Carbon–Carbon Bond Cleavage of α-Substituted Benzoin by Retro-Benzoic Condensation; A New Method of Synthesizing Ketones

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When α-benzylbenzoin (3a, α-benzyl-α-hydroxybenzyl phenyl ketone) was treated with potassium cyanide (1) in N,N-dimethylformamide at 80 °C for 1 h, the carbon-carbon bond was cleaved, resulting in the formation of deoxybenzoin (4a, benzyl phenyl ketone) and benzaldehyde (2a). This carbon-carbon bond cleavage proceeds through a retro-benzoic condensation mechanism. This method of synthesizing ketones was applied to several α-substituted benzoin (3), and the corresponding ketones (4) were formed in good yields. Further, we found that the cyanide ion-donating ability of tetrabutylammonium cyanide (6, Bu₄NCN) is more effective than that of potassium cyanide (1, KCN). As expected from the chemical analogy between cyanide ion and azolium ylide, several azolium salts (7) can also be employed in the retro-benzoic condensation as catalysts.

The benzoin derivatives 3 were synthesized in the following three ways; reaction of alkyl halide (9) with benzoin (5), Michael addition of benzoin (5) with acceptors (10), and Grignard reaction of benzils (8). Alkylation of the benzoin without isolation, followed by carbon–carbon bond cleavage, readily afforded the corresponding ketones (4).

Key words retro-benzoic condensation; ketone; potassium cyanide; benzoin; carbon–carbon bond cleavage; tetrabutylammonium cyanide

Benzoin condensation is a well-known self-condensation of two molecules of arencarbaldehyde (2) to give benzoin (5), catalyzed by cyanide ion (Chart 1). Attack of the strongly nucleophilic cyanide ion (CN⁻) on the arencarbaldehydes (2) is the first step, and the electron-withdrawing effect of the introduced cyano group allows the condensation to proceed. All of the reaction processes are reversible.¹,²

In the previous communication,³ we reported that the cyanide ion-catalyzed carbon–carbon bond cleavage of α-substituted benzoin (3) proceeded through retro-benzoic condensation, resulting in the formation of ketones (4). We showed that this retro-benzoic condensation provides a convenient method of synthesizing ketones, and further found that the cyanide ion-donating ability of tetrabutylammonium cyanide (6, Bu₄NCN) is more effective than that of potassium cyanide (1, KCN) in this retro-benzoic condensation. Based on the chemical analogy between cyanide ion and azolium ylide, we also found that several azolium salts (7) can be employed as catalysts. In this paper, we wish to report these results in detail.

It has been shown that cross-benzoic condensation products are formed from benzoin (5) and arencarbaldehyde (2) or between different arencarbaldehydes (2) in the presence of cyanide ion.⁴ Thus, while self-condensation of benzaldehyde (2a) gives benzoin (5a, α-hydroxybenzyl phenyl ketone), cross-condensation between benzoin (5a) and 2-furaldehyde (2d) gives the cross-condensation product, i.e., 2-furyl α-hydroxybenzyl ketone (5e, benzfuuroin). As mentioned above, the reaction steps are reversible, so we considered that benzoin (5a) is the most stable product in the former case, while 5e is the most stable in the latter case.

These results suggested us that synthesis of ketones might be achieved by retro-benzoic condensation from α-substituted benzoin. Namely, we considered that treatment of α-substituted benzoin derivatives 3, such as α-benzylbenzoin (3a, α-benzyl-α-hydroxybenzyl phenyl ketone), with a catalytic amount of cyanide ion would give deoxybenzoin (4a, benzyl phenyl ketone) and benzaldehyde (2a) and/or benzoin (5a) by carbon–carbon bond cleavage. Among the reaction products, the ketone 4a should be the most stable product, because the cross-benzoic condensation between benzaldehyde (2a) and deoxybenzoin (ketone, 4a) to give the corresponding cross-benzoic (3a) does not occur.⁵

When α-benzylbenzoin (3a) was treated with a catalytic amount of potassium cyanide (1, KCN) in N,N-dimethylformamide (DMF) at 80 °C for 1 h, deoxybenzoin (4a) was obtained in 98% yield together with benzaldehyde.
(2a) in 20% yield (method a). As expected, deoxybenzoin (4a) was produced through retro-benzoin condensation. Other benzylbenzoxins such as α-benzyl-4,4'-dichlorobenzoin (3b, α-benzyl-α-hydroxy-4-chlorobenzyl 4-chlorophenyl ketone) and α-benzyl-4,4'-dimethoxybenzoin (3c, α-benzyl-α-hydroxy-4-methoxybenzyl 4-methoxyphenyl ketone) afforded the corresponding deoxybenzoxins such as 4-methoxydeoxybenzoin (4b, benzyl 4-methoxyphenyl ketone) and 4-chlorodeoxybenzoin (4c, benzyl 4-chlorophenyl ketone) in good yields. Similarly, other deoxybenzoxins (4d and e) were obtained from 3d and e in good yields.

