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Synthesis of Unsymmetrical Benzil Licoagrodione

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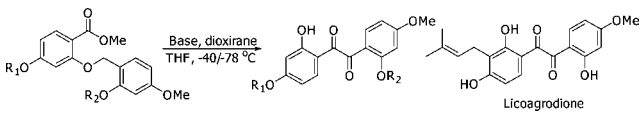
Received June 27, 2008



A synthesis of unsymmetrical 1,2-diarylethane-1,2-dione is reported involving the intramolecular cyclization of anionic benzylic ester of the aryl benzyl ether followed by oxidation employing dioxirane. With the use of microwave irradiation, licoagrodione was prepared from Claisen rearrangement of the corresponding allyl phenyl ether 1,2-diketone readily available from the Lindlar's reduction of the corresponding alkyne derivative. Subsequent removal of protecting groups then furnished the desired product.

Benzils, 1,2-diarylethane-1,2-diones, are an important class of compounds for organic synthesis as the synthetic studies of both symmetrical and unsymmetrical benzils have been reported.[1,2] Some benzils exhibited various potential biological activities including inhibition of mammalian carboxylesterases (CE).[3] They were often isolated concurrently with other flavanoids as common constituents of plants in the Leguminosae family, and have been used as intermediates for the synthesis of various flavonoids (Figure 1).[4] Licoagrodione (**1**), isolated from a Chinese herb, *Glycyrrhiza glabra* (licorice), was found to exhibit antimicrobial activity,[5] while its backbone, 2,2′,4-trihydroxy-4′-methoxybenzil (**2**), has been isolated from the wood of *Zollernia paraensis*.[6] Scandione (**3**) was isolated from the stem of a Thai medicinal plant, *Derris scandens*, and showed antibacterial, hypertensive, and radical scavenging activities.[7] Lespedezol H_1 (**4**) was isolated from the stem of *Lespedeza homoloba*,[8] and its benzil C-glycoside, vijayosin (**5**), was isolated from *Pterocarpus marsupium*, which has been used as an ayurvedic drug in India.[9] Not only isolated from various plants, the heteroaryl-1,2-diketones, 1,2-bis(1*H*-indol-3-yl)ethane-1,2-dione (**6**) and hyrtiosin B (**7**), were also isolated from marine sponges, *Smennospongia* sp.[10] and *Hyrtios erectus*,[11] respectively.

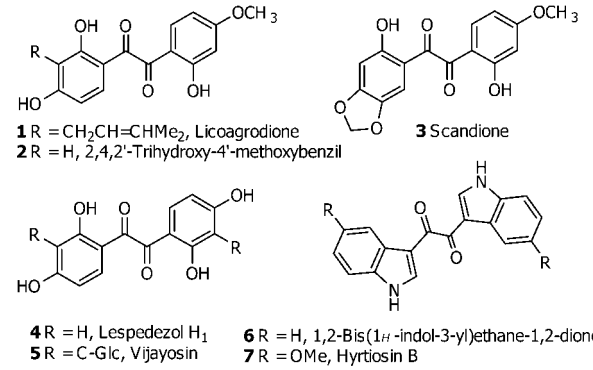


FIGURE 1. Unsymmetrical and symmetrical natural benzils.

We recently described the synthesis of 2-phenylbenzofuran-3-carboxylic acid involving the rearrangement of aromatic cyanohydrin carbonate esters and intramolecular cyclization of the benzylic carbanion using LDA.[12] With the initial intention to synthesize wrightiadione (**11**),[13] lithiation of active methylene protons of ketone **9** followed by reaction with methyl-*O*-benzylsalicylate **8a** was thought to smoothly afford 1,3-diketone **10** (Scheme 1). Unfortunately, no target compound **10** was observed, but unexpected product was obtained in moderate yield. The product was charecterized as 2-hydroxy-1,2-diphe-

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10.1021/jo8013353 CCC: $40.75
Published on Web 08/20/2008

