http://dx.doi.org/10.5012/bkcs.2012.33.9.3095

Synthesis of Versatile 1-Indanones and their Conversion to 1,2-Naphthoquinones, Key Precursors for the Construction of Perylenequinone Core

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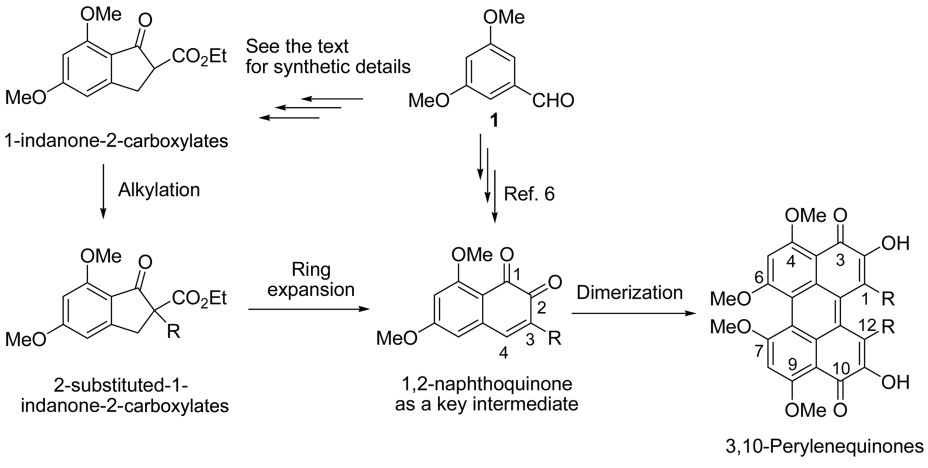
Received May 16, 2012, Accepted May 31, 2012

Key Words : Photodynamic therapy, Photosensitizer, 2-Allyl-1-indanone-2-carboxylate, 3-Allyl-1,2-naphthoquinone

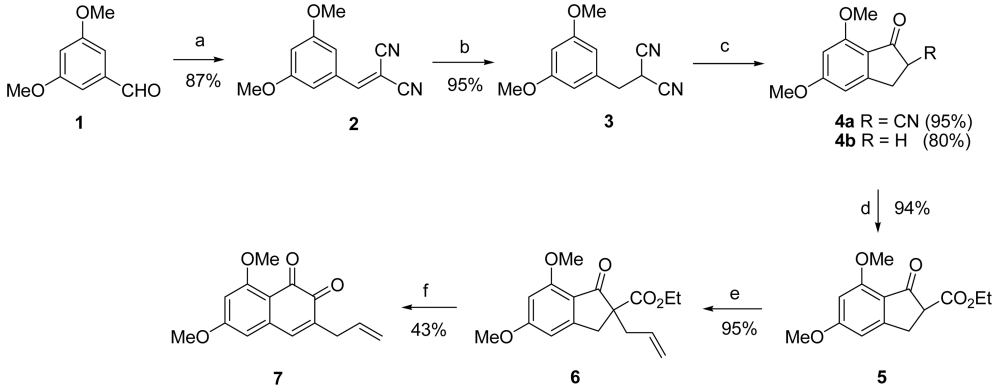
4,9-Dihyroxy-3,10-perylenequinones are natural pigments produced by a wide variety of molds, which act as photodynamic phototoxins to their hosts.[1] Due to their unique photosensitizing properties, considerable attention has been paid to the application of these perylenequinones in photodynamic therapy (PDT) as anticancer,[2] antiviral,[3] and antifungal agents,[4] particularly in developing efficient methodologies for the synthesis of naturally occurring perylenequinones and their analogues.[5] However, the reported synthetic routes are pretty lengthy (over about 20 reaction steps) to the final bioactive perylenequinones, and the introduction of diverse substituents into perylenequinone core is likely to be difficult in one specific route. Consequently, perylenequinone derivatives with diverse structural features have not prepared in sufficient quantity to allow investigation of their structure-activity relationships. In addition, our literature analysis on the structural features of perylenequinones indicated that the successful formation of perylenequinones and the variation in the yields is likely to be dependent on the diversity of substitution at the 3-position of 1,2-naphthoquinone, a key precursor for the construction of perylenequinone core in the dimerization step (Scheme 1).[5] In our previous work,[6] we prepared the novel perylenequinone core through a dimerization of 1,2-naphthoqinone (Scheme 1). While this synthetic route was pretty efficient in terms of relatively short reaction steps to the perylenequinone core (11 steps) and the satisfactory overall yield, it also is limited in the introduction of diverse substituents into the 1- and 12-positions of the perylenequinone core.

