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AN EFFICIENT $SeO_2/FeCl_3$ PROMOTED ACYLATION: INTRAMOLECULAR FRIEDEL-CRAFTS REACTION LEADING TO A ONE-POT SYNTHESIS OF WRIGHTIADIONE AND ITS DERIVATIVES

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Abstract – Wrightiadione has been shown to exhibit a broad range of biological activities. An efficient and straightforward synthetic method for generating wrightiadione and its derivatives which contain a unique tetracyclic isoflavone moiety was developed. This unprecedented one-pot route utilizes a wide spread of substrates through three-step tandem Riley oxidation/Friedel-Crafts reaction/oxidation with $SeO_2/FeCl_3$ in moderate yield.

In recent years, indanones and their structural analogues behave as key intermediates in medicine, agriculture and natural products synthesis, which display a broad spectrum of biological and pharmaceutical properties.[1] The extensive research on the biological activities of indanones has opened up more and more new application prospects, such as anticancer,[2] antibacterial,[3] antiviral and antimicrobial drugs,[4] drugs for anti-Alzheimer's disease[5] and hepatitis C treatment in medicine.[6] Specially, wrightiadione is an indanone derivative including a similar indanone fused heterocyclic structure, and isolated from the bark of *Wrightia tomentosa* medicinally in Thailand. It has been studied to exhibit a broad range of biological and pharmaceutical activities, especially the cytotoxicity against leukemia cell lines.[7]

Consequently, the development of efficient methods for the synthesis of the indanone frameworks and the unique tetracyclic isoflavone derivatives is a topic of considerable importance. Known powerful and reliable syntheses for indanone formation include classical intramolecular Friedel-Crafts acylations,[8] intramolecular [4+2] cycloaddition reactions of conjugated enynes,[9] Grignard reactions,[10] transition metal-catalyzed annulation of arylalkynes,[11] radical cyclization,[12] and base-promoted cyclization of β-alkynyl ketones.[13] In our previous study, an unexpected indanone byproduct excited our interest.[14]

Driven by the need for a more efficient synthetic route to wrightiadione derivatives, we were particularly interested in exploring a one-pot intramolecular cyclization. In this paper, we disclose the first example of a one-pot pathway through Riley oxidation/ Friedel-Crafts reaction/oxidation promoted by $SeO_2/FeCl_3$ to provide an efficient and straightforward protocol for the preparation of wrightiadione derivatives.

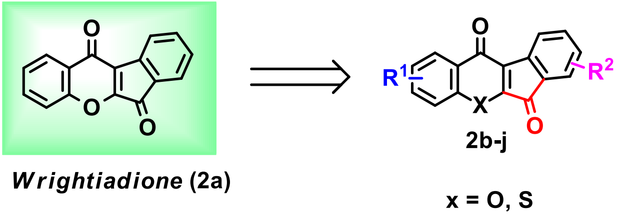
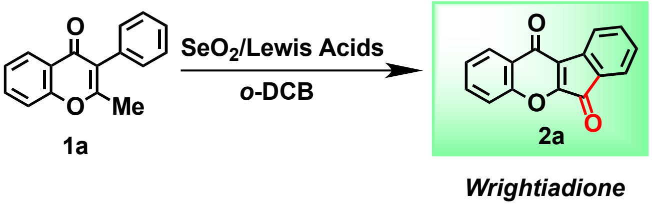


Figure 1. Structure of wrightiadione and its derivatives

In line with our hypothesis, the 2-methylchromone **1**[14] was prepared and converted to aldehyde following Riley selenium dioxide oxidation. Next acid promoted intramolecular Friedel-Crafts (F-C) reaction to generate the tetracyclic core and then subsequent aromatization and oxidation of the resulting benzyl alcohol gave corresponding wrightiadione derivatives. Based on the one-pot strategy, we studied the feasibility of the process to determine the most compatible conditions. For the fundamental study, our efforts began by exploring possible conditions using 2-methylchromone as model substrate. Oxidation/F-C reaction was conducted in the presence of SeO_2 with various Lewis acids in order to produce wrightiadione (Table 1).

