Synthesis of 5,6-dihydropyrrolo[2,1-*a*]isoquinolines by rearrangement of 5-methyleneisoxazolidines generated from 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline *N*-oxides with allenes: a novel consecutive rearrangement to fused-ring pyrrole derivatives

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5-Methyleneisoxazolidines 3, obtained by 1,3-dipolar cycloaddition of 1-methyl- and 1-(substituted methyl)isoquinoline *N*-oxides 1 with electron-deficient allenes 2, undergo thermal rearrangement when heated at 130–150 °C to afford two isomers, 4 and 5, of 5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivatives. The formation of these fused-ring pyrroles can be rationalized on the basis of two competitive consecutive rearrangements occurring, one of which, as the minor route, involves an initial 1,3-hydrogen shift to give 4-isoxazolines followed by known rearrangement *via* acylaziridine intermediates, while the other, the major one, involves transient formation of pyrrolidin-3-ones followed by their novel rearrangement *via* 3,4 bond scission and cyclocondensation.

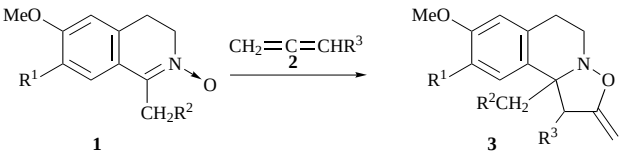
Introduction

5,6-Dihydropyrrolo[2,1-*a*]isoquinolines have attracted considerable interest in recent years because they display valuable pharmacological activities.[1] A variety of methodologies have emerged for their synthesis including: the Tschitschibabin reaction between isoquinolines and halogeno keto esters,[2] the 1,5-electrocyclization of vinyl azomethine ylides generated from imines by 1,2-prototropy and by deprotonation of iminium ions,[3] 1,3-dipolar cycloaddition of mesoionic oxazolone formed from substituted 2-(1-oxo-1,2,3,4-tetrahydroisoquinoline-2-yl)acetic acid with dimethyl acetylenedicarboxylate (DMAD),[1a] the reaction of isoquinolinium ketene dithioacetal with active methylene compounds,[4] the reaction of acetylenic tricarbonyls with β-phenylethylamine,[5] and base-catalyzed ring transformation of 1-furyl-3,4-dihydroisoquinolines.[6] Nevertheless, new and efficient methods for the synthesis of dihydropyrrolo[2,1-*a*]-isoquinolines are still needed in connection with the development of novel, biologically active compounds. In an earlier study, we have first reported that the rearrangement of 4-isoxazoline prepared by 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline *N*-oxide with alkynes provides a convenient method for the synthesis of dihydropyrrolo[2,1-*a*]isoquinolines.[7] Recently, it is also reported that the reaction of hydrazonoyl chlorides with 2-(3,4-dihydro-6,7-dimethoxyisoquinolin-1-yl)cinnamonitrile in the presence of triethylamine affords 5,6-dihydropyrrolo[2,1-*a*]isoquinoline[8] and the cyclocondensation of 1-chloromethyl-3,4-dihydroisoquinoline hydrochloride with aliphatic ketones gives 2,3-dialkyl-5,6-dihydropyrrolo[2,1-*a*]isoquinolines.[9]

Our interest in the 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline *N*-oxide arose from our ongoing program of devising simple new routes to fused-ring 5-membered heterocycles, especially dihydropyrrolo[2,1-*a*]isoquinolines. Thus, we have reported that 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline *N*-oxides with substituted allenes gives stable 5-methyleneisoxazolidines.[10] In continuation of our work in this area, we thought it worthwhile to study the thermal rearrangement of these 5-methyleneisoxazolidines at higher temperature. Our expectation was that these systems would undergo a 1,3-hydrogen shift to give 4-isoxazoline initially and then rearrange to fused-ring pyrroles. However, we obtained two kinds of dihydropyrrolo[2,1-*a*]isoquinolines, one of which was an unexpected product derived by a novel sequential rearrangement route. In this paper, we report the results of this investigation.

Results and discussion

In an earlier study,[10] we described 1,3-dipolar cycloadditions of 3,4-dihydroisoquinoline *N*-oxides such as **1a** and **1b**, with electron-deficient allenes such as **2a** and **2b**, to afford regioselectively *endo*- and *exo*-5-methyleneisoxazolidines **3** (Scheme 1). These products were quite stable and even at 80 °C no rearrangement took place.



1 **3**

a: R^1 = MeO, R^2 = H
b: R^1 = H, R^2 = H
c: R^1 = MeO, R^2 = CH_3
d: R^1 = H, R^2 = CH_3
e: R^1 = MeO, R^2 = Ph

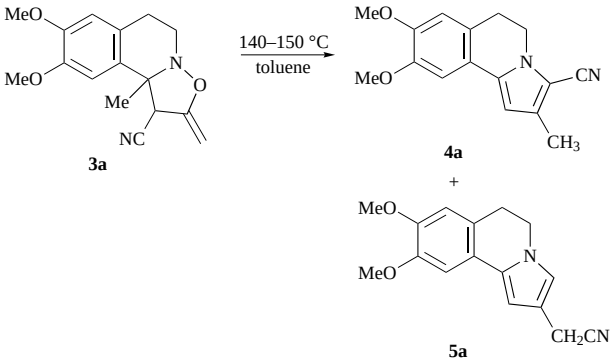
a: R^3 = CN
b: R^3 = CO_2Et

a: R^1 = MeO, R^2 = H, R^3 = CN
b: R^1 = MeO, R^2 = H, R^3 = CO_2Et
c: R^1 = H, R^2 = H, R^3 = CN
d: R^1 = H, R^2 = H, R^3 = CO_2Et
e: R^1 = MeO, R^2 = CH_3, R^3 = CN
f: R^1 = MeO, R^2 = CH_3, R^3 = CO_2Et
g: R^1 = H, R^2 = CH_3, R^3 = CN
h: R^1 = H, R^2 = CH_3, R^3 = CO_2Et
i: R^1 = MeO, R^2 = Ph, R^3 = CN

