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Copper-catalyzed cycloisomerization of alkynylaziridines to access functionalized 2-substituted-4-formylpyrroles

Anne Westermeyer ^{a, b}, Gérard Guillaumot ^b, Phannarath Phansavath ^{a, *},
Virginie Ratovelomanana-Vidal ^{a, *}

^a PSL University, Chimie ParisTech-CNRS, Institute of Chemistry for Life & Health Sciences, CSB2D Team, 11 rue Pierre et Marie Curie, 75005, Paris, France

^b SEQENS, 2-8 rue de Rouen, ZI de Limay-Porcheville, 78440, Porcheville, France

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Dedicated to Professor Nuno Maulide for his major contributions in organic synthesis.

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ABSTRACT

The copper-catalyzed cycloisomerization of alkynylaziridines has been developed to access 2-substituted-4-formylpyrroles. The reaction proved to be tolerant to aryl and alkyl-substituted substrates which were readily prepared from the corresponding enynes. This atom-economical catalytic process gives a convenient and regioselective access to a wide range of diversely 2-substituted-4-formylpyrroles in a two-step procedure.

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1. Introduction

Among the class of heteroaromatic compounds, poly-substituted pyrroles are extensively used as key synthetic intermediates in organic synthesis [1] and present a wide range of applications in pharmaceuticals [2] and materials science [3]. The pyrrole motif can also be found in numerous natural products [4] and exhibits various biological activities such as anti-fungal, anti-inflammatory and anti-tumoral among others. For example, Atorvastatin (**A**) has proven to be efficient against dyslipidemia [5] and Aloracetam (**B**) has been considered as clinical candidate for the treatment of Alzheimer's disease [6] (Fig. 1).

In this context, considerable effort has been devoted toward developing efficient syntheses of polysubstituted pyrroles. Among them, metal-catalyzed π -acid promoted alkynylaziridine cycloisomerization approaches present an excellent functional group tolerance and are atom-economical.

Following the work of Hashmi [7] on the rearrangement of

alkynylloxiranes to furans catalyzed with AuCl_3 , both groups of P. W. Davies [8] and X.-L. Hou [9] reported the synthesis of *N*-tosyl-disubstituted pyrroles through cationic-gold catalysis (Scheme 1). Davies et al. demonstrated that regioselectivity in favor of 2,4- or 2,5-disubstitution was attained by changing the solvent and the counterion in the catalytic system. In 2011, they further explored the mechanism of this rearrangement [10]. M. Yoshida et al. [11] studied the reaction using platinum chloride as catalyst and

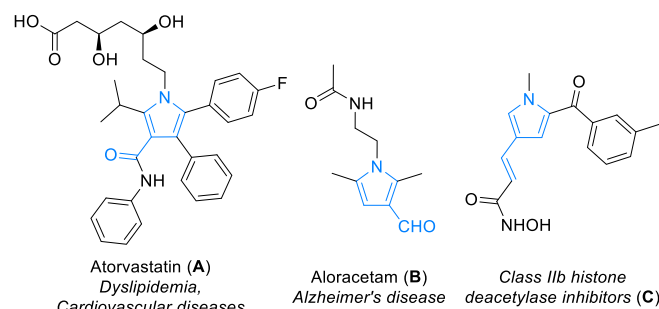
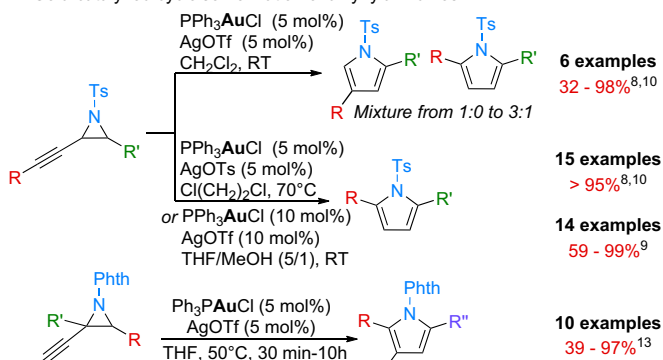


Fig. 1. Selected examples of useful compounds having a pyrrole core.

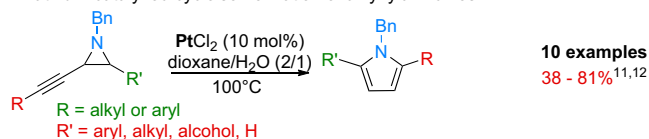
* Corresponding authors.

E-mail addresses: phannarath.phansavath@chimieparistech.psl.eu (P. Phansavath), virginie.vidal@chimie-paristech.fr (V. Ratovelomanana-Vidal).

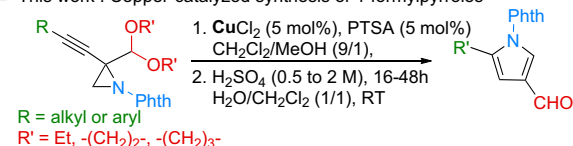
■ Gold-catalyzed cycloisomerization of alkynylaziridines



■ Platinum-catalyzed cycloisomerization of alkynylaziridines



■ This work : Copper-catalyzed synthesis of 4-formylpyrroles



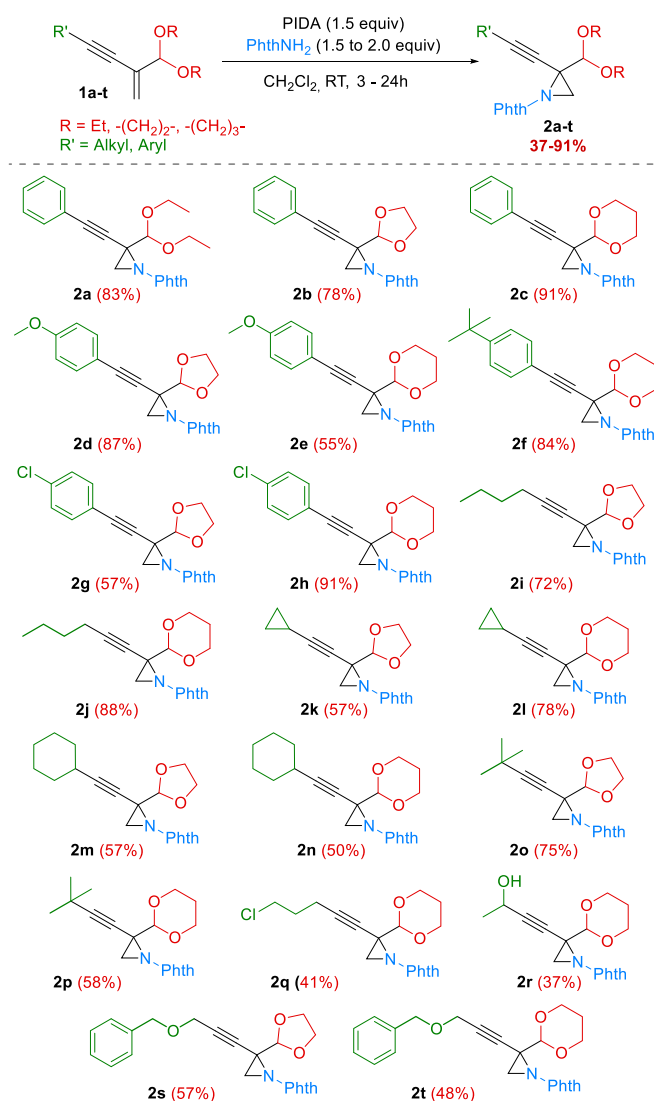
Scheme 1. Metal-catalyzed cycloisomerization of alkynylaziridines.

pointed out that 3-iodopyrroles could be obtained in the presence of NIS or I_2 [12]. Finally, Liu et al. extended the reaction scope to polysubstituted pyrroles bearing functional groups such as alcohols or esters in positions 2 and 5 [13]. However, these catalytic systems are quite expensive as they utilize precious metals. As an alternative, copper presents numerous advantages such as availability, lower toxicity and higher environmental compatibility. Moreover, to the best of our knowledge, only few examples provide a regio-selective access to 2,4-disubstituted pyrroles. Thus, we present herein the first copper-catalyzed cycloisomerization of highly diversified propargyl aziridines to 2-substituted-4-formylpyrroles in two telescoped steps using CuCl_2 as catalyst in the presence of *p*-toluenesulfonic acid (PTSA).

