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The Synthesis of 1-Aminodihydroisoquinolines by an Imine Addition-Cyclisation Reaction.

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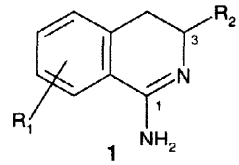
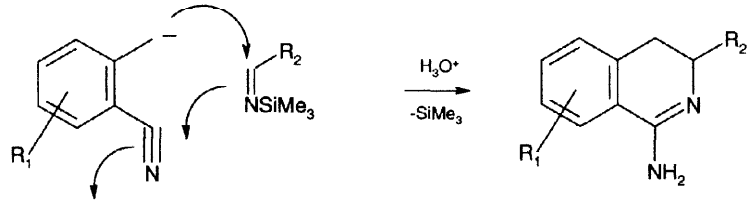
Abstract : A variety of 1-amino-3,4-dihydroisoquinolines substituted at the 3-position and related thienopyridines were prepared by lithiation of ortho-methyl aromatic nitriles, addition to N-trimethylsilylimines and spontaneous cyclisation.

Amidines are of great interest in medicinal chemistry because of their range of biological properties, e.g. in the areas of adrenergic[1] and fibrinogen receptor binding,[2] and thrombin inhibition.[3] Recently, simple cyclic amidines have been shown[4] to inhibit the isoforms of the nitric oxide synthase enzyme, which are important in blood pressure regulation, the immune response and in neurotransmission.[5] As part of a research programme in this area, we required a synthesis of some related 1-amino-3,4-dihydroisoquinolines **1** which would allow for easy substitution at the 3-position and in the benzo ring. However, there are no direct routes to this class of compound. The only reported preparations use elaboration of the corresponding lactam[6] or thiolactam,[7] in turn derived from electrophilic cyclisation onto a benzene ring at C1-C6.[8]



1

We proposed that the intermediate resulting from addition of a benzylic anion species to an imine might spontaneously cyclise onto the activating ortho nitrile group (Eq. 1). Indeed, there is an example in the literature in which a lithiated 3-cyano-4-methylpyridine is added to an N-silyliminium salt of a β-carboline (Eq. 2),[9] and aromatic 1-aminoisoquinolines have been prepared by addition of similar species to nitriles.[10,11,12] We chose to use an N-trimethylsilylimine, which is easily generated in situ[13] and which should be deprotected under the reaction conditions.



(Eq. 1)

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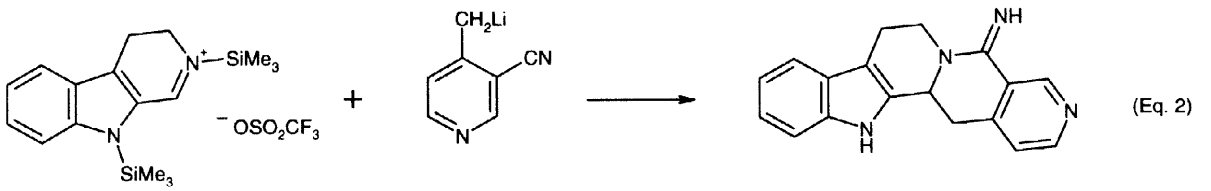
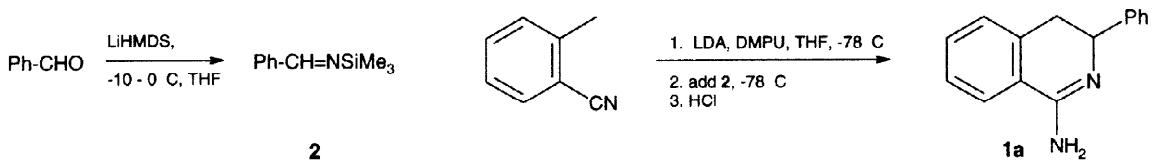


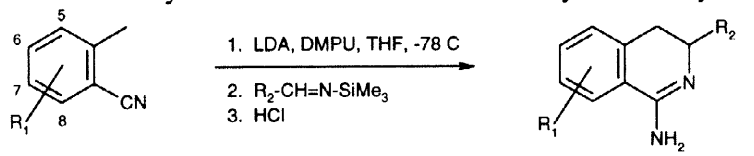
(Eq. 2)

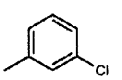
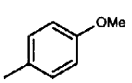
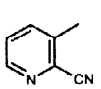
In practice, treatment of 2-methylbenzonitrile with one equivalent of n-butyllithium in THF at -78 °C in the presence of DMPU, followed by addition of the N-trimethylsilylimine **2** (generated by adding lithium bis(trimethylsilyl)amide to benzaldehyde in THF at 0 °C) to the resulting deep red anion led to rapid cyclisation. The desired amidine was obtained in 60% yield after acid work-up and chromatography.



