

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

Hyun Nam Song, Hyoung Shik Kim, and Jae Nyoung Kim\*

Department of Chemistry, Chonnam National University, Kwangju 500-757, Korea

Received January 19, 1999

Friedel-Crafts type reactions of ninhydrin (1,2,3-indantrione) have been examined by us<sup>1</sup> and other groups.<sup>2</sup> 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**.<sup>3-4</sup>

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.<sup>4a</sup>

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.

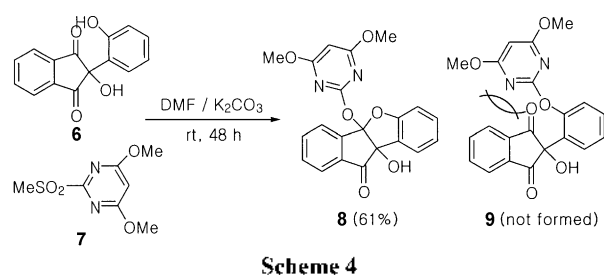
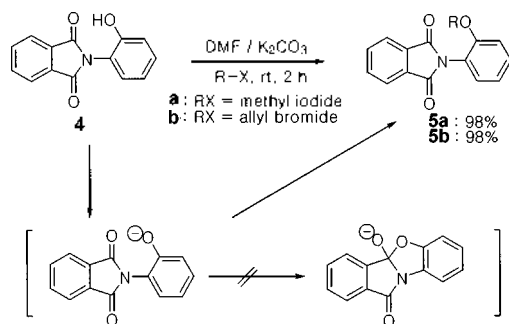
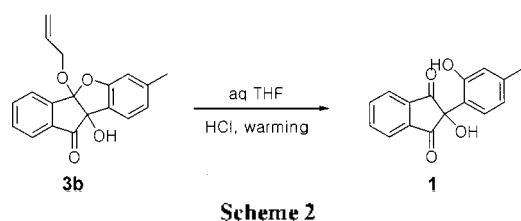
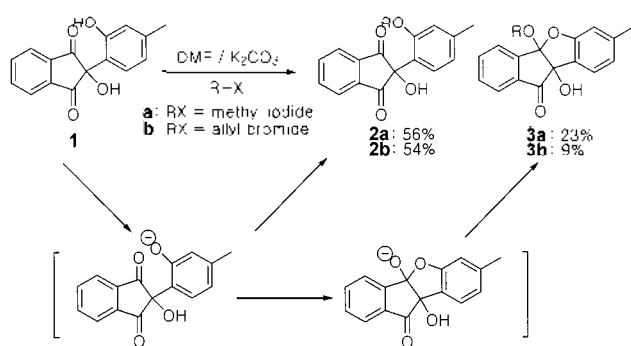
As expected the mixed ketal moiety was hydrolyzed to the starting material **1** quantitatively. Thus, the structure and the proposed mechanism (Scheme 1)<sup>4a</sup> for the formation of **3** seemed reasonable. Is it possible that such a transfer of nucleophilicity can occur to amide carbonyl group?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

ine this, we prepared *N*-(2-hydroxyphenyl)phthalimide (**4**)<sup>5</sup> 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**<sup>5</sup> 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**<sup>4</sup> 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**<sup>5</sup> in good yield (Scheme 4).

Discrimination of **8** and **9** was based on the number of carbon atoms in <sup>13</sup>C NMR<sup>5</sup> and the splitting pattern of aromatic protons in <sup>1</sup>H NMR spectrum.<sup>4</sup> The formation of the normal alkylation product **9** is restricted by the steric hindrance between the pyrimidine and indenedione moiety. Further studies on the reaction and the biological activity of prepared compounds are in progress.



**Acknowledgment.** We wish to thank the Chonnam National University Research Foundation for financial support of this work. The support of the Korea Basic Science Institute (Kwangju branch) is also acknowledged.

### References

- (a) Song, H. N.; Seong, M. R.; Son, J. S.; Kim, J. N. *Synth. Commun.* **1998**, *28*, 1865. (b) Song, H. N.; Son, J. S.; Seong, M. R.; Kim, J. N. *Synth. Commun.* **1998**, *28*, 687.
- (a) Moubasher, R. *J. Am. Chem. Soc.* **1951**, *73*, 3245. (b) Black, D. St. C.; Bowyer, M. C.; Condie, G. C.; Craig, D. C.; Kumar, N. *Tetrahedron* **1994**, *50*, 10983. (c) Bullington, J. L.; Dodd, J. H. *J. Org. Chem.* **1993**, *58*, 4833.
- (a) Schmitt, G.; An, N. D.; Poupelin, J. P.; Vebrel, J.; Laude, B. *Synthesis* **1979**, 758. (b) Poupelin, J. P.; Saint-Ruf, G.; Perche, J. C.; Roussey, J. C.; Laude, B.; Narcisse, G.; Bakri-Logcais, F.; Hubert, F. *Eur. J. Med. Chem.* **1980**, *15*, 253. (c) Poupelin, J. P.; Saint-Ruf, G.; Perche, J. C.; Lacroix, R.; Uchida-Ernouf, G.; Narcisse, G.; Hubert, F. *Eur. J. Med. Chem.* **1979**, *14*, 171.
- (a) Song, H. N.; Seong, M. R.; Lee, H. J.; Kim, J. N. "Formation of Benzo[b]indeno[2,1-d]furanone Ring System During Alkylation of 2-(2-Hydroxyaryl)-2-hydroxy-1,3-indanedione Derivatives." *Synth. Commun.* **1999**, in print. (b) Song, H. N.; Lee, H. J.; Kim, H. R.; Ryu, E. K.; Kim, J. N. "Friedel-Crafts Type Reactions of Some Activated Cyclic Ketones with Phenol Derivatives." *Synth. Commun.* **1999**, in print.
- Melting points and representative spectroscopic data of prepared compounds were as follows. **4**: mp. 230-231 °C;  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  6.94-7.36 (m, 4H), 7.88-7.96 (m, 4H), 9.81 (s, 1H);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  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;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.80 (s, 3H), 7.04-7.48 (m, 4H), 7.76-7.98 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.57 (s, 6H), 5.67 (s, 1H), 6.78-8.05 (m, 8H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  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).