CONCISE SYNTHESIS OF AZAFLUORENONE AND ITS APPLICATION TO INDENO[1,2-c]ISOQUINOLONE

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We dedicate this paper to Professor Dr. Kiyoshi Tomioka on the celebration of his 70th birthday.

Abstract – The total synthesis of azafluorenone alkaloid, an onychine isolated from Onychopetalum amazonicum, was newly achieved by constructing an azafluorene framework using thermal electrocyclization of the aza 6π-electron system. This methodology was applied for the synthesis of indeno[1,2-c]isoquinolones as an attractive scaffold for developing anticancer agents.

INTRODUCTION

Camptothecin (1) is a cytotoxic quinoline alkaloid; its derivatives, irinotecan and topotecan, are used clinically as anticancer drugs. However, the lactone hydrolysis of 1 at physiological pH values results in the loss of its biological activity.1 Much research has been performed to evaluate the synthesis and
activity of its analogs, and the indeno[1,2-c]isoquinolone (tetracyclic azafluorenone) derivative NSC 314622 (2) is considered as a potential anticancer agent with cytotoxic and topoisomerase I (Topo1) inhibitory properties.\textsuperscript{2}

Conversely, onychine (3) is an azafluorenone alkaloid that was isolated from \textit{Onychopetalum} in 1976,\textsuperscript{3} and has also been reported to exhibit potent antimicrobial activity against multiple bacterial strains.\textsuperscript{4} The first total synthesis of 3 was achieved by Prostakov and coworkers.\textsuperscript{5a} In 2010, Kraus and coworkers reported the total synthesis of 3 using an intramolecular Heck cyclization reaction of 2-bromoaryl 3-pyridyl ketones.\textsuperscript{5l} Moreover, the synthesis of 3 based on the Pd-catalyzed cross-coupling aryloboronic acid with bromonicotinate has been reported by Snieckus and coworkers.\textsuperscript{5d} Padwa and coworkers achieved its synthesis using the cyclization–deprotonation–cycloaddition cascade of imidosulfoxide.\textsuperscript{5i} Recently, Marquise and coworkers described the total synthesis of 3 using Pd-catalyzed Suzuki coupling–intramolecular arylation auto-tandem reactions.\textsuperscript{5a} Till date, the total synthesis of 3 (including formal synthesis) has been reported by 17 research groups.\textsuperscript{5} Many synthetic studies are being performed to obtain a new bioactive lead compounds for anticancer agents. Based on the above considerations, azafluorenones and indenoisoquinolones are considered as attractive scaffolds for developing anticancer agents.

We have performed the synthesis of bioactive-fused nitrogen-containing heteroaromatic compounds including natural products and search studies on anticancer agents using them.\textsuperscript{2,8} The total synthesis of bioactive-fused heteroaromatic compounds via the construction of fused pyridine ring systems using a conventional and/or microwave (MW)-assisted thermal electrocyclization of an aza 6π-electron system been reported.\textsuperscript{8}

In this study, an alternative synthesis of 3 by constructing azafluorene based on thermal electrocyclization of a 1-aza 6π electron system is described. Furthermore, this methodology is applied to the synthesis of indeno[1,2-c]isoquinolones.

**RESULTS AND DISCUSSION**

Scheme 1 illustrates our retrosynthetic strategy for synthesizing azafluorenone and its derivatives. We envisaged that azafluorenone 6 could be derived from azafluorene 7 via oxidation. The azafluorene 7 might be obtained via thermal electrocyclization of the oxime 8 (as a 1-azahexatriene system), which was derived via cleavage of the 4,4a-bond of the azafluorene framework. The oxime 8 can be easily obtained from the known indene 9.
As shown in Scheme 1, 2-(trifluoromethylsulfonyloxy)indene (10) (the starting material) was prepared according to Manabe’s procedure. 2-Alkenylindene 11 was obtained from triflate 10 and 3-(tributylstannyl)but-2-en-1-ol via the Stille reaction with 85% yield. Next, conversion from alcohol to oxime was performed using Fukuyama’s procedure. The treatment of 11 with O-TBS-N-tosylhydroxylamine via the Mitsunobu reaction, followed by the desilylative elimination of p-toluenesulfinate via treatment with CsF, resulted in 76% yield of oxime 13 (two-step yield).

