Metallation of pyridine *N*-oxides and application to synthesis

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Regio- and chemi-selective, directed *ortho*-lithiation of 2-, 2,5- or 3,4-substituted pyridine *N*-oxides has been achieved with diisopropylamide and butyllithium. Polysubstituted pyridine *N*-oxides, azaxanthone, and an isomer of orelline have been synthesized by such methods.

Compared to the directed *ortho*-metallation of pyridine,[1] little work on the lithiation of pyridine *N*-oxides has been reported apart from the pioneering studies of Abramovitch and his group between 1969 and 1972.[2–6] In this they both developed the lithiation of pyridine *N*-oxide as well as various 3-, 4- and 3,4-substituted compounds at low temperature, and proved, that in such compounds, the enhanced acidity of 2-H and the lithium-complexing effect of the oxygen lone pairs makes feasible under strongly basic conditions (treatment with lithium alkyls or lithium dialkylamides) proton abstraction *ortho* to nitrogen.

This work has remained unexploited since these studies mainly because the low selectivity of this reaction often gave mixtures of 2-, 6- and 2,6-functionalized products. Although this original work was later developed by Martin[7] using an *in situ* trap technique based on the compatibility between LTMP (lithium 2,2,6,6-tetramethylpiperidide) and such electrophiles as trimethylsilyl chloride or hexafluoroacetone, the problem of regioselectivity remained.

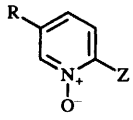
Recently, since we developed an interest in preparing 2- or 6-substituted pyridines or pyridine *N*-oxides for synthetic purposes, we have studied the metallation of pyridine *N*-oxides, particularly in respect of the 2/6-regioselectivity of such reactions.

Two different regioselective pathways are investigated in this paper: the 6-lithiation of 2-substituted pyridine *N*-oxides **1–3** for which dimetallation cannot occur since the 2 position is blocked, and the 2-lithiation of 3-substituted pyridine *N*-oxides for which the substituent at C-3 can be an *ortho*-directing group. The latter example consists of the metallation of 3,4-dimethoxypyridine *N*-oxide and some applications of this strategy are given with the synthesis of polyaromatic compounds.

Results and discussion

Metallation of 2-substituted pyridine *N*-oxides

Lithiation of 2-*N*,*N*-diisopropylcarboxamidopyridine *N*-oxide† **1** and 2-pivaloylaminopyridine *N*-oxides‡ **2** and **3** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −75 °C (Scheme 1) occurred with total regioselectivity at the C-6 position. No metallation occurred at the C-3 position, although carboxamides and pivaloylamino groups are known to be *ortho*-directing groups under other conditions.[9] Reaction of various electrophiles with the intermediate lithio species provided the corresponding 6-substituted pyridines (Table 1).



1 Z = $CONPr^i_2$, R = H
2 Z = $NHCOBu^t$, R = H
3 Z = $NHCOBu^t$, R = Me

4-20

Scheme 1 *Reagents and conditions:* LDA, THF, −75 °C; ii, electrophile, −75 °C

Table 1 Metallation of 2-substituted pyridine *N*-oxides

Compound	Electrophile	E	Product	Yield (%)[a]
1[c]	EtOD	D	**4**	100[b]
1	PhCHO	PhCH(OH)	**5**	62
1	Ph_2CO	$Ph_2CH(OH)$	**6**	60
1	Cyclohexanone	c-C_6H_{10}(OH)	**7**	54
1	CO_2	CO_2H	**8**	50
1	I_2	I	**9**	77
2[d]	EtOD	D	**10**	80[b]
2	PhCHO	PhCH(OH)	**11**	80
2	Cyclohexanone	c-C_6H_{10}(OH)	**12**	60
2	HCO_2Et	CHO	**13**	62
2	CO_2	CO_2H	**14**	48
2	I_2	I	**15**	73
3[e]	EtOD	D	**16**	100[b]
3	MeI	Me	**17**	83[b]
3	HCO_2Et	CHO	**18**	62
3	CO_2	CO_2H	**19**	83
3	TsCN	CN	**20**	57

[a] Isolated yields, unless otherwise indicated. [b] Determined by ^{1}H NMR analysis. [c] Lithiation of **1** was carried out with 1.1 equiv. of LDA for 0.5 h. [d] Lithiation of **2** was carried out with 2.2 equiv. of LDA for 0.5 h. [e] Lithiation of **3** was carried out with 2.2 equiv. of LDA for 1.5 h.

Metallation of 3,4-dimethoxypyridine *N*-oxide

We have previously reported[10] that with butyllithium, 3,4-dimethoxypyridine undergoes a regioselective metallation at C-2 without side reactions such as nucleophilic addition. 3,4-Dimethoxypyridine *N*-oxide§ **21** was lithiated with butyllithium

† 2-(*N*,*N*-Diisopropylcarboxamido) pyridine *N*-oxide **1** was prepared from the corresponding pyridinecarboxamide in 70% yield by action of hydrogen peroxide in acetic acid at 80 °C for 12 h.[8]

‡ Pyridine *N*-oxides **2** and **3** were prepared respectively from 2-aminopyridine and 5-methyl-2-aminopyridine in a two-step sequence: i, $ClCOBu^t$, NEt_3, ether, room temp., 2 h; ii, H_2O_2, $MeCO_2H$, 80 °C, 12 h. The overall yields were 65% for **2** and 73% for **3**.

§ 3,4-Dimethoxypyridine *N*-oxide **21** was prepared in a three-step sequence from 3-fluoropyridine by a literature procedure[11] (overall yield: 55%).