We endeavored to develop a novel pathway to construct the perylenequinone core with the goal of the easy introduction of diverse substituents at the 1- and 12-positions. To this end, we designed 1-indanones **4-6** as precursors, which would bear diverse substituents at the 2-position (**6**, Scheme 2) and which, in turn, could be readily converted by ring expansion to 3-substituted-1,2-naphthoquinones **7**, the key precursor to perylenequinone (Scheme 2). We also hoped that this synthetic route could shorten the reaction pathway by at least several reaction steps. We focused on the efficient synthesis of versatile 1-indanones bearing diverse substituents at the 2-position of the molecule, and their conversion to the corresponding naphthoquinones. Presently, we report the efficient synthetic methodology of versatile 2-substituted-1-indanone **6** and demonstrate that these 1-indanones are useful precursors for the efficient preparation of 1,2-naphthoquinone **7**, as we expected.

On the basis of our literature survey[7] for the preparation of multi-functionalizable 1-indanones **4-6** in mild and economic conditions, and in acceptable yields, we investigated the Hauben-Hoesch condensation reaction,[8] a kind of Friedel-Craft acylation with nitriles, which involves the electrophilic substitution of aromatic C-H bonds with intramolecular



Scheme 1. The synthetic flow to 3,10-perylenequinones *via* 1-indanone derivatives and 1,2-naphthoquinones as key precursor.



Scheme 2. The synthetic pathway to 1,2-naphthoquinine (**7**) *via* 1-indanone derivatives (**4**-**6**). (a) Malonitrile, piperidine, toluene, reflux; (b) $NaBH_4$, EtOH, −18 °C; (c) (i) HCl, $AlCl_3$, Et_2O, rt (ii) H_2O, 60 or 120 °C; (d) NaH, diethyl carbonate, benzene, reflux; (e) NaH, allyl bromide, THF; (f) SmI_2, THF, rt.

Table 1. Hauben-Hoesch condensation of 2-(3,5-dimethoxybenzyl)-malononitrile **3** with the variation of Lewis acids and their amounts

Entry	Lewis acid (eqiv.)[a]	Reaction time (hour)		Yield of **4a** (%)
		(i)	(ii)	
1	$ZnCl_2$ (1.7)	0.5	6	36
2	$ZnCl_2$ (5.0)	1	4.5	45
3	$AlCl_3$ (1.7)	3	2	52
4	$AlCl_3$ (5.0)	2	4	95
5	$FeCl_3$ (1.7)	3.5	1.5	0[b]

[a]Equivalent to the compound **3**. [b]The only unknown product was obtained: R_f = 0.3 on silica gel tlc (EtOAc:Hexane = 7:3, v/v).