Table 1. Optimization of reaction conditions



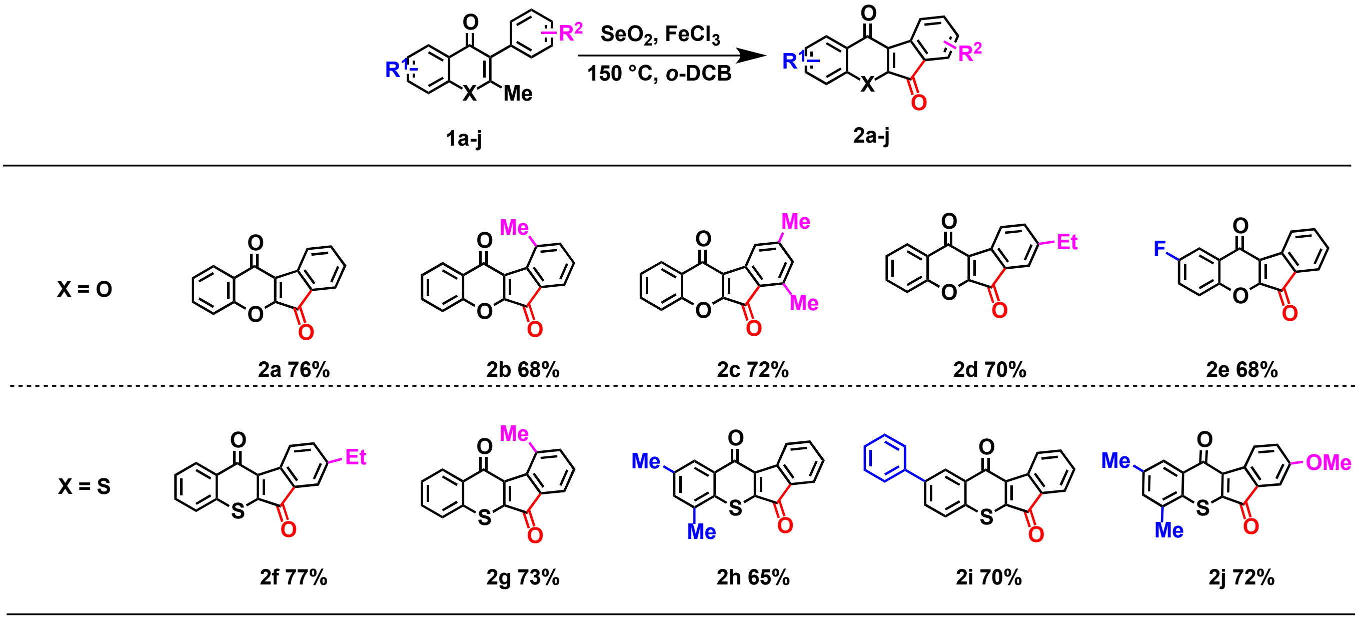
Entry	SeO_2(eq)	Additive	Temp (°C)	Time (h)	Yield (%)[a]
1	2.4	No	150	12	26
2	3.6	No	150	12	22
3	2.4	No	150	48	24
4	2.4	$AlCl_3$, 0.1	150	12	35
5	2.4	$SnCl_4$, 0.1	150	12	27
6	2.4	$FeCl_3$, 0.1	150	12	42

7	2.4	$FeCl_3$, 0.5	150	12	76
8	2.4	$FeCl_3$, 1.0	150	12	71
9	2.4	$FeCl_3$, 0.5	150	48	74
10	2.4	$FeCl_3$, 0.5	180	12	69

Reaction conditions unless specified otherwise: [a] **1a** (0.3 mmol) and SeO_2 (2.4 eq) in *o*-dichlorobenzene (4.0 mL) Under an Ar atmosphere. The reaction was stirred at 150 °C under an Ar atmosphere for 12 h. Isolated yield.

