Selective Methylation of the Ninhydrin-Phenol Adducts with I_2 in MeOH

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The formation of ninhydrin-phenol adducts and chemical transformations of them have been studied by us and other groups.[1,2] The adducts can be easily prepared from ninhydrin (**1**) and phenols **2** in acetic acid in good yields.[1,2] The structure of the ninhydrin-phenol adduct **3** is benzo[b]-indeno[2,1-d]furanone skeleton in $CDCl_3$. However, the adduct **3** existed in equilibrium with its ring-opened form **3'** in DMSO-d_6 (Scheme 1). The structure can be easily confirmed from the ^{1}H NMR spectrum. For the cyclic form **3a**, as an example, the protons at the ninhydrin moiety appeared as t, d, t, and d at around 7.49-8.02 ppm in $CDCl_3$ (a in Figure 1). Whereas, **3a** and **3a'** existed in a ratio of 65 : 35 in the ^{1}H NMR spectrum in DMSO-d_6 (b in Figure 1). The four protons of the ninhydrin moiety of **3a'** appeared as a singlet apparently at 8.00 ppm due to the symmetric nature of the compound of **3a'** (Figure 1). The characteristic peaks of **3a** (t, d, t, d) remained in about 65% with slightly different chemical shifts.

We have published the alkylation of the ninhydrin-phenol adduct **3** in DMF in the presence of K_2CO_3 (Scheme 1).[1a] As shown in Scheme 1, the formation of **5** is the major pathway. Ring-opened component **3'** existed to some extent in DMF as in DMSO-d_6 and underwent the alkylation at the more acidic phenolic OH via **A**. As the reaction proceeded, new equilibrium reached to generate the ring-opened form **3'** and can undergo further alkylation at the phenolic OH to give the product **5** as the major product. In the reaction, compound **4** was also formed as the minor product via **B**. The formation of **4** has been explained by using the concept of "transfer of nucleophilicity" as depicted in Scheme 1.[1a]

Recently we have published a facile synthetic method of benzo[b]indeno[2.1-d]furanone skeleton from the reaction of ninhydrin and cyclohexane-1,3-diones.[3] During the oxidative aromatization reaction of the intermediate with iodine in methanol we have found that the hydroxyl group at the hemiketal portion can be selectively converted into methoxy group to some extent.[3]

In these respects, we envisioned that we might control the alkylation position for the ninhydrin-phenol adducts **3** (Scheme 1). Currently we are interested in the synthesis of various types of alkylated or acylated benzo[b]indeno[2,1-d]furanone systems in order to examine their antiviral activities.[4] Actually, some compounds showed high antiviral activity against coxsackie A, coxsackie B, echovirus, and poliovirus in a 0.04-0.09 μg/mL level. Thus, in this paper we wish to report the selective methylation at the hemiketal portion of ninhydrin-phenol adducts.

