3-Hydroxypyrrolo[2,3-*b*]pyridine and related compounds – indoxyl analogues with fused electron deficient rings†

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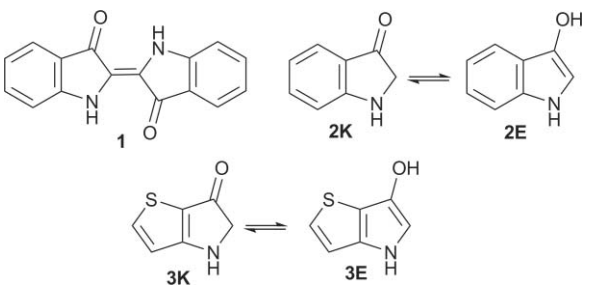
Flash vacuum pyrolysis (FVP) of 4-acetyltetrazolo[1,5-*a*]pyridine **5** at 400 °C provides 3-methyl isoxazolo[3,4-*b*]pyridine **6** whose structure was confirmed by X-ray crystallography. At higher pyrolysis temperatures, the unstable heteroindoxyl **8** was obtained, which exists as the keto form (1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one) **8K** in $CDCl_3$ solution and the enol tautomer (3-hydroxypyrrolo[2,3-*b*]pyridine) **8E** in DMSO. The heteroindoxyl **8** oxidatively dimerises to the heteroindigotin **9**, undergoes condensation reactions at the 2-position and reacts with methoxymethylene Meldrum's acid at the 1-position. FVP of the corresponding acetyltetrazolo[1,5-*a*]quinoline **19** was much more complex, with 2-(cyanophenyl)acetonitrile **30** (rather than a heteroindoxyl) the major product at 750 °C. FVP of 3-acetyl-4-azidoquinoline **24** at 400 °C gave 3-methylisoxazolo[4,3-*c*]quinoline **33**, but rearrangement to the heteroindoxyl was not observed at higher temperatures.

Introduction

Despite the wealth of information that is available on indigotin **1**[1] and its reduced monomer, indoxyl **2**,[2] the first example of a heteroindoxyl, in which the benzene ring is replaced by a heterocycle, was reported by our group in 2009.[3] This compound, 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3**, has an electron rich thiophene ring as the fused heterocycle. The synthetic strategy involved generation of an arylnitrene intermediate under flash vacuum pyrolysis (FVP) conditions, and its subsequent insertion into a CH bond of an adjacent acetyl group;[3] the method proved to be applicable to the preparation of indoxyl **2** itself.[4] In this paper, we report a further extension of the general strategy, aimed at the formation of indoxyl analogues with electron deficient fused rings (pyridine and quinoline) and the chemical properties of the products. These targets were explored to test if the synthetic strategy is robust (successful for the pyridin-2-yls; much more complex for the quinolin-2-yls) and to compare the reactivity and spectroscopic properties of the products with corresponding indoxyl and other heteroindoxyl derivatives.[3,4]



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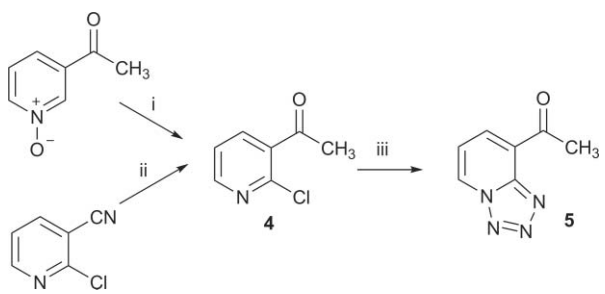
† Electronic supplementary information (ESI) available: Experimental, discussion of NMR spectra of **8** and X-ray tables. CCDC reference number 776464. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00076k

Results and discussion

Pyridine series

In the pyridine series, we successfully synthesised a precursor to 3-acetyl-2-pyridylnitrene but we were unable to develop routes to any of its isomers. Two methods were used to make 3-acetyl-2-chloropyridine **4**[5] (Scheme 1). The *N*-oxide route has been used previously[5] but the nitrile route (*cf.* ref. 6) has the advantage that only one step is required from commercially available starting materials and the overall yield and purity are higher. Treatment of the chloro-compound **4** with sodium azide in acidified aqueous ethanol gave a 90% yield of 4-acetyltetrazolo[1,5-*a*]pyridine **5**. This tetrazole is known,[7] but the published route appears to offer few advantages over the current methods.



Scheme 1 *Reagents and conditions* (i) $POCl_3$, 100 °C, 1 h, 66%; (ii) MeMgCl, THF, reflux, 1 h, 65%; (iii) NaN_3, EtOH–H_2O/HCl, 95 °C, 24 h, 90%.

As found for the previous examples,[3,4] FVP of the tetrazole **5** was strongly temperature dependent (Fig. 1) with the isoxazolo[3,4-*b*]pyridine **6** formed at low pyrolysis temperatures (80% yield from a preparative pyrolysis at 400 °C). Compound **6** is essentially the only product at furnace temperatures between 350–500 °C; 3-methylbenz[*c*]isoxazole, the benzenoid analogue of **6**, is the major product only between 300–400 °C.[4] Isoxazolo[3,4-*b*]pyridine **6** is therefore more stable to rearrangement than its benzo-analogue.

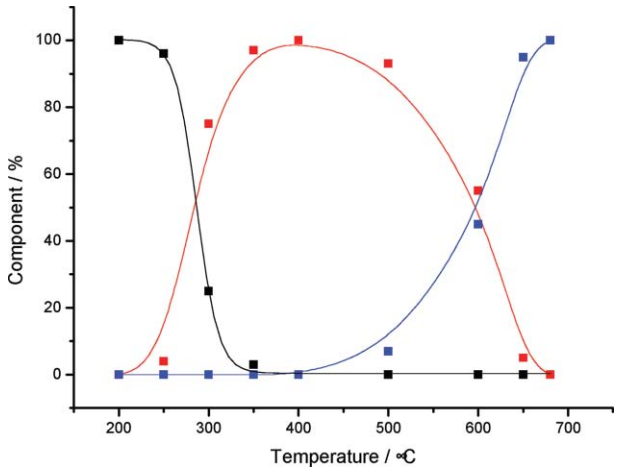
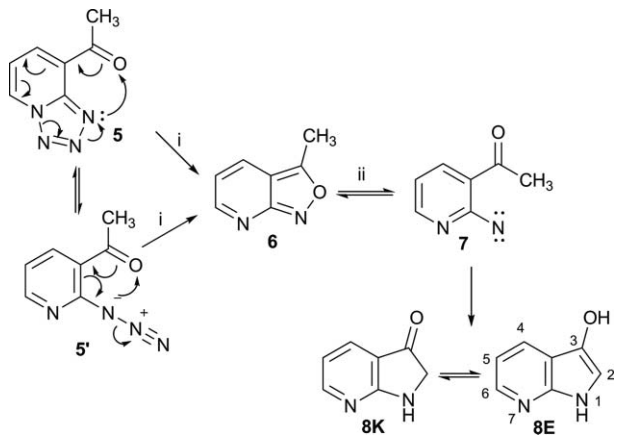


Fig. 1 Temperature-conversion graph for FVP of **5**, showing decrease of **5** (in black), appearance and subsequent disappearance of **6** (in red) and appearance of **8** (in blue).

