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o-Nitrophenylacetonitrile Michael additions and cyclocondensations: a novel quinoline synthesis

Marco R. Buccini,[a] Shi Yuan Jeow,[a,b] Glenn A. Pullella,[a] Han Chern Loh,[a] Brian W. Skelton,[a] Stephen A. Moggach,[a] and Matthew J. Piggott[a*]

[a] *Chemistry, School of Molecular Sciences, University of Western Australia, Perth, 6009, WA, Australia*
[b] *Department of Pharmacy, National University of Singapore, Singapore 117543*
Email: matthew.piggott@uwa.edu.au

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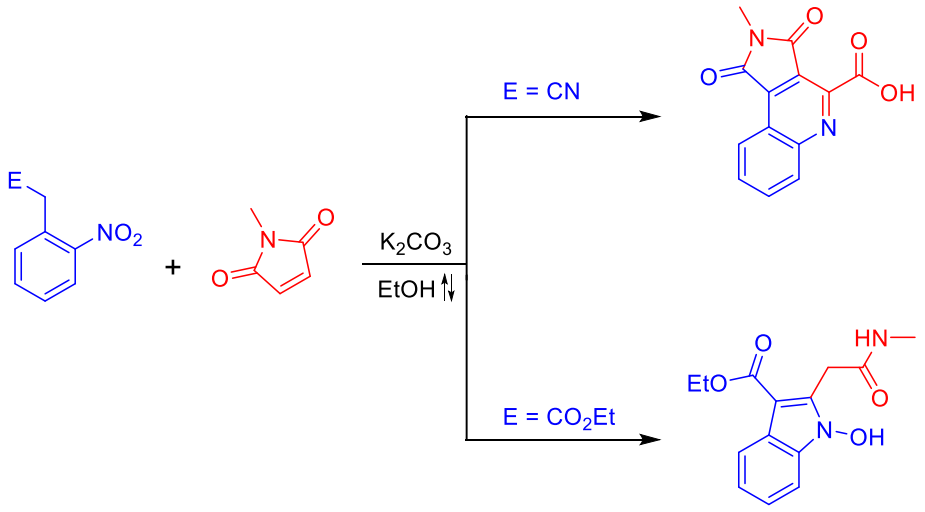
Abstract

Michael additions of *o*-nitrophenylacetonitrile have been investigated. The adducts are formed diastereoselectively under mild conditions. Higher temperatures result in an unusual annulation involving intramolecular nucleophilic attack of an enolate on the nitro group, giving rise to 2,3,4-trisubstituted quinolines. In contrast, under similar conditions ethyl *o*-nitrophenylacetic acid reacts with *N*-methylmaleimide to give an *N*-hydroxyindole. A possible explanation for the divergent chemistry, and mechanisms for these reactions are proposed.



Keywords: *o*-Nitrophenylacetonitrile, Michael addition, isoquinolines, *N*-hydroxyindoles

Introduction

o-Nitrophenylacetonitriles, *e.g.*, the parent **1**, are valuable and versatile precursors to a variety of benzo-fused heterocycles, including indoles **2**,[1-10] *N*-hydroxyindoles **3**,[11-15] quinoline-*N*-oxides **4**,[16-21] quinolines **5**,[22-26] cinnoline-1-oxides **6**,[27-29] and 2,1-benzisoxazoles (anthranils) **7**[20,30,31] (Figure 1).

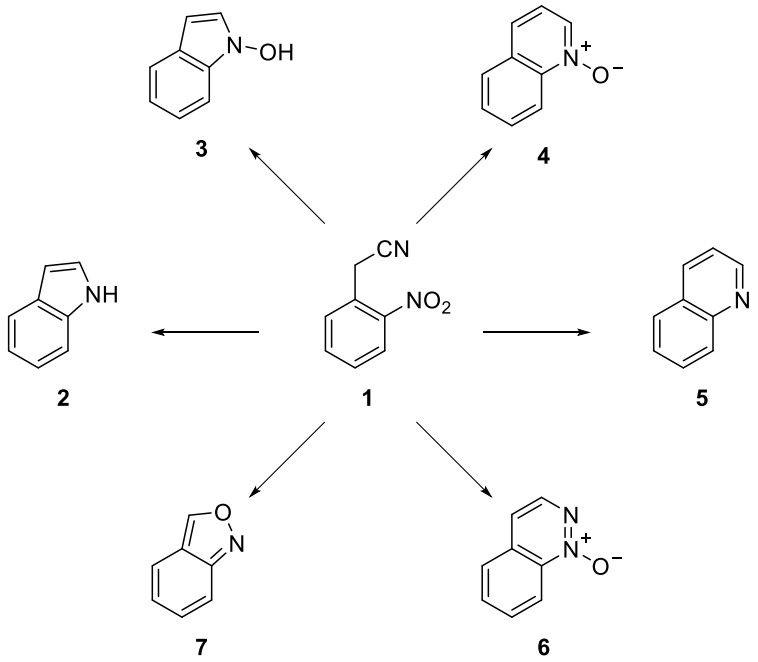


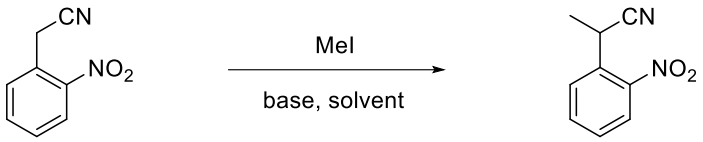
Figure 1. *o*-Nitrophenylacetonitriles as synthons for benzo-fused heterocycles.

As part of efforts to achieve the total synthesis of the marine pyrroloacridine natural product alpkinidine,[32-34] we investigated Michael addition of **1** to quinones. Somewhat surprisingly, these reactions were unsuccessful.[33] For the purposes of calibration, we explored the reactions of **1** with other Michael acceptors. In the course of these studies, we encountered some interesting and unexpected reactions affording quinolines and *N*-hydroxyindoles, which are reported here.

Results and Discussion

Our investigation into nucleophilic reactions of the anion derived from **1** began with α-methylation (Table 1). The reaction failed to go to completion with K_2CO_3 in EtOH, and it was apparent that the purple carbanion had adsorbed to the poorly soluble base, effectively sequestering it from the electrophile. A switch to the more soluble base Cs_2CO_3, or a dipolar aprotic solvent,[9] improved the yield of **8** considerably.

Table 1. α-Methylation of *o*-(nitrophenyl)acetonitrile (**1**)



1 **8**

Solvent	equiv. MeI	equiv. Base	Temp. (°C)	Time (h)	Yield (%)
EtOH	5	5 K_2CO_3	40	3	35
EtOH	1	1 Cs_2CO_3	40	1	87
DMF	2	1.5 K_2CO_3	50	1.5	80

Michael additions were then explored (Table 2). In these reactions, the combination of K_2CO_3/EtOH worked well, as expected given the requirement for only catalytic base and the stabilization of transition states imparted by the protic solvent. Reactions in MeCN were much slower and gave side-products and inferior yields. The Michael addition of **1** to methyl acrylate, using potassium *t*-butoxide in THF, has been reported to provide the corresponding adduct in 76% yield.[35] In our hands, milder conditions with ethyl acrylate (**9**) led to a higher yield of **14**.

Michael additions to *N*-methylmaleimide (**10**) or cyclohexenone (**11**), gave 10:1 and 5:1 mixtures of diastereomeric adducts **15** and **16**, respectively, as determined by ^{1}H NMR spectroscopy of the crude products. Attempts to separate the stereoisomers by chromatography resulted in significant mass losses; however, in both cases the major diastereomer was easily isolated by washing the crude solid product with Et_2O. The relative configurations of the major isomers were determined by X-ray crystallography (Figure 1).