nitriles under gaseous HCl. The straightforward synthetic route to prepare the 1-indanone compound **4** by Hauben-Hoesch condensation is shown in Scheme 2. Briefly, 3,5-dimethoxybenzaldehyde **1** and malonitrile are condensed to yield compound **2**, which is selectively reduced at a double bond with sodium borohydride to afford compound **3**, in good yields (**2**: 87% and **3**: 95%). Then, compound **3** is condensed intramolecularly under typical Hoesch reaction condition, *i.e.*, the reaction mixture containing $ZnCl_2$ (1.7 equivalent to the compound **3**) as a Lewis acid was continuously bubbled with anhydrous gaseous HCl for 2-3 hours at room temperature, and then the resulting solid was hydrolyzed by adding water at various temperature. The product, 2-cyano-1-indanone **4a** was produced, although the yield was very poor (0-36%). The best yield of **4a** (37%) was obtained when hydrolyzed at the temperature of 60 °C, while hydrolysis at higher temperatures (80-120 °C) resulted in much lower yield (0-16%). At 120 °C, the hydrolyzed product **4b** was obtained in poor yield (50%) *via* over-hydrolysis of cyano group into carboxylic acid and subsequent decarboxylation. To improve the yield of compound **4a**, we varied Lewis acids other than $ZnCl_2$, such as $AlCl_3$ and $FeCl_3$, their amount, and the reaction times for the hydrolysis. The temperature for hydrolysis was determined as 60 °C, at which the relative yield was shown to be better than those at other temperatures. The results are shown in Table 1. The reaction condition using an excess amount of $ZnCl_2$ (5 equivalents to compound **3**) contributed to the marginal improvement of yield (45%, entry 2). The use of $FeCl_3$ (3.5 equivalents to compound **3**), showing relatively better catalytic power than $ZnCl_2$, gave no desired product but just unknown materials (entry 5). In contrast, to our surprise, the reaction condition using excess $AlCl_3$ (5 equivalents to the starting material) was notable, producing a remarkable improvement of the yield (95%, entry 4), while the use of typical amount of $AlCl_3$ (1.7 equivalents) showed no distinct difference in yield (52%, entry 3). These results suggested that the use of an excess amount of Lewis acid would be necessary to form a complex with the substrate material.

The 1-indanone **4b** was prepared by one-pot reaction from the compound **3** in an acceptable yield (80%) by applying our notable condition of the Hauben-Hoesch condensation reaction and high hydrolysis temperature (120 °C). Under this reaction condition, the hydrolysis of cyano group and subsequent decarboxylation of the resultant carboxyl group led to the production of the desired compound **4b**. This one-pot reaction was advantageous compared to the preparation of the compound **4b** from direct hydrolysis of the compound **4a**, in terms of shortening the reaction pathway by one step and in achieving a relatively good yield. 1-Indanone **4b** was easily carboxylated at the 2-position of the molecule to yield ethyl 1-indanone-2-carboxylate **5** in a good yield (94%). Finally, we investigated whether 2-alkyl substituted-1-indanone-2-carboxlyate derivative **6** could be converted to diverse 1,2-naphthoquinone **7**, a crucial precursor for the construction of the perylenequinone core. As a model case, we successfully synthesized 2-allyl-1-indanone-2-carboxylate **6** in a good yield (95%) *via* the general S_N2 allylation of 1-indanone-2-carboxlyate **5**. In sequence, we scrutinized the conversion of compound **6** to the crucial precursor compound, 1,2-naphthoquinone **7** through the ring extension of compound **6**. The reaction was performed according to a previous procedure,[9] in which samarium diiodide (SmI_2) could promote intramolecular ketone-ester coupling followed by the ring extension reaction of 2-substituted-1-indanone-2-carboxylates. Thus, when compound **6** was treated with 2.2 equivalents of SmI_2 in tetrahydrofuran, an orange-colored solid was obtained. The solid was proven to be the

desired product **7**, but was obtained in a very low yield (16%), along with the considerable amount of starting material (42%). To improve the yield of the compound **7**, the amount of SmI_2 and the reaction temperature were varied. Although the yield was relatively low (43%), the best production of **7** was accomplished when 4.4 equivalents of SmI_2 to starting material was used and the reaction was run at room temperature. However, the increase of the reaction temperature to 50 °C and the use of more SmI_2 (over 4.4 equivalents) decreased the yield (27-37%). Preparation of other derivatives of compound **6** bearing diverse substituents at 2-position and their conversion to the corresponding 1,2-naphthoquinones are in progress and the reaction conditions for the ring expansion are being fine-tuned to enable better production of compound **7**.