Scheme 1

It has been reported that some 5-methyleneisoxazolidines, when heated, underwent a 1,3-hydrogen shift to give 4-isoxazolines rather than N–O bond scission to give pyrrolidinones. Thus, in the present case, it would be expected that 5-methyleneisoxazolidines **3** would undergo a 1,3-hydrogen shift to give 4-isoxazolines and that this would be followed by rearrangement to fused-ring pyrroles at higher temperature in a similar way to our previous report.[7] Therefore, our attention was focused on the rearrangement of 5-methyleneisoxazolidine generated from 1,3-dipolar cycloaddition of 1-methyl-3,4-dihydroisoquinoline *N*-oxide with substituted allenes. Initially we heated *endo*-**3a** in toluene in a sealed tube at 140–150 °C under an atmosphere of argon, monitoring the reaction by TLC until *endo*-**3a** was converted completely. The two products

formed were easily isolated by preparative TLC (silica gel) using ethyl acetate–hexane (1:2) as eluent. As expected, the fused-ring pyrrole **4a** was obtained as the minor product (29%), the major product being the unexpected fused-ring pyrrole **5a** (40%). Similarly, two products **4a** and **5a** were also obtained in the similar yields by the thermal rearrangement of *exo*-**3a**. The product structures were assigned on the basis of spectral data (Scheme 2); in the case of **4a**, the ^{1}H NMR spectrum signals at

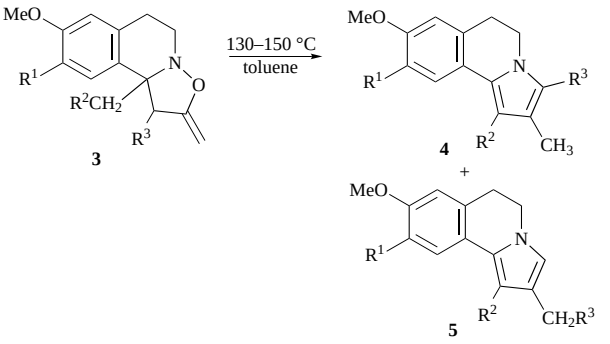


Scheme 2

δ 6.27 (s, 1-H) and 2.27 (s, 2-CH_3). The ^{1}H NMR spectrum of **5a** showed signals at δ 6.35 and 6.67 (both d, J 1.8 Hz, 1-H, 3-H) (generally, in fused-ring pyrroles, $J_{1\text{-H,2-H}} = 4.0$ or 3.5 Hz)[7,9,11,12] and 3.61 (s, strongly deshielded by the influence of the cyano group). It is valuable to notice the difference in the IR characteristics of the cyano group in **4a** and **5a**; in the former CN absorption appeared at 2197 cm^{-1} and was stronger than that of the latter (at 2247 cm^{-1}) because of conjugation.

Similarly, two fused-ring pyrroles **4b**, **4c** and **5b–d** were obtained from the corresponding 5-methyleneisoxazolidines **3b–d** by thermal rearrangement (Scheme 3). The spectral data of the products were all in accord with the structures assigned. In the case of **3d**, only **5d** was obtained as the major product.

The results mentioned above encouraged us to extend the 1,3-dipolar cycloaddition of 1-(substituted methyl)-3,4-dihydroisoquinoline *N*-oxides with allenes and their rearrangement. Thus, 1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1c**, 1-ethyl-6-methoxy-3,4-dihydroisoquinoline *N*-oxide **1d** and 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide **1e** have been allowed to react with the allenes **2a** or **2b** to give 5-methyleneisoxazolidines **3e–i** (Scheme 1) as a mixture of *endo*- and *exo*-isomers. Similar rearrangement conditions have been used for the thermal rearrangement of **3e–i** to give the fused-ring pyrroles **4e–i** and **5e–i** (Scheme 3). The conditions and



Scheme 3

results are summarized in Table 1. In the case of 10b-(substituted methyl)-5-methyleneisoxazolidine, the rearrangement showed more complex behaviour; for example, in the case of **3g**, a minor thermolysis product was obtained besides the fused-ring pyrroles **4g** and **5g**, which was identified as 6-methoxy-1-ethylisoquinoline **6a**. However, in the case of **3h**, no rearrangement product was obtained, only the thermolysis product **6a**.

