The Synthesis of Wrightiadione via Directed Remote Metalation

Nopporn Thasana,[a,b] Somsak Ruchirawat*[a,b,c]

[a] Chulabhorn Research Institute, Vipavadee Rangsit Highway, Bangkok 10210, Thailand
Fax +66(2)5740616; E-mail: somsak@tubtim.cri.or.th.

[b] Department of Chemistry, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand

[c] Programme on Research and Development of Synthetic Drugs, Institute of Science and Technology for Research and Development, Mahidol University, Salaya Campus, Thailand

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Abstract: The application of directed remote metalation (DreM) and electrophilic substitution is reported for the synthesis of wrightiadione using *N*,*N*-diethylcarboxamide as a directed metalation group (DMG) and electrophilic group. The lithiation of *N*,*N*-diethylisoflavone-2′-carboxamide with LDA gave a carbanion at C-2 which further cyclized to wrightiadione.

Key words: directed remote metalation, wrightiadione, *N*,*N*-diethylisoflavone-2′-carboxamide, directed metalation group, electrophilic substitution

Wrightiadione **1** is a rare and unusual oxygen heterocycle isolated from the bark of *Wrightia tomentosa*, a medicinal plant of Thailand, and it has been shown to exhibit cytotoxicity against a cultured murine P388 lymphocytic leukemia cell line (ED_{50} 1.1 μgmL^{-1}). The methanol extract of the dried leaves and stems of this plant also exhibited weak activity against HIV-1 reverse transcriptase.[1] Recently we have disclosed a successful synthesis of wrightiadione[2] **1** and also isowrightiadione[3] **2**, an isomeric compound.

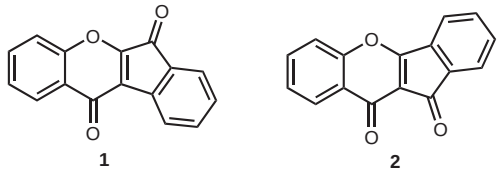
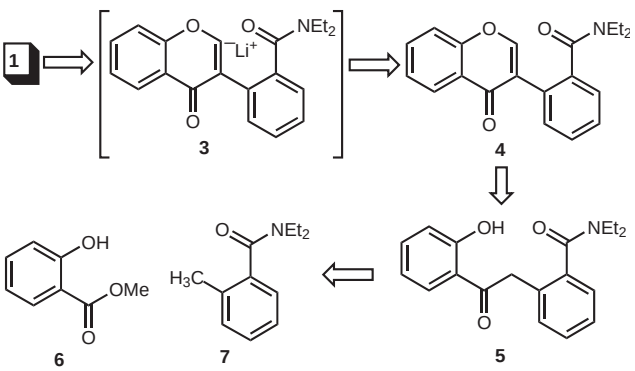


Figure 1

We wish to report another efficient route for the synthesis of wrightiadione **1** by directed remote metalation (DreM).[4] Heteroatom-facilitated metalation has become an increasingly important strategy in organic synthesis and has been widely adopted in the functionalization of both aromatic and heterocyclic systems.[4,5]

The lithiation of flavones and isoflavones has been successfully used to introduce substituents by Dean's group.[6] Isoflavone was lithiated at position 2 but it did not react easily; after carboxylation the yield of the 2-carboxylic acid was low.[6] In addition, it appeared not to react at all with the lithium bistrimethylsilylamide reagent. Chromones unsubstituted at C-2 are susceptible to ring cleavage and consequently C-2 lithiation is difficult to achieve. Although the evidence is not strong, it does support a preference for 3- over 2-lithiation. Lithiation at both positions can be improved by appropriate substituents. With an acetal at position 3, chromone derivatives were readily lithiated at position 2 and the anion could be captured with electrophiles.[7]

On the basis of this pioneering work, we have developed a strategy for the synthesis of wrightiadione **1**. We envisaged that the carbanion at C-2 of *N*,*N*-diethylisoflavone-2′-carboxamide **4** could be generated under remote metalation conditions using *N*,*N*-diethylcarboxamide as a directed metalation group (DMG). The resulting carbanion **3** could counter attack with the *N*,*N*-diethylcarboxamide functioning as an electrophile to give the product **1**. The key intermediate isoflavone **4** could be prepared from 2-hydroxybenzoin **5** using a C_1 addition procedure as shown in a general method for the synthesis of isoflavones.[8] Compound **5** could be prepared from the lateral lithiation reaction[9] of toluamide **7** with methyl salicylate **6** as shown in Scheme 1.



