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Diels–Alder cycloadditions of stabilised 2,3-pyridynes

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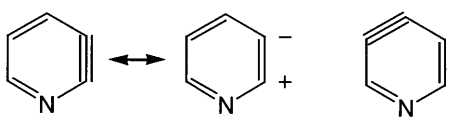
Abstract—Investigation of electron donating substituents at C-4 on 2,3-pyridyne **1** stability has revealed a novel stabilisation of these reactive species by aryloxy and thiophenoxy groups leading to a relatively high yielding [4+2] cycloaddition between 4-(*p*-methoxyphenoxy)-2,3-pyridyne and furan at low temperature.

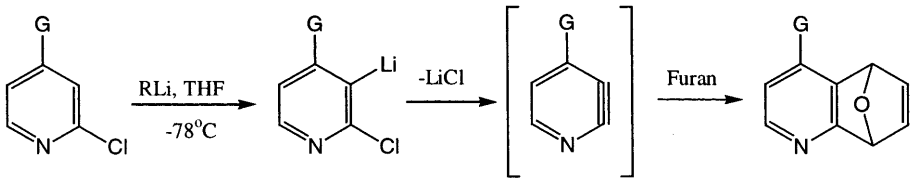
2,3-Pyridyne (**1**; 2,3-didehydropyridine) has traditionally proved to be a poorer dienophile in Diels–Alder trapping reactions than the more stable 3,4-isomer **2**[1,2] and hence has been of lower synthetic value.[3–6] We have recently shown that 3,4-pyridyne (and not its lithiated precursor) is considerably stabilised by 2- or 6-alkoxy groups, with furan trapped cycloadduct yields in the range 66–89% possible.[7] In line with this earlier work, we proposed that the instability of 2,3-pyridyne is related to the partial polarisation of the strained aryne bond due to the electron withdrawing effect of the pyridine ring nitrogen, giving 2,3-pyridyne some dipolar character **1a**, thus reducing its reactivity towards Diels–Alder cycloaddition processes.



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

The closer proximity of the aryne bond to the ring nitrogen in **1** relative to **2** would therefore account for its lower stability. Consequently our strategy for circumventing this polarisation effect involved the generation of 2,3-pyridynes with electron donating substituents '*para*' to the ring nitrogen at C-4.

Improved cycloadduct yields have been obtained from 4-methoxy-[8,9] and 4-ethoxy-[10] 2,3-pyridynes using metallation–elimination strategies, but as yet the role which the 4-alkoxy group plays in the stabilisation of either the aryne, the metallated precursor (via coordination of the metal counterion to the heteroatom), or both, remains to be established.[5] Since this question is of paramount importance in the design and synthesis of superior 2,3-pyridyne precursors, we investigated the furan trapping of various 4-substituted 2,3-pyridynes, generated via dehydrohalogenation of the corresponding 2-chloropyridines using lithiating reagents (Scheme 1).



3 G = H **6** G = OPh
4 G = Me **7** G = SPh
5 G = OMe **8** G = OPMP

9 G = H **12** G = OPh
10 G = Me **13** G = SPh
11 G = OMe **14** G = OPMP

Scheme 1.

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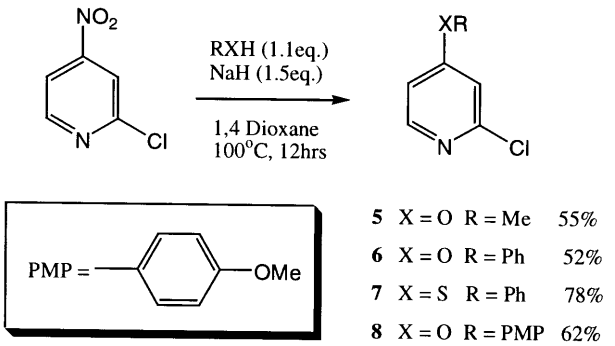


Scheme 2.

Synthesis of the required precursors was possible from simple inexpensive starting materials. Chlorination of commercially available 4-picoline-*N*-oxide with phosphorous oxychloride at 100°C overnight gave 2-chloro-4-methylpyridine **4** in 64% yield. 2-Chloro-4-alkoxy- and 4-thiophenoxypyridines **5**–**8** were conveniently prepared by treating 2-chloro-4-nitropyridine[11] with sodium alkoxide or thiophenoxide at 100°C (Scheme 2).

