Substituted 3,4-pyridynes: clean cycloadditions

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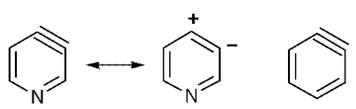
The stabilisation of 3,4-pyridyne (**1**) by an alkoxy group adjacent to the ring nitrogen is reported. The regioselective lithiation of 2-ethoxy- (**14**), 2-methoxy- (**18**), 2-isopropoxy- (**19**) and 6-isopropoxy- (**26**) -3-chloropyridines with *tert*-butyllithium at low temperatures, followed by elimination of lithium chloride affords 2- and 6-alkoxy-3,4-pyridynes. These species are trapped *in situ* with furan in a Diels–Alder reaction to give **5**–**8** in 66–89% yield, and do not give products typical of polymerisation or nucleophilic addition to the 3,4-pyridyne intermediates. As a comparison treatment of 3-chloropyridine with furan and LDA gives only 19% of adduct (**4**). We also report the novel use of the isopropoxy (rather than methoxy) group in these systems, which can act as a heteroatomic electron donating group which inhibits α-lithiation by *tert*-butyllithium because of its increased steric bulk.

Introduction

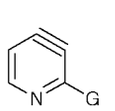
Pyridynes (didehydropyridines)[1] are reactive intermediates formally derived by the removal of two adjacent hydrogens from a pyridine ring. Of the two possible regioisomers, 3,4-pyridyne (**1**) has received the most synthetic attention.[2a–d] Many



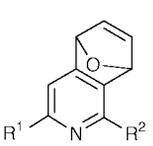
1 **1a** **2**

methods of preparing this species in solution have emerged, including dehydrohalogenation of 3- and 4-halopyridines, dehalogenation of 3,4-dihalopyridines, lead tetraacetate oxidation of 1-aminotriazolo[4.5]pyridine, loss of CO_2 and N_2 from pyridine-3-diazonium carboxylate, and fluoride induced desilylation of trialkylsilylpyridyl triflates.[3–5] 3,4-Pyridyne can be trapped in a Diels–Alder reaction with reactive dienophiles (for example, furans). However compared to its carbocyclic analogue, benzyne (**2**), generated by similar methods, the yields of trapped product remain low,[1] limiting their use as synthetic intermediates. This indicates that the relative instability of **1** compared to **2** is related to the nature of the pyridyne bond rather than how it is generated.

One possibility is that the pyridine ring nitrogen partially polarises the strained aryne bond. If 3,4-pyridyne has some dipole character (**1a**), then attack by nucleophiles may compete effectively with cyclisation. We postulated that if this effect was responsible for the lower yields of cyclised products associated with pyridynes, it could be circumvented by generation of a 3,4-pyridyne with an electron donating substituent '*ortho*' to the ring nitrogen (**3**). We chose to investigate the furan trapping of such species, generated by dehydrohalogenation of appropriate precursors with butyllithium, and used as a comparison the trapping of unsubstituted 3,4-pyridyne (**1**) generated using LDA.



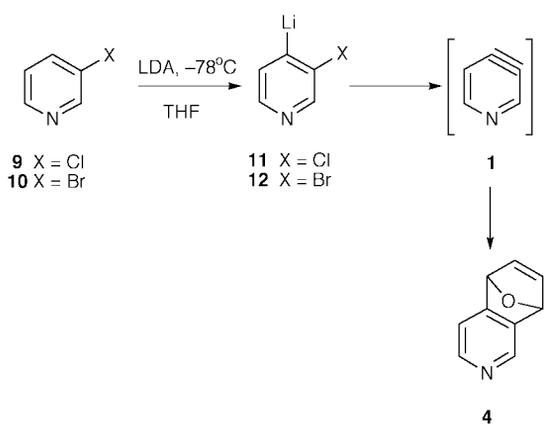
3
G = OR, NR_2



4 R^1 = H, R^2 = H
5 R^1 = H, R^2 = OMe
6 R^1 = H, R^2 = OEt
7 R^1 = H, R^2 = O^{i}Pr
8 R^1 = O^{i}Pr, R^2 = H

Results and discussion

Treatment of 3-chloropyridine (**9**) and 3-bromopyridine (**10**) with LDA at −78 °C results in regioselective lithiation at the C-4 position to give the corresponding 3-halo-4-lithiopyridines (**11**, **12**).[6] Furan is then added and the temperature allowed to rise slowly to ambient, during which time elimination of lithium halide occurs resulting in **1**, which is intercepted in a Diels–Alder reaction (Scheme 1) to give the required 5,8-epoxy-5,8-dihydroisoquinoline (**4**).



