Linear and macrocyclic ligands containing alternating pyridine and imidazolidin-2-one units[1]

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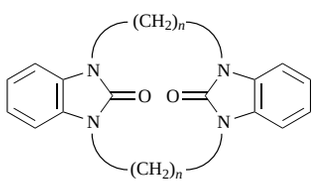
Linear oligomers of alternating 2,6-disubstituted pyridine (P) and *N*,*N*′-disubstituted imidazolidine-2-one (I) units have been made rapidly and in high yield with up to nine repeating units, terminating in either pyridine or imidazolidin-2-one units, or one of each. Synthetic methods include: (1) the sodium hydride-mediated condensation of *N*-(*tert*-butyl)imidazolidin-2-one with 2,6-difluoropyridine (F-P-F) or with higher analogues such as F-PIP-F, to give IPI, IPIPI and IPIPIPI. (The *tert*-butyl protection is readily and quantitatively removed with acid.) (2) The caesium fluoride catalysed interaction of *N*,*N*′-[dimethyl-(1,1,3-trimethylpropyl)]-protected IPI with Bu′-IP-F sequentially leads firstly to IPIPIPI which by the same method reacts with F-P-F to give F-PIPIPIPIP-F. (3) F-P-F also reacts with 1,2-ethylenediamine (E) sequentially to give F-PEP-F, EPEPE and F-PEPEPEP-F while similar reactions starting from F-PIP-F give EPIPE and F-PEPIPEP-F in sequence. Alternative routes examined include: (1) the interaction of F-P-F with imidazole to give 2,6-bis(imidazol-1-yl)pyridine and salts therefrom followed by (unsuccessful) oxidation. (2) The reaction of 2,6-diaminopyridine with 2-chloroethyl isocyanate followed by cyclisation to give IPI. (3) The interaction of 2,6-diaminopyridine with oxalate esters (O) to give OPO or H_2N-POP-NH_2, the latter of which was reduced to H_2N-PEP-NH_2.

Cyclisation of the linear assemblies was not successful. However macrocyclic systems were made by linking two IPI units with two ethoxyethyl or with two ethoxyethoxyethyl units. Also two F-PIP-F units were similarly reacted to give polyether-linked macrocycles. Mono- and bis-prop-2-ynylated IPI derivatives were made but could not be cyclised. Attempts to cyclise ethylenediamine and oxamide based systems were also unsuccessful. The linear and macrocyclic ligands showed calcium selectivity in a study of their metal complexing abilities.

Introduction

Some years ago we published the first examples of synthetic 'crown ureides', that is systems in which a macrocycle contains urea carbonyl functions as ligand units such as **1** and **2**.[2] The compounds **1** and **2** proved to be particularly effective, and in some cases, very selective for calcium ions, giving stable crystalline complexes. Later, Cram and co-workers[3] developed a number of designed crown ureides usually containing three ureides alternating with aryl units, their synthesis requiring many steps, but the ligand properties of which were of considerable interest. Weber *et al.*[4] and Shi and Thummel[5] have reported an alternative approach to compounds **1** and **2** and their analogues, and other acyclic analogues have also been examined and shown to be effective calcium ligands. Kumars and co-workers[6] and Parifer and co-workers[7] have made imidazolidin-2-one based macrocyclic systems with ether bridges, which show selective binding, while Still and co-workers[8] have incorporated imidazolidin-2-one units into complex ligands, some of which were homochiral and behave as hosts for imidazole and amino acid amides. Nolte and co-workers[9] have utilised bicyclic imidazolidin-2-one units in the design of complex ligands capable of binding alkali metal picrates.



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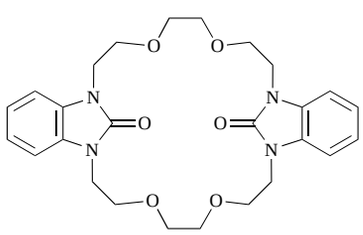

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We considered that the use of alternating 2,6-dihalopyridines with imidazolidin-2-one units would allow a rapid, more simple assembly of novel ligands for group II metal ions as well as generating interesting systems containing two types of alternating ligand atoms. To this end we first explored the synthesis of alternating pyridine–imidazolidin-2-one oligomers, secondly we investigated methods for their macrocyclisation and finally examined the ligand properties of the macrocycles.

Consideration of ring geometries suggest that a macrocycle **3** containing four units each of 2,6-disubstituted pyridine and *N*,*N*′-disubstituted imidazolidin-2-one would be almost planar and unstrained and preorganised for complexation (the sum of the external angles would be ~415°) (Scheme 1). With this target in mind, we first examined potential routes to such a system and in particular to appropriate linear precursors.

In order to simplify the nomenclature of such linear alternating systems we herein refer to the 2,6-disubstituted pyridine system as 'P' and the *N*,*N*′-disubstituted imidazolidin-2-one unit as 'I', and append terminal groups other than hydrogen. We envisaged two alternative pyridine building blocks, namely 2,6-diamino- and 2,6-dihalo-pyridines. We did not consider the *de novo* synthesis of a pyridine ring as deserving attention as a short approach to our targets. *N*,*N*′-Disubstituted imidazolidin-2-ones could be derived from the heterocycle itself or a protected derivative, from a close analogue such as imidazole followed by functional manipulation, or from a urea or

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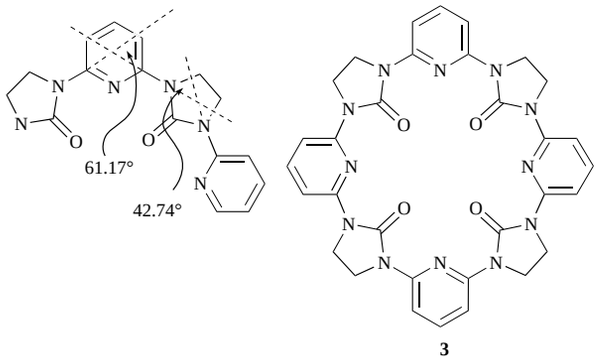
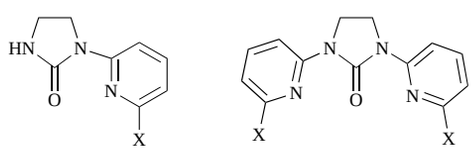


Scheme 1

an ethylenediamine unit. The above nomenclature system also utilises 'E' to imply an *N*,*N*′-disubstituted 1,2-diaminoethane unit and 'O' to indicate an *N*,*N*′-disubstituted oxamide unit. Each of these approaches have been explored, some having merit depending upon the target intermediate, and will be discussed below in order based upon the starting 2,6-disubstituted pyridine.

Synthesis of linear assemblies based on halopyridines

1. Halopyridines and imidazolidin-2-ones. Since imidazolidin-2-one is non-nucleophilic we first investigated the reaction of cheap 2,6-dichloropyridine with imidazolidin-2-one in the presence of sodium hydride in either THF or DMF. At temperatures from ambient (no action) to 150 °C no effective pathway to simple products was found, polymers being produced under forcing conditions. Thus after 5 days in refluxing THF the mono- and di-substituted products **4a** and **5a** were

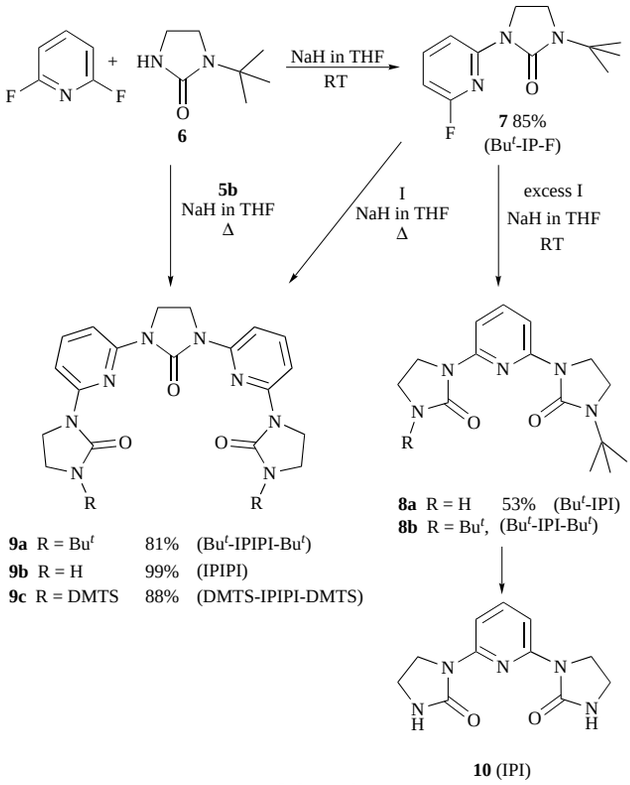


4a X = Cl
b X = F

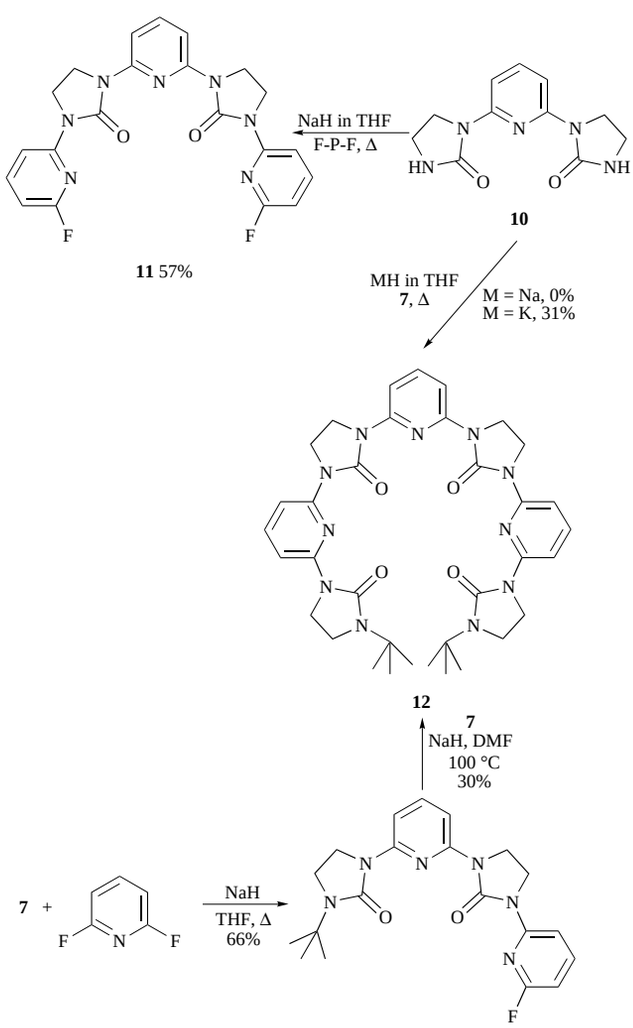
5a X = Cl
b X = F

isolated in 3 and 5%, respectively. The much more reactive 2,6-difluoropyridine gave *N*,*N*′-bis(6-fluoropyridin-2-yl)imidazolidin-2-one **5b** (F-PIP-F) in 83% yield after 20 h in refluxing THF, so long as an excess of the pyridine was utilised.

We therefore next explored the use of protected imidazolidin-2-ones. 1-*tert*-Butylimidazolidin-2-one **6** is easily made on a large scale by the sulfuric acid catalysed *tert*-butylation of imidazolidin-2-one.[10] Other workers have found that *N*,*N*′-bis(trimethylsilyl)imidazolidin-2-one readily forms a polymer with 2,6-difluoropyridine[11] in the presence of caesium fluoride. We examined both of these potentially useful approaches. Reaction of the latter imidazolidin-2-one with 2,6-difluoropyridine in DMF at 120 °C again gave F-PIP-F **5** in 79% yield. However the *tert*-butylated imidazolidin-2-one proved a versatile and key reagent, being crystalline and, unlike its parent, very soluble, easily reacted and easily deprotected. Some typical applications are shown in Scheme 2. The rapid assemblies of Bu′-IP-F **7**, Bu′-IPI **8a**, Bu′-IPI-Bu′ **8b** and Bu′-IPIPI-Bu′ **9a** were performed in high yields by interaction of 1-*tert*-butylimidazolidin-2-one **6** with sodium hydride in THF and subsequently a fluoropyridine. Deprotection of the latter two systems proceeds in almost quantitative yield with refluxing mineral acid to give IPI **10** and IPIPI **9b**. Treatment of IPI **10** with an excess of 2,6-difluoropyridine and with NaH in THF under reflux gives F-PIPIP-F **11** in 57% yield (Scheme 3). However, the increasing insolubility and unreactivity of these compounds as chain length increases made further progress using this protocol less attractive for the higher members of the series. Thus while the sodium hydride mediated reaction



Scheme 2



Scheme 3

was no longer effective, we were able to make the heptamer, Bu′-IPIPIPI-Bu′ **12** in moderate yields by using the more

reactive KH instead of NaH in the coupling reaction or alternatively by reacting two moles of mono-protected IPI with 2,6-difluoropyridine (31%) (Scheme 3). Fortunately an adaption of the above *N*-protected imidazolidin-2-one methodology proved to be an excellent method for the higher oligomers.

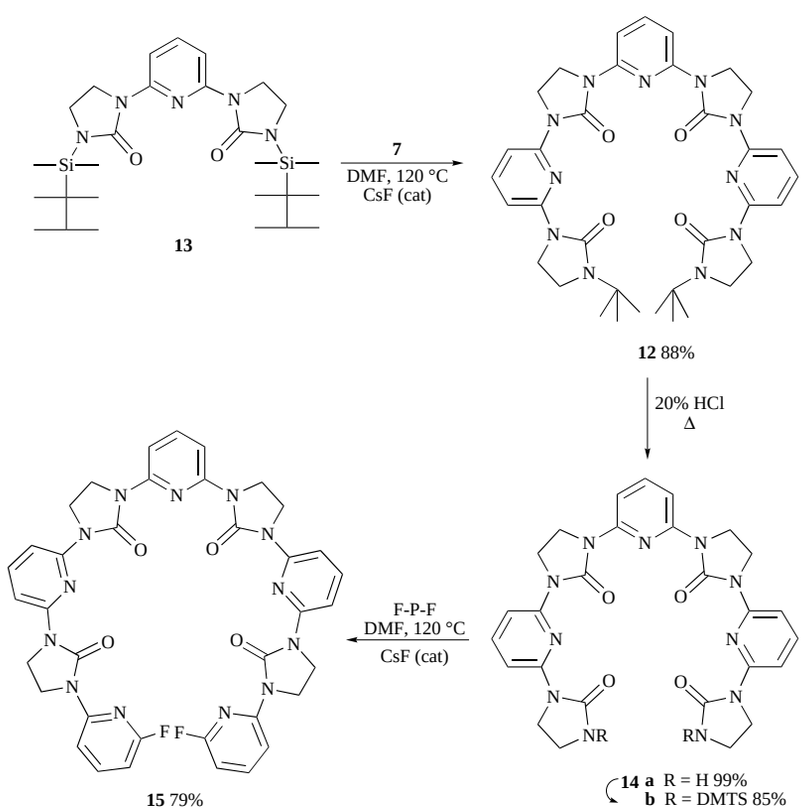
N-Silyl derivatives of amides are considerably less stable than their *O*-silylated counterparts. However, the (1,1,3-trimethylpropyl)dimethylsilyl derivatives (herein referred to as DMTS reagents) are excellent derivatives, capable of isolation, crystallisation and chromatography.[12] They were easily made by, for example, reaction of IPI **10** with DMTS chloride and triethylamine in 79% yield. This product **13**, reacted readily with Bu^t-IP-F **7** and a catalytic amount of caesium fluoride in DMF at 120 °C to give Bu^t-IPIPIPI-Bu^t **12** in 88% yield, which was again quantitatively deprotected to give IPIPIPI **14**. In a similar manner, even the nonamer, F-PIPIPIPIP-F **15** was readily made from silylated IPIPIPI **14** and an excess of 2,6-difluoropyridine in 79% yield (Scheme 4). Indeed, given the need, this methodology should allow higher members of such a series to be readily assembled.

