S_NAr Displacement of Fluorine from Pentafluoropyridine by Sodium Oximates: Unprecedented Substitution Patterns

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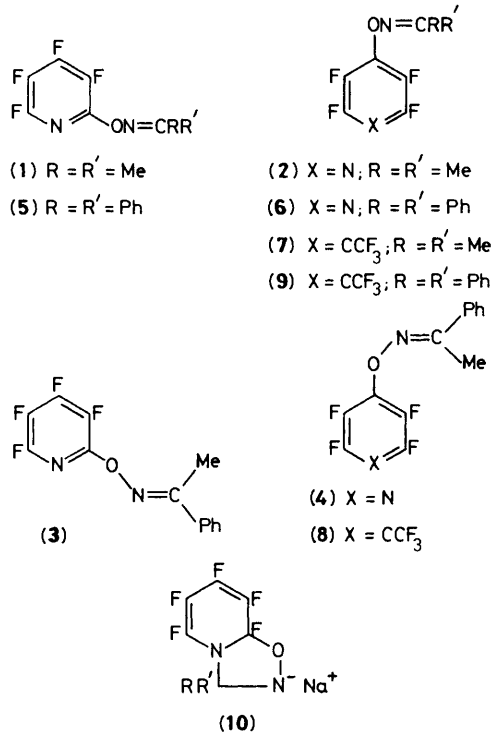
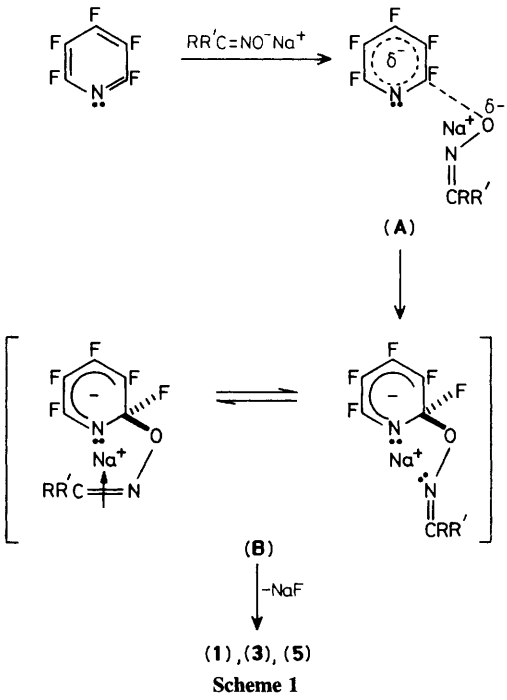
Displacement of fluorine from pentafluoropyridine under mild conditions by sodium oximates RR'C=NO$^-$Na$^+$ [R,R' = Me or Ph; R = Me, R' = Ph (*anti* isomer)] suspended in benzene or diethyl ether yields *O*-tetrafluoropyridyl oximes arising from monosubstitution at both 2- and 4-positions.

Nucleophilic attack on pentafluoropyridine has been utilised extensively in synthesis[1] since the first examples were reported twenty-five years ago.[2] 'Exclusive' 4-substitution is judged to occur first and a satisfactory rationale is available.[3] Having studied S_NAr reactions between pentafluoropyridine and the sodium salts $(CF_3)_2NO^-Na^+$ and $Et_2NO^-Na^+$, which proceeded 'normally' *via* initial displacement of 4-fluorine,[4] we have examined the situation with sodium ketoximates. The results have no precedent.

