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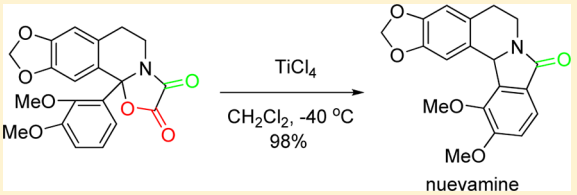
Conversion of Oxazolidinediones to Isoindoloisoquinolinones via Intramolecular Friedel–Crafts Reaction

Ji-Young Min and Guncheol Kim*

Department of Chemistry, College of Natural Science, Chungnam National University, Daejon 305-764, Korea

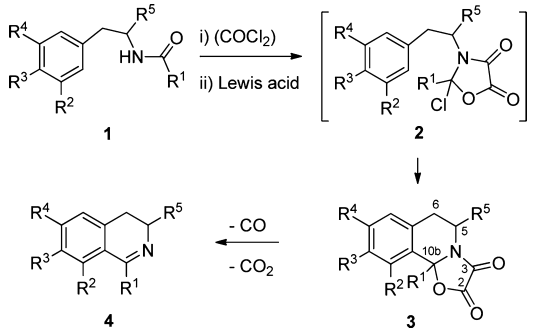
Supporting Information

ABSTRACT: Treatment of oxazolidinediones with $TiCl_4$ in CH_2Cl_2 resulted in conversion to isoindoloisoquinolinones via intramolecular Friedel–Crafts reaction with extrusion of CO_2 in the transformation. The alkaloid nuevamine has been synthesized under these conditions in a regiospecific manner.



Oxazolidine-4,5-diones were first introduced for the synthesis of 3-aryl-3,4-dihydroisoquinolines through a modified Bischler–Napieralski reaction as the application of oxalyl chloride to the reaction.[1] Treatment of amide **1** with oxalyl chloride to form **2**, subsequent addition of Lewis acid to facilitate the second cyclization, and the following reaction of **3** with an acid afforded good yields of 3-aryl-3,4-dihydroisoquinolines (Scheme 1). Formation of the dione intermediates from

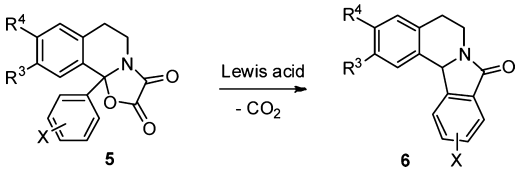
Scheme 1. Oxazolidine-4,5-diones to 3-Aryl-3,4-dihydroisoquinolines



the corresponding (1,2-diphenylethyl)amides (R^5 = Ar) was specifically intended to avoid nitrile elimination causing low yields through a retro-Ritter reaction before cyclization.[2] This process has been generally carried out without separation of intermediates, expecting that the formation of the diones would ensure the desired cyclization. While alkyl or benzylamide derivatives have been dominantly subjected to the transformation, benzamide precursors have been less explored, partly because the steric bulkiness of aromatic group on the quartenary center of **2** was assumed to cause low yields in the final acylation. Formation of imine **4** was carried out via extrusion of CO_2 and CO from **3**, and a few examples of intramolecular Friedel–Crafts reactions onto C-2 carbonyl of **3** have been reported.[3]

Aromatic groups attached on C-10b of the diones should be able to take part in some other type of reaction; however, any attempt on the derivatives has not been reported so far to our best knowledge. We envisioned that the aromatic dione compounds would result in a new transformation under Lewis acid catalysis, hopefully conversion of oxazolidinediones to isoindoloisoquinolinones[4] via Friedel–Crafts reaction onto C-3 carbonyl of **5** (Scheme 2).

Scheme 2. Conversion of Oxazolidinediones to Isoindoloisoquinolinones



First we wanted to obtain precursors having the required aromatic groups on C-10b. We could not obtain reproducible yields of compounds **5** by the known procedures.[1,2] However, slight modification of the sequential procedures provided excellent yields of purified materials: Addition of *n*-BuLi (2.5 equiv) to a solution of amide and oxalyl chloride (2.5 equiv) in THF at −78 °C, stirring for 3 h at that temperature, addition of $AlCl_3$ (3.5 equiv) at 0 °C, and warming the resulting mixture to room temperature allowed good yields of the desired products. As the aromatic ring needs to be reactive enough to overcome the steric factor on the quartenary center in the cyclization, only the compounds containing electron-donating groups at the meta and para positions on the aromatic ring (R^3 and R^4) afforded the desired products in good yields. $AlCl_3$ was found to be the best Lewis acid for the Friedel–Crafts cyclization step (Table 1).

