Recently, we are interested in the aromatization reaction of 2-acylcyclohexane-1,3-dione derivatives by using iodine in methanol. As a continuous work we wish to report herein another useful application of iodine in methanol system for the synthesis of benzo[b]indeno[2,1-d]furanone skeleton from ninhydrin and cyclohexane-1,3-dione derivatives.

Iodine in methanol has been used as a novel reagent for the conversion of 2-cyclohexen-1-ones into the corresponding anisole derivatives. Vanadium-induced synthesis of 1,3-diethoxybenzene in low yield from cyclohexane-1,3-dione was reported. Iodine in methanol was used during the synthesis of natural product, rocaglamide, for the transformation of cyclohexanedione enol ether into anisole derivative. Aromatization of alkyl group-substituted cyclohexane-1,3-diones into the corresponding dimethoxyresorcinol was reported by Kotnis.

The reaction of ninhydrin (1) and cyclohexane-1,3-dione (2a) gave the corresponding addition product 3a-c in good yield as reported. The structure of 3a is difficult to confirm due to the line-broadening in 1H NMR spectrum and rapid equilibration (vide infra, Scheme 2). The compound 3a can exist in equilibrium with its cyclic structure, which increases in acidic condition such as iodine-methanol system. Thus we can expect that we could prepare the benzo[b]indeno[2,1-d]furanone skeleton by the oxidative aromatization protocol with iodine in methanol as shown in Scheme 1.

With the addition products 3a-c in hand, we examined the oxidative aromatization process. The reaction of 3a and iodine (2.0 equiv.) in dry methanol under refluxing condition gave the anisole derivatives 4a and 5a in 66% and 11%, respectively, within 24 h. Similarly we could obtain the corresponding 4b-c and 5b-c in similar yields as shown in Table 1. The reaction of 3a in dry ethanol gave the corresponding products 6a and 7a (entry 4 in Table 1).

The formation of these compounds can be explained as exemplified by the formation of 4a and 5a in Scheme 2: conversion of 3a-cyclic form into its hemiketal by methanol, elimination of water, and iodine-assisted oxidative aromatization process as already reported in similar systems. Methylation of 4a at the hydroxyl group can be explained as shown in Scheme 2: electrophilic iodination, formation of cyclic oxonium species, and addition of methanol to give 5a.

### Table 1. Synthesis of Benzo[b]indeno[2,1-d]furanone Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Products (% Yields)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>I$_2$ (2 equiv.) MeOH, reflux 24 h</td>
<td>4a (66%) 5a (11%)</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>I$_2$ (2 equiv.) MeOH, reflux 13 h</td>
<td>4b (59%) 5b (5%)</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>I$_2$ (2 equiv.) MeOH, reflux 14 h</td>
<td>4c (52%) 5c (6%)</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>I$_2$ (2 equiv.) ETOH, reflux 13 h</td>
<td>6a (45%) 7a (12%)</td>
</tr>
</tbody>
</table>

*1,3-Dimethoxy-5-methylbenzene was obtained in 5% yield. 1,3-Dimethoxybiphenyl was isolated in 9% yield.*
Prepared compounds are under progress.

Studies on the antiviral activities of the diones was carried out for the first time with iodine in the methanol system. This work was supported by the grant (R05-2003-000-10042-0) from the Basic Research Program of the Korea Science & Engineering Foundation. Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

In summary, the facile synthesis of benzo[b]indeno[2,1-d]furanone skeleton from ninhydrin and cyclohexane-1,3-diones was carried out for the first time with iodine in methanol system. This synthesis of 3a-c existed as their enol form in CDCl3 based on its 1H NMR spectra. 13C NMR spectra of cyclohexane-1,3-dione derivatives were very complex as reported and we did not assign them.

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**References**

3. The NMR spectra of cyclohexane-1,3-diones is very complex to interpret due to the keto-enol equilibration. The starting materials 3a-c existed as their enol form in CDCl3 based on its 1H NMR spectra. 13C NMR spectra of cyclohexane-1,3-dione derivatives were very complex as reported and we did not assign them.
5. The synthesis of 4a was prepared from ninhydrin and phenol as reported more exactly, we could obtain 4a and 5a as white solids, 395 mg (66%) and 63 mg (11%), respectively. The synthesized compounds were identified from their melting points, 1H and 13C NMR spectra and mass spectra.
6. In order to confirm the structure of 4a-c and 6a more exactly, we carried out some supplementary experiments with 8 and 9. The compound 8 was prepared from ninhydrin and phenol as reported previously.\(^\text{26}\) The reaction of 8 and methanol in the presence of acid catalyst (p-TsOH) afforded the methylated derivative 9 in 71% yield. Conversely, the conversion of 9 into 8 could be carried out in the presence of water and acid catalyst (conc. HCl) in 59% yield (Scheme 3). From the experiment we could propose the structure of 4a-c and 6a as described tentatively.

![Scheme 2](image2)

![Scheme 3](image3)