2. Results and discussion

The alkynylaziridines were synthesized following the procedure developed by the groups of Yudin and Che [14]. A broad family of substrates was provided from diversely substituted-enynes **1a-t** using *N*-aminophthalimide (PhthNH₂) in the presence of phenyliodine(III) diacetate (PIDA). This method tolerated a large range of functional groups such as halogens or alcohols and allowed the formation of alkyl- and aryl-substituted alkynylaziridines **2a-t** with yields up to 91% (Scheme 2). Furthermore, the reaction was conducted on gram-scale on several substrates without a decrease of the yield.

The initial attempts for the cycloisomerization reaction were performed on (3-(diethoxymethyl)but-3-en-1-yn-1-yl)benzene **2a** as model substrate. The reaction was first carried out with $\text{AuPPh}_3\text{Cl}/\text{AgOTf}$ (5 mol%) in THF at 50 °C. Under these conditions, the corresponding pyrrole **3a** was isolated in 49% yield (Table 1, entry 1). In our efforts to replace Au by cheaper metals, AgOTf was employed in the presence of catalytic amounts of PTSA but only a low yield of 24% was attained (Table 1, entry 2). In order to access



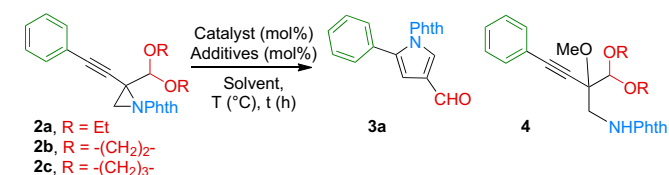
Scheme 2. Synthesis of alkynylaziridines from various enynes.

the expected aldehyde **3a** as the sole product of the reaction, an acidic treatment of the crude reaction mixture with aqueous H_2SO_4 was systematically performed before purification. $\text{Cu}(\text{OTf})_2$ failed to give the desired pyrrole and only led to the ring-opening of the aziridine with methanol affording compound **4** in 13% yield (Table 1, entry 3). The expected pyrrole **3a** was formed using 5 mol% of CuCl_2 with PTSA as additive (Table 1, entry 4). The yield (43%) was similar to the one observed with Au-catalysis. Thus, we decided to continue the optimization of the reaction conditions with CuCl_2 as copper is one of the most available and cost-effective catalysts. The influence of the nature of the acetal in compounds **2** was investigated. It appears that better yields were generally obtained with alkynylaziridines bearing cyclic acetals **2b** and **2c** (Table 1, entries 5–6) than for compound **2a** having a diethoxyacetal moiety (Table 1, entry 4). Performing the reaction with a catalyst loading of 10 mol% instead of 5 mol% did not improve the yield (Table 1, entry 7). Whereas, using 20 mol% of catalyst led to more degradation with a lower yield (Table 1, entry 8) and the same trend was observed with a longer reaction time (Table 1, entry 9).

With these optimized conditions in hand, the scope and limitations of the reaction were evaluated using 5 mol% of PTSA/ CuCl_2

Table 1

Screening of the conditions for the rearrangement of alkynyl-aziridines to 2,4-disubstituted pyrroles.



Entry	R	Catalyst	Additives	Solvent, T (°C), t (h)	Yield (%) ^a
1	2a	AuPPh ₃ Cl	AgOTf	THF	49 (3a)
2	2a	5 mol%	5 mol%	50 °C, 1h	
3	2a	AgOTf	PTSA	CH ₂ Cl ₂ /MeOH (9/1), 30 °C, 4h ^b	24 (3a)
4	2a	5 mol%	5 mol%		
5	2a	Cu(OTf) ₂	PTSA	CH ₂ Cl ₂ /MeOH (9/1), RT, 16h	13 (4)
6	2a	5 mol%	5 mol%		
7	2a	CuCl ₂	PTSA	CH ₂ Cl ₂ /MeOH (9/1), Δ, 6h ^b	43 (3a)
8	2a	5 mol%	5 mol%		
9	2b	CuCl ₂	PTSA	CH ₂ Cl ₂ /MeOH (9/1), Δ, 3h ^b	62 (3a)
10	2b	5 mol%	5 mol%		
11	2c	CuCl ₂	PTSA	CH ₂ Cl ₂ /MeOH (9/1), Δ, 4h ^b	63 (3a)
12	2c	5 mol%	5 mol%		
13	2b	CuCl ₂	PTSA	CH ₂ Cl ₂ /MeOH (9/1), Δ, 2h ^b	61 (3a)
14	2b	10 mol%	5 mol%		
15	2b	CuCl ₂	PTSA	CH ₂ Cl ₂ /MeOH (9/1), Δ, 4h ^b	40 (3a)
16	2b	20 mol%	5 mol%		
17	2b	CuCl ₂	PTSA	CH ₂ Cl ₂ /MeOH (9/1), Δ, 16h ^b	38 (3a)
18	2b	5 mol%	5 mol%		

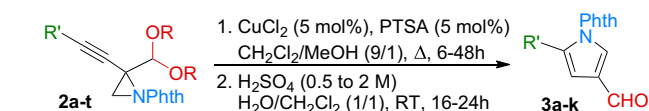
^a Isolated yield.

^b After completion, the reaction mixture was treated for 16–24 h with an aqueous solution of H₂SO₄ (0.5–2.0 M) to afford the aldehyde **3a** as the sole product of the reaction.

in a mixture of CH₂Cl₂/MeOH (9/1). The cycloisomerization was followed by an acidic treatment of the crude reaction mixture to provide the desired 4-formylpyrrole over the two steps. We initially started the exploration of the scope with alkynylaziridines **2a-h** functionalized with aryl groups. Better yields were generally reached with substrates containing the dioxane moiety (Table 2,

Table 2

Evaluation of the scope and limitations of the reaction.



