Tetrahedron 66 (2010) 519–529

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Dipyrido[1,2-*a*;3′,4′-*d*]imidazole systems

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ARTICLE INFO

Article history:
Received 27 July 2009
Received in revised form 22 October 2009
Accepted 5 November 2009
Available online 10 November 2009

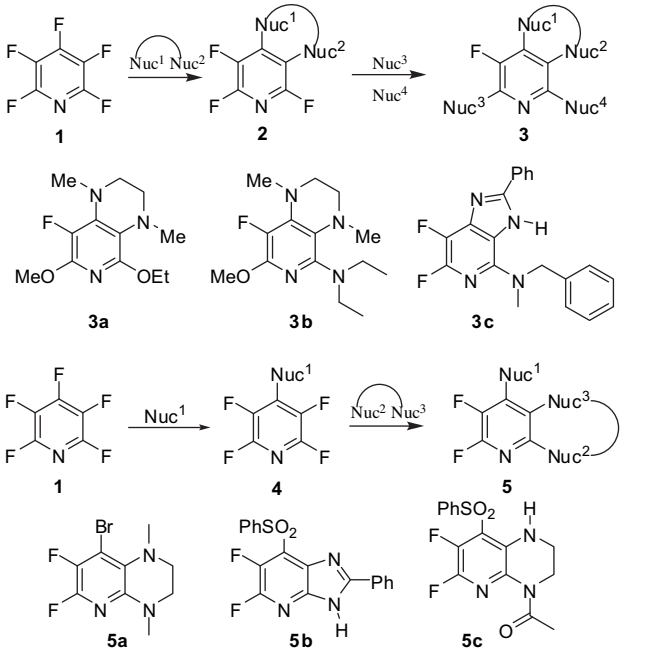
ABSTRACT

Novel tricyclic dipyridoimidazole derivatives can be readily synthesised in one pot processes from various highly fluorinated pyridine systems such as pentafluoropyridine and relatively nucleophilic 2-aminopyridine derivatives. Further nucleophilic aromatic substitution reactions of the novel tricyclic scaffolds allow the regioselective synthesis of various nitrogen, oxygen, carbon and sulfur-functionalised dipyridoimidazole products.

1. Introduction

Many pharmaceuticals and plant protection agents are based upon a heteroaromatic core scaffold[1] and, consequently, there is a continued demand for the development of methodology that provides ready access to novel polyfunctional heterocyclic architectures as part of a wide ranging drug discovery programme. Heteroaromatic systems that possess several functional groups that can be rapidly and selectively transformed into a wide range of related structural analogues are particularly useful and this approach has been reviewed extensively.[2,3]

In this context, we have been developing a general approach to the synthesis of a wide range of polyfunctional heterocyclic systems involving annelation reactions between pentafluoropyridine **1** and various difunctional nucleophiles (Scheme 1).[4–7] Initial substitution of the fluorine atom located at the most activated 4-position of pentafluoropyridine[8,9] is followed by displacement of the adjacent fluorine atom at the 3-position leading to ring fused products **2**. The heterocyclic scaffolds, such as the pyrido-pyrazine systems (**2**, Nuc^1-Nuc^2=MeNHCH$_2$CH$_2$NHMe), prepared by this developing general methodology may be further functionalised by sequential reaction with other nucleophilic species. A range of analogues **3**, e.g., pyrido-pyrazine[4] **3a** and imidazopyridine[7] **3c** derivatives, were synthesised from the novel core scaffold systems **2** (Scheme 1).[4–6] In further developments, sequential reactions of pentafluoropyridine with nucleophiles followed by subsequent annelation of tetrafluoropyridine derivatives **4** allowed the synthesis of a range of polyfunctional ring-fused systems **5** (Scheme 1).



Scheme 1. Strategy for the synthesis of functional ring-fused systems **3** and **5** from pentafluoropyridine **1**.

Previously, we targeted the synthesis of pyridopyrazine and imidazopyridine systems because of the wide ranging bioactivity possessed by some of these heterocyclic systems.[5,7] Adaptation of our general heterocyclic synthesis strategy to the synthesis of relatively unknown heterocyclic systems with unexplored biological activity was our next goal.

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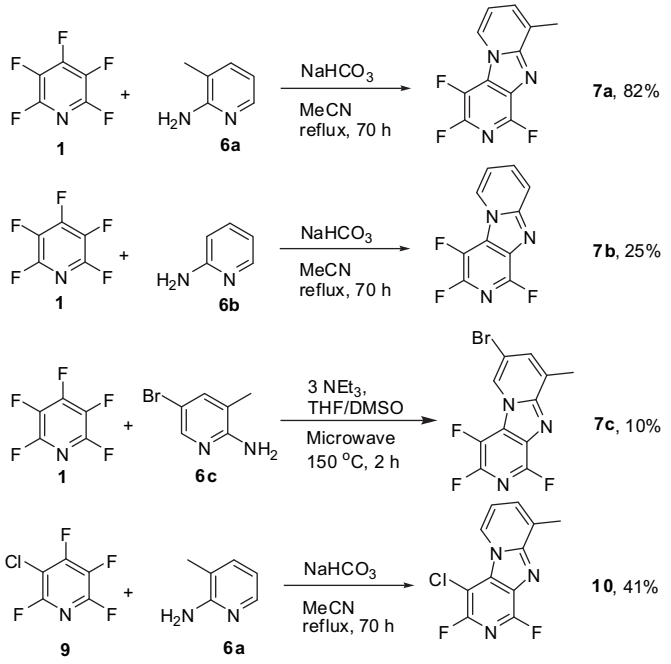
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.036

Synthetic procedures for the construction of dipyridoimidazole motifs are very rare[10] and recent publications describe syntheses involving reaction of 2-aminopyridine derivatives with an appropriate dihalogenated pyridine system catalysed by palladium acetate or palladium acetate/copper (I) iodide in Buchwald–Hartwig type processes.[11,12] Alternatively, annelation of imidazo[1,2-a]pyridine systems has allowed the synthesis of some functionalised systems, albeit in low yield.[10,13,14] In all cases, further functionalisation of the heterocyclic core scaffolds to provide analogue systems has not been reported because, in part, the multi-step synthesis of functionalised dibrominated pyridine starting materials can be very difficult indeed.

In this paper, we describe very efficient methodology for the synthesis of pyridoimidazole systems by reaction of pentafluoropyridine and various tetrafluoropyridine derivatives with appropriate 2-amino-pyridine derivatives, further establishing the use of perfluoroheteroaromatic systems for scaffold and functionalised heteroaromatic analogue synthesis.

2. Results and discussion

Reaction of pentafluoropyridine **1** with 2-amino-3-picoline **6a** under basic conditions in acetonitrile at reflux or under microwave heating gave a single product, dipyridoimidazole **7a**. Three resonances by ^{19}F NMR (−82, −105 and −164 ppm), indicate displacement of fluorine atoms attached to the 3- and 4-positions of the pyridine ring (Scheme 2). X-ray crystallography confirmed the structure of dipyridoimidazole **7a** (Fig. 1). In contrast, analogous reactions between the less nucleophilic 2-aminopyridine **6b** or 2-amino-5-bromo-3-picoline **6c** and **1** proceeded very slowly and gave low yields of the corresponding dipyridoimidazole systems **7b** and **7c**, respectively (Scheme 2).



Scheme 2. Syntheses of pyridoimidazole derivatives **7a–c**, **10**.

Initial attack of aminopyridine **6a** occurs through the more nucleophilic pyridine ring nitrogen to give the pyridinium intermediate **8**, and subsequent ring closure involving nucleophilic substitution at the adjacent 3-position gives rise to the product obtained **7a** (Scheme 3). The pyridinium group in **8** acts as an electron withdrawing substituent, activating the fluorinated ring towards nucleophilic attack and allowing ring annelation to occur very efficiently. Non-cyclised intermediate products **8** were not observed by ^{19}F NMR spectroscopic analysis of the reaction mixture, indicating that intramolecular cyclisation is a very rapid process.

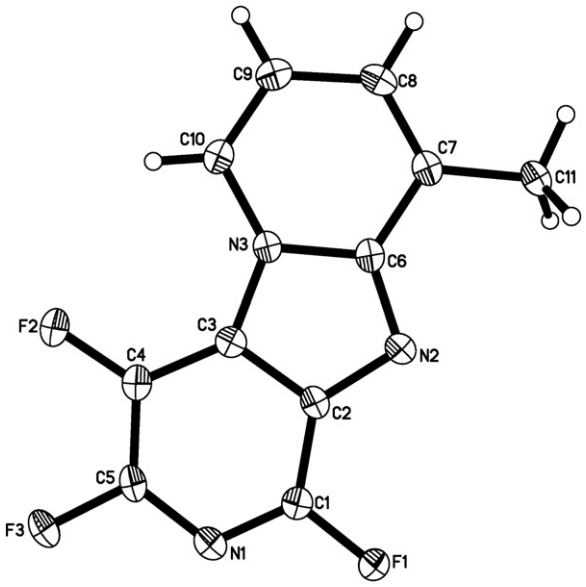
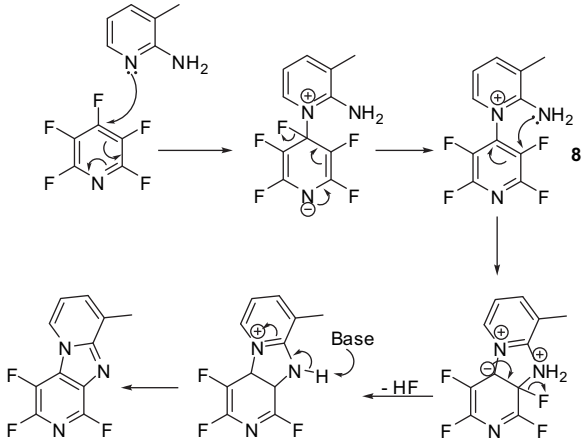


Figure 1. X-ray structure of **7a**.



Scheme 3. Mechanism of annelation.

By a similar process, 3-chlorotetrafluoropyridine **9** reacted with **6a** to give the corresponding tricyclic system **10** (Scheme 2).

In order to further develop routes to dipyridoimidazole systems following the ideas outlined in Scheme 1, we studied reactions of two tetrafluoropyridine derivatives **11** and **12** bearing phenylsulfonyl and cyano functionality at the 4-positions, respectively. However, reaction of **6a** with 4-phenylsulfonyl-tetrafluoropyridine **11** was less selective than the reactions described above and three major products, **13a**, **13b** and **7a**, were present in the reaction mixture as determined by ^{19}F NMR spectroscopy. Purification allowed the isolation of small quantities of the two major products **13a** and **13b** whose identities were confirmed by X-ray crystallography (Fig. 2). **7a** was also identified by ^{19}F NMR spectroscopy and GC–MS, but was not isolated from this product mixture.