In the initial attempt, following the previous study,[14] in the presence of 2.4 equiv SeO_2 in *o*-dichlorobenzene (*o*-DCB), the reaction proceeded at 150 °C within 12 h to give desired wrightiadione **2a** with a low yield (entry 1). Next, we tried to adjust the reaction conditions, and found that the yield could not be improved by increasing equivalent of SeO_2 and prolonging reaction time (entries 2, 3). Then, in order to improve the activity of the cyclization reaction, Lewis acids were chosen to add. $AlCl_3$ and $SnCl_4$ showed similar reactivity and gave unsatisfactory result (entries 4, 5). Further regulating the reaction conditions were achieved with $FeCl_3$, which worked to yield **2a** in moderate yield (entry 6). To our delight, when $FeCl_3$ reagent was increased to 0.5 equiv, a dramatic improvement in the yield was achieved (entry 7). It should be noted that, increasing equivalent of $FeCl_3$, prolonging reaction time and increasing reaction temperature did not improve the yield, but rather led to a decreased yield (entries 8, 9 and 10). Finally, the optimal condition was carried out in *o*-DCB with 2.4 equiv SeO_2 and 0.5 equiv $FeCl_3$ at 150 °C, after 12 h the desired transformation was successfully demonstrated.

Table 2. Scope of substituents leading to wrightiadione derivatives



With optimal conditions determined, our focus was directed toward studying the substrates. The substituent R^1 and R^2 were investigated to see the substituent effect on the reactivity (Table 2), and the tetracyclic scaffold could be easily equipped by this one-pot process. It was noticed that even the present of aryl group bearing either electron-donating or withdrawing group, such as an alkyl (**2b**, **2c**, **2d**) and halogen (**2e**), the corresponding heteroindanones were produced smoothly in moderate yields. Also, when the sulfur was introduced to the substrate replacing of oxygen, the effect was not distinct on the course of the reaction (**2f**-**2j**). A narrow yield range (65%−77%) across the substrates verified herein was an indicative of the robustness of the method. The reactions were well-tolerated and generated the respective wrightiadione derivatives in moderate yields. The molecular structure of compound **2f** was independently confirmed by X-ray crystal structure analysis.

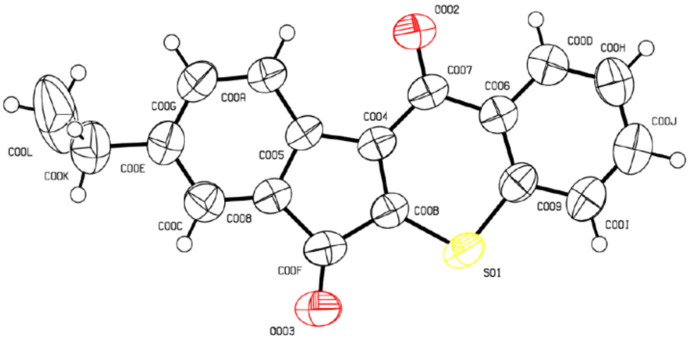
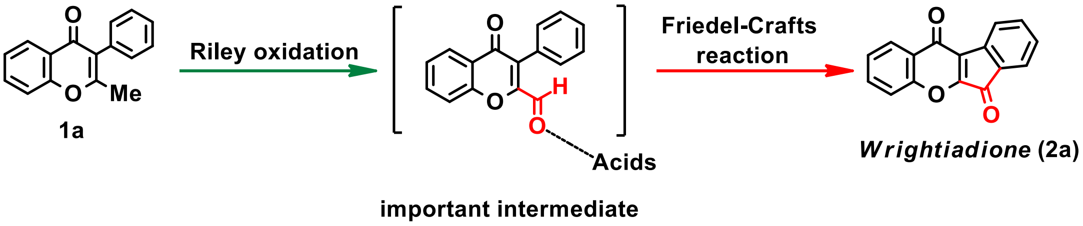