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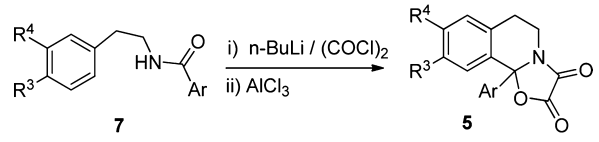
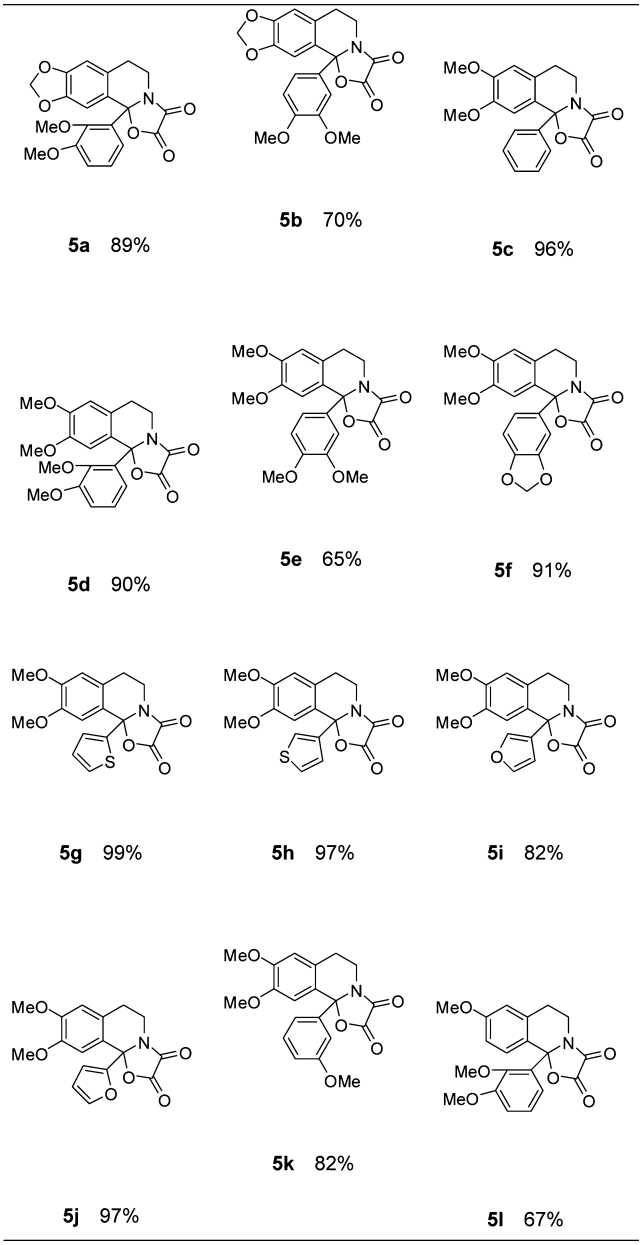
Table 1. Synthesis of Oxazolidine-2,3-dione[a]

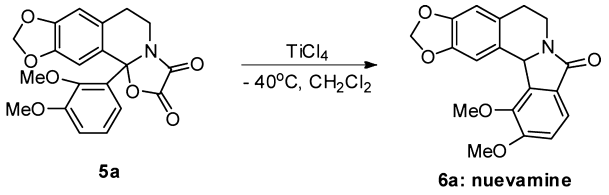




[a]Yields of the isolated product.

Conversion to the desired isoindoloisoquinolinones has been tested by using intermediate **5a** because the desired transformation would result in the synthesis of **6a**, an alkaloid nuevamine. The reaction was investigated by treatment of **5a** with several acids. When the process was carried under *p*-toluenesufonic acid catalyst, no reaction occurred even at rt (Table 2, entry 1). However, CF_3COOH and general Lewis acids provided **6a** in a regiospecific manner (entries 2–7).[5] The optimized conditions were found to be the reaction of **5a** with $TiCl_4$ in CH_2Cl_2 at −40 °C, yielding 98% (entry 3). $AlCl_3$ treatment in CH_2Cl_2 provided 11% of product (entry 5), which indicates prolonged reaction time at the dione formation step

Table 2. Reaction Optimization for Nuevamine Synthesis[a]



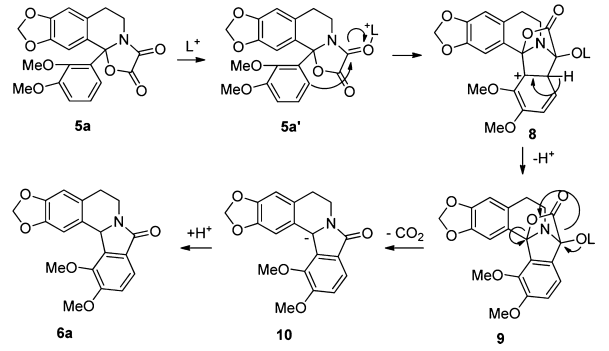
entry	acid	solvent	T (°C)	yield[b] (%)
1	TsOH	CH_2Cl_2	rt	NR
2	$SnCl_4$	CH_2Cl_2	−40	74
3	$TiCl_4$	CH_2Cl_2	−40	98
4	BF_3OEt_2	CH_2Cl_2	−40	23
5	$AlCl_3$	CH_2Cl_2	−40	11
6	$ZnCl_2$	CH_2Cl_2	−40	70
7	CF_3COOH	CH_2Cl_2	−40	93

[a]Unless otherwise noted, the reactions were performed with **5a** and acid (2.5 equiv) for 1 h, and less than 1 equiv of acid afforded very poor yields. [b]Yield of the isolated product.

would end up to the desired compound. However, the longer stirring in the previous step without separation of **5a** gave the desired product less than 5% yield.

