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Mechanisms of cyclisation of indolo oxime ethers. Part 2: Formation of ethyl 6,8-dimethoxypyrazolo[4,5,1-*hi*]indole-5-carboxylates

Kylie A. Clayton, David StC. Black, Jason B. Harper*

School of Chemistry, University of New South Wales, UNSW, Sydney, NSW 2052, Australia

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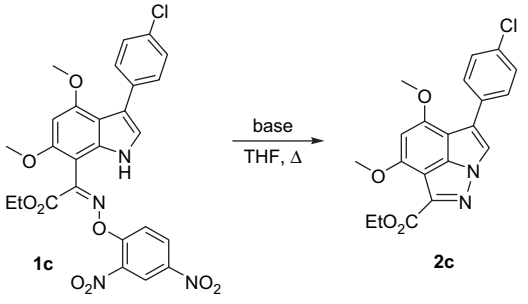
Abstract

The cyclisation of a series of ethyl 3′-phenyl-4′,6′-dimethoxyindol-7′-yl-2-(hydroxyimino)acetates was investigated using ^{1}H NMR spectroscopy to determine the mechanism of formation of the corresponding ethyl 6,8-dimethoxypyrazolo[4,5,1-*hi*]indole-5-carboxylates. The electronic requirements of the reaction were determined and used, along with the effect of removing the ester functionality, to determine that the reaction proceeds through a concerted intramolecular substitution.

Keywords: Indole; Cyclisation; Mechanism determination

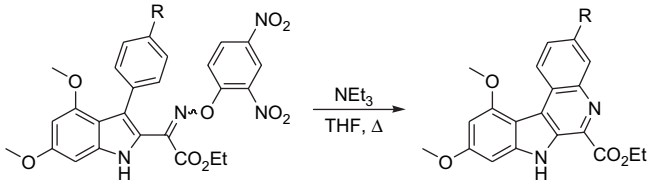
1. Introduction

Recently, we have reported the cyclisation of chlorophenyl oxime ether **1c** to the corresponding tricycle **2c** (Scheme 1).[1] It is of interest to determine the mechanism of this process, both in an effort to extend the methodology involved in the syntheses of these novel tricycles and also as a comparison to when the indoles are substituted at the 2-position (Scheme 2). This isomeric case has been shown in the preceding paper in this series[2] to proceed through an electrocyclic mechanism.



Scheme 1. Cyclisation of the oxime ether **1c** to give the corresponding tricycle **2c**.

As for the series investigated previously (Scheme 2),[2] several mechanistic pathways may be considered for the reaction outlined in Scheme 1. There is literature precedent for an intramolecular concerted substitution process[3] and this has been suggested previously for this system.[1] A polar mechanism that proceeds stepwise through a nitronium ion must also be considered. Rather than a polar mechanism, radical mechanisms need also to be considered, as both one-step[4] and two-step[5] radical processes have been reported for related systems. While an electrocyclic mechanism, which was found to be the case for the isomeric oxime cyclisation (Scheme 2),[2] is not possible in this case, a conjugate addition mechanism



Scheme 2. Cyclisation of ethyl 3′-aryl-4′,6′-dimethoxyindol-2′-yl-2-(hydroxyimino)acetates, which has been shown to proceed through an electrocyclic mechanism.[2]

* Corresponding author. Tel.: +61 2 9385 4692; fax: +61 2 9385 6141.
E-mail address: j.harper@unsw.edu.au (J.B. Harper).

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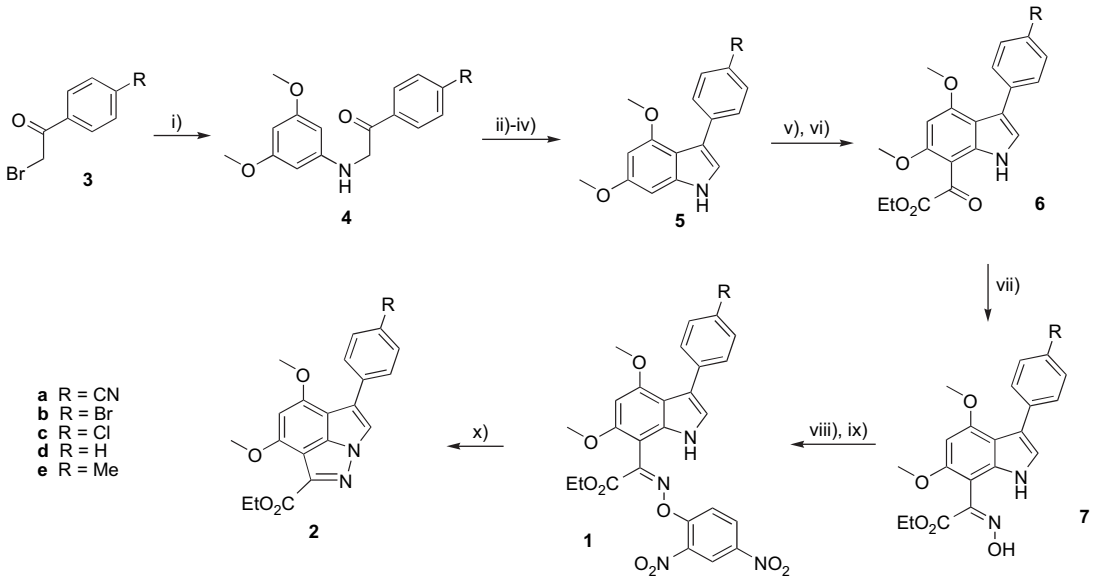


Scheme 3. Syntheses of the tricycles **2a**–**e**. Reagents: (i) 3,5-dimethoxyaniline, EtOH, $NaHCO_3$, Δ; (ii) $(CF_3CO)_2O$; (iii) CF_3CO_2H; (iv) KOH, MeOH; (v) $(COCl)_2$; (vi) EtOH; (vii) $NH_2OH{\cdot}HCl$, pyridine, EtOH, Δ; (viii) Na, EtOH; (ix) 2,4-fluorodinitrobenzene; (x) NEt_3, THF, Δ.

