

Difference in Reactivity during Alkylation of 2-(2-Hydroxyaryl)-1,3-indanedione and *N*-(2-Hydroxyphenyl)phthalimide

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Friedel-Crafts type reactions of ninhydrin (1,2,3-indantrione) have been examined by us¹ and other groups.² Besides the common arene compounds phenolic compounds could be used to prepare the corresponding 2-(2-hydroxyaryl)-2-hydroxy-1,3-indanedione derivatives such as **1**.³⁻⁴

Recently, we have reported on the unusual formation of benzo[b]indeno[2,1-d]furanone ring system **3** as well as the normally expected **2** during alkylation of 2-(2-hydroxyaryl)-2-hydroxy-1,3-indanedione derivative **1** as shown in Scheme 1.^{4a}

With the aim of shedding more light on the mechanistic aspects on the reaction, we examined further and report herein the preliminary results. The formation of **3a-b** could be explained by "transfer of nucleophilicity" as shown in Scheme 1. Initially generated phenoxide nucleophilicity is transferred to the carbonyl group to generate the corresponding indenofuranone alkoxide, which could be trapped as their alkylated derivatives **3a-b**. In order to clarify the structure of compounds **3**, we examined on the acid catalyzed hydrolysis of **3b** in aqueous tetrahydrofuran in the presence of hydrochloric acid as shown in Scheme 2.

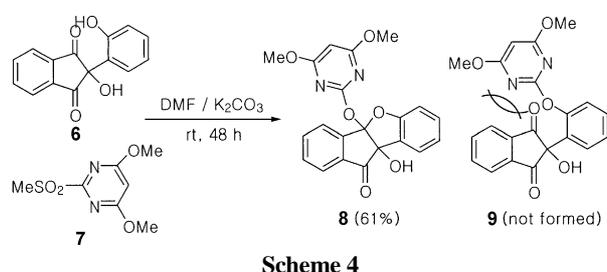
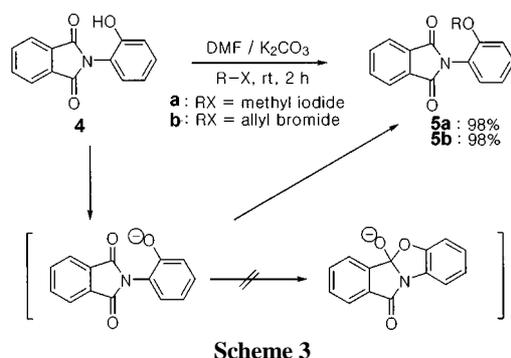
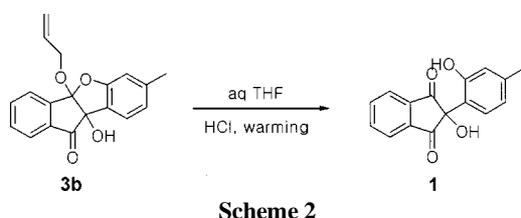
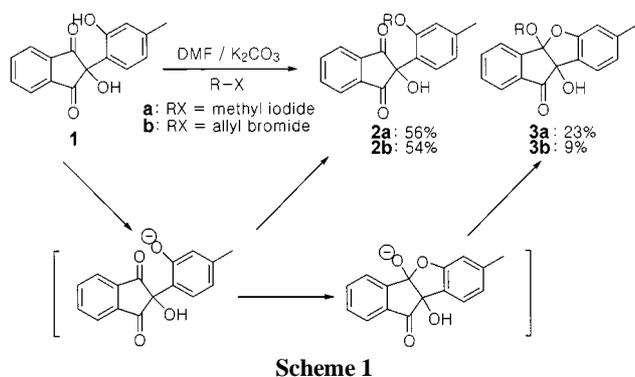
As expected the mixed ketal moiety was hydrolyzed to the starting material **1** quantitatively. Thus, the structure and the proposed mechanism (Scheme 1)^{4a} for the formation of **3** seemed reasonable. *Is it possible that such a transfer of nucleophilicity can occur to amide carbonyl group?* To exam-

ine this, we prepared *N*-(2-hydroxyphenyl)phthalimide (**4**)⁵ from phthalic anhydride and 2-aminophenol in 90% yield, and examined on their alkylation as shown in Scheme 3.