2. Halopyridines and ethanediamines. Because of the insolubility of the oligomeric pyridine–imidazolidin-2-ones we envisaged that our ultimate goal may be better realised by linking pyridines with 1,2-ethylenediamine units and only form the imidazolidin-2-ones at a late stage. This approach would have the added virtue of utilising a highly nucleophilic reagent allowing easier synthetic manipulation, as well as yielding products with greater flexibility for macrocyclisation. The ultimate carbonylation of the oligomeric ethylenediamines to give imidazolidin-2-ones is well documented in principle, using phosgene,[13] diethyl carbonate,[14] urea,[15] selenium catalysed carbonylation with carbon monoxide[16] and other methods by way of thiocarbonyl groups.[17]

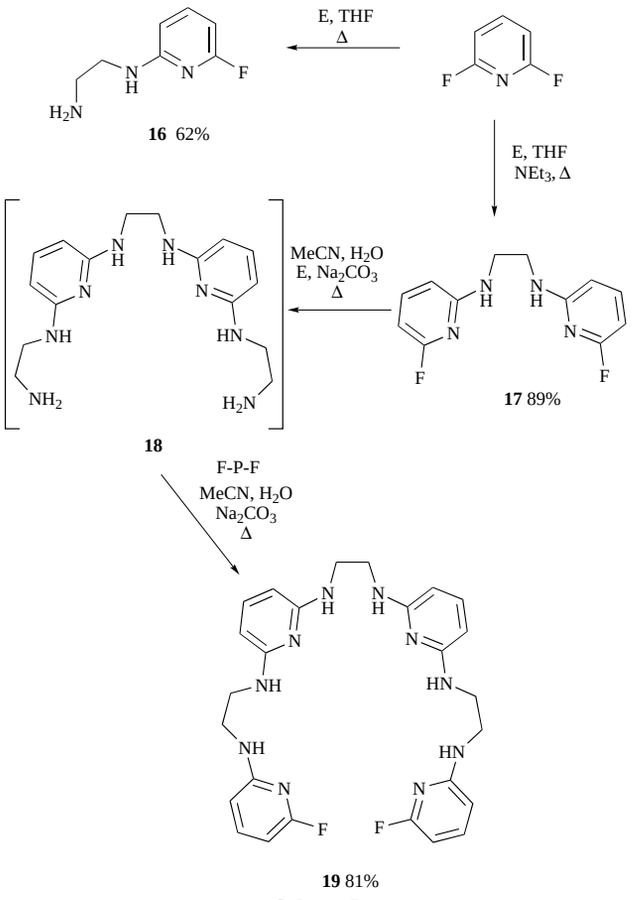
Since the amine was nucleophilically reactive, the cheaper chloro- and bromo-pyridines could possibly be utilised. Thus 2-bromopyridine reacts with ethylenediamine ('E' in our terminology) to give PE in 60% yield[18] while *N*,*N*-diisopropylethylenediamine reacts with 2,6-dichloropyridine to give the monosubstituted derivative, disubstitution being very difficult to achieve.[19] In practice, however, chloro- and bromo-pyridines resulted in polymer formation, while 2,6-difluoropyridine reacted with an excess of E in refluxing THF to give F-PE **16** in 62% yield. When two moles of 2,6-difluoropyridine were reacted with one of E in the presence of triethylamine, F-PEP-F **17** was formed in 89% yield. This product was readily transformed into EPEPE **18** with an excess of ethylenediamine, which, without purification was further reacted with 2,6-difluoropyridine to give the heptamer, F-PEPEPEP-F **19** in an overall yield of 81% (Scheme 5). It is noteworthy that oligomers terminating in E units tend to be viscous oils, not easily purified except by chromatography, while those bearing F-P termini are crystalline solids.

We also have made mixed systems containing ethylenediamine and imidazolidin-2-one units in order to obtain crystalline products for optimal isolation and purification purposes. Thus F-PIP-F **5** reacts successively with ethylenediamine, giving EPIPE **20** (in 92% yield) and then 2,6-difluoropyridine to produce F-PEPIPEP-F **21** in 85% yield, both products being crystalline solids (Scheme 6).

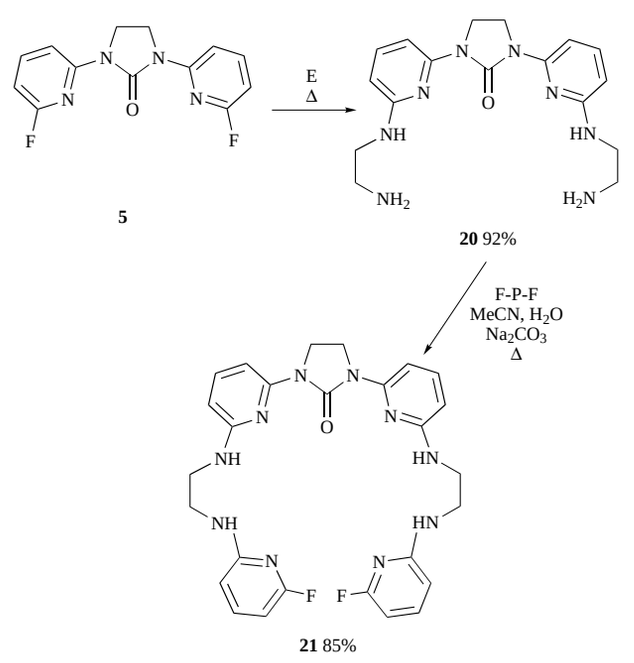
3. Halopyridines and imidazoles. One other route briefly explored as a means to build linear assemblies relied upon the considerable nucleophilicity of imidazole and its potential for conversion into an imidazol-2-one. 2,6-Dichloropyridine has been reported to react with neat imidazole at 190 °C to give 2,6-bis(imidazol-1-yl)pyridine **22** in 28% yield.[20] Using 2,6-difluoropyridine, we obtained the same product at 120 °C in 80% yield, which gave the corresponding bis-benzyl imidazolium salt **23** on warming with benzyl chloride. Surprisingly, unlike observations in the earlier reported reactions, irrespective of the ratio of the 2,6-difluoropyridine and imidazole, predominately the bis-substitution product **22** was isolated. The pure monobenzyl salt **24** was formed in 83% yield if the reaction was performed in ethyl acetate solution. However, attempts to oxidise the salt **23** to give the corresponding imidazol-2-ones, were not successful using alkaline hydrogen peroxide, sodium perborate, sulfur and base, or sodium hydride and cupric chloride with oxygen.[21] Similar failure was observed from metal-



Scheme 4



Scheme 5

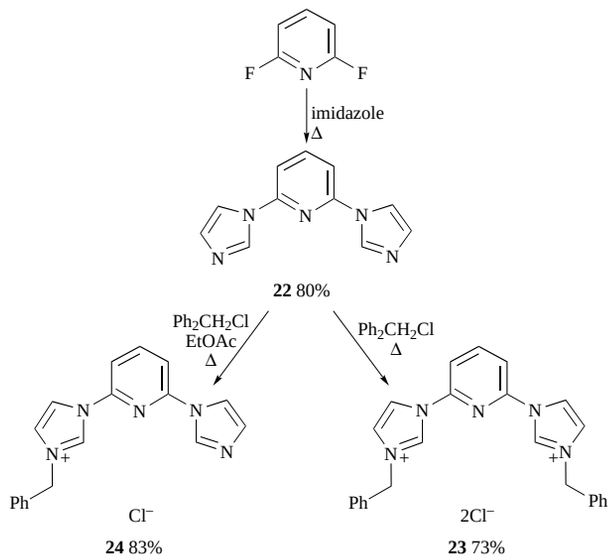


Scheme 6

lation of the bis-imidazole **22** with butyllithium followed by treatment with *tert*-butyl hydroperoxide.[22]

Synthesis of linear assemblies based on aminopyridines

The alternative, and much cheaper starting material for this work was 2,6-diaminopyridine which was readily converted into useful precursors to the desired oligomers. Reaction with commercially available 2-chloroethyl isocyanate to give 2,6-bis-[3-(2-chloroethyl)ureido]pyridine **25** in 30% yield has been reported.[23] We found that in THF solution, the reaction was rapid and efficient, giving the product in 78% yield. On the other hand, in acetonitrile, a salt was formed, which we presume is the triazepinopyridine **29**. The bis(chloroethylureido)-pyridine **25** readily cyclised with sodium hydride to give IPI **10** in 78% yield (Scheme 7). It is worth noting that the 3- and 5-



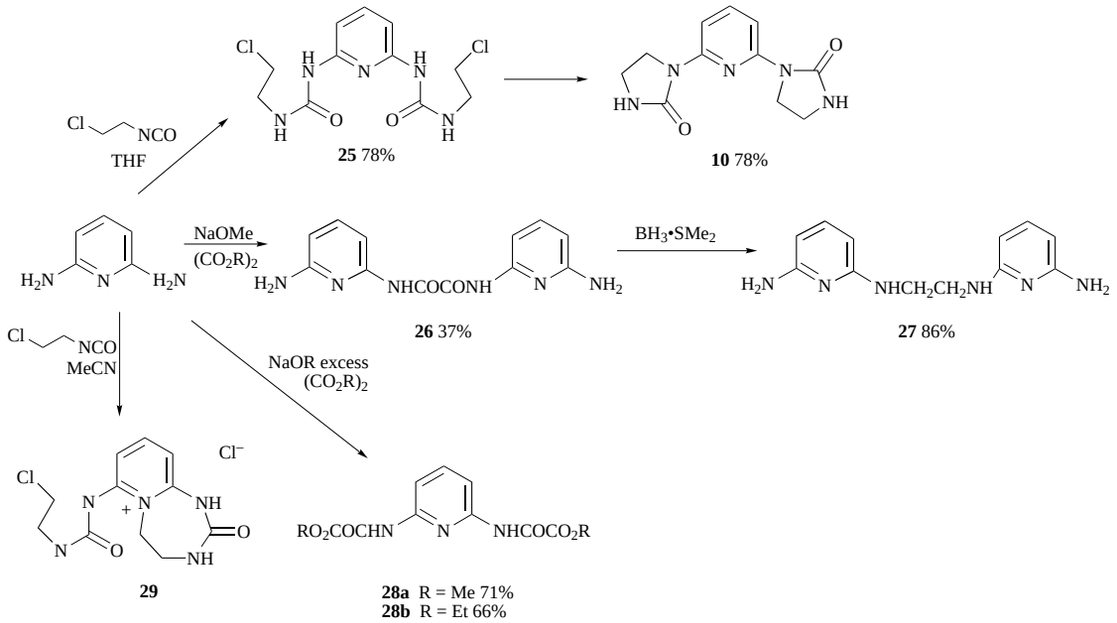
Scheme 7

H's of the pyridine ring of IPI **10** are non-equivalent, due we believe, to considerable bond fixation of the two imidazolidinonyl units in opposite but coplanar geometries (Scheme 8).

Alkylation of the diaminopyridine with, for example, 1,2-dibromoethane is fraught with potential problems of non-chemoselectivity, mixture formation, polymerisation and formation of elimination products. The literature reports that 2-aminopyridine reacts at 160–200 °C with diethyl oxalate to give *N*,*N*′-di(2-pyridyl)oxamide[24] while 2,6-diaminopyridine at 150 °C surprisingly is reported to give a 1,8-naphthyridine. On the contrary, we found that the former reaction proceeded well at ambient temperature and the latter gave the desired *N*,*N*′-bis(6-aminopyridin-2-yl)oxamide **26** (referred to as H_2N-POP-NH_2 in our nomenclature) in 37% yield. Reduction of this product with borane in THF gave the corresponding *N*,*N*′-bis(6-aminopyridin-2-yl)ethane-1,2-diamine **27** in high yield. Furthermore, the use of an excess of dimethyl or diethyl oxalate gave the bis(oxamido)pyridines **28a** and **28b**. No further chemistry was conducted with this series of precursors as a result of their limited synthetic success compared to that of other methods.

Cyclisations of the linear assemblies

Attempted synthesis of the macrocycle 3. In principle, the macrocycle **3** can be assembled from appropriate 7 + 1, 6 + 2, 5 + 3 and 4 + 4 units as well as by cyclisation of an 8 unit assembly. Of the various potential precursors, symmetry aspects would favour a 4 + 4 reaction, though this precursor is not easily assembled; precursors terminating in similar units (*i.e.* totalling an odd number of units—7 + 1 or 5 + 3) are both simpler to make and to interact. We therefore examined this protocol in detail. Of the various modes of linkage examined for the linear assemblies, the interaction of an *N*-[dimethyl-(1,1,3-trimethylpropyl)silylated] (DMTS) imidazolidinone with a 2-fluoropyridine under caesium fluoride catalysis proved most effective for the higher oligomers. We therefore studied the interaction of DMTS-IPIPIPI-DMTS **14** with 2,6-difluoropyridine (7 + 1) and DMTS-IPIPI-DMTS **9c** with F-PIP-F **5b** (5 + 3) both under high dilution conditions and with caesium fluoride catalysis (the caesium ion could also act as a template cation). The two reagents were added slowly dropwise in DMF solution to caesium fluoride in DMF at

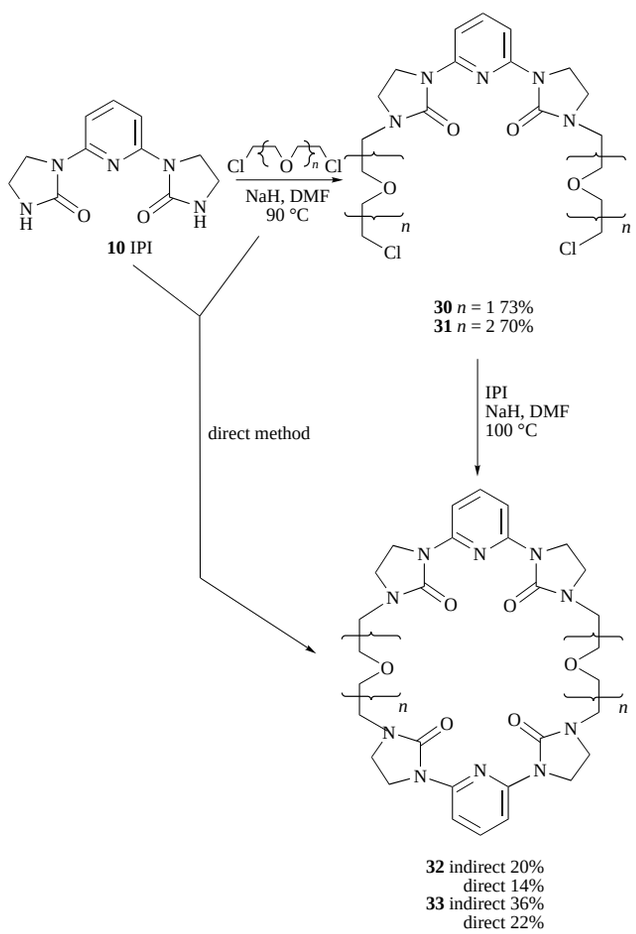


Scheme 8

120 °C. Solubility considerations required the dropping funnel to be maintained at 110–120 °C in the case of the 7 + 1 reaction. The major product apart from polymer was the nonameric system F-PIPIPIPIP-F **15**. Use of the better solvent, *N*-methylpyrrolidone, allowed the solution of reagents to be added at ambient temperature by way of a syringe pump. However, only polymer was obtained, as was also the case when the reaction temperature was raised to 160 °C with addition over two days. Similar problems were encountered with the more soluble reagents, DMTS-IPIPI-DMTS **9c** and F-PIP-F **5b**. We studied the energy difference between the ground state conformation (apparently helical; conformational NMR effects in such compounds have already been briefly addressed earlier) of F-PIP-F **5b** and IPIPI **9b** and that required for macrocyclisation, comparing the results with those for PPPPP. (It is already well established that the macrocycle, 'sexipyridine' cannot be made by cyclisation of linear precursors but requires an indirect approach.[25]) Chem-X data suggests that F-PIP-F **5b** and IPIPI **9b** have energy differences of 7.8 and 15.0 kcal mol^{-1}, respectively, compared to 12.7 kcal mol^{-1} for that of PPPPP. Clearly, the longer the precursor, the greater the energy difference and since the two-step reaction from F-PIP-F **5b** and IPIPI **9b** involves F-PIPIPIPI as the immediate potential precursor to the formation of **1**, the chance of such a cyclisation succeeding is vanishingly small in the absence of a templating effect. We have not found any effective templating metal ions that influence this process. We therefore decided to investigate the linkage of our precursors *via* either alkynic units, well known in the chemistry of annulenes, or polyether systems, or to build up the imidazolidinone unit from ethylenediamine units after macrocyclisation.