SCHEME 1. Initial Research Goal

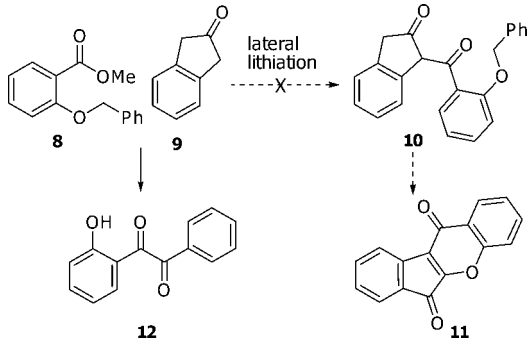
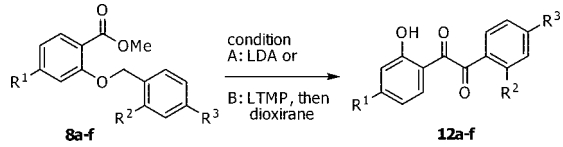


TABLE 1. Optimization of the Anionic Benzylic Ester Rearrangement



					yield (%)	
entry	**12**	R^1	R^2	R^3	A[a]	B[b]
1	**a**	H	H	H	43[c]	58
2	**b**	H	H	OMe	31	53
3	**c**	OMe	H	H	16	33
4	**d**	OMe	H	OMe	16	39
5	**e**	H	NO_2	H		NA[d]
6	**f**	H	H	NO_2		NA[e]

[a] Condition A: 2 equiv of LDA, THF, −78 °C. [b] Condition B: 3 equiv of LTMP, THF, −78 °C, then dioxirane. [c] 46% of benzil **12a** was obtained after addition of oxygen gas. [d] 4 equiv of LTMP was used and gave 27% recovery of benzyl ester **8e**. [e] 13% recovery of benzyl ester **8f**.

nylethane-1,2-dione **12a** on the basis of spectroscopic and analytical data with a singlet of hydroxy proton at δ 11.39 in the ^{1}H NMR spectrum and the dicarbonyl groups at 1677 and 1643 cm^{-1} in the IR spectrum.

This unexpected result prompted us to investigate the potential application of this finding for the construction of natural unsymmetrical benzils using the intramolecular cyclization of anionic benzylic ester of the aryl benzyl ether and subsequent oxygenation. General methods for deprotonating the benzylic ether proton involve the photochemical hydrogen atom abstraction reaction[14] or the hindered nonionic phosphazene base.[15]

Herein we developed a concise method for the synthesis of unsymmetrical benzils by the deprotonation of the benzylic ether using lithiated bases (LDA and LTMP) in anhydrous media followed by reacting the intermediate with molecular oxygen or with dioxirane to afford benzil **12**. Methyl-*O*-benzylsalicylate derivatives **8a**−**f** were used as prototypes in this study. Our results are summarized in Table 1.

Treating simple benzylic ether **8a** with 2 equiv of LDA (condition A) gave 2-hydroxybenzil **12a** in moderate yields either in the presence or the absence of the molecular oxygen gas (Table 1, condition A, entry 1). The electron-donating groups on both aromatic rings gave lower yields of the corresponding products under the same condition (Table 1, entries 2 to 4). When 3 equiv of LTMP was employed instead of 2 equiv of

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SCHEME 2. Proposed Mechanism for the Formation of 12

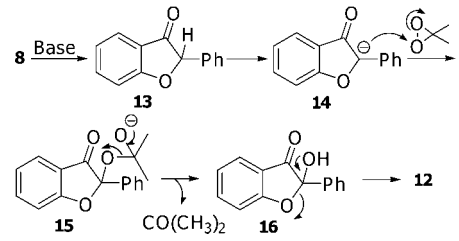
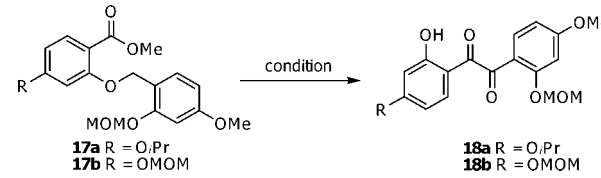


TABLE 2. Preparation of 2-Hydroxy-2′-methoxy-4′-methoxybenzil 18



entry	condition	yield of **18** (%)
1	4.0 equiv of LTMP, THF, −78 °C, then O_2	**a**, 47
2	4.0 equiv of LTMP, THF, −78 °C, dioxirane	**a**, 50
3	4.0 equiv of LTMP, THF, −78 °C, then O_2	**b**, 16
4	4.0 equiv of LTMP, THF, −40 °C, dioxirane	**b**, 48[a]
5	4.5 equiv of LTMP, THF, −40 °C, dioxirane	**b**, 54

[a] 15% recovery of benzyl ester **17b**.