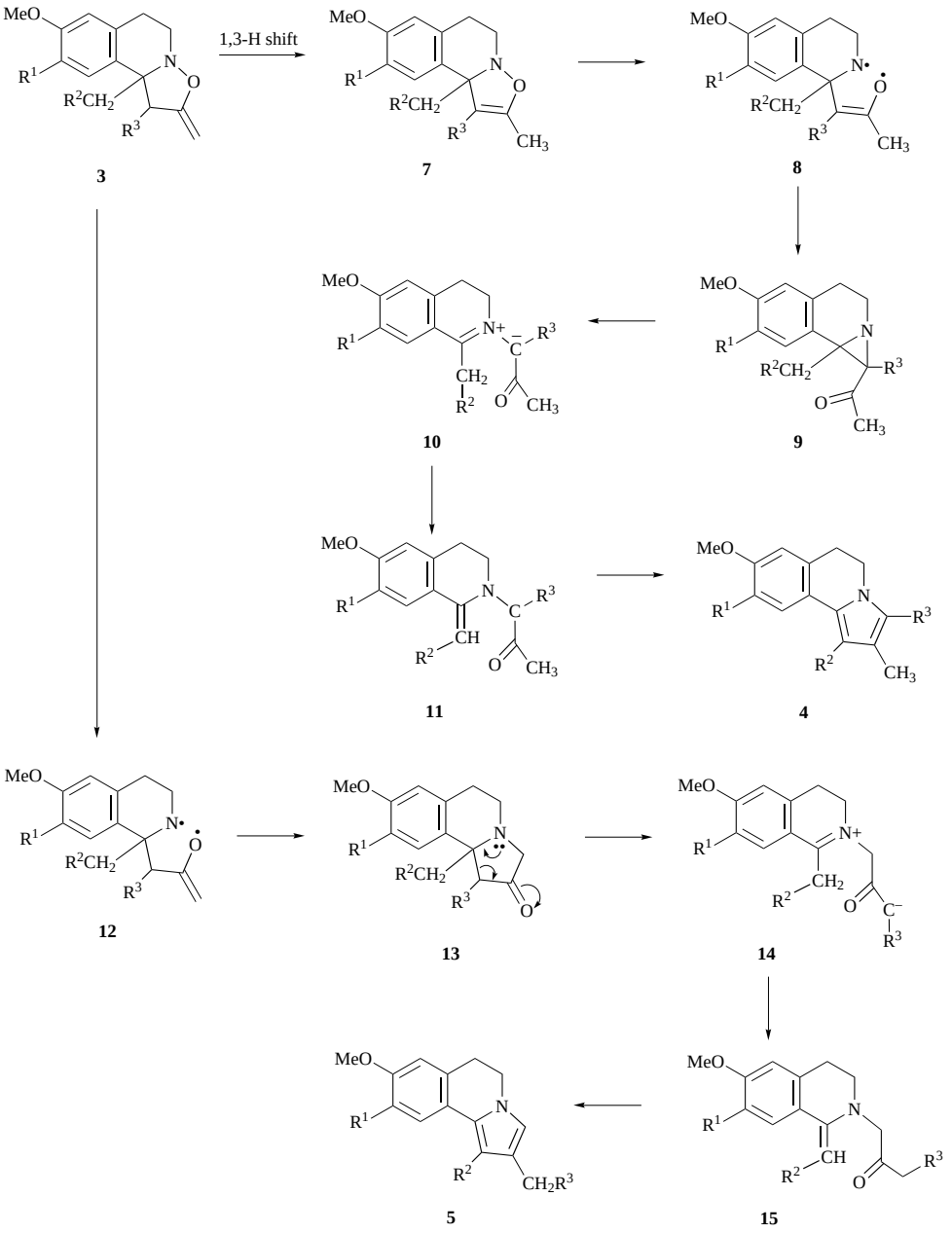
The formation of **4** can be rationalized in terms of an initial 1,3-hydrogen shift to give a transient 4-isoxazoline followed by rearrangement *via* an acylaziridine; however, the formation of **5** involves another process. The nitrogen–oxygen bond of the heterocyclic ring is expected to be readily cleaved, since such heteroatom–heteroatom bonds are known to be relatively weak.[13] Thus, at the higher temperature, besides the 1,3-hydrogen shift to give **7**, cleavage of the weak N–O bond directly gave **12**. A plausible mechanism for the formation of **4** and **5** is given in Scheme 4. The pyrrolidinone **13** formed *via* **12** upon cleavage would give **14** and this by cyclodehydration would afford the pyrrole **5** in a similar fashion to the formation of **4** from **9** and **10**.

In summary, we have demonstrated that 5-methyleneisoxazolidines formed by 1,3-dipolar cycloaddition of 3,4-dihydro-1-(substituted methyl)isoquinoline *N*-oxides with allenes rearrange thermally to fused-ring pyrrole derivatives *via* two competitive consecutive routes. The first, and major one, is a novel pyrrolidinone route and the second a route *via* a previously known 1,3-hydrogen shift followed by acylaziridine rearrangement. The route followed is dependent on the substituent present. The reaction can be effectively carried out in a one-pot procedure starting from the nitrones and allenes, thus providing an expeditious method for the synthesis of 5,6-dihydropyrrolo[2,1-*a*]isoquinolines.

Table 1 Rearrangement of 5-methyleneisoxazolidine **3** to fused-ring pyrroles **4** and **5**

Entry	Isoxazolidine **3**[a]	Temp (°C)	Time (h)	Products **4** and **5**	Yield[b] (%)
1	**3a**	150	2	**4a**	20
				5a	40
2	**3b**	130	7	**4b**	10
				5b	27
3	**3c**	130	6	**4c**	28
				5c	50
4	**3d**	130	8	**4d**	—
				5d	40
5	**3e**	140	5	**4e**	25
				5e	38
6	**3f**	130	8	**4f**	—
				5f	31
7	**3g**	130	6	**4g**	20
				5g	40
8	**3h**	130	8	**4h**	—
				5h	—
9	**3i**	130	5	**4i**	27
				5i	45

[a] Entry 1 was carried out with *endo*-**3a** and entries 2–9 were carried out with mixture of *endo*- and *exo*-isoxazolidines. [b] Isolated yield.



