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Mechanisms of cyclisation of indolo oxime ethers I. Formation of ethyl 9,11-dimethoxy indolo[2,3-*c*]quinoline-6-carboxylates

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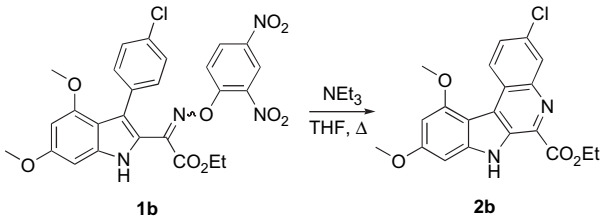
Abstract—The cyclisation of a series of ethyl 3′-aryl-4′,6′-dimethoxyindol-2′-yl-2-(hydroxyimino)acetates was investigated using ^{1}H NMR spectroscopy to determine the mechanism of formation of the corresponding ethyl 9,11-dimethoxy indolo[2,3-*c*]quinoline-6-carboxylates. The electronic requirements of the reaction were determined and, along with the observation of an intermediate in the process, indicated that the reaction proceeds through an electrocyclic mechanism. The importance of the ester moiety in such a process is discussed.

1. Introduction

We have recently observed the cyclisation of the chlorophenyl ester **1b** to give the tetracycle **2b** (Scheme 1).[1] Since structures related to the indoloquinoline **2b** have been found to have antitumour activity,[2] it is of interest to extend the synthetic methodology associated with these compounds. In order to do so, we have undertaken mechanistic studies to determine how this cyclisation occurs.



Scheme 1. Cyclisation of the oxime ether **1b** to give the corresponding tetracycle **2b**.

Several mechanistic pathways might be considered for this reaction. While substitution at an sp^2 hybridised centre is not common, significant literature precedent exists for an intramolecular concerted substitution process in closely related oxime ether systems.[3] A stepwise polar mechanism can also be envisaged, in which the reaction proceeds through a nitrenium ion intermediate. Similar one-[4] and two-step[5] radical processes have been observed for related systems and hence clearly need to be considered also. Finally, the reaction may proceed through an electrocyclic mechanism, followed by the elimination of 2,4-dinitrophenol. It is important to note that formally the first step in this process is equivalent to conjugate addition of the aromatic ring onto the nitrogen centre, since the reaction proceeds through the same intermediate.

In this paper we describe the synthesis and cyclisation of a series of analogues of the oxime ether **1b**. Through variation of the substituent on the phenyl ring, the electronic demand of the reaction was determined and the mechanism elucidated.

2. Results and discussion

The indole oxime ethers **1a–e** were synthesised as outlined in Scheme 2 from the corresponding acetophenones **3a–e**. The amino ketones **4a–e** were cyclised under Bischler-like conditions to give the phenylindoles **5a–e**. Treatment with oxalyl chloride and then ethanol gave a mixture of the desired 2-substituted keto esters **6a–e** and the corresponding 7-substituted isomer, which could be separated using column chromatography. The ketones **6a–e** were converted to the corresponding oximes **7a–e** using hydroxylamine, followed by reaction with dinitrofluorobenzene to give the cyclisation precursors **1a–e**. Spectroscopic studies on each of the oximes **7a–e** and the oxime ethers **1a–e** showed the presence of both *syn* and *anti* forms in solution. The corresponding quinolines **2a–e** were formed through heating the precursors **1a–e** at reflux in tetrahydrofuran in the presence of triethylamine.

Keywords: Indole; Cyclisation; Mechanism determination.
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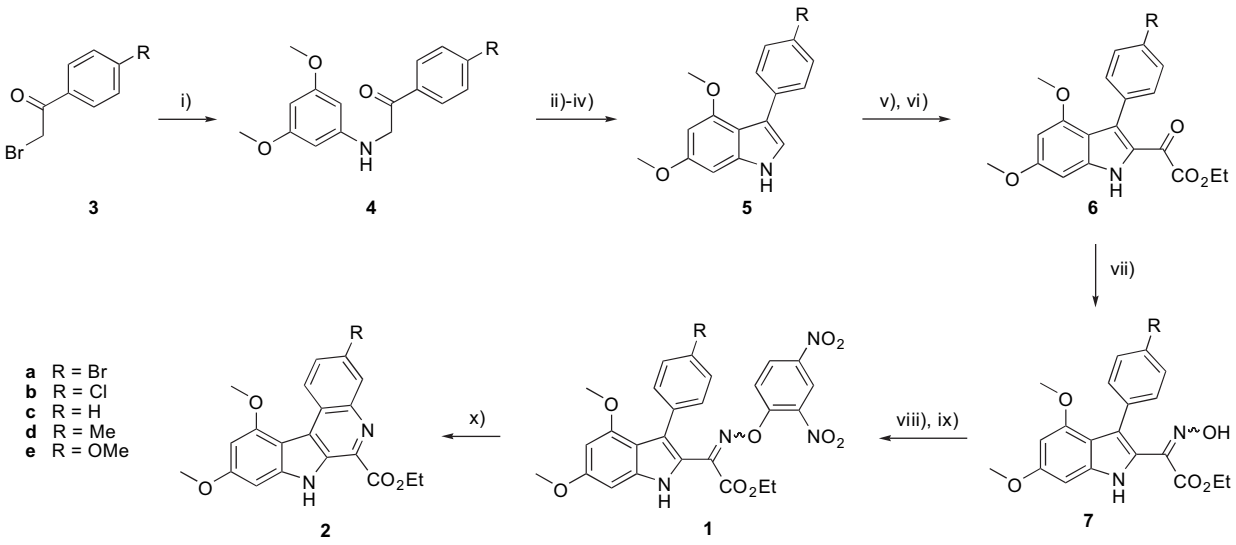


Scheme 2. Syntheses of the tetracycles **2a–e**. Reagents: (i) 3,5-dimethoxyaniline, EtOH, $NaHCO_3$, Δ; (ii) $(CF_3CO)_2O$; (iii) CF_3CO_2H; (iv) KOH, MeOH; (v) $(COCl)_2$; (vi) EtOH; (vii) $NH_2OH{\cdot}HCl$, $NaCH_3CO_2$, EtOH, Δ; (viii) Na, EtOH; (ix) 2,4-dinitrofluorobenzene and (x) NEt_3, THF, Δ.

Each of the precursors **1a–e** was treated under the same conditions as those used in the initial cyclisation studies.[1] Samples of the reaction were taken at regular intervals, immediately cooled to 77 K and the solvent removed in vacuo. The rate of disappearance of each of the starting materials **1a–e** and the rate of appearance of each of the tetracycles **2a–e** were followed using ^{1}H NMR spectroscopy. Specifically the signals due to $H_{5''}$ and $H_{7''}$ of the precursors **1a–e** and H_1 of the products **2a–e** were followed using the protons on the methoxyindole moiety as the internal standard. Each of these protons had previously been shown to have the same relaxation time, and hence integration of the signals was an appropriate quantitative measure.

Initial analysis showed that the rate of consumption of each of the starting materials **1a–e** did not follow first order kinetics. In addition, signals were observed, which could not be attributed to either the starting materials **1a–e** or the products **2a–e**. Further, these signals did not correspond to the nitrophenoxide that might be expected to be liberated during the reaction. A sample spectrum is shown in Figure 1, for the cyclisation of the methyl substituted case **1e**. The coupling pattern of the highlighted signals is characteristic of a 1,2,4-trisubstituted aromatic system and suggests that an intermediate containing the dinitrophenoxide moiety is being formed in the reaction.