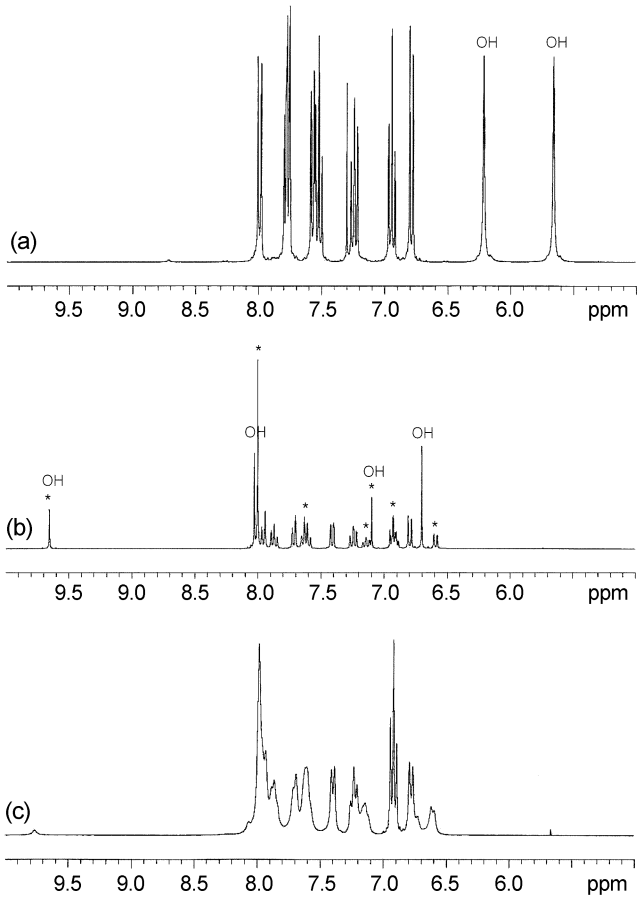

Figure 1. ^{1}H NMR spectra of ninhydrin-phenol adduct **3a** in $CDCl_3$ (a), DMSO-d_6 (b), and DMSO-d_6+D_2O (c). The peaks marked with asterisk are derived from **3a'**.

The reaction of **3a** and iodine (2.0 equiv.) in methanol gave the methylated compound **4a** in 56% yield. As expected, desired compounds **4b-e** were prepared in good to moderate yields (47-77%) with iodine in methanol or ethanol from **3b-d**, which could be easily prepared from the reaction of ninhydrin and *p*-cresol, *m*-cresol, and hydroquinone, respectively. For the *m*-cresol derivative **3c**, iodination at the aryl moiety occurred (entry 3) to give **6** to some extent. When we used ethanol in the reaction, ethylated

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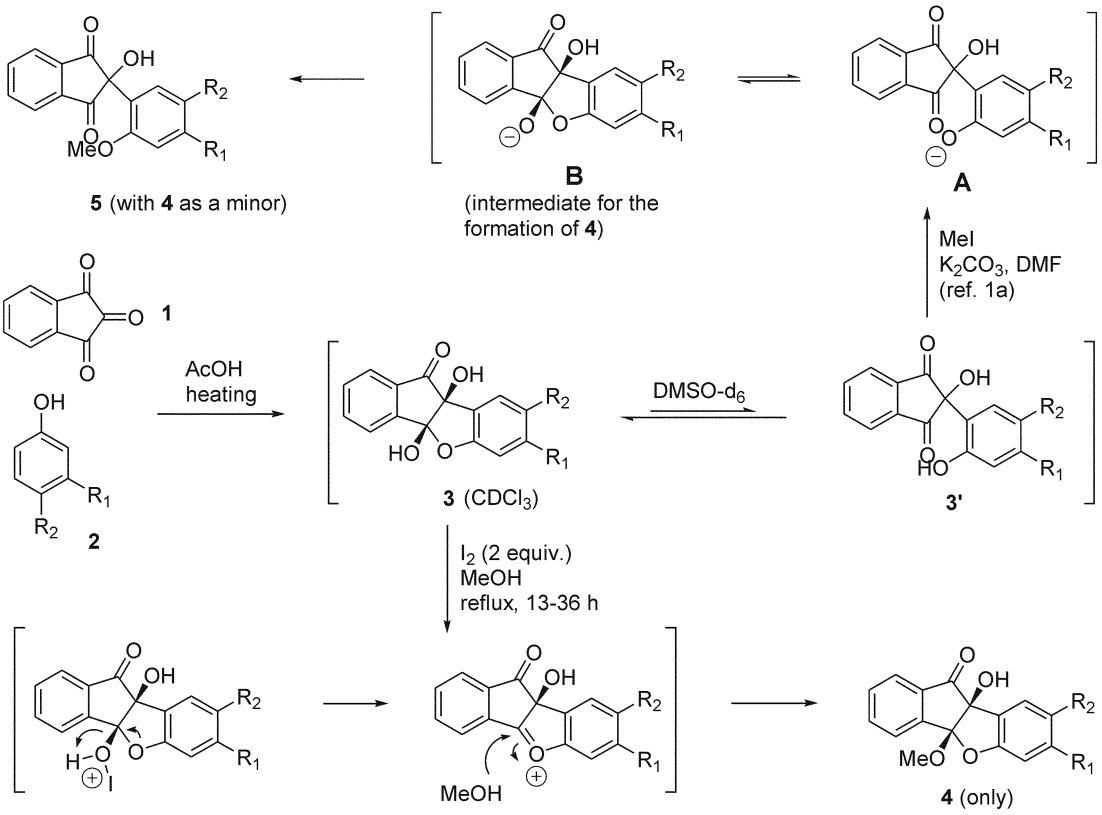
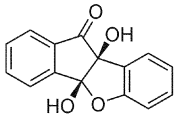
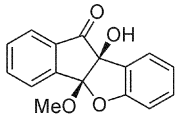
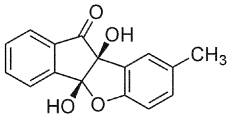
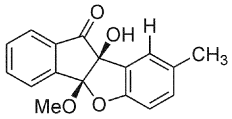
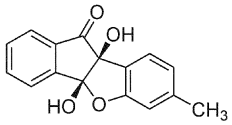
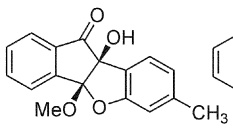
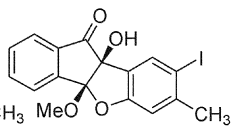
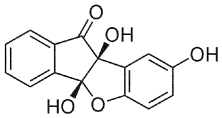
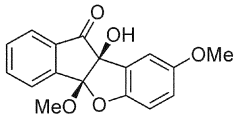
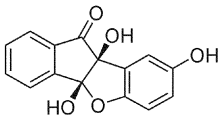
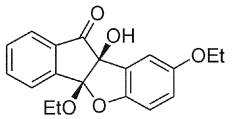