However, normally expected alkylation products **5a-b**⁵ were obtained as the sole products. These differences might be arisen from the diminished electrophilicity of the amide carbonyl group to be attacked by the phenoxide nucleophile.

The amounts of indenofuranone derivatives could be varied by the polarity of the reaction medium. However, the ratios of **2a** and **3a** did not change dramatically in *N,N*-dimethylformamide and in acetone. More important factor for determining the ratios might be the steric bulkiness of the alkylating agents. As an example, the reaction of **6**⁴ and 4,6-dimethoxy-2-methanesulfonylpyrimidine (**7**), which was easily prepared from the commercially available 4,6-dichloro-2-(methylthio)pyrimidine, in the same reaction conditions gave exclusively the corresponding indenofuranone derivative **8**⁵ in good yield (Scheme 4).

Discrimination of **8** and **9** was based on the number of carbon atoms in ¹³C NMR⁵ and the splitting pattern of aromatic protons in ¹H NMR spectrum.⁴ The formation of the normal alkylation product **9** is restricted by the steric hindrance between the pyrimidine and indanedione moiety. Further studies on the reaction and the biological activity of prepared compounds are in progress.



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5. Melting points and representative spectroscopic data of prepared compounds were as follows. **4**: mp. 230-231 °C; ^1H NMR (acetone- d_6) δ 6.94-7.36 (m, 4H), 7.88-7.96 (m, 4H), 9.81 (s, 1H); ^{13}C NMR (acetone- d_6) δ 117.39, 117.49, 120.54, 123.99, 131.18, 131.25, 133.43, 135.13, 154.89, 167.91; Mass (70 eV) m/z (rel intensity) 50 (30), 76 (66), 77 (21), 104 (41), 167 (25), 195 (100), 239 (M^+ , 69). **5a**: mp. 160-161 °C; ^1H NMR (CDCl_3) δ 3.80 (s, 3H), 7.04-7.48 (m, 4H), 7.76-7.98 (m, 4H); ^{13}C NMR (CDCl_3) δ 55.76, 112.06, 120.15, 120.79, 123.60, 129.92, 130.64, 32.17, 134.07, 155.34, 167.34; Mass (70 eV) m/z (rel intensity) 76 (41), 83 (36), 85 (39), 97 (30), 127 (22), 149 (39), 253 (M^+ , 54). **5b**: mp. 121-122 °C; ^1H NMR (CDCl_3) δ 4.55-4.58 (m, 2H), 5.12-5.30 (m, 2H), 5.83-5.96 (m, 1H), 7.01-7.44 (m, 4H), 7.75-7.96 (m, 4H); ^{13}C NMR (CDCl_3) δ 69.03, 113.42, 117.19, 120.55, 120.99, 123.58, 129.96, 130.45, 132.16, 132.57, 134.07, 154.27, 167.28; Mass (70 eV) m/z (rel intensity) 76 (100), 104 (56), 130 (23), 210 (74), 222 (22), 238 (40), 279 (M^+ , 61). **8**: mp. 163-165 °C; ^1H NMR (CDCl_3) δ 3.57 (s, 6H), 5.67 (s, 1H), 6.78-8.05 (m, 8H); ^{13}C NMR (CDCl_3) δ 54.25, 85.66, 87.83, 109.83, 110.50, 122.29, 123.76, 124.13, 125.04, 126.15, 130.99, 132.53, 134.85, 136.49, 147.67, 156.93, 162.66, 172.39, 193.90; Mass (70 eV) m/z (rel intensity) 126 (37), 152 (93), 155 (47), 157 (35), 208 (48), 236 (73), 237 (100), 392 (M^+ , 91).