Carbon–Carbon Bond Cleavage of α-Substituted Benzoins by Retro-Benzoin 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-benzoin condensation mechanism. This method of synthesizing ketones was applied to several α-substituted benzoins (3), and the corresponding ketones (4) were formed in good yields. Further, we found that the cyanide ion-donating ability of tetrabutylammonium cyanide (6, Bu_4NCN) 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-benzoin 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 benzoins without isolation, followed by carbon–carbon bond cleavage, readily afforded the corresponding ketones (4).

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

Benzoin condensation is a well-known self-condensation of two molecules of arenecarbaldehyde (**2**) to give benzoin (**5**), catalyzed by cyanide ion (Chart 1). Attack of the strongly nucleophilic cyanide ion (CN^-) on the arenecarbaldehydes (**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 benzoins (**3**) proceeded through retro-benzoin condensation, resulting in the formation of ketones (**4**). We showed that this retro-benzoin condensation provides a convenient method of synthesizing ketones, and further found that the cyanide ion-donating ability of tetrabutylammonium cyanide (**6**, Bu_4NCN) is more effective than that of potassium cyanide (**1**, KCN) in this retro-benzoin 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-benzoin condensation products are formed from benzoin (**5**) and arenecarbaldehyde (**2**) or between different arenecarbaldehydes (**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**, benzfuroin). 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-benzoin condensation from α-substituted benzoins. 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-benzoin condensation between benzaldehyde (**2a**) and deoxybenzoin (ketone, **4a**) to give the corresponding cross-benzoin (**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

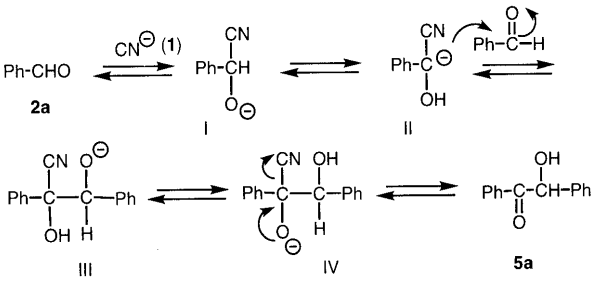

Chart 1

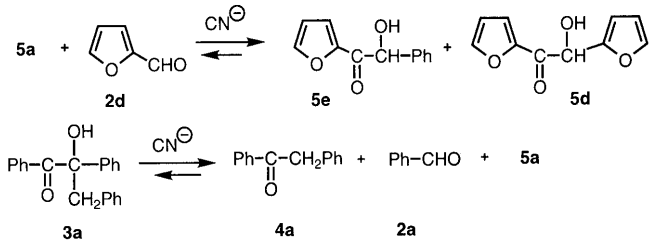

Chart 2

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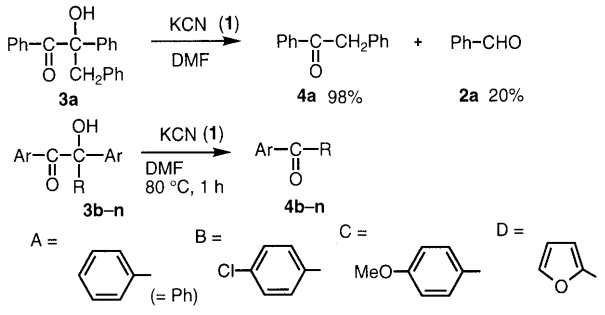
(**2a**) in 20% yield (method a).[3] As expected, deoxybenzoin (**4a**) was produced through retro-benzoin condensation. Other benzylbenzoins such as α-benzyl-4,4′-dichlorobenzoin (**3b**, α-benzyl-α-hydroxy-4-chlorobenzyl 4-chlorophenyl ketone) and α-benzyl-4,4′-dimethoxybenzoin (**3c**, α-benzyl-α-hydroxy-4-methoxybenzyl 4-methoxyphenyl ketone) afforded the corresponding deoxybenzoins such as 4-methoxydeoxybenzoin (**4b**, benzyl 4-methoxyphenyl ketone) and 4-chlorodeoxybenzoin (**4c**, benzyl 4-chlorophenyl ketone) in good yields. Similarly, other deoxybenzoins (**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 benzoins (**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-phenylbenzoins (**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 Table 1.