Scheme 1

Table 1. Selective alkylation at the hemiketal position of ninhydrin-phenol adducts **3**

entry	substrate	conditions	products (% yield)
1	 **3a**	I_2 (2 equiv.) MeOH, reflux 19 h	 **4a** (56%)
2	 **3b**	I_2 (2 equiv.) MeOH, reflux 13 h	 **4b** (77%)
3	 **3c**	I_2 (2 equiv.) MeOH, reflux 36 h	 **4c** (47%)  **6** (28%)
4	 **3d**	I_2 (2 equiv.) MeOH, reflux 14 h	 **4d** (63%)
5	 **3d**	I_2 (2 equiv.) EtOH, reflux 16 h	 **4e** (51%)

compound **4e** was synthesized in 51% yield (entry 5). The reaction mechanism for the formation of **4** was depicted in Scheme 1: electrophilic iodination,[3,5] formation of cyclic oxonium ion intermediate, and addition of methanol to give the corresponding methylated compounds **4**.[3,5] The structure including the regiochemistry and the relative stereochemistry of the OH and methoxy group (*cis* relationship) of **4b** were confirmed by NOE experiment.[6]

In summary, we have synthesized the alkylated compounds at the hemiketal part of ninhydrin-phenol adducts selectively by using the iodine-alcohol system.

Experimental Section

Typical procedure for the synthesis of the starting material 3a: A mixture of ninhydrin (356 mg, 2 mmol) and phenol (188 mg, 2 mmol) in acetic acid (5 mL) was heated to reflux for 3 h. After usual aqueous workup procedure and column chromatographic purification process (hexanes/ether, 1 : 1), desired ninhydrin-phenol adduct **3a** was obtained in 63% yield (320 mg). Other starting materials **3b-d** have been synthesized analogously and the spectroscopic data are summarized below.

Typical procedure for the selective methylation of 3a: To a stirred solution of **3a** (254 mg, 1 mmol) in dry methanol (5 mL) was added iodine (508 mg, 2 mmol) and the reaction mixture was heated to reflux for 19 h. After removal of the solvent and purification by flash column chromatography (hexanes/ether, 2:1) we obtained the desired compound **4a** in 56% yield (150 mg). Other products **4b-e** and **6** have been synthesized similarly and the spectroscopic data are summarized below.

3a (63%): mp 166-168 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 1H), 4.72 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.78-7.82 (m, 2H), 8.02 (d, J = 7.8 Hz, 1H).