Table 2 Regioselectivity of the metallation of 3,4-dimethoxypyridine *N*-oxide **21**

Entry	Electrophile[a]	E	Yield[b] of **22**, **23** and **24** (%)	Ratio of **22**:**23**:**24**		
				22	**23**	**24**
1	DCl	D	83[c]	100	—	—
2	MeCHO	MeCH(OH)	61	100	—	—
3	2-$MeOC_6H_4CHO$	2-$MeOC_6H_4CH(OH)$	60	91[d]	9[d]	—
4	I_2	I	80	81[e]	5[e]	14[e]

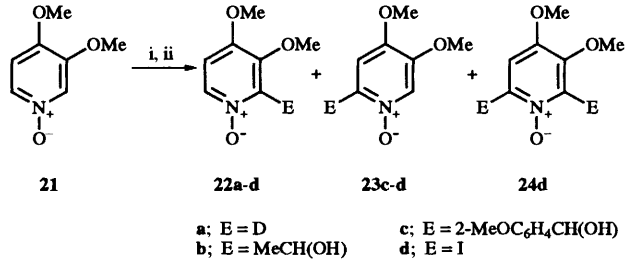
[a] Electrophiles were added and allowed to react at −75 °C. [b] Yields are for isolated products. [c] Determined by ^1H NMR analysis. [d] Ratios were determined by ^1H NMR analysis. [e] Ratios were determined by isolation of products.

Table 3 Regioselectivity of the metallation of **21** when iodine was used as electrophile

Entry	Equiv. of BuLi and I_2	Time of reaction of I_2(*t*/min)	Yields[a] (%)		
			22d	**23d**	**24d**
1	2.0	45	60	2	26
2	2.0	5	65	4	11
3	3.3	45	—	—	76

[a] Yields are for isolated products.

in THF, the reaction conditions being determined by quenching of the lithio species with deuterium chloride. With 1.2 equiv. of BuLi at 0 °C deuterium incorporation was poor¶ (< 5%). The best conditions were found to be 2.2 equiv. of BuLi in THF at 0 °C for 45 min, allowing a 83% deuterium incorporation. From these results it seems that the first equivalent of base was entirely chelated by the two methoxy groups to give an intermediate lithio species which on reaction with various electrophiles afforded the corresponding 2-, 6- or 2,6-functionalized products (Scheme 2 and Table 2).



Scheme 2 *Reagents and conditions:* i, BuLi, THF, 0 °C, 45 min; ii, electrophile, −75 °C

When DCl was used as electrophile, total regioselectivity at C-2 was observed (Table 2, entry 1). The same regioselectivity was observed with acetaldehyde (Table 2, entry 2), but not with 2-methoxybenzaldehyde (Table 2, entry 3) and iodine (Table 2, entry 4). We assume that the action of BuLi on **21** leads to an equilibrium between two lithiated species, the 2-lithio and the 6-lithio derivatives. This equilibrium is in favour of the 2-lithio derivative and the ratios of final products seem to depend on the nature of the electrophile. Nevertheless, a satisfactory regioselectivity of the metallation at C-2 was observed (see ratios in Table 2).

The particular case of iodine is more complex because a 2,6-diiodo compound **24d** was obtained together with the 2-iodo compound **22d** and a very small quantity of the 6-iodo compound **23d** (Table 3). However, the 2-iodo derivative **22d** could be conveniently obtained using a 5 min reaction time (Table 3, entry 2: 65%).

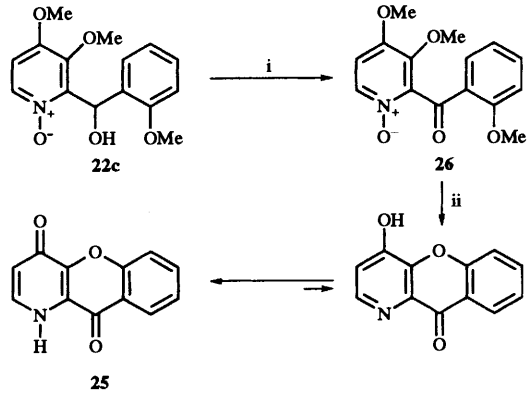
¶ Determined by ^1H NMR analysis.

Moreover, a sufficient excess of both metallating reagent and iodine selectively led to the diiodo derivative **24d** (Table 3, entry 3).

Application to synthesis

Some of the previously prepared pyridine *N*-oxides were used as key intermediates in the synthesis of polyaromatic compounds.

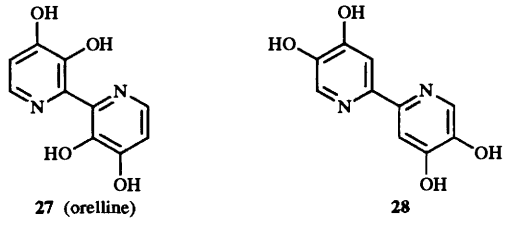
(a) Synthesis of a new 1-azaxanthone. Xanthone derivatives have potential pharmaceutical properties.[12] The synthesis of the azaxanthone **25** was achieved in two steps from the alcohol **22c**. Thus, oxidation of **22c** with manganese dioxide gave the corresponding ketone **26**, and this upon treatment with boiling pyridinium chloride (215 °C)[13] cyclized to **25** (Scheme 3).‖



Scheme 3 *Reagents and conditions:* i, MnO_2, toluene, reflux, 64%; ii, boiling pyridinium chloride, 20 min, 62%

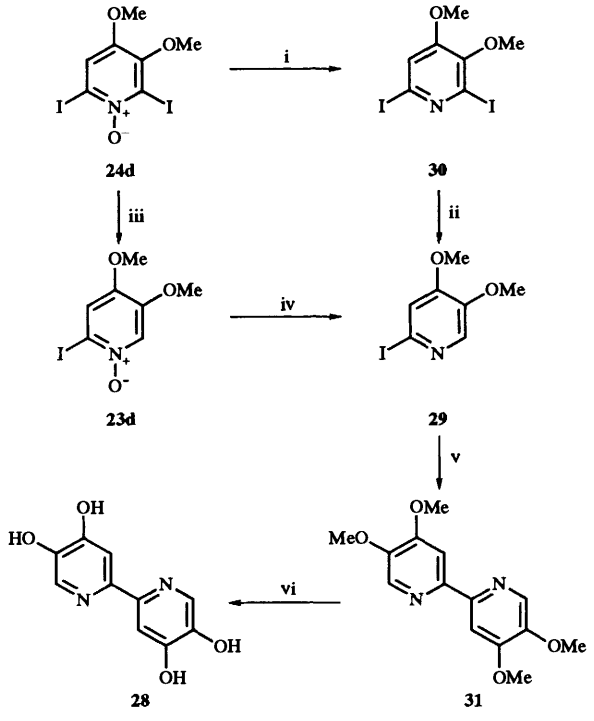
Simultaneous cleavage of the ether moiety and reduction of the *N*-oxide group are the result of the strongly acidic conditions and the excess of pyridine, respectively.