Subsequently, the synthesis of azafluorene 14 from oxime 13 via electrocyclization was investigated. In addition, the reaction conditions were optimized (solvent type, temperature, and microwave parameters) (Table 1).

First, the heating of 13 in 1,2-dichlorobenzene at 180 °C for 10 min (monitoring the disappearance of oxime 13 via TLC) led to 14 being obtained with 41% yield (run 1). Subsequently, this reaction was performed in the same solvent at 150 °C, 120 °C, and 80 °C until oxime 13 disappeared, and the heating
of 13 in the same solvent at 120 °C resulted in 14 with 60% yield (runs 2–4). Second, the use of bromobenzene and toluene as solvents (instead of 1,2-dichlorobenzene) was investigated in relation to cyclization conditions (runs 5 and 6). Heating of 13 at 120 °C in toluene afforded 14 with 64% yield (run 6).

Table 1. Synthesis of 14 via thermal electrocyclization

<table>
<thead>
<tr>
<th>Run</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>MW*</th>
<th>Time (h)</th>
<th>Yield (%) of 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,2-dichlorobenzene</td>
<td>180</td>
<td>−</td>
<td>10 min</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>1,2-dichlorobenzene</td>
<td>150</td>
<td>−</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>1,2-dichlorobenzene</td>
<td>120</td>
<td>−</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>1,2-dichlorobenzene</td>
<td>80</td>
<td>−</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>bromobenzene</td>
<td>120</td>
<td>−</td>
<td>1.5</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>120</td>
<td>−</td>
<td>12</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>1,2-dichlorobenzene</td>
<td>120</td>
<td>+</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>bromobenzene</td>
<td>120</td>
<td>+</td>
<td>1.5</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>toluene</td>
<td>120</td>
<td>+</td>
<td>5</td>
<td>42</td>
</tr>
</tbody>
</table>

*MW*: microwave.

Next, cyclization under MW irradiation was examined and compared with conventional conditions (runs 7–9). When the reaction was performed in 1,2-dichlorobenzene at 120 °C for 3 h under MW irradiation, 14 was obtained with 70% yield (run 7). From the above results, it can be seen that heating at 120 °C in 1,2-dichlorobenzene under MW irradiation was the best condition for the completion of reaction (run 7).

Finally, the oxidation of 14 with active MnO<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> afforded 3 with 80% yield (Scheme 3). As described above, we were able to establish the construction methodology of the azafluorenone framework.
In addition, we applied the above procedure to the synthesis of indeno[1,2-c]isoquinolines (tetracyclic azafluorenone). As shown in Scheme 4, the Suzuki–Miyaura reaction of indene 10 with phenylboronic acids 15a and 15b afforded 2-arylindenes 16a and 16b with 65% and 54% yields, respectively. Subsequently, the treatment of 16a and 16b with hydroxylamine afforded oximes 17a and 17b with 78% and 90% yields, respectively.