Scheme 4

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra of liquids were measured as films on sodium chloride plates and those of solids were measured in pressed potassium bromide discs on a JASCO FT/IR 5300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian GEMINI 200 spectrometer at 200 and at 50 MHz, respectively. Chemical shifts are recorded in parts per million (ppm) for samples in $CDCl_3$ solution with Me_4Si as internal standard. Coupling constants *J* are reported in Hz. Elemental analyses were carried out on a Perkin-Elmer 2400S elemental analyzer. Mass spectra (EI) were obtained using a JEOL JMS-AX505 HA mass spectrometer at 70 eV. The thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254}. 3,4-Dihydroisoquinoline *N*-oxides **1a–e** were prepared and used in the 1,3-dipolar cycloadditions with allenes according to our previous reports.[10,14]

1-Ethyl-6-methoxy-3,4-dihydroisoquinoline *N*-oxide (1d)
A white solid, yield 48%, mp 50–52 °C (Found: C, 70.13; H, 7.42; N, 6.76. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82%); ν_{max}(KBr)/cm^{-1} 1612, 1587, 1503, 1466, 1314, 1256, 1190, 1128, 1045, 881 and 804; δ_H 1.24 (3 H, t, *J* 7.4), 2.96 (2 H, q, *J* 7.4), 3.08 (2 H, t, *J* 7.6), 3.84 (3 H, s), 4.10 (2 H, t, *J* 7.6), 6.75 (1 H, d, *J* 2.6), 6.83 (1 H, dd, *J* 8.6 and 2.6) and 7.30 (1 H, d, *J* 8.6); δ_C 9.9, 19.9, 28.2, 55.6, 57.8, 112.8, 113.8, 122.6, 126.0, 134.0, 146.8 and 160.4; *m*/*z* 205 (M^+, 100%), 204 (80), 189 (12), 188 (77) and 160 (25).

10b-Ethyl-1,5,6,10b-tetrahydro-8,9-dimethoxy-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile 3e
A white solid, yield 71%, R_f 0.55 (EtOAc–hexane, 1:1); mp 127–129 °C (Found: C, 67.89; H, 6.75; N, 9.27. $C_{17}H_{20}N_2O_3$ requires C, 67.98; H, 6.71; N, 9.33%); ν_{max}(KBr)/cm^{-1} 2934, 2251, 1672, 1609, 1518, 1445, 1360, 1263, 1211, 1152, 1099, 1074, 1011, 961, 883 and 797; δ_H 0.76 (3 H, t, *J* 7.2), 1.94–2.29 (2 H, m), 2.63–2.73 (1 H, m), 2.87 (2 H, m), 3.45 (1 H, m), 3.87 (3 H, s), 3.91 (3 H, s), 4.24 (1 H, t, *J* 2.4), 4.41 (1 H, dd, *J* 3.2 and 2.4), 4.61 (1 H, dd, *J* 3.2 and 2.4), 6.59 (1 H, s) and 6.92 (1 H, s); δ_C 7.8, 28.4, 28.7, 45.9, 50.7, 56.1, 56.2, 70.9, 83.7, 108.2, 111.0, 117.3, 126.4, 126.8, 148.9 and 156.5; *m*/*z* 300 (M^+, 41%), 271 (100), 243 (54), 218 (56) and 204 (22).

Ethyl 10b-ethyl-1,5,6,10b-tetrahydro-8,9-dimethoxy-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carboxylate 3f
An inseparable mixture (1:1), yield 90%, oil, R_f 0.5 (EtOAc–hexane, 1:1) (Found: C, 65.72; H, 7.21; N, 4.06. $C_{19}H_{25}NO_5$ requires C, 65.69; H, 7.25; N, 4.03%); ν_{max}(neat)/cm^{-1} 2938, 1740, 1671, 1613, 1516, 1464, 1364, 1260, 1213, 1157, 1078, 1038, 1015, 953, 910, 962 and 797; δ_H 0.69 (3 H, t, *J* 7.2), 0.71 (3 H, t, *J* 7.2), 0.99 (3 H, t, *J* 7.2), 1.34 (3 H, t, *J* 7.0), 1.73–2.20 (4 H, m), 2.61–2.75 (2 H, m), 2.92–3.12 (4 H, m), 3.36–3.48 (2 H, m), 3.84 (3 H, s), 3.85 (6 H, s), 3.87 (3 H, s), 3.68–3.95 (2 H, m), 4.02 (1 H, t, *J* 1.8), 4.07 (1 H, t, *J* 1.6), 4.12 (1 H, t, *J* 1.6), 4.16 (1 H, t, *J* 1.8), 4.20–4.40 (2 H, m), 4.54–4.59 (2 H, m), 6.56 (1 H, s), 6.57 (1 H, s), 6.58 (1 H, s) and 6.72 (1 H, s); *m*/*z* 347 (M$^+$, 10%), 318 (100), 246 (30) and 218 (16).