Attempted generation of substituted 2,3-pyridynes from precursors **3**–**8** using *n*-, *sec*-, or *tert*-butyllithium failed due to competing substitution and halogen-exchange reactions. For example, treatment of **6** with *tert*-butyllithium at −78°C followed by quenching with water gave 4-phenoxypyridine in quantitative yield, presumably via halogen–metal exchange at C-2. This problem could be avoided using the sterically hindered lithium diisopropylamide (LDA) as the lithiating reagent, which does not undergo halogen–metal exchange reactions in these systems. The results of lithiation of these precursors with LDA at −78°C in THF and subsequent trapping with furan[12] are presented in Table 1.

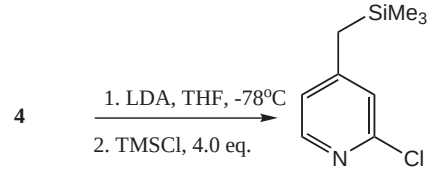
The failure of 2-chloropyridine **3** to give trapped adduct is not surprising, the main product arises from nucleophilic attack on **1** by its lithiated precursor, giving a resinous black tar. The unsuitability of **4** as a 2,3-pyridyne precursor is due to the acidity of the methyl group protons, this was confirmed by trapping the intermediate lithio species with trimethylsilylchloride (TMSCl), giving silylation of the methyl group as the only product (Scheme 3).

Reasonable to good yields of cycloadduct were obtained using 2-chloro-4-alkoxy- and 4-thiophenoxy-

Table 1. [4+2] cycloadditions of 4-substituted 2,3-pyridynes with furan

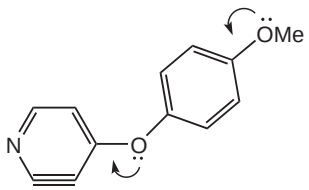
Entry	Adduct	Yield (%)[a]
3	**9**	0
4	**10**	0
5	**11**	37
6	**12**	25
7	**13**	29
8	**14**	58

[a] Refers to isolated yields after chromatography.



Scheme 3.

pyridines. The decrease in adduct yield as the C-4 substituent is changed from methoxy to the relatively weaker electron donating phenoxy and thiophenoxy groups indicates that electron donation into the pyridine ring system is the dominant factor in pyridyne stabilisation by these substituents. These reactions were relatively clean in that the only other products detected were 2-diisopropylamino-4-alkoxypyridines (derived from attack of diisopropylamine on the 2,3-pyridyne intermediate) and starting material. To our knowledge the strong stabilisation exhibited by the *p*-methoxyphenoxy group resulting in a 58% yield of **14**[13] represents a significant improvement over present literature methods and is unexpected when compared with the results obtained when the methoxy group is directly attached to the 4-position (as is the case with **5**). This could be explained in terms of the electron-rich 4-methoxy substituted benzoid ring encouraging preferential electron donation towards the ring nitrogen by the pyridyl-ether oxygen, as depicted by **15**.



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The novel use of a sulphur based stabilising group **7** holds particular promise given the possibility of cleavage of the sulphide functionality after cycloaddition.[14] Further 'tuning' of the 4-aryloxy and thiophenoxy substituents and the use of more sterically hindered bases should further increase the synthetic utility of these species. Work along these lines is currently in progress in our laboratory.

Acknowledgements

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12. For trapping experiment conditions see Ref. 7 (p. 1248, compound **4**). In these experiments 20 equivalents of trapping agent were used instead of 10.
13. All compounds gave spectral and analytical data consistent with the proposed structures. Selected data for **14**: amber oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.83 (s, 3H), 5.17 (d, 1H, $J=1.8$), 5.53 (d, 1H, $J=1.8$), 6.46 (d, 1H, $J=6.0$), 6.88 (dd, 1H, $J_1=5.5$, $J_2=1.8$), 6.94 (d, 2H, $J=6.6$), 6.99 (d, 2H, $J=6.6$), 7.05 (dd, 1H, $J_1=5.5$, $J_2=1.8$), 7.91 (d, 1H, $J=6.0$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 55.7, 80.0, 82.7, 110.2, 115.2, 121.7, 127.7, 142.1, 143.4, 146.0, 148.4, 157.2, 157.3, 175.5. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.78; H, 5.12; N, 5.46%.
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