LDA while using dimethyldioxirane (DMDO) as the source of oxygen atom (condition B),[16] the yield was dramatically improved (Table 1, condition B, entries 1 to 4). The presence of an electron-withdrawing nitro group at the ortho or para position of the aromatic benzyl ether gave the complex mixture and recovered starting material in 27% and 13% yield (Table 1, entries 5 and 6), respectively, as previously reported by Scaiano.[17] LHMDS was also studied in this condition and gave no reaction.

The proposed mechanism was shown in Scheme 2. The benzylic carbanion of benzyl ether **8** could intramolecularly cyclize to give 2-phenylbenzofuranone **13**, which could be converted to the corresponding anion **14** and reacted spontaneously with dioxirane leading to the hemiketal anion **15**. Subsequent loss of acetone gave 2-hydroxy-2-phenylbenzofuran-3-one **16**, which, upon ring opening, furnished 2-hydroxybenzil **12**.

Having successfully synthesized unsymmetrical benzils, we then applied the above approach (condition B) to the synthesis of licoagrodione (**1**). 2-Hydroxy-4-isopropoxy-2′-methoxymethoxy-4′-methoxybenzil **18a** was used as the licoagrodione backbone and was synthesized from methyl 4-isopropoxy-2-(4-methoxy-2-(methoxymethoxy)benzyloxy)benzoate **17a**. With the optimized condition, increasing the amount of base to 4 equiv of LTMP gave benzil **18a** in 47−50% yield (Table 2, entries 1 and 2).

The structure of benzil **18a** was fully supported by spectroscopic data at δ 190.0 and 197.6 in the ^{13}C NMR for the two carbonyl peaks. The "C-5" Dimethylallyl group equivalent was introduced into the molecule as the corresponding alkynyl ether of the phenolic group by reacting **18a** with 3-chloro-3-methylbut-1-yne and NaH in DMF in 92% yield.[18] The alkyne

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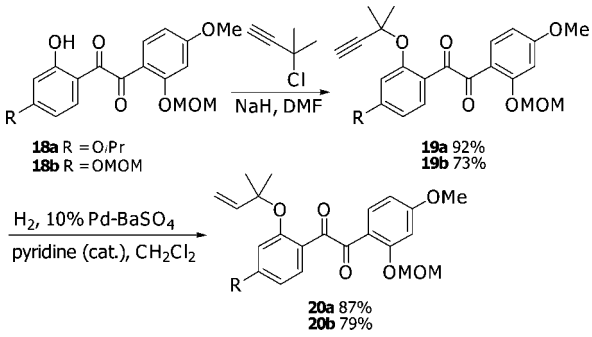
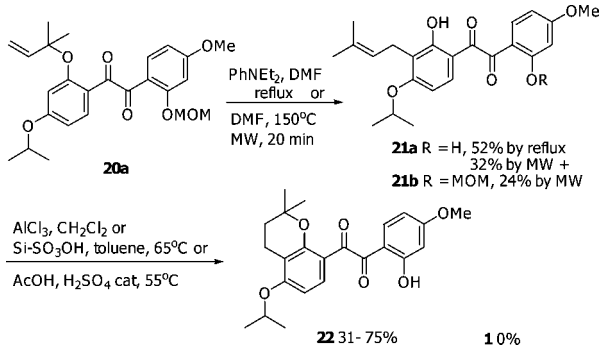
SCHEME 3. Preparation of Allyl Aryl Ether 1,2-Diketones 20



SCHEME 4. The Claisen Rearrangement and Deprotection Reactions



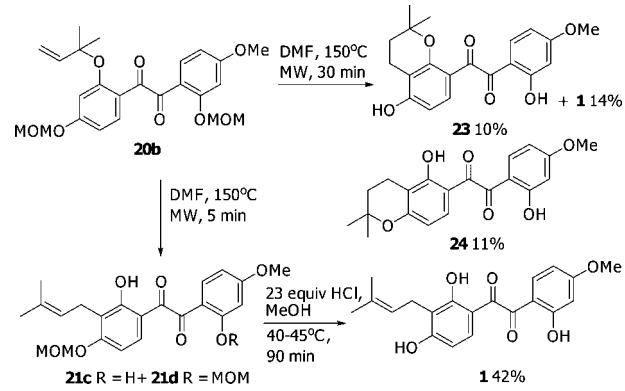
19a was characterized and the alkyne absorption was observed at 3263 cm^{-1}. Hydrogenaton of alkyne **19a** under 10% Pd-$BaSO_4$ in CH_2Cl_2 yielded the 2-methylbut-3-en-2-yloxy ether **20a** in 87% yield (Scheme 3).[19]