The reaction is suggested to be initiated by electrophilic addition of aromatic group to the activated C-3 carbonyl carbon to intermediate **8**. Proton elimination to **8** was followed by extrusion of CO_2 to **10**, and protonation would yield **6a** (Scheme 3). This process suggests a differentiated route for

Scheme 3. Mechanism of the Nuevamine Formation



tetrahydroisoquinoline skeleton from conventional synthetic protocols such as Pictet–Spengler,[6] Bischler–Napieralski,[7] Pomeranz–Fritsch–Bobbitt,[8] *N*-acyliminium ion cyclization,[9] and Parham-type cyclization.[10]

The scope of this new transformation has been investigated under the optimized conditions. Compound **5c** did not proceed to yield **6c**. In general, no desired compound has been detected from the starting materials, which do not have an electron-donating group on the aromatic nucleophile. Starting materials have been fully recovered, or complete decomposition has been detected depending on the reaction temperature. Among anisole derivatives only meta-substituted compound **5k** underwent the reaction to afford **6k** in 99% yield. In the case of 2- and 3-furans, **6i** and **6j**, only 3-furan compound **5i** reacted to provide product **6i** in 72% yield. However, both 2- and 3-thiofurans, **5g** and **5h**, provided the corresponding products **6g** and **6h** in 80% and 83% yields, respectively. Neither pyrrole nor pyridine derivatives went through the transformation at all. In terms of regioselectivity, products **6b**, **6e**, **6f**, **6h**, and **6k** have

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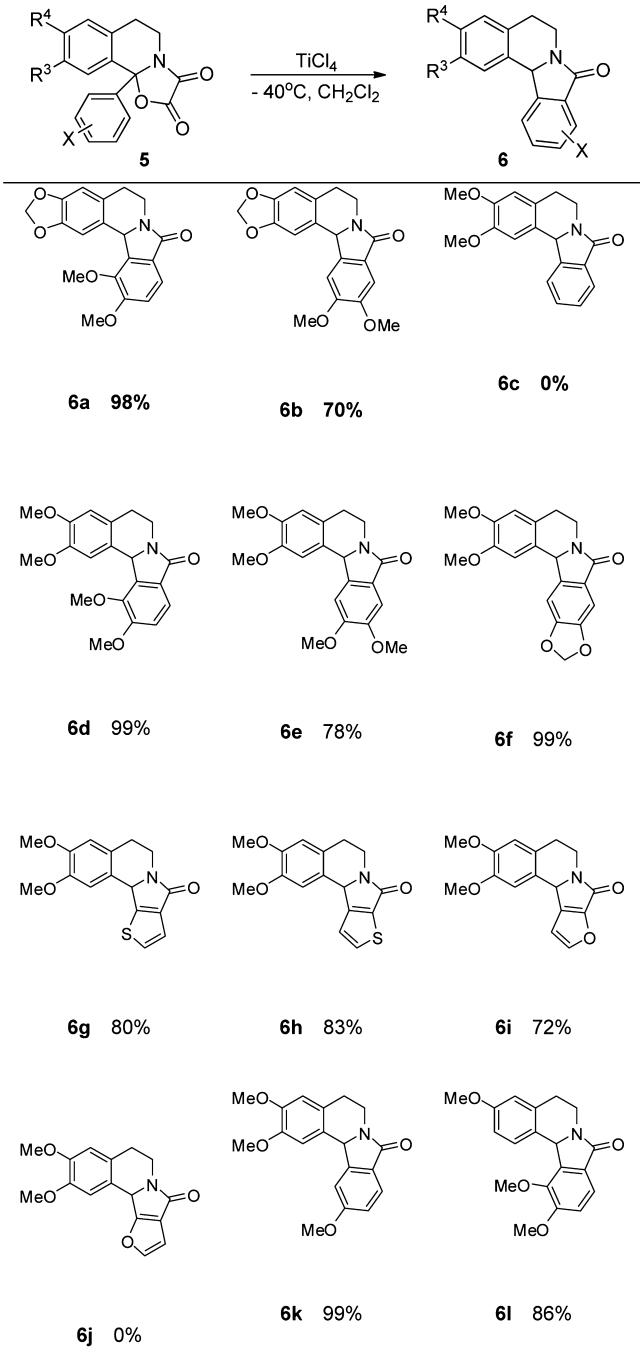
been detected as a single isomer, respectively, from the corresponding starting materials (Table 3).