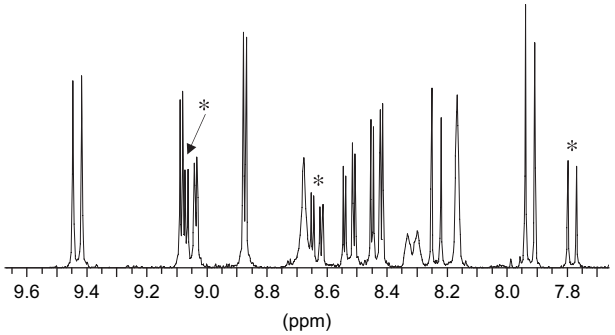


Figure 1. ^{1}H NMR spectrum of the cyclisation reaction of the precursor **1e**. The highlighted signals do not correspond to starting material, product, nitrophenol or its deprotonated form.

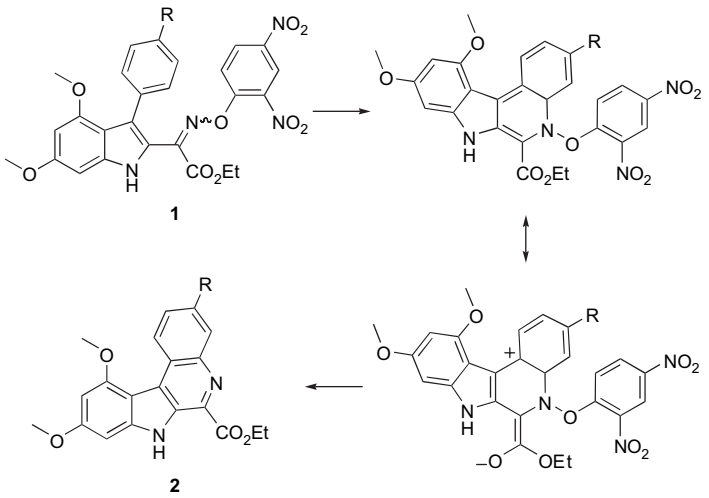
Therefore, the reaction was analysed assuming that, once it had formed, the intermediate could decompose to either starting material or product, but product formation was irreversible. The data sets fit well into this model and were integrated numerically, with the rates of formation of the intermediate calculated for the cyclisation of each of the precursors **1a–e**. These are summarised in Table 1 and show a clear trend, with the rate of reaction faster for electron donating substituents and slower for electron withdrawing substituents. The difference in the rate constant between the two extreme cases was a factor of ca. 3.

The importance of the base was also probed, with the above kinetic analyses repeated for the chloro derivative **1b** in either the absence of triethylamine or with either 0.5 or 1 equiv of triethylamine present. In the absence of triethylamine, no trace of the product **2b** was evident by ^{1}H NMR spectroscopy, though there was indication of the intermediate identified earlier. In the presence of either 0.5 or 1 equiv of the base, the reaction was observed to proceed at the same initial rate as when an excess was present, however the reaction stopped at an extent of conversion of ca. 50% and 95%, respectively, and the rate slowed as the limiting yield was approached.

The effect on the reaction of altering the concentration of the base, the observation of an intermediate and the electronic requirements of the reaction allows the mechanistic pathway

Table 1. Rate constants for the cyclisation of the precursors **1a–e**

Compound	R	Rate constant ($\times 10^{-5}$ s^{-1})
1a	Br	(1.14±0.17)
1b	Cl	(1.09±0.27)
1c	H	(1.77±0.17)
1d	Me	(2.78±0.06)
1e	OMe	(3.61±0.29)



Scheme 3. Cyclisation of the precursors **1** proceeding through an electrocylic mechanism.

to be elucidated. The cyclisation of the precursors **1a–e** occurs through an electrocyclic process, which proceeds through an intermediate that contains the dinitrophenoxide moiety followed by elimination to give the aromatic species **2a–e** (Scheme 3). A significant resonance contributor to this intermediate is also shown with a negative charge localised on the ester oxygen. The presence of an electron donating substituent at the 4″ position of the starting material stabilises this resonance form and hence the intermediate itself. This results in an increase in the rate of cyclisation, while conversely an electron withdrawing substituent at the 4″ position of the starting material destabilises the intermediate and decreases the rate of cyclisation.

3. Conclusions

In conclusion, it can be seen that the key portion of the precursors **1a–e** is the ester moiety. The presence of this group stabilises the intermediate in the electrocyclic process, facilitating the reaction. Further, it suggests that related groups might be able to perform a similar role; an amide in this position has been shown to facilitate the cyclisation.[1] The importance of the ester functionality is currently being investigated through the study of related cyclisations.

4. Experimental

4.1. General

Melting points were determined on a Köfler hot stage apparatus and are uncorrected. Elemental analyses and electrospray mass spectra were performed by Marianne Dick at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Ultraviolet spectra were measured on a Carey 100 spectrophotometer and refer to solutions in chloroform. IR spectra were obtained on a Mattson Genesis series FTIR spectrometer as Nujol mulls between sodium chloride plates unless otherwise stated. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75.5 MHz using a Bruker AC300F spectrometer with the residual protio solvent as an internal standard. Chemical shifts are reported in parts per million downfield from TMS and coupling constants (J) in hertz (Hz). The compounds **1b**, **2b**, **4a**,**c**,**e**, **5a–c**,**e**, **6b** and **7b** were prepared as described previously.[1,6,7]

4.2. Preparation of novel indole precursors

4.2.1. 1-(4′-Chlorophenyl)-2-[(3″,5″-dimethoxyphenyl)-amino]ethanone (4b). 3,5-Dimethoxyaniline (1.98 g, 12.9 mmol), 2-bromo-4′chloroacetophenone **3b** (3.01 g, 12.9 mmol) and sodium hydrogen carbonate (1.37 g, 16.1 mmol) in absolute ethanol (50 mL) were heated under reflux with stirring until TLC analysis confirmed the consumption of the starting materials (ca. 4 h). The mixture was then removed from the heat and allowed to cool. The solvent was removed in vacuo and the residue was purified using column chromatography (ethyl acetate/light petroleum, 3:7) to yield the amino ketone **4b** as a yellow solid (3.60 g, 92%). Mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 6H, OMe), 4.56 (s, 2H, CH_2), 5.88 (s, 2H, $H_{2''}$), 5.93 (s, 1H, $H_{4''}$), 7.49 (d, 2H, J=8.7 Hz, $H_{3'}$), 7.95 (d, 2H, J=8.7 Hz, $H_{2'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 50.5 (CH_2), 55.1 (OMe), 90.3 ($C_{4''}$), 92.1 ($C_{2''}$), 129.1 ($C_{3'}$), 129.2 ($C_{2'}$), 133.1 ($C_{1'}$), 140.3 ($C_{4'}$), 148.6 ($C_{1''}$), 161.8 ($C_{3''}$), 193.6 (CO); ν_{max} 3396, 1682, 1618 cm^{-1}; λ_{max} ($CHCl_3$) 262 nm (ε 8600 cm^{-1} M^{-1}); m/z (ESI) 305/307 ([M+H], 100%); found: C, 62.9; H, 5.3; N, 4.4. Calcd. for $C_{16}H_{16}ClNO_3$: C, 62.9; H, 5.3; N, 4.6.

