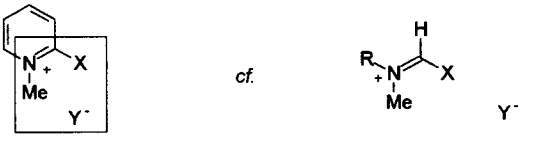
Abstract: *2-Fluoro- and 2,6-difluoropyridine are readily quaternised with methyl p-toluenesulfonate and methyl triflate respectively. These salts readily undergo substitution of fluorine by enamines, the difluoro-derivatives being capable of specific mono- or disubstitution in a symmetrical or unsymmetrical manner. The products reduced to give keto-1,2,3,6-tetrahydropyridines, can be hydrolysed to the corresponding ketopyridines or hydrogenated to give ketopiperidines.*

The regiospecific functionalisation of π-deficient heterocycles, particularly with carbon-based groups is not trivial and is particularly problematic for pyridines. Even the powerful methodologies of metalation and halogen-metal exchange are not without their serious limitations due to addition, dimerisation, halogen-dance and related diversions. We herein disclose a new approach to solve this long-standing problem. α-Halopyridinium salts may be viewed as pseudo-Vilsmeier reagents (Scheme 1). As such, they should react effectively with electrophiles such as enamines, which we have utilised widely in reaction with Vilsmeier reagents.



A pseudo-Vilsmeier reagent **A Vilsmeier reagent**

Scheme 1

2-Chloro- **1**, and 2-fluoropyridinium salts **2**, easily made by heating the halopyridine with methyl *p*-toluenesulfonate, react smoothly with a variety of enamines **3**[1] in acetonitrile solution at 80 °C as shown in Scheme 2. The chloropyridinium salts are considerably less reactive than their fluoro-analogues and require base for optimal reaction. Pyrrolidino-enamines are somewhat more reactive than their morpholino counterparts. The resulting products **4** are best isolated as their water insoluble and beautifully crystalline PF_6^- salts by addition of ammonium hexafluorophosphate.

This process is equally applicable to the 2,6-difluoropyridinium salts **5**, which require methyl triflate for quaternisation of the pyridine and are best used *in situ*, the yield of salt being essentially quantitative. These salts react at 0 °C in acetonitrile to introduce one enamine side-arm to give **6**, and at ambient temperature to allow

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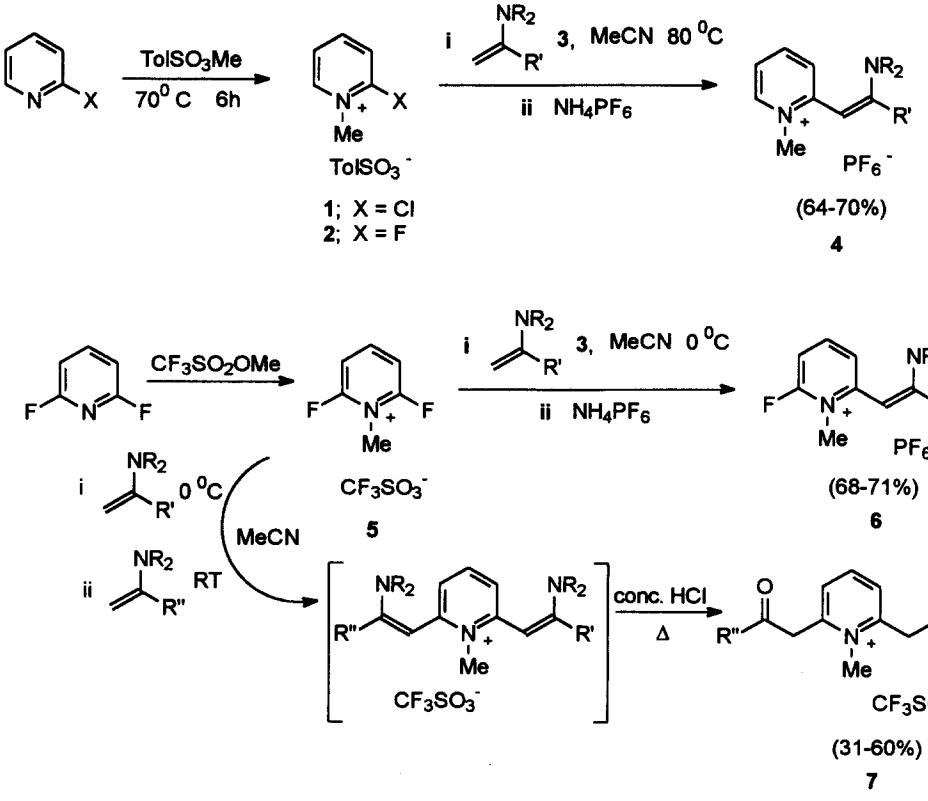
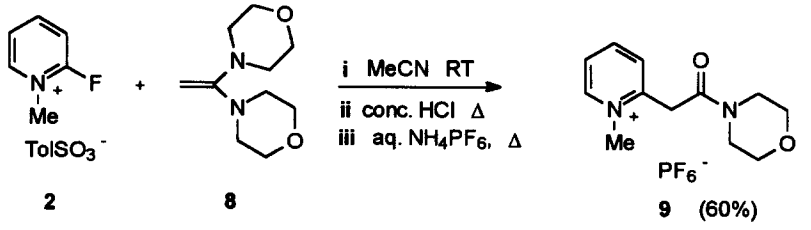
two substitutions to be performed giving 7. These two enamines may be similar or different and thus both symmetrical and unsymmetrical pyridines are accessible in good yield. Surprisingly, enol derivatives such as enol acetates and trimethylsilyl ethers, so far have proved ineffective in this process.



