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

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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-nitrophensylacetic 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

DOI: [https://doi.org/10.24820/ark.5550190.p011.850](https://doi.org/10.24820/ark.5550190.p011.850)
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 $\alpha$-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)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>equiv. Mel</th>
<th>equiv. Base</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOH</td>
<td>5</td>
<td>5 K$_2$CO$_3$</td>
<td>40</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>EtOH</td>
<td>1</td>
<td>1 Cs$_2$CO$_3$</td>
<td>40</td>
<td>1</td>
<td>87</td>
</tr>
<tr>
<td>DMF</td>
<td>2</td>
<td>1.5 K$_2$CO$_3$</td>
<td>50</td>
<td>1.5</td>
<td>80</td>
</tr>
</tbody>
</table>

Michael additions were then explored (Table 2). In these reactions, the combination of K$_2$CO$_3$/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$_2$O. The relative configurations of the major isomers were determined by X-ray crystallography (Figure 1).

![Figure 1](image_url)

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

<table>
<thead>
<tr>
<th>Michael Acceptor</th>
<th>Adduct</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>9</td>
<td>14</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>78*</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>72*</td>
</tr>
<tr>
<td>12</td>
<td>17</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44:56 % mixture of diastereomers</td>
</tr>
</tbody>
</table>

# 1 (2 mmol), Michael acceptor (2 mmol), K₂CO₃ (2 mmol), EtOH (15–20 mL).
* Major diastereomer isolated after washing crude solid product with Et₂O.
† 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$_2$O$^{11}$ (Scheme 1). Given the structural similarities, we subjected Michael adduct 15 to treatment with K$_2$CO$_3$ 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 hydrolys 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).\textsuperscript{36,37}

![Scheme 3](image)

**Scheme 3.** Base-catalyzed cyclocondensations involving a nitro group – current (top) and closest precedents\textsuperscript{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, \textit{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 \(\beta\)-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$_2$CO$_3$ 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.\(^3\) 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\(_2\)CO\(_3\) (74 mg, 0.54 mmol) was added to a stirred solution of o-nitrophenylacetacetitrile (1) (18 mg, 0.11 mmol) in dry EtOH (2 mL) under argon. Mel (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\(_2\)CO\(_3\) (429 mg, 3.11 mmol) was added to a stirred solution of o-nitrophenylacetacetitrile (1) (323 mg, 1.99 mmol) in dry DMF (15 mL) under argon. Mel (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\(_2\)CO\(_3\) (765 mg, 2.35 mmol) was added to a stirred solution of o-nitrophenylacetacetitrile (1) (318 mg, 1.96 mmol) in dry EtOH (15 mL) under argon. Mel (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%). \(\delta\) (EtOAc/hexanes, 1:4). \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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\(_2\)CO\(_3\) (288 mg, 2.08 mmol) was added to a stirred solution of o-nitrophenylacetacetitrile (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%). Rf 0.2 (EtOAc/hexanes, 1:4).

IR (neat) v̇max cm⁻¹: 2244 (w, C=O), 1731 (s, C=O). ¹H NMR (400 MHz, CDCl₃) 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'''). ¹³C NMR (100 MHz, CDCl₃) 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; C₁₃H₁₅N₂O₄⁺ [M+H]⁺ requires 263.1026.

(S*)-2-[(R*)]-1-Methyl-2,5-dioxopyrrolidin-3-yl]-2-(2-nitrophenyl)acetonitrile (15). K₂CO₃ (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 a beige solid (424 mg, 78%), which crystallized as pale-yellow prisms, mp 163–166 °C (n-BuOH). Rf 0.15 (EtOAc/hexanes, 2:3). IR (KBr disc) v̇max cm⁻¹: 2247 (w, C=O), 1774 (m, C=O, asym), 1701 (s, C=O, sym). ¹H NMR (400 MHz, CDCl₃) 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'), 7.78 (m, 1H, H₂'''). ¹³C NMR (100 MHz, CDCl₃) 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; C₁₃H₁₅N₂O₄⁺ [M+H]⁺ requires 274.0822.