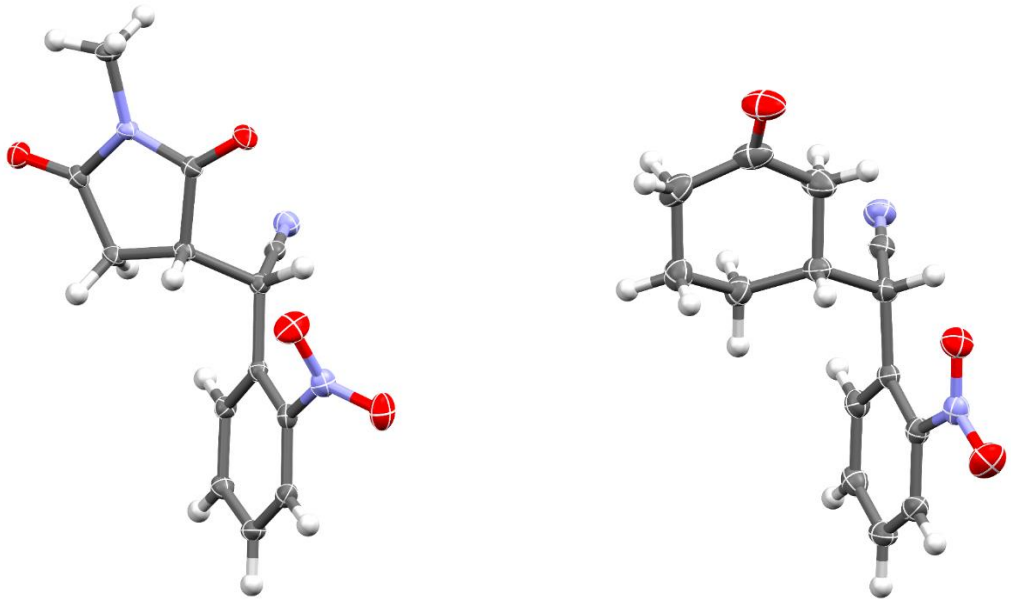
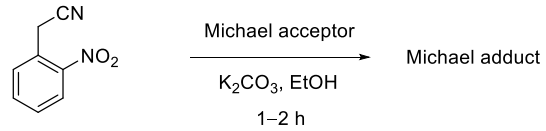
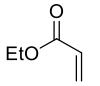
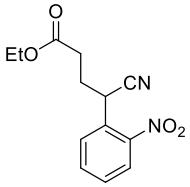
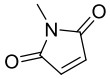
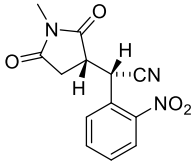
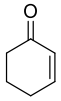
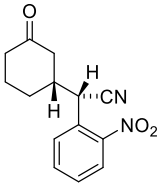
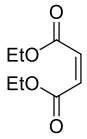
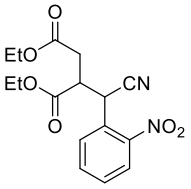
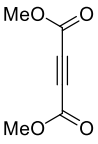


Figure 1. Representations of the X-ray crystal structures of **15** (left) and **16** (right). Crystals of **16** contained two independent molecules in the asymmetric unit. In the molecule not shown, the nitro group is slightly more twisted out of the plane of the benzene. Displacement envelopes are at 50% probability amplitude, with hydrogen atoms assigned arbitrary radii.

Table 2. Addition of *o*-(nitrophenyl)acetonitrile (**1**) to various Michael acceptors[#]



1

	Michael Acceptor		Adduct	Yield (%)
9		**14**		92
10		**15**		78*
11		**16**		72*
12		**17**	 44:56 % mixture of diastereomers	51
13†		–		–

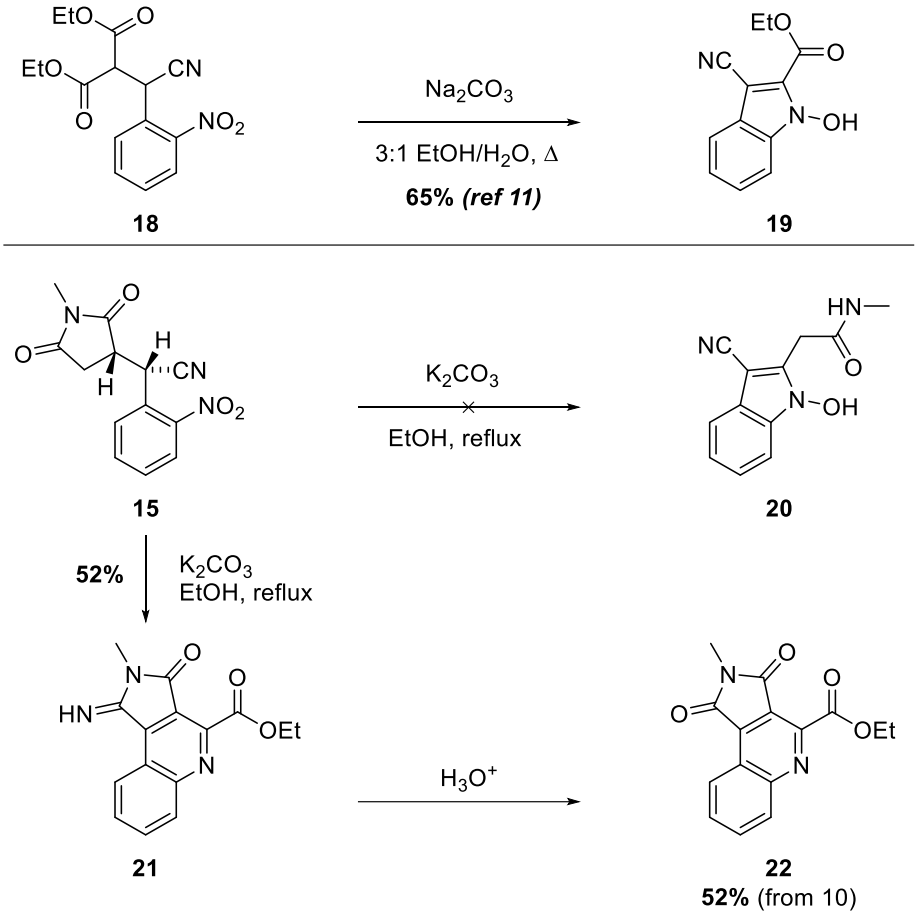
[#] **1** (2 mmol), Michael acceptor (2 mmol), K_2CO_3 (2 mmol), EtOH (15–20 mL).

* Major diastereomer isolated after washing crude solid product with Et_2O.

† MeOH used as solvent.

Michael addition to diethyl maleate (**12**) proceeded as expected, but in this case afforded a 11:14 mixture of diastereomers **17** that were neither separated nor assigned to spectroscopic features. The reaction with dimethyl acetylenedicarboxylate (DMAD, **13**) was undertaken in MeOH to exclude the possibility of transesterification. In contrast to the other examples, this reaction produced a complex array of products and attempted chromatographic separation failed to yield any identifiable compounds.

In 1960, Loudon and Wellings reported the synthesis of *N*-hydroxyindole **19** during an attempted recrystallisation of **18** from weakly basic EtOH/H_2O[11] (Scheme 1). Given the structural similarities, we subjected Michael adduct **15** to treatment with K_2CO_3 in refluxing EtOH. A new major product was isolated following acidic work-up; however, it was clearly not the expected *N*-hydroxyindole **20**. One and 2D NMR spectroscopy experiments suggested the unexpected product was a quinoline, and X-ray crystallography confirmed the structure **22** (Figure 2). It was also noted from TLC that the R_f of **22** was different from that of the major product observed in the reaction mixture, suggesting that a further transformation had occurred during acidic work-up. Thus, the reaction was repeated with a basic aqueous work-up, leading to the isolation of the imino congener **21**, again confirmed by X-ray crystallography (Figure 2). The identification of **21** shed light on a possible mechanism for the unusual reaction (Scheme 2).