9 X = Cl
10 X = Br
11 X = Cl
12 X = Br
1
4

Scheme 1

The dependence of this process on the reaction temperature, amounts of furan and base present and the order of addition (base to substrate/substrate to base) was determined. From the results of these experiments it emerged that **9** was a more robust pyridyne precursor than **10**, which is expected since α-lithiobromopyridines have a higher propensity for ring opening and competing "Base Catalysed Halogen Dance" (BCHD) reactions, making **11** more stable than **12** at −78 °C.[3,6,7]

Optimum conditions for pyridyne generation using this method involved treating **9** with 1.1 and 10 equivalents of LDA and furan, respectively. The order of addition of the base proved to be unimportant. Under these conditions, **4** was isolated in 19% yield. The other products in the crude reaction

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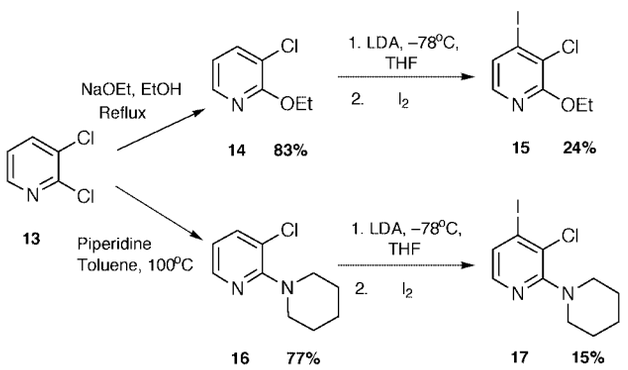
mixture arose from addition of diisopropylamine to the aryne (*ca*. 20%) and polymeric products (*ca*. 60%) derived from addition of **11** to **1**.

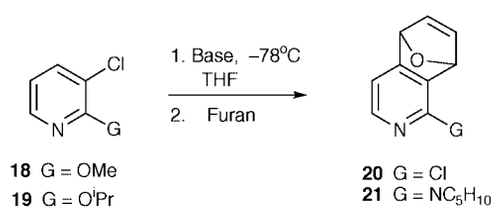
In seeking to avoid these two wasteful processes, the deprotonation route to the lithiated precursor was initially abandoned in favour of a halogen–metal exchange methodology at C-4 using the excellent protocol of Gribble and Saulnier,[6] who obtained no base derived products when **1** was generated from 3-chloro-4-iodopyridine and ^{t}BuLi, although the yield of furan trapped product remained modest (<40%). To counter the dipolar nature of these unsubstituted 3,4-pyridynes and thus discourage polymerisation, an electron donating substituent was introduced at C-2. 2-Ethoxy-3-chloro-4-iodopyridine (**15**) and 2-piperidino-3-chloro-4-iodopyridine (**17**) were prepared from 2,3-dichloropyridine (**13**) by the routes outlined in Scheme 2.



Scheme 2

Lithiation of these precursors with ^{t}BuLi and subsequent trapping with furan gave the desired adducts (**6**, **21**) in 63 and 74% yields respectively, with no polymeric products detected in the crude mixture.

Although this was a pleasing result, these precursors proved difficult to prepare in good yield owing to the inefficiency of the iodination reaction. In order to overcome this difficulty a more practical 2-substituted pyridyne precursor was required. With this in mind it was decided to generate pyridynes from 3-chloropyridines with various electron donating substituents at the 2 position using *n*- or *tert*-butyllithium as the lithiating reagent with 10 equivalents of furan trap (Scheme 3).



