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Multi-substituted heterocycles

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Abstract

Pentafluoropyridine was used as the starting material for the preparation of a range of pyridine derivatives that bear five different substituents. In this context, syntheses of penta-functional pyridine systems by sequences of nucleophilic aromatic substitution, palladium catalysed coupling and bromo-lithiation processes are described.

Keywords: Heterocycles; Heteroaromatic systems; Pentafluoropyridine

1. Introduction

Heteroaromatic systems have, of course, a vast chemistry [1] and a great number of pharmaceuticals, materials and life-science products are heterocyclic derivatives. In the ongoing search for novel biologically active ''lead'' compounds, the life-science industries have extensive discovery programmes focused upon the synthesis of a wide range of structurally diverse, multi-functional systems that, ideally, can be accessed by parallel synthesis methodologies. A particular target is the development of procedures for the synthesis of a variety of poly-substituted heteroaromatic derivatives that bear several different functionalities and, therefore, methodologies for the transformation of unsubstituted heterocyclic systems to poly-substituted derivatives is under constant development. This idea is illustrated in Scheme 1 in which pyridine is the parent of heterocyclic systems bearing up to five different substituents R_1–R_5.

The challenges involved in the synthesis of analogues of multi-substituted heteroaromatic systems have been reviewed by Collins [2] and Snieckus [3] recently and the problems associated with the use of established synthetic procedures such as low reactivity of heteroaromatics towards electrophiles and nucleophiles and low selectivity, have been discussed. Furthermore, effective synthetic strategies for the drug discovery arena should ideally be short synthetic sequences that are high yielding, selective and amenable to parallel synthesis which allow the rapid preparation of many analogue derivatives of poly-functional heterocyclic systems.

Our approach towards the synthesis of highly functionalised heteroaromatic derivatives utilises perfluorinated heterocyclic systems as starting materials.

We chose pentafluoropyridine as a suitable 'building block' for the construction of multi-functional pyridine derivatives because this system is very susceptible towards nucleophilic attack and so, in principle, all five fluorine atoms may be substituted by an appropriate nucleophile. Furthermore, it is well established [4,5] that, in general, the order of activation towards nucleophilic attack follows the sequence 4-fluorine > 2-fluorine > 3-fluorine. Therefore, for a succession of five nucleophilic substitution processes, where Nuc1 is the first nucleophile, Nuc2 the second, etc., the order of substitution is predicted to be selective as outlined in Scheme 2.

However, reactions of perfluoroheterocycles are principally those of nucleophilic substitution processes. Therefore, we sought to identify related perhalo-heterocyclic systems that could be suitable, more synthetically versatile start materials and we envisaged that related bromofluoro-heterocyclic derivatives such as **1** and **2**, would be effective starting materials for poly-functionalisation. The Durham group has previously established [6] that in reactions of **1**, ''hard'' nucleophiles such as oxyanions selectively replace fluorine whereas ''soft'' nucleophiles replace bromine (Scheme 3). Furthermore, the presence of bromine substituents should allow various bromometallation and palladium catalysed processes to be performed, thus extending the range of selective functionalisation reactions possible on these systems.

In this presentation, we describe our results which outline syntheses of penta-substituted pyridine systems derived originally from pentafluoropyridine.

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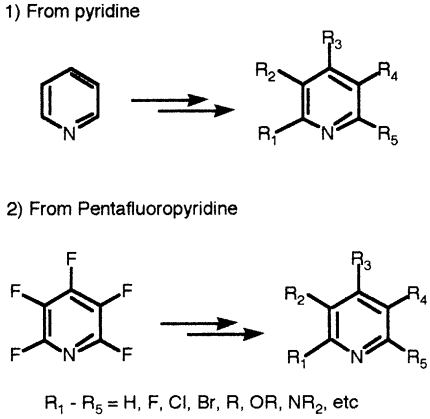
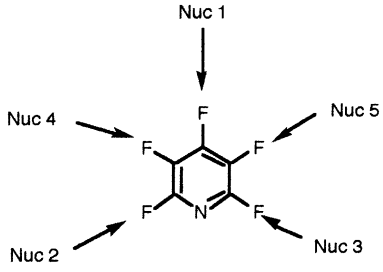


Scheme 1. Penta-functional pyridine derivatives.