10b-Ethyl-1,5,6,10b-tetrahydro-8-methoxy-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile 3g
A colourless oil, yield 92%, this was an inseparable mixture (2.5:1), R_f 0.55 (EtOAc–hexane, 1:2); ν_{max}(neat)/cm^{-1} 2938, 2245, 1676, 1657, 1612, 1580, 1505, 1464, 1331, 1285, 1263, 1221, 1036, 947 and 821; one component showed δ_H 0.74 (3 H, t, *J* 7.2), 1.97–2.29 (2 H, m), 2.69–3.58 (4 H, m), 4.22 (1 H, t, *J* 2.4), 4.41 (1 H, dd, *J* 3.4 and 2.4), 4.60 (1 H, dd, *J* 3.4 and 2.4), 6.65 (1 H, d, *J* 2.6), 6.85 (1 H, dd, *J* 2.6 and 8.8) and 7.38 (1 H, d, *J* 8.8); another minor isomer showed δ_H 0.74 (3 H, t, *J* 7.0), 1.76–2.11 (2 H, m), 2.69–3.58 (4 H, m), 4.00 (1 H, t, *J* 1.6), 4.44 (1 H, dd, *J* 1.6 and 3.0), 4.70 (1 H, dd, *J* 1.6 and 3.0), 6.68 (1 H, d, *J* 2.6), 6.87 (1 H, dd, *J* 2.6 and 8.6) and 7.12 (1 H, d, *J* 8.6).

Ethyl 10b-ethyl-1,5,6,10b-tetrahydro-8-methoxy-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carboxylate 3h
An inseparable mixture (1:1), oil, yield 88%, R_f 0.6 (EtOAc–hexane, 1:1); ν_{max}(neat)/cm^{-1} 2938, 1740, 1671, 1613, 1505, 1464, 1371, 1323, 1262, 1173, 1038, 945, 907 and 814; δ_H 0.68 (3 H, t, *J* 7.2), 0.70 (3 H, t, *J* 7.2), 0.99 (3 H, t, *J* 7.0), 1.33 (3 H, t, *J* 7.0), 1.73–1.92 (2 H, m), 1.96–2.19 (2 H, m), 2.66–2.86 (2 H, m), 2.96–3.19 (3 H, m), 3.36–3.48 (2 H, m), 3.65–3.76 (1 H, m), 3.77 (3 H, s), 3.80 (3 H, s), 3.79–3.91 (2 H, m), 4.00 (1 H, t, *J* 1.8), 4.05 (1 H, t, *J* 2.0), 4.11–4.14 (2 H, m), 4.30 (2 H, qd, *J* 1.8 and 7.0), 4.54–4.58 (2 H, m), 6.60 (1 H, d, *J* 2.8), 6.62 (1 H, d, *J* 2.8), 6.73 (1 H, dd, *J* 2.8 and 8.6), 6.78 (1 H, dd, *J* 2.6 and 8.6), 7.03 (1 H, d, *J* 8.6) and 7.10 (1 H, d, *J* 8.6).

10b-Benzyl-1,5,6,10b-tetrahydro-8,9-dimethoxy-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile 3i
A white solid, yield 65%, R_f 0.6 (EtOAc–hexane, 1:2); mp 146–148 °C (Found: C, 72.86; H, 6.05; N, 7.65. $C_{22}H_{22}N_2O_3$ requires C, 72.91; H, 6.12; N, 7.73%); ν_{max}(KBr)/cm^{-1} 2944, 2251, 1659, 1607, 1518, 1468, 1362, 1258, 1209, 1125, 1024, 945, 856, 764 and 700; δ_H 2.41–2.63 (2 H, m), 2.85–2.98 (1 H, m), 3.23–3.31 (1 H, m), 3.41–3.51 (2 H, m), 3.82 (3 H, s), 3.97 (3 H, s), 4.30 (1 H, t, *J* 2.4), 4.47 (1 H, dd, *J* 2.4 and 3.2), 4.67 (1 H, dd, *J* 2.4 and 3.2), 6.42 (1 H, s), 7.09 (1 H, s) and 6.94–7.11 (5 H, m); δ_C 28.2, 41.1, 46.3, 50.4, 55.9, 56.3, 71.0, 83.8, 108.9, 110.9, 117.3, 126.6, 126.7, 126.8, 127.8, 131.3, 135.8, 148.5 and 156.3; *m*/*z* 362 (M$^+$, 5%), 344 (18), 271 (100) and 229 (20).

General procedure for thermal rearrangement of 5-methylene-isoxazolidines 3 to fused-ring pyrroles 4 and 5
A solution of **3** (0.1 mmol) in dry toluene (1 cm^3) was heated in a sealed tube at 130–150 °C for an appropriate period of time under an atmosphere of argon. After evaporation of the solvent under a reduced pressure, the products were separated on preparative TLC (silica gel) with a mixture of ethyl acetate–hexane as eluent to give the fused-ring pyrroles **4** and **5**. For the reaction conditions and yields, see Table 1.

3-Cyano-5,6-dihydro-8,9-dimethoxy-2-methylpyrrolo[2,1-*a*]-isoquinoline 4a. A pale yellowish solid, R_f 0.62 (EtOAc–hexane, 2:1); mp 169–171 °C (Found: C, 71.68; H, 6.05; N, 10.32. $C_{16}H_{16}N_2O_2$ requires C, 71.62; H, 6.01; N, 10.44%); ν_{max}(KBr)/cm^{-1} 2951, 2193, 1518, 1468, 1412, 1332, 1275, 1233, 1148, 1032, 881, 820 and 789; δ_H 2.27 (3 H, s), 3.05 (2 H, t, *J* 6.8), 3.91 (3 H, s), 3.92 (3 H, s), 4.11 (2 H, t, *J* 6.8), 6.27 (1 H, s), 6.73 (1 H, s) and 6.99 (1 H, s); δ_C 11.9, 28.4, 42.9, 56.2, 56.3, 102.4, 104.9, 107.0, 111.6, 114.6, 120.7, 124.3, 132.6, 135.3, 148.8 and 149.4; *m*/*z* 268 (M$^+$, 100%), 253 (34), 225 (13) and 210 (12).