(b) Synthesis of an isomeric analogue of orelline. Orelline **27**, a toxin from the poisonous mushrooms *Cortinarius orellanus* and *speciosissimus*,[14] has previously been synthesised with 2-iodo-3,4-dimethoxypyridine as a key intermediate.[10]



‖ In order to establish unambiguously the structure of the azaxanthone **25**, this molecule was synthesized by another route, starting from 3,4-dimethoxypyridine: i, BuLi, THF, −70 °C, 1 h, then 2-$MeOC_6H_4$-CHO, −70 °C, 72%; ii, MnO_2, toluene, reflux, 90%; iii, boiling pyridinium chloride, 76%.

The isomeric analogue of orelline, compound **28**, was prepared from 2-iodo-4,5-dimethoxypyridine **29**, a compound itself synthesized from the corresponding pyridine *N*-oxide **23d**, in very low yield (Table 3, entry 2: 4%), by a metallation–iodination sequence with 3,4-dimethoxypyridine *N*-oxide **21**. An alternative two-step route to compound **29** was *via* the key intermediate the *N*-oxide **24d**: thus, either reduction of the *N*-oxide followed by a regioselective iodine–lithium exchange of **30** (61% overall), or by selective deiodination of **24d** followed by the reduction of the *N*-oxide **23d** (34% overall). A nickel–phosphine complex-mediated homocoupling[15,10] of **29** gave the 2,2'-bipyridine **31** in good yield (79%). Treatment of **31** in refluxing hydrobromic acid afforded the isomeric analogue of orelline **28** (Scheme 4).



Scheme 4 *Reagents and conditions:* i, PCl_3, 83%; ii, BuLi, THF, −75 °C, 0.5 h, then HCl, 74%; iii, BuLi, THF, −30 °C, 1 h, then HCl, 77%; iv, PCl_3, 44%; v, $NiCl_2$, PPh_3, Zn, DMF, 50 °C, 48 h, 79%; vi, conc. aq. HBr, reflux, 20 h, 70%

Conclusion

2-Substituted pyridine *N*-oxides **1**–**3** and 3,4-dimethoxypyridine *N*-oxide **21** have been successfully metallated with LDA and BuLi, respectively. Lithiation was *ortho* directed by the *N*-oxide group for 2-substituted pyridine *N*-oxides and by the *N*-oxide and the methoxy group for **21**. The resulting lithiopyridines were obtained in high yields as shown by reaction with various electrophiles. Some of the pyridine *N*-oxide intermediates thus obtained were used to synthesize a new azaxanthone **25** and an isomeric analogue of orelline **28**. This strategy is fully convergent, highly regioselective and allows overall yields, respectively of 40% (2 steps) for **25**, and 34% (4 steps) for **28**.

Experimental

General

All reactions involving organometallic compounds were carried out under a dry argon atmosphere. Reagents were handled with syringes through septa. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Ether refers to diethyl ether. Column chromatography was performed on silica (0.063–0.200 mm). Mps were determined on a Kofler hot-stage. ^1H NMR spectra were recorded on a 60 MHz Varian EM 360L, on a 200 MHz Bruker AC 200 F, or on a 400 MHz Bruker AM 400 spectrometer using $CDCl_3$ or deuteriated dimethyl sulfoxide as solvent with chemical shifts being reported as δ (ppm), respectively, from tetramethylsilane or from hexamethyldisiloxane; J values are recorded in Hz. ^{13}C NMR spectra were recorded at 50 MHz on a Bruker AC 200 F spectrometer. IR spectra were obtained on a Perkin-Elmer FTIR 1600 spectrophotometer. Mass spectra were recorded on a JEOL JMS-AX 500 instrument. Elemental analyses were performed on a Carlo Erba 1160 instrument.

General procedure A: metallation of 2-(*N*,*N*-diisopropylcarboxamido)pyridine *N*-oxide 1

2-(*N*,*N*-Diisopropylcarboxamido)pyridine *N*-oxide **1** (1.56 g, 7.0 mmol) in THF (20 cm^3) was slowly added to a cold (−75 °C) solution of LDA (7.7 mmol) in THF (100 cm^3). The resulting mixture was stirred for 30 min at −75 °C before addition of the required electrophile (15 mmol) in THF (20 cm^3). Stirring was continued for 2 h at the same temperature before hydrolysis of the mixture at −75 °C by water (100 cm^3) and further dilution with water (50 cm^3) at room temperature. The mixture was extracted with dichloromethane (CH_2Cl_2), and the extract dried ($MgSO_4$) and evaporated to afford a crude product which was purified by flash chromatography on silica.

2-(*N*,*N*-Diisopropylcarboxamido)-[6-$^2H_1$]pyridine *N*-oxide 4. General procedure A, using deuteriated ethanol as electrophile, gave the title compound (100%). The physical characteristics of this product were found to be identical with those described for **1**** except for the ^1H NMR spectrum where the 6-H signal had disappeared.

2-(*N*,*N*-Diisopropylcarboxamido)-6-(1-hydroxyphenylmethyl)-pyridine *N*-oxide 5. General procedure A, using benzaldehyde as electrophile, gave the *title compound* (62%) (eluent: CH_2Cl_2–ether, 5:5) as a pale yellow solid, mp 118–120 °C (Found: C, 69.4; H, 7.4; N, 8.4. $C_{19}H_{24}N_2O_3$ requires C, 69.5; H, 7.4; N, 8.5%); ν_{max}(KBr)/cm^{-1} 3340, 3080, 3015, 2970, 2870, 1640, 1495 and 1450; δ_H(60 MHz; $CDCl_3$) 1.00 to 1.85 (12 H, m, 4 CH_3), 3.30 to 3.85 (2 H, comp, 2 CH), 6.15 (1 H, s, CH), 6.30 (1 H, s, OH) and 6.70 to 7.70 (8 H, comp, 5 H phenyl + 3 H pyridine).