Entry	R	Product	Time	Yield (%) ^a
1	Et (2a)		6h	43
2	$-(CH_2)_2-$ (2b)		4h	62
3	$-(CH_2)_3-$ (2c)		3h ^b	63
4	$-(CH_2)_2-$ (2d)		4h	29
5	$-(CH_2)_3-$ (2e)		6h	42
6	$-(CH_2)_3-$ (2f)		6h ^b	64

Table 2 (continued)

Entry	R	Product	Time	Yield (%) ^a
7	$-(CH_2)_2-$ (2g)		7h ^b	57
8	$-(CH_2)_3-$ (2h)		6h ^b	65
9	$-(CH_2)_2-$ (2i)		6h	29
10	$-(CH_2)_3-$ (2j)		6h	78
11	$-(CH_2)_2-$ (2k)		6h	55
12	$-(CH_2)_3-$ (2l)		3h	80
13	$-(CH_2)_2-$ (2m)		6h	56
14	$-(CH_2)_3-$ (2n)		6h	61
15	$-(CH_2)_2-$ (2o)		48h	38 ^c
16	$-(CH_2)_3-$ (2p)		48h	45 ^c
17	$-(CH_2)_3-$ (2q)		24h	58
18	$-(CH_2)_3-$ (2r)		30h	47
19	$-(CH_2)_2-$ (2s)		24h	66
20	$-(CH_2)_3-$ (2t)		24h	48

^d R" = H in **2r** and R" = Me in **3j**.

^a Isolated yield after 2 steps.

^b After 16 h, the deprotection of the acetal was not complete and the mixture was heated to 45 °C for an additional hour.

^c Only partial conversion was observed after 48 h.

entries 3, 5 and 8) as compared to the ones having a dioxolane ring (Table 2, entries 2, 4 and 7), given the higher stability of dioxane derivatives compared to dioxolane moieties. Both electron-rich and electron-deficient substituents were reactive. However, alkynylaziridines **2g-h** bearing an electron-withdrawing group such as a chlorine atom on the phenyl ring (Table 2, entries 7–8), were more

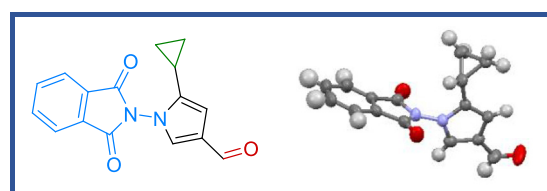
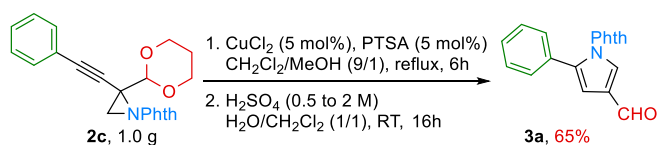


Fig. 2. X-Ray crystallographic analysis of compound **3f** (CCDC 1989300).

prone to ring expansion than electron-donating substituted analogues such as **2d-e** (Table 2, entries 4–5). A yield of 64% was obtained for the rearrangement of **2f** having a bulky *tert*-butyl group in *para* position (Table 2, entry 6). To test the substrate scope further, alkynylaziridines containing both linear and cyclic alkyl groups were evaluated (Table 2, entries 9–16). The reaction delivered the corresponding pyrroles with good yields especially with the dioxane ring (61–80%) except for compounds **2o** and **2p**. Indeed, the bulky *tert*-butyl substituent on the alkyne of these alkynylaziridines **2o** and **2p** led to poor conversions of 50% (Table 2, entries 15–16). Furthermore, the reaction conditions were tolerant to various functional groups on the alkynylaziridines such as ethers or halides (Table 2, entries 17–20). The desired 4-formylpyrroles were provided with yields ranging from 47 to 66% over the two steps. During the course of the rearrangement, compound **2r** led to the methoxylated derivative **3j** in the presence of methanol in the reaction mixture. Finally, benzyloxy-methylene substituted pyrrole **3k** was obtained with a yield of 66% from the dioxolane alkynylaziridine **2s**. Under the standard reaction conditions, *N*-tosyl-protected alkynylaziridines provided only degradation products. It should be noted that the phthalyl group can be removed using hydrazine or methylamine in ethanol [13,15–17] to give pyrroles or *N*-aminopyrroles which are key intermediates to access pyrrolo-triazines [18].

To confirm the regioselectivity of the rearrangement, the structure of the pyrrole **3f** was unambiguously determined by X-ray crystallographic analysis and we assumed that all compounds followed the same trend (Fig. 2).

Finally, a gram-scale experiment was carried out on **2c** (Scheme 3). Satisfyingly, the expected pyrrole **3a** was produced without any detrimental effect on the outcome of the reaction. A similar yield (65%) to that achieved on smaller scale (63%) was obtained demonstrating the synthetic potential of this reaction.



Scheme 3. - Gram-scale experiment on aziridine **2c**.

3. Conclusion

In summary, a new access to 2-substituted-4-formylpyrroles was achieved by copper-catalyzed π -acid promoted propargyl-aziridine cycloisomerization over two telescoped steps in good yields. The reaction tolerates both alkyl and aryl substituents on the alkyne and also accommodates functional groups such as halogen and alcohol. Moreover, this method is particularly attractive due to the low cost and high availability of Cu compared to Au and Pt catalysts.

4. Experimental part

4.1. General information

All reactions were carried out under argon atmosphere in oven-dried glassware. HPLC grade methanol and ethanol were purchased and used without further purification. THF and CH_2Cl_2 were dried over alumina columns in an Innovative Technology apparatus. Every reagent was either purified following the methods described in the literature or used without further purification. Acros Silica

Gel 60 (40–63 μm) was employed for flash column chromatography. Analytical thin layer chromatography (TLC) was carried out using commercial silica-gel plates (Merck 60 F₂₅₄), spots were detected with UV light (254 nm) and/or revealed with a KMnO_4 stain. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded using a Bruker AV400 (400 MHz) or a Bruker AV500 (500 MHz). Chemical shifts are reported in delta (δ) units part per million (ppm) relative to the signal of the residual solvent. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and brs = broad signal. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Bruker AVANCE 400 (100 MHz). NMR experiments were routinely run with broadband decoupling. Melting points were determined with a Kofler Heizbank 7841 apparatus and are uncorrected. Mass spectra (Electrospray ionization, Chemical ionization and Electronical Impact) were recorded at ENSCP Chimie ParisTech and SEQENS. Infrared spectra were measured on a spectrometer FT-4500 at ENSCP Chimie ParisTech.

4.2. Preparation of alkynylaziridines

General procedure 1 for the formation of aziridines from enynes: To an oven-dried 25 mL round bottom flask filled with argon, were introduced the enyne (1.0 equiv) and (diacetoxyiodo) benzene PIDA (1.5–2.0 equiv) in CH_2Cl_2 (10 mL). The reaction mixture was cooled to 0–5 $^\circ\text{C}$ (ice-bath) and the *N*-aminophthalimide PhthNH₂ (1.5–2.0 equiv) was added. The resulting mixture was stirred at 0 $^\circ\text{C}$ for 10 min, allowed to warm up to room temperature (22–26 $^\circ\text{C}$) and stirred until judged as complete by TLC (*ca* 3–24 h). Then it was diluted in CH_2Cl_2 and quenched with a saturated solution of NaHCO_3 (30–100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 \times 20–60 mL). The combined organic phases were dried over MgSO_4 , filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (PET/AcOEt 80/20 to 70/30, 11–45g SiO_2) to afford the desired product.