### Table 2. Synthesis of indeno[1,2-c]isoquinoline via thermal electrocyclization

<table>
<thead>
<tr>
<th>Run</th>
<th>Comd. No.</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>MW*</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17a</td>
<td>1,2-dichlorobenzene</td>
<td>180</td>
<td>−</td>
<td>15</td>
<td>19a</td>
</tr>
<tr>
<td>2</td>
<td>17a</td>
<td>1,2-dichlorobenzene</td>
<td>180</td>
<td>+</td>
<td>5</td>
<td>19a</td>
</tr>
<tr>
<td>3</td>
<td>17a</td>
<td>diphenyl ether</td>
<td>260</td>
<td>−</td>
<td>1.5</td>
<td>19a</td>
</tr>
<tr>
<td>4</td>
<td>17b</td>
<td>diphenyl ether</td>
<td>260</td>
<td>−</td>
<td>5</td>
<td>19b</td>
</tr>
<tr>
<td>5</td>
<td>18a</td>
<td>diphenyl ether</td>
<td>260</td>
<td>−</td>
<td>45 min</td>
<td>19a</td>
</tr>
<tr>
<td>6</td>
<td>18b</td>
<td>diphenyl ether</td>
<td>260</td>
<td>−</td>
<td>2</td>
<td>19b</td>
</tr>
</tbody>
</table>

*MW: microwave.
Next, to synthesize the indenoisoquinoline, oxime 17a was heated at 120 °C in 1,2-dichlorobenzene under MW irradiation (Table 1, run 7); however, the cyclization reaction did not proceed. Therefore, the optimum conditions for this reaction were further investigated (Table 2). First, 17a was reacted at 180 °C in 1,2-dichlorobenzene to afford only traces of indenoisoquinoline 19a (run 1). The same reaction was performed under MW irradiation (run 2), giving a slightly improved yield (32%) compared with run 1. Next, diphenyl ether was used as the solvent. The reaction was carried out without MW irradiation because the MW generator could not be heated to 260 °C. When 17a was heated in diphenyl ether at 260 °C (run 3), the yield of 19a was improved (62%) and the reaction time was decreased. Similarly, heating of 17b gave 2,3-dimethoxyindenoisoquinoline 19b in 50% yield (run 4). Furthermore, to improve the yield, the cyclization reaction using oxime ether instead of oxime was examined with reference to our previous work. As shown in Scheme 4, 16a and 16b were treated with O-methylhydroxylamine to give oxime ethers 18a and 18b in 90% and 88% yields, respectively. When oxime ethers 18a and 18b were heated at the same temperature, indenoisoquinolines 19a and 19b were obtained in 75% and 77% yields, respectively; moreover, the reaction times were decreased (run 3 vs. run 5 and run 4 vs. run 6). In this case, a high temperature was required for synthesis of the indenoisoquinolines, and oxime ether was a more suitable precursor than oxime. Finally, the oxidation of indenoisoquinolines 19a and 19b with active MnO₂ in CH₂Cl₂ afforded indenoisoquinolones 20a and 20b with 94% and 60% yields, respectively (Scheme 5).

Again, we applied the process to the synthesis of the indenoisoquinolone (tetracyclic azafluorenone) framework. The structures of the azafluorenones and indenoisoquinolones were supported by ¹H-NMR, ¹³C-NMR, and mass spectra.

CONCLUSIONS
In conclusion, the total synthesis of the azafluorenone alkaloid, onychine (3), was newly achieved by constructing an azafluorene framework using electrocyclization of the 1-aza 6π-electron system as the key reaction. The target compound 3 was obtained in five steps in 36.2% overall yield from 2-(trifluoromethylsulfonyloxy)indene (10). In addition, this methodology could be applied to the
synthesis of indeno[1,2-c]isoquinolones (tetracyclic azafluorenone) as an attractive scaffold for developing anticancer agents. The biologic activity of azafluorenones, indenoisoquinolones, and their derivatives is under investigation.

**EXPERIMENTAL**

**General Methods:** All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin layer chromatography was performed with Silica gel 60PF254 (Merck). Silica gel column chromatography was performed with Silica gel 60 (70–230 mesh, Kanto Chemical Co. Lit.). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a JEOL AL-300. Infrared spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. Low and high-resolution mass spectra were recorded on JEOL JMS-700 spectrometers by direct inlet system. The reaction of microwave (MW) irradiation was carried out by Discover of CEM Co. Ltd. with 2450 MHz.