2-Cyanomethyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]-isoquinoline 5a. A pale red solid, R_f 0.5 (EtOAc–hexane, 2:1); mp 188–190 °C (Found: C, 71.72; H, 5.96; N, 10.46. $C_{16}H_{16}N_2O_2$ requires C, 71.62; H, 6.01; N, 10.44%); ν_{max}(KBr)/cm^{-1} 2955, 2247, 1524, 1454, 1334, 1273, 1235, 1209, 1125, 1028 and 871; δ_H 3.00 (2 H, t, *J* 6.6), 3.61 (2 H, s), 3.89 (3 H, s), 3.92 (3 H, s), 4.02 (2 H, t, *J* 6.6), 6.35 (1 H, d, *J* 1.8), 6.63 (1 H, d, *J* 1.8), 6.70 (1 H, s) and 6.98 (1 H, s); δ_C 16.1, 28.9, 44.4, 56.2 (2 C), 102.4, 106.2, 111.7, 112.3, 119.1, 119.3, 122.1, 123.2, 131.2, 148.1 and 148.8; *m*/*z* 268 (M$^+$, 100%), 253 (49) and 185 (28).

Ethyl 5,6-dihydro-8,9-dimethoxy-2-methylpyrrolo[2,1-*a*]-isoquinoline-3-carboxylate 4b. A white solid, R_f 0.68 (EtOAc–hexane, 3:1); mp 80–82 °C (lit.,[2b] 91–92 °C from aq. EtOH) (Found: C, 68.76; H, 6.79; N, 4.38. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44%); ν_{max}(KBr)/cm^{-1} 2934, 1682, 1608, 1514, 1419, 1331, 1256, 1215, 1132, 1089, 1042, 860 and 797; δ_H 1.38 (3 H, t, *J* 7.2), 2.38 (3 H, s), 2.99 (2 H, t, *J* 6.8), 3.91 (3 H, s), 3.92 (3 H, s), 4.32 (2 H, q, *J* 7.2), 4.57 (2 H, t, *J* 6.8), 6.30 (1 H, d, *J* 0.6), 6.73 (1 H, s) and 7.02 (1 H, s); δ_C 14.6, 28.8, 42.8, 56.2, 56.3, 59.8, 106.4, 107.2, 111.3, 119.3, 121.3, 125.2, 131.0, 135.3, 148.6, 149.1 and 162.8; *m*/*z* 315 (M$^+$, 100%), 300 (29) and 272 (11).

Ethyl (5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-2-yl)acetate 5b. A yellowish solid, R_f 0.6 (EtOAc–hexane, 3:1) mp 83–85 °C (lit.,[2d] 91–93 °C from light petroleum) (Found: C, 68.65; H, 6.78; N, 4.50. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44%); ν_{max}(KBr)/cm^{-1} 2939, 1726, 1608, 1523, 1445, 1312, 1257, 1226, 1209, 1174, 1132, 1028, 862 and 799; δ_H 1.29 (3 H, t, *J* 7.2), 2.98 (2 H, t, *J* 6.8), 3.51 (2 H, s), 3.88 (3 H, s), 3.91 (3 H, s), 4.00 (2 H, t, *J* 6.8), 4.18 (2 H, q, *J* 7.2), 6.36 (1 H, d, *J* 1.6), 6.59 (1 H, d, *J* 1.6), 6.68 (1 H, s) and 6.99 (1 H, s); δ_C 14.3, 29.0, 33.3, 44.3, 56.2 (2 C), 60.9, 103.4, 106.2, 111.6, 116.2, 119.6, 122.7, 123.1, 130.4, 147.7, 148.6 and 173.1; *m*/*z* 315 (M$^+$, 100%), 300 (31) and 242 (52).

3-Cyano-5,6-dihydro-8-methoxy-2-methylpyrrolo[2,1-*a*]-isoquinoline 4c. A white solid R_f 0.5 (EtOAc–hexane, 1:2); mp 120–122 °C (Found: C, 75.67; H, 6.02; N, 11.70. $C_{15}H_{14}N_2O$ requires C, 75.61; H, 5.92; N, 11.76%); ν_{max}(KBr)/cm^{-1} 2920, 2205, 1622, 1580, 1514, 1460, 1414, 1304, 1283, 1256, 1238, 1143, 1053, 877 and 777; δ_H 2.26 (3 H, s), 3.09 (2 H, t, *J* 6.8), 3.83 (3 H, s), 4.11 (2 H, t, *J* 6.8), 6.26 (1 H, s), 6.77 (1 H, d, *J* 2.6), 6.82 (1 H, dd, *J* 2.6 and 8.4) and 7.43 (1 H, d, *J* 8.4); δ_C 11.9, 29.1, 42.6, 55.5, 102.0, 104.8, 113.4, 113.9, 114.7, 121.0, 125.3, 132.7, 133.3, 135.3 and 159.8; *m*/*z* 238 (M$^+$, 100%) and 223 (68).