The mechanism for this reaction is given in Scheme 4 and provides an indication of how the products arise from initial nucleophilic attack by **6a** at the 2-, 3- and 4-positions of the pyridine ring. Displacement of fluorine at the 2-position leads directly to product **13a**, whilst displacement of fluorine at the 3-position gives intermediate **13c,** which gives rise to **13d** or **13e** by intramolecular

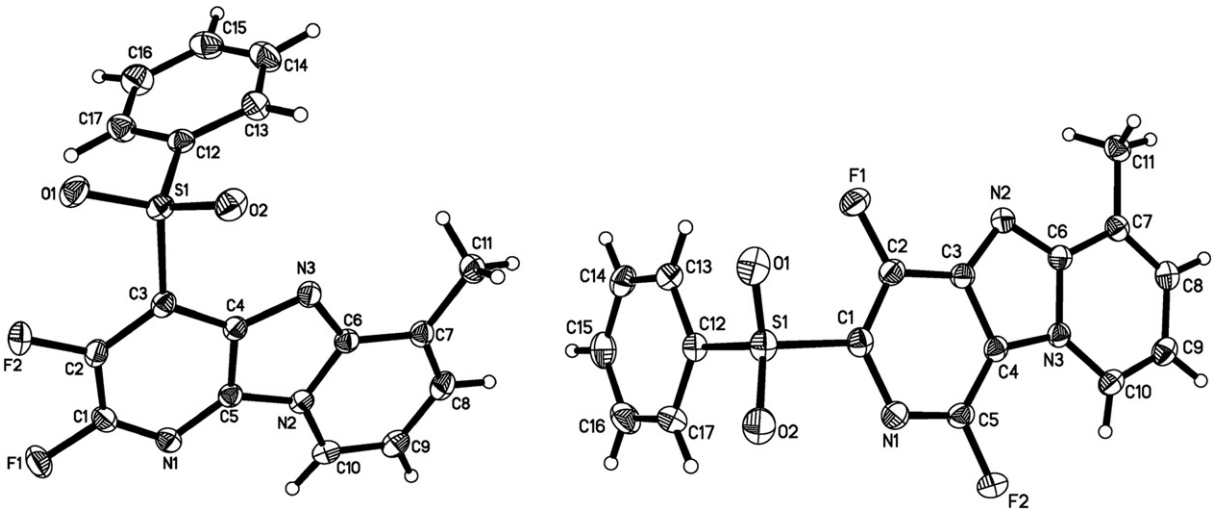
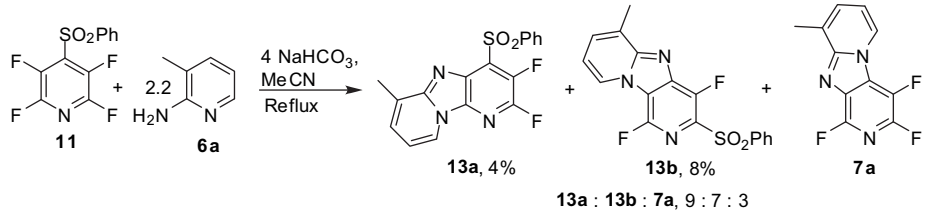
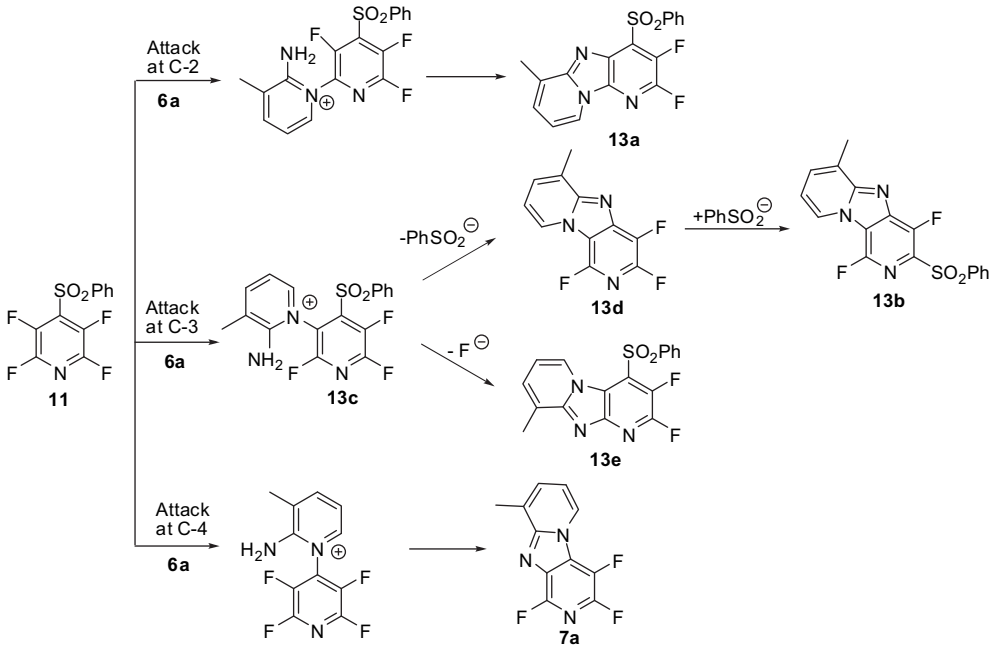
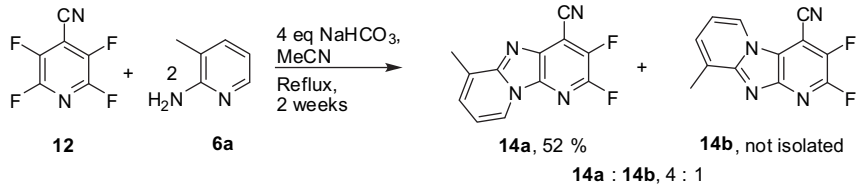


Figure 2. X-ray structures of **13a** (left) and **13b** (right).





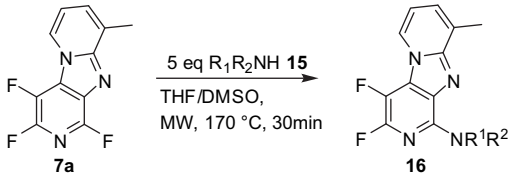
Scheme 4. Reaction of 4-phenylsulfonyl-tetrafluoropyridine **11** with **6a**.

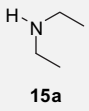
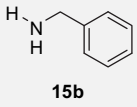
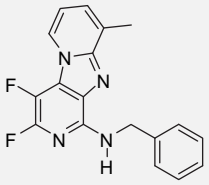
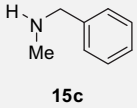
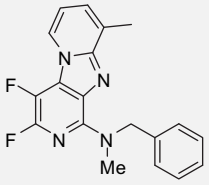
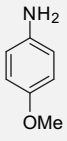
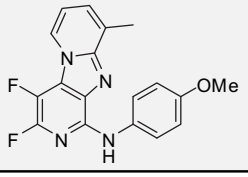


Scheme 5. Reaction of 4-cyano-tetrafluoropyridine **12** with **6a**.

cyclisation at the 4 or 2 positions, displacing phenyl-sulfonyl or fluorine, respectively. Reaction of **13d** with the phenylsulfonyl anion, which is now present in the reaction mixture, gives **13b**. This process is, therefore, complicated by the fact that the phenylsulfonyl group, which is attached to the site *para* to ring nitrogen that remains most activated towards nucleophilic attack, is labile and may be readily displaced by nucleophiles.

Table 1
Reactions of **7a** with amines **15a–d**



R_1R_2NH **15**	Product **16** (Yield %)
 **15a**	 **16a** (83)
 **15b**	 **16b** (63)
 **15c**	 **16c** (77)
 **15d**	 **16d** (12)

Subsequently, therefore, we examined the reaction of 4-cyanotetrafluoropyridine **12** with **6a** because the cyano group is a much poorer leaving group than a phenylsulfonyl group but is a strong electron withdrawing group that helps to activate the pyridine ring towards nucleophilic attack. In this case, the reaction gave a mixture of **14a** and **14b** arising from initial substitution at the 2- and 3-positions of **12** in a 4:1 ratio, respectively (Scheme 5) and this reflects the activating influence of the cyano group on adjacent sites, which competes with the activating influence of the ring nitrogen to some extent.

With the synthesis of various dipyridoimidazole scaffolds established, we turned our attention to assessing the suitability of the dipyridoimidazole derivative **7a** as a scaffold for analogue synthesis and further functionalisation by nucleophilic aromatic substitution reactions was studied. **7a** reacted very efficiently with *N*,*N*-diethylamine **15a**, benzylamine **15b**, *N*-benzylmethylamine **15c** and *p*-anisidine **15d** under either microwave or conventional heating giving, in each case, single products, **16a–d,** respectively, by ^{19}F NMR spectroscopic analysis of the crude product mixture. Recrystallisation of the crude solids obtained after work-up gave pure products **16a–d** in good to excellent yields and these results are collated in Table 1.

X-ray crystallography confirmed the structure of **16b** (Fig. 3) and the structures of other products **16a**,**c**,**d** were determined by comparison of NMR spectroscopic data with those obtained for **16b**.

Reaction of **7a** with sodium methoxide or phenylmagnesium bromide gave **17** and **18**, respectively by selective displacement of the fluorine atom located at the C-1 position (Scheme 6).

All reactions of **7a** with nucleophiles (Table 1, Scheme 6) gave products arising from selective displacement of fluorine located at the C-1 position. We would expect sites C-1 and C-3 to be activated towards nucleophilic attack because both these positions are *ortho* to the pyridine ring nitrogen, but position C-3 may be predicted to be further activated by the fluorine atom at the adjacent C-4 site since fluorine *ortho* to the site of nucleophilic attack is established to be highly activating.[8] However, the observed regioselectivity may be due to, for example, hydrogen bonding interactions between the incoming nucleophile with the ring nitrogen, directing the nucleophile towards the adjacent C-1 site, consistent with the regiochemistry of nucleophilic substitution processes in related systems.