2 **1a**

A number of substituted 2-methylbenzonitriles and aromatic aldehydes were cyclised in this way (Table 1).[14,15]

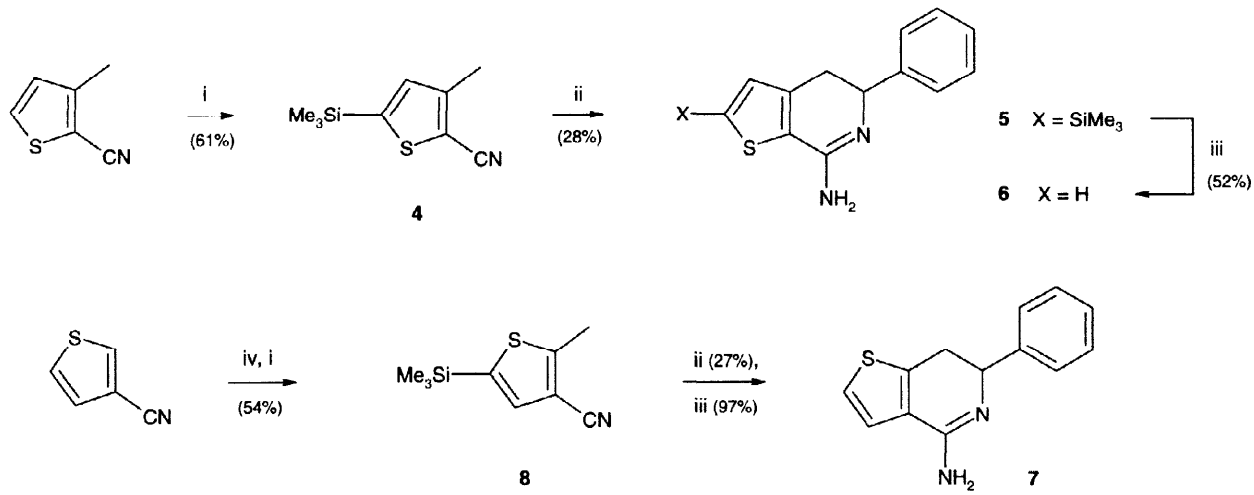


Entry	R_1	R_2	Yield / %[a,b]
1	H		60
2	H		63
3	H		11
4	H		45
5	6-Br		77
6	5-OMe		56
7	8-Cl		34
8	H		50
9	H	R_2 = 	62 (cyclopropyl)
		R_2 = 	56 (cyclobutyl)
		R_2 = 	0 (cyclopentyl)
10	nitrile used = 		56

[a] Yields refer to pure product isolated by flash chromatography on neutral alumina.
[b] All compounds isolated as hydrochloride salt

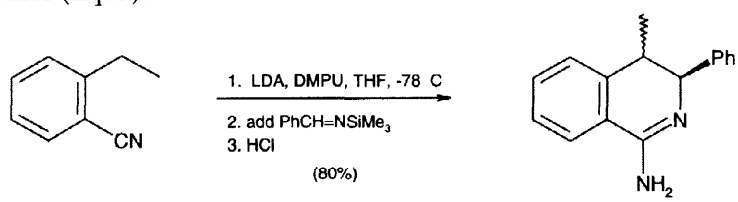
The presence of DMPU proved to be essential for reaction. Yields were generally lower with electron-rich aldehydes (Entries 3, 4, 7). Aliphatic aldehydes with no enolisable proton, such as trimethylsilylacetylene carboxaldehyde, worked well (Entry 8) but enolisable aldehydes failed to react, probably due to preferential formation of enamine rather than imine. Interestingly, imine generation and cyclisation using cyclopentylcarboxaldehyde failed but cyclopropyl and cyclobutylcarboxaldehydes cyclised successfully, presumably due to the strained nature of the enamine in the latter two cases which allows the imine to predominate (Entry 9). We were also able to access the 1,7-naphthyridine ring system by cyclising 2-cyano-3-methylpyridine (Entry 10).