(which is formally equivalent to the electrocyclic mechanism in the previous case) is also possible.

In this paper, we describe the synthesis and cyclisation of a series of analogues of the oxime ether **1c**. Through variation of the substituent on the phenyl ring, the electronic demand of the reaction was determined and used, along with observation of the effect of varying the ester substituent, to elucidate the mechanism.

2. Results and discussion

Indole oxime ethers **1a**–**e** were synthesised as outlined in Scheme 3 from the corresponding acetophenones **3a**–**e**. Bischler-like conditions were used to convert the ketones **4a**–**e** to the phenylindoles **5a**–**e**, which were subsequently acylated and esterified. This gave a mixture of the desired 7-substituted indoles **6a**–**e**, which were separated from the corresponding 2-isomers that were also produced, using column chromatography. Conversion to the corresponding oximes **7a**–**e** using hydroxylamine was followed by reaction with fluorodinitrobenzene to give the cyclisation precursors **1a**–**e**. It is interesting to note that spectroscopic analysis of both the oximes **7a**–**e** and the oxime ethers **1a**–**e** did not show any indication that both the *syn* and the *anti* forms were present, as was the case for the corresponding isomers substituted at the 2-position of the indole.[2] This is consistent with hydrogen bonding seen previously, suggesting that only the *anti* form is present in each case.[6] The corresponding tricycles **2a**–**e** were formed through heating the precursors **1a**–**e** at reflux in tetrahydrofuran in the presence of triethylamine.

Each of the precursors **1a**–**e** was treated under the same conditions as described in Scheme 3. 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 formation of each of the tricycles **2a**–**e** were followed using ^1H NMR spectroscopy, specifically the disappearance of the signals due to $H_{5'}$ of the precursors **1a**–**e** and appearance of the signals due to H_7 of the products **2a**–**e**. Each of these protons had previously been shown to have the same relaxation time and hence integration of these signals was an appropriate quantitative measure.

Initial analysis of the rate data showed that the cyclisation of the precursors **1a**–**e** followed first order kinetics. This allowed the straightforward calculation of the rate constants for the cyclisation of the precursors **1a**–**e** to the corresponding tricycles **2a**–**e** (Table 1). The trend in the rate constants for the cyclisation of the precursors **1a**–**e** is clear, with the rate of reaction being faster for electron donating substituents and slower for electron withdrawing substituents. The values calculated give rise to a linear Hammett plot (Fig. 1) with a ρ value of -0.98 ± 0.07.

While several of the possible mechanisms might be anticipated to be favoured by electron donating groups, the large value for the reaction constant is consistent with significant decrease in electron density in the transition state, as occurs in a polar mechanism. The distance of the substituents on the phenyl group in the precursors **1a**–**e** from the imino nitrogen atom would likely result in their change having little effect on the formation of a nitronium ion intermediate, suggesting that a stepwise polar mechanism is not operating. Both the intramolecular concerted substitution process and the conjugate

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

Compound	R	Rate constant (s^{-1})
1a	CN	$(2.04\pm0.01)\times10^{-6}$
1b	Br	$(5.22\pm0.14)\times10^{-6}$
1c	Cl	$(4.53\pm0.11)\times10^{-6}$
1d	H	$(8.36\pm0.30)\times10^{-6}$
1e	Me	$(13.9\pm0.1)\times10^{-6}$

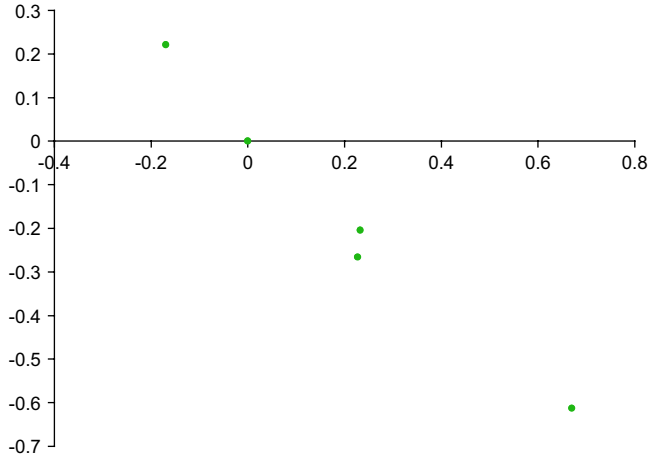
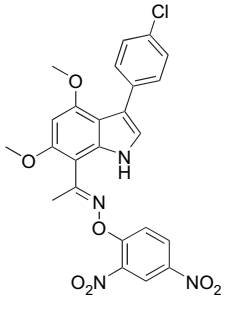


Figure 1. Hammett plot for the cyclisation of the precursors **1a–e** under the conditions outlined in Scheme 1.

addition mechanism would be anticipated to result in a negative ρ value. While no values of the reaction constant have been reported for reaction of styrylamines or related compounds, it is possible to use ρ values reported for the reaction of aniline derivatives and the attenuation ratio developed for the insertion of a vinyl group to predict ρ values for such a reaction. The reaction constants for the reaction of anilino derivatives range from -2.1 to -4.2,[7] depending on reaction conditions, though the comparison may be narrowed to the lower end of this range by recognising that the ρ value is dependent on temperature and dielectric constant of the medium.[8] Using this and the attenuation value for a vinyl group (0.48 ± 0.07[9]) suggests a reaction constant of ca. 1–1.5 for both the intramolecular concerted substitution and the conjugate addition mechanisms, which, given the approximations involved, is in reasonable agreement with that observed.