4.2.1. 2-(2-(diethoxymethyl)-2-(phenylethynyl)aziridin-1-yl)isindoline-1,3-dione **2a**

The title compound was prepared from (3-(diethoxymethyl)but-3-en-1-yn-1-yl)benzene (1.00 g, 4.34 mmol) following general procedure 1. This procedure afforded 1.41 g (83% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.78 (dd, J = 5.5, 3.1 Hz, 2H), 7.67 (dd, J = 5.5, 3.1 Hz, 2H), 7.24–7.17 (m, 1H), 7.17–7.06 (m, 4H), 4.95 (s, 1H), 3.94–3.71 (m, 4H), 3.51 (d, J = 2.2 Hz, 1H), 3.16 (d, J = 2.2 Hz, 1H), 1.28 (dt, J = 26.3, 7.1 Hz, 6H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.4, 134.2, 131.8, 130.4, 128.6, 128.2, 123.1, 122.1, 100.9, 85.8, 83.8, 64.8, 63.6, 44.8, 40.0, 15.4, 15.2. MS (ESI): m/z = 413 [$\text{M}+\text{Na}$]⁺.

4.2.2. 2-(2-(1,3-dioxolan-2-yl)-2-(phenylethynyl)aziridin-1-yl)isindoline-1,3-dione **2b**

The title compound was prepared from 2-(4-phenylbut-1-en-3-yn-2-yl)-1,3-dioxolane (2.00 g, 9.99 mmol) following general procedure 1. This procedure afforded 3.27 g (78% yield) of the title compound as a dark-yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.78 (dd, J = 5.5, 3.1 Hz, 2H), 7.67 (dd, J = 5.5, 3.1 Hz, 2H), 7.29–7.06 (m, 5H), 5.31 (s, 1H), 4.32–4.17 (m, 2H), 4.08–3.96 (m, 2H), 3.59 (d, J = 2.4 Hz, 1H), 3.01 (d, J = 2.4 Hz, 1H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.2, 134.2, 131.9, 130.3, 128.8, 128.2, 123.1, 121.7, 103.1, 86.6, 82.6, 66.2, 65.8, 44.8, 40.1. MS (CI/ NH_3): m/z = 361 [$\text{M}+\text{H}$]⁺.

4.2.3. 2-(2-(1,3-dioxan-2-yl)-2-(phenylethynyl)aziridin-1-yl)isoindoline-1,3-dione **2c**

The title compound was prepared from 2-(4-phenylbut-1-en-3-yn-2-yl)-1,3-dioxane (100 mg, 0.43 mmol) following general procedure 1. This procedure afforded 170 mg (91% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.84–7.60 (m, 4H), 7.23–7.02 (m, 5H), 5.04 (s, 1H), 4.25 (dddt, $J = 23.1, 11.5, 5.0, 1.5$ Hz, 2H), 3.93 (dddd, $J = 23.1, 12.5, 11.5, 2.6$ Hz, 2H), 3.50 (d, $J = 2.3$ Hz, 1H), 3.19 (d, $J = 2.3$ Hz, 1H), 2.17 (dtt, $J = 13.6, 12.5, 5.0$ Hz, 1H), 1.40 (dtt, $J = 13.6, 2.6, 1.5$ Hz, 1H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 134.2, 131.9, 130.4, 128.7, 128.1, 123.1, 121.9, 99.4, 86.0, 82.9, 67.5, 65.2, 44.3, 40.6, 25.7. MS (Cl/NH_3): $m/z = 375$ $[\text{M}+\text{H}]^+$.

4.2.4. 2-(2-(1,3-dioxolan-2-yl)-2-((4-methoxyphenyl)ethynyl)aziridin-1-yl)isoindoline-1,3-dione **2d**

The title compound was prepared from 2-(4-(4-methoxyphenyl)but-1-en-3-yn-2-yl)-1,3-dioxolane (300 mg, 1.30 mmol) following general procedure 1. This procedure afforded 432 mg (87% yield) of the title compound as a light-yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.78 (d, $J = 2.9$ Hz, 2H), 7.67 (d, $J = 3.4$ Hz, 2H), 7.16–6.98 (m, 2H), 6.66 (d, $J = 9.4$ Hz, 2H), 5.31 (s, 1H), 4.32–4.17 (m, 2H), 4.02 (m, 2H), 3.73 (d, $J = 2.6$ Hz, 3H), 3.58 (d, $J = 2.8$ Hz, 1H), 2.99 (d, $J = 2.8$ Hz, 1H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.3, 160.0, 134.2, 133.5, 130.4, 123.1, 113.84, 113.78, 103.2, 86.7, 81.1, 66.2, 65.8, 55.3, 44.9, 40.1. MS (ESI): $m/z = 413$ $[\text{M}+\text{Na}]^+$.

4.2.5. 2-(2-(1,3-dioxan-2-yl)-2-((4-methoxyphenyl)ethynyl)aziridin-1-yl)isoindoline-1,3-dione **2e**

The title compound was prepared from 2-(4-(4-methoxyphenyl)but-1-en-3-yn-2-yl)-1,3-dioxane (400 mg, 1.64 mmol) following general procedure 1. This procedure afforded 365 mg (55% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.82–7.73 (m, 2H), 7.71–7.63 (m, 2H), 7.07 (d, $J = 9.5$ Hz, 2H), 6.65 (d, $J = 9.5$ Hz, 2H), 5.03 (s, 1H), 4.32–4.17 (m, 2H), 3.93 (m, 2H), 3.72 (s, 3H), 3.49 (d, $J = 2.4$ Hz, 1H), 3.18 (d, $J = 2.4$ Hz, 1H), 2.18 (m, 1H), 1.45–1.36 (m, 1H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.2, 159.9, 134.1, 133.6, 130.4, 123.1, 113.9, 113.8, 99.5, 86.0, 81.4, 67.5, 67.3, 55.4, 44.4, 40.6, 25.7. MS (ESI): $m/z = 427$ $[\text{M}+\text{Na}]^+$.

4.2.6. 2-(2-((4-(tert-butyl)phenyl)ethynyl)-2-(1,3-dioxan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2f**

The title compound was prepared from 2-(4-(4-(tert-butyl)phenyl)but-1-en-3-yn-2-yl)-1,3-dioxane (1.00 g, 4.66 mmol) following general procedure 1. This procedure afforded 1.34 g (84% yield) of the title compound as a light-yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.79 (dd, $J = 5.4, 3.0$ Hz, 2H), 7.67 (dd, $J = 5.4, 3.0$ Hz, 2H), 7.19–7.11 (m, 2H), 7.12–7.04 (m, 2H), 5.06 (s, 1H), 4.32–4.17 (m, 2H), 3.93 (m, 2H), 3.48 (d, $J = 2.3$ Hz, 1H), 3.19 (d, $J = 2.3$ Hz, 1H), 2.23–2.11 (m, 1H), 1.40 (m, 1H), 1.22 (s, 9H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.2, 152.1, 134.1, 131.8, 130.5, 125.2, 123.2, 118.9, 99.4, 86.2, 82.2, 67.5, 67.2, 44.3, 40.5, 34.8, 31.2, 25.7. MS (ESI): $m/z = 453$ $[\text{M}+\text{Na}]^+$.