(S*)-2-[(2-Nitrophenyl)-2-[(S*)]-3-oxocyclohexyl]acetonitrile (16). K₂CO₃ (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). Rf 0.3 (EtOAc/hexanes, 2:3). IR (KBr disc) v̇max cm⁻¹: 2238 (w, C=O), 1702 (s, C=O). ¹H NMR (400 MHz, CDCl₃) 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, 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). ¹³C NMR (100 MHz, CDCl₃) 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; C₁₃H₁₄N₃O₃⁺ [M+H]⁺ requires 258.0999.

Diethyl 2-[cyano-(2-nitrophenyl)methyl]succinate (17). K₂CO₃ (638 mg, 4.62 mmol) was added to a stirred solution of o-nitrophenylacetanilide (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 11⁰:14⁰ mixture of diastereomers. Rf 0.45 (EtOAc/hexanes, 1:2). v̇max cm⁻¹: 1733 (s, C=O), 2247 (w, C=O). ¹H NMR (400 MHz, CDCl₃) 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, H₁''), 4.00–4.19 (m, 4H, 4 × OCH₂), 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, CH₃), 1.201* (t, J = 7.2 Hz, 3H, CH₃), 1.196* (t, J = 7.2 Hz, 3H, CH₃).
= 7.2 Hz, 3H, CH₃), 1.13₁ (t, J = 7.2 Hz, 3H, CH₃). ¹³C NMR (101 MHz, CDCl₃) 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 (CH₂O), 61.8 (CH₂O), 61.4 (CH₂O), 61.3 (CH₂O), 44.8 (C2), 44.6 (C2), 35.53 (C2'), 35.46 (C2'), 35.45 (C2'), 35.41 (C3), 33.4 (C3), 14.2 (CH₃), 14.1 (CH₃), 14.01 (CH₃), 13.98 (CH₃). HRESIMS m/z found: 335.1245; C₁₆H₁₅N₂O₆⁺ [M+H]⁺ requires 335.1238.

**Ethyl 1-imino-2-methyl-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinoline-4-carboxylate (21).** K₂CO₃ (50 mg, 0.37 mmol) was added to a stirred solution of 2-(2-nitrophenyl)acetoniitride 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 (CHCl₃/hexane). Rᵣ 0.25 (EtOAc/hexanes, 1:2). IR νₘₐₓ cm⁻¹: 1752 (s, OC=O), 1739 (s, NC=O), 1654 (C=N). ¹H NMR (400 MHz, CDCl₃) 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], J₁ = J₂ = 7.6 Hz, 1H, H7 or H8), 4.61 (q, J = 7.1 Hz, 2H, CH₂), 3.24 (s, 3H, NMe), 1.49 (t, J = 7.2 Hz, 3H, Me). ¹³C NMR (101 MHz, CDCl₃) δ 165.0 (CO₂ or C3), 164.6 (CO₂ 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 (OCH₂), 23.9 (NMe), 14.3 (Me). HRESIMS m/z found: 284.1036; C₁₅H₁₄N₃O₃⁺ [M+H]⁺ requires 284.1030.

**Ethyl 2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinoline-4-carboxylate (22).** K₂CO₃ (55 mg, 0.40 mmol) was added to a stirred solution of 2-(2-nitrophenyl)acetoniitride 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 (CHCl₃/hexane). Rᵣ 0.45 (EtOAc/hexanes, 1:2). IR νₘₐₓ cm⁻¹: 1738 (s, OC=O), 1714 (s, NC=O). ¹H NMR (400 MHz, CDCl₃) δ 8.91 (d, J = 8.3 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, CH₂O), 3.25 (s, 3H, NMe), 1.50 (t, J = 7.1 Hz, 3H, Me). ¹³C NMR (101 MHz, CDCl₃) 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 (CH₂O), 24.4 (NMe), 14.24 (Me). HRESIMS m/z found: 307.0697; C₁₅H₁₂N₂NaO₄⁺ [M+Na⁺]⁺ requires 307.0689.