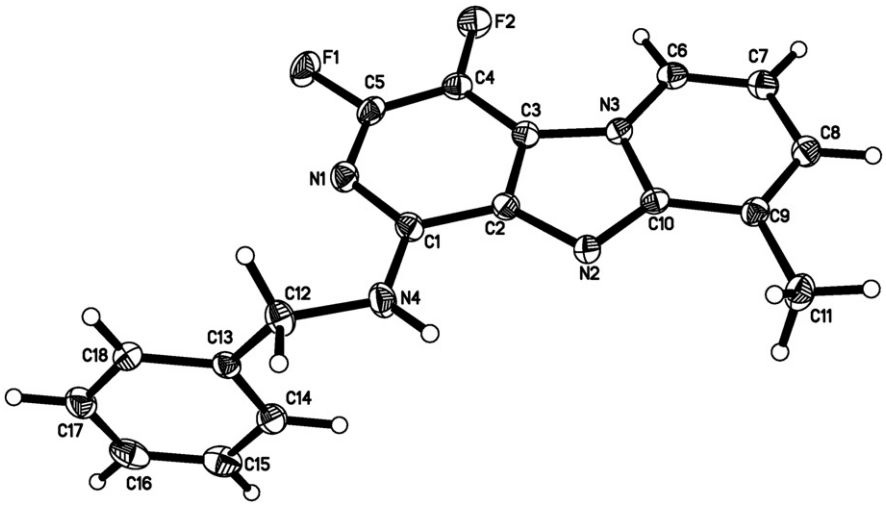
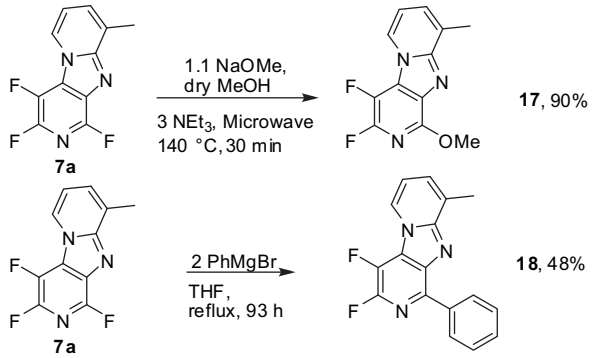
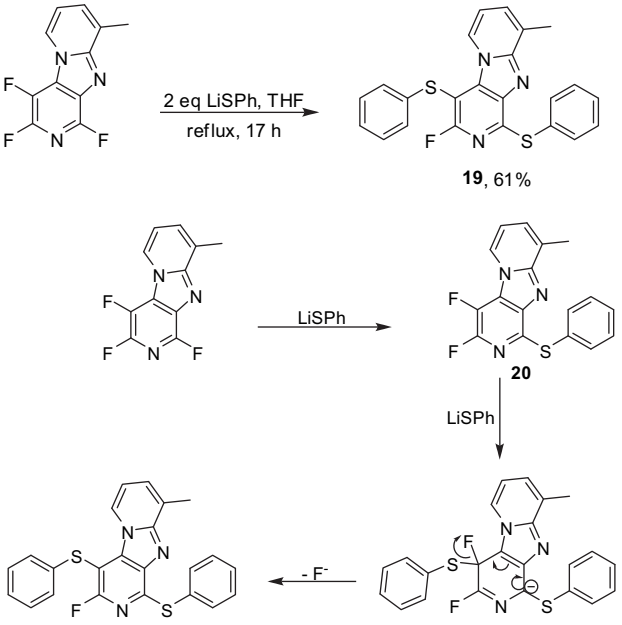


Figure 3. X-ray structure of **16b**.



Scheme 6. Reactions of **7a**.

Reaction of **7a** with only one equivalent of lithium thiophenoxide gave the disubstituted derivative **19** as the major product (44%) arising from displacement of fluorine atoms located at the C-1 and C-4 positions, with only a small amount of the monosubstituted product **20** (2%) present in the reaction mixture along with some starting material (54%, by ^{19}F NMR spectroscopy). Subsequently, reaction of **7a** with two equivalents of lithium thiophenoxide gave high yields of **19** (Scheme 7). The most effective indicator as to the regiochemistry of this substitution reaction is by ^{19}F NMR spectroscopy for which, in this case, the singlet resonance occurs at −75 ppm, indicative of a fluorine atom situated *ortho* to a ring nitrogen.

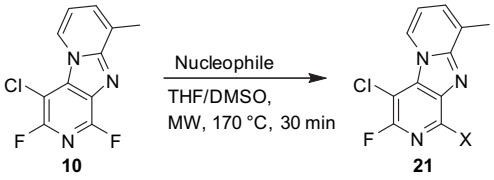


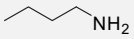
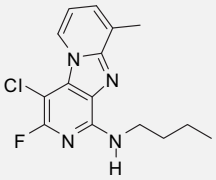
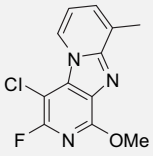
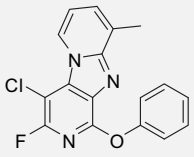
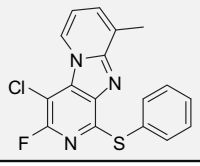
Scheme 7. Reaction of **7a** with lithium thiophenoxide.

It is reasonable to assume that initial attack on **7a** by the nucleophile occurs, as before, at the C-1 site *ortho* to the activating imine group and, therefore, the second equivalent of lithium thiophenoxide must attack the fluoropyridine scaffold *para* to the thiophenyl substituent to give the observed product **19** (Scheme 7). This reflects the advantage of delocalising negative charge developed in the Meisenheimer intermediate onto the carbon bearing the sulfur substituent, which would not be possible if attack occurred at C-3, and the activating effect of sulfur substituents *para* to sites of nucleophilic attack has been noted previously.[8]

Analogous reactions of chlorinated tricyclic system **10** with a small range of nucleophiles were performed (Table 2) and, in all cases, selective displacement of fluorine at the C-1 position, *para* to the ring chlorine, occurred to furnish products **21a–e**. In this case, reaction of **10** with thiophenoxide gave only the monosubstituted system **21e**, reflecting the lower reactivity of the carbon–chlorine bond towards nucleophilic substitution compared to the carbon–fluorine bond.

Table 2
Reactions of **10** with nucleophiles



Nucleophile	Product **21** (Yield %)	
		**21a** (97)
		**21b** (71)
NaOMe		**21c** (32)
PhONa		**21d** (76)
PhSNa		**21e** (58)

The structure of **21e** was confirmed by X-ray crystallography (Fig. 4), and all other related products **21a–d** were identified by comparison of NMR data. In particular, ^{19}F NMR spectroscopy shows the chemical shift of fluorine atoms attached to the 3-position are observed at ca. −85 ppm. The resonance attributed to the carbon atom attached to chlorine (C-4) in the ^{13}C NMR spectrum has a distinctive chemical shift (ca. 90 ppm) and two-bond carbon–fluorine coupling ($^{2}J_{CF}$ 40 Hz), which would not be observed if substitution had occurred at the C-3 site.

The chlorine atom attached to the pyridine ring in **10** provides further opportunities for functionalisation of this scaffold in addition to the nucleophilic substitution processes shown in Table 2. Reaction of **10** with ammonium formate in the presence of a palladium catalyst gives a good yield of **22** arising from substitution of

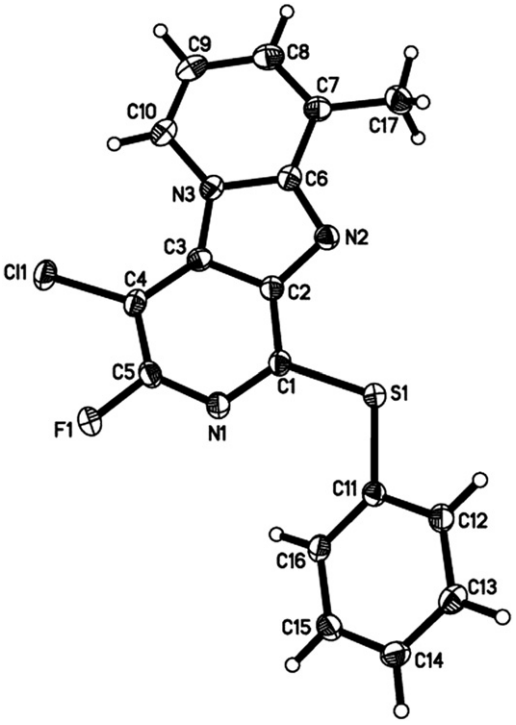
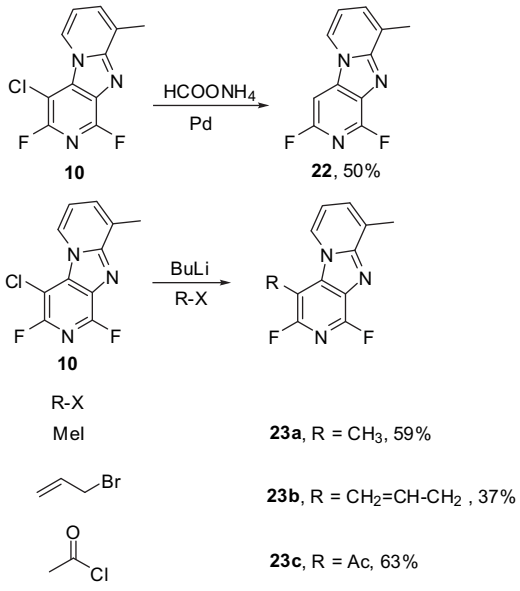


Figure 4. X-ray structure of **21e**.



Scheme 8. Substitution of chlorine in **10**.

chlorine by hydrogen (Scheme 8). Dechlorometallation of **10** by reaction with butyl lithium followed by trapping of the resulting lithiated heterocycle with electrophiles, such as methyl iodide, allyl bromide and acetyl chloride, give ready access to systems **23a–c**, respectively, functionalised at the C-4 position (Scheme 8) and X-ray crystallography confirmed the structure of **23a** (Fig. 5).

3. Conclusions

Tricyclic dipyridoimidazole scaffolds can be readily synthesised in one pot processes from pentafluoropyridine and various tetrafluoropyridine derivatives and relatively nucleophilic

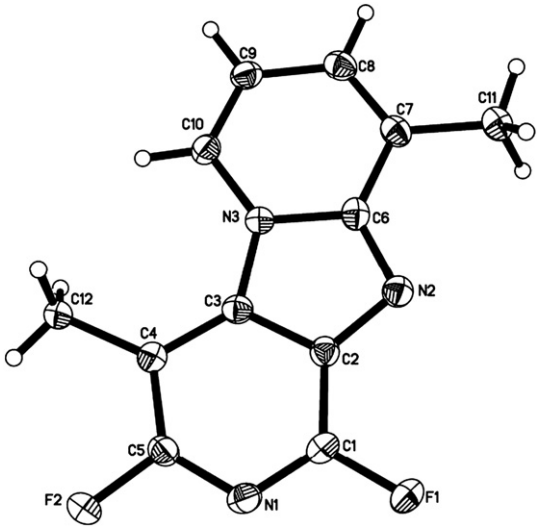


Figure 5. X-ray structure of **23a**.

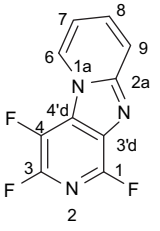
2-aminopyridine derivatives. In particular, model dipyridoimidazole systems **7a** and **10** can be utilised as scaffolds for further nucleophilic aromatic substitution, reacting regioselectively and under relatively mild conditions, to yield a series of nitrogen, oxygen, carbon and sulfur-functionalised dipyridoimidazole analogues. In addition, the carbon–chlorine bond of **10** allows functionalisation by dechlorolithiation and trapping by carbon centred electrophiles. Application of our general strategy for the synthesis of polyfunctional heterocyclic scaffolds from highly fluorinated heteroaromatic starting materials has, therefore, been extended to the synthesis of very rare polyfunctional heteroaromatic systems.

4. Experimental

4.1. General

All starting materials were obtained commercially (Sigma-Aldrich) and all solvents were dried using standard laboratory procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. Assignments were made with the aid of data collected by ^{1}H–^{1}H COSY and ^{1}H–^{13}C HETCOR experiments and coupling constants are given in Hz. Mass spectra were recorded on either a VG 7070E spectrometer or a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Elemental analyses were obtained on either a Perkin-Elmer 240 or a Carlo Erba Elemental Analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Column chromatography was carried out on silica gel (Merck No. 1-09385, 230–400 mesh) and T.L.C. analysis was performed on silica gel T.L.C. plates.

The following numbering scheme is used for indicating NMR assignments for dipyridoimidazole systems.