Polyether-linked macrocycles

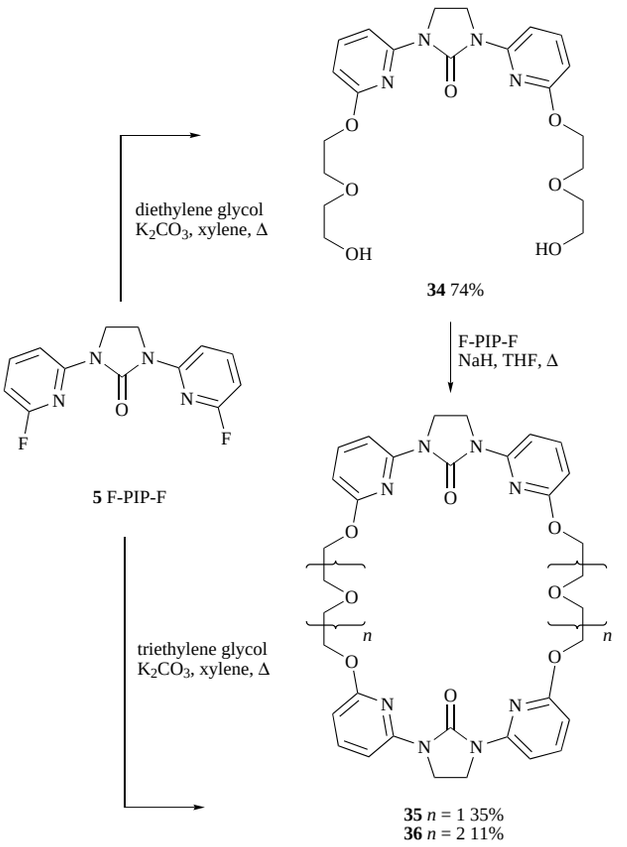
IPI **10** was readily transformed into *N*,*N*′-substituted derivatives containing either -$(CH_2)_2O(CH_2)_2Cl$ [-EOE-Cl] **30** or -$(CH_2)_2[O(CH_2)_2]_2Cl$ [-EOEOE-Cl] **31** functions in over 70% yield by reaction with an excess of the appropriate dichloroalkyl ether and base. These compounds reacted well with equimolar IPI **10** and sodium hydride in hot DMF under high dilution to give the corresponding macrocycles (c-IPI-EOE-IPI-EOE- **32** and c-IPI-EOEOE-IPI-EOEOE- **33**, respectively) in 20 and 36% yield, respectively (Scheme 9). The direct interaction of the dichloroalkyl ether with IPI **10** under the same conditions gave the macrocycles in lower yields (14 and 22%, respectively). Interestingly, the ether-linked system **33** in



Scheme 9

[$^2H_6$]DMSO solution suggests NMR evidence for a helical disposition of the imidazolidinone units since the pyridine β-protons are non-equivalent.

The analogous series of macrocycles in which two PIP **10** units are linked by polyether groups were also easily assembled utilising the interaction of di- and tri-ethylene glycol with F-PIP-F **5b** and K_2CO_3 in refluxing xylene either directly or in a stepwise manner (Scheme 10). In this way c-PIP-OEOEO-PIP-OEOEO- **35** (35% by the indirect route by way of **34**)

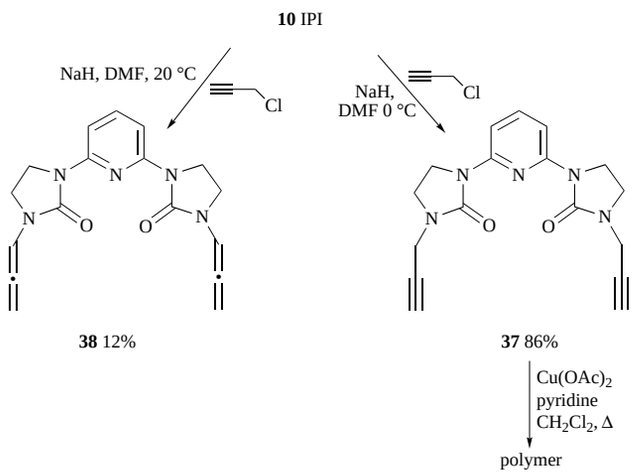


Scheme 10

and c-PIP-OEOEOEO-PIP-OEOEOEO- **36** [11% by the direct approach; an intractable gluey intermediate (*cf.* **34**) resulted from the interaction of F-PIP-F **5** and triethylene glycol].

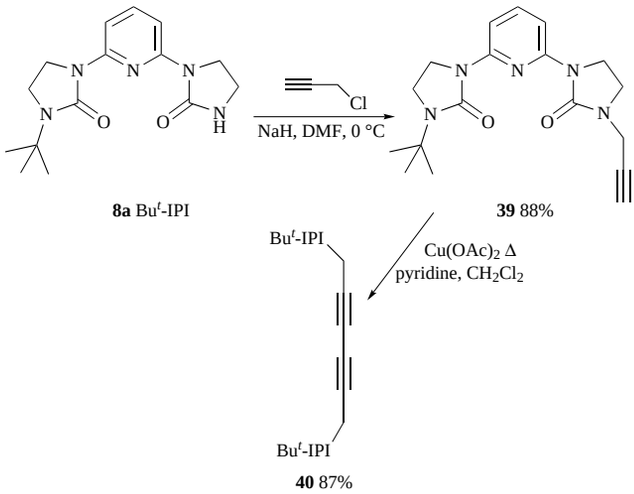
Alkyne-linked macrocycles

Recent studies by Lehn and co-workers[26] and others[27] have made the prospect of macrocyclisation by dimerisation of *N*-prop-2-ynylated IPI **37** an attractive proposition. The diprop-2-ynylated IPI **37** was readily synthesised by base-catalysed prop-2-ynylation of IPI **10** in 86% yield (Scheme 11).



Scheme 11

When the reaction was conducted at 20 °C rather than 0 °C, only a low yield of the isomeric allene **38** resulted. In a similar manner the monoprotected IPI (Bu^t-IPI **8a**) was prop-2-ynylated to give the derivative **39** in 88% yield which could be easily dimerised with copper acetate in 87% yield to give the highly insoluble dimer **40** (Scheme 12). This insolubility



Scheme 12

problem, which is much greater with the deprotected analogues, caused us to drop this stepwise approach. Furthermore, attempted dimerisation of the diprop-2-ynylated IPI **37** with copper acetate again gave solely polymeric material.

Ethylenediamine-linked macrocycles

F-PE **16**, F-PEP-F **17**, EPEPE **18**, EPIPE **20**, F-PEPEPEP-F **19** and F-PEPIPEP-F **21** were all made readily. Several different approaches to macrocycles from these precursors were examined. Thus F-PE **16** was heated in DMF with KF or solid K_2CO_3 at 130 °C without effect (we have already commented on the greatly reduced reactivity of the 2-fluoro substituent when a 6-amino group is also present). We therefore examined the interaction of F-PIP-F **5b** with EPIPE **20** under similar conditions—again without any sign of reaction! Even in *N*-methylpyrrolidone at 170 °C with the same catalysts no reaction was observed. We therefore endeavoured to increase the activity of the nucleophilic units by firstly adding KH to generate potassium amide units. The potassium ions could well also show some template benefit. Reaction at 170 °C led solely to polymer. We next studied the interaction of F-PEP-F **17** with imidazolidinone and with bis-DMTS-protected imidazolidinone. We noted in preliminary work that F-PEP-F **17** polymerised on treatment with sodium hydride, so we were not surprised that a similar result from interaction of F-PEP-F **17** and imidazolidinone in the presence of NaH in DMF was observed. Surprisingly, bis-DMTS-protected imidazolidinone remained unchanged on heating with F-PEP-F **17** at 150 °C with CsF in *N*-methylpyrrolidone, again attesting to the non-reactivity of aminofluoropyridines. Similar non-reactivity was noted from the interaction of F-PEP-F **17** and DMTS-IPI-DMTS **13**. In order to remove the deactivating effect of the amino units on the aryl fluoride we reacted the *N*,*N*′-acetyl, -trifluoroacetyl and toluene-4-sulfonyl derivatives of ethylenediamine with 2,6-difluoropyridine in DMF at 100 °C as a model for the higher analogues. Again the reaction was unsuccessful and this approach was abandoned.

Macrocyclisations based on aminopyridine precursors

H_2N-POP-NH_2 **26** was treated with methyl oxalate and sodium methylate under high dilution conditions. No reaction occurred at ambient but a polymer formed under reflux conditions. Similar problems were encountered when 2,6-bis(methoxamido)pyridine was reacted with 2,6-diaminopyridine.

Complexation studies on the macrocyclic ligands 8, 9, 12 and 13 and their acyclic precursors

Reedijk *et al.*[28] showed that imidazolidinone itself effectively forms oxygen coordinated complexes with the divalent cations of Mg, Mn, Co, Ni, Cu, Zn and Cd. Kiriakidou and Manessi-

Table 1 Dissolution test for some linear pyridine–imidazolidinone ligands compared to TDA-1[a]

Ligand	LiBr	NaBr	KBr	CsBr	$MgBr_2$	$CaBr_2$	$SrBr_2$	BaI_2
TDA-1	++	++	++	++	++	++	++	++
Bu^t-IP	+	—	—	—	+	+	+	+
Bu^t-IPI-Bu^t **8b**	+	—	—	—	+	+	+	+
F-PIP-F **5b**	+	—	—	—	+	+	+	+
Bu^t-IPIPI-Bu^t **9a**	+	—	—	—	—	—	—	—
DMTS-IPIPIPI-DMTS **14b**	+	—	—	—	—	—	—	—

[a] ++ indicates immediate change; + indicates slow dissolution; — indicates no change.

Zoupa[29] have shown that *N*,*N*′-bis(2-pyridyl)urea forms a 2:1 complex with nickel(II) nitrate. We have studied the complexation of these compounds from several standpoints, namely their ability to solubilise metal ions in organic solution,[2b] their ability to extract ions, examined both by UV and NMR spectroscopic studies, and finally their ability to generate stable, isolable complexes with metal ions. In each case we have compared the macrocycle with related acyclic precursors that could have similar ligand properties.

1. Solubilisation of metal ions in organic media. We have reported elsewhere a simple 'yes–no' test for potential ligands[2b] which involves the dissolution of a precipitated inorganic salt (from a solution of a salt in methanol by dropwise addition of toluene) by addition of the ligand. Although crude, this is a rapid first indication of a potential ligand. In our current study, this test requires ready solubilisation of the potential ligand in methanol–toluene, which precludes the macrocyclic systems. For comparison, we also examined TDA-1 [tris(3,6-dioxaheptyl)amine] and the results are collected in Table 1. TDA-1 is a general, but non-selective ligand, hence its use as a catalyst, and is much more powerful than any of our acyclic ligands. Interestingly, apart from lithium which complexes with all of our systems, only the shorter ligand units were effective, no doubt due to the large preference for a helical rather than ligand-effective conformation. Also complexation was only observed with the divalent cations, suggesting our ligand groups were 'hard'.

2. Extraction of metal ions into organic solvents. We examined the rate of extraction of metal and ammonium picrates into chloroform, following the process by UV spectrophotometry, as described by Cram and co-workers.[30] The picrates studied included the following cations: NH_4^+, Li^+, Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} and Ag^{2+}. No univalent cations showed any sign of picrate extraction. Furthermore the macrocyclic ligands tended to cause precipitation, possibly of the liganded metal picrate complex. However, the acyclic ligands proved effective for magnesium and calcium cations with a strong preference for calcium ion extraction, as we have noted elsewhere[2b] for ureido ligands (Table 2). Increased rates of extraction were noted for ligands with a greater number of ureido groups. While the cyclic ligands **8** and **9** containing four ureido ligands were the best complexes for magnesium, the cyclic systems proved less selective, and the slow rate of precipitate formation may have also indicated a slow rate of complexation.

3. NMR spectroscopic studies of complexation with alkylammonium salts. In order to check whether the cyclic ligands were capable of complexing alkylammonium salts we examined both the extraction of the salt from D_2O by a $CDCl_3$ solution of the potential ligand, as used by Timko and Cram[31] and the NMR titration method of Nolte and co-workers[32] whereby the change in chemical shift of a $CDCl_3$–[$^2H_6$]DMSO solution of the ligand and of the salt were changed on making up 1:1, 1:2 and 2:1 mixtures. Essentially no complexation was evident with the cyclic ligands.

4. Isolation of metal complexes. In line with the above findings, the interaction of a chalcogen thiocyanate salt in acetone was mixed with a chloroform solution of the ligands indicated in Table 2. Only the IPI-based macrocycles gave precipitates. Thus from the smaller macrocycle **8** only a 1:1 calcium complex was isolated while the larger ligand **9** gave both a calcium and a barium 1:1 complex, indicative of a larger cavity. Although the complexes analysed well (with chloroform of crystallisation) they were unstable to crystallisation, precluding X-ray crystallography. Complexation was also indicated by significant melting point changes (reasonably sharp melting points were observed for the complexes) and lowering of solid state infrared carbonyl absorptions (*e.g.* from 1707 to 1678–1690 cm^{-1}). Insolubility precluded ambient NMR measurements but at 120 °C not surprisingly the free ligand and its complex were identical in [$^2H_6$]DMSO solution.