4.2.2. 4,6-Dimethoxy-3-(4′-methylphenyl)indole (5d). 3,5-Dimethoxyaniline (1.48 g, 9.67 mmol), 2-bromo-4′-methylacetophenone **3d** (2.00 g, 6.94 mmol) and sodium hydrogen carbonate (1.02 g, 12.1 mmol) in absolute ethanol (35 mL) were heated under reflux with stirring until TLC analysis confirmed the consumption of the starting materials (ca. 4 h). The mixture was then removed from the heat and allowed to cool. ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated the presence of the indole **5d** and, as such, a small portion of the crude reaction mixture was purified using column chromatography (light petroleum/ethyl acetate, 7:3) and the amino ketone **4d** isolated. *2-[(3″,5″-Dimethoxyphenyl)amino]-1-(4′-methylphenyl)ethanone* ***4d***: mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s,

3H, 4-Me), 3.78 (s, 6H, OMe), 4.57 (s, 2H, CH_2), 5.94 (br s, 3H, $H_{2''}$, $H_{4''}$), 7.31 (d, 2H, J=8.3 Hz, $H_{3'}$), 7.90 (d, 2H, J=8.3 Hz, $H_{2'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.6 (4′-Me), 50.2 (CH_2), 55.1 (OMe), 90.2 ($C_{4''}$), 92.0 ($C_{2''}$), 127.8 ($C_{2'}$), 129.5 ($C_{3'}$), 132.3 ($C_{1'}$), 144.8 ($C_{4'}$), 148.8 ($C_{1''}$), 161.8 ($C_{3''}$), 194.3 (CO); ν_{max} 3392, 1682, 1621, 1600 cm^{-1}; λ_{max} ($CHCl_3$) 260 nm (ε 9400 cm^{-1} M^{-1}); *m/z* (ESI) 286 ([M+H], 100%); found: C, 71.8; H, 6.4; N, 4.9. Calcd for $C_{17}H_{19}NO_3$: C, 71.6; H, 6.7; N, 4.9.

The remainder of the mixture and triethylamine (1.94 mL, 14 mmol) in dry tetrahydrofuran (32 mL) was stirred in an ice bath before trifluoroacetic anhydride (1.98 mL, 14 mmol) was added. The mixture was allowed to come to room temperature, stirred for 1 h and the solvent was then removed in vacuo yielding a yellow oil. Trifluoroacetic acid (9.58 mL) was added to the oil and the mixture heated under reflux for 15 min. The mixture was then removed from the heat, allowed to cool and poured into ice-water (ca. 100 mL) resulting in a green precipitate. The solid was collected and left to dry in a dessicator. The dried precipitate was dissolved in methanol (19.2 mL) and potassium hydroxide was (2.03 g, 36.2 mmol) added. The mixture was then stirred for 1 h and water was added, causing precipitation. The solid was then extracted with dichloromethane and the solvent removed in vacuo to give the title compound as a grey/black solid (2.64 g, 100%) a small sample of which was recrystallised from chloroform for elemental analysis. Mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H, 4-Me), 3.80 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.26 (d, 1H, J=2.1 Hz, H_5), 6.49 (d, 1H, J=2.1 Hz, H_7), 6.98 (d, 2H, J=8.5 Hz, H_2), 7.18 (d, 2H, J=8.1 Hz, $H_{3'}$), 7.90 (d, 2H, J=8.1 Hz, $H_{2'}$), 8.06 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (4′-Me), 55.0 (6-OMe), 55.5 (4-OMe), 86.8 (C_7), 92.1 (C_5), 110.4 (C_{3a}), 118.9 (C_3), 120.1 (C_2), 128.2 ($C_{2'}$), 129.3 ($C_{3'}$), 133.0 ($C_{1'}$), 135.1 ($C_{4'}$), 138.3 (C_{7a}), 154.9 (C_4), 157.5 (C_6); ν_{max} 3357, 1618, 1580 cm^{-1}; λ_{max} ($CHCl_3$) 260 nm (ε 9400 cm^{-1} M^{-1}); *m/z* (ESI) 268 ([M+H], 100%); found: C, 73.0; H, 6.3; N, 5.0. Calcd for $C_{17}H_{17}NO_2\cdot 0.125CHCl_3$: C, 72.9; H, 6.1; N, 5.0.

4.3. Preparation of substituted indole esters

4.3.1. General procedure for the formation of the substituted indoles 6. Oxalyl chloride (1.2 mol equiv) was added to a mixture of the appropriately substituted indole **5** (1 mol equiv) partially dissolved in dry diethyl ether (8.6 L per mole of indole **5**). This mixture was stirred for 3 h at room temperature and the solvent was then removed in vacuo. Absolute ethanol (4.3 L per mole of substituted indole **5**) was then added to the solid and the mixture stirred for a further 2 h, whereupon the solvent was again removed in vacuo. The indole esters **6a–e** were then purified using column chromatography (methanol/chloroform, 1:100). Elemental analyses indicated chloroform of crystallisation.

4.3.1.1. Ethyl 2-[3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-2′-yl]glyoxylate (6a). 3-(4′-Bromophenyl)-4,6-dimethoxyindole **5a**: 2.34 g, 7.04 mmol, yield: 0.54 g, 18%, mp 187–188 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, 3H, J=7.7 Hz, CH_3), 3.64 (s, 3H, OMe), 3.66 (m, 2H, CH_2), 3.85 (s, 3H, OMe), 6.11 (d, 1H, J=1.9 Hz, $H_{5'}$), 6.39 (d, 1H, J=1.9 Hz, $H_{7'}$), 7.30 (d, 2H, J=8.5 Hz, $H_{3''}$), 7.48 (d, 2H, J=8.5 Hz, $H_{2''}$), 9.35 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.5 (CH_3), 55.1, 55.6 (OMe), 61.9 (CH_2), 85.6 ($C_{7'}$), 93.8 ($C_{5'}$), 113.3 ($C_{3a'}$), 121.9 ($C_{4''}$), 127.0 ($C_{2''}$), 128.5 ($C_{3'}$), 130.0 ($C_{2'}$), 132.4 ($C_{1''}$), 132.5 ($C_{3''}$), 139.7 ($C_{7a'}$), 157.0 ($C_{4'}$), 162.4 ($C_{6'}$), 163.9 (CO), 176.7 (OCO); ν_{max} 3000, 1739, 1630 cm^{-1}; λ_{max} ($CHCl_3$) 363 nm (ε 16,000 cm^{-1} M^{-1}), 264 (19,000); *m/z* (ESI) 432/424 ([M+H], 100%), 404/406 (9); found: C, 53.8; H, 4.5; N, 3.0. Calcd for $C_{20}H_{18}BrNO_5\cdot 0.125CHCl_3$: C, 54.1; H, 4.1; N, 3.1.