2-(*N*,*N*-Diisopropylcarboxamido)-6-(1-hydroxydiphenylmethyl)pyridine *N*-oxide 6. General procedure A, using benzophenone as electrophile, gave the *title compound* (60%) (eluent: cyclohexane–ether, 5:5) as a beige solid, mp 230–232 °C (Found: C, 74.2; H, 6.9; N, 6.8. $C_{25}H_{28}N_2O_3$ requires C, 74.2; H, 7.0; N, 6.9%); ν_{max}(KBr)/cm^{-1} 3200, 3080, 2940, 1645, 1610, 1495 and 1445; δ_H(400 MHz; $CDCl_3$) 1.02 (6 H, d, J 6.5, 2 CH_3), 1.47 (6 H, d, J 6.5, 2 CH_3), 3.20 (1 H, comp, CH), 3.47 (1 H, comp, CH), 6.69 (1 H, comp, 5-H), 7.24 (12 H, m, 3-H + 4-H + 10 H phenyl) and 8.36 (1 H, s, OH).

2-(*N*,*N*-Diisopropylcarboxamido)-6-(1-hydroxycyclohexyl)-pyridine *N*-oxide 7. General procedure A, using cyclohexanone as electrophile, gave the *title compound* (54%) (eluent: ether) as a beige solid, mp 78–80 °C (Found: C, 66.5; H, 9.0; N, 8.4. $C_{18}H_{28}N_2O_3$, 0.3 H_2O requires C, 66.35; H, 8.85; N, 8.6%); ν_{max}(KBr)/cm^{-1} 2935, 1637 and 1448; δ_H(60 MHz; $CDCl_3$) 1.00–1.30 (22 H, m, 10 H cyclohexyl + 4 CH_3), 3.10–3.90 (3 H, m, 2 CH + OH) and 7.15–7.50 (3 H, m, 3-H + 4-H + 5-H).

** Physical characteristics of compound **1**: mp 166–168 °C (Found: C, 64.9; H, 8.25; N, 12.6. $C_{12}H_{18}N_2O_2$ requires C, 64.8; H, 8.15; N, 12.6%); ν_{max}(KBr)/cm^{-1} 3430, 3120, 3080, 2980, 2940, 1640, 1610, 1560, 1500, 1480 and 1425; δ_H(60 MHz; $CDCl_3$) 1.05–1.80 (12 H, m, 4 CH_3), 3.2–3.9 (2 H, m, 2 CH), 7.27 (3 H, m, 3-H + 4-H + 5-H) and 8.14 (1 H, comp, 6-H).

2-Carboxy-6-(*N*,*N*-diisopropylcarboxamido)pyridine *N*-oxide 8. General procedure A, using solid carbon dioxide as electrophile gave, after acidification by 2 mol dm^{-3} hydrochloric acid (extraction by CH_2Cl_2 at pH 2), the *title compound* (50%) as a white solid, mp 180–182 °C (Found: C, 58.3; H, 6.55; N, 10.2. $C_{13}H_{18}N_2O_4$ requires C, 58.6; H, 6.8; N, 10.5%); ν_{max}(KBr)/cm^{-1} 3094, 2969, 1651 and 1444; δ_H(60 MHz; $CDCl_3$) 1.15–1.80 (12 H, m, 4 CH_3), 3.20–3.90 (2 H, m, 2 CH), 7.55–7.90 (2 H, m, 4-H + 5-H) and 8.50 (1 H, dd, *J* 2 and 8, 3-H).

2-(*N*,*N*-Diisopropylcarboxamido)-6-iodopyridine *N*-oxide 9. General procedure A, using iodine as electrophile, gave the *title compound* (77%) (eluent: ether) as a pale yellow solid, mp >250 °C (Found: C, 41.4; H, 5.1; N, 7.85. $C_{12}H_{17}N_2O_2$ requires C, 41.4; H, 4.9; N, 8.05%); ν_{max}(KBr)/cm^{-1} 3448, 2967, 1624, 1508 and 1442; δ_H(60 MHz; $CDCl_3$) 0.90–1.70 (12 H, m, 4 CH_3), 3.20–3.70 (2 H, m, 2 CH), 6.95 (1 H, t, *J* 8, 4-H), 7.20 (1 H, dd, *J* 2 and 8, 3-H) and 7.85 (1 H, dd, *J* 2 and 8, 5-H).

General procedure B: metallation of 2-pivaloylaminopyridine *N*-oxide 2

Procedure B was identical with general procedure A except that 15.5 mmol of LDA and electrophile were used.

2-Pivaloylamino[6-^{2}H]pyridine *N*-oxide 10. General procedure B, using deuteriated ethanol as electrophile, gave the title compound (80%). The physical characteristics of this product were found to be identical with those described for **2**†† except for the ^{1}H NMR spectrum where the 6-H signal had disappeared.

2-Pivaloylamino-6-[hydroxy(phenyl)methyl]pyridine *N*-oxide 11. General procedure B, using benzaldehyde as electrophile, gave the *title compound* (80%) (eluent: cyclohexane–ether, 7:3) as a white solid, mp 98 °C (Found: C, 67.8; H, 6.65; N, 9.1. $C_{17}H_{20}N_2O_3$ requires C, 68.0; H, 6.7; N, 9.3%); ν_{max}(KBr)/cm^{-1} 3000, 1700, 1615, 1570, 1490 and 1450; δ_H(60 MHz; $CDCl_3$) 1.30 (9 H, s, Bu^t), 6.00 (2 H, m, CH + OH), 6.60 (1 H, dd, *J* 2 and 8, 5-H), 7.30 (6 H, m, 4-H + 5 H phenyl), 8.36 (1 H, dd, *J* 2 and 8, 3-H) and 10.36 (1 H, s, NH).