The reaction could be extended further to the novel aminodihydrothienopyridines.[16] Thus, 2-cyano-3-methyl-5-trimethylsilylthiophene **4** and the imine of benzaldehyde smoothly cyclised to the 7-aminothienopyridine **5** under the same conditions, and subsequent treatment with tetrabutylammonium fluoride (TBAF) furnished the desired desilylated product **6** (Scheme 1). The 3,2 ring junction isomer **7** could be prepared in the same way from 3-cyano-2-methyl-5-trimethylsilylthiophene **8**, obtained from 3-cyanothiophene by sequential addition of LDA, methyl iodide, a second equivalent of LDA and trimethylsilylchloride.



Scheme 1. *Reagents and conditions*: **i,** LDA, THF, -78 C; TMSCl; **ii,** LDA, DMPU, THF, -78 C; add PhCH=NTMS; HCl aq.; **iii,** TBAF, THF; **iv,** LDA, THF, -78 C; MeI.

Finally, we investigated the possibility that some degree of diastereoselection would be observed on cyclisation of 2-ethylbenzonitrile with the imine of benzaldehyde. However, this resulted in a 1:1 mixture of the two diastereomers (Eq. 3).



(Eq. 3)

1:1 mixture of diastereomers

In conclusion, we have described an efficient one-pot addition-cyclisation reaction that furnishes a variety of novel cyclic amidines from simple starting materials. The interesting biological activities of these compounds will be reported in a forthcoming publication.

References and Notes

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14. The general procedure for the preparation of 1-amino-3,4-dihydroisoquinolines is illustrated by the preparation of 1-amino-3-phenyl-3,4-dihydroisoquinoline **1a** :
Lithium hexamethyldisilylazide (1.0 M in THF, 15 ml) was added dropwise to a stirred solution of benzaldehyde (15.0 mmol, 1.52 ml) in dry THF (30 ml) at -10 °C, and the imine solution allowed to warm to 0 °C over a period of 2 h. Meanwhile, n-butyllithium in hexanes (15.0 mmol, 1.45M, 10.4 ml) was added dropwise to a stirred solution of diisopropylamine (16.5 mmol, 2.33 ml) in dry THF (45 ml) at -5 - 0 °C and the solution stirred for 30 min. DMPU (22.6 mmol, 2.73 ml) was added, the mixture cooled to -78 °C and a solution of 2-methylbenzonitrile (15.0 mmol, 1.78 ml) in THF (5 ml) was added dropwise. The dark red anion was stirred for 30 min., and the freshly prepared imine solution added dropwise. After 40 min., the mixture was warmed to 0 °C over 30 min., quenched with aqueous hydrochloric acid, extracted three times with dichloromethane and the combined extracts dried over sodium sulphate and evaporated to afford a yellow oil. This was purified by flash chromatography on untreated neutral alumina, eluting with 5% methanol in dichloromethane, increasing the gradient to 10% methanol in dichloromethane to give the hydrochloride salt of compound **1a** as a white solid (2.33 g, 60%). Recrystallisation from dichloromethane/hexane afforded analytically pure compound, m.p. 204-206 °C; 360 MHz ^{1}H n.m.r. (d_6-DMSO) 10.42 (1H, br.s), 9.67 (1H, br.s), 9.16 (1H, br.s), 8.16 (1H, d, *J* 8.8 Hz), 7.69 (1H, t, *J* 7.0 Hz), 7.52 (1H, t, *J* 7.5 Hz), 7.46-7.31 (6H, m), 5.03 (1H, t, *J* 6.0 Hz), 3.40-3.25 (2H, m); MS (+EI) 222 (M+, 100%); (Found: C, 69.6; H, 5.9; N, 11.0; Cl, 13.4. $C_{15}H_{15}ClN_2$ requires C, 69.6; H, 5.8; N 10.8; Cl, 13.7%).
15. All compounds had satisfactory elemental and spectral analysis data.
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