Scheme 3

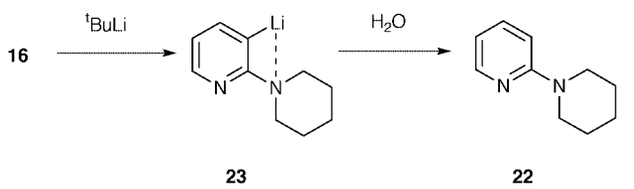
The 2-alkoxypyridines all gave good yields of trapped product with in each case a complete absence of polymer; the only other product detected was starting material (Table 1). In contrast 2,3-dichloropyridine (**13**) gave only polymer, irrespective of the base used. The failure of **16** to generate the corresponding aryne with ^{t}BuLi was surprising; instead 2-piperidinopyridine (**22**) was formed in quantitative yield. A sample of **22** was also obtained independently by treating 2-chloropyridine with piperidine in refluxing toluene overnight. This arises presumably from halogen–metal exchange at C-3 (Scheme 4).

Examples of halogen–metal exchange reactions involving chlorine with butyllithium in pyridine systems are rare, and then usually at C-4 in poly-chloro substrates.[8,9] It is possible

Table 1 Yields of adduct formed from 2-substituted 3,4-pyridynes

Precursor	Base	Adduct	Yield (%)[a]
13	^{n}BuLi	**20**	0
14	^{n}BuLi	**6**	29
16	^{n}BuLi	**21**	36
13	^{t}BuLi	**20**	0
14	^{t}BuLi	**6**	71
16	^{t}BuLi	**21**	0
18	^{t}BuLi	**5**	74
19	^{t}BuLi	**7**	66

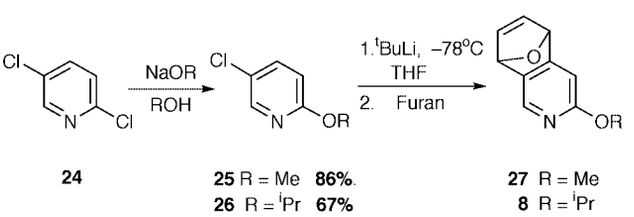
[a] Refers to isolated yields after chromatography.



Scheme 4

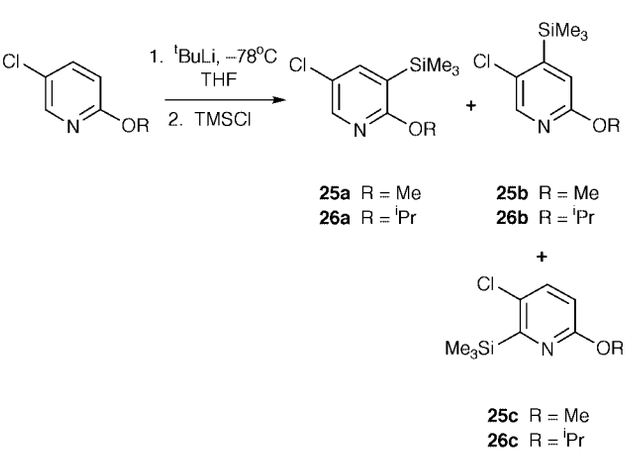
that stabilisation of the 3-anion by coordination of nitrogen to the lithium counterion (**23**) is responsible for this effect.

The small decrease in trapped product yield which was observed with increasing steric bulk at C-2 encouraged us to generate a 6-substituted 3,4-pyridyne. In this case the substituent is not in close proximity to the aryne bond but still adjacent to the ring nitrogen. With this in mind we prepared **25** and **26** from 2,5-dichloropyridine (**24**) and the appropriate alkoxides (Scheme 5).



Scheme 5

When **25** was treated with ^{t}BuLi and furan as before, the usual colourless to yellow colour change associated with lithiation was observed but only starting material was isolated on workup. Using similar reaction conditions, **26** gave only 43% yield of trapped material (**8**). The regioselectivity of lithiation in these compounds therefore seemed to be in question. In order to test this, **25** and **26** were treated with ^{t}BuLi, holding the anion at −78 °C for various times (*t*) followed by quenching with 4.0 equivalents of trimethylsilyl chloride (TMSCl) as shown in Scheme 6. ^{1}H NMR analysis of the crude reaction mixtures after workup gave the results summarised in Table 2.