Table 3. Substrate Scopes for the Transformation[a]



[a]Yield of the isolated product.

In summary, oxazolidinediones containing aromatic groups on the quaternary center have been converted to isoindoloisoquinolones through Friedel–Crafts reaction, and nuevamine was synthesized in a regiospecific manner.

EXPERIMENTAL SECTION

Representative procedure for the formation of dione 5a. To a solution of *N*-(3,4-dimethoxyphenethyl)benzamide (200 mg, 0.70 mmol) and oxalyl chloride (0.15 mL, 1.75 mmol) in THF (3 mL) was added n-BuLi (1.75 mmol) at −78 °C. The reaction mixture was stirred for 3h at −78 °C and was raised to 0 °C, and $AlCl_3$ (327 mg, 2.45 mmol) in 8 mL CH_2Cl_2 was added at 0 °C. The resulting mixture was stirred for 0.5 h at 0 °C and raised to room temperature. CH_2Cl_2 (5 mL) and H_2O (10 mL) were added to the solution and the organic layer was separated and washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, and evaporated. Purification of the residue by column chromatography (hexane/AcOEt 1/1) provided **5a** (228 mg, 96%).

11*b*-(2,3-Dimethoxyphenyl)-5,6-dihydro-2*H*-[1,3]dioxolo-[4,5-*g*]oxazolo[2,3-*a*]isoquinoline-2,3(11*bH*)-dione (5a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, J = 8.3, 1.5 Hz, 1H), 6.94 (s, 1H), 6.91 (t, J = 8.1 Hz, 1H), 6.66 (s, 1H), 6.31 (dd, J = 7.9, 1.5 Hz, 1H), 6.05 (d, J = 1.3 Hz, 1H), 6.01 (d, J = 1.3 Hz, 1H), 4.30 (ddd, J = 13.1, 7.1, 3.0 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.20 (ddd, J = 13.1, 7.1, 2.9 Hz, H), 3.13 (ddd, J = 16.6, 5.9, 2.5 Hz, 2H), 2.75 (ddd, J = 16.6, 5.9, 2.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 153.7, 152.3, 149.2, 148.9, 146.9, 128.2, 127.8, 126.9, 123.2, 122.9, 115.7, 108.3, 107.1, 101.8, 91.7, 60.7, 56.1, 36.3, 27.3 ppm; IR (KBr) γ 1731, 1831 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{17}NO_4$: 311.1158 [M−(CO + CO_2)]$^+$; found: 311.1154.

11*b*-(3,4-Dimethoxyphenyl)-5,6-dihydro-2*H*-[1,3]dioxolo-[4,5-*g*]oxazolo[2,3-*a*]isoquinoline-2,3(11*bH*)-dione(5b). (240 mg, 70%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.71 − 6.66 (m, 2H), 6.64 (dd, J = 8.5, 1.9 Hz, 1H), 6.03 (d, J = 12.4 Hz, 2H), 4.28 (ddd, J = 13.4, 5.1, 3.7 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.33 (ddd, J = 13.4, 5.1, 3.5 Hz, 1H), 3.11 (ddd, J = 16.6, 4.4, 3.3 Hz, 1H), 2.75 (ddd, J = 16.6, 5.1, 3.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 151.9, 151.0, 149.6, 149.3, 147.1, 128.9, 127.7, 127.0, 121.4, 110.7, 109.2, 108.3, 106.9, 101.8, 92.0, 56.3, 56.1, 37.0, 27.2 ppm; IR (KBr) γ 1733, 1836 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{17}NO_4$: 311.1158 [M − (CO + CO_2)]$^+$; found: 311.1154.

8,9-Dimethoxy-10*b*-phenyl-5,6-dihydro-2*H*-oxazolo[2,3-*a*]-isoquinoline-2,3(10*bH*)-dione (5c). (253 mg, 96%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, J = 8.3, 1.5 Hz, 1H), 6.94 (s, 1H), 6.91 (t, J = 8.1 Hz, 1H), 6.66 (s, 1H), 6.31 (dd, J = 7.9, 1.5 Hz, 1H), 6.05 (d, J = 1.3 Hz, 1H), 6.01 (d, J = 1.3 Hz, 1H), 4.30 (ddd, J = 13.1, 7.1, 3.0 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.41 (m, 1H), 3.21 (ddd, J = 13.1, 7.1, 2.9 Hz, 1H), 2.75 (ddd, J = 16.6, 5.9, 3.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 153.7, 152.3, 149.2, 148.9, 146.9, 128.2, 127.8, 126.9, 123.2, 122.9, 115.7, 108.3, 107.1, 101.8, 91.7, 60.7, 56.1, 36.3, 27.3 ppm; IR (KBr) γ 1735, 1830 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{17}NO_2$: 267.1259 [M − (CO + CO_2)]$^+$; found: 267.1254.