Similar results were obtained with other benzoin derivatives 3. When 3f–l, which are Michael addition products of benzoxins (5), were treated with a catalytic amount of potassium cyanide in DMF, the corresponding ketones 4f–l were formed in excellent yields. Further, several α-phenylbenzoxins (4m and n) underwent retro-benzoin condensation upon treatment with KCN in DMF to give the corresponding ketones (3m and n) in good yields. In this retro-benzoin condensation, DMF is an effective solvent, because the retro-condensation of 3f in MeOH under the same conditions gave the ketone 4f in only 49% yield. However, the α-substituted acyloin 3o did not undergo the carbon–carbon bond cleavage under similar conditions. These results are shown in Chart 3 and

![Chart 3](image)

Table 1. As shown in Chart 4, the retro-condensation of 3a using tetrabutylammonium cyanide (6, Bu₄NCN) instead of KCN (1) as the cyanide ion donor furnished the deoxybenzoin (4a), benzaldehyde (2a) and benzoin (5a) (method b). This reaction can be done in tetrahydrofuran (THF), and this condition is regarded as being milder than the reaction in DMF. The retro-condensation using Bu₄N CN (6) as the cyanide ion donor readily afforded the cleaved products, the ketone (4) and areneacarbaldheyde (2) and/or benzoin (5). The desired ketones 4 were obtained in quantitative yields by using Bu₄N CN, as shown in Chart 4 and Table 2.

In several reactions, we have shown that the chemical behavior of cyanide ion is similar to that of azolite ylide. For example, areneacarbaldheydes (2) underwent self-condensation catalyzed by azolite ylides, resulting in the formation of benzoxins (5). Namely, we reported that

![Chart 4](image)

Table 2. Synthesis of Ketones (4) by Retro-Benzoin Condensation Catalyzed by Tetrabutylammonium Cyanide (6, Bu₄N CN)

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Substituted benzoin (3)</th>
<th>Reaction conditions</th>
<th>Products (isolated yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solvent</td>
<td>Temp. (°C)a</td>
<td>Time (min)</td>
</tr>
<tr>
<td>1</td>
<td>3a</td>
<td>THF</td>
<td>Reflux</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>THF</td>
<td>r.t.</td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>THF</td>
<td>r.t.</td>
</tr>
<tr>
<td>4</td>
<td>3f</td>
<td>THF</td>
<td>r.t.</td>
</tr>
<tr>
<td>5</td>
<td>3h</td>
<td>THF</td>
<td>Reflux</td>
</tr>
<tr>
<td>6</td>
<td>3j</td>
<td>THF</td>
<td>r.t.</td>
</tr>
</tbody>
</table>

a) r.t. = room temperature.
Table 3. Synthesis of Ketones (4) by Retro-Benzoin Condensation Catalyzed by Azolium Salts (7)

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Substituted benzoin (3)</th>
<th>Catalyst Azolium salt</th>
<th>Reaction conditions</th>
<th>Ketone (4) Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Base</td>
<td>Solvent</td>
<td>Temp. (°C)</td>
</tr>
<tr>
<td>1</td>
<td>3a</td>
<td>NaNH₂</td>
<td>DMF</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>3c</td>
<td>NaNH₂</td>
<td>THF</td>
<td>Reflux</td>
</tr>
<tr>
<td>3</td>
<td>3f</td>
<td>NaH</td>
<td>DMF</td>
<td>r.t.</td>
</tr>
<tr>
<td>4</td>
<td>3m</td>
<td>NaH</td>
<td>DMF</td>
<td>r.t.</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>NaNH₂</td>
<td>DMF</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>3c</td>
<td>NaNH₂</td>
<td>THF</td>
<td>Reflux</td>
</tr>
<tr>
<td>7</td>
<td>3f</td>
<td>NaH</td>
<td>DMF</td>
<td>80</td>
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<tr>
<td>8</td>
<td>3e</td>
<td>NaH</td>
<td>DMF</td>
<td>80</td>
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<td>9</td>
<td>3g</td>
<td>NaH</td>
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<td>11</td>
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<tr>
<td>12</td>
<td>3k</td>
<td>NaH</td>
<td>DMF</td>
<td>80</td>
</tr>
</tbody>
</table>

a) r.t. = room temperature.