In order to distinguish these mechanistic possibilities, the oxime ether **8**, which is related to the ether **1c** through replacement of the ester moiety with a methyl group, was prepared by a method analogous to that described in Scheme 3. The removal of the ester group would be expected to have the greatest effect on the rate of cyclisation if the reaction proceeded through a conjugate addition mechanism, essentially halting the reaction. In the case of the intramolecular concerted processes, while removing the ester group might be expected to alter the electron density on the oxime ether nitrogen, the effect on the rate of reaction would not be expected to be as great.



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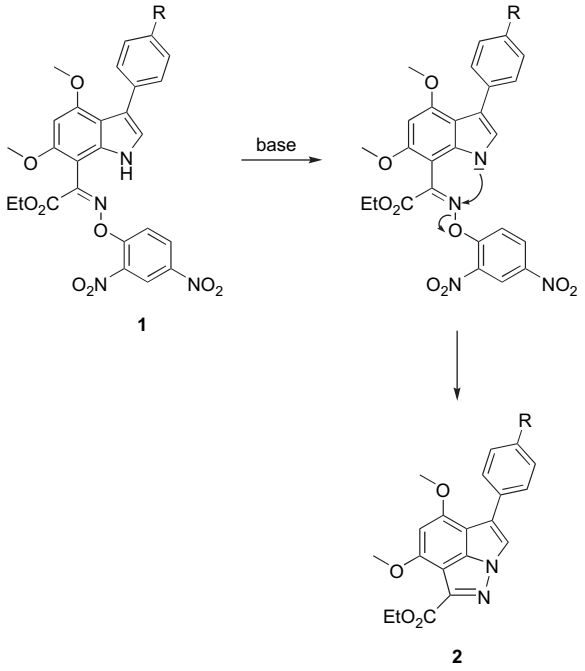
It is not possible to follow the reaction using the same signals in the ^{1}H NMR spectra as for the conversion of the precursors **1a–e** to the tricycles **2a–e** as in the case of the cyclisation of the oxime ether **8** the signals overlap.[1] As such, the cyclisation of the ether **8** was followed using the signals corresponding to the protons on the chlorophenyl substituent. Under identical conditions to those used for the cyclisation of the precursors **1a–e**, the reaction was found to go to completion in less than 12 h. This corresponds to a rate at least five times than that for the cyclisation of the fastest of the precursors **1a–e** and is consistent with the results reported previously.[1]

These results indicate that the cyclisation of the ethers **1a–e** proceeds through a concerted intramolecular cyclisation, as shown in Scheme 4. The process is shown as proceeding through the indole anion rather than the neutral indole, as the reaction has been shown not to proceed in the absence of a base but to proceed faster in the presence of a stronger base.[1]



1 **2**

Scheme 4. Cyclisation of the precursors **1** proceeding through a concerted intramolecular substitution.

3. Conclusions

Oxime ethers **1a–e** cyclise through a concerted intramolecular substitution mechanism to give the indoles **2a–e**, a process for which there is literature precedent.[3]

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. High-resolution mass spectra were recorded on a Bruker BioApex IIe 7T FT-ICRMS with an Analytico electrospray ionisation source operating in positive ion mode. Ultraviolet spectra were recorded 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). Compounds **1c**, **2c**, **4b–e**, **5b–e**, **6c**, **7c** and **8** were prepared as described previously.[1,2,10,11]

4.2. Preparation of novel indole precursors

4.2.1. 1-(4′-Cyanophenyl)-2-[(3″,5″-dimethoxyphenyl)amino]ethanone (*4a*)

3,5-Dimethoxyaniline (3.46 g, 22.6 mmol), 2-bromo-4′-cyanoacetophenone **3a** (5.06 g, 22.6 mmol) and sodium hydrogen carbonate (2.37 g, 28.3 mmol) in absolute ethanol (75 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 heating and allowed to cool. The solvent was removed in vacuo and the residue recrystallised from ethyl acetate/light petroleum to yield amino ketone **4a** as a yellow solid (4.64 g, 70%). Mp 158–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 6H, OMe), 4.54 (s, 2H, CH_2), 5.87 (s, 2H, $H_{2''}$), 5.88 (br s, 1H, $H_{4''}$), 7.49 (d, 2H, J=8.7 Hz, $H_{3'}$), 7.93 (d, 2H, J=8.7 Hz, $H_{2'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 50.8 (CH_2), 55.2 (OMe), 90.5 ($C_{4''}$), 92.4 ($C_{2''}$), 117.1 (CN), 117.5 ($C_{4'}$), 128.1 ($C_{2'}$), 132.7 ($C_{3'}$), 137.7 ($C_{1'}$), 148.3 ($C_{1''}$), 161.8 ($C_{3''}$), 193.7 (CO); ν_{max} 3396, 1682, 1618 cm^{-1}; λ_{max} ($CHCl_3$) 368 nm (ε 770 cm^{-1} M^{-1}), 259 (2900); *m/z* (ESI) 297 ([M+H]$^+$, 100%). Found: C, 67.4; H, 5.4; N, 9.1. Calcd for $C_{17}H_{16}N_2O_3\cdot 0.05CHCl_3$: C, 67.7; H, 5.4; N, 9.3.