The Claisen rearrangement of **20a** under refluxing *N*,*N*-diethylaniline followed by the deprotection of both MOM and isopropyl ethers with 6 N HCl afforded the isopropyl ether licoagrodione **21a** in 52% yield. However licoagrodione (**1**) was not obtained by using this acidic deprotection reaction.

Moody[20] reported the Claisen rearrangement of the allyl group under refluxing of DMF. We then modified the rearrangement of **20a** using microwave irradiation. Under the microwave irradiation at 150 °C for 20 min, the isopropyl ether **21a** and its congener the MOM ether **21b** were obtained in 32% and 24% yields, respectively (Scheme 4). All attempts to cleave the isopropyl ether of **21a** with use of $AlCl_3$ in CH_2Cl_2,[21] Si-tosic acid in toluene at 65 °C,[22] and acetic acid at 55 °C[23] with a catalytic amount of sulfuric acid led only to the cyclization product, dihydrobenzopyranethane-1,2-dione **22**, in moderate to good yields while none of the target licoagrodione (**1**) was obtained.

We then turned to the use 2-hydroxy-2′,4-di(methoxymethoxy)-4′-methoxybenzil **18b** as the benzil skeleton and synthesis of the required benzil then started from methyl benzoate **17b**. Under reaction condition similar to those for the synthesis of compound **18a**, the benzil **18b** was obtained in 16−48% yield (Table 2, entries 3 to 4). With the use of MOM as the protecting group in place of the isopropyl group, increasing the amount of base to 4.5 equiv of LTMP while raising the temperature to −40 °C gave the desired product **18b** in better yield (Table 2, entry 5). The *O*-alkylation of benzil **18b** with 3-chloro-3-methylbut-1-yne following Lindlar's reduction gave **20b** in good overall yield (Scheme 3).

SCHEME 5. Synthesis of Licoagrodione (1)



The microwave irradiation at 150 °C for 5 min assisted the Claisen rearrangement of **20b** to yield an inseparable mixture of **21c** and **21d**. Increasing the reaction time to 30 min furnished the ultimate target licoagrodione (**1**) in 14% yield with the cyclization congener **23** and **24** in 10% and 11% yield, respectively (Scheme 5). Subsequent hydrolysis of the MOM ether of the product from the Claisen rearrangement **21c** and **21d** with 23 equiv of HCl in MeOH at 40−45 °C for 90 min afforded the licoagrodione (**1**) in moderate yield (42%).[24]

In summary, we have developed a facile route for the unsymmetrical benzils **12** and **18**. Compounds **18a** and **18b** lend themselves to conversions to various natural benzils, and were also applied to the synthesis of licoagrodione (**1**). The key reactions are (1) the intramolecular cyclization of the anionic benzylic ester of methyl *O*-benzyl salicylate derivatives followed by the oxygenation with dioxirane, (2) the Claisen rearrangement under neutral condition using microwave irradiation, and (3) hydrolysis of the MOM ether under relatively mild conditions. This methodology should be valuable for the synthesis of unsymmetrical benzils and we are applying this methodology to the synthesis of related benzils and other biologically important oxygen heterocyclic compounds.