4.2. Synthesis of dipyridoimidazole derivatives

4.2.1. 1,3,4-Trifluoro-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazole ***7a***. Pentafluoropyridine **1** (1.69 g, 10.0 mmol), 3-methyl-pyridin-2-ylamine **6a** (2.38 g, 22.0 mmol) and sodium hydrogencarbonate (3.36 g, 40.0 mmol) were heated in dry MeCN (200 mL) at reflux temperature, under an atmosphere of argon, for 70 h. The solvent was evaporated, water (50 mL) was added and extracted with dichloromethane (3×40 mL). Drying ($MgSO_4$), solvent evaporation and recrystallisation from acetonitrile gave 1,3,4-trifluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **7a** (1.94 g, 82%) as a white solid; mp 174–176 °C (Found: C, 55.6; H, 2.5; N, 17.8. $C_{11}H_6F_3N_3$ requires: C, 55.5; H, 2.6; N, 17.7%.); δ_H 2.67 (3H, s, CH_3), 6.93 (1H, t, $^3J_{HH}$ 6.9, H-7), 7.36 (1H, dm, $^3J_{HH}$ 6.9, H-8), 8.49 (1H, d, $^3J_{HH}$ 7.1, H-6); δ_F −79.01 (1F, dd, $^3J_{FF}$ 34.8, $^4J_{FF}$ 13.7, F-3), −102.43 (1F, dd, $^5J_{FF}$ 20.1, $^4J_{FF}$ 12.8, F-1), −164.73 (1F, dd, $^3J_{FF}$ 33.7, $^5J_{FF}$ 20.1, F-4); δ_C 17.57 (s, CH_3), 113.20 (s, C-7), 124.93 (d, $^4J_{CF}$ 5.1, C-6), 127.63 (dd, $^2J_{CF}$ 35.3, $^3J_{CF}$ 3.8, C-4′d), 128.24 (m, C-3′d), 129.44 (s, C-9), 129.87 (s, C-8), 131.17 (ddd, $^1J_{CF}$ 257.1, $^2J_{CF}$ 32.8, $^4J_{CF}$ 8.7, C-4), 140.94 (ddd, $^1J_{CF}$ 233.9, $^2J_{CF}$ 13.7, $^2J_{CF}$ 13.7, C-3), 145.22 (dd, $^1J_{CF}$ 251.3, $^2J_{CF}$ 14.5, C-1), 151.07 (s, C-2a); *m*/*z* (EI^+) 237 ($[M]^+$, 60%). Crystals suitable for X-ray crystallography were grown from acetonitrile.

4.2.2. 1,3,4-Trifluoro-dipyrido[1,2-a;3′,4′-d]imidazole ***7b***. **1** (1.69 g, 10.0 mmol), 2-amino-pyridine **6b** (1.88 g, 20.0 mmol) and sodium hydrogen carbonate (3.36 g, 40.0 mmol) were stirred together in dry MeCN (200 mL) at reflux temperature, under an atmosphere of argon, for 96 h. The solvent was evaporated, water (50 mL) was added and extracted with dichloromethane (3×40 mL). Drying ($MgSO_4$) and evaporation of the solvent yielded a dark red solid, which was recrystallised from acetonitrile to give 1,3,4-trifluoro-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **7b** (0.55 g, 25 %) as a pale orange solid; mp 197–198 °C (Found: C, 53.8; H, 1.7; N, 18.9. $C_{10}H_4F_3N_3$ requires: C, 53.8; H, 1.8; N, 18.8%); δ_H 7.01–7.08 (1H, m, H-7), 7.56–7.60 (1H, m, H-8), 7.75–7.80 (1H, m, H-9), 8.64 (1H, dm, $^3J_{HH}$ 7.0, H-6); δ_F −79.05 (1F, dd, $^3J_{FF}$ 34.3, $^4J_{FF}$ 13.4, F-3), −102.07 (1F, dd, $^5J_{FF}$ 19.9, $^4J_{FF}$ 13.3, F-1), −164.36 (1F, dd, $^3J_{FF}$ 34.4, $^5J_{FF}$ 20.3, F-4); δ_C 113.08 (s, C-7), 119.30 (s, C-9), 127.44 (d, $^4J_{CF}$ 5.0, C-6), 127.73 (m, C-3′d), 128.00 (dd, $^2J_{CF}$ 35.4, $^3J_{CF}$ 3.8, C-4′d), 131.22 (ddd, $^1J_{CF}$ 256.6, $^3J_{CF}$ 32.1, $^4J_{CF}$ 8.5, C-4), 131.95 (s, C-8), 141.07 (ddd, $^1J_{CF}$ 233.7, $^2J_{CF}$ 13.6, $^2J_{CF}$ 13.6, C-3), 145.07 (dd, $^1J_{CF}$ 250.7, $^2J_{CF}$ 14.8, C-1), 150.24 (s, C-2a); *m*/*z* (EI^+) 223 ($[M]^+$, 100 %), 203 (21), 176 (24).

4.2.3. 7-Bromo-1,3,4-trifluoro-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazole ***7c***. **1** (0.30 g, 1.77 mmol), 2-amino-5-bromo-3-methylpyridine **6c** (0.50 g, 2.66 mmol) and triethylamine (0.54 g, 5.32 mmol) were stirred together in a mixture of THF (10.00 mL) and DMSO (4.00 mL) in a sealed 20 mL vial under microwave heating for 2 h at 150 °C. The resulting mixture was evaporated to dryness and purification by column chromatography using DCM/MeOH as elutant (0.5–4% MeOH gradient over 15 min) gave 7-bromo-1,3,4-trifluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **7c** (0.06 g, 10%) as a yellow solid; mp 249–251 °C ($[MH]^+$, 315.9687. $C_{11}H_5N_3F_3Br$ requires: $[MH]^+$, 315.9697); δ_H 2.72 (3H, s, CH_3), 7.45 (1H, br s, H-8), 8.65 (1H, br s, H-6); δ_F −77.80 (1F, dd, $^3J_{FF}$ 34.4, $^4J_{FF}$ 13.8, F-3), −100.90 (dd, $^5J_{FF}$ 20.1, $^4J_{FF}$ 13.2, F-1), −164.49 (dd, $^3J_{FF}$ 34.4, $^5J_{FF}$ 19.5, F-4); δ_C 17.33 (s, CH_3), 107.42 (s, C-7), 124.51 (d, $^4J_{CF}$ 5.2, C-6), 127.76 (m, C-4′d), 130.52 (s, C-9), 130.83 (ddd, $^1J_{CF}$ 257.0, $^2J_{CF}$ 32.0, $^4J_{CF}$ 8.6, C-4), 133.20 (s, C-8), 141.29 (ddd, $^1J_{CF}$ 236.0, $^2J_{CF}$ 14.0, $^2J_{CF}$ 14.0, C-3), 145.16 (dd, $^1J_{CF}$ 252.1, $^3J_{CF}$ 11.8, C-1), 149.27 (s, C-2a); *m*/*z* (ES^+) 318.0 ($[MH]^+$, 100%), 316.0 ($[MH]^+$, 100%).

4.2.4. 4-Chloro-1,3-difluoro-9-methyl-dipyrido[1,2-a; 3′,4′-d]imidazole ***10***. 3-Chlorotetrafluoropyridine **9** (2.0 g, 1.1 mmol), 2-amino-3-picoline **6a** (1.28 g, 1.2 mmol) and sodium hydrogen carbonate (1.81 g, 2.2 mmol) were heated to reflux in MeCN (200 mL) under an atmosphere of argon for 72 h. MeCN was removed under reduced pressure and the reaction mixture was poured into water (50 mL) and extracted with DCM (3×30 mL). The reaction mixture was dried ($MgSO_4$), solvent evaporated and the residue recrystallised to give 4-chloro-1,3-difluoro-9-methyl-dipyrido[1,2-*a*; 3′,4′-*d*]imidazole **10** (1.06 g, 41%) as a yellow solid; mp 193–194 °C (MeCN) (Found: C, 52.0; H, 2.3; N, 16.6. $C_{11}H_6N_3F_2Cl$ requires: C, 52.0; H, 2.3; N 16.5%); δ_H 2.63 (3H, s, CH_3), 6.86 (1H, t, $^3J_{HH}$ 7.0, H-7), 7.31 (1H, d, $^3J_{HH}$ 7.0, H-8), 9.00 (1H, d, $^3J_{HH}$ 7.0, H-6); δ_F −77.85 (1F, d, $^4J_{FF}$ 13, F-3), −86.15 (1F, d, $^4J_{FF}$ 13, F-1); δ_C 17.58 (s, CH_3), 97.33 (dd, $^2J_{CF}$ 41.29, $^4J_{CF}$ 8.13, C-4), 112.69 (s, C-7), 124.37 (s, C-6), 127.20 (dd, $^2J_{CF}$ 33.9, $^4J_{CF}$ 3.9, C-3′d), 129.43 (s, C-9), 129.66 (s, C-8), 135.60 (dd, $^3J_{CF}$ 11.12, $^3J_{CF}$ 5.9, C-4′d), 149.44 (dd, $^1J_{CF}$ 253.91, $^3J_{CF}$ 14.79, C-3), 149.71 (dd, $^1J_{CF}$ 231.79, $^3J_{CF}$ 13.97, C-1), 151.37 (s, C-2a); *m*/*z* (EI^+) 253 ($[M]^+$, 28%), 255 ($[M]^+$, 28%), 116 (39), 39 (100).

4.2.5. 4-Benzenesulfonyl-2,3-difluoro-6-methyl-dipyrido[1,2-a;3′2′-d]imidazole ***13a*** *and 3-benzenesulfonyl-1,4-difluoro-6-methyl-dipyrido[1,2-a;4′,3′-d]imidazole* ***13b***. 4-Benzenesulfonyl-2,3,5,6-tetrafluoropyridine **11** (1.46 g, 5.0 mmol), 2-amino-3-picoline **6a** (1.19 g, 11.0 mmol) and sodium hydrogen carbonate (1.68 g, 20.0 mmol) were stirred together in dry MeCN (100 mL) at reflux temperature, under argon. After one week the reaction was evaporated to dryness, poured onto a 1 M HCl solution (50 mL) and extracted into DCM (3×40 mL). Drying ($MgSO_4$), solvent evaporation and recrystallisation from MeCN gave 3-benzenesulfonyl-1,4-difluoro-6-methyl-dipyrido[1,2-*a*;4′,3′-*d*]imidazole **13b** (0.14 g, 8%) as planar yellow crystals; mp 288–290 °C; (Found: C, 56.6; H, 3.0; N, 11.8. $C_{17}H_{11}F_2N_3O_2S$ requires: C, 56.8; H, 3.1; N, 11.7%); δ_H 2.74 (3H, s, CH_3), 7.11 (1H, d, $^3J_{HH}$ 7.5, H-8), 7.52–7.56 (3H, m, H-3′,4′), 7.62 (1H, t, $^3J_{HH}$ 7.5, H-7), 8.15 (2H, d, $^3J_{HH}$ 7.2, H-2′), 8.60 (1H, d, $^3J_{HH}$ 6.8, H-9); δ_F −76.61 (1F, d, $^5J_{FF}$ 30.9, F-1), −132.08 (1F, d, $^5J_{FF}$ 31.6, F-4); *m*/*z* (ES^+) 360.1 ($[MH]^+$, 100%). Crystals suitable for X-ray crystallography were grown from MeCN.

