Doubly dearomatising intramolecular coupling of a nucleophilic and an electrophilic heterocycle†

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Isonicotinamides carrying *N*-furanylmethyl, *N*-pyrrolylalkyl or *N*-thiophenylmethyl substituents at nitrogen undergo cyclisation induced by an electrophile, giving spirocyclic compounds or doubly spirocyclic compounds in which both the nucleophilic and electrophilic heterocycles are dearomatised.

Spirocyclic piperidines are present in many biologically active compounds[1] (including the alkaloids histrionicotoxin, nakadomarin and cephalotaxine) and have been identified as "privileged scaffolds" with respect to binding at G-protein coupled receptors.[2] Compounds containing more than one adjacent spirocyclic centre are challenging to make,[3] though bis-spirocyclic heterocycles feature in the *Delphinium* and *Aconitum* alkaloids[4] and other biologically active compounds.[5]

In this paper we report a conceptually simple approach to spirocycles in which a pair of tethered aromatic heterocycles—one nucleophilic and one electrophilic—undergo a dearomatising intramolecular coupling. The reaction allows the synthesis of spirocyclic and doubly spirocyclic molecules by a remarkable cascade of electrophilicity, governed by basicity, effective concentration and steric hindrance.

Both electron-deficient and electron-rich heterocycles may be dearomatised with an appropriate electrophile–nucleophile pair (Fig. 1). Pyridines, once acylated or alkylated at N to yield pyridinium species, are electrophilic towards a variety of anionic and neutral nucleophiles,[6] including electron-rich heterocycles (Fig. 1a).[7] Likewise, bromination or nitration of furan[8] in the presence of a nucleophile may yield dihydrofuran derivatives (Fig. 1b). We envisaged a tandem reaction in which an activated pyridinium species would itself activate an electron-rich heterocycle, potentially dearomatising both in one reaction. In the face of challenging questions of regio- and chemoselectivity, we decided to tether the nucleophilic heterocycle to the pyridine, aiming to generate spirocyclic or even doubly spirocyclic heterocycles (Fig. 1c).[9]

Using standard methods for amide formation we made a series of isonicotinamides **1**, **3**, **5** *etc*. carrying electron-rich heterocyclic substituents (pyrroles, furans and thiophenes) (Scheme 1). These were treated with trifluoromethanesulfonic anhydride in order to activate the pyridine ring by N-sulfonylation:[10] electrophilic attack on the 2-position of **1**, **3** and **5** by

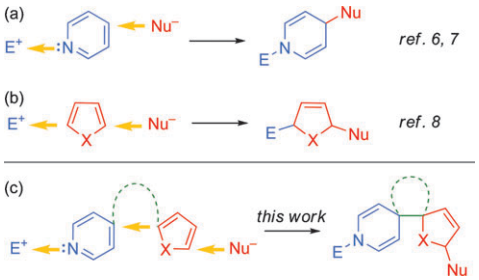
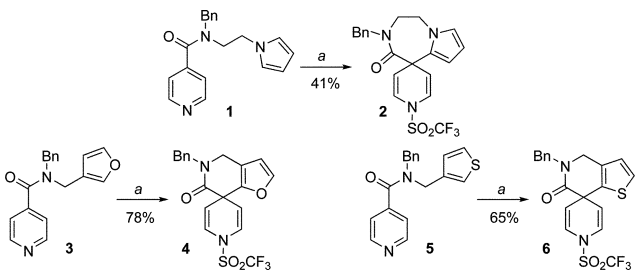


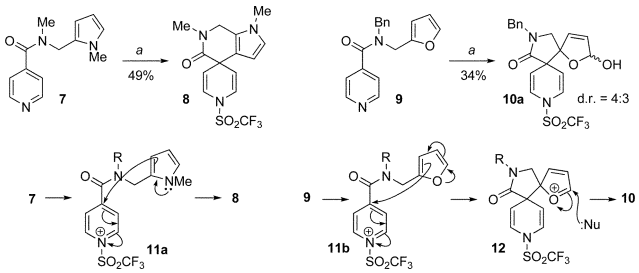
Fig. 1 Dearomatising additions to (a) electron-deficient and (b) electron-rich aromatic heterocycles; (c) tandem double dearomatisation.



Scheme 1 Spirocyclisations of 1- and 3-substituted pyrroles, furans and thiophenes. *a* $(CF_3SO_2)_2O$ (1.0 equiv.), 2,6-lutidine (1.2 equiv.), CH_2Cl_2, 0–20 °C, 30 min.

the resulting pyridinium species gave spirocyclic pyrrole **2**, furan **4** and thiophene **6** in moderate to good yield.

Pyrrole **7** and furan **9** tethered *via* their 2-positions behaved differently. Intermediate **11a** derived from pyrrole **7** cyclised onto its 3-position (either by direct attack as shown, or by rearrangement of an initial spirocyclic intermediate generated by attack at the 2-position) to yield spirocyclic ring-fused pyrrole **8** (Scheme 2). The oxonium ion **12** derived from the furylpyridinium **11b**, on the other hand, was trapped by nucleophilic attack of water, so the product isolated from **9**



Scheme 2 Spirocyclisations of 2-substituted pyrroles and furans. *a* $(CF_3SO_2)_2O$ (1.0 equiv.), 2,6-lutidine (1.2 equiv.), CH_2Cl_2, 0–20 °C, 30 min.