2-Cyanomethyl-5,6-dihydro-8-methoxypyrrolo[2,1-*a*]-isoquinoline 5c. A pale orange solid, R_f 0.4 (EtOAc–hexane, 1:2); mp 86–88 °C (Found: C, 75.58; H, 5.86; N, 11.83. $C_{15}H_{14}N_2O$ requires C, 75.61; H, 5.92; N, 11.76%); ν_{max}(KBr)/cm^{-1} 2959, 2247, 1611, 1580, 1524, 1478, 1443, 1335, 1308, 1258, 1236, 1165, 1030, 860, 821 and 802; δ_H 3.02 (2 H, t, *J* 6.6), 3.59 (2 H, s), 3.81 (3 H, s), 4.01 (2 H, t, *J* 6.6), 6.33 (1 H, d, *J* 1.8), 6.62 (1 H, d, *J* 1.8), 6.73 (1 H, d, *J* 2.6), 6.80 (1 H, dd, *J* 2.6 and 8.4) and 7.41 (1 H, d, *J* 8.4); δ_C 16.1, 29.7, 44.1, 55.5, 102.3, 112.4, 113.1, 113.9, 118.8, 119.3, 122.4, 124.1, 131.2, 132.4 and 158.6; *m*/*z* 238 (M$^+$, 100%), 223 (88), 154 (5) and 119 (7).

Ethyl (5,6-dihydro-8-methoxypyrrolo[2,1-*a*]isoquinolin-2-yl)-acetate 5d. A pale yellowish solid, R_f 0.35 (EtOAc–hexane, 2:1); mp 38–40 °C (Found: C, 71.63; H, 6.68; N, 4.85. $C_{17}H_{19}NO_3$ requires C, 71.57; H, 6.72; N, 4.91%); ν_{max}(KBr)/cm^{-1} 2938, 1740, 1611, 1524, 1475, 1329, 1236, 1180, 1038 and 829; δ_H 1.28 (3 H, t, *J* 7.2), 3.02 (2 H, t, *J* 6.4), 3.51 (2 H, s), 3.81 (3 H, s), 4.01 (2 H, t, *J* 6.4), 4.17 (2 H, q, *J* 7.2), 6.34 (1 H, d, *J* 1.8), 6.58 (1 H, d, *J* 1.8), 6.71 (1 H, d, *J* 2.2), 6.78 (1 H, dd, *J* 2.2 and 8.4)

and 7.41 (1 H, d, *J* 8.4); δ_C 14.3, 29.8, 33.3, 43.9, 55.5, 60.8, 103.4, 113.0, 113.8, 116.2, 119.3, 123.0, 124.0, 130.4, 132.3, 158.2 and 173.1; *m*/*z* 285 (M^+, 98%), 270 (22), 242 (12), 212 (100) and 197 (31).

3-Cyano-5,6-dihydro-8,9-dimethoxy-1,2-dimethylpyrrolo[2,1-*a*]isoquinoline 4e. A white solid, R_f 0.5 (EtOAc–hexane, 1:1); mp 146–148 °C (Found: C, 72.41; H, 6.38; N, 9.87. $C_{17}H_{18}N_2O_2$ requires C, 72.32; H, 6.43; N, 9.92%); ν_{max}(KBr)/cm^{-1} 2920, 2195, 1520, 1483, 1400, 1336, 1286, 1242, 1215, 1154, 1034, 954, 873 and 814; δ_H 2.19 (3 H, s), 2.28 (3 H, s), 3.01 (2 H, t, *J* 7.0), 3.92 (3 H, s), 3.93 (3 H, s), 4.08 (2 H, t, *J* 7.0), 6.78 (1 H, s) and 7.20 (1 H, s); δ_C 10.1, 11.1, 29.3, 42.9, 56.2, 56.3, 101.1, 108.3, 111.9, 114.6, 114.9, 121.9, 125.6, 131.0, 131.4, 148.4 and 148.6; *m*/*z* 282 (M^+, 100%), 267 (32), 239 (8) and 224 (18).

2-Cyanomethyl-5,6-dihydro-8,9-dimethoxy-1-methylpyrrolo-[2,1-*a*]isoquinoline 5e. A pale yellowish solid, R_f 0.42 (EtOAc–hexane, 1:1); mp 133–135 °C (Found: C, 72.26; H, 6.47; N, 9.96. $C_{17}H_{18}N_2O_2$ requires C, 72.32; H, 6.43; N, 9.92%); ν_{max}(KBr)/cm^{-1} 2959, 2245, 1530, 1497, 1466, 1408, 1333, 1285, 1246, 1208, 1159, 1028, 858 and 799; δ_H 2.33 (3 H, s), 2.96 (2 H, t, *J* 6.4), 3.54 (2 H, s), 3.90 (3 H, s), 3.93 (3 H, s), 3.98 (2 H, t, *J* 6.4), 6.64 (1 H, s), 6.75 (1 H, s) and 7.14 (1 H, s); δ_C 10.9, 14.6, 29.9, 44.6, 56.2, 56.3, 107.7, 111.6, 112.0, 112.5, 118.3, 119.1, 123.3, 124.7, 127.5, 148.4 and 151.1; *m*/*z* 282 (M^+, 100%), 267 (50) and 199 (17).

Ethyl (5,6-dihydro-8,9-dimethoxy-1-methylpyrrolo[2,1-*a*]isoquinolin-2-yl)acetate 5f. A pale yellowish oil, R_f 0.4 (EtOAc–hexane, 1:1) (Found: C, 69.18; H, 7.14; N, 4.22. $C_{19}H_{23}NO_4$ requires C, 69.28; H, 7.04; N, 4.25%); ν_{max}(neat)/cm^{-1} 2938, 1732, 1611, 1564, 1529, 1493, 1464, 1408, 1331, 1285, 1242, 1215, 1157, 1032, 945, 856 and 797; δ_H 1.28 (3 H, t, *J* 7.0), 2.32 (3 H, s), 2.94 (2 H, t, *J* 6.4), 3.48 (2 H, s), 3.89 (3 H, s), 3.91 (3 H, s), 3.97 (2 H, t, *J* 6.4), 4.17 (2 H, q, *J* 7.0), 6.58 (1 H, s), 6.73 (1 H, s) and 7.12 (1 H, s).