6-(1-Hydroxycyclohexyl)-2-pivaloylaminopyridine *N*-oxide 12. General procedure B, using cyclohexanone as electrophile, gave the *title compound* (60%) (eluent: cyclohexane–ether, 5:5) as a pale yellow solid, mp 120 °C (Found: C, 65.6; H, 8.6; N, 9.4. $C_{16}H_{24}N_2O_3$ requires C, 65.7; H, 8.3; N, 9.6%); ν_{max}(KBr)/cm^{-1} 3260, 2930, 2850, 1690, 1570 and 1485; δ_H(400 MHz; $CDCl_3$) 1.41–2.31 (19 H, m, Bu^t + 10 H cyclohexyl), 3.60 (1 H, s, OH), 7.00 (1 H, dd, *J* 2 and 8, 5-H), 7.31 (1 H, t, *J* 8, 4-H), 8.37 (1 H, dd, *J* 2 and 8, 3-H) and 10.51 (1 H, s, NH).

2-Formyl-6-pivaloylaminopyridine *N*-oxide 13. General procedure B, using ethyl formate as electrophile, gave the *title compound* (62%) (eluent: cyclohexane–ether, 5:5) as a yellow solid, mp 102 °C (Found: C, 59.65; H, 6.5; N, 12.5. $C_{11}H_{14}N_2O_3$ requires C, 59.45; H, 6.35; N, 12.6%); ν_{max}(KBr)/cm^{-1} 3280, 2960, 1700, 1610, 1530, 1500 and 1460; δ_H(60 MHz; $CDCl_3$) 1.33 (9 H, s, Bu^t), 7.40 (2 H, m, 4-H + 5-H), 8.70 (1 H, dd, *J* 2 and 8, 3-H), 10.40 (1 H, s, NH) and 10.70 (1 H, s, CHO).

2-Carboxy-6-pivaloylaminopyridine *N*-oxide 14. General procedure B, using solid carbon dioxide as electrophile gave, after acidification by 2 mol dm^{-3} hydrochloric acid (extraction by CH_2Cl_2 at pH 2), the *title compound* (48%) as a pink solid, mp 136 °C (Found: C, 55.3; H, 5.9; N, 11.5. $C_{11}H_{14}N_2O_4$ requires C, 55.45; H, 5.9; N, 11.75%); ν_{max}(KBr)/cm^{-1} 3350, 3130, 2980, 1710, 1620, 1585 and 1480; δ_H(60 MHz; $CDCl_3$) 1.33 (9 H, s, Bu^t), 7.73 (1 H, t, *J* 8, 4-H), 8.20 (1 H, dd, *J* 2 and 8, 5-H), 8.86 (1 H, dd, *J* 2 and 8, 3-H) and 10.1 (1 H, s, NH).

2-Iodo-6-pivaloylaminopyridine *N*-oxide 15. General procedure B, using iodine as electrophile, gave the *title compound* (73%) (eluent: cyclohexane–ether, 5:5) as a pale yellow solid, mp 128 °C (Found: C, 37.45; H, 3.95; N, 8.6. $C_{10}H_{13}IN_2O_2$ requires C, 37.5; H, 4.1; N, 8.75%); ν_{max}(KBr)/cm^{-1} 3270, 2960, 1685, 1595, 1550, 1495 and 1475; δ_H(400 MHz; $CDCl_3$) 1.26 (9 H, s, Bu^t), 6.97 (1 H, t, *J* 8, 4-H), 7.49 (1 H, dd, *J* 2 and 8, 5-H), 8.32 (1 H, dd, *J* 2 and 8, 3-H) and 10.34 (1 H, s, NH).

General procedure C: metallation of 5-methyl-2-pivaloylaminopyridine *N*-oxide 3

Procedure C was identical with general procedure B except that the metallation time was 1.5 h.

5-Methyl-2-pivaloylamino[6 ^{2}H]pyridine *N*-oxide 16. General procedure C, using deuteriated ethanol as electrophile, gave the title compound (100%). The physical characteristics of this product were identical with those described for **3**§§ except for the ^{1}H NMR spectrum where the 6-H signal has disappeared.

5,6-Dimethyl-2-pivaloylamino[6-^{2}H]pyridine *N*-oxide 17. General procedure C, using methyl iodide as electrophile, gave the title compound (83%, ^{1}H NMR integration). It was impossible to separate this product from the starting material and only its ^{1}H NMR spectrum is given: δ_H(200 MHz; $CDCl_3$) 1.05 (9 H, s, Bu^t), 2.01 (3 H, s, 5-CH_3), 2.23 (3 H, s, 6-CH_3), 6.80 (1 H, d, *J* 9, 4-H) and 7.85 (1 H, d, *J* 9, 5-H).

2-Formyl-3-methyl-6-pivaloylaminopyridine *N*-oxide 18. General procedure C, using ethyl formate as electrophile, gave the *title compound* (62%) (eluent: hexane–ether, 5:5) as a yellow solid, mp 108–110 °C (Found: C, 60.85; H, 7.05; N, 11.85. $C_{12}H_{16}N_2O_3$ requires C, 61.0; H, 6.85; N, 11.85%); ν_{max}(KBr)/cm^{-1} 3290, 2972, 1771, 1686, 1599, 1506 and 1438; δ_H(60 MHz; $CDCl_3$) 1.43 (9 H, s, Bu^t), 2.60 (3 H, s, CH_3), 7.20 (1 H, d, *J* 8.5, 4-H), 8.55 (1 H, d, *J* 8.5, 5-H), 10.30 (1 H, s, NH) and 10.80 (1 H, s, CHO).

2-Carboxy-3-methyl-6-pivaloylaminopyridine *N*-oxide 19. General procedure C, using solid carbon dioxide as electrophile gave, after acidification by a 2 mol dm^{-3} solution of hydrochloric acid (extraction by CH_2Cl_2 at pH 2), the *title compound* as a pale yellow solid, mp 178–180 °C (Found: C, 57.4; H, 6.4; N, 11.2. $C_{12}H_{16}N_2O_4$ requires C, 57.15; H, 6.4; N, 11.1%); ν_{max}(KBr)/cm^{-1} 3360, 2940, 1710, 1675, 1610, 1580, 1510 and 1465; δ_H(60 MHz; $CDCl_3$) 1.40 (9 H, s, Bu^t), 2.75 (3 H, s, CH_3), 7.55 (1 H, d, *J* 8.5, 4-H), 8.65 (1 H, d, *J* 8.5, 5-H) and 10.00 (1 H, s, NH).