Scheme 1. Attempted synthesis of *N*-hydroxyindole **20** and unexpected formation of quinolines **21** and **22**.

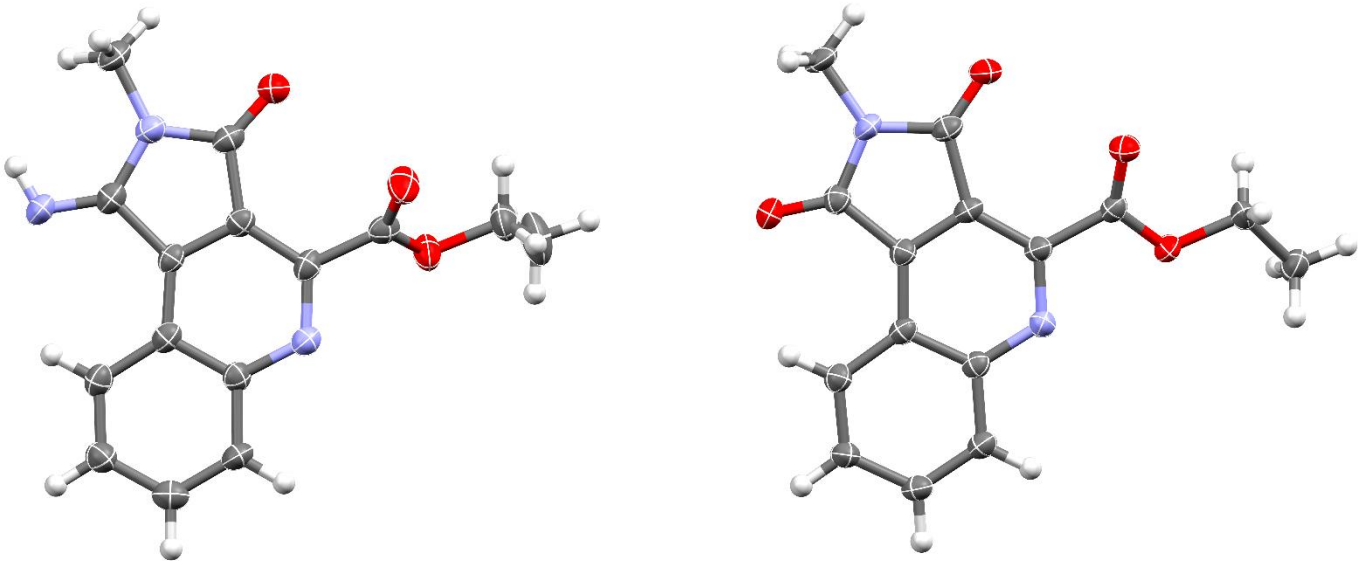
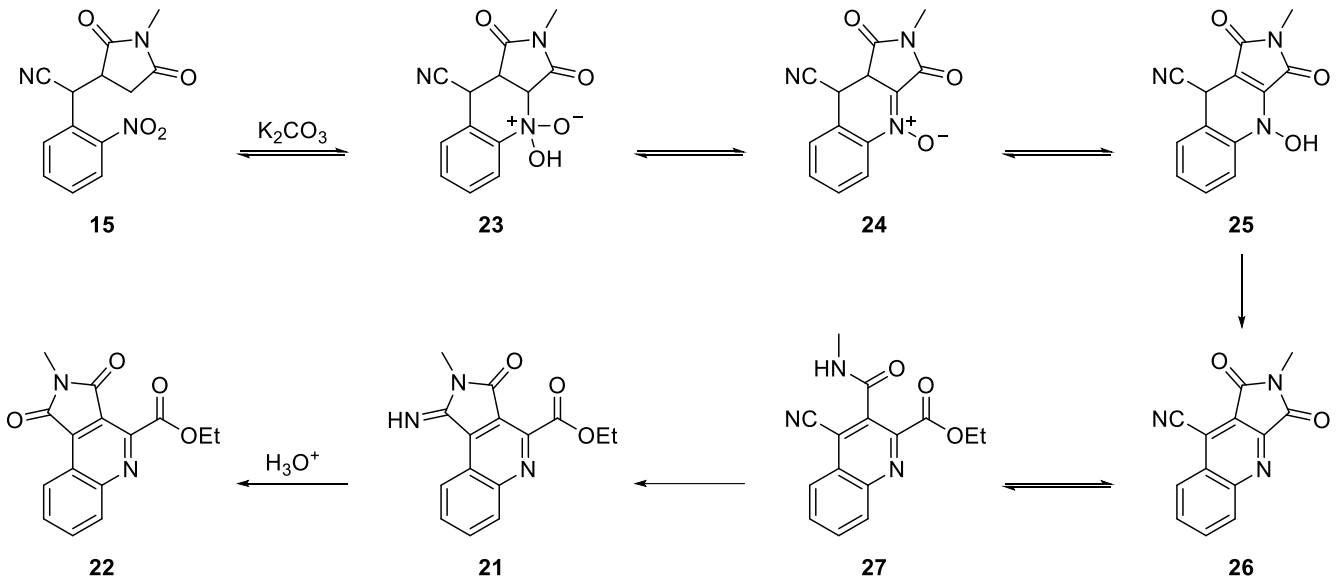


Figure 2. Representations of the X-ray crystal structures of **21** (left) and **22** (right). Displacement envelopes are at 50% probability amplitude, with hydrogen atoms assigned arbitrary radii.

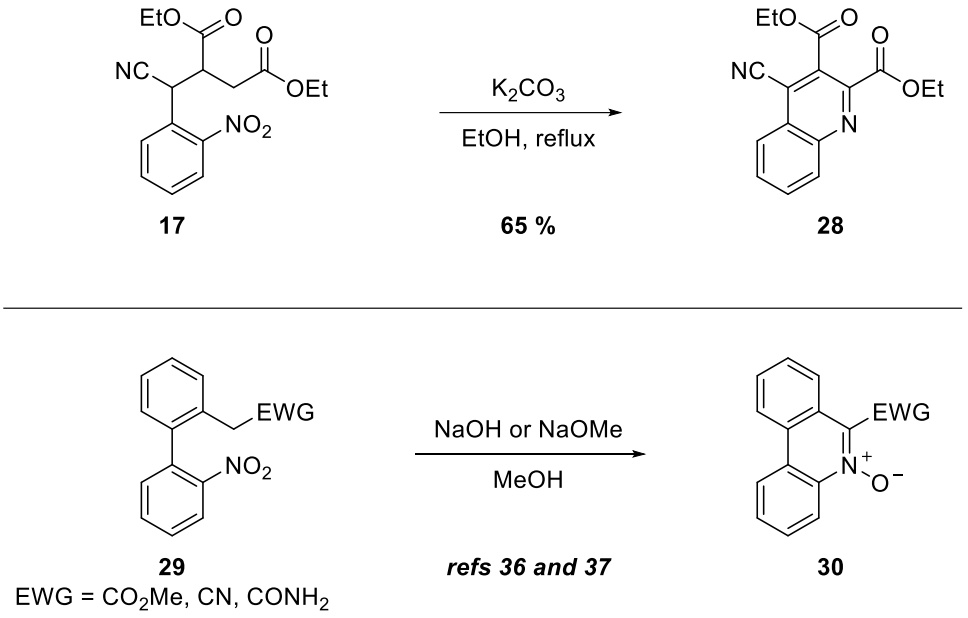
Base-catalyzed enolization of **15**, followed by intramolecular nucleophilic attack on the nitro group, gives intermediate **23**, which eliminates water (likely by an E1cb mechanism), affording nitronate **24**. Tautomerization to **25** precedes transannular dehydration, generating quinoline **26**. General base-catalyzed solvolysis of the imide in **26** gives ethyl ester **27**, followed by cyclisation of the resulting secondary amide nitrogen onto the cyano group, affording the observed product **21**. Acidic work-up hydrolyses the imino group, giving the maleimide **22**.