Column chromatography of the remaining material on silica gel using ethyl acetate: hexane (2:1) as elutant followed by recrystallisation from MeCN gave 4-benzenesulfonyl-2,3-difluoro-6-methyl-dipyrido[1,2-*a*;3′2′-*d*]imidazole **13a** (0.08 g, 4%) as a yellow solid; mp 242–244 °C; (Found: C, 56.8; H, 3.1; N, 11.9. $C_{17}H_{11}F_2N_3O_2S$ requires: C, 56.8; H, 3.1; N, 11.7%); δ_H 2.71 (3H, s, CH_3), 6.94–6.98 (1H, m, H-8), 7.34–7.40 (1H, m, H-7), 7.50–7.58 (2H, m, H-3′), 7.62–7.68 (1H, m, H-9), 8.36–8.46 (3H, m, H-2′,4′); δ_F −91.53 (1F, d, $^3J_{FF}$ 24.8, F-2), −140.24 (1F, d, $^3J_{FF}$ 24.6, F-3); δ_C 17.02 (s, CH_3), 112.87 (s, C-8), 121.95 (s, C-4′), 128.51 (m, C-3′d), 128.99 (s, C-6), 129.14 (s, C-3′), 129.26 (s, C-2′), 130.24 (s, C-7), 131.29 (d, $^4J_{CF}$ 3.1, C-1′), 133.90 (dm, $^2J_{CF}$ 15.2, C-4), 134.62 (s, C-9), 140.66 (s, C-2′d), 141.44 (dd, $^1J_{CF}$ 267.9, $^2J_{CF}$ 30.2, C-3), 147.21 (dd, $^1J_{CF}$ 243.9, $^2J_{CF}$ 19.8, C-2), 151.21 (s, C-2a); *m*/*z* (ES^+) 360.0 ($[MH]^+$, 100%). Crystals suitable for X-ray crystallography were grown from chloroform.

4.2.6. 2,3-Difluoro-6-methyl-dipyrido[1,2-a,3′,2′d]imidazole-4-carbonitrile ***14a***. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **12** (0.88 g, 5.0 mmol), 2-amino-3-picoline **6a** (1.08 g, 10.0 mmol) and sodium hydrogen carbonate (1.68 g, 20.0 mmol) were stirred together in dry MeCN at reflux temperature, under dry argon. After two weeks the reaction was cooled to room temperature and the solvent evaporated. The residue was redissolved in DCM and poured onto water (50 mL). Extraction of the organic products into DCM, drying ($MgSO_4$), solvent evaporation and column chromatography on silica gel (*n*-hexane: ethyl acetate, 1:1) gave 2,3-difluoro-6-methyl-dipyrido[1,2-*a*,3′,2′*d*]imidazole-4-carbonitrile **14a** (0.63 g, 52%) as a yellow solid; mp 197–198 °C (Found: C, 58.9; H, 2.4; N, 23.1. $C_{12}H_6N_4F_2$ requires: C, 59.2; H, 2.5; N, 22.9%); δ_H 2.73 (3H, br s, CH_3), 7.02 (1H, t, $^3J_{HH}$ 6.9, H-8), 7.45 (1H, dm, $^3J_{HH}$ 6.9, H-7), 8.53 (1H, d, $^3J_{HH}$ 6.9, H-9); δ_F −91.96 (1F, d, $^3J_{FF}$ 22.5, F-2), −135.23 (1F, d, $^3J_{FF}$ 23.1, F-3); δ_C 17.03 (s, CH_3), 101.49 (dd, $^2J_{CF}$ 13.0, $^3J_{CF}$ 4.5, C-4), 109.91

(d, $^3J_{CF}$ 5.0, CN), 113.28 (s, C-8), 122.31 (s, C-9), 128.94 (s, C-6), 131.03 (s, C-7), 133.50 (m, C-3′d), 134.72 (d, $^3J_{CF}$ 2.9, C-2′d), 145.72 (dd, $^1J_{CF}$ 268.5, $^2J_{CF}$ 31.6, C-3), 146.35 (dd, $^1J_{CF}$ 245.5, $^2J_{CF}$ 17.3, C-2), 151.79 (s, C-2a); *m*/*z* (ES^+) 243.8 ($[M]^+$, 100%).

4.3. Reactions of 1,3,4-trifluoro-9-methyl-dipyrido[1,2-*a*;3′, 4′-*d*]imidazole 7a with nucleophiles

*4.3.1. 3,4-Difluoro-(9-methyl-dipyrido[1,2-a,3′,4′-d]imidazol-1-yl)-diethyl-amine **16a**.* **7a** (0.25 g, 1.06 mmol) and diethylamine **15a** (0.39 g, 5.27 mmol) were stirred together in a mixture of DMSO (4.0 mL) and THF (10 mL) and irradiated by microwave heating for 30 min at 170 °C. The reaction mixture was evaporated to dryness, water (50 mL) was added and the organic products extracted into dichloromethane (3×40 mL). Drying ($MgSO_4$), evaporation and recrystallisation from acetonitrile gave 3,4-difluoro-(9-methyl-dipyrido[1,2-*a*,3′,4′-*d*]imidazol-1-yl)-diethyl-amine **16a** (0.51 g, 83 %) as a pale yellow solid; mp 91–93 °C (Found: C, 62.3; H, 5.5; N, 19.2. $C_{15}H_{16}N_4F_2$ requires: C, 62.1; H, 5.6; N, 19.3%); δ_H 1.28 (6H, t, $^3J_{HH}$ 6.8,–CH_2CH_3), 2.63 (3H, s, CH_3), 4.03 (4H, q, $^3J_{HH}$ 7.0, CH_2), 6.74–6.80 (1H, m, H-7), 7.15 (1H, d, $^3J_{HH}$ 6.7, H-8), 8.42 (1H, d, $^3J_{HH}$ 6.9, H-6); δ_F −102.42 (1F, d, $^3J_{FF}$ 27.0, F-3), −181.52 (1F, d, $^3J_{FF}$ 26.8, F-4); δ_C 13.79 (s, NCH_2CH_3), 17.20 (s, CH_3), 43.73 (s, CH_2), 111.66 (s, C-7), 124.42 (d, $^4J_{CF}$ 6.0, C-6), 124.45 (dd, $^1J_{CF}$ 243.6, $^2J_{CF}$ 36.7, C-4), 126.00 (m, C-4′d), 126.16 (s, C-8), 127.94 (m, C-3′d), 128.76 (s, C-9), 143.68 (dd, $^1J_{CF}$ 218.0, $^2J_{CF}$ 12.1, C-3), 144.28 (d, $^3J_{CF}$ 17.0, C-1), 146.81 (s, C-2a); *m*/*z* (EI^+) 290 ($[M]^+$, 90%), 275 ($[M\text{-}CH_3]^+$, 100), 261 (76), 247 (85), 219 (52).

*4.3.2. Benzyl-(3,4-difluoro-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazol-1-yl)-amine **16b**.* **7a** (0.50 g, 2.11 mmol) and benzylamine **15b** (1.13 g, 10.54 mmol) were stirred together in a mixture of THF (10 mL) and DMSO (2 mL) under microwave heating at 170 °C for 30 min. The reaction mixture was evaporated to dryness, water (50 mL) was added and the organic products extracted into dichloromethane (3×40 mL). Drying ($MgSO_4$), evaporation and recrystallisation from acetonitrile gave benzyl-(3,4-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazol-1-yl)-amine **16b** (0.43 g, 63%) as a yellow solid; mp 148–149 °C (Found: C, 66.7; H, 4.3; N, 17.3. $C_{18}H_{14}F_2N_4$ requires: C, 66.7; H, 4.4; N, 17.3%); δ_H 2.57 (3H, s, CH_3), 4.75 (2H, d, $^3J_{HH}$ 5.6, CH_2), 6.12 (1H, br s, NH), 6.72–6.78 (1H, m, H-7), 7.14 (1H, dm, $^3J_{HH}$ 6.8, H-8), 7.26–7.31 (3H, m, H-3′,4′), 7.39 (2H, dm, $^3J_{HH}$ 7.6, H-2′), 8.34 (1H, dm, $^3J_{HH}$ 6.8, H-6); δ_F −103.97 (1F, m, F-3), −179.55 (1F, d, $^3J_{FF}$ 23.7, F-4); δ_C 17.56 (s, CH_3), 45.60 (s, CH_2), 112.31 (s, C-7), 124.40 (dd, $^2J_{CF}$ 16.1, $^3J_{CF}$ 8.9, C-4′d), 124.89 (d, $^4J_{CF}$ 4.6, C-6), 125.65 (dd, $^1J_{CF}$ 246.2, $^2J_{CF}$ 35.3, C-4), 127.48 (s, Ar), 127.54 (s, Ar), 128.27 (s, Ar), 128.40 (m, C-3′d), 128.66 (s, Ar), 128.74 (s, Ar), 139.03 (s, C-1′), 144.40 (d, $^3J_{CF}$ 18.4, C-1), 144.77 (dd, $^1J_{CF}$ 222.0, $^2J_{CF}$ 12.7, C-3), 148.30 (s, C-2a); *m*/*z* (ES^+) 325.1 ($[MH]^+$, 100 %). Crystals suitable for X-ray crystallography were grown from acetonitrile.

*4.3.3. Benzyl-(3,4-difluoro-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazol-1-yl)-methyl-amine **16c**.* **7a** (0.50 g, 2.11 mmol) and *N*-benzylmethylamine **15c** (1.28 g, 10.54 mmol) were stirred together in a mixture of THF (10 mL) and DMSO (2 mL) at 170 °C for 30 min (MW). The reaction mixture was evaporated to dryness, water (50 mL) was added and the organic products extracted into dichloromethane (3×40 mL). Drying ($MgSO_4$), evaporation and recrystallisation from acetonitrile gave benzyl-(3,4-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazol-1-yl)-methyl-amine **16c** (0.55 g, 77%) as a dark green solid; mp 111–113 °C (Found: C, 67.7; H, 4.7; N, 16.8. $C_{19}H_{16}N_4F_2$ requires: C, 67.5; H, 4.8; N, 16.6%); δ_H 2.53 (3H, s, CH_3), 3.37 (3H, s, NCH_3), 5.46 (2H, s, CH_2), 6.64–6.70 (1H, m, H-7), 7.06 (1H, dm, $^3J_{HH}$ 6.7, H-8), 7.37–7.22 (5H, m, H-2′, 3′, 4′), 8.31 (1H, d, $^3J_{HH}$ 7.1, H-6); δ_F −102.56 (1F, d, $^3J_{FF}$ 26.3, F-3), −180.01 (1F, d, $^3J_{FF}$ 26.0, F-4); δ_C 17.21 (s, CH_3), 37.00 (s, NCH_3), 54.57 (s, CH_2), 111.79 (s, C-7), 124.28 (d, $^4J_{CF}$ 6.1, C-6), 124.98 (dd, $^1J_{CF}$ 245.4, $^2J_{CF}$ 36.3, C-4), 125.90 (dd, $^2J_{CF}$ 8.2, $^3J_{CF}$ 7.0, C-4′d), 126.50 (s, Ar), 127.06 (s, Ar), 127.99 (s, Ar), 128.12 (m, C-3′d), 128.46 (s, Ar), 128.71 (s, C-9), 139.09 (s, C-1′), 143.38 (dd, $^1J_{CF}$ 219.5, $^2J_{CF}$ 12.1, C-3), 144.88 (d, $^3J_{CF}$ 16.6, C-1),146.71 (br s, C-2a); *m*/*z* (ES^+) 339.1 ($[MH]^+$, 100%).