2-Cyano-3-methyl-6-pivaloylaminopyridine *N*-oxide 20. General procedure C, using tosyl cyanide as electrophile, gave the *title compound* (57%) (eluent: hexane–ethyl acetate, 4:6) as a white solid, mp 202–204 °C (Found: C, 61.6; H, 6.4; N, 18.2. $C_{12}H_{15}N_3O_2$ requires C, 61.8; H, 6.5; N, 18.0%); ν_{max}(KBr)/cm^{-1} 3314, 2970, 2240, 1946, 1692, 1522 and 1478; δ_H(60 MHz; $CDCl_3$) 1.33 (9 H, s, Bu^t), 2.48 (3 H, s, CH_3), 7.15 (1 H, d, *J* 9, 4-H), 8.44 (1 H, d, *J* 9, 3-H) and 10.10 (1 H, s, NH).

General procedure D: metallation of 3,4-dimethoxypyridine *N*-oxide 21

Anhydrous 3,4-dimethoxypyridine *N*-oxide (0.31 g, 2.0 mmol) was added to a cold (−75 °C) solution of butyllithium (4.4

†† Physical characteristics of compound **2**: mp 84–85 °C (Found: C, 61.7; H, 7.15; N, 14.6. $C_{10}H_{14}N_2O_2$ requires C, 61.85; H, 7.25; N, 14.4%); ν_{max}(KBr)/cm^{-1} 3250, 3120, 3050, 2960, 1685, 1600, 1560, 1490 and 1430; δ_H(60 MHz; $CDCl_3$) 1.36 (9 H, s, Bu^t), 7.05 (1 H, ddd, *J* 2, 6 and 8, 5-H), 7.40 (1 H, dt, *J* 2 and 8, 4-H), 8.33 (1 H, dd, *J* 2 and 6, 6-H), 8.53 (1 H, dd, *J* 2 and 8, 3-H) and 10.50 (1 H, s, NH).

§§ Physical characteristics of compound **3**: mp 80–82 °C (Found: C, 63.15; H, 8.0; N, 13.5. $C_{11}H_{16}N_2O_2$ requires C, 63.45; H, 7.75; N, 13.45%); ν_{max}(KBr)/cm^{-1} 3280, 2970, 2870, 1680, 1620, 1570, 1535 and 1490; δ_H(60 MHz; $CDCl_3$) 1.20 (9 H, s, Bu^t), 2.14 (3 H, s, CH_3), 7.02 (1 H, d, *J* 8, 4-H), 7.95 (1 H, s, 6-H), 8.17 (1 H, d, *J* 8, 3-H) and 10.14 (1 H, s, NH).

mmol) in THF (50 cm^3). The mixture was allowed to warm to 0 °C at which temperature it was stirred for 45 min. It was then cooled to −75 °C and the required electrophile was added to it. Stirring was continued for 2 h at the same temperature before the mixture was hydrolysed at −75 °C by the addition of hydrochloric acid, ethanol and THF (1:1:2; 8 cm^3). After the solution had been warmed to room temperature, it was diluted with water (10 cm^3), neutralized with potassium carbonate and then extracted with dichloromethane. The extract was dried ($MgSO_4$) and evaporated to leave the crude product, which was purified by column chromatography on silica (eluent is given in the product description).

3,4-Dimethoxy[2-^{2}H]pyridine *N*-oxide 22a. General procedure D, using deuterium chloride (1 cm^3) as electrophile afforded 83% (eluent: CH_2Cl_2–methanol, 9:1) of the title compound. The physical characteristics of this product were identical with those described for **21**[10] except for the ^{1}H NMR spectrum: δ_H(200 MHz; $CDCl_3$) 3.93 (3 H, s, OMe), 4.00 (3 H, s, OMe), 6.73 (1 H, d, *J* 7, 5-H) and 7.93 (1 H, d, *J* 7, 6-H).

2-(1-Hydroxyethyl)-3,4-dimethoxypyridine *N*-oxide 22b. General procedure D, using 2-methoxybenzaldehyde as electrophile afforded 60% (eluent: CH_2Cl_2–methanol, 95:5) the *title compound* as a pale yellow solid (61%) mp 89–90 °C (Found: C, 54.6; H, 6.7; N, 6.7. $C_9H_{13}NO_4$ requires C, 54.3; H, 6.7; N, 7.0%); ν_{max}(KBr)/cm^{-1} 3500, 2980, 1615, 1487 and 1444; δ_H(200 MHz; $CDCl_3$) 1.53 (3 H, d, *J* 6.8, CHC*H*$_3$), 3.82 (3 H, s, OMe), 3.86 (3 H, s, OMe), 5.20 (1 H, q, *J* 6.8, C*H*CH$_3$), 6.72 (1 H, d, *J* 7.3, 5-H), 7.5 (1 H, br s, OH) and 7.89 (1 H, d, *J* 7.3, 6-H).

2-[Hydroxy(2-methoxyphenyl)methyl]-3,4-dimethoxypyridine *N*-oxide 22c. General procedure D, using 2-methoxybenzaldehyde as electrophile afforded 60% (eluent: CH_2Cl_2–methanol, 97:3) a mixture of the *title compound* and 2-[hydroxy(2-methoxyphenyl)methyl]-4,5-dimethoxypyridine *N*-oxide **23c** (ratio: 91:9). The title compound was obtained in pure form as a white solid by recrystallization from acetone, mp 137 °C (Found: C, 62.0; H, 5.8; N, 4.7. $C_{15}H_{17}NO_5$ requires C, 61.85; H, 5.9; N, 4.8%); ν_{max}(KBr)/cm^{-1} 2940, 1600, 1490, 1470 and 1450; δ_H(200 MHz; $CDCl_3$) 3.76 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.90 (3 H, s, OMe), 6.61 [1 H, s, C*H*(OH)], 6.78 (1 H, d, *J* 7.3, 5-H), 6.87 (1 H, d, *J* 7.8, 3′-H), 6.89 (1 H, t, *J* 7.6, 5′-H), 7.24 (1 H, dt, *J* 7.8 and 1.7, 4′-H), 7.57 (1 H, dd, *J* 7.6 and 1.7, 6′-H), 7.98 (1 H, d, *J* 7.3, 6-H) and 8.15 (1 H, s, OH).