Scheme 2. Key intermediates in the proposed mechanism for the cyclocondensation of **15** to **21** and **22**.

The proposed mechanism is supported by the reaction of the crude diastereomeric mixture of adducts **17** under the same conditions, which afforded quinoline **28** (Scheme 3). To the best of our knowledge, the closest precedent to this rare and unusual cyclocondensation, initiated by nucleophilic attack of an enolate on a nitro

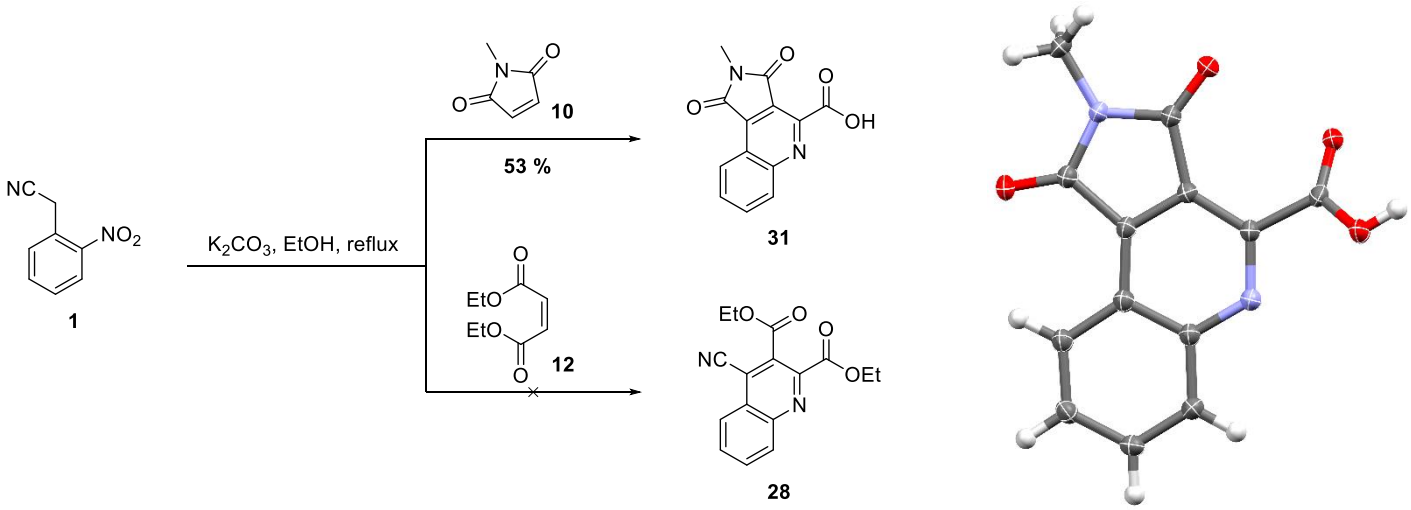
group, involves 2'-nitrobiphenyl-2-acetic acid derivatives **29**, which cyclize under strongly basic conditions to give the phenanthridine-*N*-oxides **30** (Scheme 3).[36,37]



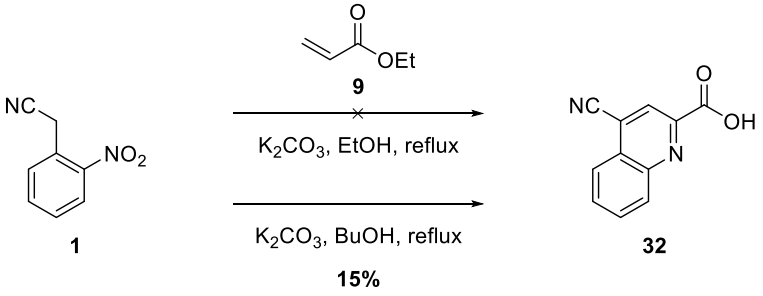
Scheme 3. Base-catalyzed cyclocondensations involving a nitro group – current (top) and closest precedents[36,37] (bottom).

Many years later, and in a different lab, we investigated the one-pot Michael addition/cyclocondensation of *o*-nitrophenylacetonitrile (**1**) with *N*-methylmaleimide (**10**) (Scheme 4). Surprisingly, this reaction gave the quinaldic acid **31** in moderate yield, after acidic workup. It seems likely in this case that adventitious water either provided an alternative nucleophile for the ring opening of intermediate **26** (Scheme 2), or led to saponification of **21**/**27** under the reaction conditions. However, drying of the K_2CO_3 (overnight 400 °C) and ethanol (over freshly activated sieves for >24 h) had no bearing on the outcome of the reaction, which raises the possibility that carbonate is the nucleophile that ring-opens intermediate **26** in these instances. In contrast to the two-step synthesis of **28** (Table 2 and Scheme 3), heating **1**, diethyl maleate (**12**) and K_2CO_3 from the outset gave a complex mixture of products, suggesting that, with some electrophiles, one-pot annulations of this type may best be carried out with a room-temperature Michael-addition step prior to heating to induce the cyclocondensation reaction.

An attempt to effect an analogous one-pot annulation reaction of **1** with ethyl acrylate (**9**) gave predominantly the Michael adduct **14** (Table 2). The slow/lack of annulation of adduct **14** in refluxing ethanol suggests that: 1) intramolecular nucleophilic attack of enolates on the nitro group is reversible; and, 2) an adjacent electron-withdrawing group facilitates tautomerization, *e.g.*, step **24** $\rightarrow$ **25** in scheme 2, enabling irreversible dehydration/aromatization. In line with these hypotheses, a switch to the higher boiling solvent 1-butanol gave 4-cyanoquinaldic acid (**32**) (Scheme 5); once again, ester saponification due to adventitious water seems likely. Difficult multistep purification exacerbated by poor solubility contributed to the low isolated yield of **32**; nevertheless, further experimentation is required to make the annulation of **1** with Michael acceptors lacking a β-electron-withdrawing group synthetically viable.



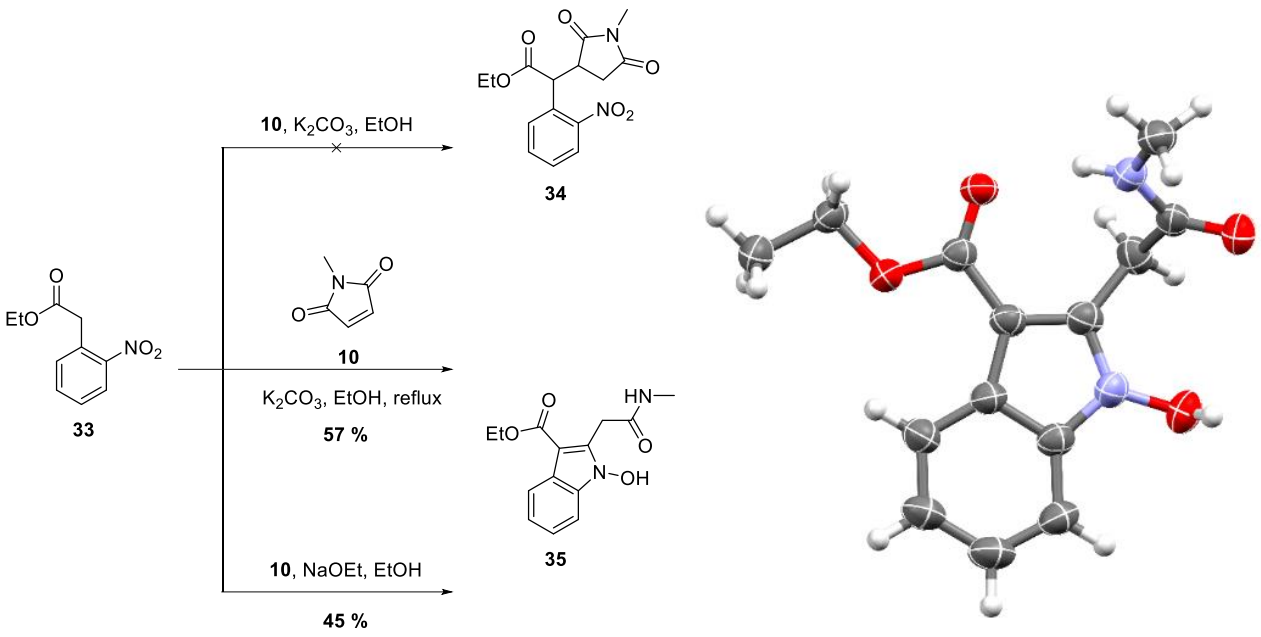
Scheme 4. Successful and attempted annulation reactions of **1** with Michael acceptors. Each reaction was followed by a weakly acidic aqueous work-up. A representation of the X-ray crystal structure of **31** is shown on the right. Displacement envelopes are at 50% probability amplitude, with hydrogen atoms assigned arbitrary radii.