4.3.1.2. Ethyl 2-[3′-phenyl-4′,6′-dimethoxyindol-2′-yl]-glyoxylate (6c). 4,6-Dimethoxy-3-phenylindole **5c**: 1.64 g, 6.48 mmol, yield: 0.84 g, 37%, mp 138–139 °C, appearance: pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, 3H, J=7.1 Hz, CH_3), 3.62 (s, 3H, OMe), 3.66 (q, 2H, J=7.1 Hz, CH_2), 3.92 (s, 3H, OMe), 6.11 (d, 1H, J=1.9 Hz, $H_{5'}$), 6.40 (d, 1H, J=1.9 Hz, $H_{7'}$), 7.34–7.45 (m, 5H, $H_{2''}$, $H_{3''}$, $H_{4''}$), 9.21 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.5 (CH_3), 55.1, 55.5 (OMe), 61.8 (CH_2), 85.5 ($C_{7'}$), 93.6 ($C_{5'}$), 113.5 ($C_{3a'}$), 126.8 ($C_{2''}$), 127.2 ($C_{3''}$), 127.5 ($C_{4''}$), 130.0 ($C_{2'}$), 130.8 ($C_{3''}$), 130.9 ($C_{1''}$), 139.7 ($C_{7a'}$), 157.2 ($C_{4'}$), 162.3 ($C_{6'}$), 164.0 (CO), 177.5 (OCO); ν_{max} 3340, 1730, 1612 cm^{-1}; λ_{max} ($CHCl_3$) 365 nm (ε 6600 cm^{-1} M^{-1}), 261 (6900); *m/z* (ESI) 354 ([M+H], 100%); found: C, 65.9; H, 5.4; N, 3.8. Calcd for $C_{20}H_{19}NO_5\cdot 0.125CHCl_3$: C, 65.6; H, 5.2; N, 3.8.

4.3.1.3. Ethyl 2-[4′,6′-dimethoxy-3′-(4″-methylphenyl)-indol-2′-yl]glyoxylate (6d). 4,6-Dimethoxy-3-(4′-methylphenyl)indole **5d**: 2.60 g, 9.73 mmol, yield: 1.57 g, 44%, mp 181–183 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, 3H, J=7.2 Hz, CH_3), 2.40 (s, 3H, 4″-Me), 3.64 (s, 3H, OMe), 3.68 (q, 2H, J=7.2 Hz, CH_2), 3.86 (s, 3H, OMe), 6.11 (d, 1H, J=1.9 Hz, $H_{5'}$), 6.39 (d, 1H, J=1.9 Hz, $H_{7'}$), 7.16 (d, 2H, J=7.9 Hz, $H_{3''}$), 7.31 (d, 2H, J=7.9 Hz, $H_{2''}$), 9.20 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4 (CH_3), 21.2 (4″-Me), 55.1, 55.5 (OMe), 61.9 (CH_2), 85.5 ($C_{7'}$), 93.5 ($C_{5'}$), 113.4 ($C_{3a'}$), 127.3 ($C_{3'}$), 127.6 ($C_{2''}$), 130.2 ($C_{2''}$), 130.8 ($C_{3''}$), 134.2 ($C_{1''}$), 137.2 ($C_{4''}$), 139.8 ($C_{7a'}$), 157.3 ($C_{4'}$), 162.2 ($C_{6'}$), 164.1 (CO), 176.4 (OCO); ν_{max} 3301, 1739, 1630 cm^{-1}; λ_{max} ($CHCl_3$) 358 nm (ε 8600 cm^{-1} M^{-1}), 261 (8400); *m/z* (ESI) 368 ([M+H], 100%), 268 (8); found: C, 67.1; H, 5.5; N, 3.7. Calcd for $C_{21}H_{21}NO_5\cdot 0.1CHCl_3$: C, 66.8; H, 5.6; N, 3.7.

4.3.1.4. Ethyl 2-[4′,6′-dimethoxy-3′-(4″-methoxyphenyl)indol-2′yl]glyoxylate (6e). 4,6-Dimethoxy-3-(4′-methoxyphenyl)indole **5e**: 1.90 g, 6.71 mmol, yield: 2.08 g, 81%, mp 182–183 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, 3H, J=7.2 Hz, CH_3), 3.65 (s, 3H, OMe), 3.74 (q, 2H, J=7.2 Hz, CH_2), 3.85 (s, 3H, OMe), 3.87 (s, 3H, 4″-OMe), 6.11 (d, 1H, J=1.7 Hz, $H_{5'}$), 6.39 (d, 1H, J=1.7 Hz, $H_{7'}$), 6.90 (d, 2H, J=8.7 Hz, $H_{3''}$), 7.35 (d, 2H, J=8.7 Hz, $H_{2''}$), 9.21 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4 (CH_3), 55.1, 55.5 (OMe), 55.2 (4″-OMe), 61.9 (CH_2), 85.5 ($C_{7'}$), 93.5 ($C_{5'}$), 112.4 ($C_{2''}$), 113.5 ($C_{3a'}$), 125.5 ($C_{3'}$), 127.3 ($C_{2'}$), 130.0 ($C_{1''}$), 132.2 ($C_{3''}$), 139.8 ($C_{7a'}$), 157.3 ($C_{4'}$), 159.2 ($C_{6'}$), 162.2 ($C_{4''}$), 164.1 (CO), 177.4 (OCO); ν_{max} 3295, 1739, 1620 cm^{-1}; λ_{max} ($CHCl_3$) 409 nm (ε 4300 cm^{-1} M^{-1}), 314 (5400), 264 (6300); *m/z* (ESI) 384 ([M+H], 100%), 312

(6), 284 (9); found: C, 64.5; H, 5.4; N, 3.5. Calcd for $C_{20}H_{18}BrNO_5 \cdot 0.1CHCl_3$: C, 64.1; H, 5.4; N, 3.5.

4.4. Preparation of 3-arylindole-2-ketoximes

4.4.1. General procedure for the formation of the indole oximes 7. The appropriate indole ester **6** (1 mol equiv), hydroxylamine hydrochloride (5.2 mol equiv) and sodium acetate (2.9 mol equiv) in absolute ethanol (40 L per mol of indole ester **6**) were heated under reflux for 7 h. The mixture was allowed to cool to room temperature and water (50 L per mol indole ester **6**) was added. The aqueous layer was extracted with dichloromethane, washed with water and dried. The solvent was removed in vacuo and ^{1}H NMR analysis of the crude reaction mixture was performed. If there was evidence of the ester **6**, the reaction was repeated. Upon consumption of the starting material, the crude oxime mixture was purified using column chromatography (chloroform/methanol, 9.7:0.3). It should be noted that due to the presence of the *syn* and *anti* forms of the oximes **7a–e**, signals in the NMR spectra are doubled. Elemental analyses indicated chloroform of crystallisation.

4.4.1.1. Ethyl 3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-2′-yl-2-(hydroxyimino)acetate (7a). Ethyl 2-[3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-2′-yl]glyoxylate **6a**: 0.45 g, 1.05 mmol, yield: 0.45 g, 96%, mp 128–129 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (m, 6H, CH_3), 3.72 (m, 16H, OMe, CH_2), 6.11, 6.17 (2d, 2H, J=1.9 Hz, $H_{5'}$), 6.36, 6.43 (2d, 2H, J=1.9 Hz, $H_{7'}$), 7.24 (m, 4H, $H_{2''}$), 7.38 (m, 4H, $H_{3''}$), 8.85, 9.62 (2br s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 13.5 (CH_3), 55.0, 55.0 (6′-OMe), 55.5, 55.5 (4′-OMe), 61.9, 62.2 (CH_2), 86.0, 86.1 ($C_{7'}$), 92.6, 92.8 ($C_{5'}$), 110.8, 112.7 ($C_{3a'}$), 120.1, 122.2 ($C_{3'}$), 120.9, 121.5 ($C_{2'}$), 129.8, 130.1 ($C_{2''}$), 132.7, 132.9 ($C_{3''}$), 133.0, 133.9 ($C_{4''}$), 137.9, 138.1 ($C_{1''}$), 144.0, 145.7 ($C_{7a'}$), 155.1, 155.3 ($C_{4'}$), 159.6, 159.6 ($C_{6'}$), 161.6, 163.2 (C=N), 175.6, 177.3 (OCO); ν_{max} 3419, 1733, 1716, 1683 cm^{-1}; λ_{max} ($CHCl_3$) 326 nm (ε 11,000 cm^{-1} M^{-1}), 264 (19,000); *m/z* (ESI) 446/448 ([M+H], 100%), 429/431 (34), 356/358 (27); found: C, 48.4; H, 3.8; N, 5.5. Calcd for $C_{20}H_{19}BrN_2O_5 \cdot 0.5CHCl_3$: C, 48.6; H, 3.9; N, 5.5.