azolium salts (7), such as 1,3-dimethylimidazolium iodide (7a) and 1,3-dimethylbenzimidazolium iodide (7b), are effective catalysts in benzoin condensation.6a These results indicated that the azolium salts should be effective as catalysts for this retro-benzoin condensation (method c). As expected, benzylbenzoins 3a and 3c were cleaved into the corresponding deoxybenzoins 4a and 4c in the presence of the azolium salts (7). But, the yields were moderate, because purification of the produced deoxybenzoins 4 from the reaction mixture was not easy. Nevertheless, several azolium salts (7) catalyze the retro-benzoin condensation, as they do the benzoin condensation (Chart 5 and Table 3).

The benzoin derivatives (3) used in this paper were prepared in the following three ways. Alkylation of benzoin, that is, benzylation of the benzoin 5 with benzyl bromide (9a), gave β-benzylbenzoins 3a—d.7 Further, the α-substituted benzoin 3e was synthesized by reaction of benzoin (5a) with p-methylbenzyl bromide (9b). Michael addition of the anion derived from benzoin (5a) with acrylonitrile (10a) gave α-(2-cyanoethyl)benzoin [3f, α-(2-cyanoethyl)-α-hydroxybenzyl phenyl ketone]. Similarly, the benzoin derivatives (3g—l) were obtained by Michael addition of the benzins 5a—e with acrylonitrile (10a), 2-butenonitrile (10b), ethyl acrylate (10c), and methyl vinyl ketone (10d). Finally, Grignard reaction of benzils (8) with phenylmagnesium bromide (11a) or benzylmagnesium bromide (11b) gave α-substituted benzozins (3a, b, m, and n).8 These results are shown in Chart 6.

Stetter and co-workers reported the preparation of ketones from aldehydes and Michael addition acceptors catalyzed by cyanide ion. This reaction proceeds through the formation of the active aldehydes (II) derived from aldehydes (2) and cyanide ion (CN⁻). However, the reaction is often not efficient.9 In contrast, our method of synthesizing ketones by retro-benzoin condensation is easy and certain, because the corresponding products can be isolated at each reaction step. Further, the ketones (4), which include the Stetter reaction products (4f—l), could be obtained by one-pot arylation starting with benzoin (5); some examples are shown in Chart 7.

In conclusion, based on the concept that benzoin condensation is a reversible reaction catalyzed by cyanide ion, in which the most stable compound is finally formed, we have developed a new method of synthesizing ketones (4) by retro-condensation from benzoin derivatives (3). Cyanide ion is an effective catalyst in this reaction (methods a and b), and azolium salts (7) can also be
used effectively \( \text{method c) } \).

**Experimental**

All melting points are uncorrected. IR spectra were recorded on a JASCO A-102 diffraction grating IR spectrophotometer. \(^1\)H-NMR spectra were measured at 60 MHz on a JEOL PMX60S NMR spectrometer and at 270 MHz on a JEOL JNM-GSX270 FT-NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethyliamline as an internal standard, and coupling constants \( J \) are given in Hz.

**Reaction of \( \text{n-Benzenbenzyl(3a)} \) with Potassium Cyanide (1)**

A mixture of \( \text{n-benzylbenzyl (3a, \text{a-benzyl-a-hydroxybenzyl phenyl ketone, 936 mg, 3.00 mmol}) and KCN (1, 39 mg, 0.6 mmol) in DMF (20 ml) \( \text{was stirred at 80}^\circ \text{C for 1 h, then poured into ice-H}_2\text{O and extracted with AcOEt. The organic layer was washed with H}_2\text{O, dried over Na}_2\text{SO}_4, and concentrated. The residue was purified by column chromatography on SiO}_2 with n-hexane and CHCl}_3. The fraction eluted with n-hexane-CHCl}_3 (7:1) gave benzaldehyde (2a) in 20% yield (64 mg). The fraction eluted with n-hexane-CHCl}_3 (7:3) gave deoxybenzoin (4a, benzyl phenyl ketone) in 98% yield (576 mg).