**3-(Inden-2-yl)but-2-en-1-ol (11):** A solution of 3-(tributylstannyl)but-2-en-1-ol (273 mg, 0.76 mmol) in DMF (5 mL) was added to the mixture of triflate 10 (100 mg, 0.38 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ (39 mg, 0.038 mmol), and AsPh$_3$ (23 mg, 0.076 mmol) in DMF (5 mL). After being stirred at rt for 24 h, the mixture was quenched with an aqueous KF solution (30%), and then the mixture was stirred at rt for 30 min. The mixture was filtered through a Celite pad, and extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc-hexane (3:7, v/v) as an eluent to give 2-alkenylindene 11 (60 mg, 85%) as yellow solid. mp 85–86 °C (EtOAc). $^1$H-NMR (CDCl$_3$) δ: 7.44 (1H, d, J = 7.6 Hz), 7.38 (1H, d, J = 7.6 Hz), 7.27 (1H, t, J = 7.6 Hz), 7.17 (1H, t, J = 7.6 Hz), 6.75 (1H, s), 5.68 (1H, t, J = 6.6 Hz), 4.41 (2H, d, J = 6.6 Hz), 3.56 (2H, s), 2.06 (3H, s), 1.43 (1H, br s). $^{13}$C-NMR (CDCl$_3$) δ: 145.8, 144.5, 143.2, 134.0, 130.5, 128.1, 126.6, 124.8, 123.5, 121.1, 60.4, 40.8, 24.0. MS m/z: 186 (M$^+$). HRMS (EI) calcd for C$_{13}$H$_{14}$O 186.1045; found 186.1036.

**3-(Inden-2-yl)but-2-enal oxime (13):** DEAD (40% in toluene, 0.15 mL, 0.32 mmol) was added slowly to a mixture of 2-alkenylindole 11 (150 mg, 0.81 mmol), O-TBS-N-tosylhydroxylamine (218 mg, 0.72 mmol), and PPh$_3$ (424 mg, 1.62 mmol) in toluene (6 mL) and THF (2 mL) at 0 °C. After stirring at the temperature for 10 min, the solvent was evaporated to half an amount. The mixture was dissolved in MeCN (10 mL) and CsF (245 mg, 1.62 mmol) was added. After stirring at rt for 1 h, saturated NH$_4$Cl aq. was added and extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc-hexane (3:7, v/v) as an eluent to give the oxime 13 (123 mg, 76%) as yellow solid. $^1$H-NMR (CDCl$_3$) δ: 8.23 (2/3H, d, J =
10.4 Hz), 7.61 (1/3H, d, J = 10.4 Hz), 7.46 (1/3H, d, J = 7.2 Hz), 7.42 (2/3H, d, J = 7.2 Hz), 7.41 (1H/3, d, J = 7.2 Hz), 7.36 (2/3H, d, J = 7.2 Hz), 7.30 (1/3H, t, J = 7.2 Hz), 7.27 (1/3H, t, J = 7.2 Hz), 7.23 (2/3H, d, J = 7.2 Hz), 7.19 (2/3H, d, J = 7.2 Hz), 7.00 (2/3H, s), 6.98 (1/3H, s), 6.72 (1/3H, d, J = 10.4 Hz), 6.43 (2/3H, d, J = 10.4 Hz), 3.64 (4/3H, s), 3.63 (2/3H, s), 2.20 (3/3H, s), 2.18 (6/3H, s), one proton (OH) was not observed. MS m/z: 199 (M+). HRMS (EI) calcd for C_{13}H_{13}NO 199.0997; found 199.0988.

1-Methyl-4-azafluorene (14): The solution of the oxime 13 (40 mg, 0.21 mmol) in 1,2-dichlorobenzene (3 mL) was heated under microwave irradiation at 120 °C for 3 h. After removal of solvent, the residue was purified by column chromatography using EtOAc/hexane (2:8, v/v) as an eluent to give the azafluorene 14 (27 mg, 70%) as orange solid. mp 82–83 °C (EtOAc).