4.4.1.2. Ethyl 3′-phenyl-4′,6′-dimethoxyindol-2′-yl-2-(hydroxyimino)acetate (7c). Ethyl 2-[3′-phenyl-4′,6′-dimethoxyindol-2′-yl]glyoxylate **6c**: 0.58 g, 1.65 mmol, yield: 0.59 g, 97%, mp 92–93 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (m, 6H, CH_3), 3.73 (m, 16H, OMe, OCH_2), 6.10, 6.16 (2d, 2H, J=1.9 Hz, $H_{5'}$), 6.36, 6.43 (2d, 2H, J=1.9 Hz, $H_{7'}$), 7.31 (m, 10H, $H_{2''}$, $H_{3''}$, $H_{4''}$), 8.86, 9.67 (2br s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 13.5 (CH_3), 55.0, 55.0 (6′-OMe), 55.4, 55.5 (4′-OMe), 61.7, 62.1 (CH_2), 86.0, 86.1 ($C_{7'}$), 92.5, 92.7 ($C_{5'}$), 111.0, 113.0 ($C_{3a'}$), 120.2, 123.0 ($C_{3'}$), 121.7, 122.1 ($C_{2'}$), 126.7, 126.8 ($C_{2''}$), 126.8, 127.0 ($C_{3''}$), 131.2, 131.4 ($C_{4''}$), 137.9, 138.1 ($C_{1''}$), 144.3, 146.0 ($C_{7a'}$), 155.6, 155.8 ($C_{4'}$), 159.4, 159.4 ($C_{6'}$), 161.9, 163.2 (C=N), 176.8, 177.6 (OCO); ν_{max} 3419, 1716, 1634 cm^{-1}; λ_{max} ($CHCl_3$) 359 nm (ε 7600 cm^{-1} M^{-1}), 331 (12,000), 262 (15,000); *m/z* (ESI) 369 ([M+H], 100%), 351 (17), 279 (18); found: C, 60.7; H, 5.4; N, 6.8. Calcd for $C_{20}H_{20}N_2O_5 \cdot 0.25CHCl_3$: C, 61.1; H, 5.1; N, 7.0.

4.4.1.3. Ethyl 4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-2′-yl-2-(hydroxyimino)acetate (7d). Ethyl 2-[4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-2′-yl]glyoxylate **6d**: 1.28 g, 3.48 mmol, yield: 1.02 g, 77%, mp 98–99 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (m, 6H, CH_3), 2.40 (s, 3H, 4″-Me), 3.69 (m, 16H, OMe, CH_2), 6.10, 6.16 (2d, 2H, J=1.9 Hz, $H_{5'}$), 6.35, 6.40 (2d, 2H, J=1.9 Hz, $H_{7'}$), 7.11–7.34 (m, 8H, $H_{2''}$, $H_{3''}$), 8.97, 9.67 (2br s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 13.4 (CH_3), 21.1, 21.2 (4″-Me), 55.0, 55.1 (4′-OMe), 55.4, 55.4 (6′-OMe), 61.7, 62.1 (CH_2), 86.1, 86.2 ($C_{7'}$), 92.5, 92.9 ($C_{5'}$), 111.0, 113.0 ($C_{3a'}$), 120.2, 123.1 ($C_{3'}$), 121.8, 122.2 ($C_{2'}$), 127.4, 127.8 ($C_{2''}$), 130.7, 131.9 ($C_{4''}$), 131.1, 131.3 ($C_{3''}$), 136.2, 138.1 ($C_{1''}$), 144.4, 146.1 ($C_{7a'}$), 155.8, 155.8 ($C_{4'}$), 159.3, 159.4 ($C_{6'}$), 162.0, 163.7 (C=N), 175.9, 177.5 (OCO); ν_{max} 3416, 1717, 1627 cm^{-1}; λ_{max} ($CHCl_3$) 329 nm (ε 12,000 cm^{-1} M^{-1}), 262 (18,000); *m/z* (ESI) 383 ([M+H], 100%), 365 (11), 293 (34); found: C, 63.1; H, 5.57 N, 6.8. Calcd for $C_{21}H_{22}N_2O_5 \cdot 0.15CHCl_3$: C, 63.2; H, 5.6; N, 7.0.

4.4.1.4. Ethyl 4′,6′-dimethoxy-3′-(4″-methoxyphenyl)-indol-2′-yl-2-(hydroxyimino)acetate (7e). Ethyl 2-[4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-2′-yl]glyoxylate **6e**: 1.98 g, 5.17 mmol, yield: 1.17 g, 57% (recovered 0.22 g, 0.57 mmol starting material), mp 89–90 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (m, 6H, CH_3), 3.71 (m, 22H, 4′-, 6′- and 4″-OMe), 6.08, 6.15 (2d, 2H, J=1.5 Hz, $H_{5'}$), 6.31, 6.40 (2d, 2H, J=1.5 Hz, $H_{7'}$), 6.87 (m, 4H, $H_{2''}$), 7.31 (m, 4H, $H_{3''}$), 9.03, 9.66 (2br s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.5, 13.6 (CH_3), 55.0, 55.1 (6′-OMe), 55.2 (4″-OMe), 55.5, 55.5 (4′-OMe), 61.6, 62.0 (CH_2), 86.0, 86.0 ($C_{7'}$), 92.5, 92.6 ($C_{5'}$), 111.2, 113.1 ($C_{3a'}$), 112.2, 112.5 ($C_{2''}$), 120.1, 122.8 ($C_{3'}$), 121.4, 122.2 ($C_{2'}$), 126.1, 127.2 ($C_{1''}$), 132.3, 132.4 ($C_{3''}$), 137.9, 138.1 ($C_{4''}$),144.7, 146.0 ($C_{7a'}$), 155.7, 155.9 ($C_{4'}$), 158.6, 159.5 ($C_{6'}$), 161.4, 164.1 (C=N), 170.7, 179.1 (OCO); ν_{max} 3420, 1716, 1646 cm^{-1}; λ_{max} ($CHCl_3$) 358 nm (ε 9500 cm^{-1} M^{-1}), 329 (15,000), 260 (20,000); *m/z* (ESI) 399 ([M+H], 100%), 381 (23), 309 (42); found: C, 60.3; H, 5.3; N, 6.2. Calcd for $C_{21}H_{22}N_2O_6 \cdot 0.2CHCl_3$: C, 60.3; H, 5.3; N, 6.6.