Figure 2. X-Ray crystal structure of **2f**

With these results, the reaction pathway was shown in Scheme 1. Firstly, the aldehyde was formed following Riley selenium dioxide oxidation from starting material 2-methylchromone (**1a**) and the selenous acid was generated from SeO_2 and H_2O at the same time. Next, under acid condition, promoted by $FeCl_3$ and selenous, the tetracyclic core was obtained by intramolecular Friedel-Crafts reaction. Lastly, wrightiadione (**2a**) was produced through subsequent aromatization and oxidation.



Scheme 1. One-pot pathway to access wrightiadione

In conclusion, we have developed an efficient one-pot pathway for constructing the wrightiadione derivatives through Riley oxidation/Friedel-Crafts reaction/oxidation with SeO_2/$FeCl_3$ in moderate yields. This method can provide a new convenient preparation of fused heterocycles and exploration of their uses in synthetic organic chemistry. Further studies to broaden the bioevaluation of the newly synthesized compounds are in progress.

EXPERIMENTAL

Unless otherwise stated, all chemicals and solvents were of analytical grade and used without further purification. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer and a JEOL JNM-ECP500 spectrometer with tetramethylsilane (TMS) as the internal standard. The chemical shifts were recorded in ppm and the following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectra were measured by an HP-1100 LC-MS spectrometer. X-Ray crystallography was performed on Rigaku R-AXIS RAPID/S imaging plate diffractometer. Flush column chromatography was performed by MERCK Silica gel 60. The progress of reactions was monitored by silica gel thin layer chromatography plates (MERCKTLC Silicagel 60 F_{254}).

Starting materials. 2-Methylchromone (**1**) was prepared using previously reported procedures.[14] All other chemicals in this study were commercially available.

General procedure for the synthesis of wrightiadione derivatives 2

Under an Ar atmosphere, to a dichlorobenzene (4.0 mL) solution of **1** (0.2 mmol) were added SeO_2 (2.4 equiv) and $FeCl_3$ (0.5 equiv). The reaction mixture was stirred at 150 °C for 12 h. After the reaction was complete (monitored with TLC), the reaction was quenched by adding sodium thiosulfate and the aqueous layer was extracted with CH_2Cl_2. The combined organic extract was washed with water and brine, and then dried over anhydrous $MgSO_4$. The solvent was evaporated and the obtained residue was purified by flash chromatography on silica gel (Hexane–EtOAc) to obtain pure product.

Indeno[2,1-*b*]chromene-6,11-dione (2a, Wrightiadione): (37.6 mg, 76%). Orange solid. mp 242-243 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.46 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.23 (dd, *J* = 7.2, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.8, 175.3, 156.6, 140.9, 136.4, 135.4, 131.6, 129.1, 127.7, 127.5, 126.9, 126.8, 125.1, 124.2, 120.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_9O_3$ 249.0552 found 249.0546.

10-Methylindeno[2,1-*b*]chromene-6,11-dione (2b): (35.5 mg, 68%). Orange solid. mp 262-265 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.61 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.45 (td, *J* = 8.0, 0.8 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 2.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.5, 175.6, 156.6, 156.4, 141.0, 140.3, 135.4, 134.6, 131.8, 126.5, 126.4, 126.2, 126.0, 124.9, 122.8, 120.0, 18.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{11}O_3$ 263.0708 found 263.0714.

7,9-Dimethylindeno[2,1-*b*]chromene-6,11-dione (2c): (39.8 mg, 72%). Orange solid. mp 263-267 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.53 (m, 2H), 6.83 (s, 1H), 2.55 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.9, 175.5, 156.6, 156.5, 144.3, 142.2, 138.3, 137.3, 136.3, 135.6, 126.4, 125.9, 125.6, 125.1, 124.1, 119.9, 21.5, 19.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{13}O_3$ 277.0865 found 277.0860.

