

Synthesis of Benzo[b]indeno[2,1-d]furanone Skeleton from Ninhydrin and Cyclohexane-1,3-dione Derivatives

Jeong Eun Na, Jeong Mi Kim, Sangku Lee,[†] and Jae Nyoung Kim^{*}

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea

[†]Korea Research Institute of Bioscience and Biotechnology, 52 Oun, Yusong, Daejeon 305-333, Korea

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Recently, we are interested in the aromatization reaction of 2-acylcyclohexane-1,3-dione derivatives by using iodine in methanol.¹ 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.²

Iodine in methanol has been used as a novel reagent for the conversion of 2-cyclohexen-1-ones into the corresponding anisole derivatives.³⁻⁶ However, aromatization of cyclohexane-1,3-dione system has not been studied much.^{1,4,7} Vanadium-induced synthesis of 1,3-dimethoxybenzene in low yield from cyclohexane-1,3-dione was reported.⁷ Iodine in methanol was used during the synthesis of natural product, rocaglamide,^{8a} for the transformation of cyclohexanedione enol ether into anisole derivative. Aromatization of alkyl group-substituted cyclohexane-1,3-diones into the corresponding dimethoxyresorcinols with iodine and methanol was reported by Kotnis.^{1b}

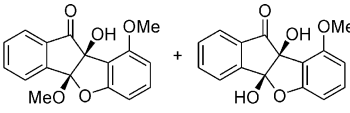
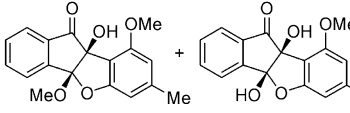
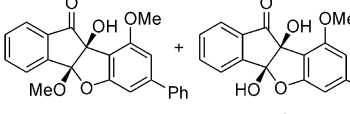
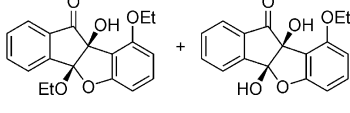
The reaction of ninhydrin (**1**) and cyclohexane-1,3-dione (**2a**) gave the corresponding addition product **3a** in good yield as reported.⁸ The structure of **3a** is difficult to confirm due to the line-broadening in ¹H NMR spectrum and rapid equilibration (vide infra, Scheme 2).⁹ The compound **3a** can exist in equilibrium with its cyclic structure, which increases in acidic condition such as iodine in methanol system. Thus we can expect that we could prepare the benzo[b]indeno[2,1-d]furanone skeleton by the oxidative aromatization

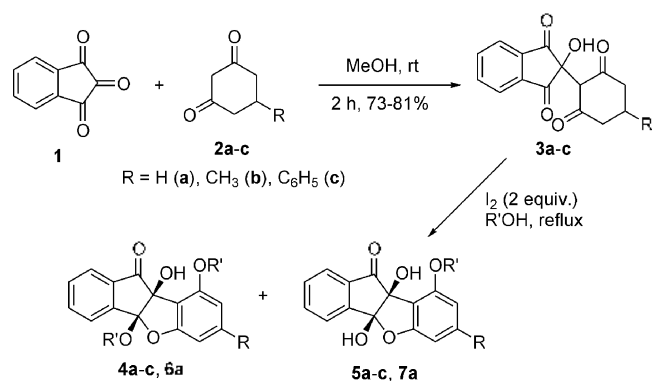
protocol with iodine in methanol as shown in Scheme 1.

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.¹⁰ 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.^{1,3-7} Methylation of **4a** at the hydroxyl group can be explained as shown in Scheme 2: electrophilic iodination,^{11,12} formation of cyclic oxonium species, and addition of methanol to give **5a**.^{11,12}