1H-NMR (CDCl₃) δ: 8.47 (1H, d, J = 4.8 Hz), 8.09 (1H, d, J = 7.5 Hz), 7.58 (1H, d, J = 7.5 Hz), 7.45 (1H, t, J = 7.5 Hz), 7.40 (1H, t, J = 7.5 Hz), 7.01 (1H, d, J = 4.8 Hz), 3.77 (2H, s), 2.42 (3H, s). 13C-NMR (CDCl₃) δ: 159.8, 148.3, 143.3, 143.1, 141.1, 136.0, 128.4, 127.2, 125.1, 122.4, 120.9, 33.2, 18.5. MS m/z: 181 (M+). HRMS (EI) calcd for C_{13}H_{11}N 181.0891; found 181.0902.

Onychine (3): A suspension of the azafluorene 14 (45 mg, 0.25 mmol) and active MnO₂ (392 mg, 2.5 mmol) in CH₂Cl₂ (10 mL) was stirred at rt for 15 h. The reaction mixture was filtrated through a Celite pad. The filtrate was evaporated in vacuo. The residue was purified by column chromatography using EtOAc-hexane (3:7, v/v) as an eluent to give onychine (3) (39 mg, 80%) as yellow solid. mp 124–125 °C (EtOAc) (Lit. mp 125–127 °C). IR (ATR) ν: 1701, 1566 cm⁻¹. 1H-NMR (CDCl₃) δ: 8.43 (1H, d, J = 5.3 Hz), 7.84 (1H, d, J = 7.5 Hz), 7.70 (1H, d, J = 7.5 Hz), 7.59 (1H, t, J = 7.5 Hz), 7.43 (1H, t, J = 7.5 Hz), 6.97 (1H, d, J = 5.3 Hz), 2.64 (3H, s). 13C-NMR (CDCl₃) δ: 193.2, 165.2, 152.8, 147.5, 143.0, 135.0, 134.9, 130.8, 125.9, 125.8, 123.7, 120.7, 17.3. MS m/z: 195 (M+). HRMS (EI) calcd for C_{13}H₉NO 195.0684; found 195.0699.

2-(Inden-2-yl)benzaldehyde (16a): A mixture of triflate 10 (140 mg, 0.52 mmol), phenylboronic acid 15a (117 mg, 0.78 mmol), Ba(OH)₂ (265 mg, 0.78 mmol), P(o-tolyl)₃ (30 mg, 0.1 mmol), and Pd(OAc)₂ (12 mg, 0.052 mmol) in DME/H₂O (4.3/0.7 mL) was stirred at 50 °C for 2 h. The reaction mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na₂SO₄, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc-hexane (1:9, v/v) as an eluent to give the arylindene 16a (74 mg, 65%) as orange oil. IR (ATR) ν: 1682 cm⁻¹. 1H-NMR (CDCl₃) δ: 10.26 (1H, s), 7.98 (1H, d, J = 8.0 Hz), 7.63 (1H, t, J = 8.0 Hz), 7.50–7.54 (2H, m), 7.42–7.47 (2H, m), 7.34 (1H, t, J = 7.8 Hz), 7.24–7.29 (1H, m), 6.85 (1H, s), 3.87 (2H, s). 13C-NMR (CDCl₃) δ: 192.2, 144.5, 143.4, 142.8, 140.8, 135.3, 134.6, 133.4, 129.4, 128.3, 127.5, 126.9, 125.6, 123.8, 121.5, 41.9. MS m/z: 220 (M+). HRMS (EI) calcd for C_{16}H₁₂O 220.0888; found 220.0856.
2-(Inden-2-yl)-4,5-dimethoxybenzaldehyde (16b): The same procedure as above was carried out using phenylboronic acid 15b (100 mg, 0.76 mmol) to give arylindene 16b (114 mg, 54%) as white solid. mp 187–188 °C (EtOAc). IR (ATR) ν: 1658 cm⁻¹. ¹H-NMR (CDCl₃) δ: 10.13 (1H, s), 7.53 (1H, d, J = 7.2 Hz), 7.52 (1H, s), 7.46 (1H, d, J = 7.2 Hz), 7.34 (1H, t, J = 7.2 Hz), 7.26 (1H, t, J = 7.2 Hz), 6.90 (1H, s), 6.85 (1H, s), 3.99 (3H, s), 3.98 (3H, s), 3.85 (2H, s). ¹³C-NMR (CDCl₃) δ: 190.6, 153.3, 148.6, 144.4, 143.2, 142.2, 136.4, 134.7, 127.9, 126.8, 125.4, 123.7, 121.3, 110.9, 109.1, 56.1, 56.0, 42.3. MS m/z: 280 (M⁺). HRMS (EI) calcd for C₁₈H₁₆O₃ 280.1099; found 280.1078.