4.2.7. 2-(2-((4-chlorophenyl)ethynyl)-2-(1,3-dioxolan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2g**

The title compound was prepared from 2-(4-(4-chlorophenyl)but-1-en-3-yn-2-yl)-1,3-dioxolane (300 mg, 1.28 mmol) following general procedure 1. This procedure afforded 288 mg (57% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.86–7.72 (m, 2H), 7.72–7.61 (m, 2H), 7.19–7.09 (m, 2H), 7.09–6.98 (m, 2H), 5.30 (s, 1H), 4.35–4.12 (m, 2H), 4.10–3.95 (m, 2H), 3.58 (d, $J = 2.4$ Hz, 1H), 3.00 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.2, 134.9, 134.3, 133.1, 130.3, 128.6, 123.1, 120.2, 102.9, 85.5, 83.7, 66.2, 65.8, 44.7, 40.1. MS (ESI): $m/z = 417$

$[\text{M}+\text{Na}]^+$.

4.2.8. 2-(2-((4-chlorophenyl)ethynyl)-2-(1,3-dioxan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2h**

The title compound was prepared from 2-(4-(4-chlorophenyl)but-1-en-3-yn-2-yl)-1,3-dioxane (500 mg, 2.01 mmol) following general procedure 1. This procedure afforded 725 mg (91% yield) of the title compound as a light-yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.77 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.67 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.16–7.00 (m, 4H), 5.01 (s, 1H), 4.24 (dddt, $J = 23.9, 11.4, 5.0, 1.7$ Hz, 2H), 3.92 (dddd, $J = 23.9, 12.5, 11.4, 2.6$ Hz, 2H), 3.50 (d, $J = 2.4$ Hz, 1H), 3.18 (d, $J = 2.4$ Hz, 1H), 2.17 (dtt, $J = 13.6, 12.5, 5.0$ Hz, 1H), 1.45–1.35 (m, 1H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 134.8, 134.3, 133.2, 130.3, 128.5, 123.2, 120.3, 99.3, 84.9, 83.9, 67.5, 67.3, 44.2, 40.5, 25.7. MS (ESI): $m/z = 431$ $[\text{M}+\text{Na}]^+$.

4.2.9. 2-(2-(1,3-dioxolan-2-yl)-2-(hex-1-yn-1-yl)aziridin-1-yl)isoindoline-1,3-dione **2i**

The title compound was prepared from 2-(oct-1-en-3-yn-2-yl)-1,3-dioxolane (300 mg, 1.66 mmol) following general procedure 1. This procedure afforded 407 mg (72% yield) of the title compound as a light-yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.78 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.68 (dd, $J = 5.4, 3.1$ Hz, 2H), 5.19 (s, 1H), 4.27–4.06 (m, 2H), 4.06–3.91 (m, 2H), 3.47 (d, $J = 2.4$ Hz, 1H), 2.87 (d, $J = 2.4$ Hz, 1H), 2.03 (t, $J = 6.8$ Hz, 2H), 1.22–0.96 (m, 4H), 0.57 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.2, 134.1, 130.4, 123.0, 103.1, 88.1, 73.3, 66.1, 65.7, 44.5, 39.7, 30.3, 21.7, 18.5, 13.5. MS (ESI): $m/z = 363$ $[\text{M}+\text{Na}]^+$.

4.2.10. 2-(2-(1,3-dioxan-2-yl)-2-(hex-1-yn-1-yl)aziridin-1-yl)isoindoline-1,3-dione **2j**

The title compound was prepared from 2-(oct-1-en-3-yn-2-yl)-1,3-dioxane (300 mg, 1.54 mmol) following general procedure 1. This procedure afforded 482 mg (88% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.84–7.70 (m, 2H), 7.73–7.62 (m, 2H), 4.87 (s, 1H), 4.23 (dddt, $J = 20.1, 11.4, 5.2, 1.7$ Hz, 2H), 3.89 (dddd, $J = 20.1, 12.4, 11.4, 2.6$ Hz, 2H), 3.40 (d, $J = 2.3$ Hz, 1H), 3.03 (d, $J = 2.3$ Hz, 1H), 2.24–2.07 (m, 1H), 2.08–1.99 (m, 2H), 1.38 (d, $J = 13.6$ Hz, 1H), 1.17–0.91 (m, 4H), 0.55 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.0, 133.9, 122.9, 99.6, 87.4, 77.2, 73.3, 67.4, 67.1, 44.0, 40.1, 30.2, 25.6, 21.6, 18.5, 13.3. MS (ESI): $m/z = 377$ $[\text{M}+\text{Na}]^+$.

4.2.11. 2-(2-(cyclopropylethynyl)-2-(1,3-dioxolan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2k**

The title compound was prepared from 2-(4-cyclopropylbut-1-en-3-yn-2-yl)-1,3-dioxolane (400 mg, 2.44 mmol) following general procedure 1. This procedure afforded 454 mg (57% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.77 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.69 (dd, $J = 5.5, 3.1$ Hz, 2H), 5.16 (s, 1H), 4.24–4.08 (m, 2H), 4.05–3.86 (m, 2H), 3.42 (d, $J = 2.4$ Hz, 1H), 2.83 (d, $J = 2.4$ Hz, 1H), 1.09–0.96 (m, 1H), 0.58–0.44 (m, 2H), 0.37–0.16 (m, 2H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 134.1, 130.3, 123.0, 103.0, 91.1, 68.3, 66.1, 65.7, 44.7, 39.7, 8.3, 0.4. MS (EI, 70 eV): $m/z = 324$.

4.2.12. 2-(2-(cyclopropylethynyl)-2-(1,3-dioxan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2l**

The title compound was prepared from 2-(4-cyclopropylbut-1-en-3-yn-2-yl)-1,3-dioxane (1.00 g, 5.61 mmol) following general procedure 1. This procedure afforded 1.49 g (78% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.81 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.71 (dd, $J = 5.4, 3.1$ Hz, 2H), 4.88 (s, 1H), 4.32–4.13 (dddt, $J = 21.0, 11.5, 4.9, 1.6$ Hz, 2H), 3.90 (dddd, $J = 21.0, 12.5, 11.4, 2.6$ Hz, 2H), 3.39 (d, $J = 2.3$ Hz, 1H), 3.04 (d, $J = 2.3$ Hz, 1H),

2.16 (dtt, $J = 13.6, 12.5, 4.9$ Hz, 1H), 1.39 (dtt, $J = 13.6, 2.6, 1.6$ Hz, 1H), 1.07 (tt, $J = 8.3, 5.0$ Hz, 1H), 0.59–0.45 (m, 2H), 0.38–0.18 (m, 2H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 134.1, 130.4, 123.0, 99.6, 90.5, 68.6, 67.5, 67.2, 44.3, 40.2, 25.7, 8.3, –0.4. MS (ESI): $m/z = 361$ $[\text{M}+\text{Na}]^+$.

4.2.13. 2-(2-(cyclohexylethynyl)-2-(1,3-dioxolan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2m**

The title compound was prepared from 2-(4-cyclohexylbut-1-en-3-yn-2-yl)-1,3-dioxolane (400 mg, 1.94 mmol) following general procedure 1. This procedure afforded 405 mg (57% yield) of the title compound as a dark-yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.77 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.67 (dd, $J = 5.4, 3.1$ Hz, 2H), 5.19 (s, 1H), 4.26–4.11 (m, 2H), 4.04–3.90 (m, 2H), 3.49 (d, $J = 2.5$ Hz, 1H), 2.86 (d, $J = 2.5$ Hz, 1H), 2.25 (m, 1H), 1.47–1.20 (m, 5H), 1.17–0.95 (m, 5H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 133.9, 130.3, 122.9, 103.0, 91.7, 73.3, 66.0, 65.6, 44.6, 39.7, 31.8, 28.6, 25.6, 24.2. MS (ESI): $m/z = 389$ $[\text{M}+\text{Na}]^+$.