4.3. Preparation of substituted indole esters

4.3.1. Ethyl 2-(3′-(4″-cyanophenyl)-4′,6′-dimethoxyindol-7′-yl)glyoxylate (*6a*)

1-(4′-Cyanophenyl)-2-[(3″,5″-dimethoxyphenyl)amino]-ethanone **4a** (4.57 g, 15.4 mmol) and triethylamine (4.26 mL, 30.8 mmol) in dry tetrahydrofuran (70 mL) were stirred in an ice bath before trifluoroacetic anhydride (4.32 mL, 30.8 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 (21 mL) was added to the oil and the mixture heated under reflux for 15 min. The mixture was then removed from heating, 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 desiccator. The dried precipitate was dissolved in methanol (42 mL) and potassium hydroxide (4.2 g, 74.9 mmol) was added. The mixture was then stirred for 1 h and water was added, causing precipitation. The solid was then extracted with dichloromethane until the organic extracts were colourless. The organic extracts were then combined, dried over magnesium sulfate and the solvent removed in vacuo. This gave the indole **5a**, which was used without further purification. *3-(4′-Cyanophenyl)-4,6-dimethoxyindole* ***5a***. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.27 (d, 1H, J=1.9 Hz, H_5), 6.51 (d, 1H, J=1.9 Hz, H_7), 7.07 (d, 1H, J=2.3 Hz, H_2), 7.67 (d, 2H, J=8.3 Hz, $H_{3'}$), 7.79 (d, 2H, J=8.3 Hz, $H_{2'}$), 8.35 (br s, 1H, NH).

Oxalyl chloride (1.26 mL, 14.7 mmol) was added to a mixture of the indole **5a** (3.40 g, 12.2 mmol) partially dissolved in dry diethyl ether (105 mL). This mixture was stirred for 3 h at room temperature and the solvent was then removed in vacuo. Absolute ethanol (52 mL) was then added to the solid and the mixture stirred for further 2 h, whereupon the solvent was again removed in vacuo. The residue was purified using column chromatography (methanol/chloroform, 1:1000) to give the indole ester **6a** as a yellow solid (0.70 g, 12%). Mp 186–187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3H, J=7.2 Hz, CH_3), 3.92 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.40 (q, 2H, J=7.2 Hz, CH_2), 6.20 (s, 1H, $H_{5'}$), 7.14 (d, 1H, J=2.3 Hz, $H_{2'}$), 7.61 (br s, 4H, $H_{2''}$, $H_{3''}$), 10.66 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (CH_3), 55.5, 56.9 (OMe), 61.5 (CH_2), 87.7 ($C_{5'}$), 100.9 ($C_{7'}$), 109.3 ($C_{3'}$), 110.3 ($C_{3a'}$), 117.7 ($C_{4''}$), 119.3 (CN), 122.9 ($C_{2'}$), 129.7 ($C_{2''}$), 131.4 ($C_{3''}$), 138.7 ($C_{7a'}$), 140.1 ($C_{1''}$), 161.8 ($C_{4'}$), 162.2 ($C_{6'}$), 165.9 (CO), 185.1 (OCO); ν_{max} 3390, 2223, 1737, 1608 cm^{-1}; λ_{max} ($CHCl_3$) 360 nm (ε 10,000 cm^{-1} M^{-1}), 325 (17,000); *m/z* (ESI) 379 ([M+H], 100%), 357 (12), 305 (47), 279 (47). Found: C, 66.5; H, 5.0; N, 7.3. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.7; H, 4.8; N, 7.4.

4.3.2. General procedure for the formation of the substituted indoles *6b*, *d* and *e*

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 further 2 h, whereupon the solvent was again removed in vacuo. Indole esters **6b**, **d** and **e** were then purified using column chromatography (methanol/chloroform, 1:100). Elemental analyses indicated chloroform of crystallisation in one case.

*4.3.2.1. Ethyl 2-[3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-7′-yl]glyoxylate (**6b**).* 3-(4′-Bromophenyl)-4,6-dimethoxyindole **5b**: 2.34 g, 7.04 mmol, yield: 0.48 g, 16%, mp 162–163 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, J=7.1 Hz, CH_3), 3.92 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.40 (q, 2H, J=7.1 Hz, CH_2), 6.18 (s, 1H, $H_{5'}$), 7.09 (d, 1H, J=2.3 Hz, $H_{2'}$), 7.45 (m, 4H, $H_{2''}$, $H_{3''}$), 10.56 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (CH_3), 55.4, 56.9 (OMe), 61.4 (CH_2), 87.7 ($C_{5'}$), 100.8 ($C_{7'}$), 110.6

($C_{3'}$), 118.0 ($C_{1''}$), 120.1 ($C_{4''}$), 121.9 ($C_{2'}$), 130.7 ($C_{2''}$), 131.0 ($C_{3''}$), 134.1 ($C_{3a'}$), 138.5 ($C_{7a'}$), 162.0 ($C_{4'}$), 162.1 ($C_{6'}$), 165.9 (CO), 185.1 (OCO); ν_{max} 3426, 1728, 1615 cm^{-1}; λ_{max} ($CHCl_3$) 368 nm (ε 11,000 $cm^{-1}M^{-1}$), 258 (22,000); *m/z* (ESI) 432/434 ([M+H], 100%), 404/406 (47), 358/360 (23). Found: C, 55.3; H, 4.2; N, 3.2. Calcd for $C_{20}H_{18}BrNO_5$: C, 55.6; H, 4.3; N, 3.2.

*4.3.2.2. Ethyl 2-[3′-phenyl-4′,6′-dimethoxyindol-7′-yl]glyoxylate (**6d**).* 4,6-Dimethoxy-3-phenylindole **5d**: 1.64 g, 6.48 mmol, yield: 0.37 g, 16%, mp 134–135 °C, appearance: pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, *J*=7.2 Hz, CH_3), 3.92 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.42 (q, 2H, *J*=7.1 Hz, CH_2), 6.19 (s, 1H, $H_{5'}$), 7.11 (d, 1H, *J*=2.3 Hz, $H_{2'}$), 7.28 (tt, 1H, *J*=1.5, 8.7 Hz, $H_{4''}$), 7.37 (m, 2H, $H_{3''}$), 7.61 (dd, 2H, *J*=1.5, 7.2 Hz, $H_{2''}$), 10.56 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (CH_3), 53.3, 55.4 (OMe), 61.4 (CH_2), 87.4 ($C_{5'}$), 100.8 ($C_{7'}$), 110.8 ($C_{3'}$), 119.2 ($C_{1''}$), 121.9 ($C_{4''}$), 126.0 ($C_{2'}$), 127.6 ($C_{2''}$), 128.7 ($C_{3''}$), 135.1 ($C_{3a'}$), 138.5 ($C_{7a'}$), 162.1 ($C_{4'}$), 162.2 ($C_{6'}$), 166.0 (CO), 185.0 (OCO); ν_{max} 3409, 1746, 1728, 1625 cm^{-1}; λ_{max} ($CHCl_3$) 378 nm (ε 5700 $cm^{-1}M^{-1}$), 341 (9600), 265 (12,000); *m/z* (ESI) 354 ([M+H], 100%), 282 (14), 254 (19). Found: C, 67.8; H, 5.8; N, 3.6. Calcd for $C_{20}H_{19}NO_5$: C, 68.0; H, 5.4; N, 4.0.