Scheme 6

Table 2 Lithiation of 2-alkoxy-5-chloropyridines

Compound	*t*/min	**25a**, **26a** (%)	**25b**, **26b** (%)	**25c**, **26c** (%)
25	10	82	10	8
25	20	96	4	0
25	60	100	0	0
26	10	0	56	44
26	20	0	68	32
26	60	0	100	0

It is clear that in the case of **25**, that the strong directing ability of the methoxy group towards '*ortho*' lithiation[7] governs the regioselectivity. Deprotonation at position C-3 is predominant initially and then becomes total to form **25a**, even if one might expect the proton at C-4 to be more acidic than its counterpart at C-3.[10] In the isopropyl analogue **26**, however, the bulky isopropoxy group prevents α lithiation by the large ^{t}BuLi molecule. Here the kinetic **26c** and thermodynamic **26b** products are present in almost equal amounts if the reaction is quenched after 10 min, indicating initial lithiation at C-6 and C-4. This converts over time to the more stable C-4 anion, giving only **26b** after quenching. With this isopropoxypyridine (**26**), no deprotonation at C-3 is observed. With a method of generating a 6-substituted 3,4-pyridyne now in hand, **26** was lithiated and trapped with furan to give adduct **8** as the sole product in 89% yield.

In summary, 2-alkoxy (**14, 18, 19**) and 6-isopropoxypyridines (**26**), have been shown to serve as excellent precursors for substituted 3,4-pyridynes under direct lithiation conditions at low temperatures. The high sensitivity of **1** to substituents at both C-2 and C-6 appears to support the proposal of aryne 'triple' bond polarisation by the ring nitrogen, as none of the ubiquitous polymeric material was formed in cases where the precursor contained an electron donating group at these positions. Since the only other product detected in the cases reported here was starting material, this also shows that the 3,4-pyridynes derived from these species are resistant to nucleophilic attack by their lithiated precursors. The ease of preparation of these compounds by direct lithiation, in addition to superior yields of cycloadduct with furan, may make them of more synthetic value than present literature methods.

Experimental

General

^{1}H NMR spectra were recorded at 270 MHz on a JEOL JMN-GX270 FT spectrometer using tetramethylsilane as a reference. Chemical shifts quoted in ppm and coupling constants in Hz. ^{13}C decoupled spectra were recorded at 67.8 MHz on this instrument. A VG analytical 7070 mass spectrometer, with attached INCOS 2400 data system, in the EI mode, was used for recording mass spectra. Thin layer chromatography (TLC) was performed on Merck precoated Kieselgel 60F_{254} slides, and Merck silica 9385, particle size 0.04–0.063 mm, was used for flash chromatography. Reaction solvents were dried according to standard literature procedures.[11] Microanalyses were carried out by the Microanalytical Laboratory, University College Dublin.

Note: unless otherwise specified 'work-up' refers to concentration of the reaction mixture *in vacuo*, taking up the residue in chloroform, washing with 10% $NaHCO_3$, water, and brine followed by drying (Na_2SO_4) of the organic layer and removal of the solvent *in vacuo*.

Precursors: 2-ethoxy-3-chloropyridine (14)

Procedure A. In a 100 cm^3 round-bottomed flask fitted with a stirring bar at 0 °C, sodium metal (*ca*. 0.5 g) was added to dry ethanol (20 cm^3) and the resulting suspension was stirred for 30 min, or until the sodium had disappeared and hydrogen liberation ceased. 2,3-Dichloropyridine (0.88 g, 5.95 mmol) was added and the resulting mixture refluxed overnight. The reaction vessel was allowed to cool to room temperature and quenched with saturated aqueous NH_4Cl (10 cm^3) and extracted with $CHCl_3$ (4 × 25 cm^3). The organic extracts were combined, dried (Na_2SO_4), and the solvent removed *in vacuo* to give a yellow liquid (0.92 g). Purification by flash chromatography (90 : 10 light petroleum–EtOAc, R_f 0.55) gave 2-ethoxy-3-chloropyridine[12] (782 mg, 83%) as a colourless liquid (Found: C, 53.2; H, 5.0; Cl, 22.6; N, 8.7. C_7H_8ClNO requires: C, 53.35; H, 5.1; Cl, 22.5; N, 8.9%); δ_H ($CDCl_3$) 1.44 (t, 3H, J = 7.2), 4.43 (q, 2H, J = 7.2), 6.81 (dd, 1H J_1 = 7.7, J_2 = 5.0), 7.61 (dd, 1H, J_1 = 7.7, J_2 = 1.7), 8.04 (dd, 1H, J_1 = 5.0, J_2 = 1.7); δ_C ($CDCl_3$) 14.1, 61.4, 116.9, 116.9, 138.1, 144.6, 159.0; *m*/*z* 157 (M^+), 142, 129, 113, 94, 78.