4.2.14. 2-(2-(cyclohexylethynyl)-2-(1,3-dioxan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2n**

The title compound was prepared from 2-(4-cyclohexylbut-1-en-3-yn-2-yl)-1,3-dioxane (400 mg, 1.82 mmol) following general procedure 1. This procedure afforded 348 g (50% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.78 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.68 (dd, $J = 5.5, 3.1$ Hz, 2H), 4.92 (s, 1H), 4.21 (dddt, $J = 25.0, 11.4, 5.0, 1.7$ Hz, 2H), 3.89 (dddd, $J = 25.0, 12.5, 11.4, 2.6$ Hz, 2H), 3.41 (d, $J = 2.3$ Hz, 1H), 3.06 (d, $J = 2.3$ Hz, 1H), 2.26 (m, 1H), 2.22–2.01 (m, 1H), 1.49–1.20 (m, 6H), 1.04 (m, 5H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.0, 133.9, 130.4, 122.9, 99.4, 91.1, 73.5, 67.3, 67.0, 44.1, 40.1, 31.8, 28.6, 25.7, 25.6, 24.2. MS (ESI): $m/z = 403$ $[\text{M}+\text{Na}]^+$.

4.2.15. 2-(2-(3,3-dimethylbut-1-yn-1-yl)-2-(1,3-dioxolan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2o**

The title compound was prepared from 2-(5,5-dimethylhex-1-en-3-yn-2-yl)-1,3-dioxolane (400 mg, 2.22 mmol) following general procedure 1. This procedure afforded 568 mg (75% yield) of the title compound as a light-yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.83–7.74 (m, 2H), 7.73–7.65 (m, 2H), 5.18 (s, 1H), 4.28–4.13 (m, 2H), 4.04–3.92 (m, 2H), 3.52 (d, $J = 2.4$ Hz, 1H), 2.86 (d, $J = 2.4$ Hz, 1H), 0.91 (s, 9H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.2, 134.1, 130.4, 123.0, 103.2, 95.8, 72.0, 66.1, 65.7, 44.8, 39.8, 30.4, 27.4. MS (ESI): $m/z = 363$ $[\text{M}+\text{Na}]^+$.

4.2.16. 2-(2-(3,3-dimethylbut-1-yn-1-yl)-2-(1,3-dioxan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2p**

The title compound was prepared from 2-(5,5-dimethylhex-1-en-3-yn-2-yl)-1,3-dioxane (400 mg, 2.06 mmol) following general procedure 1. This procedure afforded 422 mg (58% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.81–7.71 (m, 2H), 7.71–7.62 (m, 2H), 4.95 (s, 1H), 4.26–4.11 (m, 2H), 3.94–3.79 (m, 2H), 3.40 (d, $J = 2.3$ Hz, 1H), 3.05 (d, $J = 2.3$ Hz, 1H), 2.19–2.02 (m, 1H), 1.36 (brd, $J = 13.5$ Hz, 1H), 0.88 (s, 9H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 134.0, 130.4, 122.9, 99.1, 95.0, 77.4, 67.4, 67.1, 44.1, 40.1, 30.4, 27.3, 25.7. MS (ESI): $m/z = 377$ $[\text{M}+\text{Na}]^+$.

4.2.17. 2-(2-(5-chloropent-1-yn-1-yl)-2-(1,3-dioxan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2q**

The title compound was prepared from 2-(4-(4-(*tert*-butyl)phenyl)but-1-en-3-yn-2-yl)-1,3-dioxane (400 mg, 1.86 mmol) following general procedure 1. This procedure afforded 296 mg (41% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.80 (d, $J = 4.5$ Hz, 2H), 7.73–7.66 (d, $J = 4.5$ Hz, 2H), 4.88 (s, 1H), 4.23 (m, 2H), 3.90 (m, 2H), 3.38 (m, 1H), 3.37–3.29

(m, 2H), 3.05 (s, 1H), 2.30–2.20 (m, 2H), 2.20–2.04 (m, 1H), 1.68–1.59 (m, 2H), 1.39 (d, $J = 13.6$ Hz, 1H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 134.2, 130.2, 123.2, 99.7, 85.4, 74.6, 67.4, 67.2, 43.9, 43.3, 40.1, 30.9, 25.6, 16.4. MS (ESI): $m/z = 397$ $[\text{M}+\text{Na}]^+$.

4.2.18. 2-(2-(1,3-dioxan-2-yl)-2-(3-hydroxybut-1-yn-1-yl)aziridin-1-yl)isoindoline-1,3-dione **2r**

The title compound was prepared from 5-(1,3-dioxan-2-yl)hex-5-en-3-yn-2-ol (200 mg, 1.12 mmol) following general procedure 1. This procedure afforded 141 mg (37% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.79 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.69 (dd, $J = 5.5, 3.0$ Hz, 2H), 4.89 (d, $J = 7.1$ Hz, 1H), 4.35 (m, 1H), 4.22 (m, 2H), 3.97–3.80 (m, 2H), 3.40 (dd, $J = 2.4, 1.1$ Hz, 1H), 3.07 (dd, $J = 2.4, 1.6$ Hz, 1H), 2.28–2.06 (m, 1H), 1.44–1.35 (m, 1H), 1.05 (dd, $J = 11.7, 6.6$ Hz, 3H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 134.3, 130.3, 123.2, 99.5, 88.4, 77.4, 67.5, 67.3, 58.2, 43.7, 40.3, 25.6, 23.7. MS (ESI): $m/z = 365$ $[\text{M}+\text{Na}]^+$.

4.2.19. 2-(2-(3-(benzyloxy)prop-1-yn-1-yl)-2-(1,3-dioxolan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2s**

The title compound was prepared from 2-(5-(benzyloxy)pent-1-en-3-yn-2-yl)-1,3-dioxolane (160 mg, 0.66 mmol) following general procedure 1. This procedure afforded 155 mg (57% yield) of the title compound as a dark-yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.76 (m, 2H), 7.67 (m, 2H), 7.33–7.23 (m, 3H), 7.18–7.09 (m, 2H), 5.28 (s, 1H), 4.33 (s, 2H), 4.31–4.17 (m, 2H), 4.10–3.94 (m, 4H), 3.51 (d, $J = 2.4$ Hz, 1H), 2.96 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 137.2, 134.2, 130.3, 128.4, 128.0, 127.9, 123.2, 102.9, 83.1, 80.0, 71.2, 66.2, 65.7, 57.2, 43.9, 39.7. MS (ESI): $m/z = 427$ $[\text{M}+\text{Na}]^+$.