Experimental Section

1-(2-Hydroxy-4-isopropoxyphenyl)-2-(4-methoxy-2-*O*-methoxymethylphenyl)ethane-1,2-dione (18b). A solution of LTMP (2.25 mmol, 4.5 equiv) was prepared by dropwise addition of *n*-BuLi (2.62 M in hexane) (0.86 mL, 2.25 mmol) into tetramethylpiperidine (0.79 mL, 4.5 mmol) in dry THF (5 mL) under argon atmosphere at −78 °C. The mixture was then warmed to 0 °C and stirred at this temperature for 1 h. The ice−water bath was replaced with a dry ice/CH_3CN bath, and a solution of methyl 2-(4-methoxy-2-*O*-methoxymethylbenzyloxy)-4-*O*-alkoxylbenzoate **17b** (196 mg, 0.5 mmol, 1 equiv) in dry THF (1 mL) was added and the solution was stirred at this temperature for 1 h. The pale yellow solution

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turned orange and dimethyldioxirane (5 mL) was added dropwise at −40 °C. The resulting mixture was quenched with saturated NH_4Cl and extracted with EtOAc (3 × 25 mL), washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated to give yellow oil, which was purified by PLC using 20% EtOAc in hexane as developing solvent to afford 2′-hydroxy-1,2-diarylethanediones **18b** (102.2 mg, 54%) as a pale yellow oil: IR (UATR) ν_{max} 2959, 2927, 1620, 1595, 1573, 1501, 1245, 1217, 1152, 1120, 1077, 984, 922, 865, 781, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.66 (s, 1H), 8.05 (d, J = 8.9 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.71 (dd, J = 8.9, 2.2 Hz, 1H), 6.67 (d, J = 2.3 Hz, 1H), 6.61 (d, J = 2.2 Hz, 1H), 6.51 (dd, J = 8.8, 2.3 Hz, 1H), 5.21 (s, 2H), 4.95 (s, 2H), 3.87 (s, 3H), 3.47 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 190.0, 166.8, 165.3, 163.9, 159.9, 133.4, 132.6, 116.8, 111.4, 108.7, 108.5, 103.8, 99.9, 94.1, 94.0, 56.4 (2C), 55.8; EI-MS m/z (%) 375 ($M^+ - 1$, 1), 195 (100), 181 (13), 167 (8), 165 (52), 151 (23); HRMS (microTOF) calcd for $C_{19}H_{20}O_8Na$ 399.1050, found 399.1054.

Licoagrodione (1). In a 10 mL microwave vessel, 1-[2-(1,1-dimethylallyloxy)-4-*O*-methoxymethylphenyl]-2-(4-methoxy-2-*O*-methoxymethylphenyl)ethane-1,2-dione **20b** (48.5 mg, 0.109 mmol) was dissolved in DMF (1 mL). The solution was heated in a microwave reactor (200 W) at 150 °C for 5 min. The solution was then diluted in ethyl acetate (15 mL) and washed with water (3 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to give red-brown oil as a mixture of **21c** and **21d**. The mixture was then treated with a solution of (23 equiv) HCl in MeOH (2.3 mL) and heated at 40−45 °C for 90 min. The reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give red-brown oil. The crude product was then purified by PLC using 30% EtOAc in hexane as developing solvent to give yellow oil which was recrystallized with CH_2Cl_2 and hexane to furnish licoagrodione (**1**) (16.3 mg, 42%) as a yellow solid: mp 126−127 °C (CH_2Cl_2−hexane); IR (UATR) ν_{max} 3357, 1633, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.12 (s, 1H), 11.84 (s, 1H), 7.39 (d, J = 9.0, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 9.0, 1H), 6.44 (dd, J = 9.0, 2.4 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 5.31−5.25 (m, 1H), 3.87 (s, 3H), 3.47 (d, J = 7.2 Hz, 1H), 1.84 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7 (2C), 167.7, 166.7, 163.8, 163.3, 136.2, 134.1, 132.2, 120.5, 114.5, 111.0, 110.8, 109.2, 108.9, 101.1, 55.8, 25.8, 21.5, 17.9; EI-MS m/z (%) 356 (M^+, 8), 205 (100), 151 (28), 149 (31); HRMS (microTOF) calcd for $C_{20}H_{21}O_6$ $(M + H)^+$ 357.1333, found 357.1334.

Acknowledgment. Financial support from the Thailand Research Fund (TRF; RMU4980048 for N.T.) and The Center for Toxicology, Environmental Health and Management of Toxic Chemicals (CTEM) is gratefully acknowledged.

Supporting Information Available: General methods, experimental procedures, as well as spectroscopic data and copies of NMR spectra of compounds (**12a**−**d**, **18a**,**b**, **19a**,**b**, **20a**,**b**, **21a**, **22**, and **1**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO8013353