10b-(2,3-Dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydro-2H-oxazolo[2,3-*a*]isoquinoline-2,3(10*bH*)-dione (5d). (268 mg, 90%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, J = 8.3, 1.1 Hz, 1H), 6.96 − 6.91 (m, 2H), 6.74 (s, 1H), 6.28 (dd, J = 7.9, 1.2 Hz, 1H), 4.35 (m, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.20 (ddd, J = 13.1, 7.1, 3.0 Hz, 1H), 3.17 (ddd, J = 13.1, 7.1, 3.1 Hz, 1H), 2.82 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 153.4, 152.0, 150.2, 148.6, 147.9, 128.2, 126.2, 125.3, 123.0, 122.9, 115.5, 110.7, 109.3, 91.5, 60.5, 56.0, 55.9, 36.2, 26.7, 14.0 ppm; IR (KBr) γ 1738, 1835 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{21}NO_4$: 327.1471 [M − (CO + CO_2)]$^+$; found: 327.1469.

10b-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydro-2*H*-oxazolo[2,3-*a*]isoquinoline-2,3(10*bH*)-dione (5e). (219 mg, 65%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.71 (d, J = 2.7 Hz, 2H), 6.62 (dd, J = 8.4, 2.2 Hz, 1H), 4.35 (ddd, J = 13.4, 5.1, 3.7 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.31 (ddd, J = 13.4, 5.1, 3.5 Hz, 1H), 3.16 (ddd, J = 16.9, 4.4, 3.3 Hz, 1H), 2.81 (ddd, J = 16.9, 5.1, 2.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 151.7, 150.8, 150.5, 149.5, 148.3, 129.1, 126.3, 125.4, 121.4, 110.7, 110.6, 109.4, 109.2, 92.0, 56.2, 56.1, 56.1, 56.0, 37.0, 26.9 ppm; IR (KBr) γ 1732, 1837 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{21}NO_4$: 327.1471 [M − (CO + CO_2)]$^+$; found: 327.1469.

10b-(Benzo[*d*][1,3]dioxol-5-yl)-8,9-dimethoxy-5,6-dihydro-2*H*-oxazolo[2,3-*a*]isoquinoline-2,3(10*bH*)-dione (5f). (240 mg, 91%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.70 (s, 1H), 6.67 − 6.64 (m, 1H), 6.63 − 6.58 (m, 1H), 6.01 (s, 2H), 4.33 (ddd, J = 13.4, 7.1, 2.9 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H),

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3.32 (ddd, J = 13.5, 7.1, 3.1 Hz, 1H), 3.15 (ddd, J = 16.9, 5.9, 3.6 Hz, 1H), 2.81 (ddd, J = 16.9, 5.9, 2.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 151.6, 150.6, 149.4, 148.5, 148.3, 130.8, 126.2, 122.2, 110.8, 109.2, 108.1, 107.2, 102.0, 91.8, 56.2, 56.1, 36.9, 26.8 ppm; IR (KBr) γ 1734, 1840 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{17}NO_4$: 311.1158 [M − (CO + CO_2)]$^+$; found: 311.1155.

8,9-Dimethoxy-10*b*-(thiophen-2-yl)-5,6-dihydro-2*H*-oxazolo[2,3-*a*]isoquinoline-2,3(10*bH*)-dione (5g). (280 mg, 99%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 5.1, 1.2 Hz, 1H), 7.04 (s, 1H), 6.98 (ddd, J = 5.0, 3.7, 1.0 Hz, 1H), 6.89 − 6.86 (m, 1H), 6.68 (s, 1H), 4.42 (ddd, J = 13.4, 7.1, 2.9 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.45 (ddd, J = 13.4, 10.5, 3.2 Hz, 1H), 3.17 (ddd, J = 16.9, 5.9, 4.2 Hz, 1H), 2.83 (ddd, J = 16.9, 5.9, 2.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 151.3, 150.8, 148.3, 141.9, 130.2, 129.4, 127.4, 125.9, 125.4, 110.8, 109.2, 89.6, 56.3, 56.1, 37.2, 26.9 ppm; IR (KBr) γ 1733, 1837 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}NO_2S$: 273.0824 [M − (CO + CO_2)]$^+$; found: 273.0826.

8,9-Dimethoxy-10*b*-(thiophen-3-yl)-5,6-dihydro-2*H*-oxazolo[2,3-*a*]isoquinoline-2,3(10*bH*)-dione (5h). (215 mg, 97%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 5.0, 3.0 Hz, 1H), 7.05 (s, 1H), 6.96 (s, 2H), 6.68 (s, 1H), 4.41 (ddd, J = 13.6, 7.0, 2.8 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.42 (ddd, J = 13.6, 7.0, 3.2 Hz, 1H), 3.20 (ddd, J = 16.9, 5.9, 4.2 Hz, 1H), 2.83 (ddd, J = 16.9, 5.9, 2.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 151.5, 150.7, 148.4, 139.7, 128.1, 128.1, 125.9, 125.5, 125.3, 110.8, 109.2, 89.3, 56.3, 56.1, 37.2, 27.1 ppm; IR (KBr) γ 1730, 1833 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}NO_2S$: 273.0824 [M − (CO + CO_2)]$^+$; found: 273.0824.