In a two-phase solid–liquid system, reaction (exothermic) between pentafluoropyridine and an approximately equimolar amount of the ketoximate $Me_2C{=}NO^-Na^+$ in diethyl ether at −35 °C yields a 1 : 9 mixture (crude product analysed by ^{19}F n.m.r. spectroscopy) of acetone *O*-(tetrafluoro-2-pyridyl)oxime (**1**) and its 4-pyridyl isomer (**2**) from which the components can be isolated chromatographically in at least 7.5 and 80% yield, respectively. Under virtually identical conditions, the oximate *anti*-MeCPh=NO$^-$Na$^+$ gives the corresponding *O*-tetrafluoropyridyl derivatives (**3**) and (**4**) in 30 and 52% (isolated material), respectively. Use of benzene as a suspending agent/solvent instead of diethyl ether, and a reaction temperature of 20 °C, increased the ratio (**3**) : (**4**) to





Scheme 1

1:1. Also at 20 °C, the sodium salt of benzophenone oxime attacks pentafluoropyridine in diethyl ether with displacement of fluorine at both the 2- and 4-positions [→ (**5**) + (**6**), ratio by ^{19}F n.m.r. 33:67; yields after chromatography 22 and 56%, respectively].

By contrast, 'normal' substitution[5] occurred, *i.e.* displacement of only the 4-fluorine was detected when octafluorotoluene in diethyl ether was treated (at −10, 20, and 20 °C, respectively) with the salts $Me_2C{=}NO^-Na^+$ [→ (**7**), 87%], *anti*-MeCPh=NO^-Na^+ [→ (**8**), 70%], or $Ph_2C{=}NO^-Na^+$ [→ (**9**), 73%]. Hence the abnormal orientation of attack by an oximate anion–sodium cation ion-pair on pentafluoropyridine seems to demand the presence of the ring nitrogen with its associated, though tightly held,† lone-pair electrons. Presumably,‡ poor solvation of the sodium cation is also required because *homogeneous* reactions between equimolar amounts of pentafluoropyridine and the *anti*-ketoximate MeCPh=NO^-Na^+ in solvents (EtOH, Me_2CO, or tetrahydrothiophene-1,1-dioxide) capable of solvating sodium cations proceeded with displacement of fluorine from only the 4-position [→ (**4**)] according to ^{19}F n.m.r. analysis of the crude products. Furthermore, formation of the 2-isomer (**3**) in heterogeneous C_5F_5N/*anti*-MeCPh=NO^-K^+/Et_2O systems [ratio of (**3**):(**4**) at −35 °C 1:5] was eliminated by the inclusion of 18-crown-6 ether.

At present, therefore, 2-substitution in pentafluoropyridine by sodium (or potassium) ketoximates in benzene or diethyl ether is suggested to proceed as shown in Scheme 1. Since pentafluoropyridine is virtually non-basic,† the sodium cation clearly cannot begin to play its role in lowering the activation energy for formation of the resonance-stabilized σ-complex (**B**) (presumably[3] the rate determining step) until an incipient bond arises between C-2 and the ketoximate oxygen, see (**A**). Detailed mechanistic studies are in progress, including attempts to determine whether [3 + 2]-cycloadducts (**10**) are involved.

Extrapolation of the above work to include structural analogues of alkali metal ketoximates is also underway: the lithium salt of benzophenone hydrazone ($Ph_2C{=}N\bar{N}H\ Li^+$) in diethyl ether, for example, has been found to attack pentafluoropyridine to give a *ca.* 1:1 mixture of 2- and 4-$(Ph_2C{=}NNH)C_5F_4N$. Conversion of the former product and of the corresponding ketoximes [(**1**), (**3**), (**5**)] to synthetically-important 2-substituted tetrafluoropyridines (2-$H_2NC_5F_4N$, 2-$H_2NNHC_5F_4N$, and 2-HOC_5F_4N) will be reported in detail elsewhere.

All the new ketoximes [(**1**)—(**9**)] possessed correct elemental compositions and spectroscopic properties consistent with the structures assigned. To make absolutely certain that nitrone formation {*e.g.* 4-$[Ph_2C{=}\overset{+}{N}(O^-)]C_5F_4N$} had not occurred, and to check on the retention of geometrical integrity of the oximate moiety MeCPh=NO^-, crystals of compounds (**3**) and (**6**) were subjected to *X*-ray analysis.

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† Pentafluoropyridine forms salts only with superacids.[1b]

‡ A seemingly less likely alternative is to invoke differential solvation of the two anionic (Meisenheimer) σ-complexes[6] involved in 2- and 4-substitution in pentafluoropyridine.

References

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