*4.3.2.3. Ethyl 2-[4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-7′-yl]glyoxylate (**6e**).* 4,6-Dimethoxy-3-(4′-methylphenyl)indole **5e**: 2.60 g, 9.73 mmol, yield: 0.13 g, 4%, mp 134–136 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, *J*=7.2 Hz, CH_3), 2.40 (s, 3H, 4″-Me), 3.90 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.42 (q, 2H, *J*=7.2 Hz, CH_2), 6.17 (s, 1H, $H_{5'}$), 7.07 (d, 1H, *J*=2.3 Hz, $H_{2'}$), 7.18 (d, 2H, *J*=7.9 Hz, $H_{3''}$), 7.45 (d, 2H, *J*=7.9 Hz, $H_{2''}$), 10.54 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (CH_3), 21.0 (4″-Me), 55.5, 56.8 (OMe), 61.3 (CH_2), 87.3 ($C_{5'}$), 100.7 ($C_{7'}$), 110.9 ($C_{3'}$), 119.1 ($C_{1''}$), 122.2 ($C_{4''}$), 122.7 ($C_{2'}$), 128.4 ($C_{2''}$), 129.2 ($C_{3''}$), 135.6 ($C_{3a'}$), 138.4 ($C_{7a'}$), 162.0 ($C_{4'}$), 162.3 ($C_{6'}$), 166.0 (CO), 185.0 (OCO); ν_{max} 3775, 3684, 3621, 1708, 1603 cm^{-1}; λ_{max} ($CHCl_3$) 335 nm (ε 4300 $cm^{-1}M^{-1}$), 259 (8100), 265 (12,000); *m/z* (ESI) 354 ([M+H], 100%), 282 (14), 254 (19). Found: C, 66.4; H, 5.8; N, 3.3. Calcd for $C_{21}H_{21}NO_5\cdot 0.1CHCl_3$: C, 66.8; H, 5.6; N, 3.7.

4.4. Preparation of 3-arylindole-7-ketoxime ethers

*4.4.1. General procedure for the formation of the cyclisation precursors **1***

The appropriate indole ester **6** (1 mol equiv) and hydroxylamine hydrochloride (2.1 mol equiv) were dissolved in a mixture of pyridine (4.4 L per mole of indole ester **6**) and absolute ethanol (2.8 L per mole of indole ester **6**). The mixture was heated under reflux until TLC analysis confirmed consumption of the starting material **6**. The solvent was then removed in vacuo, the residue dissolved in dichloromethane and the organic layer extracted twice with water, once with 1 M hydrochloric acid and then dried. The solvent was removed in vacuo to give the oximes **7**, which were characterised using NMR spectroscopy and used without further purification.

The appropriate indole oxime **7** (1 mol equiv) was dissolved in absolute ethanol (38 L per mole of oxime **7**) and sodium metal (1.5 mol equiv) was added. This mixture was stirred for 30 min to ensure complete reaction of sodium. The mixture was then cooled in an ice bath before 2,4-fluorodinitrobenzene (1.5 mol equiv) was added dropwise, resulting in immediate precipitation of a yellow-brown solid. The reaction mixture was stirred overnight whereupon the solid was collected under suction and washed with absolute ethanol. The resulting solid was recrystallised from either chloroform or chloroform/light petroleum to yield the appropriate cyclisation precursor **1**. The yields calculated are based upon two steps from the ester. Elemental analyses indicated chloroform of crystallisation.

*4.4.1.1. Ethyl 3′-(4″-cyanophenyl)-4′,6′-dimethoxyindol-2′-yl-2-(hydroxyimino)acetate (**7a**).* Ethyl 2-[3′-(4″-cyanophenyl)-4′,6′-dimethoxyindol-2′-yl]glyoxylate **6a**: 0.19 g, 0.50 mmol, appearance: yellow solid; ^{1}H NMR (300 MHz, CD_3OD) δ 1.35 (t, 3H, *J*=7.2 Hz, CH_3), 3.93 (br s, 6H, OMe), 4.35 (q, 2H, *J*=7.2 Hz, CH_2), 6.40 (s, 1H, $H_{5'}$), 7.26 (s, 1H, $H_{2'}$), 7.70–7.90 (m, 4H, $H_{2''}$, $H_{3''}$), 10.35 (br s, 1H, NH).