The mechanism of isoxazole formation is likely to involve anchimeric assistance by the acetyl group rather than generation of the free nitrene,[3,4] but such assistance can occur either *via* the tetrazole **5** itself, or *via* the ring-opened azide **5′** (Scheme 2). The isoxazolo[3,4-*b*]pyridine **6** was characterised by its spectra (Experimental section) and by X-ray crystallography (PELGET) (Fig. 2) Data are listed in the ESI†. The crystal structure shows expected similarities to that of 3-phenylbenz[*c*]isoxazole.[8]



Scheme 2 *Reagents and conditions* (i) FVP, 400 °C, 80%; (ii) FVP, 680 °C, 57%.

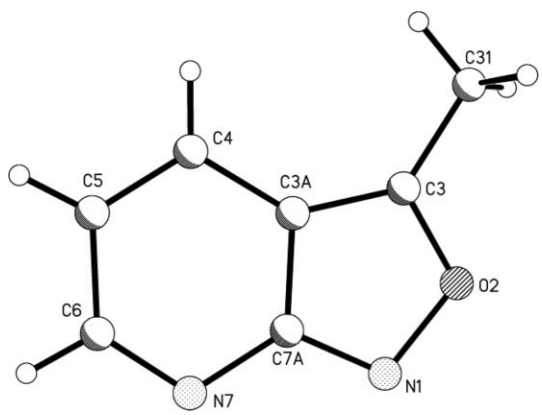
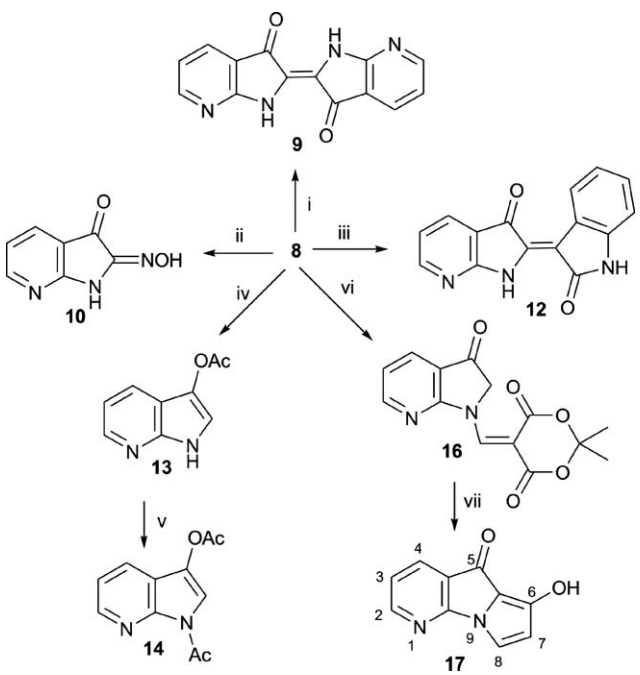


Fig. 2 Plot of **6** showing crystallographic numbering scheme.

At higher temperatures (*e.g.* 680 °C) electrocyclic ring opening of the isoxazolo[3,4-*b*]pyridine **6** generates the nitrene intermediate **7** which provides the heteroindoxyl **8** (57%) by CH insertion. This product was characterised by its solvent-dependent NMR spectra which showed the exclusive presence of the keto tautomer (1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one) **8K** in $CDCl_3$ solution (δ_H 3.90, CH_2) and of the enol tautomer (3-hydroxypyrrolo[2,3-*b*]pyridine) **8E** in DMSO solution [δ_H 6.62, H(2)]. A full analysis of the NMR spectra of the enol form **8E** is given in the ESI†. This compound is only the second parent heteroindoxyl to be reported,[3] though a few (mostly 1-substituted) derivatives are known.[9]

The general stability of the 1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one **8K** was low (half life in $CDCl_3$ solution in air *ca.* 3.5 h), due to oxidative dimerisation to the known[10] heteroindigitin species **9** which could be filtered off (*m*/*z* 264). The half-life of the enol form **8E** in DMSO was *ca.* three times longer. As mentioned above, the ratio of **8E**:**8K** is solvent dependent (see ESI†); in solvents of intermediate polarity the heteroindoxyl **8** shows a greater tendency to adopt the enol tautomer **8E** than indoxyl **2** itself. Deuterium exchange at the 2-position takes place readily in [$^2H_4$]methanol ($t_{\frac{1}{2}}$ *ca.* 90 min) and is *ca.* five times faster than for indoxyl **2** itself. Protonation of **8** probably occurs at N(7) in TFA solution (ESI†), rather than at the carbonyl group which is the normal behaviour of indoxyls.[3]

Despite its low stability, a number of successful reactions were carried out on freshly prepared samples of **8** (Scheme 3), though products were often isolated in very low yields. Reactions were observed to take place at the active methylene group, or at the nitrogen atom of the 5-membered ring, or at the oxygen atom. Thus, preparative oxidative dimerisation to the diazaindigotin **9**[10] (53%) was achieved with potassium ferricyanide. The EI-MS of **9** showed close correspondence to that of indigotin **1** (ESI†)



Scheme 3 *Reagents and conditions* (i) $K_3[Fe(CN)_6]$, 50 °C, 30 min, 53%; (ii) $NaNO_2$, 20 °C, 60 min, 22%; (iii) isatin **11**, Hunig's base, 20 °C, 30 min, 17%; (iv) Ac_2O 20 °C; (v) Ac_2O, reflux, 10 min, 88%; (vi) methoxymethylene Meldrum's acid **15** 20 °C, 20 h, 14%; (vii) FVP, 650 °C, 27%.

the UV-vis spectrum of **9** showed λ_{max} (DMSO) 567 nm; (DMF) 562 nm [lit.,[10] (ethanol) 556 nm], all solvents showed substantial hypsochromic shifts relative to indoxyl **2** itself [lit.,[11] λ_{max} (ethanol) 606 nm]. Reaction of **8** with nitrite ions gave the oxime **10** (22%), as found for indoxyl **2** (though *N*-nitrosation was observed with **3**). Condensation of **8** with isatin **11** in the presence of base gave the azaindirubin **12** (17%) λ_{max} (methanol) 505 nm; [λ_{max} (indirubin itself, methanol) 540 nm[12]]; again the aza-derivative shows a hypsochromic shift with respect to the parent compound.

Treatment of **8** with an excess of acetic anhydride gave the *N*,*O*-diacetylated product **14**; the *O*-acetylated product **13** could be observed as the major component of a mixture under milder conditions. This suggests that the initial reaction with the anhydride takes place at the oxygen atom. In contrast, reaction of **8** with methoxymethylene Meldrum's acid **15** gave the *N*-'Meldrumsated' product **16**, though again only in very low yield (14%) due to competitive formation of the diazaindigotin **9**. The regiochemistry of the reaction with **15** is the same as found in indoxyl **2** itself,[4] though a corresponding pyrrolone reacts instead at the 2-position.[13] FVP of **16** at 650 °C provided the unusual heterocyclic system 6-hydroxypyrido[3,2-*b*]pyrrolizin-5-one **17**, by a hydrogen transfer – electrocyclisation mechanism after methyleneketene formation, analogous to the pyrolyses of aminomethylene Meldrum's acid derivatives of other secondary amines.[14] The corresponding derivative of indoxyl **2** undergoes a similar reaction upon FVP and the product shows the same tautomeric form.[4]

Quinoline series

Two nitrene precursors were successfully synthesised in the quinoline series. 3-Acetyl-2-chloroquinoline **18** was made in two steps from 2-chloroquinoline-3-carboxaldehyde by adapting a literature method (ESI†).[15] Conversion to the tetrazole **19** by reaction with sodium azide in dilute ethanolic HCl took place at 95 °C and was complete in 3 h (91%) (Scheme 4). The product was characterised by its crystal structure (Fig. 3 and ESI†) which showed close similarities in the tetrazoloquinoline region to a related, heavily substituted, structure.[16]