In summary, we prepared the versatile ethyl 2-allyl-1-indanone-2-carbolyate **6** and converted it to 3-allyl-1,2-naphthoquinone **7** by ring expansion of compound **6**. We successfully synthesized the 1-indanone derivatives **4** in an economic way and in a relatively high yield by adopting $AlCl_3$ as an unexpected and alternative Lewis acid of Hauben-Hoesch condensation reaction. The 1-indanone derivatives **4-6** are versatile precursors to the preparation of structurally diverse 3-substituted-1,2-naphthoquinones **7**.

Experimental Section

2-(3,5-Dimethoxybenzylidene)malononitrile (2). To a solution of 3,5-dimethoxybenzaldehyde (300 mg, 1.80 mmol) and malonitrile (120 mg, 1.80 mmol) in dried toluene (10 mL) were added piperidine (27 uL, 0.27 mmol) and benzoic acid (22 mg, 0.18 mmol). The reaction mixture was refluxed for 1 h with the removal of water using a Dean-Stark apparatus. The mixture was cooled to room temperature and diluted with ethyl acetate (EtOAc, 50 mL). The organic layer was washed with 5% aqueous HCl (25 mL) and saturated $NaHCO_3$ (50 mL), dried over Na_2CO_3, filtered, and evaporated *in vacuo* to give oily residue. The residue was subjected to flash silica gel column chromatography to afford **2** (335 mg, 87%) as a yellow solid: mp 91 °C; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 7.65 (s, 1H, H-2), 7.00 (d, 2H, J = 2.0 Hz, H-2',6'), 6.67 (t, 1H, J = 2.0 Hz, H-4'), 3.81 (s, 6H, -OCH_3×2); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 161.18, 160.02, 132.28, 113.59, 112.57, 108.17, 107.11, 82.99, 55.61; APCIMS m/z $(M+H)^+$ calcd 215.0821 for $C_{12}H_{11}N_2O_2$: Found: 215.0820.

2-(3,5-Dimethoxybenzyl)malononitrile (3). The solution of compound **2** (335 mg, 1.56 mmol) in ethanol (3 mL) was pre-cooled at −18 °C, then $NaBH_4$ (30 mg, 0.78 mmol) was added to this solution. The mixture was stirred for 20 min and glacial acetic acid (1.5 mL) was added cautiously. The mixture was concentrated *in vacuo* and the residue was taken up in EtOAc (50 mL). This organic layer was washed with 1 N aqueous HCl (10 mL), sat. $NaHCO_3$ (2 × 20 mL) and brine, dried over Na_2CO_3, filtered and evaporated *in vacuo* to give oily residue. The residue was subjected to flash silica gel column chromatography to afford **3** (320 mg, 95%) as a colorless sticky solid: mp 50 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.44 (s, 3H, H-2', 4', 6'), 3.90 (t, 1H, J = 7.2 Hz, H-1), 3.79 (s, 6H, -OCH_3×2), 3.21 (d, 2H, J = 7.2 Hz, H_a-2, H_b-2); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 161.34, 135.00, 112.18 (-CN), 107.06, 100.45, 55.40 (-OCH_3), 36.96, 24.78; APCIMS m/z $(M+H)^+$ calcd 216.0899 for $C_{12}H_{13}N_2O_2$: Found: 217.0977.