As shown in Chart 4, the retro-condensation of **3a** using tetrabutylammonium cyanide (**6**, Bu_4NCN) 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 Bu_4NCN (**6**) as the cyanide ion donor readily afforded the cleaved products, the ketone (**4**) and arenecarbaldehyde (**2**) and/or benzoin (**5**). The desired ketones **4** were obtained in quantitative yields by using Bu_4NCN, 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 azolium ylide.[6] For example, arenecarbaldehydes (**2**) underwent self-condensation catalyzed by azolium ylides, resulting in the formation of benzoins (**5**). Namely, we reported that



3 and **4**;
b: Ar = B, R = $PhCH_2$, **c**: Ar = C, R = $PhCH_2$, **d**: Ar = D, R = $PhCH_2$, **e**: Ar = A, R = *p*-$MeC_6H_4CH_2$, **f**: Ar = A, R = $NCCH_2CH_2$, **g**: Ar = B, R = $NCCH_2CH_2$, **h**: Ar = C, R = $NCCH_2CH_2$, **i**: Ar = C, R = $NCCH_2(CH_3)CH$, **j**: Ar = C, R = $EtOOCCH_2CH_2$, **k**: Ar = A, R = $MeCOCH_2CH_2$, **l**: Ar = C, R = $MeCOCH_2CH_2$, **m**: Ar = A, R = Ph, **n**: Ar = B, R = Ph,

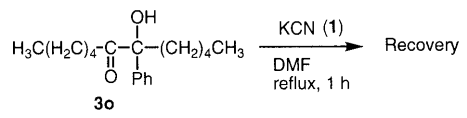
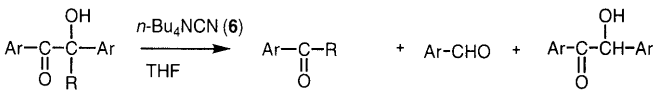


Chart 3

Table 1. Synthesis of Ketones (**4**) by Retro-Benzoin Condensation Catalyzed by Potassium Cyanide (**1**)

Entry	α-Substituted benzoin (**3**)	Reaction conditions: Solvent	Temp. (°C)[a]	Time (min)	Ketone (**4**) Isolated yield (%)	
1	**3b**	DMF	80	60	**4b**	96
2	**3c**	DMF	80	60	**4c**	95
3	**3d**	DMF	r.t.	90	**4d**	69
4	**3e**	DMF	r.t.	60	**4e**	99
5	**3f**	DMF	80	60	**4f**	95
6	**3f**	MeOH	Reflux	60	**4f**	49
7	**3g**	DMF	80	60	**4g**	87
8	**3h**	DMF	80	60	**4h**	99
9	**3i**	DMF	r.t.	30	**4i**	97
10	**3j**	DMF	80	15	**4j**	98
11	**3k**	DMF	r.t.	30	**4k**	94
12	**3l**	DMF	r.t.	30	**4l**	98
13	**3m**	DMF	r.t.	60	**4m**	63
14	**3n**	DMF	80	60	**4n**	69

a) r.t. = room temperature.



2 and **5**;
a: Ar = A, **b**: Ar = B, **c**: Ar = C

Chart 4

Table 2. Synthesis of Ketones (**4**) by Retro-Benzoin Condensation Catalyzed by Tetrabutylammonium Cyanide (**6**, Bu_4NCN)

Entry	α-Substituted benzoin (**3**)	Reaction conditions: Solvent	Temp. (°C)[a]	Time (min)	Products (isolated yield, %): Ketone (**4**)		Aldehyde (**2**)		Benzoin (**5**)	
1	**3a**	THF	Reflux	60	**4a**	(100)	**2a**	(6)	**5a**	(38)
2	**3a**	THF	r.t.	60	**4a**	(100)	**2a**	(21)	**5a**	(49)
3	**3b**	THF	r.t.	90	**4b**	(100)	**2b**	(trace)	**5b**	(12)
4	**3f**	THF	r.t.	60	**4f**	(100)	**2a**	(2)	**5a**	(75)
5	**3h**	THF	Reflux	60	**4h**	(98)	**2c**	(46)	**5c**	(43)
6	**3j**	THF	r.t.	60	**4j**	(86)	**2c**	(12)	**5c**	—

a) r.t. = room temperature.

Table 3. Synthesis of Ketones (**4**) by Retro-Benzoin Condensation Catalyzed by Azolium Salts (**7**)

Entry	α-Substituted benzoin (**3**)	Catalyst Azolium salt	Reaction conditions				Ketone (**4**) Isolated yield (%)	
			Base	Solvent	Temp. (°C)[a]	Time (min)		
1	**3a**	**7a**	$NaNH_2$	DMF	80	60	**4a**	87
2	**3c**	**7a**	$NaNH_2$	THF	Reflux	120	**4c**	53
3	**3f**	**7a**	NaH	DMF	r.t.	30	**4f**	55
4	**3m**	**7a**	NaH	DMF	r.t.	60	**4m**	82
5	**3a**	**7b**	$NaNH_2$	DMF	80	120	**4a**	44
6	**3c**	**7b**	$NaNH_2$	THF	Reflux	120	**4c**	43
7	**3f**	**7b**	NaH	DMF	80	60	**4f**	71
8	**3f**	**7c**	NaH	DMF	80	60	**4f**	67
9	**3f**	**7d**	NaH	DMF	80	60	**4f**	63
10	**3f**	**7e**	NaH	DMF	80	90	**4f**	60
11	**3f**	**7f**	NaH	DMF	80	180	**4f**	71
12	**3f**	**7g**	NaH	DMF	80	60	**4f**	90

a) r.t. = room temperature.