Scheme 2

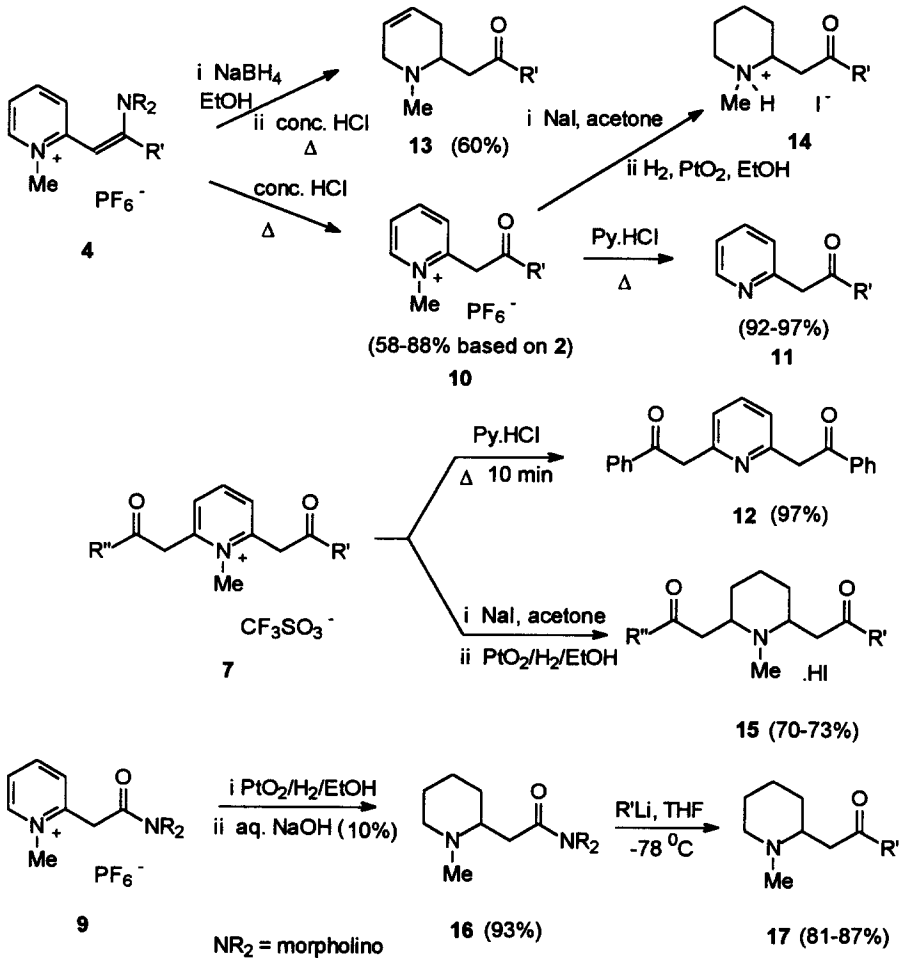


Scheme 3

Since enamines of many unsymmetrical aliphatic ketones are a mixture of isomers, an alternative approach has been developed using the easily made[2] enediamines **8**. These potent nucleophiles readily substitute the pyridinium salts **1**, **2** and **5** to give morpholino-amides **9** (Scheme 3), derivatives of which react efficiently with

organolithiums to give ketones (Scheme 4).