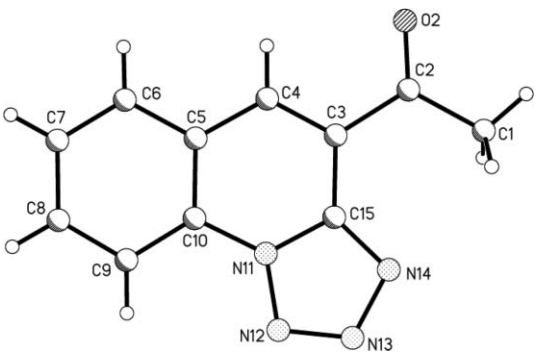
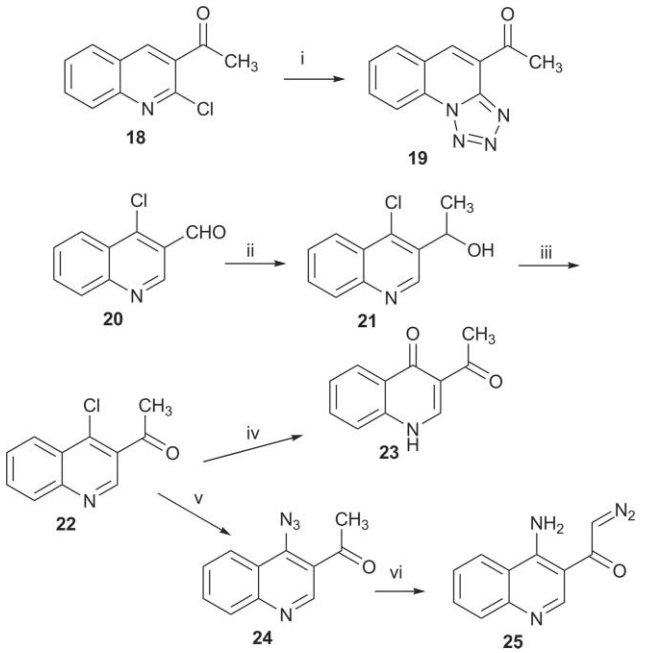


Fig. 3 Plot of **19** showing crystallographic numbering scheme.

A four-step route was used to generate 4-azido-3-acetylquinoline **24**. 4-Chloroquinoline-3-carboxaldehyde **20**, available in one step by Vilsmeier formylation of 2-aminoacetophenone,[17] gave the alcohol **21** (77%) by reaction with methylmagnesium chloride. Oxidation of **21** by activated manganese dioxide provided 3-acetyl-4-chloroquinoline **22** (62%) (Scheme 4).

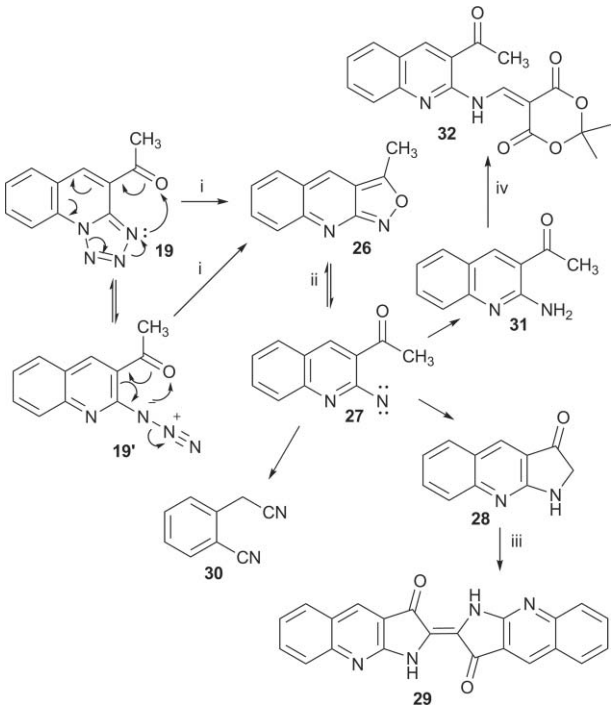


Scheme 4 *Reagents and conditions*: (i) NaN_3, EtOH–H_2O/HCl, 95 °C, 3 h, 91%; (ii) CH_3MgCl, THF, 20 °C, 30 min, 77%; (iii) MnO_2, toluene, 110 °C, 3 h, 62%; (iv) NaN_3, EtOH–H_2O/HCl, 95 °C, 24 h, 50%; (v) NaN_3, DMSO, 60 °C, 2.5 h, 57%; (vi) as (v), but 8 h at 60 °C, 24%.

Treatment with sodium azide under the aqueous conditions previously described caused unwanted hydrolysis of the chloro-substituent to give 3-acetylquinolin-4-one **23**[18] (50%) (ESI†), but the azide **24** was successfully obtained (57%) when the reaction was carried out in DMSO at 60 °C for 2.5 h (*cf.* ref. 19).

If the reaction of **22** with sodium azide in DMSO was allowed to proceed for a longer time (8 h at 60 °C) a product isomeric with the azide **24** could be isolated by chromatography in 24% yield. The product showed a CH signal in the ^{13}C NMR spectrum at δ_C 53.87 which is characteristic of diazoketones.[20] It therefore appears that the methyl group of **24** is sufficiently activated to undergo a diazo-transfer by an inter- or intra-molecular process, resulting in the formation of **25**.

Tetrazole **19** is a benzannelated-analogue of **5** and it was expected to show similar properties upon pyrolysis. In fact, FVP of **19** proved to be much more complex than that of **5** and the only product which could be isolated (at temperatures above 550 °C was 2-(cyanophenyl)acetonitrile **30** (see below; 40% preparative yield at 750 °C) (Scheme 5). In the first place the tetrazole **19** proved to be more thermally stable than **5**. The temperature profile (Fig. 4) shows that **19** comprises *ca.* 30% of the product mixture at 400 °C whereas **5** has been completely consumed at this temperature. Some of the isoxazoloquinoline **26** was tentatively identified from the chemical shift of its methyl group [δ_H(**26**) 3.04; δ_H(**6**) 2.82] but this was present in significant quantities (*ca.* 50% of the total pyrolysate) only at 400 °C. The low relative stability of **26** may be rationalised by the loss of aromaticity of both 6-membered rings. There is better evidence for the formation of 1,2-dihydropyrrolo[2,3-*b*]quinolin-3-one **28**, the heteroindoxyl (maximum 45% of the pyrolysate at 450 °C). A characteristic CH_2 signal at [δ_H(**28**) 4.04; δ_H(**8**) 3.90] was observed in the ^1H NMR spectrum of the pyrolysate mixture. If the pyrolysate (450 °C) was



Scheme 5 *Reagents and conditions*: (i) FVP, 350–750 °C; (ii) FVP, 450 °C; (iii) O_2; (iv) methoxymethylene Meldrum's acid **15** 20 °C, 30 min, 33%.