*4.4.1.2. Ethyl 3′-(4″-cyanophenyl)-4′,6′-dimethoxyindol-7′-yl-2-(O-2,4-dinitrophenoxyimino)acetate (**1a**).* Yield: 0.10 g, 36%, mp 131–133 °C, appearance: orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, 3H, *J*=7.2 Hz, CH_3), 3.85 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.43 (q, 2H, *J*=7.2 Hz, CH_2), 6.25 (s, 1H, $H_{5'}$), 7.05 (br s, 1H, $H_{2'}$), 7.60–7.70 (m, 4H, $H_{2''}$, $H_{3''}$), 8.16 (d, 1H, *J*=9.4 Hz, $H_{6'''}$), 8.43 (dd, 1H, *J*=2.6, 9.4 Hz, $H_{5'''}$), 8.96 (d, 1H, *J*=2.6 Hz, $H_{3'''}$), 10.12 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8 (CH_3), 55.0, 57.4 (OMe), 60.6 (CH_2), 88.9 ($C_{5'}$), 90.0 ($C_{7'}$), 106.5 ($C_{3a'}$), 113.8 ($C_{4''}$), 117.5 ($C_{3'}$), 117.6 (CN), 117.7 ($C_{6'''}$), 122.0 ($C_{3'''}$), 123.1 ($C_{2'}$), 126.1 ($C_{2''}$), 129.6 ($C_{3''}$), 129.9 ($C_{5'''}$), 135.9 ($C_{2'''}$), 136.0 ($C_{7a'}$), 139.5 ($C_{1''}$), 140.2 ($C_{4'''}$), 156.6 ($C_{6'}$), 157.0 ($C_{1'''}$), 157.9 ($C_{4'}$), 164.7 (C=N), 175.1 (OCO); ν_{max} ($CHCl_3$) 3684, 3620, 1736, 1712, 1603 cm^{-1}; λ_{max} ($CHCl_3$) 260 nm (ε 6900 $cm^{-1}M^{-1}$), 385 (5200); *m/z* (ESI) 560 ([M+H], 5%), 376 (100). HRMS found: 560.1426. Calcd for $C_{27}H_{22}N_5O_9$ ($[M+H]^+$): 560.1418. Found: C, 56.3; H, 3.5; N, 11.9. Calcd for $C_{27}H_{21}N_5O_9\cdot 0.2CHCl_3$: C, 56.0; H, 3.7; N, 12.0.

*4.4.1.3. Ethyl 3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-7′-yl-2-(hydroxyimino)acetate (**7b**).* Ethyl 2-[3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-7′-yl]glyoxylate **6b**: 0.11 g, 0.25 mmol, appearance: yellow solid; ^{1}H NMR (300 MHz, CD_3OD) δ 1.35 (t, 3H, *J*=7.1 Hz, CH_3), 3.74 (s, 3H, OMe), 3.76 (s, 3H, OMe), 4.35 (q, 2H, *J*=7.1 Hz, CH_2), 6.29 (s, 1H, $H_{5'}$), 7.10 (s, 1H, $H_{2'}$), 7.36 (br s, 4H, $H_{2''}$, $H_{3''}$), 10.51 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.2 (CH_3), 54.4, 56.8 (OMe), 61.1 (CH_2), 88.0 ($C_{5'}$) 89.0 ($C_{7'}$), 110.8 ($C_{3a'}$), 117.0 ($C_{3'}$), 119.0 ($C_{2'}$), 122.1 ($C_{4''}$), 126.9 ($C_{2''}$), 130.2 ($C_{3''}$), 135.4 ($C_{1''}$), 135.6 ($C_{7a'}$), 156.1 ($C_{4'}$), 156.8 ($C_{6'}$), 165.3 (C=N), 165.5 (OCO).

*4.4.1.4. Ethyl 3′-(4″-bromophenyl)-4′,6′-dimethoxyindol-7′-yl-2-(O-2,4-dinitrophenoxyimino)acetate (**1b**).* Yield: 0.09 g, 59%, mp 197–198 °C, appearance: orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, 3H, J=7.2 Hz, CH_3), 3.91 (s, 3H, OMe), 3.92 (s, 3H, OMe), 4.53 (q, 2H, J=7.2 Hz, CH_2), 6.28 (s, 1H, $H_{5'}$), 7.14 (d, 1H, J=7.2 Hz, $H_{2'}$), 7.43 (d, 2H, J=8.3 Hz, $H_{2''}$), 7.51 (d, 2H, J=8.3 Hz, $H_{3''}$), 7.86 (d, 1H, J=9.0 Hz, $H_{6'''}$), 8.49 (dd, 1H, J=2.6, 9.0 Hz, $H_{5'''}$), 8.91 (d, 1H, J=2.6 Hz, $H_{3'''}$), 9.82 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3 (CH_3), 54.8, 57.0 (OMe), 61.5 (CH_2), 89.4 ($C_{5'}$) 93.7 ($C_{7'}$), 110.9 ($C_{3a'}$), 117.4 ($C_{6'''}$), 117.7 ($C_{3'}$), 121.2 ($C_{3'''}$), 122.8 ($C_{2'}$), 127.2 ($C_{2''}$), 129.2 ($C_{5'''}$), 131.0 ($C_{3''}$), 134.3 ($C_{4''}$), 134.7 ($C_{1''}$), 135.2 ($C_{7a'}$), 136.5 ($C_{2'''}$), 141.8 ($C_{4'''}$), 155.6 ($C_{1'''}$), 159.0 ($C_{4'}$), 159.7 ($C_{6'}$), 160.1 (C=N), 161.6 (OCO); ν_{max} 3733, 1733, 1716, 1657 cm^{-1}; λ_{max} ($CHCl_3$) 376 nm (ε 8400 cm^{-1} M^{-1}), 334 (10,000), 256 (15,000); *m/z* (ESI) 613/615 ([M+H], 8%), 429/431 (100), 368 (22), 338 (10). Found: C, 44.0; H, 3.2; N, 8.0. Calcd for $C_{26}H_{21}BrN_4O_9\cdot 1CHCl_3$: C, 44.3; H, 3.0; N, 7.6.