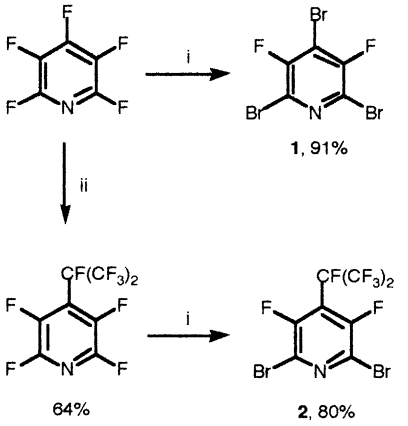


Scheme 2.

2. Results and discussion

Bromofluoro-heterocycles **1** and **2** were prepared as shown in Scheme 4. Perfluoroalkylation of pentafluoropyridine was achieved by reaction with hexafluoropropene and a tertiary amine, following methodology previously established by the Durham group [7]. Brominations of pentafluoro- and perfluoro-4-isopropyl-pyridine were carried out [6] by heating each substrate with an excess of hydrogen bromide gas and aluminium tribromide in an autoclave at 140°C giving **1** and **2**, respectively.

We investigated reactions of bromofluoropyridine derivative **2** with both 'hard' and 'soft' nucleophiles (Scheme 5). Substitution of fluorine by the relatively hard methoxide nucleophile occurs in **2** selectively to give the mono- and dimethoxylated derivatives **3** and **4** upon reaction with 1.5 and 3.0 equivalents of sodium methoxide, respectively. However, if an excess of methoxide is used, replacement of



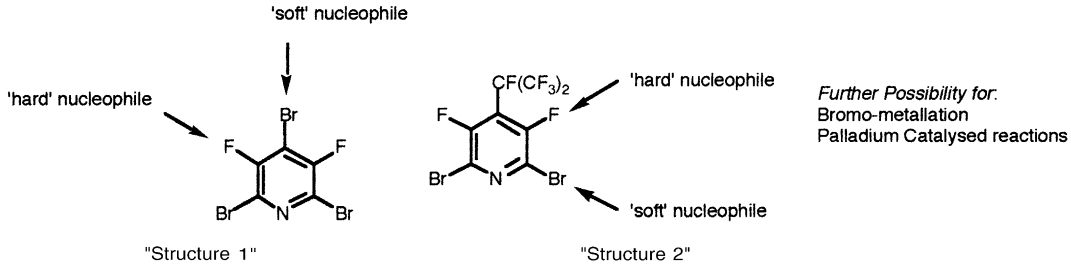
Scheme 4. Reagents and conditions: (i) HBr, $AlBr_3$, 140°C, 24 h; (ii) CF_2=CF–CF_3, NMe_3, 60°C.

bromine can also occur to give the trimethoxylated product **5** on prolonged heating in methanol. In contrast, bromine is selectively replaced by 'softer' nitrogen nucleophiles because **6** was obtained from reaction between **2** and piperidine. Therefore, the selectivity of the nucleophilic substitution processes involving perbromofluoro-heterocycles is controlled, quite simply, by the nature ('hard' or 'soft') of the nucleophile.

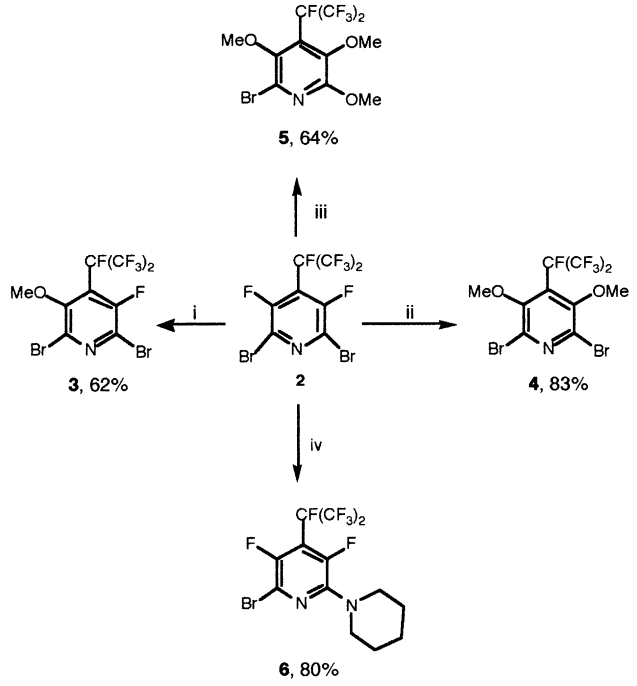
In order to widen the range of selective functionalisation reactions possible for bromofluoro-heterocycles **1** or **2** beyond nucleophilic aromatic substitution processes, we next focussed our attention on the use of the bromine substituents as functional groups in various metallation and palladium catalysed processes.