*4.3.4. (3,4-Difluoro-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazol-1-yl)-(4-methoxy-phenyl)-amine **16d**.* **7a** (0.10 g, 0.42 mmol), *p*-anisidine **15d** (0.08 g, 0.63 mmol) and triethylamine (0.13 g, 1.26 mmol) were stirred together in THF (1.0 mL) and DMSO (0.2 mL) at 170 °C for 2 h (MW). Solvent was evaporated and purification of the residue by mass directed HPLC gave (3,4-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazol-1-yl)-(4-methoxy-phenyl)-amine **16d** (0.02 g, 12%) as a yellow solid; mp 161–162 °C ($[MH]^+$, 341.1208. $C_{18}H_{14}N_4OF_2$ requires: $[MH]^+$, 341.1214); δ_H 2.65 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 6.81 (1H, t, $^3J_{HH}$ 6.9, H-7), 6.93 (2H, AX, $^3J_{AX}$ 9.0, Ar-H), 7.21 (1H, dm, $^3J_{HH}$ 6.8, H-8), 7.63 (1H, br s, NH), 7.74 (2H, AX, $^3J_{AX}$ 8.8, Ar-H), 8.42 (1H, d, $^3J_{HH}$ 6.9, H-6); δ_F −102.9 (1F, d, $^3J_{FF}$ 24.3, F-3), −176.5 (1F, d, $^3J_{FF}$ 24.1, F-4); *m*/*s* (ES^+) 341.1 ($[MH]^+$, 100%).

*4.3.5. 3,4-Difluoro-1-methoxy-9-methyl-dipyrido[1,2-a,3′,4′-d]imidazole **17**.* **7a** (0.40 g, 1.69 mmol), sodium methoxide (0.10 g, 1.86 mmol) and triethylamine (0.51 g, 5.08 mmol) were stirred together in anhydrous MeOH (10 mL) under microwave irradiation for 30 min at 140 °C. The reaction mixture was poured into water (10 mL) and evaporation under reduced pressure gave a white crude product, which was triturated with water to give 3,4-difluoro-1-methoxy-9-methyl-dipyrido[1,2-*a*;3′4′-*d*]imidazole **17** (0.38 g, 90%) as a white solid; mp 187–188 °C (Found: C, 57.6; H, 3.5; N, 16.6. $C_{12}H_9F_2N_3O$ requires: C, 57.8; H, 3.6; N, 16.9%); δ_H 2.68 (3H, s, CH_3), 4.16 (3H, s, OCH_3), 6.80–6.87 (1H, m, H-7), 7.21–7.28 (1H, m, H-8), 8.41–8.52 (1H, m, H-6); δ_F −104.3 (1F, d, $^3J_{FF}$ 22.0, F-3), −172.8 (1F, d, $^3J_{FF}$ 21.9, F-4); δ_C 17.73 (s, CH_3), 54.87 (s, OCH_3), 112.64 (s, C-7), 124.82 (d, $^4J_{CF}$ 5.2, C-6), 126.04 (m, C-4′d), 128.38 (s, C-8), 128.49 (dd, $^1J_{CF}$ 251.5, $^2J_{CF}$ 33.7, C-4), 128.71 (m, C-3′d), 129.35 (s, C-9), 142.70 (dd, $^1J_{CF}$ 227.0, $^2J_{CF}$ 14.0, C-3), 148.55 (dd, $^3J_{CF}$ 13.8, $^4J_{CF}$ 1.2, C-1), 149.51 (s, C-2a); *m*/*z* (ES^+) 250.1 ($[MH]^+$, 100%).

*4.3.6. 3,4-Difluoro-9-methyl-1-phenyl-dipyrido[1,2-a;3′,4′-d]imidazole **18**.* **7a** (0.41 g, 1.70 mmol) and phenylmagnesium bromide (3.49 mL 1 M soln in THF, 3.50 mmol) were heated at reflux in THF (40 mL) for 93 h. The resulting mixture was poured into 0.5 M HCl solution (50 mL) and extracted with DCM (3×10 mL). Drying ($MgSO_4$), evaporation of solvent and recrystallisation from acetonitrile gave 3,4-difluoro-9-methyl-1-phenyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **18** (0.25 g, 48%) as a pale yellow solid; mp 188–189 °C (Found: C, 69.2; H, 3.7; N, 14.2. $C_{17}H_{11}F_2N_3$ requires: C, 69.2; H, 3.8; N, 14.2%); δ_H 2.66 (3H, s, CH_3), 6.78 (1H, t, $^3J_{HH}$ 6.7, H-7), 7.24 (1H, dm, $^3J_{HH}$ 6.7, H-8), 7.41–7.48 (1H, m, H-4′), 7.50–7.54 (2H, m, H-3′), 8.42 (1H, d, $^3J_{HH}$ 6.9, H-6), 8.79 (2H, dm, $^3J_{HH}$ 8.3, H-2′); δ_F −99.8 (1F, d, $^3J_{FF}$ 28.2, F-3), −162.9 (1F, d, $^3J_{FF}$ 27.5, F-4); δ_C 17.49 (s, CH_3), 112.29 (s, C-7), 125.19 (d, $^4J_{CF}$ 5.5, C-6), 125.84 (m, C-4′d), 128.52 (s, Ar), 129.10 (s, Ar), 129.20 (s, C-9), 129.39 (s, Ar), 129.52 (s, Ar), 131.68 (dd, $^1J_{CF}$ 264.5, $^2J_{CF}$ 36.6, C-4), 136.19 (s, C-1′), 139.35 (m, C-3′d), 140.26 (dd, $^3J_{CF}$ 13.5, $^4J_{CF}$ 5.6, C-1), 144.03 (dd, $^1J_{CF}$ 223.7, $^2J_{CF}$ 11.9, C-3), 150.60 (s, C-2a); *m*/*z* (EI^+) 295 ($[M]^+$, 100%).

*4.3.7. 3-Fluoro-9-methyl-1,4-bis-phenylsulfanyl-dipyrido[1,2-a;3′, 4′-d]imidazole **19**.* **7a** (0.47 g, 2.0 mmol) and lithium thiophenoxide (4.00 mL 1 M solution in THF, 4.0 mmol) in THF (10 mL) were heated at reflux for 17 h. Evaporation of the solvent was followed by addition of 0.5 M HCl solution (50 mL), extraction into DCM (3×40 mL), drying ($MgSO_4$), evaporation and recrystallisation from acetonitrile gave 3-fluoro-9-methyl-1,4-bis-phenylsulfanyl-

dipyrido[1,2-*a*;3′,4′-*d*]imidazole **19** (0.51 g, 61%) as a yellow solid; mp 174–176 °C (Found: C, 65.9; H, 3.8; N, 10.2. $C_{23}H_{16}N_3FS_2$ requires: C, 66.2; H, 3.9; N, 10.1%); δ_H 2.70 (3H, s, CH_3), 6.70–6.73 (1H, m, H-7), 7.15–7.09 (3H, m, Ar-H), 7.24–7.17 (3H, m, H-9, Ar-H), 7.49–7.45 (3H, m, Ar-H), 7.75–7.72 (2H, m, Ar-H), 9.31 (1H, d, $^3J_{HH}$ 7.1, H-6); δ_C 17.71 (s, CH_3), 93.13 (d, J_{CF} 44.3, C-4), 112.06 (s, C-7), 125.26 (s, C-6), 126.62 (s, Ar), 127.11 (s, Ar), 127.99 (s, C-9), 128.76 (s, Ar), 128.98 (s, Ar), 129.36 (s, Ar), 129.51 (s, C-8), 129.58 (s, Ar), 134.86 (d, $^3J_{CF}$ 5.9, C-4′d), 135.25 (br s, C-3′d), 135.58 (s, Ar), 136.74 (d, $^4J_{CF}$ 1.9, C-1′), 150.60 (d, $^5J_{CF}$ 1.8, C-2a), 152.00 (d, J_{CF} 17.7, C-1), 158.57 (d, $^1J_{CF}$ 230.6, C-3); δ_F -75.6 (1F, s, F-3); *m*/*z* (ES^+) 418 ($[MH]^+$, 100%).

4.4. Reactions of 4-chloro-1,3-trifluoro-9-methyl-dipyrido-[1,2-*a*;3′,4′-*d*]imidazole 10 with nucleophiles

4.4.1. Butyl-(4-chloro-3-fluoro-9-methyl-dipyrido[1,2-a;3′-4′d]-imidazol-1-yl)amine ***21a***. 4-Chloro-1,3-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **10** (0.3 g, 0.1 mmol), *n*-butylamine (0.17 g, 0.2 mmol) and sodium hydrogen carbonate (1.81 g, 2.2 mmol) were heated at reflux in MeCN (40 mL) under an atmosphere of argon for 21 h. MeCN was removed under reduced pressure, the reaction mixture was poured into water (50 mL) and extracted with DCM (3×30 mL). The reaction mixture was dried ($MgSO_4$), solvent evaporated and the residue recrystallised to give butyl-(4-chloro-3-fluoro-9-methyl-dipyrido[1,2-*a*;3′-4′*d*]imidazol-1-yl)amine **21a** (0.35 g, 97%) as a white solid; mp 104.8–105.6 °C (MeCN) (Found: C, 58.4; H, 5.1; N, 16.9. $C_{15}H_{16}N_4FCl$ requires: C, 58.7; H, 5.2; N, 18.2); δ_H 0.99 (3H, t, $^3J_{HH}$ 7.0, CH_3), 1.45–1.55 (2H, m, CH_2), 1.70–1.76 (2H, m, CH_2), 2.66 (3H, s, CH_3), 3.58–3.66 (2H, m, CH_2), 6.70–6.76 (1H, m, H-7), 7.09–7.15 (1H, m, H-8), 8.90–8.96 (1H, m, H-6); δ_F −86.78 (s); δ_C 14.02 (s, C-14), 17.55 (s, C-10), 20.34 (s, C-13), 31.82 (s, C-12), 41.14 (s, C-11), 85.36 (d, $^2J_{CF}$ 43.60, C-4), 111.75 (s, C-7), 124.41 (s, C-6), 127.10 (s, C-9), 127.12 (s, C-8), 130.15 (d, $^4J_{CF}$ 6.34, C-4′d), 148.03 (d, $^3J_{CF}$ 19.92, C-3′d), 148.18 (m, C-1), 153.84 (d, $^1J_{CF}$ 221, C-3); *m*/*z* (EI^+) 305.9 ($[M]^+$, 46%), 262.9 (100).