*4.4.1.5. Ethyl 3′-phenyl-4′,6′-dimethoxyindol-7′-yl-2-(hydroxyimino)acetate (**7d**).* Ethyl 2-(3′-phenyl-4′,6′-dimethoxyindol-7′-yl)glyoxylate **6d**: 0.27 g, 0.75 mmol; appearance: yellow solid; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 1.36 (t, 3H, J=7.5 Hz, CH_3), 3.85 (br s, 6H, OMe), 4.36 (q, 2H, J=7.5 Hz, CH_2), 6.41 (br s, 1H, $H_{5'}$), 7.17 (br s, 1H, $H_{2'}$), 7.25–7.38 (br s, 3H, $H_{3''}$, $H_{4''}$), 7.56 (d, 2H, J=7.1 Hz, $H_{2''}$), 11.29 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 13.4 (CH_3), 54.5, 57.0 (OMe), 61.2 (CH_2), 89.0 ($C_{5'}$), 96.6 ($C_{7'}$), 110.9 ($C_{3'}$), 122.0 ($C_{2'}$), 125.4 ($C_{2''}$), 129.2 ($C_{3''}$), 132.7 ($C_{4''}$), 135.9 ($C_{1''}$), 135.9 ($C_{7a'}$, $C_{3a'}$), 156.0 ($C_{4'}$), 156.9 ($C_{6'}$), 165.2 (C=N), 166.1 (OCO).

*4.4.1.6. Ethyl 3′-phenyl-4′,6′-dimethoxyindol-7′-yl-2-(O-2,4-dinitrophenoxyimino)acetate (**1d**).* Yield: 0.15 g, 37%, mp 192–193 °C, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, 3H, J=7.2 Hz, CH_3), 3.90 (s, 3H, OMe), 3.92 (s, 3H, OMe), 4.53 (q, 2H, J=7.2 Hz, CH_2), 6.27 (s, 1H, $H_{5'}$), 6.91 (s, 1H, $H_{2'}$), 7.15–7.50 (m, 5H, $H_{2''}$, $H_{3''}$, $H_{4''}$), 7.88 (d, 1H, J=9.4 Hz, $H_{6'''}$), 8.50 (dd, 1H, J=2.6, 9.4 Hz, $H_{5'''}$), 8.92 (d, 1H, J=2.6 Hz, $H_{3'''}$), 9.81 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 13.4 (CH_3), 54.8, 57.2 (OMe), 61.7 (CH_2), 89.5 ($C_{5'}$) 93.6 ($C_{7'}$), 111.2 ($C_{3a'}$), 117.8 ($C_{6'''}$), 118.8 ($C_{3'}$), 121.1 ($C_{3'''}$), 122.7 ($C_{2'}$), 125.7 ($C_{4''}$), 127.3 ($C_{3''}$), 129.4 ($C_{2''}$), 129.8 ($C_{5'''}$), 135.2 ($C_{1''}$), 135.6 ($C_{7a'}$), 135.6 ($C_{2'''}$), 141.7 ($C_{4'''}$), 156.1 ($C_{1'''}$), 159.4 ($C_{4'}$), 159.9 ($C_{6'}$), 160.0 (C=N), 161.5 (OCO); ν_{max} 3440, 1732, 1600 cm^{-1}; λ_{max} ($CHCl_3$) 395 nm (ε 8500 cm^{-1} M^{-1}), 334 (13,000), 258 (17,000); *m/z* (ESI) 535 ([M+H], 8%), 385 (27), 252 (100), 280 (24). Found: C, 38.7; H, 3.1; N, 6.7. Calcd for $C_{26}H_{22}N_4O_9\cdot 3CHCl_3$: C, 39.0; H, 2.8; N, 6.3.

*4.4.1.7. Ethyl 4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-7′-yl-2-(hydroxyimino)acetate (**7e**).* Ethyl 2-[4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-7′-yl]glyoxylate **6e**: 0.02 g, 0.07 mmol, appearance: yellow solid; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 1.35 (t, 3H, J=6.8 Hz, CH_3), 2.13 (s, 3H, 4″-Me), 3.80 (br s, 6H, OMe), 4.45 (q, 2H, J=6.8 Hz, CH_2), 6.35 (s, 1H, $H_{5'}$), 6.90–7.30 (m, 5H, $H_{2'}$, $H_{2''}$, $H_{3''}$), 10.42 (br s, 1H, NH).

*4.4.1.8. Ethyl 4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-7′-yl-2-(O-2,4-dinitrophenoxyimino)acetate (**1e**).* Yield: 0.04 g, 74%, mp 170–171 °C, appearance: yellow-orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, 3H, J=7.2 Hz, CH_3), 2.41 (s, 3H, 4″-Me), 3.91 (s, 3H, OMe), 3.92 (s, 3H, OMe), 4.31 (q, 2H, J=7.2 Hz, CH_2), 6.26 (s, 1H, $H_{5'}$), 7.12 (s, 1H, $H_{2'}$), 7.16 (d, 2H, J=7.9 Hz, $H_{3''}$), 7.46 (d, 2H, J=7.9 Hz, $H_{2''}$), 7.87 (d, 1H, J=9.4 Hz, $H_{6'''}$), 8.41 (dd, 1H, J=2.6, 9.4 Hz, $H_{5'''}$), 8.72 (d, 1H, J=2.6 Hz, $H_{3'''}$), 9.75 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.1 (4″-Me), 55.3, 57.4 (OMe), 62.3 (CH_2), 85.4 ($C_{5'}$) 88.7 ($C_{7'}$), 103.0 ($C_{3a'}$), 116.5 ($C_{3'}$), 119.7 ($C_{6'''}$), 121.4 ($C_{3'''}$), 122.0 ($C_{2'}$), 127.7 ($C_{5'''}$), 128.4 ($C_{2''}$), 129.2 ($C_{3''}$), 129.4 ($C_{1''}$), 132.1 ($C_{4''}$), 135.8 ($C_{2'''}$), 136.1 ($C_{7a'}$), 141.0 ($C_{4'''}$), 156.7 ($C_{6'}$), 159.2 ($C_{1'''}$), 160.0 ($C_{4'}$), 166.9 (C=N), 169.9 (OCO); ν_{max} 3776, 3684, 3621, 1708, 1598 cm^{-1}; λ_{max} ($CHCl_3$) 386 nm (ε 1400 cm^{-1} M^{-1}), 329 (2800), 243 (4700). HRMS found: 549.1625. Calcd for $C_{27}H_{25}N_4O_9$ ($[M+H]^+$): 549.1616.