3-Cyano-5,6-dihydro-8-methoxy-1,2-dimethylpyrrolo[2,1-*a*]-isoquinoline 4g. A white solid, R_f 0.5 (EtOAc–hexane, 1:2); mp 107–109 °C (Found: C, 76.25; H, 6.28; N, 11.02. $C_{16}H_{16}N_2O$ requires C, 76.16; H, 6.39; N, 11.10%); ν_{max}(KBr)/cm^{-1} 2948, 2197, 1620, 1578, 1512, 1466, 1418, 1335, 1304, 1283, 1250, 1153, 1136, 1045, 864 and 804; δ_H 2.18 (3 H, s), 2.24 (3 H, s), 3.04 (2 H, t, *J* 6.6), 3.84 (3 H, s), 4.08 (2 H, t, *J* 6.6), 6.80 (1 H, d, *J* 2.8), 6.85 (1 H, dd, *J* 2.8 and 8.6) and 7.58 (1 H, d, *J* 8.6); δ_C 10.1, 11.1, 30.0, 42.7, 55.5, 100.8, 112.8, 114.4, 114.8, 115.0, 122.3, 125.9, 131.1, 131.4, 134.6 and 159.0; *m*/*z* 252 (M^+, 100%) and 237 (85).

2-Cyanomethyl-5,6-dihydro-8-methoxy-1-methylpyrrolo[2,1-*a*]isoquinoline 5g. A pale reddish solid, R_f 0.43 (EtOAc–hexane, 1:2); mp 95–97 °C (Found: C, 76.09; H, 6.42; N, 11.17. $C_{16}H_{16}N_2O$ requires C, 76.16; H, 6.39; N, 11.10%); ν_{max}(KBr)/cm^{-1} 2953, 2250, 1620, 1568, 1527, 1489, 1464, 1395, 1335, 1289, 1246, 1173, 1132, 1103, 1047, 885 and 808; δ_H 2.29 (3 H, s), 2.99 (2 H, t, *J* 6.6), 3.53 (2 H, s), 3.82 (3 H, s), 3.98 (2 H, t, *J* 6.6), 6.63 (1 H, s), 6.78 (1 H, d, *J* 2.8), 6.84 (1 H, dd, *J* 2.8 and 8.4) and 7.52 (1 H, d, *J* 8.4); δ_C 10.9, 14.6, 30.7, 44.3, 55.5, 111.5, 112.6, 112.7, 114.3, 117.9, 119.1, 123.6, 124.9, 126.7, 133.9 and 157.9; *m*/*z* 252 (M^+, 100%) and 237 (78).

3-Cyano-5,6-dihydro-8,9-dimethoxy-2-methyl-1-phenyl-pyrrolo[2,1-*a*]isoquinoline 4i. A pale yellowish solid, R_f 0.5 (EtOAc–hexane, 1:1); mp 188–190 °C (Found: C, 76.81; H, 5.94; N, 8.04. $C_{22}H_{20}N_2O_2$ requires C, 76.72; H, 5.85; N, 8.13%); ν_{max}(KBr)/cm^{-1} 2934, 2203, 1605, 1512, 1468, 1397, 1339, 1258, 1215, 1161, 1039, 868, 802, 773, 739 and 710; δ_H 2.13 (3 H, s), 3.08 (2 H, t, *J* 6.8), 3.30 (3 H, s), 3.87 (3 H, s), 4.15 (2 H, t, *J* 6.8), 6.51 (1 H, s), 6.71 (1 H, s) and 7.30–7.49 (5 H, m); δ_C 10.4, 28.8, 43.2, 55.3, 56.1, 101.9, 108.3, 111.4, 114.7, 120.8, 121.8, 125.2, 127.7, 129.1, 130.9, 131.0, 131.2, 135.4, 147.9 and 148.7; *m*/*z* 344 (M^+, 100%) and 329 (20).

2-Cyanomethyl-5,6-dihydro-8,9-dimethoxy-1-phenyl-pyrrolo[2,1-*a*]isoquinoline 5i. A colourless oil, R_f 0.37 (EtOAc–hexane, 1:1) (Found: C, 76.67; H, 5.81; N, 8.20. $C_{22}H_{20}N_2O_2$ requires C, 76.72; H, 5.85; N, 8.13%); ν_{max}(neat)/cm^{-1} 2936, 2247, 1605, 1532, 1508, 1476, 1408, 1335, 1256, 1219, 1170, 1123, 1057, 961, 864, 795, 768 and 704; δ_H 3.03 (2 H, t, *J* 6.6), 3.31 (3 H, s), 3.44 (2 H, d, *J* 0.8), 3.85 (3 H, s), 4.06 (2 H, t, *J* 6.6), 6.50 (1 H, s), 6.68 (1 H, s), 6.79 (1 H, s) and 7.33–7.49 (5 H, m); δ_C 14.6, 29.4, 44.8, 55.2, 56.1, 107.5, 111.5, 111.7, 118.8, 119.4, 112.0, 122.0, 124.2, 126.7, 127.6, 129.2, 131.0, 135.7, 147.5 and 147.9; *m*/*z* 344 (M^+, 100%) and 329 (47).

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