4.4.2. (4-Chloro-3-fluoro-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazol-1-yl)-diethyl-amine ***21b***. 4-Chloro-1,3-difluoro-9-methyl-dipyrido[1,2-*a*; 3′,4′-*d*]imidazole **10** (0.3 g, 0.1 mmol), diethylamine (0.17 g, 0.2 mmol) and sodium hydrogen carbonate (1.81 g, 2.2 mmol) were heated at reflux in MeCN (40 mL) under an atmosphere of argon for 21 h. MeCN was removed under reduced pressure, the reaction mixture was poured into water (50 mL) and extracted with DCM (3×30 mL). The reaction mixture was dried ($MgSO_4$), solvent evaporated and the residue recrystallised from ethyl acetate to give (4-chloro-3-fluoro-9-methyl-dipyrido [1,2-*a*;3′4′-*d*]imidazol-1-yl)-diethyl-amine **21b** (0.2 g, 71%) as a yellow solid; mp 101–102.5 °C (MeCN) (Found: C 58.61; H 5.15; N 18.08. $C_{15}H_{16}N_4ClF$ requires: C 58.82; H 5.22; N 18.30%); δ_H 1.29 (6H, m, CH_2CH_3), 2.57 (3H, s, CH_3), 4.00–4.09 (4H, m, CH_2), 6.65–6.71 (1H, m, H-7), 7.04–7.11 (1H, m, H-8), 8.94–9.00 (1H, m, H-6); δ_F −85.71 (s); δ_C 13.79 (s, CH_2CH_3), 17.28 (s, CH_3), 43.99 (s, CH_2), 83.94 (d, $^2J_{CF}$ 45.14, C-4), 111.31 (s, C-7), 124.09 (s, C-6), 126.08 (s, C-8), 127.82 (d, $^3J_{CF}$ 2.56, C-4′d), 128.66 (s, C-9), 132.07 (d, $^3J_{CF}$ 6.54, C-1), 146.82 (d, $^5J_{CF}$ 1.75, C-2a), 147.21 (d, $^3J_{CF}$ 18.95, C-1), 152.79 (d, $^1J_{CF}$ 219.39, C-3); *m*/*z* (EI^+) 306.0 ($[M]^+$, 75%), 291.0 (88), 276.9 (75), 262.8 (100), 234.6 (55).

4.4.3. 4-Chloro-3-fluoro-1-methoxy-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazole ***21c***. 4-Chloro-1,3-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **10** (0.3 g, 0.1 mmol) and sodium methoxide (0.13 g, 0.2 mmol) were heated at reflux in MeOH (30 mL) under an atmosphere of argon for 23 h. MeOH was removed under reduced pressure, the reaction mixture was poured onto water (50 mL) and extracted with DCM (3×30 mL). The reaction mixture was dried ($MgSO_4$), solvent evaporated and recystallisation of the residue gave 4-chloro-3-fluoro-1-methoxy-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **21c** (0.1 g, 32%) as a white solid; mp 229–230 °C (MeOH) (Found: C, 53.9; H, 3.3; N, 15.4. $C_{12}H_9N_3OFCl$ requires: C, 54.2; H, 3.4, N, 15.8%); δ_H 2.63 (3H, s, CH_3), 4.13 (3H, s, OCH_3), 6.75–6.81 (1H, m, H-7), 7.18–7.23 (1H, m, H-8), 8.94–9.01 (1H, m, H-6); δ_F −87.47 (s); δ_c 17.78 (s, CH_3), 54.97 (s, OMe), 92.00 (d, $^2J_{CF}$ 41.69, C-4), 112.15 (s, C-7), 124.33 (s, C-6), 128.11 (s, C-8), 128.70 (d, $^4J_{CF}$ 3.37, C-3′d), 129.35 (s, C-9), 132.67 (d, $^3J_{CF}$ 6.08, C-4′d), 149.82 (d, $^5J_{CF}$ 1.81, C-2a), 151.64 (d, $^1J_{CF}$ 227.37, C-3), 152.52 (d, $^3J_{CF}$ 15.25, C-1); *m*/*z* (EI^+) 265.0 ($[M]^+$, 100%), 249.9 (55).

4.4.4. 4-Chloro-3-fluoro-9-methyl-1-phenoxy-dipyrido[1,2-a;3′,4′-d]imidazole ***21d***. 4-Chloro-1,3-difluoro-9-methyl-dipyrido[1,2-*a*; 3′,4′-*d*]imidazole **10** (0.5 g, 1.97 mmol) and sodium phenoxide (0.34 g, 2.9 mmol) were heated at reflux in dry MeCN for 24 h under an atmosphere of argon. The reaction mixture was evaporated under reduced pressure, water (50 mL) was added and extracted with DCM (3×50 ml). Drying ($MgSO_4$), solvent evaporation and recrystallisation from ethyl acetate gave 4-chloro-3-fluoro-9-methyl-1-phenoxy-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **21d** (0.49 g, 76%) as a white solid; mp 170.5–171.2 °C; (Found: C, 62.3; H, 3.6; N, 12.5. $C_{17}H_{11}ClFN_3O$ requires C, 62.3; H, 3.4; N, 12.8%); δ_H 2.64 (3H, s, CH_3), 6.82 (1H, t, $^3J_{HH}$ 7.00, H-7), 7.23 (1H, t, $^3J_{HH}$ 7.50, H-14), 7.24 (2H, d, $^3J_{HH}$ 7.50, H-12,16), 7.25 (1H, d, $^3J_{HH}$ 7.00, H-8), 7.39 (2H, t, $^3J_{HH}$ 7.50, H-13,15), 9.02 (1H, d, $^3J_{HH}$ 7.00, H-6); δ_F −85.75 (s); δ_C 17.95 (s, CH_3), 93.71 (d, $^2J_{CF}$ 41.72, C-4), 112.6 (s, C-7), 118.87 (s, Ar), 122.12 (s, Ar), 124.54 (s, C-6), 124.89 (d, $^3J_{CF}$ 11.94, C-4′d), 125.76 (s, C-8), 129.22 (m, C-4′d), 129.52 (s, C-9), 129.78 (s, Ar), 133.83 (m, C-3′d), 149.66 (s, C-2a), 153.17 (s, C-1), 154.41 (d, $^1J_{CF}$ 247.94, C-3); *m*/*z* (EI^+) 327.0 ($[M]^+$, 100%), 292.0 (60).

4.4.5. 4-Chloro-3-fluoro-9-methyl-1-phenylsulfanyl-dipyrido[1,2-a;3′,4′-d]imidazole ***21e***. 4-Chloro-1,3-difluoro-9-methyl-dipyrido [1,2-*a*;3′,4′-*d*]imidazole **10** (0.5 g, 1.99 mmol) and sodium thiophenolate (0.34 g, 2.59 mmol) were heated at reflux in dry MeCN for 120 h under an atmosphere of argon. The reaction mixture was evaporated under reduced pressure, water (50 mL) was added and extracted with DCM (3×50 mL). Drying ($MgSO_4$), solvent evaporation and recrystallisation from acetonitrile gave 4-chloro-3-fluoro-9-methyl-1-phenylsulfanyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **21e** (0.40 g, 58%) as green crystals; mp 149–150 °C; (Found: C, 59.2; H, 3.2; N, 12.3%. $C_{17}H_{11}ClFN_3S$ requires C, 59.4; H, 3.2; N, 12.2%); δ_H 2.66 (3H, s, CH_3), 6.82 (1H, t, $^3J_{HH}$ 6.00, H-7), 7.24 (1H, d, $^3J_{HH}$ 6.00, H-8), 7.39 (1H, t, $^3J_{HH}$ 6.50, H-14), 7.40 (2H, t, $^3J_{HH}$ 6.50, H-13,15), 7.63 (2H, d, $^3J_{HH}$ 6.50, H-12,16), 8.96 (1H, d, $^3J_{HH}$ 7.00, H-6); δ_F -84.0 (s); δ_C 17.85 (s, CH_3), 96.43 (d, $^2J_{CF}$ 43.61, C-4), 112.27 (s, C-7), 116.19 (s, Ar), 118.87 (s, Ar), 124.85 (s, C-6), 128.59 (s, C-4′d), 129.02 (s, C-8), 129.44 (s, Ar), 129.48 (s, C-9), 131.10 (m, C-3′d), 135.53 (s, Ar), 137.61 (s, C-1), 147.44 (d, $^5J_{CF}$ 15.46, C-2a), 153.18 (d, $^1J_{CF}$ 228.71, C-3); *m*/*z* (EI^+) 343.0 ($[M]^+$, 100%), 308.0 (95).

4.5. Reactions of 10 involving displacement of ring chlorine

4.5.1. 1,3-Difluoro-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazole ***22***. 4-Chloro-1,3-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **10** (4.01 g, 1.57 mol), ammonium formate (0.89 g, 1.57 mol) and 30% palladium on charcoal were heated at reflux in THF (160 mL) for 48 h. The reaction mixture was filtered, poured into water (100 mL) and extracted with DCM (4×30 ml). Drying ($MgSO_4$), solvent evaporation and recrystallisation gave 1,3-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **22** (1.38 g, 50%) as a white solid; mp 234–235 °C (MeOH) (Found: C 60.06; H 3.26; N 19.15. $C_{11}H_7N_3F_2$ requires: C 60.27; H 3.19; N 19.17%); δ_H (DMSO) 2.47 (3H, s, CH_3), 6.97–7.03 (1H, m, H-7), 7.41–7.48 (1H, m, H-8), 8.00–8.06 (1H, m, H-4), 8.78–8.84 (1H, m, H-6); δ_F −74.92 (1F, d, $^4J_{FF}$ 13.03), −79.47 (1F, d, $^4J_{FF}$ 12.80); δ_C 16.68 (s, CH_3), 90.59 (dd,

$^{2}J_{CF}$ 43.73, $^{4}J_{CF}$ 7.37, C-4), 112.17 (s, C-7), 124.83 (dd, $^{2}J_{CF}$ 32.60, $^{4}J_{CF}$ 3.87, C-3′d), 125.10 (s, C-6), 127.62 (s, C-9), 130.22 (s, C-8), 140.83 (dd, $^{3}J_{CF}$ 12.4, $^{3}J_{CF}$ 12.4, C-3′d), 149.97 (dd, $^{1}J_{CF}$ 248.82, $^{3}J_{CF}$ 16.30, C-3), 150.61 (s, C-2a), 153.03 (dd, $^{1}J_{CF}$ 229.95, $^{3}J_{CF}$ 13.72, C-1); *m*/*z* (EI^{+}) 219.0 ([M]$^{+}$, 100%).

4.5.2. 1,3-Difluoro-4,9-dimethyl-dipyrido[1,2-a;3′,4′-d]imidazole ***23a***. BuLi (0.139 g, 1.35 mL 1.6 M soln in hexanes, 2.17 mmol) was added slowly to a stirred solution of 4-chloro-1,3-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **10** (0.5 g, 1.97 mmol) in dry THF (50 mL) at −78 °C. After stirring for 1 h, methyl iodide (0.31 g, 2.17 mmol) was added and the reaction mixture was left to stir for 72 h. The reaction mixture was concentrated under reduced pressure, 1.0 M HCl (50 ml) was added and extracted with DCM (3×50 mL). Drying ($MgSO_4$), solvent evaporation and purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave 1,3-difluoro-4,9-dimethyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **23a** (0.272 g, 59%) as off-white crystals; mp 241.1–241.5 °C; (Found: C, 61.5; H, 3.6; N, 17.9. $C_{12}H_9F_2N_3$ requires: C, 61.8; H, 3.9; N, 18.0%); δ_H 2.70 (3H, s, CH_3), 2.71 (3H, s, CH_3), 6.92 (1H, t, $^{3}J_{HH}$ 7.00, H-7), 7.36 (1H, d, $^{3}J_{HH}$ 7.00, H-8), 9.07 (1H, d, $^{3}J_{HH}$ 7.00, H-6); δ_F −80.87 (1F, $^{4}J_{FF}$ 13.17, F-1), 89.52 (1F, $^{4}J_{FF}$ 13.74, F-3); δ_C 16.58 (s, CH_3), 17.72 (s, CH_3), 97.54 (d, $^{2}J_{CF}$ 41.21, C-4), 112.74 (s, C-7), 124.23 (s, C-6), 128.49 (d, $^{2}J_{CF}$ 33.61, C-3′d), 129.66 (s, C-8), 129.87 (s, C-9), 135.45 (m, C-4′d), 149.03 (s, C-2a), 151.85 (dd, $^{1}J_{CF}$ 251.37, $^{3}J_{CF}$ 13.19, C-3), 153.71 (dd, $^{1}J_{CF}$ 223.27, $^{3}J_{CF}$ 13.92, C-1); *m*/*z* (EI^{+}) 233.0 ([M]$^{+}$, 100%).