2-Ethoxy-3-chloro-4-iodopyridine (15)

Procedure B. An oven dried, 25 cm^3 three-neck round-bottomed flask fitted with an internal thermometer, addition funnel, nitrogen adapter, rubber septum and magnetic stirring bar was charged with dry THF (5 cm^3) and dry diisopropylamine (0.49 cm^3, 3.49 mmol) at −78 °C under N_2 with stirring. To this was added *n*-butyllithium (1.7 cm^3 of 2.5 M solution in hexane; 4.19 mmol) *via* a syringe. This was stirred at −78 °C for 20 min, and then over 15 min 2-ethoxy-3-chloropyridine (0.55 g, 3.49 mmol) in THF (2 cm^3) was added, keeping the internal temperature at −78 °C to give a bright yellow solution. This mixture was stirred for 20 min at −78 °C and a solution of iodine (1.06 g, 4.19 mmol) in THF (6 cm^3) was added *via* syringe. The mixture was allowed to warm to room temperature overnight and poured into 8% aqueous (10 cm^3) sodium bisulfite and extracted with Et_2O (3 × 15 cm^3). The combined organic extracts were washed with 10% $NaHCO_3$ (20 cm^3), water (20 cm^3) and brine (50 cm^3), dried (Na_2CO_3), and concentrated *in vacuo* to give crude material (0.62 g) consisting of mostly **14** and **15**. These were carefully separated by flash chromatography (90 : 10 light petroleum–EtOAc, R_f 0.64) to give 2-ethoxy-3-chloro-4-iodopyridine (0.24 g, 24%) as a colourless oil (Found: C, 29.5; H, 2.6; N, 5.2. C_7H_7ClINO requires: C, 29.7; H, 2.5; N, 4.9%); δ_H ($CDCl_3$) 1.44 (t, 3H, J = 7.2), 4.43 (q, 2H, J = 7.2), 7.23 (d, 1H, J = 5.3), 7.56 (d, 1H, J = 5.3); δ_C ($CDCl_3$) 14.2, 63.5, 110.8, 123.4, 127.5, 144.3, 158.9; *m*/*z* 283 (M^+), 268, 255, 239.

2-Piperidino-3-chloropyridine (16)

In a 50 cm^3 round-bottomed flask 2,3-dichloropyridine (1.43 g, 9.66 mmol) was dissolved in dry toluene (10 cm^3), and distilled piperidine (3 cm^3, 30.38 mmol) was added. A condenser was fitted and the resulting solution was heated under reflux overnight. Work-up and purification by flash chromatography ($CHCl_3$, R_f 0.88) gave 2-piperidino-3-chloropyridine (1.46 g, 77%) as a colourless liquid (Found: C, 61.25; H, 6.7; Cl, 17.8; N, 14.45. $C_{10}H_{13}ClN_2$ requires: C, 61.1; H, 6.7; Cl, 18.0; N, 14.2%); δ_H 1.59 (m, 6H), 3.14 (m, 4H), 6.63 (dd, 1H, J_1 = 7.7, J_2 = 4.8), 7.42 (dd, 1H, J_1 = 7.7, J_2 = 1.7), 8.04 (dd, 1H, J_1 = 4.8, J_2 = 1.7); *m*/*z* 196 (M^+), 161, 113, 84.