5,7-Dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carbonitrile (4a) and 5,7-Dimethoxy-2,3-dihydroinden-1-one (4b). To a solution of compound **3** (200 mg, 0.92 mmol) in dried ethyl ether (10 mL) was added $AlCl_3$ (617 mg, 4.62 mmol) at room temperature. HCl gas was passed through the mixture for 2 h. The solvent was removed *in vacuo*, and the resultant white precipitate was resolved in water (7 mL) and the mixture was refluxed for 4 h at 60 °C. On cooling, the mixture was diluted with water and extracted with CH_2Cl_2 (30 mL). The organic layer was dried over Na_2CO_3, filtered and evaporated *in vacuo* to give pale yellow solid. The residue was applied to flash silica gel column chromatography to afford compound **4a** (192 mg, 95%) as a colorless solid. The compound **4b** was prepared by the same procedure for **4a** except for increasing the hydrolysis temperature to 120 °C. The yield of **4b** was 80%:

4a: mp 167 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.46 (s, 1H, H-6), 6.32 (s, 1H, H-4), 3.90 (s, 3H, -OCH_3), 3.87 (s, 3H, -OCH_3), 3.64 (dd, 1H, J = 8.8; 5.4 Hz, H-2), 3.44 (dd, 1H, J = 17.2; 8.8 Hz, H_a-3), 3.31 (dd, 1H, J = 17.2; 5.4 Hz, H_b-3); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 190.06 (-CO-), 168.31, 160.40, 156.25, 117.42 (-CN), 116.29, 101.79, 98.23, 55.98, 55.94, 37.48, 31.00; APCIMS m/z $(M+H)^+$ calcd 218.0817 for $C_{12}H_{12}NO_3$: Found: 218.0837:

4b: mp 78 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.46 (d, 1H, J = 1.9 Hz, H-6), 6.28 (d, 1H, J = 1.9 Hz, H-4), 3.89 (s, 3H, -OCH_3), 3.85 (s, 3H, -OCH_3), 3.01-2.98 (m, 2H, H_a-3, H_b-3), 2.64-2.61 (m, 2H, H_a-2, H_b-2); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 202.92 (-C=O), 166.84, 160.30, 159.25, 119.32, 101.56, 97.29, 55.62, 36.82, 25.80: APCIMS m/z $(M+H)^+$ calcd 193.0865 for $C_{11}H_{13}O_3$: Found: 193.0864.

Ethyl 5,7-Dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (5). To a suspension of sodium hydride (437 mg, 13.0 mmol, 60% dispersion in mineral oil, washed three times with benzene) in benzene (10 mL) was added diethyl carbonate (0.63 mL, 5.2 mmol) under Ar atmosphere. The mixture was refluxed and then the solution of compound **4b** (500 mg, 2.6 mmol) dissolved in benzene (10 mL) was slowly dropped over 1 h. After checking the completeness of the reaction by the disappearance of the compound **4b** by thin layer chromatography, the reaction mixture was cooled to room temperature and quenched by adding acetic acid. The mixture was diluted with water (60 mL) and partitioned with CH_2Cl_2 (3 × 60 mL). The combined organic layer was with brine, dried over Na_2CO_3, filtered and evaporated *in vacuo* to give oily residue. The residue was subjected to flash silica gel column chromatography to afford **5** (648 mg, 94%) as a colorless solid: mp 91 °C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.45 (d, 1H, J = 1.4 Hz, H-6), 6.24 (d, 1H, J = 1.4 Hz, H-4), 4.16 (q, 1H, J = 7.3 Hz, -CH_2-), 4.15 (q, 1H, J = 7.3 Hz, -CH_2-), 3.83 (s, 3H, -OCH_3), 3.82 (s, 3H, -OCH_3),

3.60 (dd, 1H, J = 8.3; 3.9 Hz, H-2), 3.36 (dd, 1H, J = 17.0; 3.9 Hz, H_a-3), 3.16 (dd, 1H, J = 17.0; 8.3 Hz, H_b-3), 1.23 (t, 3H, J = 7.3 Hz, -CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 195.05 (-C=O), 169.52 (-COO-), 167.46, 159.89, 158.68, 117.48, 101.50, 97.65, 61.44, 55.71, 55.68, 53.75, 30.07, 14.12. APCIMS m/z $(M+H)^+$ calcd 265.1076 for $C_{14}H_{17}O_5$: Found: 265.1076.