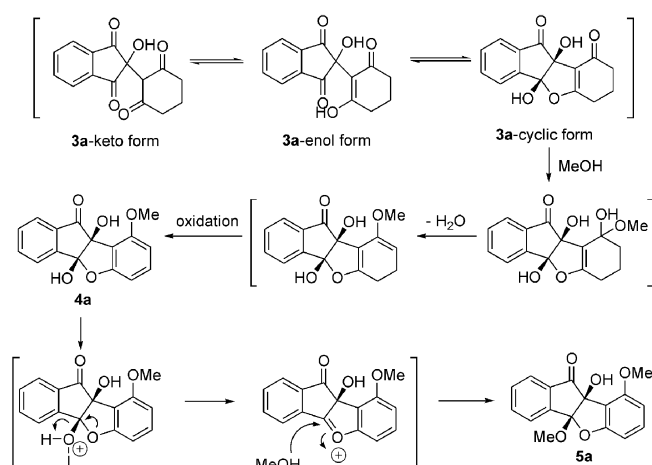
Table 1. Synthesis of Benzo[b]indeno[2,1-d]furanone Derivatives

Entry	Substrate 3	Conditions	Products (% Yields)
1	3a	I ₂ (2 equiv.) MeOH, reflux 24 h	 4a (66%) 5a (11%)
2 ^a	3b	I ₂ (2 equiv.) MeOH, reflux 13 h	 4b (59%) 5b (5%)
3 ^b	3c	I ₂ (2 equiv.) MeOH, reflux 14 h	 4c (52%) 5c (6%)
4	3a	I ₂ (2 equiv.) EtOH, reflux 13 h	 6a (45%) 7a (12%)



^{*}Corresponding author. Phone: +82-62-530-3381, e-mail: kimjn@chonnam.ac.kr

^a1,3-Dimethoxy-5-methylbenzene was obtained in 5% yield. ^b1,3-Dimethoxybiphenyl was isolated in 9% yield.



Scheme 2

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. Studies on the antiviral activities of the prepared compounds are under progress.

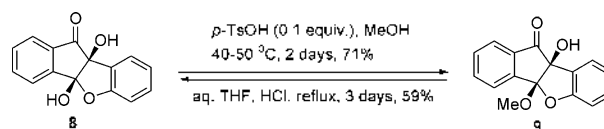
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- The NMR spectra of cyclohexane-1,3-diones is very complex to interpret due to the keto-enol equilibration. The starting materials **3a-c** existed as their enol form in CDCl₃ based on its ¹H NMR spectra. ¹³C NMR spectra of cyclohexane-1,3-dione derivatives were very complex as reported and we did not assign them. (a) Im, Y. J.; Lee, C. G.; Kim, H. R.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 2987. (b) Imashiro, F.; Maeda, S.; Takegoshi, K.; Terao, T.; Saika, A. *J. Am. Chem. Soc.* **1987**, *109*, 5213. (c) Eiter, M. C.; Urbanczyk-Lipkowska, Z.; Jahn, D. A.; Frye, J. S. *J. Am. Chem. Soc.* **1986**, *108*, 5871.
- The synthesis of **4a** and **5a** is typical. A solution of **3a** (545 mg, 2.0 mmol) and iodine (1016 mg, 4.0 mmol) in methanol (10 mL) was heated at reflux for 24 h. The reaction mixture was diluted with methylene chloride and washed with aqueous NaHSO₃ solution and brine. After removal of solvent and flash column chromatographic separation process (hexane/ether, 1:3), 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. The selected spectroscopic data of the compounds is as follows: **4a**: mp 187-189 °C; ¹H NMR (CDCl₃) δ 3.76 (s, 3H), 3.82 (br s, 1H), 3.90 (s, 3H), 6.47 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.56-7.92 (m, 4H); ¹³C NMR (CDCl₃) δ 53.56, 55.78, 84.36, 103.53, 104.06, 110.03, 112.15, 124.01, 125.37, 131.21, 132.78, 134.58, 136.26, 147.51, 157.89, 158.19, 198.12; Mass (70 eV) *m/z* (rel. intensity) 251 (57), 266 (100), 298 (M⁺, 14). **5a**: mp 177-178 °C; ¹H NMR (CDCl₃) δ 3.86 (s, 3H), 4.60 (br s, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.52-7.99 (m, 4H); ¹³C NMR (CDCl₃) δ 55.73, 82.92, 103.81, 103.93, 108.96, 111.02, 123.99, 124.80, 131.07, 133.17, 134.33, 136.64, 147.70, 158.11, 158.75, 197.40; Mass (70 eV) *m/z* (rel. intensity) 104 (52), 151 (76), 251 (66), 266 (73), 284 (M⁺, 100).
- 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.^{2b-c} 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 3

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