**Synthesis of Ketones (4) by Retro-Benzo Condensation of \( \text{a-Substituted Benzoxs (3) Catalyzed by Potassium Cyanide (1) (Method a)** General Procedure: A mixture of \( \text{a-substituted benzox (3, 3.00 mmol}) and KCN (39 mg, 0.6 mmol) in DMF (20 ml) was stirred under appropriate conditions (reaction conditions are shown in Table 1). The reaction mixture was poured into ice-H}_2\text{O and extracted with AcOEt. The organic layer was washed with H}_2\text{O, dried over Na}_2\text{SO}_4, and concentrated. The residue was purified by column chromatography on SiO}_2 with n-hexane, AcOEt and/or CHCl}_3.

**Synthesis of Ketones (4) by Retro-Benzo Condensation of \( \text{a-Substituted Benzoxs (3) Catalyzed by Potassium Cyanide (1) (Method a)** General Procedure: A mixture of \( \text{a-substituted benzox (3, 3.00 mmol}) and KCN (39 mg, 0.6 mmol) in DMF (20 ml) was stirred under appropriate conditions (reaction conditions are shown in Table 1). The reaction mixture was poured into ice-H}_2\text{O and extracted with AcOEt. The organic layer was washed with H}_2\text{O, dried over Na}_2\text{SO}_4, and concentrated. The residue was purified by column chromatography on SiO}_2 with n-hexane, AcOEt and/or CHCl}_3.

**Synthesis of Ketones (4) by Retro-Benzo Condensation of \( \text{a-Substituted Benzoxs (3) Catalyzed by Potassium Cyanide (1) (Method a)** General Procedure: A mixture of \( \text{a-substituted benzox (3, 3.00 mmol}) and Bu}_2\text{NCN (6, 161 mg, 0.6 mmol) in THF (20 ml) was stirred (reaction conditions are shown in Table 2). The reaction mixture was poured into ice-H}_2\text{O and extracted with CHCl}_3. The organic layer was washed with H}_2\text{O, dried over Na}_2\text{SO}_4, and concentrated. The residue was purified by column chromatography on SiO}_2 with n-hexane and AcOEt.

**Preparation of Azolium Salts (7) 1,3-Dimethylimidazolium iodide (7a), 1,3-dimethylimidazolium iodide (7b), 1,4-dimethyl-1,2,4-triazolium iodide (7e)**

1,4-Dimethyl-1,2,4-triazole-3-ylidene (5a) 2,5-dimethyl-1H-3,4-triazolium iodide (7d)

**Preparation of Azolium Salts (7) 1,3-Dimethylimidazolium iodide (7a), 1,3-dimethylimidazolium iodide (7b), 1,4-dimethyl-1,2,4-triazolium iodide (7e)**

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**Preparation of Azolium Salts (7) 1,3-Dimethylimidazolium iodide (7a), 1,3-dimethylimidazolium iodide (7b), 1,4-dimethyl-1,2,4-triazolium iodide (7e)**
IR (KBr) cm⁻¹: 1668 (CO), 3520 (OH). ¹H-NMR (CDCl₃): δ: 3.60 (IH, d, J=14 Hz, a proton signal of CH₂), 3.96 (1H, d, J=14 Hz, a proton signal of CH₂), 3.95 (1H, s, OH), 6.81—7.77 (1H, m, aromatic H).

- Benzyl-2,4-dichlorobenzo[3,4,5]triazol-2-yl: Yield 99%, colorless needles (MeOH), mp 137—138°C. Anal. Calcd for C₁₂H₁₀Cl₂N₂: C, 76.94; H, 5.43. Found: C, 76.24; H, 5.08. IR (KBr) cm⁻¹: 1657 (CO), 3420 (OH). ¹H-NMR (CDCl₃): δ: 3.34 (1H, d, J=14 Hz, a proton signal of CH₂), 3.83 (1H, d, J=14 Hz, a proton signal of CH₂), 3.45 (1H, s, OH), 6.94—7.44 (1H, m, aromatic H).

- Benzyl-2,4-dimethoxybenzene [3e, 3,4-benzyl-2,4-dimethoxybenzene]: Yield 72%, yellow needles (MeOH), mp 165—167°C (from EtOH). IR (KBr) cm⁻¹: 1659 (CO), 3440 (OH). ¹H-NMR (CDCl₃): δ: 3.45 (1H, d, J=14 Hz, a proton signal of CH₂), 3.73 (1H, d, J=14 Hz, a proton signal of CH₂), 3.74 (1H, s, OMe), 3.82 (1H, s, OMe), 4.22 (1H, s, OH), 6.58—8.03 (1H, m, aromatic H).