Table 2 Extraction rates (%)[a] for some linear and cyclic pyridine–imidazolidin-2-one ligands[b]

Ligand	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
Bu^t-IPI-Bu^t **8b**	—	20.6	—	—
Bu^t-IPIPI-Bu^t **9a**	—	38	—	—
Bu^t-IPIPIPI-Bu^t **12**	—	47.1	—	—
Compound **30**	2.9	11.8	—	—
Compound **31**	2.2	37	—	—
Compound **32**	3.3	ppt	ppt	ppt
Compound **33**	3.1	ppt	ppt	ppt
Compound **34**	2.5	19.3	—	ppt
Compound **35**	insoluble	insoluble	insoluble	insoluble
Compound **36**	—	2.5	ppt	ppt

[a] This percentage is the ion to ligand ratio in the chloroform solution. [b] — indicates no extraction and 'ppt' indicates that a precipitate formed.

Experimental

General conditions

Melting points were determined on either an Electrothermal capillary or a Reichert Hot-stage Microscope melting point apparatus and are uncorrected. Infrared spectra were recorded on a UNICAM Research Series 1 FT-IR spectrophotometer as liquid films or KBr discs, and ultra-violet spectra on a UNICAM UV-2 spectrophotometer. NMR spectra were taken on a JEOL GSX 270 MHz FT NMR spectrophotometer. Chemical shifts are quoted to higher frequency of $SiMe_4$ as internal standard and are given in ppm, with coupling constants in Hz.

Elemental analyses and accurate mass spectra were conducted at Newcastle University on a Carlo Erba 1106 Elemental Analyser and a Kratos MS80RF mass spectrometer, respectively. Silica gel TLC was performed on E. Merck plastic plates coated with 0.2 mm silica 60 F254. Flash chromatography was performed with Janssen or Merck silica gel, particle size 35–70 mm.

Commercial reagents were normally used without further purification. For air sensitive reactions, solid reagents were dried over phosphorus pentoxide in a dessicator under reduced pressure for one day prior to use; liquid reagents were dried and distilled according to standard methods.[33] Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. *N*,*N*-Dimethylformamide (DMF) was dried by stirring over P_2O_5 for 24 h, followed by distillation. The fraction boiling at 153–155 °C was collected and kept over 4 Å molecular sieves in the dark. Toluene and xylene were distilled with the first 10% being discarded and the remainder collected and stored over

4 Å molecular sieves. Chloroform, methanol and ethanol were distilled from calcium hydride and stored over 3 Å molecular sieves. Other solvents were purified by standard procedures as necessary. Light petroleum refers to the fraction of boiling range 60–80 °C, and ether implies diethyl ether. Sodium hydride or potassium hydride was dispensed in oil, and was washed three times with dried hexane prior to use. Reactions requiring anhydrous conditions were performed in oven-dried apparatus under nitrogen. Reaction solutions were dried using magnesium sulfate ($MgSO_4 \cdot 1H_2O$).

1-*tert*-Butylimidazolidin-2-one 6[10]

This is an adaption of the literature method.[10] To a 500 cm^3 three-necked flask equipped with a fast mechanical stirrer, a 200 cm^3 dropping funnel and a thermometer and surrounded by an ice-bath, was added sulfuric acid (98%, 75 cm^3). Finely powdered imidazolidin-2-one (60.0 g, 0.67 mol) was then added slowly at such a rate that the temperature remained between 0–15 °C, followed by the dropwise addition of *tert*-butyl alcohol (125 cm^3, 98.70 g, 1.33 mol) at 20–25 °C. After the addition was complete, the mixture was stirred for 30 min, and then poured with stirring into ~1.0 kg ice–water. The mixture was brought to pH 6 by slow addition of a solution of 4 M NaOH, while the temperature was kept below 25 °C. The mixture was cooled to 15 °C (**CAUTION:** $Na_2SO_4 \cdot 10H_2O$ precipitates below this temperature). The product, a colourless solid (17.0 g) was collected by filtration. The filtrate was extracted with chloroform (4 × 150 cm^3) and the combined organic layers were dried and evaporated under reduced pressure. The filtered product and the extract were combined (62.0 g) and recrystallised from ethyl acetate–light petroleum giving 1-*tert*-butylimidazolidin-2-one **6** as colourless plates (58.0 g, 61.5%), mp 138.5–139 °C (lit.,[10] mp 135–136 °C).

1,3-Bis(trimethylsilyl)imidazolidin-2-one[11]

This is an adaption of the literature method.[11] To a stirred mixture of imidazolidin-2-one (3.30 g, 38 mmol) and hexamethyldisilazane (9.60 g, 50 mmol) was added 4 drops trimethylsilyl chloride at ambient temperature. The mixture was heated to 110 °C for 6 h, and then cooled and distilled *in vacuo* on a Kugelrohr apparatus. 1,3-Bis(trimethylsilyl)imidazolidin-2-one was collected at 130 °C/0.01 mbar, which solidified as colourless needles (7.40 g, 81%), mp 67–68 °C (lit.,[11] mp 52–54 °C); ν_{max}(KBr)/cm^{-1} 2957 (C–H, aliphatic), 1655 (C=O); δ_H($CDCl_3$) 0.25 (18H, s, 6 × Me), 3.42 (4H, s, CH_2).

1,3-Bis[dimethyl(1,1,3-trimethylpropyl)silyl]imidazolidin-2-one

To a stirred mixture of imidazolidin-2-one (2.20 g, 25 mmol) and dimethyl(1,1,3-trimethylpropyl)silyl chloride (13.72 g, 75 mmol) in DMF (30 cm^3) was added triethylamine (15.0 g, 150 mmol). The mixture was heated at 90 °C for 12 h. Most of the solvent was removed under reduced pressure. The residue was then distilled *in vacuo* on a Kugelrohr apparatus. Pure 1,3-*bis*[*dimethyl*(1,1,3-*trimethylpropyl*)*silyl*]*imidazolidin*-2-*one* was collected at 170 °C/0.1 mbar which solidified as colourless crystals (6.90 g, 74%), mp 62–63 °C (Found: C, 61.5; H, 11.4; N, 7.6. $C_{19}H_{42}N_2OSi_2$ requires C, 61.6; H, 11.4; N, 7.6%); ν_{max}(KBr)/cm^{-1} 2959 (C–H, aliphatic), 1670 (C=O); δ_H($CDCl_3$) 0.21 (12H, s, SiMe), 0.84 (12H, d, CH*Me*), 0.92 (12H, s, CMe), 1.52–1.67 (2H, m, CH), 3.38 (4H, s, CH_2).

Synthesis of 2,6-bis(2-oxoimidazolidin-1-yl)pyridine (IPI) 10

The reaction of 2,6-dichloro- or 2,6-difluoro-pyridine with imidazolidin-2-one. The reaction of 2,6-dichloropyridine (or 2,6-difluoropyridine) and imidazolidin-2-one with added sodium hydride was performed under a variety of different conditions (the use of DMF or THF as solvent, with temperatures from 60 to 150 °C and various molar ratios of reagents). After completion of the reaction, the mixture was concentrated, poured into ice–water and neutralised with 2 M hydrochloric acid. The resulting precipitate was filtered, the solid extracted with chloroform using a Soxhlet apparatus, and the extract evaporated and purified by chromatography if necessary. Only one reaction gave non-polymeric products, conducted as follows. To a stirred mixture of sodium hydride (1.06 g, 50% in oil, 22 mmol) in THF (100 cm^3) was added imidazolidin-2-one (8.60 g, 10 mmol). The mixture was heated under reflux for 0.5 h when 2,6-dichloropyridine (1.48 g, 10 mmol) was added and reflux continued until the dichloropyridine was minimal (~5 days). The solvent was removed and water (~100 cm^3) added and the solution neutralised with 2 M hydrochloric acid. The precipitate was filtered and extracted with chloroform in a Soxhlet apparatus and the evaporated extract subjected to flash chromatography with dichloromethane–ethyl acetate as eluent. Two products, 2-*chloro*-6-(2-*oxoimidazolidin*-1-*yl*)*pyridine* **4a** (0.06 g, 3%) and 2,6-*bis*(2-*oxoimidazolidin*-1-*yl*)*pyridinium chloride* **10**·HCl (0.10 g, 5%) were isolated.

2-*Chloro*-6-(2-*oxoimidazolidin*-1-*yl*)*pyridine* (IP-Cl) **4a**.—Mp 235–236 °C (Found: C, 48.9; H, 4.2; N, 21.0. $C_8H_8N_3ClO$ requires C, 48.6; H, 4.1; N, 21.3%); ν_{max}(KBr)/cm^{-1} 3239 (NH), 1706 (C=O), 1591, 794 (Py); δ_H([$^2H_6$]DMSO) 3.79 (2H, t, CH_2), 3.95 (2H, t, CH_2), 7.03 (1H, d, *J* 8.1, Py H *ortho* to Cl), 7.31 (1H, br, NH), 7.72 (1H, t, *J* 8.1, Py-4-H), 8.14 (d, 1H, *J* 8.1, Py-5-H).

2,6-*Bis*(2-*oxoimidazolidin*-1-*yl*)*pyridinium chloride* (IPI·HCl) **10**·HCl.—Mp 183–184 °C (Found: C, 46.85; H, 5.1; N, 24.4. $C_{11}H_{14}N_5ClO_2$ requires C, 46.6; H, 5.0; N, 24.7%); ν_{max}(KBr)/cm^{-1} 3260 (NH), 1710 (C=O), 1579, 768 (Py); δ_H([$^2H_6$]DMSO) 3.29 (6H, t, CH_2), 3.73 (2H, t, CH_2), 6.42 (1H, d, *J* 8.0, Py-3-H), 6.48 (1H, d, *J* 8.0, Py-5-H), 6.99 (1H, br, NH), 7.37 (1H, t, *J* 8.0, Py-4-H), 7.45 (1H, br, NH), 8.21 (1H, br, PyN′H).

2,6-Bis(3-*tert*-butyl-2-oxoimidazolidin-1-yl)pyridine Bu^t-IPI-Bu^t 8b

(1). To a stirred mixture of NaH (9.60 g, 50% in oil, 200 mmol) in THF (250 cm^3) was added 1-*tert*-butylimidazolidin-2-one **6** (25.56 g, 180 mmol) with gas evolution. Then 2,6-difluoropyridine (9.20 g, 80 mol) was added and the mixture was heated at reflux under N_2 for 40 h. The mixture was then concentrated to ~50 cm^3 and ice–water (~200 g) was added. The precipitate was filtered and recrystallised from ethyl acetate to give *Bu^t-IPI-Bu^t* **8b** as colourless plates (21.10 g, 73%), mp 248–249 °C (sublimes above 240 °C) (Found: C, 63.5; H, 8.2; N, 19.4. $C_{19}H_{29}N_5O_2$ requires C, 63.5; H, 8.1; N, 19.5%); ν_{max}(KBr)/cm^{-1} 2974 (C–H, aliphatic), 1701 (C=O), 1583, 797 (Py); δ_H($CDCl_3$) 1.35 (18H, s, Bu^t), 3.37 (4H, t, CH_2), 3.81 (4H, t, CH_2), 7.43 (1H, t, *J* 8.1, Py-4-H), 7.71 (2H, d, *J* 8.1, Py-3-H and Py-5-H).

(2). In a similar manner 2,6-bis(3-*tert*-butyl-2-oxoimidazolidin-1-yl)pyridine **8b** could be obtained from 2,6-dichloropyridine instead of 2,6-difluoropyridine in DMF (100 °C, 24 h) in 52% yield together with 2-chloro-6-(3-*tert*-butyl-2-oxoimidazolidin-1-yl)pyridine (34%); δ_H($CDCl_3$) 1.42 (9H, s, Bu^t), 3.47 (2H, t, CH_2), 3.91 (2H, t, CH_2), 6.86 (1H, d, *J* 8.1, Py-3-H), 7.52 (1H, t, *J* 8.1, Py-4-H), 8.17 (1H, d, *J* 8.1, Py-5-H).

2,6-Bis(2-oxoimidazolidin-1-yl)pyridine 10 by hydrolysis of Bu^t-IPI-Bu^t 8b

A mixture of Bu^t-IPI-Bu^t **8b** (8.0 g, 22 mmol) in aqueous hydrochloric acid (20%, 80 cm^3) was heated at reflux overnight. The mixture was cooled and neutralised with 4 M NaOH. The precipitate was filtered to give 2,6-*bis*(2-*oxoimidazolidin*-1-*yl*)-*pyridine* **10** as colourless crystals from DMSO (5.40 g, 98%), mp >320 °C (Found: C, 53.3; H, 5.4; N, 28.1. $C_{11}H_{13}N_5O_2$ requires C, 53.4; H, 5.3; N, 28.3%); ν_{max}(KBr)/cm^{-1} 3257 (N–H), 1697 (C=O), 1583, 790 (Py); δ_H([$^2H_6$]DMSO, 120 °C) 3.50 (4H, t, $NHCH_2$), 4.11 (4H, t, CH_2), 6.73 (2H, br, NH), 7.63 (1H, dd, *J* 7.5 and 8.7, Py-4-H), 7.77 (1H, d, *J* 7.5, PyH), 7.78 (1H, d, *J* 8.7, PyH).

1,3-Bis(6-fluoropyridin-2-yl)imidazolidin-2-one (F-PIP-F) 5b

(1). To a stirred mixture of NaH (5.28 g, 50% in oil, 110 mmol) in THF (80 cm^3) was added imidazolidin-2-one (4.48 g,

50 mmol) at ambient temperature. The mixture was heated at reflux for 30 min and then 2,6-difluoropyridine (12.19 g, 110 mmol) was added. After 20 h, most of the solvent was removed under reduced pressure and water (~500 cm^3) was added to precipitate a solid which was filtered and recrystallised from ethyl acetate (effective for small amounts of product) or DMF (better for large amounts of product) to give *F-PIP-F* **5b** as colourless plates (11.47 g, 83%), mp 267–268 °C (sublimes above 200 °C, plates change slowly to needles) (Found: C, 56.4; H, 3.6; N, 20.05. $C_{13}H_{10}N_4F_2O$ requires C, 56.5; H, 5.65; N, 20.28%); ν_{max}(KBr)/cm^{-1} 1714 (C=O), 1575, 797 (Py); δ_H($CDCl_3$) 4.08 (4H, s, CH_2), 6.52 (2H, dd, J_{HH} 8.1, $^5J_{HF}$ 2.4, Py-5-H), 7.68 (2H, q, *J* 8.1, Py-4-H), 8.10 (2H, dd, $^5J_{HH}$ 8.1, $^4J_{HH}$ 2.4, Py-3-H).

(2). F-PIP-F **5b** was also obtained from 1,3-bis(trimethylsilyl)imidazolidin-2-one as follows. To a stirred mixture of 2,6-difluoropyridine (4.60 g, 40 mmol) and 1,3-bis(trimethylsilyl)imidazolidin-2-one (2.40 g, 10 mmol) in DMF (50 cm^3) at 110 °C was added a catalytic amount of caesium fluoride (~10 mg). After overnight heating at this temperature, the solvent was removed under reduced pressure and water was added. Filtration gave 1,3-bis(6-fluoropyridin-2-yl)imidazolidin-2-one **5b** (2.81 g, 79%).