10b-(Furan-3-yl)-8,9-dimethoxy-5,6-dihydro-2*H*-oxazolo-[2,3-*a*]isoquinoline-2,3(10*bH*)-dione (5i). (278 mg, 82%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, J = 1.7 Hz, 1H), 7.12 (s, 1H), 6.99 (s, 1H), 6.68 (s, 1H), 6.36 (d, J = 0.9 Hz, 1H), 4.45 (ddd, J = 13.4, 7.5, 2.0 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.36 (ddd, J = 13.4, 7.5, 4.0 Hz, 1H), 3.18 (ddd, J = 16.1, 7.6, 4.9 Hz, 1H), 2.84 (ddd, J = 16.1, 7.6, 1.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 151.5, 150.6, 148.2, 145.1, 144.3, 125.8, 125.4, 124.8, 110.8, 109.0, 107.7, 88.0, 56.1, 56.0, 37.0, 27.0 ppm; IR (KBr) γ 1732, 1836 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{15}NO_3$: 257.1052 [M − (CO + CO_2)]$^+$; found: 257.1049.

10b-(Furan-2-yl)-8,9-dimethoxy-5,6-dihydro-2*H*-oxazolo-[2,3-*a*]isoquinoline-2,3(10*bH*)-dione (5j). (297 mg, 97%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 1.8, 0.8 Hz, 1H), 7.04 (s, 1H), 6.69 (s, 1H), 6.36 (dd, J = 3.3, 1.8 Hz, 1H), 6.20 (dd, J = 3.4, 0.8 Hz, 1H), 4.46 (ddd, J = 13.3, 6.8, 1.8 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.31 (ddd, J = 13.3, 8.1, 4.4 Hz, 1H), 3.19 (ddd, J = 16.5, 6.3, 2.7 Hz, 1H), 2.84 (ddd, J = 16.5, 5.3, 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 151.6, 151.0, 148.3, 148.1, 145.3, 126.5, 122.9, 114.7, 111.0, 110.9, 109.4, 87.0, 56.2, 56.1, 37.2, 27.2 ppm; IR (KBr) γ 1737, 1839 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}NO_3$: 257.1052 [M − (CO + CO_2)]$^+$; found: 257.1049.

8,9-Dimethoxy-10*b*-(3-methoxyphenyl)-5,6-dihydro-2*H*-oxazolo[2,3-*a*]isoquinoline-2,3(10*bH*)-dione (5k). (211 mg, 82%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 − 7.28 (m, 1H), 6.93 (dd, J = 21.7, 9.6 Hz, 2H), 6.80 − 6.65 (m, 3H), 4.34 (m, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 3.32 (m, 1H), 3.14 (m, 1H), 2.82 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.1, 151.6, 150.6, 148.4, 138.8, 130.1, 126.3, 125.1, 119.4, 115.1, 113.6, 110.8, 109.3, 91.6, 56.2, 56.1, 55.5, 37.0, 26.9 ppm; IR (KBr) γ 1730, 1832 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{19}NO_3$: 297.1365 [M − (CO + CO_2)]$^+$; found: 297.1361.

10b-(2,3-Dimethoxyphenyl)-8-methoxy-5,6-dihydro-2H-oxazolo[2,3-*a*]isoquinoline-2,3(10*bH*)-dione (5l). (278 mg, 67%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.7 Hz, 1H), 7.04 (dd, J = 8.3, 1.4 Hz, 1H), 6.93 − 6.87 (m, 2H), 6.76 (d, J = 2.5 Hz, 1H), 6.24 (dd, J = 8.0, 1.5 Hz, 1H), 4.32 (ddd, J = 12.6, 6.9, 3.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.28 − 3.10 (m, 2H), 2.85 (ddd, J = 8.9, 5.5, 2.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 159.5, 153.4, 152.2, 148.6, 135.1, 128.4, 128.3, 125.9, 122.9, 122.7, 115.4, 113.1, 91.6, 60.4, 55.9, 55.3, 36.1, 27.2 ppm; IR (KBr) γ 1738, 1835 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{19}NO_3$: 297.1365 [M − (CO + CO_2)]$^+$; found: 297.1362.

Representative procedure for the formation of isoindoloisoquinolinone, nuevamine 6a. To a solution of **5a** (100 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) was added $TiCl_4$ (0.46 mL, 0.63 mmol) at −40 °C. The reaction mixture was stirred for 1h at −40 °C, Quenching with H_2O (0.5 mL) was followed by washing with saturated $NaHCO_3$ solution and brine. After dry over $MgSO_4$ and evaporation, purification of the residue by short column chromatography (hexane/AcOEt 1/1) provided **6a** (98 mg, 98%).