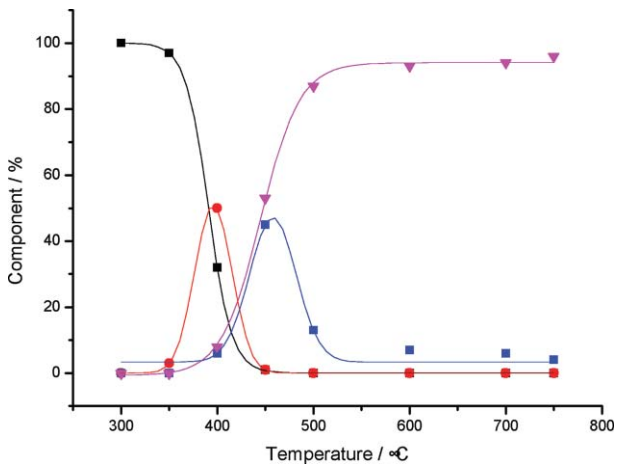


Fig. 4 Temperature-conversion graph for FVP of **19**, showing decrease of **19** (in black), increase and subsequent decrease of **26** (red) and **28** (blue) and increase of **30** (magenta); compounds **19**, **26**, **28** and **30** normalised to 100%.

allowed to stand in $CDCl_3$ solution for 3 days, the mass spectrum of the precipitate (*m*/*z* 364) which formed was consistent with the generation of the unknown heteroindigotin **29**, obtained by oxidative dimerisation of **28**. The region of the temperature profile between 350 °C and 450 °C shows the presence of all four species, **19**, **26**, **28** and **30**; in view of the reactivity of **28** with oxygen, it was therefore not surprising that neither **26** nor **28** (which show their maximum levels in this region) could be isolated by chromatography.

The pyrolysate was further complicated by the formation of 3-acetyl-2-aminoquinoline **31**, by hydrogen atom capture by the nitrene **27**; **31** could be isolated in 11% yield at 400 °C and was characterised by the formation of its methylene Meldrum's acid derivative **32**. The amount of (intermolecular) formation of **31** proved to be dependent on the throughput rate, with rapid throughput rate (corresponding to the presence of more material in the furnace at any instant) favouring formation of the amino-compound **31** (Fig. 5). Because of this variability, **31** was not included in the temperature profile (Fig. 4).

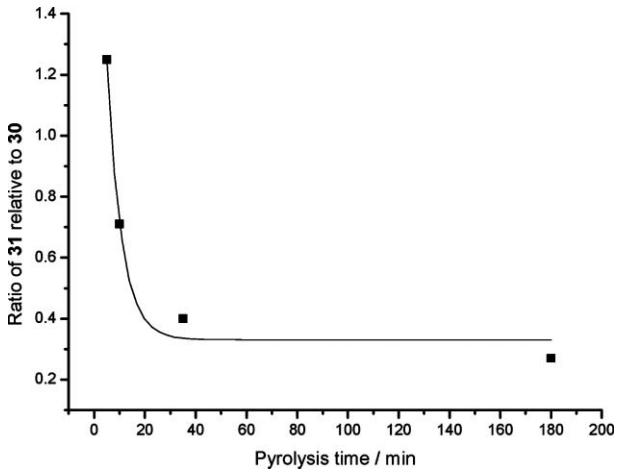
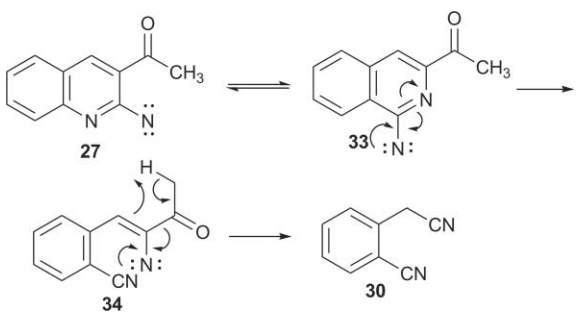


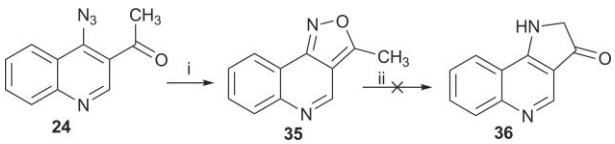
Fig. 5 Relative formation of **30** and **31** as a function of pyrolysis time.

2-(Cyanophenyl)acetonitrile **30** is a known product, along with indole-4-carbonitrile, from FVP of tetrazolo[1,5-*a*]quinoline itself.[21] Since no indole derivative could be detected in the pyrolysis reactions of **19**, it is clear that different intermediate(s) must be involved. A viable mechanism involves, first, an insertion-extrusion cycle, known for quinoline-2-nitrenes,[22] to generate the isoquinolinylnitrene **33**, followed by ring-opening to the vinylnitrene intermediate **34**. Collapse of the vinylnitrene to **30**, with concomitant loss of the acetyl group as ketene, must be faster than CH-insertion to form the indole (Scheme 6).



Scheme 6 Proposed mechanism for formation of **30**.

FVP of the 4-azido-compound **24** proceeded smoothly between 300–500 °C to provide 3-methylisoxazolo[4,3-*c*]quinoline **35** (73% preparative yield at 400 °C) (Scheme 7). Unfortunately, the expected rearrangement to the heteroindoxyl **36** at higher temperatures was complicated by a large number of competing reactions and no products could be isolated by chromatography of a 600 °C pyrolysate.



Scheme 7 *Reagents and conditions*: (i) FVP, 400 °C, 73%; (ii) FVP, 600 °C.

Conclusions

The work described in this paper has developed a viable synthetic route to the first electron-deficient heteroindoxyl **8** by FVP of 4-acetyltetrazolo[1,5-*a*]pyridine **5**. 3-Methylisoxazolo[3,4-*b*]pyridine **6** is obtained if the pyrolysis is carried out at a lower temperature. The thermal behaviour of **5** mirrors that of the anthranil-indoxyl system[4] and a thiophene analogue[3] and establishes that the synthetic route has some generality for bicyclic systems. The chemical properties of **8** show close similarities to indoxyl itself **2**[2] and to the electron-rich heteroindoxyl **3**.[3] In contrast, FVP of the quinolinyl analogues **19** and **24** do not provide a viable route to heteroindoxyls; addition of the fused benzene ring dramatically increases the scope for competitive rearrangements at high temperatures.

Experimental

^{1}H and ^{13}C NMR spectra were recorded at 200 (or 250) and 50 (or 63) MHz respectively for solutions in [^{2}H]chloroform unless otherwise stated. ^{13}C NMR signals refer to one CH unless otherwise stated. Coupling constants are quoted in Hz. Mass spectra were recorded under electron impact conditions.

4-Acetyltetrazolo[1,5-*a*]pyridine 5

3-Acetyl-2-chloropyridine **4** (see ESI†) (3.30 g, 21.2 mmol) and sodium azide (3.61 g, 55.6 mmol) were dissolved in aqueous ethanol (10%, 50 cm^3) containing hydrochloric acid (10%, 5 cm^3), and heated for 24 h at 95 °C. The solvent was removed by rotary evaporation, and water (10 cm^3) was added. The precipitate was collected, and washed with water to give 4-acetyltetrazolo[1,5-*a*]pyridine **5** (3.09 g, 90%); mp 96–98 °C (from ethanol) (lit.,[7] 134–136 °C, though spectra are in accord with published data); (Found: M$^+$, 162.0547. $C_7H_6N_4O$ requires *M* 162.0541); ν_{max} 3422, 1685 (C═O), 1617, 1552, 1276, 1217, 1096, 771 and 721 cm^{-1}; δ_H 3.15 (3H, s, CH_3), 7.45 (1H, t, $J_{6,5} = J_{6,7}$ 7.0), 8.32 (1H, dd, *J* 7.0 and $J_{5,7}$ 1.2) and 9.11 (1H, dd, *J* 7.0 and $J_{7,5}$ 1.2); δ_C 31.6 (CH_3), 116.8, 125.9 (quat), 129.4, 134.5, 147.9 (quat) and 193.9 (quat); *m*/*z* 162 (M$^+$, 21%), 134 (100), 125 (21), 91 (37) and 64 (61) (NMR spectra in close agreement with literature values[7]).