2-(Inden-2-yl)benzaldehyde oxime (17a): A mixture of arylindene 16a (100 mg, 0.43 mmol), NH₂OH·HCl (59 mg, 0.86 mmol), and AcONa (71 mg, 0.86 mmol) in EtOH (5 mL) was stirred at rt for 2 h. After removal of solvent, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na₂SO₄, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc/hexane (3:7, v/v) as an eluent to give the oxime 17a (79 mg, 78%) as white solid. mp 187–188 °C (EtOAc). ¹H-NMR (CDCl₃) δ: 8.42 (1H, s), 7.84 (1H, d, J = 7.2 Hz), 7.59 (1H, br s), 7.50 (1H, d, J = 7.2 Hz), 7.42–7.46 (3H, m), 7.29–7.36 (2H, m), 7.24 (1H, t, J = 7.2 Hz), 6.84 (1H, s), 3.79 (2H, s). ¹³C-NMR (CDCl₃) δ: 150.3, 144.9, 144.5, 143.2, 137.3, 133.0, 129.9, 129.7, 128.9, 127.5, 127.2, 126.7, 125.2, 123.7, 121.4, 42.1. MS m/z: 235 (M⁺). HRMS (EI) calcd for C₁₆H₁₃NO 235.0997; found 235.0976.

2-(Inden-2-yl)-4,5-dimethoxybenzaldehyde oxime (17b): The same procedure as above was carried out using arylindene 16b (40 mg, 0.14 mmol) to give the oxime 17b (37 mg, 90%) as white solid. mp 165–167 °C (EtOAc). ¹H-NMR (CDCl₃) δ: 8.39 (1H, s), 8.10 (1H, br s), 7.48 (1H, d, J = 7.4 Hz), 7.43 (1H, d, J = 7.4 Hz), 7.37 (1H, s), 7.31 (1H, t, J = 7.4 Hz), 7.22 (1H, t, J = 7.4 Hz), 6.87 (1H, s), 6.78 (1H, s), 3.94 (3H, s), 3.93 (3H, s), 3.76 (2H, s). ¹³C-NMR (CDCl₃) δ: 150.3, 149.9, 148.5, 144.9, 144.2, 143.0, 132.5, 131.1, 126.8, 125.0, 123.6, 122.5, 121.3, 111.2, 108.7, 56.0, 56.0, 42.4. MS m/z: 295 (M⁺). HRMS (EI) calcd for C₁₈H₁₇NO₃ 295.1208; found 295.1222.