Nuevamine (6a).[5e] White solid: mp 213-214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 1H), 7.32 (s, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.67 (s, 1H), 5.93 − 5.92 (m, 1H), 5.86 (d, J = 1.4 Hz, 1H), 5.63 (s, 1H), 4.00 (s, 3H), 3.99 (m, 1H), 3.98 (s, 3H), 3.56 (dt, J = 12.5, 6.1 Hz, 1H), 3.02 (dt, J = 15.4, 6.1 Hz, 1H), 2.87 (dt, J = 15.4, 6.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 155.7, 147.0, 146.6, 144.5, 136.3, 129.0, 128.6, 126.8, 119.9, 113.3, 108.6, 107.6, 101.1, 60.6, 58.5, 56.4, 38.8, 28.9. IR (KBr) γ 1675 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{17}NO_5$: [M]$^+$ 339.1107; found: 339.1109.

10,11-Dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoindolo-[1,2-*a*]isoquinolin-8(12*bH*)-one (6b). (101 mg, 70%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.22 (s, 1H), 7.04 (s, 1H), 6.67 (s, 1H), 5.98 (d, J = 1.2 Hz, 1H), 5.92 (d, J = 1.1 Hz, 1H), 5.48 (s, 1H), 4.32 (dt, J = 12.6, 5.1 Hz, 1H), 4.04 (s, 3H), 3.94 (s, 3H), 3.47 − 3.39 (m, 1H), 3.01 − 2.91 (m, 1H), 2.77 (dt, J = 15.7, 4.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 152.7, 150.1, 146.9, 146.7, 137.9, 128.5, 127.7, 125.3, 109.3, 105.6, 105.4, 105.4, 101.3, 58.9, 56.5, 56.3, 38.6, 29.6 ppm; IR (KBr) γ 1673 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{17}NO_5$: [M]$^+$ 339.1107; found: 339.1109.

2,3,11,12-Tetramethoxy-5,6-dihydroisoindolo[1,2-*a*]-isoquinolin-8(12*bH*)-one (6d). (108 mg, 99%) White solid: mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.58 (dd, J = 8.2, 1.0 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.66 (s, 1H), 5.73 (s, 1H), 4.33 − 4.25 (m, 1H), 4.03 (d, J = 1.1 Hz, 3H), 3.96 (s, 3H), 3.85 (d, J = 8.3 Hz, 6H), 3.51 − 3.41 (m, 1H), 3.09 − 2.99 (m, 1H), 2.80 (dt, J = 15.7, 4.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 155.8, 148.2, 147.8, 144.5, 136.9, 127.2, 127.1, 126.6, 120.0, 113.2, 111.5, 110.8, 60.9, 58.5, 56.3, 56.0, 55.9, 38.6, 28.5 ppm; IR (KBr) γ 1675 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}NO_5$: [M]$^+$ 355.1420; found: 355.1418.

2,3,10,11-Tetramethoxy-5,6-dihydroisoindolo[1,2-*a*]-isoquinolin-8(12*bH*)-one (6e). (110 mg, 78%) White solid: mp 162−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.28 (s, 1H), 7.08 (s, 1H), 6.68 (s, 1H), 5.52 (s, 1H), 4.42 (ddd, J = 12.8, 5.6, 3.8 Hz, 1H), 4.02 (s, 3H), 3.93 (s, 6H), 3.86 (s, 3H), 3.44 − 3.35 (m, 1H), 2.98 (ddd, J = 15.9, 10.0, 5.9 Hz, 1H), 2.76 (dt, J = 15.9, 4.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 152.6, 150.1, 148.5, 147.9, 138.3, 127.2, 126.4, 125.3, 112.1, 108.8, 105.6, 105.5, 58.7, 56.3, 56.2, 56.2, 56.0, 38.5, 29.0 ppm; IR (KBr) γ 1672 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}NO_5$: [M]$^+$ 355.1420; found: 355.1417.

2,3-Dimethoxy-5,6-dihydro-[1,3]dioxolo[4′,5′:5,6]isoindolo-[1,2-*a*]isoquinolin-8(13*bH*)-one (6f). (95 mg, 99%) White solid: mp 161−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.22 (s, 1H), 7.02 (s, 1H), 6.67 (s, 1H), 6.10 (s, 1H), 6.06 (s, 1H), 5.51 (s, 1H), 4.45 (dd, J = 8.1, 4.2 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.41 − 3.31 (m, 1H), 3.03 − 2.93 (m, 1H), 2.74 (d, J = 15.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 151.6, 148.6, 148.4, 147.9, 140.3, 127.0, 126.9, 126.1, 112.0, 108.5, 103.6, 103.6, 102.2, 58.8, 56.2, 55.9, 38.5, 29.1 ppm; IR (KBr) γ 1672 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{17}NO_5$: [M]$^+$ 339.1107; found: 339.1104.