Flash vacuum pyrolysis reactions

The precursor was volatilized through an empty, electrically heated silica tube (35 × 2.5 cm) and the products were collected in a U-tube, cooled with liquid nitrogen, situated at the exit point of the furnace. CAUTION: aryl azides and tetrazoles are potentially explosive when heated. Although we experienced no problems with any of the reactions reported here, the following precautions were always taken. 1. Each individual pyrolysis was carried out on a scale no greater than 250 mg. 2. A metal inlet heater was always used. 3. The apparatus was protected by a blast shield while in use. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent and removed from the trap. The precursor, pyrolysis conditions [quantity of precursor, furnace temperature (T_f), inlet temperature (T_i), pressure (P) and pyrolysis time (t)] and products are quoted.

3-Methylisoxazolo[3,4-*b*]pyridine 6

Conditions were established by a temperature profile (ESI†). Low temperature FVP of 4-acetyltetrazolo[1,5-*a*]pyridine **5** (211 mg, 1.30 mmol, T_f 400 °C, T_i 45 °C, P 2×10^{-2} Torr, t 15 min) yielded 3-methylisoxazolo[3,4-*b*]pyridine **6** (140 mg, 80%); mp 72–74 °C; (Found: M$^+$, 134.0480. $C_7H_6N_2O$ requires *M* 134.0480); ν_{max} 1641, 1512, 1261, 1091, 1020, 802, 722 cm^{-1}; δ_H 2.82 (3H, s, CH_3), 6.93 [1H, dd, $J_{5,4}$ 9.0 and $J_{5,6}$ 3.9, H(5)], 7.88 [1H, dd, $J_{4,5}$ 9.0 and $J_{4,6}$ 1.6, H(4)] and 8.73 [1H, dd, $J_{6,4}$ 1.6 and $J_{6,5}$ 3.9, H(6)]; δ_C 13.12 (CH_3), 109.14 (quat), 119.39, 130.18, 158.55, 165.75 (quat) and 168.31 (quat); *m*/*z* 134 (M$^+$, 68%), 92 (32), 64 (44), 51 (46) and 43 (100).

3-Hydroxypyrrolo[2,3-*b*]pyridine 8E (1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one 8K)

Conditions were established by a temperature profile (ESI†). FVP of 4-acetyltetrazolo[1,5-*a*]pyridine **5** (209 mg, 1.29 mmol, T_f 680 °C, T_i 45 °C, P 2×10^{-2} Torr, t 15 min) yielded 1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one **8K** as a buff coloured sticky solid (100 mg, 57%); (Found: M$^+$, 134.0481. $C_7H_6N_2O$ requires *M* 134.0480); δ_H ($CDCl_3$ – keto tautomer); 3.90 (2H, s, CH_2), 5.66 (1H, s, NH), 6.72 [1H, dd, $J_{5,4}$ 7.3 and $J_{5,6}$ 5.1, H(5)], 7.83 [1H, dd, $J_{4,5}$ 7.3 and $J_{4,6}$ 1.5, H(4)] and 8.32 [1H, dd, $J_{6,4}$ 1.5 and $J_{6,5}$ 5.1, H(6)]; (^{13}C spectrum in $CDCl_3$ unavailable due to instability in this solvent).

The product was present as the enol tautomer (3-hydroxypyrrolo[2,3-*b*]pyridine **8E**) when dissolved in DMSO; δ_H ([$^2H_6$]DMSO – enol tautomer, 360 MHz); 6.62 [1H, s, H(2)], 6.80 [1H, dd, $J_{5,6}$ 4.7 and $J_{5,4}$ 7.9, H(5)], 7.76 [1H, dd, $J_{6,5}$ 4.7 and $J_{6,4}$ 1.6, H(6)], 7.97 [1H, dd, $J_{4,6}$ 1.6 and $J_{4,5}$ 7.9, H(4)], 8.57 (1H, s, OH) and 10.60 (1H, s, NH); δ_C ([$^2H_6$]DMSO, 90 MHz) 107.49 [C(2)], 114.30 [quat, C(3a)], 116.56 [C(5)], 126.09 [C(4)], 132.16 [quat, C(3)], 142.82 [C(6)] and 146.43 [quat, C(7a)]; *m*/*z* 134 (M$^+$, 100%), 119 (78), 106 (53), 94 (47), 92 (45), 79 (88), 67 (44) and 52 (71).

(*E*)-1*H*,1′*H*-[2,2′]Bi[pyrrolo[2,3-*b*]pyridinylidene]-3,3′-dione 9

1,2-Dihydropyrrolo[2,3-*b*]pyridin-3-one **8K** (46 mg, 0.34 mmol) was dissolved in a mixture of phosphate buffer (pH 7, 5.5 cm^3) and methanol (1 cm^3), and heated to 50 °C under a nitrogen atmosphere. A solution of potassium ferricyanide (113 mg, 0.42 mmol) in water (1 cm^3) was added dropwise over 10 min, and the mixture stirred for a further 30 min, keeping the temperature at 50 °C. The sample was cooled, stored overnight in a freezer, and the resulting precipitate collected and washed with water to give a purple solid identified as (*E*)-1*H*,1′*H*-[2,2′]bi[pyrrolo[2,3-*b*]pyridinylidene]-3,3′-dione **9** (24 mg, 53%); (Found: M$^+$ 264.0647. $C_{14}H_8N_4O_2$ requires *M* 264.0647); λ_{max} (DMSO) 567 nm [lit.,[10] (ethanol) 556 nm]; *m*/*z* 265 (45%), 264 (M$^+$, 100), 236 (30), 208 (30), 104 (39), 78 (56) and 77 (49). No NMR data were available due to insolubility.

1*H*-Pyrrolo[2,3-*b*]pyridine-2,3-dione-2-oxime 10

To a suspension of 1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one **8K** (140 mg, 1.04 mmol) in water (40 cm^3) and acetic acid (0.2 cm^3) was added sodium nitrite (135 mg, 1.73 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was filtered, the filtrate extracted with dichloromethane (3 × 100 cm^3), the organic extracts dried ($MgSO_4$) and the solvent removed by rotary evaporation to yield crude 1*H*-pyrrolo[2,3-*b*]pyridine-2,3-dione-2-oxime **10** (38 mg, 22%); (Found: M^+ 163.0382, $C_7H_5N_3O_2$ requires *M* 163.0382); δ_H ([$^2H_6$]DMSO) 7.00 [1H, dd, $J_{5,6}$ 5.6 and $J_{5,4}$ 7.6, H(5)], 7.95 [1H, dd, $J_{4,6}$ 1.7 and $J_{4,5}$ 7.6, H(4)], 8.42 [1H, dd, $J_{6,5}$ 5.6 and $J_{6,4}$ 1.7, H(6)], 10.97 (1H, br s) and 11.97 (1H, br s); δ_C ([$^2H_6$]DMSO) 109.31 (quat), 113.53 (quat), 116.64, 132.80, 155.93, 163.08 (quat) and 179.29 (quat); *m*/*z* 163 (M^+, 83%), 146 (54), 134 (58), 119 (100), 118 (49) and 91 (44).