2-Piperidino-3-chloro-4-iodopyridine (17)

Procedure B was followed using dry THF (5 cm^3), diisopropylamine (0.28 cm^3, 2.05 mmol), *n*-butyllithium (1.28 cm^3 of 1.6 M solution in hexane, 2.05 mmol), 2-piperidino-3-chloropyridine (402 mg, 2.05 mmol). Work-up gave crude material (451 mg) consisting of mostly **16** and **17**. These were carefully separated by flash chromatography (90 : 10 light petroleum–EtOAc, R_f 0.75) to give 2-piperidino-3-chloro-4-iodopyridine (101 mg, 15%) as a viscous colourless liquid (Found: C, 37.2; H,

3.6; N, 8.8. $C_{10}H_{12}ClIN_2$ requires: C, 37.2; H, 3.75; N, 8.7%); δ_H ($CDCl_3$) 1.63 (m, 6H), 3.24 (m, 4H), 7.32 (d, 1H, J = 5.1), 7.74 (d, 1H, J = 5.1); δ_C ($CDCl_3$) 25.4, 25.8, 25.9, 50.7, 51.0, 111.9, 127.3, 128.0, 145.3, 159.8; *m*/*z* 322 (M^+), 287, 239, 159.

2-Methoxy-3-chloropyridine (18)

Procedure A was followed using 2,3-dichloropyridine (0.71 g, 4.8 mmol) and dry methanol (20 cm^3). Purification by flash chromatography (90 : 10 light petroleum–EtOAc, R_f 0.59) gave 2-methoxy-3-chloropyridine[13] (572 mg, 83%) as a colourless liquid (Found: C, 50.1; H, 4.15; Cl, 24.95; N, 10.0. C_6H_6ClNO requires: C, 50.2; H, 4.2; Cl, 24.7; N, 9.8%); δ_H ($CDCl_3$) 3.94 (s, 3H), 6.76 (dd, 1H, J_1 = 7.7, J_2 = 4.9), 7.61 (dd, 1H, J_1 = 7.7, J_2 = 1.7), 8.04 (dd, 1H, J_1 = 4.9, J_2 = 1.7); *m*/*z* 143 (M^+), 129, 113, 101, 78.

2-Isopropoxy-3-chloropyridine (19)

Procedure A was followed using 2,3-dichloropyridine (0.65 g, 4.39 mmol) and dry propan-2-ol (20 cm^3). To generate the alkoxide, heating to 50 °C was required. Purification by flash chromatography (90 : 10 light petroleum–EtOAc, R_f 0.48) gave 2-isopropoxy-3-chloropyridine (535 mg, 71%) as a colourless oil (Found: C, 56.4; H, 5.9; Cl, 20.5; N, 8.0. $C_8H_{10}ClNO$ requires: C, 56.0; H, 5.9; Cl, 20.7; N, 8.2%); δ_H ($CDCl_3$) 1.38 (d, 6H, J = 6.2), 5.35 (septet, 1H, J = 6.2), 6.77 (dd, 1H, J_1 = 7.7, J_2 = 5.0), 7.60 (dd, 1H, J_1 = 7.7, J_2 = 1.6), 8.02 (dd, 1H, J_1 = 5.0, J_2 = 1.6); *m*/*z* 171 (M^+), 129, 101, 94, 78.

5-Chloro-2-methoxypyridine (25)

Procedure A was followed using 2,5-dichloropyridine (1.22 g, 8.24 mmol) and dry methanol (20 cm^3). Purification by flash chromatography (90 : 10 light petroleum–EtOAc, R_f 0.6) gave 5-chloro-2-methoxypyridine[13] (1.02 g, 86%) as a colourless liquid (Found: C, 50.3; H, 4.35; Cl, 24.55; N, 9.9. C_6H_6ClNO requires: C, 50.1; H, 4.1; Cl, 24.7; N, 9.8%); δ_H ($CDCl_3$) 3.88 (s, 3H), 6.67 (dd, 1H, J_1 = 8.8, J_2 = 0.7), 7.46 (dd, 1H, J_1 = 8.8, J_2 = 2.6), 8.07 (dd, 1H, J_1 = 2.6, J_2 = 0.7); *m*/*z* 143 (M^+), 129, 113, 101, 78.