Scheme 1

The lateral lithiation reaction[10] of toluamide **7** using LDA as base in THF at –78 °C followed by reaction with methyl salicylate (**6**) provided 2-hydroxybenzoin **5**[11] in 58% yield as shown in Scheme 2. However, the tolyl anion **8** could also react with another molecule of **7** to give the deoxybenzoin intermediate **9** which further lactonized to isocoumarin[12] **10** (11%). Similar coupling of the anion of methyl *ortho*-toluate to the corresponding isocoumarin has been reported by Hauser.[13]

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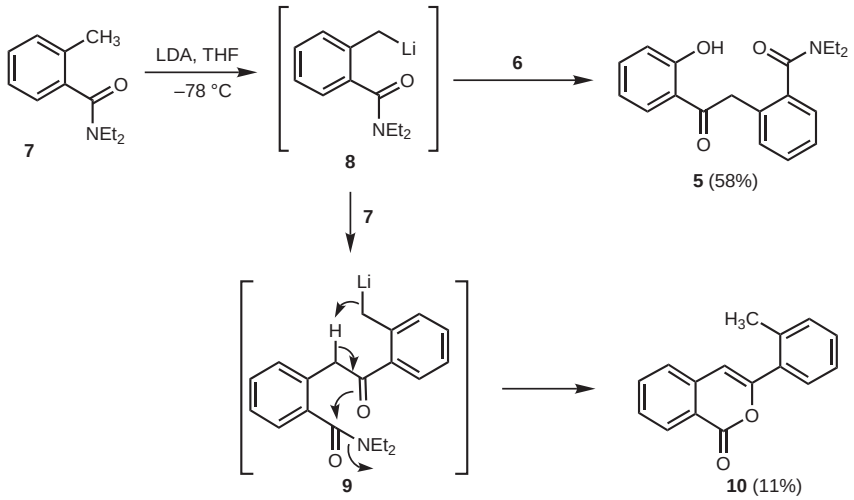

Scheme 2

Compound **5** was converted to the desired isoflavone[15] **4** in 48% yield accompanied by the spiro compound[16] **12** in 14% yield by reaction with a mixture of DMF–$MeSO_2Cl$ and $BF_3{\cdot}Et_2O$ at 70 °C.[14]

The spiro lactone **12** was probably formed by autooxidation at the benzylic position of deoxybenzoin **5** to produce intermediate benzoin **11** which could further cyclize in a tandem fashion to compound **12** as shown in Scheme 3.[17] The lithiation of isoflavone **4** was carried out by using LDA (5 equiv) in THF at –78 °C.[18] The carbanion intermediate **3** thus formed then reacted with the carboxamide group to give the desired wrightiadione **1** in moderate yield (49%). The identity of wrightiadione was proved by comparison of the spectroscopic data with that of the previously synthesized product.[2]

In conclusion, we have described an alternative approach to the synthesis of wrightiadione **1** via a basic directed remote metalation strategy. The synthesis is highly concise and employs the rarely used isoflavone metalation.