2-Iodo-3,4-dimethoxypyridine *N*-oxide 22d. General procedure D, using iodine in THF (quickly added) at −70 °C, with stirring for 5 min, afforded (eluent: CH_2Cl_2–methanol, 95:5) the *title compound* (65%), mp 167–168 °C (Found: C, 29.6; H, 2.8; N, 4.8. $C_7H_8INO_3$ requires C, 29.9; H, 2.9; N, 5.0%); ν_{max}(KBr)/cm^{-1} 2940, 1600, 1470 and 1425; δ_H(200 MHz; [$^2H_6$]-DMSO) 3.75 (3 H, s, OMe), 3.88 (3 H, s, OMe), 7.15 (1 H, d, *J* 7.3, 5-H) and 8.27 (1 H, d, *J* 7.3, 6-H).

2,6-Diiodo-3,4-dimethoxypyridine *N*-oxide 24d. Anhydrous 3,4-dimethoxypyridine *N*-oxide (1.25 g, 8.0 mmol) was added to a cold (−75 °C) solution of BuLi (26.5 mmol) in THF (120 cm^3). After the mixture had warmed to 0 °C it was stirred for 0.75 h at this temperature before being cooled to −75 °C. A solution of iodine (6.75 g, 26.5 mmol) in THF was then added to the mixture after which it was stirred for 1 h at this temperature. After dilution with ethanol (25 cm^3), the solution was warmed to room temperature, diluted with water (40 cm^3), treated with sodium thiosulfate to remove the iodine (bleaching) and then extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to leave the crude product, which was purified by column chromatography on silica gel using CH_2Cl_2–ethanol (97:3) as eluent to afford the *title compound* as a pale yellow solid (76%), mp 218–219 °C (Found: C, 20.9; H, 1.7; N, 3.5. $C_7H_7I_2NO_3$ requires C, 20.65; H, 1.7; N, 3.45%); ν_{max}(KBr)/cm^{-1} 2940, 1575, 1470 and 1420; δ_H(200 MHz; [$^2H_6$]-DMSO) 3.73 (3 H, s, OMe), 3.88 (3 H, s, OMe) and 7.70 (1 H, s, 5-H).

2-Iodo-4,5-dimethoxypyridine *N*-oxide 23d. 2,6-Diiodo-3,4-dimethoxypyridine *N*-oxide **24d** (0.407 g, 1.0 mmol) was added to a cold (−75 °C) solution of BuLi (3.3 mmol) in THF (25 cm^3). The mixture was stirred at −30 °C for 1 h and then hydrolysed by addition of hydrochloric acid, ethanol and THF (1:1:2; 4 cm^3). It was warmed to room temperature, treated with water (10 cm^3) and with potassium carbonate, and then extracted with dichloromethane. The extract was dried ($MgSO_4$) and evaporated to leave the crude product, which was purified by column chromatography on silica gel using CH_2Cl_2–methanol (96:4) as eluent to afford the *title compound* as a white solid (77%), mp 171 °C (Found: C, 29.7; H, 2.85; N, 4.8. $C_7H_8INO_3$ requires C, 29.9; H, 2.85; N, 5.0%); ν_{max}(KBr)/cm^{-1} 2920, 1600, 1510 and 1430; δ_H(200 MHz; [$^2H_6$]-DMSO) 3.78 (3 H, s, OMe), 3.83 (3 H, s, OMe), 7.50 (1 H, s, 5-H) and 8.28 (1 H, s, 2-H).

3,4-Dimethoxy-2-(*o*-methoxybenzoyl)pyridine *N*-oxide 26. A solution of the alcohol **22c** (1.10 g, 0.004 mol) in dry toluene (25 cm^3) was oxidized by active MnO_2 (3.48 g, 0.04 mol) at reflux in a Dean–Stark apparatus, the reaction being monitored by TLC. When the reaction was complete, the mixture was filtered through Celite and the filter cake was washed by chloroform. The combined filtrate and washings were dried and evaporated to give a crude product which was purified by chromatography on silica gel using CH_2Cl_2–methanol (95:5) as eluent to afford the *title compound* as a beige solid (64%), mp 169 °C (Found: C, 62.3; H, 5.2; N, 4.8. $C_{15}H_{15}NO_5$ requires C, 62.0; H, 5.3; N, 4.6%); ν_{max}(KBr)/cm^{-1} 2940, 1670, 1600, 1490, 1465 and 1430; δ_H(200 MHz; $CDCl_3$) 3.66 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.95 (3 H, s, OMe), 6.82 (1 H, d, *J* 7.1, 5-H), 6.92 (1 H, d, *J* 7.6, 3′-H), 7.06 (1 H, t, *J* 7.7, 5′-H), 7.53 (1 H, dt, *J* 7.6 and 1.5, 4′-H), 7.95 (1 H, d, *J* 7.1, 6-H) and 8.06 (1 H, dd, *J* 7.7, 6′-H); δ_C(50 MHz; $CDCl_3$) 56.2 (OMe), 56.3 (OMe), 61.7 (OMe), 107.8, 112.2, 120.9, 125.0, 131.2, 134.7, 135.5, 143.3, 146.8, 151.7, 160.1 and 184.5 (C=O).