2-[2-Oxo-1,2-dihydro-indol-(3*Z*)-ylidene]-1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one 12

To a solution of isatin **11** (87 mg, 0.58 mmol) in methanol (10 cm^3) was added solid 1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one **8K** (81 mg, 0.60 mmol) followed by *N*,*N*-diisopropylethylamine (*ca.* 0.066 cm^3) and the mixture was stirred at room temperature for 30 min. The resulting precipitate was collected and washed with methanol to yield 2-[2-oxo-1,2-dihydro-indol-(3*Z*)-ylidene]-1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one **12** (27 mg, 17%); mp > 330 °C; (Found: M^+ 263.0696, $C_{15}H_9N_3O_2$ requires *M* 263.0695); λ_{max} (methanol) 505 nm (ε 7900 mol^{-1} cm^{-1}); δ_H ([$^2H_6$]DMSO) 6.93 (1H, m, Ar–H), 7.05 (1H, m, Ar–H), 7.12 [1H, dd, $J_{5,4}$ 7.5 and $J_{5,6}$ 5.1, H(5)], 7.30 (1H, m, Ar–H), 8.11 [1H, dd, $J_{4,5}$ 7.5 and $J_{4,6}$ 1.7, H(4)], 8.50 (1H, dd, $J_{6,4}$ 1.7 and $J_{6,5}$ 5.1, H(6)], 8.68 (1H, m, Ar–H), 10.79 (1H, br s, NH) and 11.04 (1H, br s, NH); δ_C ([$^2H_6$]DMSO) 108.59 (quat), 110.32, 113.23 (quat), 118.17, 121.28 (quat), 121.98, 125.22, 130.55, 133.98, 137.94 (quat), 141.72 (quat), 156.06, 163.29 (quat), 171.40 (quat) and 186.45 (quat); *m*/*z* 264 (77%), 263 (M^+, 100), 236 (20), 235 (57), 207 (15) and 78 (50).

3-Acetoxy-1*H*-pyrrolo[2,3-*b*]pyridine 13

1,2-Dihydropyrrolo[2,3-*b*]pyridin-3-one **8K** (32 mg, 0.24 mmol) was placed in a 10 cm^3 round bottomed flask, and acetic anhydride (0.5 cm^3) added. The contents were swirled, and immediately evacuated to 2.8 × 10^{-2} Torr. After removal of solvent, ^{1}H NMR analysis of the product mixture showed a 1 : 2 ratio of 3-acetoxy-1-acetyl-1*H*-pyrrolo[2,3-*b*]pyridine **14** (see below) and 3-acetoxy-1*H*-pyrrolo[2,3-*b*]pyridine **13** identified by its ^{1}H NMR spectrum; δ_H 2.36 (3H, s, acetyl), 7.09 [1H, dd, $J_{5,4}$ 7.9 and $J_{5,6}$ 4.8, H(5)], 7.44 [1H, s, H(2)], 7.90 [1H, dd, $J_{4,5}$ 7.9 and $J_{4,6}$ 1.4, H(4)] and 8.26 [1H, dd, $J_{6,4}$ 1.4 and $J_{6,5}$ 4.8, H(6)].

3-Acetoxy-1-acetyl-1*H*-pyrrolo[2,3-*b*]pyridine 14

1,2-Dihydropyrrolo[2,3-*b*]pyridin-3-one **8K** (36 mg, 0.27 mmol) was dissolved in acetic anhydride (2 cm^3) and heated with a hot air blower for 10 min. The excess reagent was evaporated under reduced pressure to yield 3-acetoxy-1-acetyl-1*H*-pyrrolo[2,3-*b*]pyridine **14** (52 mg, 88%); (Found: M^+ 218.0691. $C_{11}H_{10}N_2O_3$ requires *M* 218.0691); δ_H 2.37 (3H, s, acetyl), 3.04 (3H, s, acetyl), 7.22 (1H, dd, $J_{5,4}$ 7.9 and $J_{5,6}$ 4.7, H(5)], 7.82 [1H, dd, $J_{4,5}$ 7.9 and $J_{4,6}$ 1.6, H(4)], 8.06 [1H, s, H(2)] and 8.39 [1H, dd, $J_{6,4}$ 1.6 and $J_{6,5}$ 4.7, H(6)]; δ_C 21.19 (CH_3), 26.53 (CH_3), 114.27, 117.64 (quat), 119.09, 127.23, 132.63 (quat), 145.20, 147.88 (quat), 168.20 (quat) and 169.03 (quat); *m*/*z* 218 (M^+, 4%), 176 (19), 134 (100), 133 (31), 79 (21) and 78 (30).

2,2-Dimethyl-5-(3-oxo-2,3-dihydropyrrolo[2,3-*b*]pyridin-1-ylmethylene)-1,3-dioxane-4,6-dione 16

Methoxymethylene Meldrum's acid **15** (142 mg, 0.76 mmol) was added to a suspension of 1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one **8K** (122 mg, 0.91 mmol) in acetonitrile (7 cm^3) and the mixture was stirred at room temperature for 20 h. The resulting solution was filtered through Celite, the solvent concentrated to 0.5 cm^3 and the precipitate collected to yield 2,2-dimethyl-5-(3-oxo-2,3-dihydropyrrolo[2,3-*b*]pyridin-1-ylmethylene)-1,3-dioxane-4,6-dione **16** (30 mg, 14%); (Found: M^+ 288.0746, $C_{14}H_{12}N_2O_5$ requires *M* 288.0746); δ_H 1.99 (6H, s, 2 CH_3), 4.87 (2H, s, CH_2), 7.37 [1H, dd, $J_{5,4}$ 6.6 and $J_{5,6}$ 4.9, H(5)], 8.13 [1H, dd, $J_{4,5}$ 6.6 and $J_{4,6}$ 1.8, H(4)], 8.71 [1H, dd, $J_{6,4}$ 1.8 and $J_{6,5}$ 4.9, H(6)] and 9.79 (1H, s, alkene); δ_C 26.95 (2CH_3), 59.10 (CH_2), 92.19 (quat), 103.94 (quat), 117.10 (quat), 122.04, 133.70, 146.00, 156.34, 160.03 (quat), 163.17 (quat), 163.32 (quat) and 191.62 (quat); *m*/*z* 288 (M^+, 0.4%), 230 (55), 186 (23), 158 (33), 152 (21) and 119 (100).

6-Hydroxypyrido[3,2-*b*]pyrrolizin-5-one 17

FVP of 2,2-dimethyl-5-(3-oxo-2,3-dihydropyrrolo[2,3-*b*]pyridin-1-ylmethylene)-1,3-dioxane-4,6-dione **16** (29 mg, 0.10 mmol, T_f 650 °C, T_i 160 °C, P 2.3 × 10^{-2} Torr, t 10 min) yielded 6-hydroxypyrido[3,2-*b*]pyrrolizin-5-one **17** (5 mg, 27%); (Found: M^+ 186.0429. $C_{10}H_6N_2O_2$ requires *M* 186.0429); δ_H ([$^2H_6$]DMSO) 5.94 [1H, d, $J_{7,8}$ 3.0, H(7)], 7.17 [1H, dd, $J_{3,4}$ 7.4 and $J_{3,2}$ 5.1, H(3)], 7.50 [1H, d, $J_{8,7}$ 3.0, H(7)], 7.91 [1H, dd, $J_{4,3}$ 7.4 and $J_{4,2}$ 1.6, H(4)] and 8.36 [1H, dd, $J_{2,4}$ 1.6 and $J_{2,3}$ 5.1, H(2)]; δ_C ([$^2H_6$]DMSO) 106.92, 116.35 (quat), 120.04, 121.71, 123.64 (quat), 132.10, 151.28, 151.48 (quat), 154.19 (quat) and 172.75 (quat); *m*/*z* 187 (12%), 186 (M^+, 100), 160 (12), 104 (17), 103 (11) and 77 (12).