8-Ethylindeno[2,1-*b*]chromene-6,11-dione (2d): (38.8 mg, 70%). Orange solid. mp 264-268 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.65 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.1, 178.7, 157.6, 156.0, 138.7, 135.8, 132.4 131.9, 129.1, 126.2, 126.0, 125.6, 124.9, 121.9, 119.4, 116.2, 28.9, 15.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{13}O_3$ 277.0865 found 277.0872.

2-Fluoroindeno[2,1-*b*]chromene-6,11-dione(2e): (36.2 mg, 68%). Orange solid. mp 259-262 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.75(d, *J* = 8.0 Hz, 1H), 7.65 – 7.62 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 7.6, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 187.8, 174.1, 163.2 (d, J_{CF} = 15.0 Hz), 160.3, 158.6, 157.0, 152.1, 139.8, 135.8, 128.7, 127.0, 124.6 (d, J_{CF} = 10.0 Hz), 123.0, 122.8 (d, J_{CF} = 8.0 Hz), 122.4 (d, J_{CF} = 5.0 Hz), 110.0 (d, J_{CF} = 15.0 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_8FO_3$ 267.0457 found 267.0464.

8-Ethylindeno[2,1-*b*]thiochromene-6,11-dione(2f): (45.5 mg, 77%). Red solid. mp 197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.46 (s, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.5, 177.8, 145.1, 142.7, 141.9, 138.2, 135.7, 134.8, 134.2, 131.9, 130.5, 129.0, 128.7, 128.4, 124.5, 124.0, 28.6, 15.2. HRMS (FAB) *m/z*: $[M+ H]^+$ calcd for $C_{18}H_{13}O_2S$ 293.0636, found 293.0630.

10-Methylindeno[2,1-*b*]thiochromene-6,11-dione(2g): (40.3 mg, 73%). Red solid. mp 206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 7.6Hz, 1H), 7.67 – 7.58 (m, 2H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.16 (dd, *J* = 7.2 Hz, 7.6 Hz, 1H), 2.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.4, 177.3, 144.1, 142.6, 141.0, 140.3, 135.4, 134.6, 131.8, 131.3, 129.6, 128.4, 128.1, 122.8, 23.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{11}O_2S$ 279.0480, found 279.0475.

2,4-Dimethylindeno[2,1-*b*]thiochromene-6,11-dione(2h): (38.7 mg, 65%). Red solid. mp 211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.22 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.49 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.30 (s, 1H), 7.24 (dd, *J* = 7.6, 8.0 Hz, 1H), 2.53 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.5, 178.1, 144.3, 142.2, 138.3, 137.3, 136.3, 135.6, 134.7, 134.5, 132.3, 130.2, 128.2, 126.8, 124.5, 124.1, 21.2 19.6. HRMS (FAB) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{13}O_2S$ 293.0636, found 293.0644.

2-Phenylindeno[2,1-*b*]thiochromene-6,11-dione(2i): (47.5 mg, 70%). Red solid. mp 214-215 °C. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.73 – 7.71 (m, 2H), 7.63 (d, *J* = 8.0Hz, 1H), 7.54 – 7.49 (m, 3H), 7.43 (dd, *J* = 8.4, 6.4 Hz, 1H), 7.29 – 7.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.2, 177.8, 144.3, 143.1, 141.5, 138.9, 137.7, 135.7, 134.5, 134.3, 130.8, 130.1, 129.9, 129.2, 129.1, 129.0, 128.4, 127.2, 126.9, 126.8, 124.7, 124.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{13}O_2S$ 341.0636 found 341.0641.

8-Methoxy-2,4-dimethylindeno[2,1-*b*]thiochromene-6,11-dione(2j): (46.5 mg, 72%). Red solid. mp 229 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31(s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.20 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 2.56 (s, 3H), 2.48 (s, 3H). HRMS (FAB) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{15}O_3S$ 323.0742 found 323.0735.

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