4.5. Preparation of 3-arylindole-2-ketoxime ethers

4.5.1. General procedure for the formation of the cyclisation precursors 1. The appropriate indole oxime **7** (1 mol equiv) was dissolved in absolute ethanol (38 L per mol of oxime **7**) and sodium metal (1.5 mol equiv) was added. This mixture was stirred for 30 min to ensure complete reaction of the sodium. The mixture was then cooled in an ice bath before 2,4-dinitrofluorobenzene (1.5 mol equiv) was added dropwise, resulting in immediate precipitation of a yellow-orange solid. The reaction mixture was stirred until TLC analysis confirmed consumption of the indole oxime **7** whereupon the solid was collected under suction and washed with absolute ethanol. The solid was dried in a dessicator and reacted further without the need for purification (a small sample was recrystallised from chloroform for elemental analysis). It should be noted that due to the presence of the *syn* and *anti* forms of the cyclisation precursors **1a–e**, signals in the NMR spectra may be doubled.

4.5.1.1. Ethyl 3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-2′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate (1a). Ethyl 3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-2′-yl-2-(hydroxyimino)acetate **7a**: 0.28 g, 0.63 mmol, yield: 0.29 g, 75%, mp 214–215 °C, appearance: yellow-orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.27 (m, 6H, CH_3), 3.58–3.93 (m, 16H, OMe, CH_2), 6.15 (br s, 2H, $H_{5'}$), 6.47, 6.61 (2d, 2H, J=1.9 Hz, $H_{7'}$), 7.26 (m, 4H, $H_{2''}$), 7.48–7.61 (m, 4H, $H_{3''}$), 7.90, 8.23 (2d, 2H, J=9.4 Hz, $H_{6'''}$), 8.45, 8.53 (2dd, 2H, J=2.6, 9.4 Hz, $H_{5'''}$), 8.30, 9.12 (2d, 2H, J=2.6 Hz, $H_{3'''}$), 8.70, 10.77 (2br s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.5, 14.6 (CH_3), 55.7, 55.8 (4′-OMe), 56.1, 56.4 (4′-OMe), 62.0, 62.7 (CH_2), 86.7, 88.7 ($C_{7'}$), 93.1, 93.2 ($C_{5'}$), 106.1 ($C_{3a'}$), 117.4 ($C_{6'''}$), 119.7 ($C_{3'''}$), 121.3, 122.2 ($C_{2'}$), 124.0, 125.3 ($C_{4''}$), 126.8, 127.8 ($C_{1''}$), 130.1, 130.2 ($C_{2''}$), 130.3, 130.7 ($C_{5'''}$), 132.9, 133.5 ($C_{3''}$), 136.2 ($C_{2'''}$), 139.8 ($C_{7a'}$), 141.4, 141.6 ($C_{4'''}$), 151.2 ($C_{6'}$), 155.6, 155.7 ($C_{4'}$), 160.1 ($C_{1'''}$), 160.6, 161.9 (C=N), 165.6, 170.8 (OCO); ν_{max} 3382, 1738, 1626, 1606 cm^{-1}; λ_{max} ($CHCl_3$) 386 nm (ε 16,000 cm^{-1} M^{-1}), 262 (23,000); *m/z* (ESI) 614/616 ([M+H], 4%), 429/431 (100); found: C, 42.3; H, 2.9; N, 7.5. Calcd for $C_{26}H_{21}BrN_4O_9\cdot 1.4CHCl_3$: C, 42.2; H, 2.9; N, 7.2.

4.5.1.2. Ethyl 3′-phenyl-4′,6′-dimethoxyindol-2′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate (1c). Ethyl 3′-phenyl-4′,6′-dimethoxyindol-2′-yl-2-(hydroxyimino)acetate **7c**: 0.37 g, 1.01 mmol, yield: 0.23 g, 43%, mp 165–166 °C, appearance: yellow-orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08–1.27 (m, 6H, CH_3), 3.47–3.97 (m, 16H, OMe, OCH_2), 6.13 (br s, 2H, $H_{5'}$), 6.46, 6.61 (2d, 2H, J=1.9 Hz, $H_{7'}$), 7.24–7.43 (m, 10H, $H_{2''}$, $H_{3''}$, $H_{4''}$), 7.90, 8.23 (2d, 2H, J=9.4 Hz, $H_{6'''}$), 8.42, 8.52 (2dd, 2H, J=2.6, 9.4 Hz, $H_{5'''}$), 8.30, 9.12 (2d, 2H, J=2.6 Hz, $H_{3'''}$), 8.73, 10.77 (2br s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 13.4 (CH_3), 55.0, 55.1 (4′-OMe), 55.5, 55.7 (6′-OMe), 62.7, 62.8 (CH_2), 85.6, 85.7 ($C_{7'}$), 93.1, 93.5 ($C_{5'}$), 110.5, 112.3 ($C_{3a'}$), 116.7, 116.8 ($C_{6'''}$), 118.0, 118.3 ($C_{3'}$), 119.2, 119.4 ($C_{3'''}$), 122.0, 122.6 ($C_{2'}$), 126.8, 127.0 ($C_{2''}$), 129.1, 130.2 ($C_{5'''}$), 131.2, 131.4 ($C_{3''}$), 132.8, 133.7 ($C_{4''}$), 135.5 ($C_{2'''}$), 138.9, 139.8 ($C_{1''}$), 140.7 ($C_{7a'}$), 141.6 ($C_{4'''}$), 149.2, 151.5 ($C_{4'}$), 155.1, 155.3 ($C_{6'}$), 156.0, 156.1 ($C_{1'''}$), 160.1, 161.3 (C=N), 161.4, 173.3 (OCO); ν_{max} 3380, 1726, 1624, 1608 cm^{-1}; λ_{max} ($CHCl_3$) 385 nm (ε 16,000 cm^{-1} M^{-1}), 257 (23,000); *m/z* (ESI) 535 ([M+H], 9%), 451 (6), 351 (100), 279 (6); found: C, 57.2; H, 4.5; N, 9.9. Calcd for $C_{26}H_{22}N_4O_9\cdot 0.125CHCl_3$: C, 57.1; H, 4.1; N, 10.2.

4.5.1.3. Ethyl 4′,6′-dimethoxy-3′-(4″-methylphenyl)-indol-2′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate (1d). Ethyl 4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-2′-yl-2-(hydroxyimino)acetate **7d**: 1.01 g, 2.65 mmol, yield: 1.07 g, 74%, mp 170–171 °C, appearance: yellow-orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09–1.27 (m, 6H, CH_3), 2.40 (s, 6H, 4″-Me), 3.50–3.95 (m, 16H, OMe, CH_2), 6.11, 6.14 (2d, 2H, J=1.5 Hz, $H_{5'}$), 6.44, 6.60 (2d, 2H, J=1.5 Hz, $H_{7'}$), 7.14–7.31 (m, 8H, $H_{2''}$, $H_{3''}$), 7.90, 8.23 (2d, 2H, J=9.4 Hz, $H_{6'''}$), 8.41, 8.52 (2dd, 2H, J=2.6, 9.4 Hz, $H_{5'''}$), 8.83, 9.11 (2d, 2H, J=2.6 Hz, $H_{3'''}$), 8.71, 10.73 (2br s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 13.4 (CH_3), 21.1, 21.2 (4″-Me), 55.0, 55.1 (4′-OMe), 55.5, 55.7 (6′-OMe), 62.6, 62.8 (CH_2), 85.7 ($C_{7'}$), 93.0, 93.4 ($C_{5'}$), 113.5, 113.6 ($C_{3a'}$), 116.6 ($C_{6'''}$), 118.0, 118.3 ($C_{3'}$), 119.3, 119.5 ($C_{3''}$), 121.9, 122.5 ($C_{2'}$), 127.5, 127.6 ($C_{2''}$), 129.1, 129.6 ($C_{4''}$), 130.2, 130.7 ($C_{5''}$), 131.0, 131.4 ($C_{3''}$), 135.9, 137.1 ($C_{2'''}$), 139.0, 139.21 ($C_{1''}$), 139.8, 140.1 ($C_{7a'}$), 140.1, 141.4 ($C_{4'''}$), 149.4, 151.6 ($C_{6'}$), 155.1, 155.3 ($C_{4'}$), 156.8, 157.0 ($C_{1'''}$), 160.0, 161.1 (C=N), 161.5, 173.5 (OCO); ν_{max} 3385, 1739, 1626, 1607 cm^{-1}; λ_{max} ($CHCl_3$) 408 nm (ε 29,000 cm^{-1} M^{-1}), 333 (50,000), 252 (53,000); *m/z* (ESI) 549 ([M+H], 9%), 365 (100), 293 (13); found: C, 58.3; H, 4.5; N, 9.9. Calcd for $C_{27}H_{24}N_4O_9\cdot 0.1CHCl_3$: C, 58.1; H, 4.3; N, 10.0.