Ethyl 2-Allyl-5,7-dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (6). To a suspension of sodium hydride (650 mg, 19.3 mmol, 60% dispersion in mineral oil, washed three times with benzene) in THF (30 mL) was added compound **5** (1.02 g, 3.86 mmol) dissolved in THF (20 mL) under Ar atmosphere at room temperature. Allyl bromide (0.65 mL, 7.734 mmol) was added to the reaction mixture and stirred for 2 h at the same temperature. After checking the completeness of the reaction by the disappearance of the starting material **5** by TLC, the reaction mixture was quenched by adding acetic acid (6 mL). The reaction solvent was removed *in vacuo*, the resultant sticky residue was resolved in EtOAc (150 mL). The organic layer was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ filtered and evaporated *in vacuo* to give oily residue. The residue was subjected to flash silica gel column chromatography to afford **6** (1.16 g, 95%) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.45 (d, 1H, J = 1.5 Hz, H-6), 6.27 (d, 1H, J = 1.5 Hz, H-4), 5.69-5.59 (m, 1H, H-2'), 5.11-4.99 (m, 2H, H_a-3', H_b-3'), 4.11 (q, 2H, J = 7.3 Hz, -CH_2-), 3.87 (s, 3H, -OCH_3), 3.85 (s, 3H, -OCH_3), 3.49 (d, 1H, J = 17.6 Hz, H_a-3), 2.97 (d, 1H, J = 17.6 Hz, H_b-3), 2.83 (dd, 1H, J = 14.1; 7.3 Hz, H_a-1'), 2.54 (dd, 1H, J = 14.1; 7.3 Hz, H_b-1'), 1.18 (t, 3H, J = 7.3 Hz, -CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 197.63, 171.05, 167.52, 159.97, 158.18, 133.28, 118.90, 117.44, 101.45, 97.72, 61.53, 60.38, 55.79, 55.76, 39.04, 35.73, 14.07. APCIMS m/z $(M+Na)^+$ calcd 327.1208 for $C_{17}H_{21}NaO_5$: Found: 327.1216.

3-Allyl-6,8-dimethoxynaphthalene-1,2-dione (7). The SmI_2 was prepared as follows. The solution of samarium powder (683 mg, 4.54 mmol) and iodoform (1.190 g, 3.02 mmol) in anhydrous THF (25 mL) was sonicated with conventional cleaner sonicator (Wiseclean ultrasound laboratory cleaner; 220 V, 50 W, 50/60 Hz) for 0.5 h at ambient temperature under an Ar atmosphere to afford a fresh deep blue solution of SmI_2. To this solution, the compound **6** (314 mg, 1.032 mmol) dissolved in THF (5 mL) was added through glass syringe over 10 min. After checking the completeness of the reaction by the disappearance of the compound **6** by thin layer chromatography, the reaction mixture was quenched by adding sat. $NaHCO_3$ (5 mL). The mixture was extracted with diethyl ether (3 × 50 mL), and the combined organic layer was washed with brine, dried over Na_2CO_3, filtered and evaporated *in vacuo* to give an oily residue. The residue was subjected to flash silica gel column chromatography to afford **7** (116 mg, 43%) as a orange solid: mp 150-162 °C (decomposed); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.99 (s, 1H, H-4), 6.39-6.38 (m, 2H, H-5, 7), 5.90-5.80 (m, 1H, H-2'), 5.17-5.12 (m, 2H, H_a-3', H_b-3'), 3.93 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 3.16-3.14 (m, 2H, H_a-1', H_b-1'); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 181.37, 176.08, 166.47, 165.49, 141.02, 139.20, 138.80, 133.90, 118.01, 112.88, 109.11, 98.61, 56.29, 55.81, 32.97. APCIMS m/z $(M+H)^+$ calcd 259.0970 for $C_{15}H_{15}O_4$: Found: 259.0966.

Acknowledgments. This research was supported by the Bio-industry Technology Development Program, Ministry for Food, Agriculture, Forestry and Fisheries, Republic of Korea.

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