Scheme 5. One-pot annulation reaction of **1** and **9** requires a higher boiling solvent.

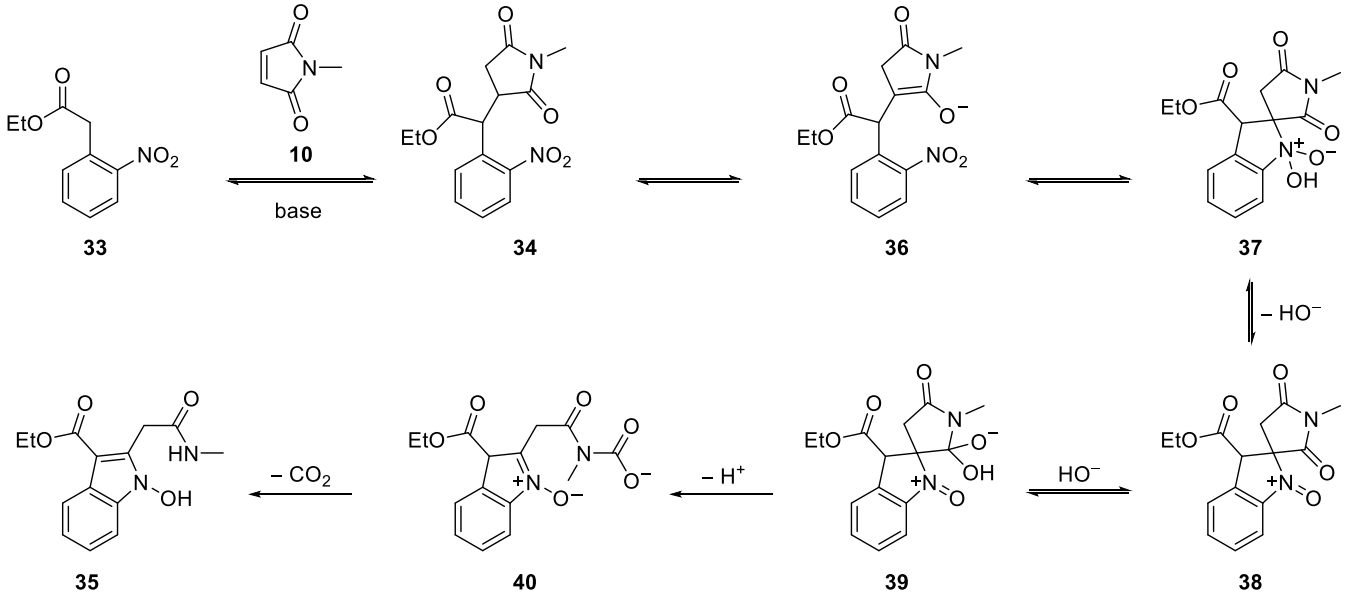
We also briefly investigated reactions of the related enolate generated from ethyl *o*-nitrophenylacetate (**33**), with *N*-methylmaleimide (**10**) (Scheme 6). Interestingly, with K_2CO_3 in ethanol at room temperature, no color associated with the relevant carbanion was observed, and no Michael adduct **34** was detected. Upon heating under reflux, *N*-hydroxyindole **35** was the predominant product, as confirmed with an X-ray crystal structure (Scheme 6). The same transformation was achieved in higher yield at room temperature with stronger base.

Key intermediates in the proposed mechanism for the formation of **35** are shown in Scheme 7. Michael addition of ester **33** to **10** gives adduct **34**. A second deprotonation generates enolate **36**, which cyclizes onto the nitro group, affording spirocycle **37**. This species is presumably in equilibrium with the oxoammonium ion **38**. Reversible attack of liberated, or adventitious, hydroxide on the more sterically hindered succinimide carbonyl group of **38** gives **39**, which is poised to undergo a retro-Claisen-like ring scission, affording nitronate **40**. Decarboxylation and tautomerization/protonation then give the observed *N*-hydroxyindole **35**.



Scheme 6. Annulation reactions of **33** and *N*-methylmaleimide (**10**). The representation of the X-ray crystal structure of *N*-hydroxyindole **35** has displacement envelopes at 50% probability amplitude, with hydrogen atoms assigned arbitrary radii.

The two different annulation pathways – quinolines from **1** and an *N*-hydroxyindole from **33** – probably result from the different steric demands of the benzylic cyano and ethoxycarbonyl groups, which influence which nucleophilic center of the possible enolate intermediates can achieve the geometry required for nucleophilic attack on the nitro group.



Scheme 7. Key intermediates in the proposed mechanism for the formation of *N*-hydroxyindole **35**.

Conclusions

The carbanion mildly generated from *o*-nitrophenylacetonitrile is a good nucleophile for diastereoselective Michael additions. More forcing conditions result in an unusual cyclocondensation affording 2,(3),4-trisubstituted quinolines in moderate to good yields. Analogous isoquinoline syntheses involving other *o*-nitrobenzylic carbanions are likely possible, provided the benzylic substituent is not too sterically demanding. In contrast, higher temperatures or stronger bases are required to elicit reaction of ethyl *o*-nitrophenylacetate with *N*-methylmaleimide (and presumably other Michael acceptors), and an *N*-hydroxyindole product predominates in this case. The reactions described herein provide rapid access to substituted benzo-fused heterocycles that would otherwise require multi-step synthetic routes, and expand the rich chemistry of the carboxylic acid derivatives of *o*-nitrophenylacetic acid.

Experimental Section

General. General experimental details are as reported previously.[33,38] Reactions were conducted under ambient conditions unless otherwise indicated. Stated temperatures refer to the temperature of the heating bath. Dry solvents were stored in sealed bottles over activated type 3A sieves for at least 24 h before use.

2-(2-Nitrophenyl)propanenitrile (8). Method 1. K_2CO_3 (74 mg, 0.54 mmol) was added to a stirred solution of *o*-nitrophenylacetonitrile (**1**) (18 mg, 0.11 mmol) in dry EtOH (2 mL) under argon. MeI (0.03 mL, 0.5 mmol) was added to the purple suspension and stirring was continued at 40 °C for 3 h, over which time the solution turned pale yellow. The reaction mixture was acidified with 1 M HCl (5 mL) and diluted with water (10 mL), then extracted with EtOAc (4 × 5 mL). The extract was dried and evaporated to give a yellow oil, which was purified by flash chromatography. Elution (EtOAc/hexanes, 3:17) gave **8** as a yellow oil (6 mg, 35%), identical with the material described below.

Method 2. K_2CO_3 (429 mg, 3.11 mmol) was added to a stirred solution of *o*-nitrophenylacetonitrile (**1**) (323 mg, 1.99 mmol) in dry DMF (15 mL) under argon. MeI (0.24 mL, 4.0 mmol) was added to the purple suspension and stirring was continued at 50 °C for 90 min, over which time the solution turned pale yellow. The mixture was acidified with 1 M HCl (10 mL) and diluted with water (20 mL), then extracted with EtOAc (3 × 15 mL). The extract was dried and evaporated to give a yellow oil, which was purified by flash chromatography. Elution (EtOAc/hexanes, 3:17) gave **8** as a yellow oil (288 mg, 80%), identical with the material described below.