4.5.3. 4-Allyl-1,3-difluoro-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazole ***23b***. BuLi (0.15 g, 1.48 mL 1.6 M soln in hexanes, 2.37 mmol) was added slowly to a stirred solution of 4-chloro-1,3-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **10** (0.5 g, 1.97 mmol) in dry THF (50 mL) at −78 °C. After stirring for 1 h, allyl bromide (0.29 g, 2.37 mmol) was added and the reaction mixture was left to stir for 20 h. The reaction mixture was evaporated under reduced pressure, 1.0 M HCl (50 mL) was added and extracted with DCM (3×50 mL). Drying (MgSO4), solvent evaporation and purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave 4-allyl-1,3-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **23b** (0.19 g, 37%) as a white solid; (Found: C, 65.2; H, 4.2; N, 16.0%. $C_{14}H_{11}F_2N_3$ requires: C, 64.9; H, 4.3; N, 16.2%); δ_H 2.68 (3H, s, CH_3), 3.03–3.12 (2H, m, CH_2), 4.13 (1H, d, $^{3}J_{HH}$ 14.68, C=CH_2), 4.49 (1H, d, $^{3}J_{HH}$ 9.09, C=CH_2), 5.21–5.35 (1H, m,=C–H), 6.89 (1H, t, $^{3}J_{HH}$ 7.00, H-7), 7.46 (1H, d, $^{3}J_{HH}$, H-8), 9.05 (1H, d, $^{3}J_{HH}$ 7.00, H-6); δ_F −80.42 (1F, $^{4}J_{FF}$ 14.83, F-1),−87.48 (1F, $^{4}J_{FF}$ 14.48, F-3); δ_C 14.31 (s, CH_3), 30.85 (dd, $^{3}J_{CF}$ 37.03, $^{5}J_{CF}$ 6.86, CH_2), 97.62 (dd, $^{2}J_{CF}$ 33.67, $^{4}J_{CF}$ 8.35, C-4), 116.54 (s,=CH_2), 112.36 (s, C-7), 122.08 (s, C-6), 124.43 (s, C-8), 126.85 (d, $^{2}J_{CF}$ 34.55, $^{4}J_{CF}$ 8.23, C-3′d), 128.90 (d, $^{5}J_{CF}$ 5.45, C-9), 130.26 (m, C-4′d), 133.42 (s,=CH), 143.48 (s, C-2a), 146 (dd, $^{1}J_{CF}$ 253.13, $^{3}J_{CF}$ 14.63, C-3), 152.57 (dd, $^{1}J_{CF}$ 239.32, $^{3}J_{CF}$ 13.04, C-1); *m*/*z* (EI^{+}) 259.0 ([M]$^{+}$, 100%).

4.5.4. 1-(1,3-Difluoro-9-methyl-dipyrido[1,2-a;3′,4′-d]imidazol-4-yl)-ethanone ***23c***. BuLi (1.34 mL 1.6 M soln in hexanes, 2.20 mmol) was added slowly to a stirred solution of 4-chloro-1,3-difluoro-dipyrido[1,2-*a*;3′,4′-*d*]imidazole **10** (0.5062 g, 2.00 mmol) in dry THF (50 mL) at −78 °C. After stirring for 1 h, acetyl chloride (0.18 g, 2.4 mmol) was added and the reaction mixture was stirred for a further 72 h. The reaction mixture was evaporated under reduced pressure, 1.0 M HCl (50 mL) was added and the organic products extracted with DCM (3×50 mL). Drying ($MgSO_4$), solvent evaporation and purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave 1-(1,3-difluoro-9-methyl-dipyrido[1,2-*a*;3′,4′-*d*]imidazol-4-yl)-ethanone **23c** (0.323 g, 63%) as a white solid; mp 223–225 °C (Found: C, 59.7; H, 3.3; N, 15.9%. $C_{13}H_9F_2N_3O$ requires: C, 59.8; H, 3.5; N, 16.1 %); δ_H 2.15 (3H, s, CH_3), 2.68 (3H, s, $COCH_3$), 6.90 (1H, t, $^{3}J_{HH}$ 7.50, H-7), 7.34 (1H, d, $^{3}J_{HH}$ 7.50, H-8), 9.04 (1H, d, $^{3}J_{HH}$ 7.50, H-6); δ_F −77.25 (1F, d, $^{4}J_{FF}$ 13.17, F-1), −85.60 (1F, d, $^{4}J_{FF}$ 13.17, F-3); δ_C 14.43 (s, CH_3), 31.18 (s, CH_3CO), 97.46 (dd, $^{2}J_{CF}$ 31.66, $^{4}J_{CF}$ 8.55, C-4), 112.34 (s, C-7), 124.51 (s, C-6), 127.34 (dd, $^{2}J_{CF}$ 33.55, $^{4}J_{CF}$ 9.43, C-3′d), 129.62 (s, C-8), 129.74 (s, C-9), 135.68 (m, C-4′d), 149.63 (dd, $^{1}J_{CF}$ 253.16, $^{3}J_{CF}$ 14.45, C-3), 149.90 (dd, $^{1}J_{CF}$ 233.99, $^{3}J_{CF}$ 13.82, C-1), 151.51 (s, C-2a), 207.24 (s, C=O); *m*/*z* (EI^{+}) 261.0 ([M]$^{+}$, 100%).

4.6. X-ray structures of 7a, 13a, 13b, 16b, 21e and 23a

Single crystal X-ray data for the structures were collected on a Bruker Proteum-M (**7a**, **13b**, **16b**) and Bruker SMART CCD 6000 (**13a**, **21e**, **23a**) diffractometers equipped with Cryostream (Oxford Cryosystems) nitrogen cooler at 120 K using graphite monochromated MoK_{α} radiation (λ=0.71073 Å, ω-scan, 0.3°/frame). All structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 741321–741326.

4.6.1. Crystal data for ***7a***. $C_{11}H_6F_3N_3$, *M*=237.19, orthorhombic, space group P nma, *a*=13.5814(7), *b*=6.4202(3), *c*=10.6503(5) Å, U=928.66(8) Å^3, *F*(000)=968, *Z*=4, D_c=1.696 mg m^{-3}, μ=0.148 mm^{-1}. 8647 reflections yielded 1342 unique data (R_{merg}=0.046). Final $wR_2(F^2)$=0.1144 for all data (119 refined parameters), conventional $R_1(F)$=0.0414 for 1016 reflections with $I \geq 2\sigma$, *GOF*=0.955.

4.6.2. Crystal data for ***13a***. $C_{17}H_{11}F_2N_3O_2S$, *M*=359.35, monoclinic, space group P 2$_1$/c, *a*=14.3633(6), *b*=10.1474(4), *c*=10.2507(4) Å, β=93.70(1)°, *U*=1490.9(1) Å^3, *F*(000)=736, *Z*=4, D_c=1.601 mg m^{-3}, μ=0.258 mm^{-1}. 17242 reflections yielded 4146 unique data (R_{merg}=0.0589). Final $wR_2(F^2)$=0.1006 for all data (270 refined parameters), conventional $R_1(F)$=0.0360 for 3161 reflections with $I \geq 2\sigma$, *GOF*=0.995.

4.6.3. Crystal data for ***13b***. $C_{17}H_{11}F_2N_3O_2S$, *M*=359.35, triclinic, space group P -1, *a*=8.3285(3), *b*=8.7801(3), *c*=11.6055(4) Å, α=72.64(2), β=82.70(2), γ=66.35(1)°, *U*=741.92(4)Å^3, *F*(000)=368, *Z*=4, D_c=1.609 mg m^{-3}, μ=0.259 mm^{-1}. 7607 reflections yielded 3971 unique data (R_{merg}=0.0327). Final $wR_2(F^2)$=0.1205 for all data (270 refined parameters), conventional $R_1(F)$=0.0469 for 3653 reflections with $I \geq 2\sigma$, *GOF*=1.078.

4.6.4. Crystal data for ***16b***. $C_{18}H_{14}F_2N_4$, *M*=324.33, monoclinic, space group P 2$_1$/n, *a*=8.5739(2), *b*=17.9700(4), *c*=10.3211(2) Å, β=110.42(1)°, *U*=1490.25(6) Å^3, *F*(000)=672, *Z*=4, D_c=1.446 mg m^{-3}, μ=0.107 mm^{-1}. 13265 reflections yielded 4130 unique data (R_{merg}=0.0296). Final $wR_2(F^2)$=0.1153 for all data (273 refined parameters), conventional $R_1(F)$=0.0454 for 3632 reflections with $I \geq 2\sigma$, *GOF*=1.052.

4.6.5. Crystal data for ***21e***. $C_{17}H_{11}ClFN_3S$, *M*=343.80, monoclinic, space group P 2$_1$/c, *a*=12.0775(4), *b*=17.1203(5), *c*=7.0518(2) Å, β=93.06(2)°, *U*=1456.02(8) Å^3, *F*(000)=704, *Z*=4, D_c=1.568 mg m^{-3}, μ=0.418 mm^{-1}. 17174 reflections yielded 4234 unique data (R_{merg}=0.0602). Final $wR_2(F^2)$=0.0896 for all data (252 refined parameters), conventional $R_1(F)$=0.0379 for 2875 reflections with $I \geq 2\sigma$, *GOF*=0.988.

4.6.6. Crystal data for ***23a***. $C_{12}H_9F_2N_3$, *M*=233.22, monoclinic, space group P 2$_1$/n, *a*=6.8959(3), *b*=13.8687(5), *c*=10.8782(4) Å, β=107.05(1)°, *U*=994.66(7) Å^3, *F*(000)=480, *Z*=4, D_c=1.557 mg m^{-3}, μ=0.123 mm^{-1}. 12194 reflections yielded 2904 unique data

(R_{merg}=0.0685). Final $wR_2(F^2)$=0.0982 for all data (190 refined parameters), conventional $R_1(F)$=0.0409 for 1865 reflections with $I \geq 2\sigma$, *GOF*=1.023.

Acknowledgements

We thank EPSRC and GlaxoSmithKline Pharmaceuticals for a studentship (MWC) and the Durham University M.Chem. Undergraduate Degree Programme for funding.

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