3b (63%): mp 160-162 °C; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 3.93 (s, 1H), 4.74 (s, 1H), 6.73 (d, J = 8.3 Hz, 1H), 7.06 (t, J = 8.3 Hz, 1H), 7.29 (s, 1H), 7.57 (t, J = 7.1 Hz, 1H), 7.77-7.81 (m, 2H), 8.00 (d, J = 6.9 Hz, 1H).

3c (78%): mp 162-164 °C; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 4.35 (s, 1H), 5.00 (s, 1H), 6.62 (s, 1H), 6.75 (d, J = 7.4 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.74-7.82 (m, 2H), 7.99 (d, J = 7.8 Hz, 1H).

3d (65%): mp 215-216 °C; ^{1}H NMR ($CDCl_3$ + 1 drop of DMSO-d_6) δ 5.97 (s, 1H), 6.60 (d, J = 8.7 Hz, 1H), 6.71 (s, 1H), 6.74 (d, J = 8.7 Hz, 1H), 7.06 (s, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.73-7.81 (m, 2H), 7.96 (d, J = 7.8 Hz, 1H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$ + 1 drop of DMSO-d_6) δ 83.18, 109.83, 110.57, 111.88, 118.80, 123.27, 125.01, 125.54, 130.55, 134.53, 136.29, 149.22, 149.97, 152.21, 198.73.

4a (56%): mp 152-154 °C; ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 1H), 3.76 (s, 3H), 6.87 (d, J = 8.4 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 7.25-7.32 (m, 1H), 7.52-7.60 (m, 2H), 7.76-7.83 (m, 2H), 7.93 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 53.57, 83.41, 110.83, 111.71, 122.28, 124.08, 125.03, 125.10, 125.68, 131.28, 131.93, 134.63, 136.54, 147.70, 157.70, 198.96; Mass (70 eV) *m/z* (rel intensity) 76 (9), 104 (6), 121 (8), 152 (9), 181 (4), 208 (28), 225 (35), 236 (100), 268 (M^+, 5).

4b (77%): mp 176-178 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 3.43 (s, 1H), 3.75 (s, 3H), 6.75 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.75-7.82 (m, 2H), 7.92 (d, J = 7.8 Hz, 1H); Mass 77 (11), 165 (12), 222 (20), 239 (52), 250 (100), 282 (M^+, 15).

4c (47%): ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 3.50 (s, 1H), 3.76 (s, 3H), 6.68 (s, 1H), 6.81 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.76-7.81 (m, 2H), 7.92 (d, J = 7.2 Hz, 1H).

4d (63%): mp 155-156 °C; ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 6.77 (d, J = 9 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 7.05 (s, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.78-7.83 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 53.48, 55.96, 84.26, 108.47, 111.43, 111.78, 119.31, 124.02, 125.08, 125.63, 131.22, 134.56, 136.52, 147.77, 151.07, 155.26, 198.89.

4e (51%): ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 6.7 Hz, 3H), 1.36 (t, J = 6.7 Hz, 3H), 3.59 (s, 1H), 3.92-4.12 (m, 4H), 6.74 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H), 7.05 (s, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.76-7.81 (m, 2H), 7.92 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.80, 15.66, 61.93, 64.27, 84.07, 109.38, 111.29, 111.84, 119.77, 123.94, 125.07, 125.62, 131.08, 134.52, 136.46, 148.06, 151.00, 154.49, 199.04.

6 (28%): ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.48 (s, 1H), 3.76 (s, 3H), 6.80 (s, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.78-7.83 (m, 2H), 7.90-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.80, 53.67, 83.21, 90.82, 112.18, 112.26, 124.15, 124.76, 125.61, 131.45, 134.36, 134.75, 136.69, 145.31, 147.36, 157.32, 198.55.

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References and Notes

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6. When we irradiate the OH proton signal (δ = 3.43 ppm), the methoxy group (δ = 3.75 ppm) and the aromatic singlet proton (δ = 7.33 ppm) showed 0.5% and 0.3% NOE increments, respectively.