2,3-Dimethoxy-5,6-dihydrothieno[2′,3′:3,4]pyrrolo[2,1-*a*]-isoquinolin-8(11*bH*)-one (6g). (89 mg, 80%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 4.9 Hz, 1H), 7.18 (s, 1H), 7.07 (d, J = 4.9 Hz, 1H), 6.59 (s, 1H), 4.17 (dd, J = 13.4, 5.9 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.39 (td, J = 12.7, 4.0 Hz, 1H), 2.91 (ddd, J = 17.9, 12.1, 6.0 Hz, 1H), 2.68 (dd, J = 16.1, 3.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 157.6, 149.6, 148.3, 138.9, 131.4, 127.2, 126.9, 120.0, 111.3, 110.2, 85.4, 56.2, 56.0, 35.3, 29.1 ppm; IR (KBr) γ 1663 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{15}NO_3S$: [M]$^+$ 301.0773; found: 301.0769.

2,3-Dimethoxy-5,6-dihydrothieno[3′,2′:3,4]pyrrolo[2,1-*a*]-isoquinolin-8(11*bH*)-one (6h). (95 mg, 83%) White solid: mp 133−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 4.8 Hz, 1H), 7.32

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(d, J = 4.8 Hz, 1H), 6.96 (s, 1H), 6.66 (s, 1H), 5.57 (s, 1H), 4.44 (ddd, J = 13.1, 6.0, 2.8 Hz, 1H), 3.92 (s, 3H), 3.84 (d, J = 6.2 Hz, 3H), 3.34 (ddd, J = 13.4, 10.8, 4.4 Hz, 1H), 2.98 (ddd, J = 16.1, 10.4, 6.0 Hz, 1H), 2.77 − 2.69 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 154.7, 148.5, 148.1, 136.1, 135.3, 126.5, 125.4, 121.0, 112.0, 108.8, 58.3, 56.2, 56.0, 38.7, 29.2 ppm; IR (KBr) γ 1667 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{15}NO_3S$: [M]$^+$ 301.0773; found: 301.0771.

2,3-Dimethoxy-5,6-dihydrofuro[3′,2′:3,4]pyrrolo[2,1-*a*]isoquinolin-8(11*bH*)-one (6i). (94 mg, 72%) White solid: mp 103−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 − 7.59 (m, 1H), 7.11 (s, 1H), 6.78 − 6.76 (m, 1H), 6.59 (s, 1H), 4.15 − 4.09 (m, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.42 (td, J = 12.9, 4.3 Hz, 1H), 2.89 (ddd, J = 17.7, 11.9, 6.1 Hz, 1H), 2.70 (dd, J = 16.2, 3.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 158.4, 150.6, 148.2, 144.4, 127.0, 111.5, 111.4, 110.4, 110.3, 107.0, 82.5, 56.2, 56.0, 35.2, 29.2 ppm; IR (KBr) γ 1669 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{15}NO_4$: [M]$^+$ 285.1001; found: 285.0999.

2,3,11-Trimethoxy-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12*bH*)-one (6k). (100 mg, 99%) White solid: mp 86−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 1H), 7.09 (s, 1H), 7.00 (dd, J = 8.4, 2.0 Hz, 1H), 6.66 (s, 1H), 5.54 (s, 1H), 5.29 (d, J = 1.0 Hz, 1H), 4.44 (ddd, J = 12.9, 5.8, 3.3 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.40 − 3.32 (m, 1H), 2.97 (ddd, J = 16.0, 10.0, 5.7 Hz, 1H), 2.73 (dt, J = 15.8, 3.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 162.9, 148.4, 147.9, 147.0, 127.2, 126.1, 125.5, 125.4, 113.9, 112.0, 109.3, 108.6, 58.8, 56.2, 56.0, 55.8, 38.3, 29.1 ppm; IR (KBr) γ 1670 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{19}NO_4$: [M]$^+$ 325.1314; found: 325.1310.

3,11,12-Trimethoxy-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12*bH*)-one (6l). (89 mg, 86%) White solid: mp 96−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 9.4 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H), 6.77 − 6.72 (m, 2H), 5.68 (s, 1H), 4.12 − 4.03 (m, 1H), 3.98 (d, J = 9.9 Hz, 6H), 3.77 (s, 3H), 3.59 (dt, J = 12.5, 6.1 Hz, 1H), 3.12 − 2.90 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.0, 155.6, 144.6, 136.9, 136.5, 128.0, 127.6, 126.8, 119.8, 113.7, 113.2, 112.3, 60.5, 58.1, 56.3, 55.3, 38.7, 29.2 ppm; IR (KBr) γ 1668 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{19}NO_4$: [M]$^+$ 325.1314; found: 325.1311.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new products. This material is available free for charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: guncheol@cnu.ac.kr.

Notes

The authors declare no competing financial interest.

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