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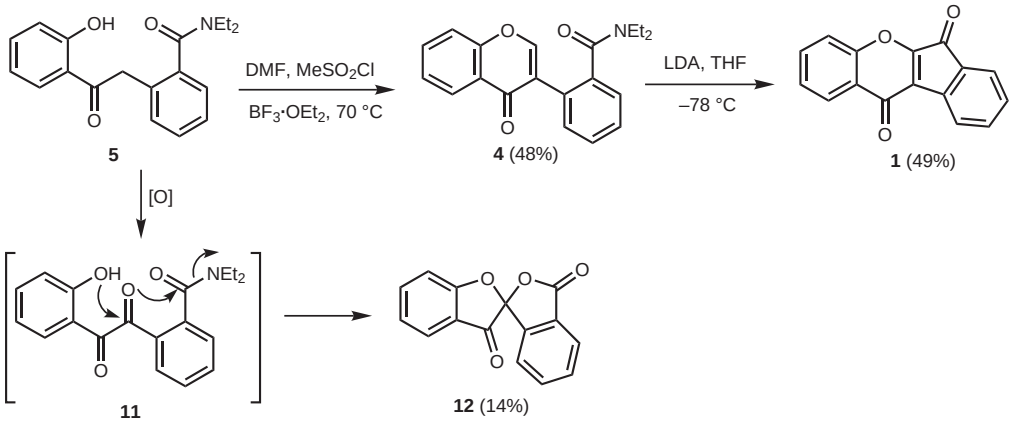