1-*tert*-Butyl-3-(6-fluoropyridin-2-yl)imidazolidin-2-one (Bu^t-IP-F) 7

To a stirred mixture of NaH (2.64 g, 50% in oil, 55 mmol) in THF (100 cm^3) was added 1-*tert*-butylimidazolidin-2-one **6** (7.0 g, 50 mmol) with gas evolution. Then 2,6-difluoropyridine (6.80 g, 59 mmol) was added and the mixture was heated at reflux under N_2 for 20 h. The mixture was concentrated and water (~500 cm^3) was added. The precipitate was filtered and recrystallised from light petroleum to give *Bu^t-IP-F* **7** as colourless needles (10.80 g, 85%), mp 103–104 °C (Found: C, 60.65; H, 6.8; N, 17.65. $C_{12}H_{16}N_3FO$ requires C, 60.7; H, 6.80; N, 17.7%); ν_{max}(KBr)/cm^{-1} 2982 (C–H, aliphatic), 1692 (C=O), 1572, 801 (Py); δ_H($CDCl_3$) 1.43 (9H, s, Bu^t), 3.49 (2H, t, CH_2), 3.89 (2H, t, CH_2), 6.45 (1H, dd, J_{HH} 8.1, $^5J_{HF}$ 2.7, Py-5-H), 7.65 (1H, q, *J* 8.1, Py-4-H), 8.11 (1H, dd, $^5J_{HH}$ 8.1, $^3J_{HF}$ 2.7, Py-3-H).

1,3-Bis[6-(3-*tert*-butyl-2-oxoimidazolidin-1-yl)pyridin-2-yl]-imidazolidin-2-one (Bu^t-IPIPI-Bu^t) 9a

(1). To a stirred mixture of NaH (3.20 g, 50% in oil, 66 mmol, washed with hexane) in THF (150 cm^3) was added 1-*tert*-butylimidazolidin-2-one **6** (9.37 g, 66 mmol) at ambient temperature with gas evolution. F-PIP-F **5b** (8.28 g, 30 mmol) was then added and the mixture heated at reflux for 48 h, most of the solvent removed and water (~500 cm^3) added. The precipitate was filtered and recrystallised from toluene to give *Bu^t-IPIPI-Bu^t* **9a** as colourless crystals (12.60 g, 81%), mp 298–299 °C (Found: C, 62.2; H, 7.1; N, 21.2. $C_{27}H_{36}N_8O_3$ requires C, 62.3; H, 7.0; N, 21.5%); ν_{max}(KBr)/cm^{-1} 2973 (C–H, aliphatic), 1709 (C=O), 1584, 792 (Py); δ_H($CDCl_3$) 1.42 (18H, s, Bu^t), 3.45 (4H, t, CH_2), 3.88 (4H, t, CH_2), 4.02 (4H, s, CH_2), 7.58 (2H, t, *J* 8.1, Py-H), 7.85 (2H, d, *J* 8.1, Py-H), 7.87 (2H, d, *J* 8.1, Py-H).

(2). Using similar conditions to those above, Bu^t-IPIPI-Bu^t **9a** was also produced in 81% yield from the reaction of 2 mol of compound **7** (Bu^t-IP-F) with 1 mol of imidazolidin-2-one.

1,3-Bis[6-(2-oxoimidazolidin-1-yl)pyridin-2-yl]imidazolidin-2-one (IPIPI) 9b

Bu^t-IPIPI-Bu^t **9a** (4.10 g) in aqueous HCl (20%, 80 cm^3) was heated at reflux overnight. The mixture was cooled and neutralised with 4 M NaOH to give *IPIPI* **9b** which was recrystallised from aqueous TFA as a colourless solid (3.18 g, 99%), mp 320 °C (Found: C, 55.6; H, 4.9; N, 27.2. $C_{19}H_{20}N_8O_3$ requires C, 55.9; H, 4.9; N, 27.45%); ν_{max}(KBr)/cm^{-1} 3232 (N–H), 1697 (C=O), 1586, 793 (C–H, Py); δ_H(TFA) 3.45 (4H, t, CH_2), 3.78 (4H, t, CH_2), 3.95 (4H, s, CH_2), 6.48 (2H, d, *J* 8.1, Py-H), 6.51 (2H, d, *J* 8.1, Py-H), 7.90 (2H, t, *J* 8.1, Py-H).

2-(2-Oxoimidazolidin-1-yl)-6-(3-*tert*-butyl-2-oxoimidazolidin-1-yl)pyridine (Bu^t-IPI) 8a

Bu^t-IP-F **7** (6.50 g, 27 mmol) in DMF (80 cm^3) was added dropwise to a stirred solution of imidazolidin-2-one (5.80 g, 0.067 mol) and NaH (2.0 g, 60%, 50 mmol) in DMF (100 cm^3) at 100 °C over 1 h. After a further 8 h heating, the solvent was removed under reduced pressure and water was added and the precipitate filtered. Flash silica chromatography using ethyl acetate–dichloromethane (from 10→30%) gave firstly *Bu^t-IPIPI-Bu^t* **9a** (2.90 g), and then Bu^t-IPI **8a** which was recrystallised from ethyl acetate as colourless crystals (4.80 g, 73%), mp 267–268 °C (Found: C, 59.4; H, 6.8; N, 23.2. $C_{15}H_{21}N_5O_2$ requires C, 59.4; H, 7.0; N, 23.1%); ν_{max}(KBr)/cm^{-1} 3210 (N–H), 2976 (C–H, aliphatic), 1701 (C=O), 1584, 804 (Py); δ_H($CDCl_3$) 1.43 (9H, s, Bu^t), 3.46 (2H, t, CH_2), 3.52 (2H, t, CH_2), 3.89 (2H, t, CH_2), 4.11 (2H, t, CH_2), 5.13 (1H, br, NH), 7.56 (1H, t, *J* 8.1, Py-H), 7.77 (2H, d, *J* 8.1, Py-H), 7.83 (2H, d, *J* 8.1, Py-H).

2,6-Bis[3-(6-fluoropyridin-2-yl)-2-oxoimidazolidin-1-yl]pyridine (F-PIPIP-F) 11

To a stirred mixture of NaH (1.20 g, 50% in oil, 25 mmol) in THF (80 cm^3) was added IPI **10** (2.47 g, 10 mmol). The mixture was heated at reflux for 1 h and then 2,6-difluoropyridine (2.79 g, 24 mmol) was added and heating under reflux continued. After 40 h, the mixture was concentrated, water (~100 cm^3) was added and the precipitate was filtered and recrystallised from DMF to give *F-PIPIP-F* **11** as colourless crystals (2.50 g, 57%), mp 318–319 °C (Found: C, 57.66; H, 3.92; N, 22.69. $C_{21}H_{17}N_7F_2O_2$ requires C, 57.67; H, 3.91; N, 22.41%); ν_{max}(KBr)/cm^{-1} 1730, 1714 (C=O), 1586, 788 (Py); δ_H(TFA) 4.44 (4H, t, CH_2), 4.51 (4H, t, CH_2), 7.11 (2H, d, *J* 8.1, Py-H), 7.16 (2H, d, *J* 8.1, Py-5-H), 7.72 (2H, d, *J* 8.1, Py-3-H), 8.32 (2H, q, *J* 8.1, Py-4-H), 8.49 (1H, t, *J* 8.1, Py-H).

2,6-Bis{3-[dimethyl(1,1,3-trimethylpropyl)silyl]-2-oxoimidazolidin-1-yl}pyridine (DMTS-IPI-DMTS) 13

To a stirred mixture of IPI **10** (2.60 g, 10.5 mmol) and triethylamine (5.0 g, 49.4 mmol) in DMF (50 cm^3) was added dimethyl(1,1,3-trimethylpropyl)silyl chloride (5.36 g, 30.1 mmol) at 90 °C under nitrogen. The mixture was heated at 90 °C with stirring for a further 16 h. The cooled solution was poured into ice–water (~200 g) and the precipitate was collected and recrystallised from ethyl acetate to give 2,6-*bis*{3-[*dimethyl*(1,1,3-*trimethylpropyl*)*silyl*]-2-*oxoimidazolidin*-1-*yl*}-*pyridine* **13** as colourless plates (4.40 g, 79%), mp 217–218 °C (Found: C, 61.2; H, 9.5; N, 13.2. $C_{27}H_{49}N_5O_2Si_2$ requires C, 61.0; H, 9.3; N, 13.2%); ν_{max}(KBr)/cm^{-1} 2959 (C–H, aliphatic), 1690 (C=O), 1582, 801 (Py); δ_H($CDCl_3$) 0.29 (12H, s, SiMe), 0.82–0.85 (12H, d, CH*Me*), 0.92 (12H, s, C*Me*), 1.65 (2H, m, CH), 3.43 (4H, t, CH_2), 3.97 (4H, t, CH_2), 7.46 (1H, t, *J* 8.1, Py-4-H), 7.73 (2H, d, *J* 8.1, Py-3-H and Py-5-H).

2,6-Bis{3-[6-(3-*tert*-butyl-2-oxoimidazolidin-1-yl)pyridin-2-yl]-2-oxoimidazolidin-1-yl}pyridine (Bu^t-IPIPIPI-Bu^t) 12

(1). To a stirred mixture of DMTS-IPI-DMTS **13** (4.26 g, 8 mmol) and Bu^t-IP-F **7** (4.18 g, 17.6 mmol) in DMF (100 cm^3) was added caesium fluoride (0.20 g, 1.3 mmol). The mixture was heated at 110 °C for 48 h, cooled, and poured into water (~500 cm^3). The precipitate was filtered and recrystallised from toluene to give *Bu^t-IPIPIPI-Bu^t* **12** as colourless crystals (4.80 g, 88%), mp >320 °C (Found: C, 61.8; H, 6.1; N, 22.7. $C_{35}H_{43}N_{11}O_4$ requires C, 61.7; H, 6.4; N, 22.6%); ν_{max}(KBr)/cm^{-1} 2969 (C–H, aliphatic), 1712 (C=O), 1585, 796 (Py); δ_H($CDCl_3$) 1.44 (18H, s, Bu^t), 3.49 (4H, t, CH_2), 3.94 (4H, t, CH_2), 4.14 (8H, s, CH_2), 7.62 (2H, t, *J* 8.1, Py-γ-H), 7.69 (1H, t, *J* 8.1, Py-γ-H), 7.88 (2H, d, *J* 8.1, Py-β-H), 7.92 (2H, d, *J* 8.1, Py-β-H), 7.98 (2H, d, *J* 8.1, Py-β-H).

(2). A mixture of IPI **10** (2.0 g, 8.1 mmol), Bu^t-IP-F **7** (4.20 g, 17.7 mmol) and NaH (0.80 g, 60%, 20 mmol) in THF (50 cm^3)

was heated at reflux for 24 h. TLC indicated no reaction. Potassium hydride (2.30 g, 35%, 20 mmol) was then added. The mixture was heated at reflux for a further two days, concentrated to 20 cm^3 and poured into ice–water (~80 g). The precipitate was filtered and separated through a silica flash chromatography column with ethyl acetate–dichloromethane (v/v 15:85) as eluent. Bu^t-IPIPIPI-Bu^t **12** was obtained (1.70 g, 31%).

The reaction of Bu^t-IPI 8a with 2,6-difluoropyridine—synthesis of Bu^t-IPIP-F

A mixture of Bu^t-IPI **8a** (4.62 g, 15 mmol), 2.6-difluoropyridine (0.88 g, 7.5 mmol) and sodium hydride (0.80 g, 60%, 20 mmol) in THF (100 cm^3) was heated at reflux for 40 h. Most of the solvent was removed and ice–water (~80 g) was added. The resulting solid was filtered and separated through silica flash chromatography with ethyl acetate–dichloromethane (v/v 10:90→30:70) as eluent to give firstly *Bu^t-IPIP-F* (3.80 g, 66%), mp 178–179 °C (Found: C, 60.2; H, 6.0; N, 21.2. $C_{20}H_{23}N_6FO_2$ requires C, 60.3; H, 5.8; N, 21.1%); ν_{max}(KBr)/cm^{-1} 2978 (C–H, aliphatic), 1709 (C=O), 1585, 792 (Py); δ_H($CDCl_3$) 1.44 (9H, s, Bu^t), 3.48 (2H, t, CH_2), 3.91 (2H, t, CH_2), 4.10 (4H, m, CH_2), 6.56 (1H, dd, J_{HH} 8.1, J_{HF} 2.7, Py-H, α to F), 7.58–7.64 (t, 1H, *J* 8.1, Py-H), 7.73 (1H, q, *J* 8.1, Py-H α to F), 7.83 (1H, d, *J* 8.1, Py-H), 7.92 (1H, d, *J* 8.1, Py-H), 8.20 (1H, dd, J_{HH} 8.1, J_{HH} 2.7, Py-H γ to F). This was followed by Bu^t-IPIPIPI-Bu^t **12** (0.40 g, 7.8%) and starting material, Bu^t-IPI (1.0 g).

The reaction of Bu^t-IPI 8a with Bu^t-IPIP-F to give Bu^t-IPIPIPI-Bu^t 12

A mixture of Bu^t-IPIP-F (2.70 g, 7.0 mmol), Bu^t-IPI **8a** (2.12 g, 7.0 mmol) and sodium hydride (0.80 g, 60%, 20 mmol) in DMF (100 cm^3) was heated at 100 °C overnight. Most of the solvent was removed under reduced pressure and ice–water (~80 g) was added. Filtration gave a solid which was separated through silica flash chromatography with ethyl acetate–dichloromethane (v/v 10:90—30:70) as eluent to give Bu^t-IPIPIPI-Bu^t **12** (1.30 g, 30%).

2,6-Bis{3-[6-(2-oxoimidazolidin-1-yl)pyridin-2-yl]-2-oxoimidazolidin-1-yl}pyridine (IPIPIPI) 14a

A mixture of Bu^t-IPIPIPI-Bu^t **12** in aqueous HCl (20%, 80 cm^3) was heated at 80 °C overnight. The cooled solution was neutralised with aqueous NaOH (4 M) to give IPIPIPI **14** as a colourless solid (99%), mp >350 °C; ν_{max}(KBr)/cm^{-1} 3297 (N–H), 1714 (C=O), 1583, 798 (C–H, Py); δ_H($CDCl_3$, 50 °C) 4.01 (4H, br, CH_2), 4.33 (4H, br, CH_2), 4.53 (8H, br, CH_2), 7.05 (4H, br, Py-H), 7.32 (2H, br, Py-H), 8.45 (2H, br, Py-H), 8.54 (1H, br, Py-H); *m*/*z* (EI) 569. This compound was not capable of ready crystallisation and was thus used without further purification and characterisation.

1,3-Bis(6-{3-[dimethyl(1,1,3-trimethylpropyl)silyl]-2-oxoimidazolidin-1-yl}pyridin-2-yl)imidazolidin-2-one (DMTS-IPIPI-DMTS) 9c and 2,6-bis[3-(6-{3-[dimethyl(1,1,3-trimethylpropyl)-silyl]-2-oxoimidazolidin-2-yl}pyridin-2-yl)-2-oxoimidazolidin-1-yl]pyridine (DMTS-IPIPIPI-DMTS) 14b

DMTS-IPIPI-DMTS **9c** and DMTS-IPIPIPI-DMTS **14b** were synthesised from IPIPI **9b** and IPIPIPI **14a** respectively, utilising the same method used for the synthesis of DMTS-IPI-DMTS **13** and were recrystallised from ethyl acetate as colourless crystals.