2-(Inden-2-yl)-4,5-dimethoxybenzaldehyde O-methyloxime (18a): A mixture of arylindene 16a (146 mg, 0.43 mmol), NH₂OMe·HCl (60 mg, 0.86 mmol), and AcONa (71 mg, 0.86 mmol) in EtOH (5 mL) was stirred at rt for 2 h. After removal of solvent, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na₂SO₄, and evaporated in vacuo. The residue was purified by column chromatography using EtOAc/hexane (3:7, v/v) as an eluent to give the oxime ether 18a (96 mg, 90%) as white solid. mp 68–69 °C (EtOAc). ¹H-NMR (CDCl₃) δ: 8.35 (1H, s), 7.89 (1H, d, J = 7.7 Hz), 7.49 (1H, d, J = 7.7 Hz), 7.40–7.45 (3H, m), 7.28–7.35 (2H, m), 7.20–7.25 (1H, m), 6.82 (1H, s), 3.99 (3H, s), 3.77 (2H, s). ¹³C-NMR (CDCl₃) δ: 148.4, 144.9, 144.5, 143.2, 137.1, 132.9, 129.9, 129.5, 128.8, 127.4, 127.1, 126.7, 125.1, 123.6, 121.3, 61.9, 42.3. MS m/z: 249 (M⁺). HRMS (EI) calcd for C₁₇H₁₅NO 249.1154; found 249.1143.
2-(Inden-2-yl)-4,5-dimethoxybenzaldehyde \( O \)-methyloxime (18b): The same procedure as above was carried out using arylindene 16b (180 mg, 0.58 mmol) to give the oxime ether 18b (158 mg, 88%) as yellow solid. mp 138–140 °C (EtOAc). \( ^1H \)-NMR (CDCl\(_3\)) \( \delta \): 8.31 (1H, s), 7.48 (1H, d, \( J = 7.6 \) Hz), 7.43 (1H, d, \( J = 7.6 \) Hz), 7.41 (1H, s), 7.30 (1H, t, \( J = 7.6 \) Hz), 7.21 (1H, t, \( J = 7.6 \) Hz), 6.85 (1H, s), 6.76 (1H, s), 3.98 (3H \( \times 2 \), s), 3.93 (3H, s), 3.75 (2H, s). \( ^{13}C \)-NMR (CDCl\(_3\)) \( \delta \): 150.1, 148.4, 148.0, 144.8, 144.2, 143.0, 132.3, 130.9, 126.6, 124.9, 123.5, 122.6, 121.1, 111.1, 108.6, 61.8, 55.9, 55.8, 42.3. MS m/z: 309 (M\(^+\)). HRMS (EI) calcd for C\(_{19}\)H\(_{19}\)NO\(_3\) 309.1365; found 309.1334.

Indeno[1,2-c]isoquinoline (19a): The solution of the oxime ether 18a (40 mg, 0.17 mmol) in diphenyl ether (3 mL) was heated at 260 °C for 45 min. After removal of solvent, the residue was purified by column chromatography using EtOAc/hexane (2:8, v/v) as an eluent to give the indenoisoquinoline 19a (28 mg, 75%) as yellow solid. mp 157–158 °C (EtOAc). \( ^1H \)-NMR (CDCl\(_3\)) \( \delta \): 9.23 (1H, s), 8.12 (1H, d, \( J = 7.4 \) Hz), 8.01 (1H, d, \( J = 8.3 \) Hz), 7.91 (1H, d, \( J = 8.3 \) Hz), 7.70 (1H, t, \( J = 7.4 \) Hz), 7.60 (1H, d, \( J = 7.4 \) Hz), 7.53 (1H, t, \( J = 7.4 \) Hz), 7.47 (1H, t, \( J = 7.4 \) Hz), 7.37 (1H, t, \( J = 7.4 \) Hz), 4.06 (2H, s). \( ^{13}C \)-NMR (CDCl\(_3\)) \( \delta \): 154.0, 152.5, 142.8, 142.0, 133.5, 131.2, 130.7, 128.8, 127.5, 127.2, 126.2, 125.0, 124.9, 123.1, 120.2, 33.1. MS m/z: 217 (M\(^+\)). HRMS (EI) calcd for C\(_{16}\)H\(_{11}\)N 217.0891; found 217.0883.