4-Acetyltetrazolo[1,5-*a*]quinoline 19

3-Acetyl-2-chloroquinoline **18** (1.60 g, 7.79 mmol) (ESI†) and sodium azide (1.23 g, 19.1 mmol) were suspended in a mixture of aqueous ethanol (10%, 110 cm^3) and hydrochloric acid (10%, 5.5 cm^3) and heated at 95 °C for 3 h. The solvents were removed by rotary evaporation, water (*ca.* 35 cm^3) was added and the resulting precipitate collected and washed with water to yield 4-acetyltetrazolo[1,5-*a*]quinoline **19** (1.53 g, 91%); mp 186–188 °C (from acetonitrile); (Found: M^+ 212.0698. $C_{11}H_8N_4O$ requires *M* 212.0698); δ_H 3.12 (3H, s, acetyl), 7.79 (1H, ddd, *J* 0.9, 7.2 and 8.1, Ar–H), 8.01 (1H, ddd, *J* 0.6, 7.2 and 7.8, Ar–H), 8.14 (1H, dd, *J* 0.9 and 7.8, Ar–H), 8.67 [1H, s, H(4)] and 8.72 (1H, dd, *J* 0.6 and 8.1, Ar–H); δ_C 30.95 (CH_3), 116.88, 122.49 (quat), 122.69 (quat), 128.50, 130.94, 131.79 (quat), 133.46, 135.97, 146.17 (quat) and 193.72 (quat); ν_{max} 1693 (acetyl), 1618, 1599, 1561, 1465, 1409 and 1091 cm^{-1}; *m*/*z* 212 (M^+, 21%), 184 (100), 142 (62), 129 (45), 115 (65) and 114 (50).

1-(4-Chloroquinolin-3-yl)-ethanol 21

A solution of 4-chloroquinoline-3-carboxaldehyde[17] (ESI†) **20** (524 mg, 2.74 mmol) dissolved in anhydrous THF (10 cm^3) was added dropwise at room temperature under a nitrogen atmosphere to a solution of methyl magnesium chloride (9 mmol) in anhydrous THF (5.5 cm^3), and stirred for 30 min. The solution was quenched with dilute aqueous ammonium chloride solution (10%, 20 cm^3), extracted with ethyl acetate (3 × 20 cm^3), the organic extracts were dried ($MgSO_4$) and the solvent removed to yield 1-(4-chloroquinolin-3-yl)-ethanol **21** as an oil (438 mg, 77%); bp 155 °C (12 Torr); (Found: M^+ 207.0450 and 209.0420, $C_{11}H_{10}ClNO$ requires *M* 207.0451 and 209.0421); δ_H 1.58 (3H, d, *J* 6.5, CH_3), 5.52 (1H, q, *J* 6.5, CH), 7.59 (1H, ddd, *J* 1.2, 8.1 and 9.3, Ar–H), 7.70 (1H, ddd, *J* 1.5, 7.8 and 9.3, Ar–H), 8.03 (1H, dd, *J* 1.2 and 7.8, Ar–H), 8.15 (1H, dd, *J* 1.5 and 8.1, Ar–H) and 9.05 [1H, s, H(2)]; δ_C 23.60 (CH_3), 65.93, 123.93, 125.61 (quat), 127.61, 129.10, 129.79, 135.39 (quat), 138.71 (quat), 147.64 (quat) and 148.67; *m*/*z* 209 (M^+, 55%), 207 (M^+, 58), 194 (58), 192 (100), 164 (48), 128 (58) and 101 (52).

3-Acetyl-4-chloroquinoline 22

1-(4-Chloroquinolin-3-yl)-ethanol **21** (100 mg, 0.48 mmol) and manganese dioxide (512 mg, 5.95 mmol) were heated under reflux in toluene (4 cm^3) for 3 h. The mixture was cooled to room temperature, filtered through Celite and the solvent removed to yield 3-acetyl-4-chloroquinoline **22** (62 mg, 62%); bp 175 °C (30 Torr); (Found: M^+ 205.0296 and 207.0262. $C_{11}H_8ClNO$ requires *M* 207.0294 and 207.0265); δ_H 2.79 (3H, s, acetyl), 7.71 (1H, m, Ar–H), 7.84 (1H, m, Ar–H), 8.13 (1H, m, Ar–H), 8.35 (1H, m, Ar–H) and 8.97 [1H, s, H(2)]; δ_C 31.23 (CH_3), 124.94, 125.58 (quat), 128.38, 129.67, 130.87 (quat), 131.67, 140.56 (quat), 148.80, 149.24 (quat) and 198.67 (quat); *m*/*z* 207 (M^+, 67%), 205 (M^+, 65), 192 (54), 190 (100), 162 (70), 135 (27) and 127 (17).

3-Acetyl-4-azidoquinoline 24

3-Acetyl-4-chloroquinoline **22** (1.05 g, 4.95 mmol) and sodium azide (1.06 g, 16.3 mmol) were dissolved in DMSO (50 cm^3) and the solution was heated at 60 °C for 2.5 h (*cf.* ref. 19). Water (50 cm^3) was added, and the resulting precipitate was collected and washed with water to yield 3-acetyl-4-azidoquinoline **24** (614 mg, 57%); mp 138–139 °C (from methanol); (Found: M^+, 212.0698, $C_{11}H_8N_4O$ requires *M* 212.0698); δ_H 2.80 (3H, s, acetyl), 7.61 (1H, m, Ar–H), 7.82 (1H, m, Ar–H), 8.07 (1H, m, Ar–H), 8.36 (1H, m, Ar–H) and 9.17 [1H, s, H(2)]; δ_C 29.57 (CH_3), 123.55 (quat), 123.94, 127.39, 129.09, 131.03 (quat), 132.08, 146.81 (quat) 149.58 (quat), 150.69 and 197.09 (quat); *m*/*z* 212 (M^+, 10%), 184 (100), 169 (45), 156 (41), 155 (53) and 102 (33).

1-(4-Aminoquinolin-3-yl)-2-diazo-ethanone 25

3-Acetyl-4-chloroquinoline **22** (107 mg, 0.52 mmol) and sodium azide (103 mg, 1.58 mmol) were dissolved in DMSO (10 cm^3) and heated at 60 °C for 8 h. The solution was quenched with water (5 cm^3) extracted with dichloromethane (5 × 20 cm^3), the organic extracts back-washed with water, dried ($MgSO_4$) and the solvent removed. The residue was purified by dry flash chromatography (50% ethyl acetate in hexane) to yield the chloro- and azido- compounds **22** and **24**, spectroscopic data for both as previously reported. Further elution of the column with methanol yielded 1-(4-aminoquinolin-3-yl)-2-diazo-ethanone **25** (26 mg, 24%); (Found: M^+, 212.0693, $C_{11}H_8N_4O$ requires *M* 212.0698); δ_H ([$^2H_6$]DMSO) 7.12 (1H, s, CH-diazo), 7.45 (1H, m, Ar–H), 7.61–7.83 (2H, m, 2Ar–H), 8.37 (1H, m Ar–H) and 8.72 [1H, s, H(2)]; δ_C ([$^2H_6$]DMSO) 53.87, 106.58 (quat), 118.13 (quat), 123.15, 124.91, 128.72, 131.20, 148.22 (quat), 149.83, 152.61 (quat) and 187.17 (quat); *m*/*z* 212 (M^+, 18%), 184 (99), 156 (50), 155 (100) and 129 (42).