Method 3. Cs_2CO_3 (765 mg, 2.35 mmol) was added to a stirred solution of *o*-nitrophenylacetonitrile (**1**) (318 mg, 1.96 mmol) in dry EtOH (15 mL) under argon. MeI (0.122 mL, 1.96 mmol) was added to the purple suspension and stirring was continued at 40 °C for 1 h, over which time the solution turned pale yellow. The mixture was acidified with 1 M HCl (10 mL) and diluted with water (20 mL), then extracted with EtOAc (3 × 15 mL). The extract was dried and evaporated to give a yellow oil, which was purified by flash chromatography. Elution (EtOAc/hexanes, 15:85) gave **8** as a yellow oil (301 mg, 87%). R_f 0.3 (EtOAc/hexanes, 1:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (m, 1H, H3'), 7.81 (dd, J = 7.0, 1.0 Hz, 1H, H6'), 7.72 (m, 1H, H5'), 7.53 (ddd [app. dt], $J_1 = J_2$ = 7.0, 1.0 Hz, 1H, H4'), 4.76 (q, J = 7.0 Hz, 1H, H2), 1.72 (d, J = 7.0 Hz, 3H, CH_3). The ^{1}H NMR data are similar to those reported at 400 MHz.[9]

Ethyl 4-cyano-4-(2-nitrophenyl)butanoate (14). K_2CO_3 (288 mg, 2.08 mmol) was added to a stirred solution of *o*-nitrophenylacetonitrile (**1**) (320 mg, 1.97 mmol) in dry EtOH (15 mL) under argon. Ethyl acrylate (**9**) (0.22 mL, 2.1 mmol) was then added to the purple suspension. After 2 h, the solution had turned pale yellow, and the

mixture was acidified with 1 M HCl (10 mL) and diluted with water (20 mL), then extracted with EtOAc (3 × 15 mL). The extract was dried and evaporated to yield a brown oil, which was subjected to flash chromatography. Elution (EtOAc/hexanes, 15:85) gave the adduct **14** as a yellow oil (428 mg, 92%). R_f 0.2 (EtOAc/hexanes, 1:4). IR (neat) ν_{max} cm^{-1}: 2244 (w, C≡N), 1731 (s, C=O). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.07 (d, *J* = 8.2 Hz, 1H, H3'), 7.79 (m, 1H, H6'), 7.73 (m, 1H, H5'), 7.56 (m, 1H, H4'), 4.83 (dd, *J* = 5.4, 3.8 Hz, 1H, H4), 4.15 (q, *J* = 7.1, 2H, H1'''), 2.60 (t, *J* = 7.5 Hz, 2H, H2), 2.41–2.15 (m, 2H, H3), 1.27 (t, *J* = 7.1 Hz, 3H, H2'''). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.8 (C1), 147.9 (C2'), 134.6 (C3'), 130.8 (C1'), 130.6 (ArH), 130.0 (ArH), 126.1 (ArH), 119.7 (C5), 61.3 (C1''') 33.3, 32.0, 30.8, 14.5 (C2'''). HRCIMS *m/z* found: 263.1020; $C_{13}H_{15}N_2O_4^+$ $[M+H]^+$ requires 263.1026.

(*S)-2-[(*R**)-1-Methyl-2,5-dioxopyrrolidin-3-yl]-2-(2-nitrophenyl)acetonitrile (15).** K_2CO_3 (274 mg, 1.99 mmol) was added to a stirred solution of *o*-nitrophenylacetonitrile (**1**) (322 mg, 1.99 mmol) in dry EtOH (20 mL) under argon. *N*-Methylmaleimide (**10**) (228 mg, 2.05 mmol) was added to the purple solution. After 1 h, the solution had turned pale yellow, and the mixture was acidified with 1 M HCl (10 mL) and diluted with water (20 mL), then extracted with EtOAc (3 × 15 mL). The extract was dried and evaporated to yield a light brown solid, which was washed with ether (5 × 10 mL) to give the adduct **15** as beige solid (424 mg, 78%), which crystallized as pale-yellow prisms, mp 163–166 °C (*n*-BuOH). R_f 0.15 (EtOAc/hexanes, 2:3). IR (KBr disc) ν_{max} cm^{-1}: 2247 (w, C≡N), 1774 (m, C=O, asym), 1701 (s, C=O, sym). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.19 (m, 1H, H3''), 7.74–7.82 (m, 2H, 2 × Ar), 7.58–7.68 (m, 1H, Ar), 5.50 (d, *J* = 4.8 Hz, 1H, H2), 3.50–3.59 (m, 1H, H3'), 3.05 (s, 3H, NMe), 2.83 (dd, *J* = 18.1, 6.0 Hz, 1H, H4a'), 2.72 (dd, *J* = 18.1, 9.0 Hz, 1H, H4b'). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.9 (C=O), 174.1 (C=O), 147.6 (C2''), 134.8 (C3''), 130.7 (ArH), 130.6 (ArH), 127.8 (C1''), 126.6 (ArH), 116.9 (C1), 43.7 (C3' or C2), 35.2 (C2 or C3'), 31.5 (C4'), 25.5 (NMe). HRCIMS *m/z* found: 274.0820; $C_{13}H_{15}N_2O_4^+$ $[M+H]^+$ requires 274.0822.

(*S)-2-(2-Nitrophenyl)-2-[(*S**)-3-oxocyclohexyl]acetonitrile (16).** K_2CO_3 (280 mg, 2.02 mmol) was added to a stirred solution of *o*-nitrophenylacetonitrile (**1**) (324 mg, 2.00 mmol) in dry EtOH (18 mL) under argon. 2-Cyclohexene-1-one (**11**) (0.21 mL, 2.2 mmol) was added to the purple suspension. After 2 h, the solution has turned pale yellow and the reaction mixture was acidified with 1 M HCl (10 mL) and diluted with water (20 mL), then extracted with EtOAc (3 × 15 mL). The extract was dried and evaporated to yield a light brown solid, which was washed with ether (5 × 10 mL) to give the adduct **16** as a beige solid (370 mg, 72%), which crystallized as colorless needles, mp 141–144 °C (*n*-BuOH). R_f 0.3 (EtOAc/hexanes, 2:3). IR (KBr disc) ν_{max} cm^{-1}: 2238 (w, C≡N), 1702 (s, C=O). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.11 (m, 1H, H3'), 7.69–7.79 (m, 2H, 2 × ArH), 7.58 (m, 1H, ArH), 4.80 (d, *J* = 5.2 Hz, 1H, H2), 2.23–2.55 (m, 5H, H2''/H3''/H6''), 2.09–2.20 (m, 1H, H5''a or H5''b), 1.93–2.04 (m, 1H, m, H5''a or H5''b), 1.64–1.79 (m, 1H, H4''a or H4''b), 1.48–1.64 (m, 1H, H4''a or H4''b). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 208.4 (C=O), 147.9 (C2'), 134.2 (C3'), 131.0 (ArH), 130.1 (ArH), 128.9 (C1'), 126.3 (ArH), 118.4 (C1), 46.1 (C2'' or C6''), 42.6 (C2 or C3''), 40.9 (C2'' or C6''), 39.5 (C2 or C3''), 27.4 (C4'' or C5''), 24.3 (C4'' or C5''). HREIMS *m/z* found: 258.1000; $C_{14}H_{14}N_2O_3^{\bullet+}$ $[M]^{\bullet+}$ requires 258.0999.