4.5. Preparation of pyrrolo[3,2,1-hi]indazoles

*4.5.1. General preparation of the tricycles **2***

The appropriately substituted 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 solid dissolved in dichloromethane before extracting with water, followed by 2 M sodium hydroxide, 2 M hydrochloric acid and finally 2 M sodium hydroxide again. Each extraction was performed until the aqueous layer was no longer coloured. The organic layer was dried over magnesium sulfate and the solvent removed in vacuo. The remaining solid was then purified using preparative TLC (methanol/chloroform, 1:100). Due to the small amounts of the tricycles **2** produced, they were characterised using NMR spectroscopy and HRMS.

*4.5.1.1. Ethyl 1-(4′-cyanophenyl)-6,8-dimethoxypyrazolo[4,5,1-hi]indole-5-carboxylate (**2a**).* Ethyl 3′-(4″-cyanophenyl)-4′,6′-dimethoxyindol-7′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate **1a**: 0.098 g, 0.175 mmol, yield: 0.030 g, 45%, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, 3H, J=7.2 Hz, CH_3), 3.88 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.35 (q, 2H, J=7.2 Hz, CH_2), 6.55 (s, 1H, H_7), 7.72 (d, 2H, J=8.7 Hz, $H_{3'}$), 7.74 (s, 1H, H_2), 7.87 (d, 2H, J=8.7 Hz, $H_{2'}$); ν_{max} ($CHCl_3$) 3687, 3614, 1814, 1794, 1713, 1647, 1602 cm^{-1}. HRMS found: 376.1303. Calcd for $C_{21}H_{18}N_3O_4$ ($[M+H]^+$): 376.1297.

*4.5.1.2. Ethyl 1-(4′-bromophenyl)-6,8-dimethoxypyrazolo[4,5,1-hi]indole-5-carboxylate (**2b**).* Ethyl 3′-(4″-bromophenyl)-

4′,6′-dimethoxyindol-7′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate **1b**: 0.040 g, 0.065 mmol, yield: 0.0052 g, 19%, appearance: orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, J=7.2 Hz, CH_3), 4.09 (s, 3H, OMe), 4.24 (s, 3H, OMe), 4.54 (q, 2H, J=7.2 Hz, CH_2), 6.47 (s, 1H, H_7), 7.56 (d, 2H, J=8.7 Hz, $H_{3'}$), 7.70–7.80 (m, 3H, H_2, $H_{2'}$); ν_{max} ($CHCl_3$) 3686, 3604, 1817, 1794, 1722, 1644 cm^{-1}; HRMS found: 429.0442. Calcd for $C_{20}H_{18}BrN_2O_4$ ($[M+H]^+$): 429.0445.

*4.5.1.3. Ethyl 6,8-dimethoxy-1-phenylpyrazolo[4,5,1-hi]indole-5-carboxylate (**2d**).* Ethyl 3′-phenyl-4′,6′-dimethoxyindol-7′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate **1d**: 0.021 g, 0.039 mmol, yield: 0.0044 g, 32%, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, J=7.2 Hz, CH_3), 4.08 (s, 3H, OMe), 4.13 (s, 3H, OMe), 4.54 (q, 2H, J=7.2 Hz, CH_2), 6.48 (s, 1H, H_7), 7.60–7.80 (m, 6H, H_2, $H_{2'}$, $H_{3'}$, $H_{4'}$); ν_{max} ($CHCl_3$) 3688, 3614, 1818, 1794, 1713, 1647, 1601 cm^{-1}. HRMS found: 373.1162. Calcd for $C_{20}H_{18}N_2O_4$ ($[M+Na]^+$): 373.1164.

*4.5.1.4. Ethyl 6,8-dimethoxy-1-(4′-methylphenyl)pyrazolo[4,5,1-hi]indole-5-carboxylate (**2e**).* Ethyl 4′,6′-dimethoxy-3′-(4″-methylphenyl)indol-7′-yl-2-(*O*-2,4-dinitrophenoxyimino)acetate **1e**: 0.030 g, 0.055 mmol, yield: 0.0059 g, 20%, appearance: yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, J=7.2 Hz, CH_3), 2.41 (s, 3H, 4″-Me), 4.07 (s, 3H, OMe), 4.13 (s, 3H, OMe), 4.53 (q, 2H, J=7.2 Hz, CH_2), 6.47 (s, 1H, H_7), 7.56 (d, 2H, J=7.9 Hz, $H_{3'}$), 7.70 (s, 1H, H_2), 7.77 (d, 2H, J=7.9 Hz, $H_{2'}$); ν_{max} ($CHCl_3$) 3687, 3609, 1818, 1794, 1712, 1646, 1602 cm^{-1}. HRMS found: 365.1495. Calcd for $C_{21}H_{21}N_2O_4$ ($[M+H]^+$): 365.1496.

4.6. Calculation of rate constants for the cyclisation of 3-arylindole-7-ketoxime ethers

Each of the precursors **1a–e** and **8** (1 mol equiv) was added to a solution of triethylamine (10 mol equiv) in tetrahydrofuran (42 L per mole of precursor **1**) being heated at reflux. Aliquots of the reaction mixtures (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 the $H_{5'}$ signal in the precursors **1a–e** and **8**, and the H_7 signal in the corresponding tricycles. The data were then fitted to a first order exponential decay curve to obtain the rate constant for the formation of the tricycles.

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