Scheme 3

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(10) Reaction of *N*,*N*-diethyl-*O*-toluamide (**7**) with methyl salicylate (**6**) in the presence of LDA: A solution of LDA in dry THF (200 mL) was prepared by adding diisopropylamine (14.7 mL, 0.10 mol) dropwise to a 0.95 M solution of *n*-BuLi (95 mL, 0.10 mol) in hexane under argon at 0 °C. The ice-water bath was replaced by a dry ice/acetone bath. The stirring was continued for 30 min at –78 °C, and then *N*,*N*-diethyl-*O*-toluamide (**7**, 14.4 g, 75.0 mmol) in dry THF (30 mL) was added. The pale yellow solution turned to deep red, indicating anion formation. The reaction mixture was allowed to warm to 0 °C with an ice-water bath, stirred for 10 min and the ice-water bath was replaced by a dry ice/acetone bath. The stirring was continued for 1 h. A solution of methyl salicylate (**6**, 11.4 g, 75.0 mmol) in dry THF (30 mL) was added slowly via syringe to the above mixture. Stirring at this temperature was continued for 2 h and then the reaction mixture was warmed to room temperature. 2 N HCl was added and the entire mixture was stirred for 1 h. Removal of solvent under reduced pressure gave a residue which was extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous sodium carbonate solution, water and brine solution, and dried over anhydrous sodium sulfate. After removal of solvent, the residue was column chromatographed on silica gel using EtOAc and hexane as eluents to provide the desired 2-(2-*N*,*N*-diethylcarboxamidephenyl)-1-(2-hydroxyphenyl)ethan-1-one (**5**) as the major adduct (13.5 g, 58%) and 3-(2-methylphenyl) isochromen-1-one (**10**) as the minor adduct (1.9 g, 11%).
(11) Compound **5**: colorless crystals: mp 168–169 °C (EtOAc:hexane); IR (KBr) 3061 (OH), 1744 (C=O), 1648 (C=O), 1628, 1603, 1486, 1272, 1215 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (t, 3 H, *J* = 7.2 Hz), 1.09 (t, 3 H, *J* = 7.2 Hz), 3.15 (q, 2 H, *J* = 7.2 Hz), 3.45 (m, 2 H), 4.44 (br s, 2 H), 6.95 (m, 2 H), 7.30 (m, 4 H), 7.47 (dd, 1 H, *J* = 1.2 Hz, 7.6 Hz), 7.90 (dd, 1 H, *J* = 1.0 Hz, 8.1 Hz), 12.09 (s, 1 H); ^{13}C NMR (50 MHz, CDC l_3) δ 12.1, 13.7, 38.5, 42.0, 42.8, 118.3, 119.0, 119.2, 125.6, 127.0, 128.9, 130.3, 131.2, 131.3, 136.6, 137.3, 162.4, 170.3 (CON), CO not observed; MS (EI) *m/z* 311 (M^+, 0), 238 (68), 210 (85), 181 (100), 152 (21). HRMS (FAB) calcd for $C_{19}H_{21}NO_3$ [MH^+]: 312.1560; found 312.1560.
(12) Compound **10**: white solid: mp 80–82 °C (EtOH); IR (KBr) 1719 (C=O), 1648 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 6.56 (s, 1 H), 7.26 (m, 3 H), 7.46 (m, 3 H), 7.69 (dd, 1 H, *J* = 1.2 Hz, 7.2 Hz), 8.28 (dd, 1 H, *J* = 0.8 Hz, 8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 105.9, 120.3, 125.8, 126.0, 128.2, 129.2, 129.5, 129.8, 131.0, 132.7, 134.8, 136.7, 137.5, 155.5, 162.6; MS (EI) *m/z* 236 (M^+, 100), 208 (83), 207 (39), 193 (27), 179 (43) Anal. calcd. for $C_{16}H_{12}O_2$: C, 81.34; H 5.12. Found: C, 80.94; H 4.87.
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(14) 3-(2-*N*,*N*-Diethylcarboxamidephenyl)-4*H*-chromen-4-one (**4**). 2-Hydroxydeoxybenzoin (**6**, 0.62 g. 2.0 mmol) was dissolved in distilled $BF_3{\cdot}Et_2O$ (5 mL) under argon. A solution of methanesulfonyl chloride (3 mL) in dry DMF (15 mL) was slowly added and the mixture was heated at 70 °C for 2 h. The reaction was cooled to room temperature and poured into an ice-cold aq sodium acetate. The mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and dried over anhydrous sodium sulfate. Solvent was removed under vacuum and the residue was purified by preparative layer chromatography on silica gel (elution with CH_2Cl_2) to give isoflavone **4** as a white solid (0.30 g, 48%).
(15) Compound **4**: mp 173–175 °C (EtOH); IR (KBr) 1639 (C=O), 1595, 1471, 1386, 1359, 1299, 1228 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (m, 6 H), 3.04 (m, 4 H), 7.35 (m, 6 H), 7.63 (ddd, 1 H, *J* = 0.6 Hz, 1.2 Hz, 7.2 Hz), 7.57 (dd, 1 H, *J* = 1.2 Hz, 7.2 Hz), 7.61 (dd, 1 H, *J* = 1.6 Hz, 7.0 Hz, 8.6 Hz), 8.06 (s, 1 H), 8.18 (ddd, 1 H, *J* = 0.4 Hz, 1.6 Hz, 8.0 Hz); ^{13}C NMR [50(16) MHz, $CDCl_3$] δ 12.1, 13.7, 38.5, 42.8, 118.2, 123.5, 124.2, 125.3, 126.0, 126.1, 128.3, 128.7, 131.4, 133.8, 137.5, 154.7, 156.3, 170.2, 176.2; MS (EI) *m/z* 321 (M^+, 13), 320 (24), 249 (100), 221 (55), 192 (6), 165 (25) Anal. calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H 5.96 N, 4.36. Found: C, 74.95; H 5.54 N, 4.07.
(16) Compound **12**: white solid (14%): mp 183–185 °C (EtOH); IR (KBr) 1719 (C=O), 1649 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.19 (m, 2 H), 7.33 (m, 1 H), 7.70 (m, 2 H), 7.78 (m, 2 H), 7.92 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.2, 113.7, 118.6, 122.6, 123.6, 125.8, 126.2, 127.1, 132.0, 135.2, 139.8, 142.3, 167.0, 171.3, 192.6; MS (EI) *m/z* 252 (M^+, 62), 224 (41), 223 (23), 196 (26), 195 (15), 180 (100), 168 (37) Anal. calcd. for $C_{15}H_8O_4$: C, 71.43; H 3.20. Found: C, 71.74; H 3.10.
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(18) Wrightiadione **1**: A solution of LDA in dry THF (10 mL) was prepared as in ref.[10] using diisopropylamine (0.4 mL, 2.6 mmol) and 0.7 M solution of *n*-BuLi (3.0 mL, 2.5 mmol) in hexane. The LDA was stirred for 30 min at –78 °C, and then isoflavone **4** (0.15 g, 0.5 mmol) in dry THF (5 mL) was added. Stirring at this temperature was continued for 2 h and then the reaction mixture was warmed to room temperature. Water was added and the mixture was stirred for 30 min. The organic layer was separated and washed again with water, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting orange residue was purified by preparative layer chromatography on silica gel using CH_2Cl_2 as eluent to give crystals of wrightiadione **1** (0.07 g, 49%).