Pyridyl lithium derivative **7**, which was prepared in situ by adding *n*-butyl lithium solution to **2** in THF at low temperature, was trapped by a variety of electrophiles such as protons (from ethanol) and trimethylsilyl (from trimethylsilyl chloride) to give **8** and **9**, respectively (Scheme 6).

However, reaction of lithio derivative **11** with acetyl chloride was not as straightforward because, in this case, the di-pyridyl system **10** was isolated as the major product (Scheme 7). Initial reaction of lithio derivative **11** with acetyl chloride gives the expected ketone **12** as an intermediate (Scheme 7) but, here, the carbonyl group is very activated towards nucleophilic attack due to the presence of the highly electron withdrawing pyridine ring and further reaction involving nucleophilic attack by **11** at the carbonyl



Scheme 3.

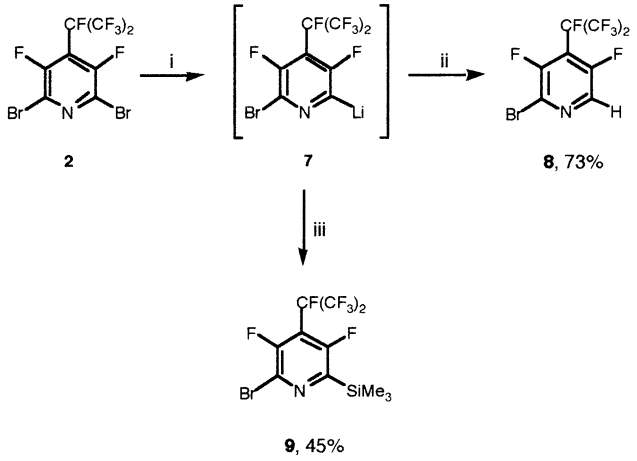


Scheme 5. Reagents and conditions: (i) NaOMe (1.5 eq.), MeOH, reflux, 24 h; (ii) NaOMe (3 eq.), MeOH, reflux, 24 h; (iii) NaOMe (6 eq.), MeOH, reflux, 24 h; (iv) piperidine (2 eq.), MeCN, 80°C, 24 h.

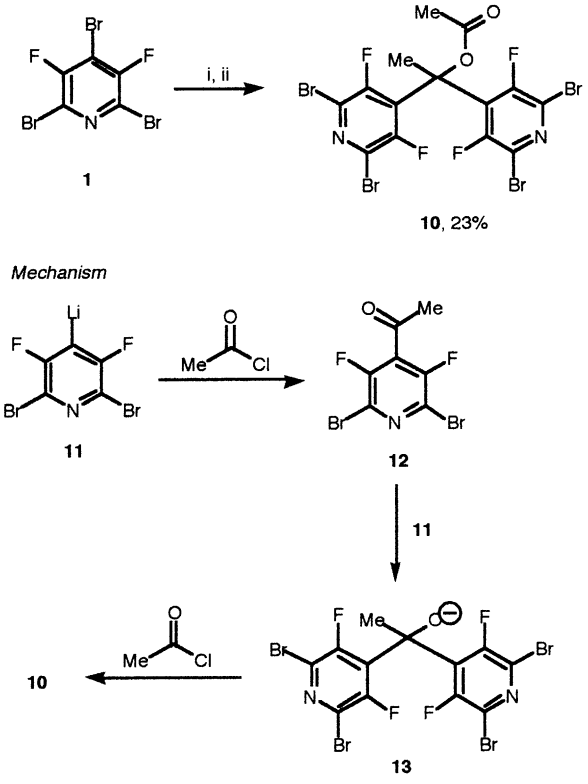
site occurs to give oxyanion **13** which, in turn, is acetylated to give product **10**.