1*H*-Benzopyrano[3,2-*b*]pyridine-4,10-dione 25. Anhydrous boiling (215 °C) pyridinium chloride (20 g) was added to the ketone **26** (1.5 mmol) and the mixture was heated under reflux for 20 min after which it was poured on ice. The resulting precipitate was filtered off, washed with chloroform and dried. The pure *title compound* was obtained as a white solid by sublimation at 190 °C/3 mmHg (62%), mp >260 °C (Found: C, 67.4; H, 3.1; N, 6.4. $C_{12}H_7NO_3$ requires 67.6; H, 3.3; N, 6.6%); ν_{max}(KBr)/cm^{-1} 3430 (NH), 2920, 1665 (C=O), 1610, 1560 and 1465; δ_H(200 MHz; [$^2H_6$]-DMSO) 6.46 (1 H, d, *J* 7.3, 3-H), 7.53 (1 H, t, *J* 7.9, 8-H), 7.75–7.96 (3 H, m, 2-H, 6-H and 7-H) and 8.18 (1 H, dd, *J* 7.9 and 1.5, 9-H); δ_C(50 MHz, [$^2H_6$]-DMSO-d_6) 116.2, 119.0, 131.3, 125.1, 127.9, 136.0, 137.8, 146.9, 155.0, 170.5 and 173.0; *m/z* (FAB) 214 (M + 1, 100%).

2,6-Diiodo-3,4-dimethoxypyridine 30. Phosphorus trichloride (1.80 g, 12 mmol, diluted in 8 cm^3 of chloroform) was slowly added at 40 °C to a stirred solution of 2,6-diiodo-3,4 dimethoxypyridine *N*-oxide **24d** (1.63 g, 4.0 mmol) in chloroform (40 cm^3). The mixture was heated under reflux for 1.5 h and then cooled and poured into ice. The crude product was purified by chromatography on silica gel using CH_2Cl_2–hexane (3:2) as eluent to afford the *title compound* as a white solid (83%), mp 97 °C (Found: C, 21.5; H, 1.8; N, 3.65. $C_7H_7I_2NO_2$ requires C, 21.5; H, 1.8; N, 3.6%); ν_{max}(KBr)/cm^{-1} 2940, 1550, 1525, 1470 and 1415; δ_H(200 MHz; $CDCl_3$) 3.80 (3 H, s, OMe), 3.88 (3 H, s, OMe) and 7.13 (1 H, s, 5-H).

2-Iodo-4,5-dimethoxypyridine 29. *Method A: from* 2,6-*diiodo*-3,4-*dimethoxypyridine* **30**.—A solution of compound **30** (2.30 g, 5.9 mmol) in THF (25 cm^3) was added to a cold (−75 °C) solution of BuLi (13.0 mmol) in THF (140 cm^3) and the mixture was stirred for 0.5 h at −75 °C. It was then hydrolysed at this

temperature by a mixture of hydrochloric acid, ethanol and THF (1:1:1; 15 cm^3). After being warmed to room temperature, was diluted with water (20 cm^3), treated with sodium carbonate and sodium thiosulfate, and then extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated to leave the crude product, which was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to afford the *title compound* as a white solid (74%), mp 103–104 °C (Found: C, 31.9; H, 3.0; N, 5.1. $C_7H_8INO_2$ requires C, 31.7; H, 3.05; N, 5.3%); ν_{max}(KBr)/cm^{-1} 2970, 1575, 1500 and 1435; δ_H(200 MHz; $CDCl_3$) 3.85 (6 H, 2 s, 2 OMe), 7.07 (1 H, s, 5-H) and 7.80 (1 H, s, 6-H).

Method B: from 2-*iodo* 4,5-*dimethoxypyridine* N-*oxide* **23d**.—Phosphorus trichloride (0.5 g, 3.6 mmol, diluted in 5 cm^3 of chloroform) was slowly added at 40 °C to a stirred solution of **23d** (0.281 g, 1.0 mmol) in chloroform (10 cm^3). The mixture was heated under reflux for 1.5 h and then cooled and poured into ice. The title compound, obtained as a white solid (44%), was identical with compound **29** prepared by Method A.

4,4',5,5'-Tetramethoxy-2,2'-bipyridyl 31. Zinc powder (0.230 g, 3.5 mmol) was added to a stirred mixture of nickel(II) chloride hexahydrate (0.832 g, 3.5 mmol) and triphenylphosphine (3.67 g, 14 mmol) in dimethylformamide (20 cm^3) under argon at 50 °C. After 1 h, 2-iodo-4,5-dimethoxypyridine **29** (0.880 g, 3.32 mmol) was added to the stirred mixture and stirring continued for 48 h. The mixture was then treated with ammonia and extracted with hydrochloric acid (2 mol dm^{-3}). The aqueous layer was treated with potassium carbonate and then extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated to afford the crude product which was purified by chromatography on silica gel using ethyl acetate–methanol (97:3) as eluent to afford the *title compound* as a white solid (79%), mp 222 °C (Found: C, 60.9; H, 5.8; N, 10.1%; M^+, 276. $C_{14}H_{16}N_2O_4$ requires C, 60.9; H, 5.7; N, 9.9%; *M*, 276); ν_{max}(KBr)/cm^{-1} 2920, 1560, 1490 and 1435; δ_H(200 MHz; $CDCl_3$) 3.99 (6 H, s, OMe), 4.04 (6 H, s, OMe), 7.96 (2 H, s, 3-H and 3'-H) and 8.15 (2 H, s, 6-H and 6'-H); δ_C(50 MHz; $CDCl_3$) 55.8 (OMe), 56.5 (OMe), 103.2, 132.0, 145.7, 150.8 and 155.5.

2,2'-Bipyridyl-4,4',5,5'-tetraol 28. A solution of 4,4',5,5'-tetramethoxy-2,2'-bipyridyl **31** (0.215 g, 0.78 mmol) in 47% hydrobromic acid (4 cm^3) was heated under reflux for 20 h after which the excess of acid was distilled off and the residue was diluted with water and then evaporated. The residue was dissolved in water and the solution adjusted to pH 7 by addition of potassium carbonate. The resulting precipitate was filtered off and washed with distilled water, to afford the *title compound* (70%), mp >260 °C (Found: C, 54.8; H, 3.4; N, 12.5. $C_{10}H_8N_2O_4$ requires C, 54.6; H, 3.65; N, 12.7%); ν_{max}(KBr)/cm^{-1} 3312 (OH), 2731, 1630, 1608, 1542, 1480 and 1444; δ_H(200 MHz, [$^2H_6$]-DMSO) 7.05 (2 H, s, 3-H and 3'-H) and 7.68 (2 H, s, 6-H and 6'-H); *m/z* (CI, Bu^{t}H) 221 (M + 1, 100%).

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