These new α-functionalised pyridinium salts are very useful precursors to a variety of pyridine and reduced pyridine intermediates, as shown in Scheme 4. Acidic hydrolysis yields the ketopyridinium salts **10** and **7**, demethylation of which is readily achieved in high yield by brief heating of the salts in refluxing pyridinium[3] chloride[3] giving **11** and **12**. Reduction of the enamines **4** with sodium borohydride[4] gives exclusively the tetrahydropyridines **13**, while hydrogenation of the salts **10** and **7** using PtO_2 and hydrogen yields the ketopiperidines **14** and **15** respectively, best isolated as their salts.



Scheme 4

The amidopyridiniums **9** are similarly easily reduced and the resulting piperidino-amides **16** react with organolithiums to give the ketones **17**.

These products have been applied to the concise synthesis of piperidine alkaloids in the accompanying paper.

Typical method for the synthesis of 2-substituted pyridinium salts: To a solution of 2-fluoropyridinium tosylate (**2**) (5.66g, 20mmol) made *in situ* in acetonitrile (15 ml), was added dropwise a solution of 1-phenyl-1-pyrrolidinoethene (3.81g, 22 mmol) in 10 ml of acetonitrile at r.t.under a nitrogen atmosphere. The reaction mixture was stirred at 80°C for 2h. The deep red solution was then concentrated under vacuum and the viscous red residue refluxed with conc. hydrochloric acid (30 ml) for 3h. The dark brown solution was cooled to room temperature, and ammonium hexafluorophosphate (3.59g, 22 mmol) added causing immediate precipitation of the product, which was filtered and washed with cold water and ethyl acetate. Recrystallisation of the crude product from ethanol afforded **10** (R' = Ph) as white crystals, yield: 6.28g (88%). M.p. 163-165°C (ethanol). (Found: C 47.18; H 3.88; N 3.81. $C_{14}H_{14}F_6NOP$ requires: C 47.05; H 3.95; N 3.92). IR (KBr): ν 1685 (C=O), 840 (PF_6^-) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 4.24 (s, 3H), 5.29 (s, 2H), 7.64 (t, 2H), 7.76 (t, 1H), 8.12 (m, 4H), 8.57 (t, 1H), 9.04 (d, 1H). ^{13}C-NMR: δ 43.55, 45.61, 126.37, 128.87, 130.67, 134.23, 135.29, 145.27, 147.04, 152.89, 194.19. MS (ES): 212 (M^+).

Typical method for the synthesis of 2,6-substituted pyridinium salts: to a solution of 2,6-difluoro-1-methylpyridinium triflate (**5**) (5.58g , 20 mmol) made *in situ* in dry acetonitrile (15 ml) was added dropwise a solution of 1-phenyl-1-pyrrolidinoethene (3.81g, 22 mmol) in acetonitrile (10 ml) at 0°C under a nitrogen atmosphere. The reaction mixture was allowed to warm to r.t. and stirred for 3h. To this solution was then added dropwise at r.t. a solution of 1-(4-methylphenyl)-1-pyrrolidinoethene (4.11g, 22mmol) in acetonitrile (10ml) and the solution stirred for another 14h. The deep red solution was concentrated under vacuum and to the viscous red residue was added conc. hydrochloric acid (50 ml). The resulting aqueous solution was refluxed for 3 h, cooled to room temperature and left to stand for several hours, when **7** (R' = Ph; R" = 4-MeC_6H_4) precipitated as white needles, which were collected by filtration and washed with water and ethyl acetate. An analytical sample was obtained by recrystallisation of the crude product from ethanol, yield: 4.10g (42%). M.p. 188-190°C. (Found: C 58.54; H 4.76; N 2.78. $C_{24}H_{22}F_3NO_5S$ requires: C 58.40, H 4.50; N 2.84) . IR (KBr): ν 1689 (C=O), 1276 (S=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.40 (s, 3H), 3.90 (s, 3H), 5.29 (s, 2H), 5.33 (s, 2H), 7.37 (d, 2H), 7.55 (t, 3H), 7.67 (t, 1H), 7.90 (d, 2H), 8.01 (m, 4H), 8.47 (t, 1H). ^{13}C-NMR: δ 21.17, 41.12, 41.16, 44.73, 128.50, 128.62, 128.85, 129.38, 129.75, 132.81, 134.22, 135.25, 144.54, 144.91, 154.02, 154.22, 193.56, 194.05. MS (ES^+): 344 (M^+).

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References and Notes

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