DMTS-IPIPI-DMTS **9c** (86%), mp 270–273 °C (Found: C, 60.9; H, 7.9; N, 16.4. $C_{35}H_{56}N_8O_3Si_2$ requires C, 60.7; H, 8.1; N, 16.2%); ν_{max}(KBr)/cm^{-1} 2960 (C–H, aliphatic), 1710, 1687 (C=O), 1583, 804 (Py); δ_H($CDCl_3$) 0.36 (12H, s, SiMe), 0.90 (12H, d, CH*Me*), 0.98 (s, 12H, C*Me*), 1.71 (2H, m, CH), 3.51 (4H, t, CH_2), 4.05 (4H, t, CH_2), 4.07 (4H, s, CH_2), 7.57 (2H, t, *J* 8.1, Py-H), 7.87 (2H, d, *J* 8.1, Py-H), 7.88 (d, 2H, *J* 8.1, Py-H).

DMTS-IPIPIPI-DMTS **14b** (85%), mp 285–288 °C (Found: C, 60.6; H, 7.2; N, 18.3. $C_{43}H_{63}N_{11}O_4Si_2$ requires C, 60.5; H, 7.4; N, 18.0%); ν_{max}(KBr)/cm^{-1} 2960 (C–H, aliphatic), 1718, 1695 (C=O), 1583, 798 (Py); δ_H($CDCl_3$) 0.36 (12H, s, Si*Me*), 0.90 (12H, d, CH*Me*), 0.98 (12H, s, C*Me*), 1.71 (2H, m, CH), 3.51 (4H, t, CH_2), 4.05 (4H, t, CH_2), 4.05 (8H, s, CH_2), 7.59 (2H, t, *J* 8.1, Py-γ-H), 7.65 (1H, t, *J* 8.1, Py-γ-H), 7.84 (2H, d, *J* 8.1, Py-β-H), 7.87 (2H, d, *J* 8.1, Py-β-H), 7.94 (2H, d, *J* 8.1, Py-β-H).

2,6-Bis(3-{6-[3-(6-fluoropyridin-2-yl)-2-oxoimidazolidin-1-yl]-pyridin-2-yl}-2-oxoimidazolidin-1-yl)pyridine (F-PIPIPIPIP-F) 15

To a stirred mixture of DMTS-IPIPIPI-DMTS **14b** (0.48 g, 0.5 mmol) and 2,6-difluoropyridine (0.13 g, 1.1 mmol) in DMF (100 cm^3) at 110–120 °C was added caesium fluoride (~10 mg). The reaction mixture was heated at this temperature for a further 24 h, the solvent was removed under reduced pressure, and water (~30 cm^3) added and the precipitate filtered. Recrystallisation from DMF gave *F-PIPIPIPIP-F* **15** as very fine colourless crystals (0.58 g, 79%), mp >320 °C (Found: C, 58.4; H, 4.2; N, 24.0. $C_{37}H_{31}N_{13}F_2O_4$ requires C, 58.5; H, 4.1; N, 24.0%); ν_{max}(KBr)/cm^{-1} 1720 (C=O), 1583, 798 (Py); δ_H(TFA) 3.86 (4H, t, CH_2), 4.06 (4H, t, CH_2), 4.35 (8H, s, CH_2), 6.73 (2H, d, *J* 8.1, mid-Py-H), 6.84 (2H, d, *J* 8.1, Py-H), 7.02 (2H, d, *J* 8.1, Py-H), 7.19 (2H, d,† *J* 8.1, Py-H), 7.42 (2H, d,† *J* 8.1, Py-H), 7.70 (2H, 2 × d,† *J* 8.1, Py-β-H), 8.22–8.39 (3H, m, mid-Py-γ-H); *m*/*z* (EI) 759.

***N*,*N*′-Bis(6-fluoropyridin-2-yl)ethane-1,2-diamine (F-PEP-F) 17**

To a stirred mixture of 1,2-ethylenediamine (2.10 g, 35 mmol) and triethylamine (10.10 g, 100 mmol) in THF (30 cm^3) at 55 °C was added 2,6-difluoropyridine (8.60 g, 75 mmol) and the mixture heated at this temperature for a further 14 h. Solvent was removed, water (~30 cm^3) added and the resulting precipitate filtered and washed with water to give N,N′-*bis*(6-*fluoropyridin*-2-*yl*)*ethane*-1,2-*diamine* **17** which was recrystallised from toluene as colourless plates (7.78 g, 89%), mp 170–171 °C (Found: C, 57.6; H, 4.8; N, 22.4. $C_{12}H_{12}N_4F_2$ requires C, 57.6; H, 4.8; N, 22.4%); ν_{max}(KBr)/cm^{-1} 3282 (N–H), 1586, 771 (Py); δ_H($CDCl_3$, 55 °C) 3.55 (4H, s, CH_2), 4.50 (2H, br, NH), 6.12 (2H, dd, $^5J_{HH}$ 8.1, $^4J_{HH}$ 2.4, Py-3-H), 6.22 (2H, dd, $^5J_{HH}$ 8.1, $^5J_{HF}$ 2.4, Py-5-H), 7.42 (2H, q, *J* 8.1, Py-4-H).

***N*-(6-Fluoropyridin-2-yl)ethane-1,2-diamine (F-PE) 16**

2,6-Difluoropyridine (4.60 g, 0.04 mmol) and 1,2-ethylenediamine (7.0 g, 116 mmol) in THF (20 cm^3) were stirred at 45 °C overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure. Aqueous sodium hydroxide (2 M, 30 cm^3) was added and the mixture was extracted with dichloromethane. The combined organic layer was dried with magnesium sulfate, filtered, the solvent removed and the residue separated by flash chromatography using ethyl acetate and ethyl acetate–methanol (v/v, 1:1) as eluent. F-PEP-F **17** was obtained as colourless crystals (0.30 g, 6%), followed by N-(6-*fluoropyridin*-2-*yl*)*ethane*-1,2-*diamine* **16** as a colourless viscous liquid (3.80 g, 62%), δ_H($CDCl_3$) 2.88 (2H, t, NH_2CH_2), 2.90 (2H, br, NH_2), 3.35 (2H, q, $NHCH_2$), 5.80 (1H, br, NH), 6.07 (1H, dd, $^5J_{HH}$ 8.1, $^4J_{HH}$ 2.4, Py-3-H), 6.23 (1H, dd, $^5J_{HH}$ 8.1, $^5J_{HF}$ 2.4, Py-5-H), 7.40 (1H, q, *J* 8.1, Py-4-H); *m*/*z* (EI) 155.

***N*,*N*′-Bis[6-(2-aminoethylamino)pyridin-2-yl]ethane-1,2-diamine (EPEPE) 18 and *N*,*N*′-bis(6-{2-[(6-fluoropyridin-2-yl)amino]-ethylamino}pyridin-2-yl)ethane-1,2-diamine (F-PEPEPEP-F) 19**

To a stirred suspension of sodium carbonate (3.20 g, 30 mmol) in 1,2-ethylenediamine (50 cm^3) was added PEP (2.0 g, 8 mmol).

† No H–F coupling evident probably due to hydrolysis of fluorides in TFA solution.

The mixture was heated under reflux overnight, the solvent removed under reduced pressure and the residue vacuum dried. To the residue {which contained *EPEPE* **18** $\delta_H([^2H_6]DMSO)$ 2.74 (4H, t, NH_2CH_2), 3.08 (br, NH_2), 3.21 (4H, q, NH_2CH_2-CH_2), 3.36 (4H, s, mid-CH_2), 5.66 (4H, d, *J* 8.1, Py-β-H), 5.95 (2H, br, NH), 6.05 (2H, br, NH), 7.08 (2H, t, *J* 8.1, Py-γ-H)} was added acetonitrile (50 cm^3), water (10 cm^3), 2,6-difluoropyridine (3.0 g, 26 mmol) and extra sodium carbonate (1.6 g). The mixture was heated at reflux again for 10 h. The solvent was removed and water (~30 cm^3) added, and the mixture was extracted with dichloromethane (4 × 30 cm^3). The combined organic layer was dried with magnesium sulfate, the solvent removed and the residue separated by flash chromatography with ethyl acetate as eluent. *F-PEPEPEP-F* **19** was obtained as a brown glue which later solidified as low-melting, dark crispy prisms (2.60 g, 81%) (Found: C, 59.8; H, 6.0; N, 27.1. $C_{26}H_{30}N_{10}F_2$ requires C, 60.0; H, 5.8; N, 26.9%); ν_{max}(KBr)/cm^{-1} 3330 (N–H), 1568, 775 (Py); $\delta_H(CDCl_3)$ 3.39 (12H, s, CH_2), 5.03 (6H, br, NH), 5.64 (2H, d, $^5J_{HH}$ 8.1, Py-β-H), 5.66 (2H, d, $^5J_{HH}$ 8.1, Py-β-H), 6.01 (2H, dd, $^5J_{HH}$ 8.1, $^3J_{HF}$ 2.4, Py-H γ to F), 6.07 (2H, dd, $^5J_{HH}$ 8.1, $^5J_{HF}$ 2.4, Py-H α to F), 7.11 (2H, t, *J* 8.1, Py-H), 7.30 (2H, q, *J* 8.1, Py-H β to F); *m*/*z* (EI) 520.

1,3-Bis[6-(2-aminoethylamino)pyridin-2-yl]imidazolidin-2-one (EPIPE) 20

To a stirred solution of 1,2-ethylenediamine (15 cm^3) was added F-PIP-F **5b** (2.80 g, 10 mmol), the mixture was heated to 100 °C for 4 h, when the solvent was removed under reduced pressure. Aqueous sodium hydroxide (2 M, 15 cm^3) was added and the mixture stirred for a few minutes then extracted with chloroform (4 × 50 cm^3). The combined organic layer was dried with magnesium sulfate and the solvent removed to give 1,3-*bis*[6-(2-*aminoethylamino*)*pyridin*-2-*yl*]*imidazolidin*-2-*one* **20** as a colourless glassy solid which could not be recrystallised (3.30 g, 92%), mp 120–125 °C; ν_{max}(KBr)/cm^{-1} 3363 (N–H), 1706 (C=O), 1597, 782 (Py); $\delta_H(CDCl_3)$ 1.52 (4H, br, NH_2), 2.95 (4H, t, *J* 5.7, NH_2CH_2), 3.37 (4H, q, *J* 5.8, $NHCH_2$), 4.08 (4H, s, CH_2), 4.69 (2H, t, NH), 6.09 (2H, d, *J* 8.1, Py-H), 7.41 (2H, t, *J* 8.1, Py-H), 7.57 (2H, d, *J* 8.1, Py-H); $\delta_H([^2H_6]DMSO)$ 2.71 (4H, t, *J* 6.2, NH_2CH_2), 3.18 (4H, t, *J* 6.0, $NHCH_2$), 3.22 (4H, NH_2 and $NHCH_2$), 4.0 (4H, s, CH_2), 6.11 (d, 2H, *J* 8.1, Py-H), 4.69 (2H, br, NH), 732 (2H, d, *J* 8.1, Py-H), 7.34 (2H, t, *J* 8.1, Py-H)

1,3-Bis(6-{2-[(6-fluoropyridin-2-yl)amino]ethylamino}pyridin-2-yl)imidazolidin-2-one (F-PEPIPEP-F) 21

To a stirred mixture of sodium carbonate (0.53 g, 5 mmol) in MeCN–H_2O (5:1, 60 cm^3) was added EPIPE **20** (0.36 g, 1 mmol). The mixture was heated at 80 °C overnight. The acetonitrile was removed under reduced pressure and water (~20 cm^3) was added. The mixture was extracted with dichloromethane (4 × 20 cm^3). The combined organic layer was dried with magnesium sulfate and filtered. Removal of solvent gave *F-PEPIPEP-F* **21** which was recrystallised from ethyl acetate as colourless crystals (0.45 g, 85%), mp 139–140 °C (Found: C, 59.4; H, 5.2; N, 25.7. $C_{27}H_{28}N_{10}F_2O$ requires C, 59.3; H, 5.2; N, 25.6%); ν_{max}(KBr)/cm^{-1} 3305 (N–H), 1706 (C=O), 1565, 777 (Py); $\delta_H(CDCl_3)$ 3.34 (4H, t, *J* 4.3, CH_2), 3.55 (4H, t, *J* 4.3, CH_2), 4.08 (4H, s, CH_2), 4.69 (2H, br, NH), 5.15 (2H, br, NH), 6.08 (2H, d, $^5J_{HH}$ 8.1, Py-H), 6.12 (2H, dd, $^5J_{HH}$ 8.1, $^3J_{HF}$ 2.4, Py-H γ to F), 6.18 (2H, dd, $^5J_{HH}$ 8.1, $^5J_{HF}$ 2.4, Py-H α to F), 7.40 (2H, t, J_{HH} 8.1, Py-H), 7.43 (2H, q, *J* 8.1, Py-H β to F), 7.57 (2H, d, J_{HH} 8.1, Py-H); $\delta_H([^2H_6]DMSO)$ 3.37 (8H, br s, CH_2), 3.98 (4H, s, CH_2), 6.04 (2H, dd, $^5J_{HH}$ 8.1, $^3J_{HF}$ 2.4, Py-H γ to F), 6.13 (2H, d, $^5J_{HH}$ 8.1, Py-H), 6.30 (2H, dd, $^5J_{HH}$ 8.1, $^5J_{HF}$ 2.4, Py-H α to F), 6.59 (2H, br, NH), 7.02 (2H, br, NH), 7.26 (2H, d, $^5J_{HH}$ 8.1, Py-H), 7.33 (2H, t, $^5J_{HH}$ 8.1, Py-H), 7.44 (2H, q, *J* 8.1, Py-H β to F); *m*/*z* (ES^+, MH^+) 547.

2,6-Bis(imidazol-1-yl)pyridine 22

A mixture of 2,6-difluoropyridine (1.50 g, 13 mmol) and imidazole (4.40 g, 65 mmol) was heated to 90 °C with stirring for 5 h and then at 120 °C for a further 30 h. The mixture was cooled and water was added (~100 cm^3). The precipitate was filtered and recrystallised from ethyl acetate to give 2,6-bis(imidazol-1-yl)pyridine **22** as colourless crystals (2.20 g, 80%), mp 150.5–151.5 °C (lit.,[20] mp 152 °C); ν_{max}(KBr)/cm^{-1} 1604 (Im), 1588, 792 (Py); $\delta_H([^2H_6]DMSO$, 50 °C) 7.14 (2H, t, *J* 1.1, =NCHC*H* of imidazole), 7.73 (2H, d, *J* 8.1, Py-H), 8.08 (2H, t, *J* 1.4, =NC*H*CH of imidazole), 8.17 (1H, t, *J* 8.1, Py-H), 8.70 (2H, br s, imidazole =NCHN); $\delta_H(CDCl_3)$ 7.23 (2H, t, *J* 1.4, =NCHC*H* of imidazole), 7.28 (2H, d, *J* 8.1, Py-H), 7.26 (2H, t, *J* 1.4, =NC*H*CH of imidazole), 7.94–7.80 (1H, t, *J* 8.1, Py-H), 8.38 (2H, br s, imidazole =NCHN).