By an analogous bromo-metallation process, difunctionalisation can also be achieved by addition of excess *n*-BuLi to **2** which may generate a dianion equivalent **14** that can be trapped by, for example, trimethylsilyl chloride giving **15** (Scheme 8).

Palladium catalysed coupling processes involving halo-heterocyclic derivatives have found many applications in organic synthesis [8] and we are interested in developing the use of such methodology for use in organofluorine chemistry. Bromo-heteroycles **1** and **2** were used as model



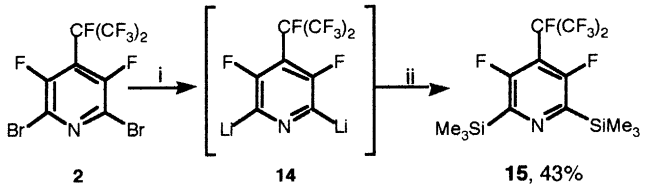
Scheme 6. Reagents and conditions: (i) *n*-BuLi (1.2 eq.), THF, −78°C; (ii) excess EtOH, −78°C to RT; (iii) Me_3SiCl (4 eq.), −78°C to RT.



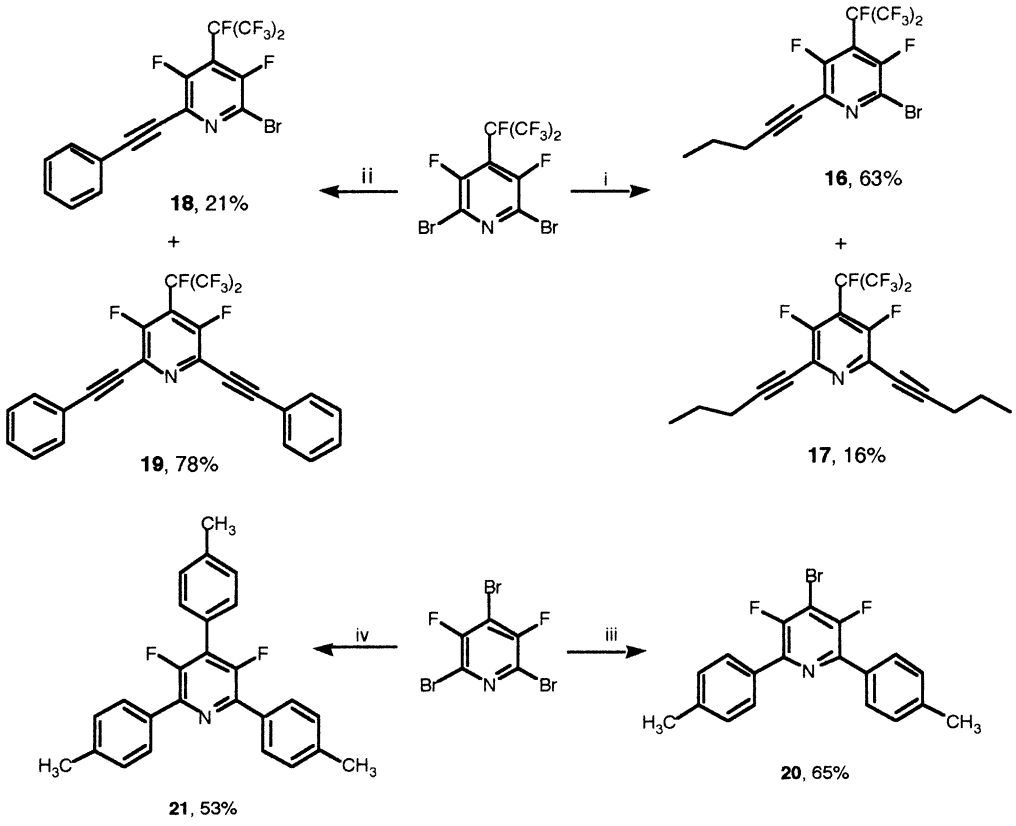
Scheme 7. Reagents and conditions: (i) *n*-BuLi (1.2 eq.), THF, −78°C; (ii) CH_3COCl, −78°C to RT.