4.2.20. 2-(2-(3-(benzyloxy)prop-1-yn-1-yl)-2-(1,3-dioxan-2-yl)aziridin-1-yl)isoindoline-1,3-dione **2t**

The title compound was prepared from 2-(5-(benzyloxy)pent-1-en-3-yn-2-yl)-1,3-dioxane (250 mg, 0.97 mmol) following general procedure 1. This procedure afforded 192 mg (48% yield) of the title compound as a yellow solid. ^1H NMR: (400 MHz, CDCl_3) δ 7.73 (dd, $J = 5.5, 2.9$ Hz, 2H), 7.63 (dt, $J = 5.5, 2.9$ Hz, 2H), 7.29–7.21 (m, 3H), 7.14–7.06 (m, 2H), 4.95 (d, $J = 2.4$ Hz, 1H), 4.32–4.16 (m, 4H), 4.04 (m, 2H), 3.98–3.83 (m, 2H), 3.41 (d, $J = 2.4$ Hz, 1H), 3.11 (d, $J = 2.4$ Hz, 1H), 2.24–2.10 (m, 1H), 1.40 (m, 1H). ^{13}C NMR: (100 MHz, CDCl_3) δ 165.1, 137.3, 134.2, 130.3, 128.4, 128.0, 127.9, 123.2, 99.5, 82.6, 80.2, 71.2, 67.5, 67.3, 57.4, 43.5, 40.2, 25.7. MS (ESI): $m/z = 441$ $[\text{M}+\text{Na}]^+$.

4.3. Cycloisomerisation of alkynylaziridines to 2,4-disubstituted pyrroles

General procedure 2 for the formation of pyrroles: In a 10 mL sealed tube under argon were introduced the alkynylaziridines (100 mg, 1.0 eq.) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1 (2 mL). To the reaction mixture, CuCl_2 (0.05 equiv) and PTSA (0.05 equiv) were added. The resulting mixture was stirred at reflux (oil bath at 75 °C) until completion followed by TLC. The reaction mixture was quenched with a saturated solution of NaHCO_3 (15 mL) and the aqueous phase extracted with dichloromethane (3×10 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated in vacuo. The crude product was diluted into 5 mL of CH_2Cl_2 and treated overnight with an aqueous solution of H_2SO_4 (0.5–2.0 M). The mixture was quenched with a saturated solution of NaHCO_3 (15 mL) and the aqueous phase extracted with dichloromethane (3×10 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (Toluene/dichloromethane/ AcOEt 50/50/0 to 45/45/10, 12 g SiO_2) to afford the desired product.

Sometimes, an additional diisopropylether trituration was needed to obtain the pure product.

4.3.1. 1-(1,3-dioxoisindolin-2-yl)-5-phenyl-1H-pyrrole-3-carbaldehyde **3a**

The title compound was prepared following general procedure 2 from **2a** (100 mg, 0.256 mmol) with 43% yield (35 mg), from **2b** (100 mg, 0.277 mmol) with 62% yield (52 mg) and from **2c** (100 mg, 0.267 mmol) with 63% yield (53 mg) as a light-yellow solid. mp: 168–170 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.83 (s, 1H), 7.94–7.84 (m, 2H), 7.84–7.75 (m, 2H), 7.39 (d, *J* = 1.9 Hz, 1H), 7.31–7.20 (m, 5H), 6.80 (d, *J* = 1.9 Hz, 1H). ¹³C NMR: (100 MHz, CDCl₃) δ 185.1, 163.9, 137.8, 135.5, 130.7, 129.4, 129.2, 128.9, 128.3, 126.0, 124.7, 106.6. IR (film): ν = 3123, 2804, 2725, 1741, 1671, 1468, 1407, 1294, 1186, 1079 cm⁻¹. MS (CI/NH₃): *m/z* = 317 [M+H]⁺.

4.3.2. 1-(1,3-dioxoisindolin-2-yl)-5-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde **3b**

The title compound was prepared following general procedure 2 from **2d** (100 mg, 0.256 mmol) with 29% yield (26 mg) and from **2e** (100 mg, 0.253 mmol) with 42% yield (44 mg) as a dark-yellow solid. mp: 210–215 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.86 (s, 1H), 7.96–7.88 (m, 2H), 7.87–7.80 (m, 2H), 7.40 (d, *J* = 1.9 Hz, 1H), 7.25–7.20 (m, 2H), 6.83–6.78 (m, 2H), 6.78 (d, *J* = 1.9 Hz, 1H), 3.74 (s, 3H). ¹³C NMR: (100 MHz, CDCl₃) δ 185.1, 164.0, 160.1, 137.7, 135.5, 130.3, 129.9, 129.2, 126.0, 124.8, 121.8, 114.3, 106.1, 55.4. IR (film): ν = 3154, 2942, 2809, 2742, 1489, 1250, 1167, 1081, 1028 cm⁻¹. MS (CI/NH₃): *m/z* = 347 [M+H]⁺.

4.3.3. 5-(4-(tert-butyl)phenyl)-1-(1,3-dioxoisindolin-2-yl)-1H-pyrrole-3-carbaldehyde **3c**

The title compound was prepared following general procedure 2 from **2f** (100 mg, 0.232 mmol) with 64% yield (55 mg) as a light-brown solid. mp: 135–140 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.86 (s, 1H), 7.95 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.40 (d, *J* = 1.9 Hz, 1H), 7.30–7.87 (m, 2H), 7.25–7.22 (m, 2H), 6.82 (d, *J* = 1.9 Hz, 1H), 1.23 (s, 9H). ¹³C NMR: (100 MHz, CDCl₃) δ 185.0, 163.9, 151.8, 137.7, 135.4, 130.7, 129.1, 127.7, 126.4, 125.9, 125.8, 124.6, 106.2, 34.6, 31.2, 31.1. IR (film): ν = 2954, 2865, 1743, 1673, 1465, 1362, 1289, 1185, 1107, 1080 cm⁻¹. MS (CI/NH₃): *m/z* = 373 [M+H]⁺.

4.3.4. 5-(4-chlorophenyl)-1-(1,3-dioxoisindolin-2-yl)-1H-pyrrole-3-carbaldehyde **3d**

The title compound was prepared following general procedure 2 from **2g** (100 mg, 0.253 mmol) with 57% yield (51 mg) and from **2h** (100 mg, 0.245 mmol) with 65% yield (56 mg) as a white solid. mp: 250–255 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.87 (s, 1H), 7.93 (m, 2H), 7.86 (m, 2H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.26 (m, 4H), 6.84 (d, *J* = 2.0 Hz, 1H). ¹³C NMR: (100 MHz, CDCl₃) δ 185.0, 163.8, 136.6, 135.7, 135.1, 130.8, 129.7, 129.3, 129.1, 127.9, 126.1, 124.9, 107.0. IR (film): ν = 3081, 2778, 2694, 2346, 1741, 1667, 1294, 1183, 1089, 1016 cm⁻¹. MS (CI/NH₃): *m/z* = 351 [M+H]⁺.

4.3.5. 5-Butyl-1-(1,3-dioxoisindolin-2-yl)-1H-pyrrole-3-carbaldehyde **3e**

The title compound was prepared following general procedure 2 from **2i** (100 mg, 0.294 mmol) with 29% yield (25 mg) and from **2j** (100 mg, 0.282 mmol) with 78% yield (65 mg) as a light-orange solid. mp: 96–98 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.77 (s, 1H), 8.02 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.28 (d, *J* = 2.0 Hz, 1H), 6.53 (dt, *J* = 2.0, 1.1 Hz, 1H), 2.33 (ddd, *J* = 8.3, 7.3, 1.1 Hz, 2H), 1.57 (m, 2H), 1.36–1.26 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). ¹³C NMR: (100 MHz, CDCl₃) δ 185.0, 163.8, 137.5, 135.6, 129.4, 129.3, 125.7, 124.8, 104.1, 29.6, 24.6, 22.2, 13.9. IR (film): ν = 3054, 2948, 2933, 2780, 2676, 1746, 1681, 1520, 1290, 1078 cm⁻¹. MS (CI/NH₃):

m/z = 297 [M+H]⁺.