4.5.1.4. Ethyl 4′,6′-dimethoxy-3′-(4″-methoxyphenyl)-indol-2′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate (1e). Ethyl 4′,6′-dimethoxy-3′-(4″-methoxyphenyl)indol-2′-yl-2-(hydroxyimino)acetate **7e**: 0.78 g, 1.95 mmol, yield: 0.78 g, 71%, mp 173–174 °C, appearance: yellow-orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10–1.26 (m, 6H, CH_3), 3.56–3.92 (m, 22H, 4′-, 6′- and 4″-OMe), 6.10, 6.12 (2d, 2H, J=1.9 Hz, $H_{5'}$), 6.42, 6.58 (2d, 2H, J=1.9 Hz, $H_{7'}$), 6.89 (m, 4H, $H_{2''}$), 7.30 (m, 4H, $H_{3''}$), 7.90, 8.21 (2d, 2H, J=9.4 Hz, $H_{6'''}$), 8.39, 8.50 (2dd, 2H, J=2.6, 9.4 Hz, $H_{5'''}$), 8.87, 9.09 (2d, 2H, J=2.6 Hz, $H_{3'''}$), 8.72, 10.69 (2br s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 13.5 (CH_3), 55.0, 55.1 (4′-OMe), 55.2 (4″-OMe), 55.5, 55.7 (6′-OMe), 62.7, 62.8 (CH_2), 85.6, 85.7 ($C_{7'}$), 93.0, 93.4 ($C_{5'}$), 112.2, 112.3 ($C_{3''}$), 112.4, 113.7 ($C_{3a'}$), 116.6 ($C_{6'''}$), 118.0, 118.3 ($C_{3'}$), 121.9, 122.5 ($C_{2'}$), 124.9, 126.0 ($C_{1''}$), 129.0, 130.2 ($C_{5'''}$), 132.2, 132.7 ($C_{2''}$), 135.4, 135.9 ($C_{2'''}$), 139.8, 139.9 ($C_{7a'}$), 141.0, 141.5 ($C_{4'''}$), 149.4, 151.6 ($C_{6'}$), 155.3, 156.1 ($C_{4'}$), 157.0 ($C_{1'''}$), 159.1, 160.2 ($C_{4''}$), 161.1, 161.2 (C=N), 161.6, 173.0 (OCO); ν_{max} 3388, 1739, 1605 cm^{-1}; λ_{max} ($CHCl_3$) 333 nm (ε 7000 cm^{-1} M^{-1}), 248 (12,000); *m/z* (ESI) 565 ([M+H], 8%), 381 (100); found: C, 54.3; H, 4.4; N, 8.9. Calcd for $C_{21}H_{22}N_2O_6\cdot 0.33CHCl_3$: C, 54.3; H, 4.1; N, 9.3.

4.6. Preparation of indolo[2,3-*c*]quinolines

4.6.1. General procedure for the formation of the tetracycles 2. The appropriate cyclisation precursor **1** (1 mol equiv) and triethylamine (10 mol equiv) in dry tetrahydrofuran (42 L per mole of cyclisation precursor **1**) were heated at reflux until TLC analysis showed consumption of the starting material. The solvent was then removed in vacuo and the residue dissolved in dichloromethane whereupon it was slowly added to 2 M hydrochloric acid resulting in precipitation. The precipitate was collected and the aqueous layer separated. The organic layer was again extracted with 2 M hydrochloric acid and the aqueous washings and the precipitate combined. Dichloromethane was added to the aqueous mixture, which was subsequently adjusted to pH 12 with concentrated sodium hydroxide solution, resulting in the suspended solid dissolving. The organic phase was separated and the aqueous layer was then extracted again with dichloromethane. The combined organic phases were dried over magnesium sulfate and the solvent removed in vacuo to yield the tetracycles **2a–e**. Where necessary a small sample was recrystallised from chloroform for elemental analysis.

4.6.1.1. Ethyl 3-bromo-9,11-dimethoxy indolo[2,3-*c*]-quinoline-6-carboxylate (2a). Ethyl 3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-2′-yl-2-(*O*-2,4-dinitrophenoxyimino)-acetate **1a**: 0.0503 g, 0.082 mmol, yield: 0.033 g, 94%, mp 199–200 °C, appearance: yellow-orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, J=7.2 Hz, CH_3), 3.95,

4.12 (2s, 6H, OMe), 4.67 (q, J=7.2 Hz, OCH_2), 6.42 (d, 1H, J=1.9 Hz, H_{10}), 6.67 (d, 1H, J=1.9 Hz, H_8), 7.68 (dd, 1H, J=1.9, 9.4 Hz, H_2), 8.57 (d, 1H, J=1.9 Hz, H_4), 9.38 (d, 1H, J=9.4 Hz, H_1), 10.37 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3 (CH_3), 55.4, 55.6 (OMe), 62.4 (CH_2), 86.9 (C_8), 92.9 (C_{10}), 119.8 (C_{6a}), 124.0 (C_3), 125.6 (C_{11c}), 128.6 (C_1), 130.6 (C_4), 132.0 (C_{11a}), 132.4 (C_{7a}, C_{11b}), 132.9 (C_2), 142.7 (C_{4a}), 143.4 (C_6), 155.9 (C_9), 162.1 (C_{11}), 166.7 (OCO); ν_{max} 3411, 1690, 1614 cm^{-1}; λ_{max} ($CHCl_3$) 404 nm (ε 1900 cm^{-1} M^{-1}), 363 (3300), 275 (8400); *m/z* (ESI) 429/431 ([M+H], 100%); found: C, 46.4; H, 3.7; N, 5.2. Calcd for $C_{20}H_{17}BrN_2O_4\cdot CHCl_3$: C, 46.0; H, 3.3; N, 5.1.