compounds in the development of various palladium catalysed processes and in Scheme 9, our initial results in this area are outlined. Sonogashira-type coupling processes gave mono- or bis-alkylethynyl products depending on reaction conditions. For example, reaction of **2** with one equivalent of pentyne and a Pd(0) catalyst gave predominantly the mono-alkylethynyl derivative **16** whereas reaction of **2** with two equivalents of phenylacetylene and a Pd(0) catalyst gave the bis-phenylethynyl system **19** as the major product. In related processes, Suzuki coupling of 4-methylboronic acid with **2** gave the di- and tri-phenylated systems **20** and **21**.

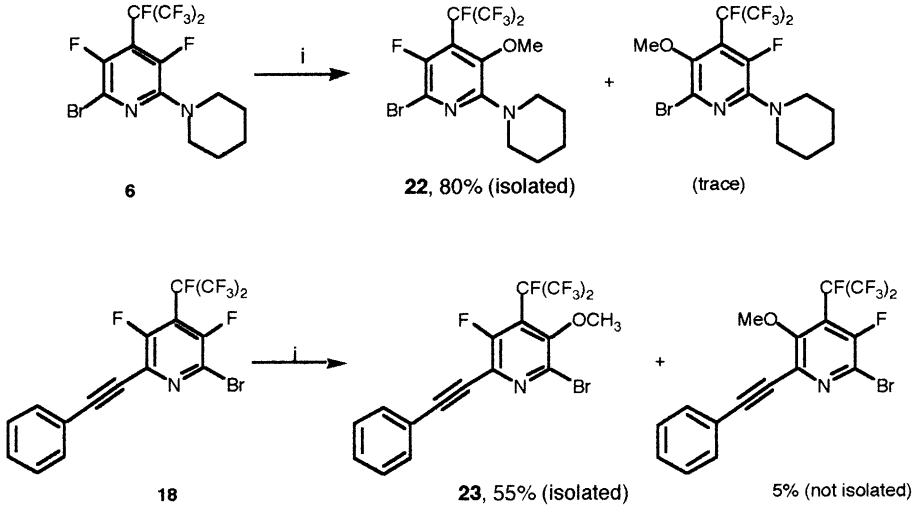
A combination, therefore, of nucleophilic substitution and palladium catalysed processes leads readily to a variety of pyridine derivatives such as **6** and **18** which bear four different ring substituents. Synthesis of penta-derivatised pyridine systems was achieved by reaction of, for example, **6** and **18** with sodium methoxide (Scheme 10). Although these reactions were not entirely regioselective, the major products **22** and **23** were isolated in good yield by column



Scheme 8. Reagents and conditions: (i) *n*-BuLi (2.4 eq.), THF, −78°C; (ii) Me_3SiCl, −78°C to RT.



Scheme 9. Reagents and conditions: (i) pent-1-yne (2 eq.), CuI, $Pd(OAc)_2$, PPh_3, Et_3N, RT, 3 days; (ii) phenylacetylene (2 eq.), CuI, $(Ph_3P)_2PdCl_2$, Et_3N, RT, 16 h; (iii) *p*-CH_3–C_6H_4–$B(OH)_2$, $Ba(OH)_2$ (2 eq.), $Pd(PPh_3)_4$, monoglyme, reflux; (iv) *p*-CH_3–C_6H_4–$B(OH)_2$, $Ba(OH)_2$ (3.5 eq.), $Pd(PPh_3)_4$, monoglyme, reflux.



Scheme 10. Reagents and conditions: (i) NaOMe (1.7 eq.), MeOH, reflux, 24 h.

chromatography and identified by a combination of NMR spectroscopy and single crystal X-ray analysis.

In summary, in this presentation we have shown that pentafluoropyridine may be used as a starting material for short, efficient and potentially flexible syntheses of pyridine derivatives that bear five different substituents. A sequence of nucleophilic substitution, novel palladium catalysed coupling and bromo-metallation processes could, therefore, be used to access a great range of multi-functional heterocyclic systems all originally derived from highly fluorinated heterocyclic starting materials.

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