5-Chloro-2-isopropoxypyridine (26)

Procedure A was followed using 2,5-dichloropyridine (0.98 g, 6.62 mmol) and dry propan-2-ol (20 cm^3). To generate the alkoxide, heating to 50 °C was required. Purification by flash chromatography (90 : 10 light petroleum–EtOAc, R_f 0.46) gave 5-chloro-2-isopropoxypyridine (761 mg, 67%) as a colourless oil (Found: C, 55.8; H, 5.75; Cl, 20.9; N, 8.4. $C_8H_{10}ClNO$ requires: C, 56.0; H, 5.9; Cl, 20.7; N, 8.2%); δ_H ($CDCl_3$) 1.33 (d, 6H, J = 6.2), 5.23 (septet, 1H, J = 6.2), 6.62 (dd, 1H, J_1 = 8.9, J_2 = 0.7), 7.48 (dd, 1H, J_1 = 8.9, J_2 = 2.8), 8.06 (dd, 1H, J_1 = 2.8, J_2 = 0.7); *m*/*z* 171 (M^+), 129, 101, 94, 78.

Trapped products: 5,8-epoxy-5,8-dihydroisoquinoline (4)

Note: as these compounds slowly aromatise over time, immediate analysis is advised.

An oven dried, 100 cm^3 three-neck round-bottomed flask fitted with an internal thermometer, addition funnel, nitrogen adapter, rubber septum and magnetic stirring bar was charged with dry THF (20 cm^3) and dry diisopropylamine (3.7 cm^3, 26.4 mmol) at −78 °C under N_2 with stirring. To this was added *n*-butyllithium (16.5 cm^3 of 1.6 M solution in hexane, 30 mmol) dropwise, *via* syringe. This was stirred at −78 °C for 20 min and then to this solution of LDA was added over 15 min 3-chloropyridine (2.51 cm^3, 26.4 mmol) in THF (5 cm^3), keeping the internal temperature at −78 °C. The resulting 3-chloro-4-lithiopyridine partially precipitated as a white solid in a yellow solution. This mixture was stirred for 20 min at −78 °C and freshly distilled furan (19.2 cm^3, 264 mmol) was added *via* a syringe. The mixture was allowed to warm to room temperature overnight. The insoluble polymeric material was removed by filtration and washed well with ether. The washings were combined and after work-up the crude product (3.74 g) was purified by flash chromatography (EtOAc, R_f 0.22) to give 5,8-epoxy-5,8-dihydroisoquinoline (0.743 g, 19%) as a light amber oil (Found: C, 74.2; H, 4.8; N, 9.5. C_9H_7NO requires: C, 74.5; H, 4.9; N, 9.65%); δ_H ($CDCl_3$) 5.72 (s, 1H), 5.82 (s, 1H), 6.97 (dd, 1H, J_1 = 5.5, J_2 = 1.8), 7.04 (dd, 1H, J_1 = 5.5, J_2 = 1.8), 7.23 (d, 1H, J = 4.6), 8.28 (d, 1H, 4.6), 8.44 (s, 1H).

1-Methoxy-5,8-epoxy-5,8-dihydroisoquinoline (5)

Procedure C. An oven dried 25 cm^3 round-bottomed flask under N_2 fitted with a stirring bar and a septum was charged with a solution of 2-methoxy-3-chloropyridine (327 mg, 2.28 mmol) in dry THF (5 cm^3) under N_2 and cooled to −78 °C. After 20 min at −78 °C, *tert*-butyllithium (1.5 cm^3 of a 1.7 M solution in hexane, 2.51 mmol) was added slowly with stirring to give a cloudy bright yellow solution. After 60 min at −78 °C, freshly distilled furan (1.66 cm^3, 22.8 mmol) was added and the mixture allowed to warm to room temperature overnight. After work-up the crude product was purified by flash chromatography ($CHCl_3$, R_f 0.26) to give 1-methoxy-5,8-epoxy-5,8-dihydroisoquinoline (294 mg, 74%) as a light amber oil (Found: C, 68.85; H, 5.3; N, 7.8. $C_{10}H_9NO_2$ requires: C, 68.6; H, 5.2; N, 8.0%); δ_H ($CDCl_3$) 3.95 (s, 3H), 5.72 (s, 1H), 5.9 (s, 1H), 6.95 (d, 1H, J = 4.8), 7.02 (dd, 1H, J_1 = 5.1, J_2 = 2.0), 7.10 (dd, 1H, J_1 = 5.1, J_2 = 2.0), 7.92 (d, 1H, J = 4.8); δ_C ($CDCl_3$) 53.4, 79.7, 82.3, 111.1, 130.0, 142.3, 143.8, 145.4, 157.1, 163.4; *m*/*z* 175 (M^+), 146, 133, 117.