- Benzylfluorone [3d, 12,2-(difuryl)-2-hydroxyanthrone]: The fraction eluted with n-hexane-CHCl₃ (1:1) gave 3d. Yield 31%, colorless prisms (acetone-n-hexane), mp 87—88°C. Anal. Calcd for C₂₃H₁₇O₂: C, 72.33; H, 5.00. Found: C, 72.33; H, 4.95. IR (KBr) cm⁻¹: 1670 (CO), 3450 (OH). ¹H-NMR (CDCl₃): δ: 3.30 (1H, d, J=14 Hz, a proton signal of CH₂), 3.95 (1H, d, J=14 Hz, a proton signal of CH₂), 4.43 (1H, s, OH), 6.25—7.52 (1H, m, aromatic H).

- 4-(Methylbenzyl)benzene [3e, 3-(methylbenzyl)-1-(2-methylbenzyl) phenyl ketone]: The fraction eluted with n-hexane-CHCl₃ (1:1) gave 3e. Yield 61%, colorless prisms (acetone-n-hexane), mp 120—121°C. Anal. Calcd for C₂₉H₂₄O: C, 83.51; H, 6.37. Found: C, 83.65; H, 6.55. IR (KBr) cm⁻¹: 1667 (CO), 3420 (OH). ¹H-NMR (CDCl₃): δ: 2.37 (1H, s, Me), 3.40 (1H, d, J=14 Hz, a proton signal of CH₂), 3.73 (1H, d, J=14 Hz, a proton signal of CH₂), 3.88 (1H, s, OH), 6.65—7.72 (1H, m, aromatic H).

**Reaction of Benzoxides (5) with Michael Acceptors (10)**

**General Procedure:** A base [DBU, 0.5 ml or NaH (60% in oil), 20 mg (0.5 mmol)] was added to a solution of benzoxides (5, 5.0 mmol) and a Michael acceptor (10, 5.0 mmol) in MeOH (2 ml). After the green color of the reaction solution turned yellow, the reaction mixture was poured into 10% brine and extracted with benzene. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by chromatography on SiO₂ with n-hexane and EtOAc.

- **Benzyl-2,4-dichlorobenzene [3b]:** Yield 76%. IR (KBr) cm⁻¹: 1670 (CO), 3470 (OH). ¹H-NMR (CDCl₃): δ: 4.40 (1H, s, OH), 7.10—7.15 (1H, m, aromatic H).

- **Phenyl-2,4-dichlorobenzene [3b]:** IR (KBr) cm⁻¹: 1670 (CO), 3470 (OH). ¹H-NMR (CDCl₃): δ: 7.08—7.90 (1H, m, aromatic H). 7-Hydroxy-7-phenyl-6-dodecanone (30): Yield 84%, colorless oil (bp 155—165°C/770 mmHg). Anal. Calcd for C₂₁H₂₀O₄: C, 75.37; H, 7.21. Found: C, 75.41; H, 7.21. IR (KBr) cm⁻¹: 1700 (CO), 3450 (OH). ¹H-NMR (CDCl₃): δ: 0.72—2.51 (2H, m, aliphatic H), 2.53 (1H, s, OH), 7.16—7.56 (3H, m, aromatic H). Compound 3b was similarly prepared from 6,7-dodecadienone.

**One-Pot Synthesis of Ketones (4) by Alkylation of Benzoxides (5) Followed by Retro-Benzo-Condensation**

**General Procedure:** Sodium hydride [50% in oil, 156g (3.9 mmol) for reaction with benzyl bromide (9) or 24% (0.6 mmol) for Michael addition] was added to a solution of benzoxides (5a, 5.0 mmol) and an alkylating agent (3.0 mmol) in DMF (20 ml). The mixture was stirred for 30 min at room temperature, then KCN (1, 39 mmol, 6.6 mmol) was added to the resulting mixture, and stirring was continued for 1 h at 80°C. The reaction mixture was poured into 10% brine and extracted with benzene. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with n-hexane and EtOAc.

**References and Notes**

1. Ide V., Buck J. S., Org. React., 4, 269—304 (1948), and references cited therein.
5. The calculated results for the differences of the heat of formation (ΔHᵢ) were as follows: formation of benzylbenzene (3a) from benzenaldehyde (2a) and deoxybenzoin (4a), −7.914 kcal/mol.
formation of benzoin (5a) from two molecules of benzaldehyde (2a). +2.444 kcal/mol. These results support our approach. The calculations were performed by MOPAC Ver 6.0 (PM3) on a Cash system (SONY Techtronix).