Oxidation of 2,6-bis(imidazol-1-yl)pyridine 22

To a stirred mixture of 2,6-bis(imidazol-1-yl)pyridine **22** (2.11 g, 10 mmol) in THF (50 cm^3) at room temperature was added *n*-butyllithium (in hexane, 21 mmol) slowly through a syringe under nitrogen. The mixture became dark-brown and was stirred for a further 2 h, and then cooled with an ice-bath and *tert*-butyl peroxide (3.30 g, 22 mmol) in THF (20 cm^3) was added dropwise to the mixture through a pressure equalised-dropping funnel over 45 min. The mixture was then stirred overnight at room temperature. 2,2′-Thiodiethanol (2.3 cm^3) and water (80 cm^3) were added (**CAUTION**: before proceeding further, negative tests with KI-starch test paper are essential to ensure no peroxide remains). The mixture was extracted with ether (3 × 50 cm^3). The combined organic layer was dried with magnesium sulfate, filtered and the solvent was removed. Starting material (0.77 g) was obtained.

2,6-Bis(3-benzylimidazol-3-ium-1-yl)pyridine dichloride 23

A mixture of 2,6-bis(imidazol-1-yl)pyridine **22** (6.33 g, 30 mmol) and benzyl chloride (38.0 g, 300 mmol) was heated to 100 °C for 1 h. The excess of benzyl chloride was removed under reduced pressure, the mixture cooled to ambient temperature and ethanol (80 cm^3) was added. After heating to reflux, ethyl acetate was slowly added until precipitation just occurred and the mixture slowly cooled. 2,6-*Bis*(3-*benzylimidazol*-3-*ium*-1-*yl*)*pyridine dichloride* **23** was collected as colourless crystals (10.10 g, 73%), mp >320 °C (Found: C, 64.65; H, 5.1; N, 15.2. $C_{25}H_{23}N_5Cl_2$ requires C, 64.8; H, 5.0; N, 15.1%); ν_{max}(KBr)/cm^{-1} 1611 (Im), 1535, 811 (Py), 712 (Ph); $\delta_H([^2H_6]DMSO$, 50 °C) 5.66 (4H, s, benzyl CH_2), 7.44 (10H, m, Ph), 8.14 (2H, t, *J* 2.0, $=N^+CHCH$ of imidazole), 8.29 (2H, d, *J* 8.1, Py-H), 8.56 (1H, t, *J* 8.1, Py-H), 8.88 (2H, t, *J* 2.0, $=N^+CHCH$ of imidazole), 11.55 (2H, br s, imidazole N^+CHN); $\delta_H(D_2O$, 80 °C) 6.16 (4H, s, benzyl CH_2), 8.11 (10H, br, Ph), 8.32 (2H, d, *J* 2.2, $=N^+CHCH$ of imidazole), 8.56 (2H, d, *J* 8.1, Py-H), 8.88 (2H, d, *J* 2.2, $=N^+CHCH$ of imidazole), 9.03 (1H, t, *J* 8.1, Py-H).

Oxidation of 2,6-bis(3-benzylimidazol-3-ium-1-yl)pyridine dichloride 23

(1). To a stirred mixture of 2,6-bis(3-benzylimidazol-3-ium-1-yl)pyridine dichloride (1.30 g, 2.8 mmol) in water (30 cm^3) at 50 °C was added sodium perborate tetrahydrate (1.35 g, 8.4 mmol). The mixture was stirred for a further 18 h. 2,2′-Thiodiethanol (1.0 cm^3) was added (**CAUTION**: before proceeding further negative tests with KI-starch test paper are essential to ensure no peroxide remains). The mixture was extracted with chloroform (3 × 20 cm^3). The combined organic layer was dried with magnesium sulfate, filtered and the solvent removed. A sticky purple inseparable mixture (0.58 g) was obtained. Following the same procedure as above, but using hydrogen peroxide as oxidant with 2.5 mol equiv. of sodium hydroxide, a similar result was observed.

(2). A mixture of 2,6-bis(3-benzylimidazol-3-ium-1-yl)pyridine dichloride salt (1.16 g, 2.5 mmol), sulfur (0.16 g, 5.0 mmol) and potassium carbonate in methanol (50 cm^3) was heated at reflux for one day. TLC indicated that no reaction had occurred.

6-(Imidazol-1-yl)-2-(3-benzylimidazol-3-ium-1-yl)pyridine chloride 24

The reaction of 2,6-bis(imidazol-1-yl)pyridine **22** (0.90 g, 4.3 mmol) and benzyl chloride (1.10 g, 8.7 mmol) in ethyl acetate (30 cm^3) at reflux for 40 h gave 6-(imidazol-1-yl)-2-(3-benzylimidazol-3-ium-1-yl)pyridine chloride **24** as colourless crystals (1.20 g, 83%) from ethyl acetate, mp 242–243 °C (Found: C, 64.0; H, 4.85; N, 20.9. $C_{18}H_{16}N_5Cl$ requires C, 64.1; H, 4.8; N, 20.8%); ν_{max}(KBr)/cm^{-1} 1614 (Im), 1536, 816 (Py), 709 (benzene); δ_H([$^2H_6$]DMSO, 50 °C) 5.62 (2H, s, benzyl CH_2), 7.18 (1H, t, *J* 1.1, =NCHC*H* of imidazole), 7.41–7.59 (5H, m, Ph), 8.02 (1H, d, *J* 8.1, Py-3-H), 8.03 (1H, d, *J* 8.1, Py-5-H), 8.09 (1H, t, *J* 1.8, =NC*H*CH of imidazole), 8.22 (1H, t, *J* 1.5, =N^+CHC*H* of imidazole), 8.37 (1H, t, *J* 8.1, Py-4-H), 8.75 (2H, t, *J* 2.0, =N^+C*H*CH of imidazole), 8.85 (1H, br s, imidazole NCHN), 10.78 (1H, br s, imidazole N^+CHN).

2-Fluoro-6-(imidazol-1-yl)pyridine

A mixture of 2,6-difluoropyridine (23.10 g, 200 mmol) and imidazole (1.36 g, 20 mmol) was heated to 100 °C and stirred for 3 h. The excess of 2,6-difluoropyridine was removed under reduced pressure, the residue cooled and water added (50 cm^3). The precipitate was filtered and then added to light petroleum (50 cm^3). The mixture was then heated to reflux and filtered. The insoluble solid which was recrystallised from ethyl acetate and found to be 2,6-bis(imidazol-1-yl)pyridine (0.78 g, 38%). Removal of the solvent from the filtrate gave 2-*fluoro*-6-(*imidazol*-1-*yl*)*pyridine* (0.66 g, 20%) as colourless needles from light petroleum, mp 80–81 °C (Found: C, 58.9; H, 3.7; N, 25.6. $C_8H_6N_3F$ requires C, 58.9; H, 3.71; N, 25.75); ν_{max}(KBr)/cm^{-1} 1603 (Im), 1580, 793 (Py); δ_H([$^2H_6$]DMSO, 50 °C) 7.13 (1H, dd, $^3J_{HH}$ 8.1, $^3J_{HF}$ 2.4, Py-3-H), 7.13 (1H, t, *J* 1.2, =NCHC*H* of imidazole), 7.75 (1H, dd, $^3J_{HH}$ 8.1, $^5J_{HF}$ 2.4, Py-5-H), 7.90 (1H, t, *J* 1.6, =NC*H*CH of imidazole), 8.17 (1H, q, *J* 8.1, Py-4-H), 8.48 (br s, 2H, N=CHN).

Preparations based on 2,6-diaminopyridine

***N*,*N*′-Bis(pyridin-2-yl)oxamide (F-POP-F).** In a 50 cm^3 thoroughly dried two-necked flask equipped with reflux condenser, calcium chloride guard-tube, a magnetic stirrer and an ice-bath, was added methanol (15 cm^3) and clean sodium pieces (0.69 g, 30 mmol). When all the sodium had dissolved, 2-aminopyridine (1.88 g, 20 mmol) was added and the clear solution slowly raised to ambient temperature. Diethyl oxalate (1.46 g, 10 mmol) in methanol (10 cm^3) was added slowly through a dropping funnel to the mixture with stirring, which was continued for 1 h after the addition was complete. Hydrochloric acid (36%, 2 cm^3) was added dropwise to the mixture, most of the methanol removed under reduced pressure at 35 °C and cold water (~30 cm^3) added. The precipitate was filtered and washed with water and then a little methanol. The solid was recrystallised from ethanol to give *N*,*N*-bis(pyridin-2-yl)oxamide as colourless crystals (0.96 g, 40%), mp 161–162 °C (lit.,[34] mp 161–162 °C).

2,6-Bis[3-(2-chloroethyl)ureido]pyridine 25 and its cyclisation to IPI 10. 2-Chloroethyl isocyanate (17.10 g, 160 mmol) was added dropwise to a stirred solution of 2,6-diaminopyridine (7.80 g, 71 mmol) in THF (50 cm^3) at 0–5 °C, and the mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure. The resulting solid was recrystallised from ethanol to give 2,6-bis[3-(2-chloroethyl)ureido]pyridine **25** as white plates (17.50 g, 78%), mp 169–170 °C (lit.,[23] mp 171–174 °C); ν_{max}(KBr)/cm^{-1} 3214 (N–H), 1690 (C=O), 1572, 793 (Py); δ_H([$^2H_6$]DMSO) 3.57 (4H, q, $NHCH_2$), 3.77 (4H, t, $ClCH_2$), 7.29 (2H, d, *J* 8.1, Py-β-H), 7.58–7.64 (t, 1H, *J* 8.1, Py-γ-H), 7.93–7.98 (2H, t, CH_2NH), 9.22 (2H, s, Py-NH).

To a stirred mixture of NaH (0.96 g, 50% in oil, 20 mmol) in THF (50 cm^3) was added 2,6-bis[3-(2-chloroethyl)ureido]-pyridine **25** (2.15 g, 6.7 mmol). The mixture was heated under reflux for 40 h, the solvent removed under reduced pressure and water added. The precipitate was filtered to give IPI **10** (1.30 g, 78%).

***N*,*N*′-Bis(6-aminopyridin-2-yl)oxamide (H_2N-POP-NH_2) 26.** In a 150 cm^3 thoroughly dried two-necked flask equipped with reflux condenser with calcium chloride guard-tube, a magnetic stirrer and ice-bath, was added methanol (50 cm^3) and clean sodium pieces (1.20 g, 50 mmol). When all the sodium had dissolved, 2,6-diaminopyridine (6.60 g, 60 mmol) was added which dissolved slowly while being raised to ambient temperature. Diethyl oxalate (2.92 g, 20 mmol) in methanol (20 cm^3) was added dropwise to the mixture with stirring and the stirring was continued for a further hour after the addition was complete. Hydrochloric acid (36%, 5 cm^3) was added dropwise to the mixture, most of the methanol removed under reduced pressure at 35 °C and cold water (~50 cm^3) was added. The precipitate was filtered and washed with water and a little methanol to give N,N′-*bis*(6-*aminopyridin*-2-*yl*)*oxamide* **26** which was collected as a grey solid (2.0 g, 37%). Recrystallisation was unsuccessful, mp >320 °C (Found: C, 52.7; H, 4.5; N, 31.0. $C_{11}H_{12}N_6O_2$ requires C, 52.9; H, 4.4; N, 30.9%); ν_{max}(KBr)/cm^{-1} 3371, 3202 (N–H), 1694 (C=O), 1573, 791 (Py); δ_H([$^2H_6$]DMSO) 6.08 (4H, br, NH_2), 6.33 (2H, d, *J* 8.1, Py-5-H), 7.23 (2H, d, *J* 8.1, Py-3-H), 7.50 (2H, t, *J* 8.1, Py-4-H), 9.30 (2H, br, NH); *m*/*z* (ES^+, MH^+) 273.

***N*,*N*′-Bis(6-aminopyridin-2-yl)ethane-1,2-diamine (H_2N-PEP-NH_2) 27.** To a 150 cm^3 two-necked round bottomed flask equipped with a pressure equalised-dropping funnel, a condenser and magnetic stirrer, was added THF (50 cm^3) and *N*,*N*-bis(6-aminopyridin-2-yl)oxamide **26** (0.27 g, 1 mmol), and the mixture heated to reflux. Borane·dimethyl sulfide (0.44 cm^3, 0.44 mmol) in THF (20 cm^3) was added dropwise through a syringe to the mixture over 10 min. After stirring for a further 3 h at reflux, the solvent was removed, hydrochloric acid (3 M, 10 cm^3) was added and the mixture was stirred at ambient temperature for 10 min, neutralised with sodium hydroxide (5 M), and extracted with ether (3 × 20 cm^3). The combined organic layer was dried with magnesium sulfate, filtered and evaporated. The *title compound* **27** was obtained as a dark, crispy solid (0.21 g, 86%), ν_{max}(KBr)/cm^{-1} 3354, 3230 (N–H), 1567, 813 (Py); δ_H($CDCl_3$) 3.35 (4H, s, CH_2), 4.21 (4H, br, NH_2), 4.80 (2H, br, NH), 5.69 (2H, d, *J* 8.1, Py-5-H), 5.72 (2H, d, *J* 8.1, Py-3-H), 7.11 (2H, t, *J* 8.1, Py-4-H); *m*/*z* (EI^+) 244.

2,6-Bis(methoxamido)pyridine 28a. In a 500 cm^3 thoroughly dried two-necked flask equipped with reflux condenser with calcium chloride guard-tube, a magnetic stirrer and an ice-bath, was added methanol (150 cm^3) and clean sodium pieces (4.60 g, 200 mmol). When all the sodium had dissolved, 2,6-diaminopyridine (11.0 g, 100 mmol) was added and to the clear solution dimethyl oxalate (47.27 g, 400 mmol) in methanol (100 cm^3) was added dropwise. The mixture was slowly raised to ambient temperature and stirred for a further 2 h, cooled with an ice-bath and aqueous hydrochloric acid (20%) was slowly added to neutralise the mixture. Most of the methanol was removed under reduced pressure at 35 °C, cold water (~100 cm^3) added and the precipitate filtered, washed with water, and then recrystallised from methanol to give 2,6-*bis*(*methoxamido*)-*pyridine* **28a** as colourless crystals (20.10 g, 71%), mp 208–209 °C (Found: C, 46.9; H, 3.9; N, 15.0. $C_{11}H_{11}N_3O_6$ requires C, 47.0; H, 3.9; N, 14.9%); ν_{max}(KBr)/cm^{-1} 3396, 3330 (N–H), 1735, 1711 (C=O), 1591, 801 (Py); δ_H($CDCl_3$) 4.0 (6H, s, Me), 7.85 (1H, t, *J* 8.1, Py-H), 8.06 (2H, d, *J* 8.1, Py-H), 9.22 (2H, s, NH).

2,6-Bis(ethoxamido)pyridine 28b. Using the same method as

above but replacing methyl oxalate with ethyl oxalate gave 2,6-*bis*(*ethoxamido*)*pyridine* **28b** as colourless crystals (20.40 g, 66%), mp 176–177 °C (Found: C, 50.4; H, 4.95; N, 13.7. $C_{13}H_{15}N_3O_6$ requires C, 50.5; H, 4.9; N, 13.6%); ν_{max}(KBr)/cm^{-1} 3402, 3331 (N–H), 1723, 1705 (C=O), 1590, 803 (Py); δ_H($CDCl_3$) 1.44 (6H, t, *Me*CH_2), 4.45 (4H, q, MeC*H*$_2$), 7.84 (1H, t, *J* 8.1, Py-4-H), 8.04 (2H, d, *J* 8.1, Py-3-H and Py-5-H), 9.26 (2H, s, NH).