1-Ethoxy-5,8-epoxy-5,8-dihydroisoquinoline (6)

Procedure C was followed using 2-ethoxy-3-chloropyridine (403 mg, 2.56 mmol), *tert*-butyllithium (1.65 cm^3 of a 1.7 M solution in hexane, 2.81 mmol), furan (1.86 cm^3, 25.6 mmol) and THF (5 cm^3). Work-up and flash chromatography ($CHCl_3$, R_f 0.2) gave 1-ethoxy-5,8-epoxy-5,8-dihydroisoquinoline (341 mg, 71%) as an amber oil (Found: C, 70.0; H, 5.9; N, 7.1. $C_{11}H_{11}NO_2$ requires: C, 69.8; H, 5.9; N, 7.4%); δ_H ($CDCl_3$) 1.37 (t, 3H, J = 7.1), 4.40 (q, 2H, J = 7.1), 5.69 (s, 1H), 5.89 (s, 1H), 6.91 (d, 1H, J = 4.8), 6.97 (dd, 1H, J_1 = 5.5, J_2 = 2.1), 7.09 (dd, 1H, J_1 = 5.5, J_2 = 2.1), 7.88 (d, 1H, J = 4.8); δ_C ($CDCl_3$) 15.5, 62.5, 80.5, 83.2, 111.7, 130.7, 143.0, 144.6, 146.2, 157.8, 164.1; *m*/*z* 189 (M^+), 146, 133, 117.

1-Isopropoxy-5,8-epoxy-5,8 dihydroisoquinoline (7)

Procedure C was followed using 2-isopropoxy-3-chloropyridine (288 mg, 1.68 mmol), *tert*-butyllithium (1.1 cm^3 of a 1.7 M solution in hexane, 1.85 mmol), furan (1.22 cm^3, 16.8 mmol) and THF (5 cm^3). Work-up and flash chromatography ($CHCl_3$, R_f 0.2) gave 1-isopropoxy-5,8-epoxy-5,8-dihydroisoquinoline (226 mg, 66%) as an amber oil (Found: C, 71.0; H, 6.5; N, 7.1. $C_{12}H_{13}NO_2$ requires: C, 70.9; H, 6.45; N, 6.9%); δ_H ($CDCl_3$) 1.33 (d, 6H, J = 6.2), 5.30 (septet, 1H, J = 6.2), 5.67 (s, 1H), 5.87 (s, 1H), 6.89 (d, 1H, J = 4.8), 6.97 (dd, 1H, J_1 = 5.5, J_2 = 2.0), 7.11 (dd, 1H, J_1 = 5.5, J_2 = 2.0), 7.88 (d, 1H, J = 4.8); *m*/*z* 203 (M^+), 188, 146, 133, 117.

3-Isopropoxy-5,8-epoxy-5,8-dihydroisoquinoline (8)

Procedure C was followed using 2-isopropoxy-5-chloropyridine (479 mg, 2.79 mmol), *tert*-butyllithium (1.8 cm^3 of a 1.7 M solution in hexane, 3.07 mmol), furan (2 cm^3, 27.9 mmol) and THF (7 cm^3). Work-up and flash chromatography ($CHCl_3$, R_f 0.18) gave 3-isopropoxy-5,8-epoxy-5,8-dihydroisoquinoline (505 mg, 89%) as an amber oil (Found: C, 71.2; H, 6.3; N, 6.6. $C_{12}H_{13}NO_2$ requires: C, 70.9; H, 6.45; N, 6.9%); δ_H ($CDCl_3$) 1.31 (d, 6H, J = 6.2), 5.24 (septet, 1H, J = 6.2), 5.63 (s, 1H), 5.73 (s, 1H), 6.63 (s, 1H), 6.89 (dd, 1H, J_1 = 5.5, J_2 = 2.1), 7.13 (dd, 1H,

J_1 = 5.5, J_2 = 2.1), 7.85 (s, 1H); δ_C ($CDCl_3$) 22.0, 29.9, 68.2, 80.2, 81.5, 105.8, 111.5, 135.3, 139.4, 143.3, 161.1, 162.4; *m*/*z* 203 (M^+), 188, 146, 133, 117.

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