4.3.6. 5-Cyclopropyl-1-(1,3-dioxoisindolin-2-yl)-1H-pyrrole-3-carbaldehyde **3f**

The title compound was prepared following general procedure 2 from **2k** (100 mg, 0.308 mmol) with 42% yield (37 mg) and from **2l** (100 mg, 0.296 mmol) with 80% yield (71 mg) as a light-yellow solid. mp: 128–132 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.76 (s, 1H), 8.07–7.96 (m, 2H), 7.95–7.86 (m, 2H), 7.31 (d, *J* = 1.9 Hz, 1H), 6.42 (d, *J* = 1.9, 1.2 Hz, 1H), 1.50–1.38 (m, 1H), 0.73–0.67 (m, 2H), 0.66–0.60 (m, 2H). ¹³C NMR: (100 MHz, CDCl₃) δ 185.0, 163.9, 139.3, 135.6, 129.8, 129.5, 125.3, 124.8, 103.6, 5.5, 5.4. IR (film): ν = 3073, 2825, 1741, 1663, 1519, 1316, 1276, 1187, 1083 cm⁻¹. MS (CI/NH₃): *m/z* = 281 [M+H]⁺.

4.3.7. 5-Cyclohexyl-1-(1,3-dioxoisindolin-2-yl)-1H-pyrrole-3-carbaldehyde **3g**

The title compound was prepared following general procedure 2 from **2m** (100 mg, 0.273 mmol) with 56% yield (50 mg) and from **2n** (100 mg, 0.263 mmol) with 61% yield (53 mg) as a light-yellow solid. mp: 180–184 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.78 (s, 1H), 8.03 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.92 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.22 (d, *J* = 1.9 Hz, 1H), 6.57–6.51 (m, 1H), 2.16 (tt, *J* = 11.8, 3.4 Hz, 1H), 1.85 (brd, *J* = 13.5 Hz, 2H), 1.78–1.70 (m, 2H), 1.44–1.09 (m, 6H). ¹³C NMR: (100 MHz, CDCl₃) δ 185.1, 164.0, 143.0, 135.7, 129.3, 129.1, 125.7, 124.9, 102.5, 34.8, 33.1, 26.3, 25.8. IR (film): ν = 3134, 29224, 2850, 2814, 1738, 1662, 1518, 1304, 1110, 1080 cm⁻¹. MS (CI/NH₃): *m/z* = 323 [M+H]⁺.

4.3.8. 5-(tert-butyl)-1-(1,3-dioxoisindolin-2-yl)-1H-pyrrole-3-carbaldehyde **3h**

The title compound was prepared following general procedure 2 from **2o** (100 mg, 0.294 mmol) with 38% yield (33 mg) and from **2p** (100 mg, 0.282 mmol) with 45% yield (38 mg) as a light-yellow solid. mp: 168–170 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.75 (s, 1H), 8.08–7.98 (m, 2H), 7.96–7.86 (m, 2H), 7.15 (d, *J* = 2.0 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 1.25 (s, 9H). ¹³C NMR: (100 MHz, CDCl₃) δ 185.1, 164.4, 145.8, 135.7, 131.4, 129.6, 124.9, 124.8, 103.9, 32.0, 30.0. IR (film): ν = 3228, 2965, 2918, 2839, 2349, 1746, 1715, 1671, 1467, 1362, 1287, 1194, 1101, 1076 cm⁻¹. MS (CI/NH₃): *m/z* = 351 [M+H]⁺.

4.3.9. 5-(3-chloropropyl)-1-(1,3-dioxoisindolin-2-yl)-1H-pyrrole-3-carbaldehyde **3i**

The title compound was prepared following general procedure 2 from **2q** (100 mg, 0.267 mmol) with 58% yield (49 mg) as a light brown solid. mp: 110–116 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.77 (s, 1H), 8.01 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.30 (d, *J* = 1.8 Hz, 1H), 6.56 (d, *J* = 1.8 Hz, 1H), 3.52 (t, *J* = 6.1 Hz, 2H), 2.60–2.52 (t, *J* = 7.4 Hz, 2H), 2.08–1.97 (m, 2H). ¹³C NMR: (100 MHz, CDCl₃) δ 184.9, 163.8, 135.7, 132.6, 129.7, 129.3, 125.7, 124.8, 104.7, 43.9, 30.7, 21.9. IR (film): ν = 3101, 2948, 2708, 2316, 1747, 1674, 1519, 1309, 1283, 1112, 1079 cm⁻¹. MS (CI/NH₃): *m/z* = 317 [M+H]⁺.

4.3.10. 1-(1,3-dioxoisindolin-2-yl)-5-(1-methoxyethyl)-1H-pyrrole-3-carbaldehyde **3j**

The title compound was prepared following general procedure 2 from **2r** (100 mg, 0.292 mmol) with 47% yield (41 mg) as a white solid. mp: 136–138 °C. ¹H NMR: (400 MHz, CDCl₃) δ 9.82 (s, 1H), 8.06–7.96 (m, 2H), 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.36 (d, *J* = 1.9 Hz, 1H), 6.74 (dd, *J* = 1.9, 0.8 Hz, 1H), 4.38 (qd, *J* = 6.6, 0.8 Hz, 1H), 3.04 (s, 3H), 1.45 (d, *J* = 6.6 Hz, 3H). ¹³C NMR: (100 MHz, CDCl₃) δ 185.0, 163.9, 136.6, 135.5, 131.4, 129.6, 125.1, 124.7, 106.4, 70.3, 54.4, 18.3. IR (film): ν = 3112, 2823, 2726, 2320, 1746, 1669, 1314, 1283, 1199, 1140, 1113, 1074 cm⁻¹. MS (CI/NH₃): *m/z* = 299 [M+H]⁺.

4.3.11. 5-((benzyloxy)methyl)-1-(1,3-dioxoisindolin-2-yl)-1H-pyrrole-3-carbaldehyde **3k**

The title compound was prepared following general procedure 2 from **2s** (100 mg, 0.247 mmol) with 66% yield (59 mg) and from **2t** (100 mg, 0.239 mmol) with 48% yield (41 mg) as a white solid. mp: 200–204 °C ¹H NMR: (400 MHz, CDCl₃) δ 9.83 (s, 1H), 7.91 (td, *J* = 5.3, 2.1 Hz, 2H), 7.85 (td, *J* = 5.3, 2.1 Hz, 2H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.24–7.14 (m, 3H), 7.14–7.04 (m, 2H), 6.76 (d, *J* = 1.9 Hz, 1H), 4.40 (s, 2H), 4.29 (s, 2H). ¹³C NMR: (100 MHz, CDCl₃) δ 184.9, 163.8, 137.1, 135.4, 132.2, 131.6, 129.6, 128.4, 128.2, 127.9, 125.2, 124.7, 108.4, 71.6, 62.6. IR (film): ν = 3112, 2924, 2880, 1739, 1673, 1515, 1300, 1136, 1045 cm⁻¹. MS (CI/NH₃): *m/z* = 361 [M+H]⁺.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.tet.2020.131221>.

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