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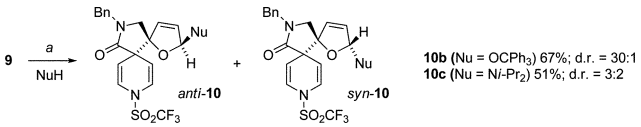


Scheme 3 Nucleophilic trapping of the doubly dearomatised intermediate. *a* $(CF_3SO_2)_2O$ (1.0 equiv.), 2,6-lutidine (1.2 equiv.), CH_2Cl_2, −20 °C, 1 min then NuH, −20 °C, 1 h.

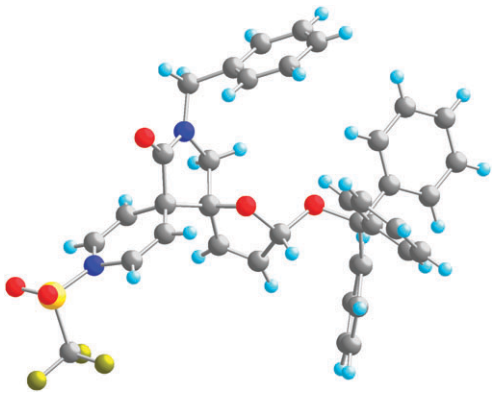
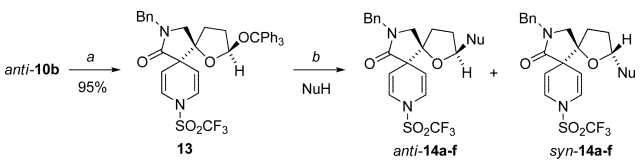


Fig. 2 X-Ray crystal structure of *anti*-**10b**.[11]

was the doubly dearomatised, doubly spirocyclic dihydropyridine-γ-lactam-dihydrofuran **10a**.

Initial yields of **10a** were low, probably due to the instability of the intermediate oxonium ion **12**. However, we found that adding a nucleophile to the reaction mixture allowed interception of the intermediate **12** to yield derivatives **10b** and **10c** (Scheme 3). For example, addition of triphenylmethanol to the reaction mixture immediately after the trifluoromethanesulfonic anhydride allowed formation of the doubly dearomatised acetal **10b** in good yield and with excellent (>30 : 1) diastereoselectivity. The stereochemistry of the major diastereoisomer of **10b**, in which the trityloxy group occupies the less



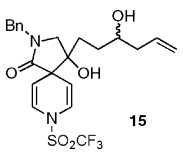
Scheme 4 Derivatives of the spirocycles. *a* H_2, 10% Pd/C, EtOAc, EtOH (continuous flow). *b* Lewis acid, NuH (see Table 1).

hindered face of the dihydrofuran, was established by X-ray crystallography (Fig. 2).[11]

The two adjacent spirocyclic centres arise from direct coupling between the 4-position of the pyridine and the 2-position of the furan, and **10b** represents a rare[12] doubly dearomatised structure arising from the coupling of two aromatic heterocycles. The chemoselectivity evident in the cascade of electrophilicity leading from **9** to **10b** is also noteworthy, with each of three nucleophiles (the pyridine *via* its nitrogen atom, the furan ring and the trityl alcohol) waiting its turn to react selectively with each of three electrophiles (the sulfonic anhydride, the pyridinium **11b** and the oxonium ion **12b**).

Diisopropylamine was also successful as a nucleophilic trap, giving **10c**, but less hindered nucleophiles were less effective (for example, methanol and furan gave only 26% and 25% yield, respectively, of the trapped products) presumably because of competing attack on electrophilic species other than **12** within the reaction mixture.

Nonetheless, by chemoselectively reducing the dihydrofuran **10b** to the tetrahydrofuran **13** and re-subjecting this acetal to a mixture of Lewis acid and nucleophile,[13] it was possible to derivatise the doubly spirocyclic scaffold with a range of nucleophiles to yield **14a–f** (Scheme 4 and Table 1).



In this paper we have demonstrated that molecules containing tethered electron-deficient and electron-rich heteroaromatic rings may be activated towards intramolecular coupling by addition of a sufficiently mutually unreactive electrophile–nucleophile pair (for example, triflic anhydride and triphenylmethanol). In common with other bicyclic systems made by dearomatisation, many of which have been used in the synthesis of biologically important structures,[14] the products display rich functionality amenable to further elaboration. The doubly dearomatised products are bis-spirocyclic, and we envisage such reactions, especially if applied as part of a diversity orientated synthetic strategy,[15] as being of value for the generation of new spirocyclic scaffolds for the discovery of biologically active molecules.

Table 1 Nucleophilic substitution of the trityl group

Entry	Nu =	Conditions	Product	Yield (%)	Ratio *anti*-**14** : *syn*-**14**
1	OH	CF_3CO_2H, Et_3SiH	**14a**	100	2 : 1[a]
		or Et_3AlCl	**14a**	87	2 : 1[a]
2	Allyl	$AllylSiMe_3$, $InCl_3$, Me_3SiBr	**14b**	85	5 : 4[a]
3	H	Et_3SiH, $InCl_3$, Me_3SiBr	**14c**	98	—
4	$CH_2C(=O)Ph$	$PhC(OSiMe_3)=CH_2$, $InCl_3$, Me_3SiBr	**14d**	51	4 : 3[b]
5	OCHO	HCO_2H	**14e**	55	2 : 1[a]
6	OAc	Ac_2O, py (on **14a**)	**14f**	88	5 : 4[b]
7	—	$AllylSnBu_3$, Et_2AlCl	**15**	81	1 : 1[a]

[a] Inseparable mixture of diastereoisomers. [b] Separable mixture of diastereoisomers.

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