2-(Cyanophenyl)acetonitrile 30

Conditions were established by a temperature profile (ESI†) of **19**. FVP of 4-acetyltetrazolo[1,5-*a*]quinoline **19** (161 mg, 0.76 mmol, T_f 750 °C, T_i 90 °C, P 3.8×10^{-2} Torr, t 22 min) yielded a mixture that was purified by dry flash chromatography (50% ethyl acetate in hexane) to yield 2-(cyanophenyl)acetonitrile **30** as the major product (41 mg, 46%); δ_H 4.02 (2H, s, CH_2), 7.51 (1H, m, Ar–H) and 7.68–7.84 (3H, m, 3Ar–H) (compatible with literature data[21]) δ_C 22.46 (CH_2), 112.06 (quat), 115.82 (quat), 116.36 (quat), 127.51 (quat), 128.66, 126.86, 133.08 and 133.57; *m*/*z* 142 (M^+, 100%), 141 (54), 115 (85), 114 (43), 88 (29) and 71 (34).

The FVP also yielded small amounts of 3-methyl-2-oxa-1,9-diazacyclopenta[*b*]naphthalene **26** and 1,2-dihydropyrrolo[2,3-*b*]quinolin-3-one **28**, assigned from the ^1H NMR spectroscopic data of the crude pyrolysate, although these products could not be isolated. Characteristic signals of 3-methyl-2-oxa-1,9-diazacyclopenta[*b*]naphthalene **26**; δ_H 3.04 (3H, s, CH_3); those of 1,2-dihydropyrrolo[2,3-*b*]quinolin-3-one **28** were δ_H 4.04 (2H, s, CH_2).

FVP of 4-acetyltetrazolo[1,5-*a*]quinoline **19** at a lower temperature (330 mg, 1.56 mmol, T_f 400 °C, T_i 95 °C, P 2.4×10^{-2} Torr, t 25 min) yielded a mixture which was purified by dry flash chromatography (25% ethyl acetate in hexane) to yield 3-acetyl-2-aminoquinoline **31** (33 mg, 11%); mp 155–157 °C; (Found: M^+ 186.0797, $C_{11}H_{10}N_2O$ requires *M* 186.0793); δ_H 2.71 (3H, s, acetyl), 7.24 (1H, m, Ar–H), 7.56–7.68 (3H, m, Ar–H) and 8.52 [1H, s, H(4)]; δ_C 27.36 (CH_3), 116.67 (quat), 121.96 (quat), 122.66, 125.26, 129.00, 132.97, 143.14, 150.00 (quat), 156.07 (quat) and 199.28 (quat); *m*/*z* 186 (M^+, 100%), 171 (47), 144 (69), 143 (60), 116 (81) and 89 (47).

(E)-1*H*,1′*H*-[2,2′]Bi[pyrrolo[2,3-*b*]quinolinylidene]-3,3′-dione 29

An NMR sample containing *ca* 20 mg of the product(s) from FVP of 4-acetyltetrazolo[1,5-*a*]quinoline **19** (65 mg, 0.31 mmol, T_f 450 °C, T_i 85 °C, P 2.8×10^{-2} Torr, t 15 min) was dissolved in $CDCl_3$ and left at room temperature for three days, and the resulting precipitate collected. Analysis by mass spectrometry showed the presence of (*E*)-1*H*,1′*H*-[2,2′]bi[pyrrolo[2,3-*b*]quinolinylidene]-3,3′-dione **29**; (Found: M^+ 364.0963, $C_{22}H_{14}N_4O_2$ requires *M* 364.0963); *m*/*z* 364 (M^+, 31%), 144 (54), 143 (98), 129 (51), 115 (55) and 81 (100).

5-[(3-Acetylquinolin-2-ylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione 32

To a solution of 3-acetyl-2-aminoquinoline **31** (crude, 30 mg, 0.16 mmol) in acetonitrile (5 cm^3) was added a solution of methoxymethylene Meldrum's acid **15** (30 mg, 0.16 mmol) in

acetonitrile (1 cm^3) and the mixture was stirred at room temperature for 30 min. The resulting solution was concentrated to 2 cm^3 and the precipitate collected and washed with acetonitrile to yield 5-[(3-acetylquinolin-2-ylamino)-methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **32** (18 mg, 33%); (Found: M^+ 340.1063, $C_{18}H_{16}N_2O_5$ requires *M* 340.1059); δ_H 1.78 (6H, s, $2CH_3$), 2.85 (3H, s, acetyl), 7.59 (1H, m, Ar–H), 7.84 (3H, m, 3Ar–H), 8.50 [1H, s, H(4)] 9.83 (1H, d, *J* 13.3, alkene) and 13.65 (1H, br. d, *J* 13.3, NH); δ_C 27.15 ($2CH_3$), 27.55 (CH_3), 91.15 (quat), 104.75 (quat), 118.19 (quat), 125.00 (quat), 126.73, 128.07, 128.85, 133.83, 143.12, 146.77 (quat), 148.14 (quat), 150.64, 163.75 (quat), 163.85 (quat) and 190.04 (quat); *m*/*z* 340 (M^+, 34%), 282 (78), 238 (58), 210 (100), 186 (26) and 168 (26).

3-Methylisoxazolo[4,3-*c*]quinoline 35

The pyrolysate from the FVP of 3-acetyl-4-azidoquinoline **24** (81 mg, 0.38 mmol, T_f 400 °C, T_i 75 °C, P 4.6×10^{-2} Torr, t 10 min) was dissolved in chloroform to yield 3-methylisoxazolo[4,3-*c*]quinoline **35** (51 mg, 73%); mp 115–116 °C (from toluene); (Found: M^+ 184.0631, $C_{11}H_8N_2O$ requires *M* 184.0631); δ_H 2.91 (3H, s, CH_3), 7.62 (1H, m, Ar–H), 7.76 (1H, m, Ar–H), 8.04 (1H, m, Ar–H), 8.39 (1H, m, Ar–H) and 8.97 [1H, s, H(4)]; δ_C 12.18 (CH_3), 111.06 (quat), 116.21 (quat), 123.60, 127.99, 129.76, 131.13, 144.99 (quat), 146.53, 155.27 (quat) and 168.74 (quat); *m*/*z* 185 (89%), 184 (M^+, 100), 169 (68), 156 (75), 155 (82),142 (60) and 129 (46).

Crystallography

Crystal data for **6** have been previously deposited with the Cambridge Crystallographic Data Centre, and are available as refcode PELGET.

Crystal data for 19. $C_{11}H_8N_4O$, $M = 212.21$. Monoclinic, space group $P2_1/n$. a = 9.6400(4), b = 5.6225(2), c = 17.8376(7) Å, β = 100.381(2)°, V = 950.99(6) $Å^3$, T = 150 K, Z = 4. Data were collected with Mo-Kα radiation on a Bruker Smart Apex diffractometer equipped with an Oxford cryosystems low-temperature device. The structure was solved by direct methods and refined by full matrix least squares against F^2.[23] All non-H atoms were refined with anisotropic displacement parameters and H-atoms were placed in calculated positions. The final *R* factor, based on *F* and 1913 out of 2259 data with $F > 4\sigma(F)$ was 0.0491. The final difference map extremes were + 0.33 and –0.26 $eÅ^{-3}$.

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