2,3-Dimethoxyindeno[1,2-c]isoquinoline (19b): The same procedure as above was carried out using the oxime ether 18b (55 mg, 0.18 mmol) to give the indenoisoquinoline 19b (38 mg, 77%) as yellow solid. mp 218–220 °C (EtOAc). \( ^1H \)-NMR (CDCl\(_3\)) \( \delta \): 9.05 (1H, s), 8.09 (1H, d, \( J = 7.6 \) Hz), 7.61 (1H, d, \( J = 7.6 \) Hz), 7.47 (1H, t, \( J = 7.6 \) Hz), 7.37 (1H, t, \( J = 7.6 \) Hz), 7.28 (1H, s), 7.12 (1H, s), 4.09 (3H, s), 4.05 (3H, s), 4.04 (2H, s); \( ^{13}C \)-NMR (CDCl\(_3\)) \( \delta \): 153.2, 152.9, 149.6, 142.4, 142.2, 130.2, 130.1, 127.1, 124.9, 123.5, 123.4, 119.9, 106.3, 101.5, 56.0, 55.9, 33.1. MS m/z: 277 (M\(^+\)). HRMS (EI) calcd for C\(_{18}\)H\(_{15}\)NO\(_2\) 277.1103; found 277.1111.

Indeno[1,2-c]isoquinolin-11-one (20a): A suspension of the indenoisoquinoline 19a (18 mg, 0.053 mmol) and active MnO\(_2\) (22 mg, 0.25 mmol) in CH\(_2\)Cl\(_2\) (3 mL) was stirred at rt for 15 h. The reaction mixture was filtrated through a Celite pad. The filtrate was evaporated in vacuo. The residue was purified by column chromatography using EtOAc/hexane (1:1, v/v) as an eluent to give the indenoisoquinolone 20a (12 mg, 94%) as white solid. mp 218–220 °C (EtOAc). \( ^1H \)-NMR (CDCl\(_3\)) \( \delta \): 9.27 (1H, s), 8.78 (1H, d, \( J = 8.3 \) Hz), 7.95 (1H, d, \( J = 8.3 \) Hz), 7.76–7.82 (2H, m), 7.67 (1H, d, \( J = 7.0 \) Hz), 7.51–7.58 (2H, m), 7.36 (1H, t, \( J = 7.0 \) Hz). \( ^{13}C \)-NMR (CDCl\(_3\)) \( \delta \): 194.1, 162.3, 158.2, 143.7, 134.8, 134.5, 133.5, 132.4, 130.3, 129.1, 128.6, 127.5, 123.7, 123.4, 120.5, 119.6. MS m/z: 231 (M\(^+\)). HRMS (EI) calcd for C\(_{16}\)H\(_9\)NO\(_2\) 231.0684; found 231.0688.

2,3-Dimethoxyinden[1,2-c]isoquinolin-11-one (20b): The same procedure as above was carried out using indenoisoquinoline 19b (30 mg, 0.14 mmol) to give the indenoisoquinolone 20b (24 mg, 60%) as
yellow solid. mp 262−263 °C (EtOAc). 1H-NMR (CDCl₃) δ: 8.97 (1H, s), 8.03 (1H, s), 7.74 (1H, d, J = 7.2 Hz), 7.61 (1H, d, J = 7.2 Hz), 7.51 (1H, t, J = 7.2 Hz), 7.32 (1H, t, J = 7.2 Hz), 7.12 (1H, s), 4.10 (3H, s), 4.02 (3H, s). 13C-NMR (CDCl₃) δ: 194.5, 160.9, 156.0, 154.5, 150.6, 143.9, 134.7, 134.6, 129.9, 129.8, 125.7, 123.4, 120.1, 118.8, 105.9, 101.3, 56.5, 56.0. MS m/z: 291 (M⁺). HRMS (EI) calcd for C₁₈H₁₃NO₃ 291.0895; found 291.0867.

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REFERENCES AND NOTES