4.6.1.2. Ethyl 9,11-dimethoxy indolo[2,3-*c*]quinoline-6-carboxylate (2c). Ethyl 3′-phenyl-4′,6′-dimethoxyindol-2′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate **1c**: 0.052 g, 0.098 mmol, yield: 0.034 g, 99%, mp 189–191 °C, appearance: yellow-orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, 3H, J=7.1 Hz, CH_3), 3.90, 4.14 (2s, 6H, OMe), 4.68 (q, J=7.1 Hz, OCH_2), 6.43 (s, 1H, H_{10}), 6.70 (s, 1H, H_8), 7.68 (m, 2H, H_3, H_4), 8.43 (m, 1H, H_2), 9.53 (d, 1H, J=7.9 Hz, H_1), 10.40 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3 (CH_3), 55.5, 55.6 (OMe), 62.4 (CH_2), 87.0 (C_8), 92.9 (C_{10}), 125.8 (C_{6a}), 126.3 (C_1), 127.1 (C_2), 127.7 (C_3), 127.8 (C_4), 131.0 (C_{11a}), 132.1 (C_{7a}), 132.2 (C_{11b}), 135.1 (C_{11c}), 143.7 (C_{4a}), 145.0 (C_6), 156.1 (C_9), 162.0 (C_{11}), 166.8 (OCO); ν_{max} 3430, 2693, 1620 cm^{-1}; λ_{max} ($CHCl_3$) 398 nm (ε 750 cm^{-1} M^{-1}), 359 (1200), 272 (3000); *m/z* (ESI) 351 ([M+H], 100%); found: C, 60.7; H, 7.4; N, 6.5. Calcd for $C_{20}H_{18}N_2O_{11}\cdot 3.5CHCl_3$: C, 61.0; H, 7.0; N, 6.1.

4.6.1.3. Ethyl 9,11-dimethoxy-3-methyl indolo[2,3-*c*]quinoline-6-carboxylate (2d). Ethyl 4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-2′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate **1d**: 0.308 g, 0.055 mmol, yield: 0.20 g, 100%, mp 181–183 °C, appearance: yellow-orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, J=7.1 Hz, CH_3), 3.94, 4.13 (2s, 6H, OMe), 4.65 (q, J=7.1 Hz, OCH_2), 6.42 (d, 1H, J=1.9 Hz, H_{10}), 6.68 (d, 1H, J=1.9 Hz, H_8), 7.52 (dd, 1H, J=1.9, 8.7 Hz, H_2), 8.16 (br s, 1H, H_4), 9.41 (d, 1H, J=8.7 Hz, H_1), 10.33 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3 (CH_3), 21.3 (3-Me), 55.4, 55.6 (OMe), 62.2 (CH_2), 86.9 (C_8), 92.6 (C_{10}), 123.5 (C_{11c}), 125.6 (C_{6a}), 126.8 (C_1), 130.0 (C_2), 130.2 (C_4), 131.9 (C_{11a}), 132.0 (C_{7a}, C_{11b}), 135.9 (C_3), 142.6 (C_{4a}), 143.2 (C_6), 156.1 (C_9), 161.8 (C_{11}), 167.1 (OCO); ν_{max} 3424, 1698, 1623 cm^{-1}; λ_{max} ($CHCl_3$) 406 nm (ε 3400 cm^{-1} M^{-1}), 262 (4400); *m/z* (ESI) 381 ([M+H], 100%); found: C, 60.4; H, 5.3; N, 6.9. Calcd for $C_{21}H_{20}N_2O_{11}\cdot 0.8CHCl_3$: C, 60.6; H, 5.0; N, 6.5.

4.6.1.4. Ethyl 3,9,11-trimethoxy indolo[2,3-*c*]quinoline-6-carboxylate (2e). Ethyl 4′,6′-dimethoxy-3′-(4″-methoxyphenyl)indol-2′-yl-2-(*O*-2,4-dinitrophenoxyimino)-acetate **1e**: 0.195 g, 0.035 mmol, yield: 0.066 g, 51%, mp 159–161 °C, appearance: yellow-orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (t, 3H, J=7.2 Hz, CH_3), 3.92, 4.09 (2s, 6H, OMe), 4.66 (q, J=7.2 Hz, OCH_2), 6.36 (d, 1H, J=1.5 Hz, H_{10}), 6.61 (d, 1H, J=1.5 Hz, H_8), 7.33 (dd, 1H, J=3.0, 9.4 Hz, H_2), 8.16 (d, 1H, J=3.0 Hz, H_4), 9.39 (d, 1H, J=9.4 Hz, H_1), 10.37 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.4 (CH_3), 55.3 (3-OMe), 55.4, 55.6 (OMe), 62.3 (CH_2), 86.9 (C_8), 92.5 (C_{10}), 108.6 (C_4), 120.6 (C_{11c}), 120.7 (C_1), 125.4 (C_{6a}), 128.2 (C_2), 131.2 (C_{11a}), 131.6 (C_{7a}, C_{11b}), 143.0 (C_{4a}), 144.3 (C_6), 156.2 (C_9), 158.0 (C_3), 162.0 (C_{11}), 166.9 (OCO); ν_{max} 3431, 1726, 1687, 1620 cm^{-1}; λ_{max} ($CHCl_3$) 416 nm (ε 5000 cm^{-1} M^{-1}), 363 (8300), 260 (13,000); *m/z* (ESI) 365 ([M+H], 100%); found: C, 58.7; H, 5.0; N, 6.4. Calcd for $C_{21}H_{20}N_2O_5\cdot 0.5CHCl_3$: C, 58.7; H, 4.7; N, 6.4.

4.7. Calculation of rate constants for the cyclisation of 3-arylindole-2-ketoxime ethers

The precursors **1a–e** (1 mol equiv) were each added to a solution of triethylamine (10 mol equiv) in tetrahydrofuran (42 L per mol of precursor **1**) being heated at reflux. Aliquots of the reaction mixture (ca. 0.3 mL) were taken periodically, cooled to 77 K to quench the reaction and the solvent then removed in vacuo at that temperature. The aliquots were subsequently analysed using ^{1}H NMR spectroscopy. The extent of reaction in each case was calculated by comparing the integrations corresponding to either the $H_{5‴}$ or $H_{6‴}$ signal in the precursor **1**, the $H_{5′}$ or $H_{6′}$ signal in the intermediate and the H_1 signal in the tetracycle **2**. The data was fitted using a numerical integration to obtain the rate constant for the formation of the intermediate from each of the starting materials **1a–e**.

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References and notes

1. Wahyuningsih, T. D.; Kumar, N.; Black, D., StC. *Tetrahedron* **2007**, *63*, 6713–6719.
2. Sugumi, H.; Niijima, J.; Kotake, Y.; Okada, T.; Kamata, J.-i.; Yoshimatsu, K.; Nagasu, T.; Nakamura, K.; Uenaka, T.; Yamaguchi, A.; Yoshino, H.; Koyanagi, N.; Kito, K. Int. Patent 9638446, 1996; *Chem. Abstr.* **1996**, *126*, 89394.
3. For examples, see: Narasaka, K. *Pure Appl. Chem.* **2003**, *75*, 19–28 and references cited therein.
4. Mikami, T.; Narasaka, K. *Chem. Lett.* **2000**, 338–339.
5. Uchiyama, K.; Ono, A.; Hayashi, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2945–2955.
6. Black, D. StC.; Gatehouse, B. M. K. C.; Théobald, F.; Wong, L. C. H. *Aust. J. Chem.* **1980**, *33*, 343–350.
7. Black, D. StC.; Bowyer, M. C.; Bowyer, P. K.; Ivory, A. J.; Kim, M.; Kumar, N.; McConnell, D. B.; Popiolek, M. *Aust. J. Chem.* **1994**, *47*, 1741–1750.