Diethyl 2-[cyano(2-nitrophenyl)methyl]succinate (17). K_2CO_3 (638 mg, 4.62 mmol) was added to a stirred solution of *o*-nitrophenylacetonitrile (**1**) (752 mg, 4.62 mmol) in dry EtOH (24 mL) under argon. Diethyl maleate (**12**) (800 mg, 4.62 mmol) was added to the purple suspension. After 1 h the solution had turned pale-yellow, and the reaction mixture was acidified with 1 M HCl (30 mL), then extracted with EtOAc (3 × 10 mL). The extract was washed with brine (10 mL), dried and evaporated to give an amber oil, which was subjected to flash chromatography. Elution (EtOAc/hexanes, 1:4) gave the adducts **17** as a yellow oil (1.03 g, 62%) as a 11$^{\#}$:14* mixture of diastereomers. R_f 0.45 (EtOAc/hexanes, 1:2). ν_{max} cm^{-1}: 1733 (s, C=O), 2247 (w, C≡N). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.12 (ddd [app. dt], *J* = 8.2, 1.2 Hz, 2H, 2 × H3''), 7.74–7.78 (m, 2H, 2 × H6''), 7.68–7.73 (m, 2H, 2 × H5''), 7.55–7.60 (m, 2H, 2 × H4''), 5.40* (d, *J* = 6.3 Hz, 1H, H2'), 5.19$^{\#}$ (d, *J* = 6.0 Hz, 1H, H2'), 4.00–4.19 (m, 4H, 4 × OCH_2), 3.56* (ddd, *J* = 8.3, 6.3, 5.2 Hz, 1H, H2), 3.46$^{\#}$ (ddd [app. dt], *J* = 9.2, 5.6 Hz, 1H, H2), 2.90–3.04 (m, 2H, 2 × H3a), 2.63–2.73 (m, 1H, 2 × H3b), 1.24$^{\#}$ (t, *J* = 7.2 Hz, 3H, CH_3), 1.201* (t, *J* = 7.2 Hz, 3H, CH_3), 1.196* (t, *J*

= 7.2 Hz, 3H, CH_3), 1.13[#] (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 170.4 (C=O), 170.2 (C=O), 170.16 (C=O), 170.15 (C=O), 148.0 (C2''), 147.8 (C2''), 134.2 (C5''), 134.1 (C5''), 131.5 (C6''), 131.3 (C6''), 130.31 (C4''), 130.27 (C4''), 128.4 (C1''), 128.1 (C1''), 126.2 (C3''), 126.1 (C3''), 117.7 (C1'), 117.5 (C1'), 62.2 (CH_2O), 61.8 (CH_2O), 61.4 (CH_2O), 61.3 (CH_2O), 44.8 (C2), 44.6 (C2), 35.53 (C2'), 35.46 (C2'), 35.1 (C3), 33.4 (C3), 14.2 (CH_3), 14.1 (CH_3), 14.01 (CH_3), 13.98 (CH_3). HRESIMS *m*/*z* found: 335.1245; $C_{16}H_{19}N_2O_6^+$ $[M+H]^+$ requires 335.1238.

Ethyl 1-imino-2-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinoline-4-carboxylate (21). K_2CO_3 (50 mg, 0.37 mmol) was added to a stirred solution of 2-(2-nitrophenyl)acetonitrile **15** (200 mg, 0.732 mmol) in dry EtOH (30 mL) and the mixture was then heated under reflux under argon for 1 h. The solvent was evaporated to give an amber residue, which was subjected to flash chromatography. Elution (EtOAc/hexanes, 33:67) gave the quinoline **21** as a colorless solid (107 mg, 52%), which crystallized as colorless needles, mp 133–138 °C ($CHCl_3$/hexane). R_f 0.25 (EtOAc/hexanes, 1:2). IR ν_{max} cm^{-1}: 1752 (s, OC=O), 1739 (s, NC=O), 1654 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.23 (d, *J* = 8.3 Hz, 1H, H9), 8.72 (s, 1H, NH), 8.29 (d, *J* = 8.5 Hz, 1H, H6), 7.85–8.01 (m, 1H, H7 or H8), 7.78 (dd [app. t], $J_1 = J_2$ = 7.6 Hz, 1H, H7 or H8), 4.61 (q, *J* = 7.1 Hz, 2H, CH_2), 3.24 (s, 3H, NMe), 1.49 (t, *J* = 7.2 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 165.0 (CO_2 or C3), 164.6 (CO_2 or C3), 157.8 (C1), 150.1 (C5a or C4), 146.3 (C5a or C4), 141.0 (9b), 132.8 (ArH), 130.6 (ArH), 130.5 (ArH), 126.1 (ArH), 122.8 (C3a or C9a), 121.5 (C3a or C9a), 62.9 (OCH_2), 23.9 (NMe), 14.3 (Me). HRESIMS *m*/*z* found: 284.1036; $C_{15}H_{14}N_3O_3^+$ $[M+H]^+$ requires 284.1030.

Ethyl 2-methyl-1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinoline-4-carboxylate (22). K_2CO_3 (55 mg, 0.40 mmol) was added to a stirred solution of 2-(2-nitrophenyl)acetonitrile **15** (220 mg, 0.81 mmol) in dry EtOH (30 mL). The reaction mixture was then heated under reflux under argon for 1 h, then cooled and acidified with 1 M HCl (5 mL) and diluted with water (10 mL), then extracted with EtOAc (4 × 10 mL). The extract was dried and evaporated to give an amber residue, which was subjected to flash chromatography. Elution (EtOAc/hexanes, 20:80) gave the quinoline **22** as a colorless solid (108 mg, 52%), which crystallized as colorless needles, mp 129–130 °C ($CHCl_3$/hexane). R_f 0.45 (EtOAc/hexanes, 1:2). IR ν_{max} cm^{-1}: 1738 (s, OC=O), 1714 (s, NC=O). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.91 (d, *J* = 8.4 Hz, 1H, H9), 8.31 (d, *J* = 8.6 Hz, 1H, H6), 7.96 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H, H7 or H8), 7.84 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H, H7 or H8), 4.61 (q, *J* = 7.1 Hz, 2H, CH_2O), 3.25 (s, 3H, NMe), 1.50 (t, *J* = 7.1 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 167.6 (C=O), 165.8 (C=O), 164.5 (C=O), 150.9 (C4 or C5a), 145.8 (C4 or C5a), 137.4 (C9b), 133.5 (ArH), 131.3 (ArH), 130.7 (ArH), 125.1 (ArH), 122.2 (C3a or C9a), 121.8 (C3a or C9a), 63.1 (CH_2O), 24.4 (NMe), 14.24 (Me). HRESIMS *m*/*z* found: 307.0697; $C_{15}H_{12}N_2NaO_4^+$ $[M+Na]^+$ requires 307.0689.

Diethyl 4-cyanoquinoline-2,3-dicarboxylate (28). K_2CO_3 (41 mg, 0.30 mmol) was added to a stirred solution of diethyl 2-[cyano(2-nitrophenyl)methyl]succinate (**17**) (200 mg, 0.60 mmol) in dry EtOH (30 mL). The reaction mixture was heated under reflux under argon for 6 h, then cooled and acidified with 1 M HCl (5 mL), diluted with water (10 mL), and extracted with EtOAc (3 × 10 mL). The extract was dried and evaporated to give a yellow oil, which was subjected to flash chromatography. Elution (EtOAc/hexanes, 25:75) gave the quinoline **28** as a yellow solid (116 mg, 65%), which crystallized as yellow needles, mp 62–67 °C ($CHCl_3$/hexane). R_f 0.45 (EtOAc/hexanes, 1:2). IR ν_{max} cm^{-1}: 2242 (w, C≡N), 1740 (s, OC=O), 1720 (s, OC=O). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.20–8.50 (m, 2H, H5/8), 7.99 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, H6), 7.91 (ddd, J = 8.2, 7.0, 1.3, 1H, H7), 4.43–4.68 (m, 4H, 2 × CH_2O), 1.45–1.51 (m, 6H, 2 × Me). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 164.6 (C=O), 164.3 (C=O), 148.0 (C2 or C8a), 147.3 (C2 or C8a), 133.1 (ArH), 131.7 (ArH), 131.2 (ArH), 129.1 (Ar), 125.9 (Ar), 125.8 (ArH), 119.5 (Ar), 113.4 (C≡N), 63.5 (OCH_2), 63.2 (OCH_2), 14.3 (Me), 14.1 (Me). HRESIMS *m*/*z* found: 299.1029; $C_{15}H_{12}N_2O_4^+$ $[M+H]^+$ requires 299.1026.