Macrocyclisations of chloroethoxyethyl derivatives

2,6-Bis{3-[2-(2-chloroethoxy)ethyl]-2-oxoimidazolidin-1-yl}-pyridine 30 and its macrocyclisation to give 32. To a stirred mixture of sodium hydride (0.40 g, 60% in oil, 10 mmol) in dry DMF (50 cm^3) was added IPI **5** (0.96 g, 3.9 mmol). The mixture was heated at 110 °C for 30 min and cooled to ambient temperature. Chloroethyl ether (5.6 g, 39 mmol) was added and the mixture heated at 90 °C with stirring for 14 h, the solvent removed under reduced pressure and water added. The precipitate was filtered dried and flash chromatographed using ethyl acetate to give the *title compound* **30** as colourless crystals (1.30 g, 73%), mp 102–103 °C (Found: C, 49.5; H, 6.0; N, 15.2. $C_{19}H_{27}Cl_2N_5O_4$ requires C, 49.7; H, 5.9; N, 15.25%); ν_{max}(KBr)/cm^{-1} 1699 (C=O), 1583, 794; δ_H($CDCl_3$) 3.51 (4H, t, *J* 5.1, ClCH_2), 3.63 (4H, t, *J* 8.1, NCH_2CH_2N), 3.64 (4H, t, *J* 5.1, OCH_2), 3.71 (4H, t, *J* 5.1, OCH_2), 3.74 (4H, t, *J* 5.1, OCH_2), 4.02 (4H, t, *J* 8.1, NCH_2CH_2N), 7.58 (1H, t, *J* 8.1, Py-4-H), 7.81 (2H, d, *J* 8.1, Py-3,5-H); *m*/*z* (EI) 459.

To a stirred mixture of sodium hydride (0.40 g, 60% in oil, 10 mmol) in dry DMF (100 cm^3) was added IPI **10** (0.62 g, 2.5 mmol). The mixture was heated at 100 °C for 30 min and the chloroethoxyethyl ether **30** (1.15 g, 2.5 mmol) in DMF (30 cm^3) was added through a syringe pump over 10 h at the same temperature with stirring. The mixture was heated at 100 °C with stirring for a further 24 h, the solvent removed under reduced pressure and water added. The precipitate was filtered, dried and extracted in a Soxhlet apparatus with dichloromethane for 5 h and the extract flash chromatographed using methanol–ethyl acetate (20 : 80) to give the *title compound* **32** as colourless crystals from ethyl acetate and chloroform (0.32 g, 20%), mp >320 °C (Found: C, 56.6; H, 6.15; N, 22.3. $C_{30}H_{38}N_{10}O_6$ requires C, 56.8; H, 6.0; N, 22.1%); ν_{max}(KBr)/cm^{-1} 1707 (C=O), 1584, 791; δ_H($CDCl_3$) 3.42–3.60 (24H, m, CH_2), 3.66 (4H, t, *J* 8.1, NCH_2CH_2N), 7.56 (2H, t, *J* 8.1, Py-4-H), 7.84 (4H, d, *J* 8.1, Py-3,5-H); *m*/*z* (ES, MH$^+$) 635.

Using the above method, addition of an equimolar amount of bis(2-chloroethyl) ether to IPI **10** in DMF by way of a syringe pump gave the same macrocycle **32** in 14% yield.

2,6-Bis{3-{2-[2-(2-chloroethoxy)ethoxy]ethyl}-2-oxoimidazolidin-1-yl}pyridine 31 and its macrocyclisation to give 33. In an exactly analogous manner but utilising IPI **10** (1.93 g, 2.5 mmol) and 1,2-bis(2-chloroethoxy)ethane (19.0 g, 100 mmol) was obtained the *title product* **31** (3.0 g, 70%) as colourless crystals from ethyl acetate, mp 65–66 °C (Found: C, 50.45; H, 6.4; N, 12.7. $C_{23}H_{35}Cl_2N_5O_6$ requires C, 50.4; H, 6.45; N, 12.8%); ν_{max}(KBr)/cm^{-1} 1705 (C=O), 1584, 802; δ_H($CDCl_3$) 3.50 (4H, t, *J* 5.4, ClCH_2), 3.63–3.77 (20H, m, CH_2), 4.0 (4H, t, *J* 8.1, NCH_2CH_2N), 7.57 (1H, t, *J* 8.1, Py-4-H), 7.81 (2H, d, *J* 8.1, Py-3,5-H).

Similarly to the above macrocyclisation, from IPI and the compound **31** treated in exactly the same manner was obtained the *title product* **33** as the fine colourless crystals from ethyl acetate and chloroform (36%), mp 275–276 °C (Found: C, 56.4; H, 6.5; N, 19.5. $C_{34}H_{46}N_{10}O_8$ requires C, 56.6; H, 6.4; N, 19.4%); ν_{max}(KBr)/cm^{-1} 1707 (C=O), 1584, 792; δ_H($CDCl_3$) 3.48–3.55 (16H, m, CH_2), 3.63 (8H, t, *J* 8.1, OCH_2CH_2O), 3.66 (8H, t, *J* 5.1, NC*H*$_2$CH_2O), 3.83 (8H, t, *J* 8.1, NCH_2CH_2N), 7.59 (2H, t, *J* 8.1, Py-4-H), 7.83 (4H, d, *J* 8.1, Py-3,5-H); δ_H([$^2H_6$]DMSO) 3.36 (8H, t, *J* 5.4, NCH_2C*H*$_2$O), 3.46 (8H, t, *J* 8.1, NC*H*$_2$-CH_2O), 3.57 (8H, s, OCH_2CH_2O), 3.61 (8H, t, *J* 5.4, NC*H*$_2$-CH_2O), 3.78 (8H, t, *J* 8.1, NCH_2CH_2N), 7.52 (2H, dd, *J* 7.5 and 8.7, Py-4-H), 7.67 (2H, d, *J* 7.5, Py-3-H), 7.68 (2H, d, *J* 8.7, Py-5-H); *m*/*z* (ES, MH$^+$) 723.

The direct approach to this product **33** performed as above using 1,2-bis(2-chloroethoxy)ethane and IPI **10** gave a yield of 22%.

1,3-Bis{6-[2-(2-hydroxyethoxy)ethoxy]pyridin-2-yl}imidazolidin-2-one 34 and its macrocyclisation to give 35

To a flask fitted with a Dean and Stark water separator was added F-PIP-F **5b** (1.25 g, 4.5 mmol), diethylene glycol (4.80 g, 45 mmol), potassium carbonate (5.0 g, 36 mmol) and xylene (80 cm^3) and the mixture was heated under reflux for 6 h. The solvent was removed and water and dichloromethane added and the organic layer was evaporated to give the *title product* **34** as colourless crystals from light petroleum and ethyl acetate (1.50 g, 74%), mp 76–77 °C (Found: C, 56.4; H, 6.35; N, 12.4. $C_{21}H_{28}N_4O_7$ requires C, 56.2; H, 6.3; N, 12.5%); ν_{max}(KBr)/cm^{-1} 3417 (OH), 1712 (C=O), 1592, 784; δ_H($CDCl_3$) 2.28 (2H, br, OH), 3.67 (4H, m, OC*H*$_2$CH_2OH), 3.78 (4H, m, OCH_2-C*H*$_2$OH), 3.86 (4H, t, *J* 4.9, OCH_2CH_2OPy), 4.13 (8H, s, NCH_2CH_2N), 4.44 (4H, t, *J* 4.9, PyOCH_2CH_2O), 6.46 (2H, d, *J* 7.8, Py-3-H), 7.59 (2H, t, *J* 7.8, Py-4-H), 7.85 (2H, d, *J* 7.8, Py-5-H).

To a flask fitted with a Soxhlet extractor was added sodium hydride (0.20 g, 60% in oil, 5 mmol) and dry THF (150 cm^3). F-PIP-F **5b** (0.28 g, 1 mmol) was placed in the extractor and the mixture heated to reflux. Through a syringe pump was added the above compound **34** (0.45 g, 1 mmol) in THF (30 cm^3) over 10 h and the mixture refluxed for a further 16 h. Removal of the solvent and addition of water precipitated a solid which was subjected to Soxhlet extraction with dichloromethane for 5 h. The extract was evaporated and the residue subjected to flash chromatography on silica gel using ethyl acetate as eluent to give the *title compound* **35** (0.12 g, 35%) as a colourless solid, mp 280–283 °C (Found: C, 59.5; H, 5.4; N, 16.4. $C_{34}H_{36}N_8O_8$ requires C, 59.6; H, 5.3; N, 16.4%); ν_{max}(KBr)/cm^{-1} 1717 (C=O), 1592, 790; δ_H($CDCl_3$, 50 °C) 3.80 (8H, t, *J* 5.4, PyOCH$_2$C*H*$_2$O), 4.01 (8H, s, NCH_2CH_2N), 4.40 (8H, t, *J* 5.4, PyOC*H*$_2$CH$_2$O), 6.27 (4H, d, *J* 8.1, Py-3-H), 7.44 (2H, t, *J* 8.1, Py-4-H), 7.71 (2H, d, *J* 8.1, Py-5-H); *m*/*z* (ES, MH$^+$) 685.

Synthesis of the macrocycle 36

To a stirred mixture of F-PIP-F **5b** (1.38 g, 5 mmol) and sodium hydride (0.5 g, 60% in oil, 12.5 mmol) in DMF (30 cm^3), triethylene glycol (0.75 g, 5 mmol) was added through a syringe pump over 10 h. The mixture was stirred for a further 24 h, the solvent removed under reduced pressure and water and dichloromethane added and the organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue with ethyl acetate as the eluent gave the *title product* **36** as colourless crystals (10.21 g, 11%), mp 189–191 °C (Found: C, 58.9; H, 5.80; N, 14.6. $C_{38}H_{44}N_8O_{10}$ requires C, 59.1; H, 5.7; N, 14.5%); ν_{max}(KBr)/cm^{-1} 1712 (C=O), 1592, 785; δ_H($CDCl_3$) 3.76 (8H, s, CH_2), 3.88 (8H, t, *J* 5.4, PyOCH$_2$C*H*$_2$O), 4.11 (8H, s, NCH_2-CH_2N), 4.44 (8H, t, *J* 5.4, PyOC*H*$_2$CH$_2$O), 6.41 (4H, d, *J* 8.1, Py-3-H), 7.54 (2H, t, *J* 8.1, Py-4-H), 7.81 (2H, d, *J* 8.1, Py-5-H); *m*/*z* (ES, MH$^+$) 773.

2,6-Bis(3-propargyl-2-oxoimidazolidin-1-yl)pyridine 37

To a stirred mixture of sodium hydride (0.24 g, 60% in oil, 6 mmol) in DMF (15 cm^3) was added IPI (0.312 g, 1.1 mmol). The mixture was heated at 110 °C for 0.5 h and then cooled to 0 °C with an ice-bath. Propargyl chloride (0.33 cm^3, 70% in toluene, 33 mmol) was added slowly through a 1 cm^3 syringe to the mixture then the ice-bath was withdrawn and the mixture stirred for a further 2 h, and poured into ice-water (~50 g). The precipitate was filtered and recrystallised from ethyl acetate to give 2,6-*bis*(3-*propargyl*-2-*oxoimidazolidin*-1-*yl*)*pyridine* **37** as white crystals (0.31 g, 86%), mp 232–234 °C (Found: C, 63.0; H, 5.4; N, 21.8. $C_{17}H_{17}N_5O_2$ requires C, 63.15; H, 5.3; N,

21.7%); ν_{max}(KBr)/cm^{-1} 3296 (C≡CH), 1714 (C=O), 1584, 802; δ_H($CDCl_3$) 2.25 (2H, t, *J* 2.4, CH), 3.54 (4H, t, *J* 8.1, Im CH_2), 4.03 (4H, t, *J* 8.1, Im CH_2), 4.12 (4H, d, *J* 2.4, CH_2), 7.59 (1H, t, *J* 8.1, Py-H), 7.84 (2H, d, *J* 8.1, Py-H).

Propargyl chloride should be added slowly at 0 °C. If it was added in one portion at ambient temperature, the mixture became black. The mixture was poured into ice-water and the resulting black oil which was purified by silica chromatography. Only *bis*(3-*allenyl*-2-*oxoimidazolidin*-1-*yl*)*pyridine* **38** was obtained (12%) as an oil, δ_H($CDCl_3$) 3.40 (4H, t, *J* 8.1, Im CH_2), 3.98 (4H, t, *J* 8.1, Im CH_2), 5.38 (4H, d, *J* 6.2, =CH_2), 7.01 (2H, t, *J* 6.2, =CH), 7.55 (1H, t, *J* 8.1, Py-H), 7.81 (2H, d, *J* 8.1, Py-H).

2-(3-*tert*-Butyl-2-oxoimidazolidin-1-yl)-6-(3-propargyl-2-oxoimidazolidin-1-yl)pyridine (Bu′-IPI-Pg) 39

The title compound was synthesised exactly as for the synthesis of **37** utilising Bu′-IPI **8a** as starting material. Recrystallisation from ethyl acetate gave *title compound* **39** as white needle crystals (88%), mp 200–201 °C (Found: C, 63.35; H, 6.8; N, 20.6. $C_{18}H_{23}N_5O_2$ requires C, 63.3; H, 6.8; N, 20.5%); ν_{max}(KBr)/cm^{-1} 3231 (C≡CH), 2971 (Bu′), 1709, 1693 (C=O), 1582, 798; δ_H($CDCl_3$) 1.43 (9H, s, Bu′), 2.27 (2H, t, *J* 2.4, CH), 3.47 (4H, t, *J* 8.1, Im CH_2), 3.55 (4H, t, *J* 8.1, Im CH_2), 3.90 (4H, t, *J* 8.1, Im CH_2), 4.04 (4H, d, *J* 2.4, CH_2), 7.58 (1H, t, *J* 8.1, Py-H), 7.84 (2H, d, *J* 8.1, Py-H).

Coupling reaction of Bu′-IPI-Pg 39, to give 40

Bu′-IPI-Pg (0.80 g, 2.34 mmol) and copper(II) acetate monohydrate (4.0 g, 20 mmol) were added to 25:5 (v/v) dichloromethane–pyridine (30 cm^3) solution. The mixture was heated at reflux overnight, cooled and dichloromethane (100 cm^3) added, and the solution was washed with aqueous ammonium hydroxide solution (3 × 30 cm^3, *d* 0.880) and then with distilled water (3 × 30 cm^3). The organic layer was dried with sodium sulfate and filtered to obtain a cloudy solution. The solvent was removed and the *dimer* **40** was obtained as a brown solid which was insoluble in common solvents (0.69 g, 87%), mp 240–243 °C; ν_{max}(KBr)/cm^{-1} 2969 (Bu′), 1710, 1693 (C=O), 1581, 802 (Py); δ_H(TFA) 2.00 (18H, s, Bu′), 4.37–4.67 (16H, m, Im CH_2), 4.81 (4H, s, C≡CCH_2), 7.15 (1H, d, *J* 8.4, Py-H), 7.16 (2H, d, *J* 8.4, Py-H), 8.70 (2H, t, *J* 8.4, Py-H); MS (EI$^+$) Found: M, 680.3547. $C_{36}H_{44}N_{10}O_4$ requires *M*, 680.3547.

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