**Diethyl 4-cyanoquinoline-2,3-dicarboxylate (28).** K₂CO₃ (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 (CHCl₃/hexane). Rᵣ 0.45 (EtOAc/hexanes, 1:2). IR νₘₐₓ cm⁻¹: 2242 (w, C=N), 1740 (s, OC=O), 1720 (s, OC=O). ¹H NMR (400 MHz, CDCl₃) 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 × CH₂O), 1.45–1.51 (m, 6H, 2 × Me). ¹³C NMR (101 MHz, CDCl₃) 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 (OCH₂), 63.2 (OCH₂), 14.3 (Me), 14.1 (Me). HRESIMS m/z found: 299.1029; C₁₃H₁₂N₂O₄⁺ [M+H]⁺ requires 299.1026.

**2-Methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinoline-4-carboxylic acid (31).** N-Methylmaleimide (10) (68 mg, 0.61 mmol) was added to a stirred mixture of K₂CO₃ (128 mg, 0.926 mmol) and α-nitrophenylacetoniitride (1) (95 mg, 0.59 mmol) in dry EtOH (20 mL). The reaction mixture was heated under reflux under N₂ 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 (/-PrOH). Rf 0.15 (AcOH/MeOH/DCM, 3:5:92). IR v_max cm⁻¹: 1705 (s, C=O). ¹H NMR (400 MHz, DMSO-d₆) δ 14.16 (br s, 1H, OH), 8.77 (m, 1H), 8.25 (d, J = 8.3 Hz, 1H), 8.07 (dd, J = 8.6, 6.9, 1.5 Hz, 1H), 7.96 (dd, J = 8.4, 6.9, 1.2 Hz, 1H), 3.09 (s, 3H, NCH₃). ¹³C NMR (100 MHz, DMSO-d₆) 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 (NCH₃). HRESIMS m/z found: 257.0552; C₁₃H₃N₂O₄⁺ [M+H]^+ requires 257.0557.

4-Cyanoquinaline-2-carboxylic acid (4-cyanoquinaldic acid) (32). Ethyl acrylate (9) (68 μL, 0.64 mmol) was added to a stirred mixture of K₂CO₃ (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 N₂ 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 CHCl₃. The remaining brown solid was dissolved in EtOAc (20 mL) and extracted with half-saturated NaHCO₃ (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/CH₂Cl₂, 3:5:92) afforded the quinaldic acid 32 as a tan solid (18 mg, 15%), mp 310 °C (dec.) [lit. 39 214 °C (dec.)]. Rf 0.2 (AcOH/MeOH/DCM, 3:5:92). IR v_max cm⁻¹: 2235 (w, C=N), 1733 (s, C=O). ¹H NMR (400 MHz, DMSO-d₆) 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). ¹H NMR (500 MHz, CD₃OD) 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], J₁ = J₂ = 7.5 Hz, 1H, H6 or H7). ¹³C NMR (125 MHz, CD₃OD) 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; C₁₁H₉N₂O⁺ [M+H]^+ requires 199.0502.

2-(1-Hydroxy-3-carbethoxy-1H-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. Euton (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 K₂CO₃ (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 N₂ 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). Rf 0.2 (MeOH/DCM, 1:19). IR (KBr disc) v_max cm⁻¹: 3433 (br. m, OH), 1674 (s, C=O), 1650 (s, C=O). ¹H NMR (400 MHz, CDCl₃) 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, CH₂O) 4.30 (s, 2H, H2'), 2.75 (d, J = 5.2 Hz, 3H, NMe₁), 1.47 (t, J = 7.0 Hz, Me). ¹³C NMR (100 MHz, CDCl₃) 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 (OCH2), 32.6 (C2'), 26.8 (NMe), 14.61 (Me). HRESIMS m/z found: 276.1118; C14H16N2O4 [M+H]+ requires 276.1105.

Acknowledgements

We thank Drs Lindsay Byrne and Gareth Nealon, and Dr Tony Reeder, from the Centre for Microscopy, Characterization and Analysis, UWA, for assistance with NMR spectroscopy, and mass spectrometry, respectively. Prof. Christina Chai and Dr Nguyen Tuan Minh are gratefully acknowledged for co-supervision of SYJ at NUS. Thanks also to colleagues from the Institute of Sustainability for Chemicals, Energy and Environment, Singapore, Chia Sze Chen and Dr Venugopal Rao, and Chen Qian Han, for assistance with X-ray crystallography and acquisition of mass spectra, respectively.

Supplementary Material

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

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