2-Methyl-1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]quinoline-4-carboxylic acid (31). *N*-Methylmaleimide (**10**) (68 mg, 0.61 mmol) was added to a stirred mixture of K_2CO_3 (128 mg, 0.926 mmol) and *o*-nitrophenylacetonitrile (**1**) (95 mg, 0.59 mmol) in dry EtOH (20 mL). The reaction mixture was heated under reflux under N_2 for 2 h, then

cooled and acidified with 1 M HCl (10 mL), diluted with water (30 mL) and extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated to give a pale brown powder, which crystallized to afford the quinoline **31** as pale-yellow granules (76 mg, 51%), mp 177–179 °C (*i*-PrOH). R_f 0.15 (AcOH/MeOH/DCM, 3:5:92). IR ν_{max} cm^{-1}: 1705 (s, C=O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.16 (br s, 1H, OH), 8.77 (m, 1H), 8.25 (d, J = 8.3 Hz, 1H), 8.07 (ddd, J = 8.6, 6.9, 1.5 Hz, 1H), 7.96 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H), 3.09 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5 (C1 or C3), 166.0 (C=O), 165.9 (C=O), 149.8 (C9a), 147.0 (C4), 137.4 (C9b), 133.4 (C7), 130.8 (C8), 129.7 (C6), 124.4 (C9), 121.2 (C9a), 120.8 (C3a), 24.0 (NCH_3). HRESIMS m/z found: 257.0552; $C_{13}H_9N_2O_4^+$ $[M+H]^+$ requires 257.0557.

4-Cyanoquinoline-2-carboxylic acid (4-cyanoquinaldic acid) (32). Ethyl acrylate (**9**) (68 µL, 0.64 mmol) was added to a stirred mixture of K_2CO_3 (125 mg, 0.902 mmol) and *o*-nitrophenylacetonitrile (**1**) (97 mg, 0.60 mmol) in dry *n*-butanol (20 mL). The reaction mixture was then heated under reflux under N_2 for 24 h, then cooled and acidified with 1 M HCl (10 mL), diluted with water (30 mL) and extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated to give a brown residue (92 mg), which was triturated with minimal $CHCl_3$. The remaining brown solid was dissolved in EtOAc (20 mL) and extracted with half-saturated $NaHCO_3$ (3 × 20 mL). The basic extract was acidified with 4 M HCl (20 mL) and extracted with EtOAc (3 × 20 mL). The organic extract was dried and evaporated to give a brown solid, which was subjected to preparative TLC. Development (AcOH/MeOH/CH_2Cl_2, 3:5:92) afforded the quinaldic acid **32** as a tan solid (18 mg, 15%), mp 310 °C (dec.) [lit.[39] 214 °C (dec.)]. R_f 0.2 (AcOH/MeOH/DCM, 3:5:92). IR ν_{max} cm^{-1}: 2235 (w, C≡N), 1733 (s, C=O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (br s, 1H), 8.67 (br s, 1H), 8.22 (br s, 1H), 8.07 (br s, 1H), 7.97 (br s, 1H). ^{1}H NMR (500 MHz, CD_3OD) δ 8.48 (s, 1H, H3), 8.33 (br d, J = 8.3 Hz, 1H, H5 or H8), 8.22 (d, J = 8.1 Hz, 1H, H5 or H8), 7.94 (dd, J = 8.0, 6.5 Hz, 1H, H6 or H7), 7.85 (dd [app. t], $J_1 = J_2$ = 7.5 Hz, 1H, H6 or H7). ^{13}C NMR (125 MHz, CD_3OD) δ 170.6 (C=O), 161.5, 148.3, 132.5 (ArH), 131.7 (ArH), 131.1 (ArH), 127.2, 126.5 (ArH), 125.6 (ArH), 120.5, 116.5 (C≡N). HRESIMS m/z found: 199.0501; $C_{11}H_7N_2O_2^+$ $[M+H]^+$ requires 199.0502.

2-(1-Hydroxy-3-carbethoxy-1*H*-indol-2-yl)-*N*-methylacetamide (35). Method 1. NaH 60% dispersion in mineral oil (24 mg, 0.61 mmol) was added to dry EtOH (6 mL) with stirring. Ester **33** (191 mg, 0.913 mmol) was added portion-wise. No color change was observed. After 5 min, *N*-methylmaleimide (**10**) (59 mg, 0.53 mmol) was added to the solution. After 24 h TLC indicated the reaction was incomplete and a second portion of *N*-methylmaleimide (**10**) (51 mg, 0.46 mmol) was added and the reaction mixture was stirred for a further 24 h. The reaction mixture was acidified with 1 M HCl (10 mL), diluted with water (20 mL) and extracted with EtOAc (3 × 10 mL). The extract was dried and evaporated to yield a pale-brown oil, which was subjected to flash chromatography. Elution (EtOAc/hexanes, 1:4) and recrystallisation from DCM/hexanes gave the *N*-hydroxyindole **35** as a pale-yellow solid (114 mg, 45%), identical with the material described below.

Method 2. *N*-Methylmaleimide (**10**) (138 mg, 1.24 mmol) was added to a stirred mixture of K_2CO_3 (127 mg, 0.919 mmol) and ester **33** (124 mg, 0.595 mmol) in dry EtOH (20 mL). The reaction mixture was then heated under reflux under N_2 for 16 h, cooled to rt, and treated with additional *N*-methylmaleimide (**10**) (71 mg, 0.64 mmol) before being heated under reflux for a further 24 h. The reaction mixture was cooled, acidified with 1 M HCl (5 mL), diluted with water (30 mL) and extracted with EtOAc (3 × 20 mL). The extract was dried and evaporated to yield an orange-red oil, which was subjected to flash chromatography. Elution (EtOAc/hexanes, 25:75) gave the *N*-hydroxyindole **35** as a pale-yellow solid (94 mg, 57%), mp 180–184 °C (DCM/hexanes). R_f 0.2 (MeOH/DCM, 1:19). IR (KBr disc) ν_{max} cm^{-1}: 3433 (br. m, OH), 1674 (s, C=O), 1650 (s, C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (br. s, 1H, OH), 8.15 (d, J = 7.6 Hz, 1H, H4), 7.56 (d, J = 8.0 Hz, 1H, H7), 7.17–7.35 (m, 2H, H5/H6), 7.00 (br. s, 1H, NH), 4.40 (q, J = 7.0 Hz, 2H, CH_2O) 4.30 (s, 2H, H2'), 2.75 (d, J = 5.2 Hz, 3H, NMe), 1.47 (t, J = 7.0 Hz, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C=O), 166.9 (C=O), 137.0 (C2 or C7a), 133.0 (C2 or C7a), 123.0 (ArH), 122.1 (ArH),

122.0 (C3a), 121.2 (ArH), 109.3 (ArH), 99.2 (C3), 60.1 (OCH_2), 32.6 (C2'), 26.8 (NMe), 14.61 (Me). HRESIMS *m/z* found: 276.1118; $C_{14}H_{16}N_2O_4^{\bullet+}$ $[M+H]^{\bullet+}$ requires 276.1105.

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Supplementary Material

Skeleton-numbered structures of all compounds for NMR assignments, ^{1}H and ^{13}C NMR spectra of compounds **17**, **31** and **35**, and X-ray crystallographic data.

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