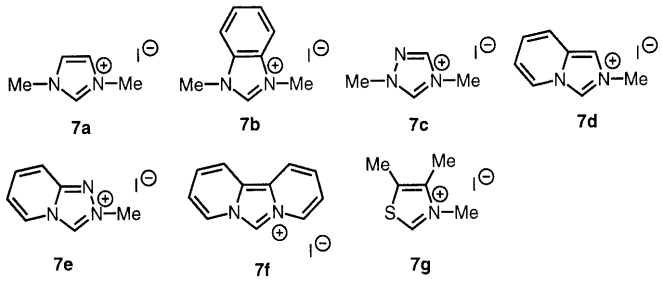


Chart 5

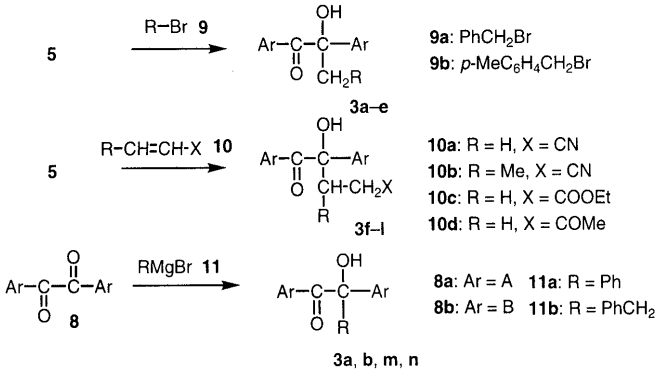
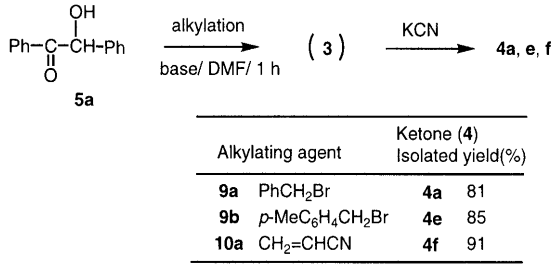


Chart 6



Alkylating agent		Ketone (**4**) Isolated yield(%)	
9a	$PhCH_2Br$	**4a**	81
9b	p-$MeC_6H_4CH_2Br$	**4e**	85
10a	CH_2=CHCN	**4f**	91

Chart 7

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 **c** were cleaved into the corresponding deoxybenzoins **4a** and **c** 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 benzoins, that is, benzylation of the benzoins **5** with benzyl bromide (**9a**), gave α-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 benzoins **5a**—**c** 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 benzoins (**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 aroylation 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 (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 PMX60SI NMR spectrometer and at 270 MHz on a JEOL JNM-GSX270 FT-NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (J) are given in Hz.

Reaction of α-Benzylbenzoin (3a) with Potassium Cyanide (1) A mixture of α-benzylbenzoin (**3a**, α-benzyl-α-hydroxybenzyl phenyl ketone, 936 mg, 3.0 mmol) and KCN (**1**, 39 mg, 0.6 mmol) in DMF (20 ml) was stirred at 80 °C for 1 h, then poured into ice–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_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).

Deoxybenzoin (**4a**): Colorless scales (*n*-hexane), mp 57—60 °C (lit.,[10a] 55—56.5 °C).

Synthesis of Ketones (4) by Retro-Benzoin Condensation of α-Substituted Benzoins (3) Catalyzed by Potassium Cyanide (1) (Method a) General Procedure: A mixture of α-substituted benzoin (**3**, 3.0 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_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane, AcOEt and/or $CHCl_3$.

4-Chlorodeoxybenzoin (**4b**, benzyl 4-chlorophenyl ketone)[10b]: The fraction eluted with *n*-hexane–$CHCl_3$ (8 : 2) gave **4b** in 96% yield (444 mg).

4-Methoxydeoxybenzoin (**4c**, benzyl 4-methoxyphenyl ketone)[7a]: The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 1) gave **4c** in 95% yield (644 mg).

Benzyl 2-furyl ketone (**4d**): The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 1) gave **4d** in 69% yield (385 mg). Red-brown oil (lit.,[10c] bp 168—169 °C). MS m/z: 186 (M^+). IR (neat) cm^{-1}: 1668 (CO). ^{1}H-NMR ($CDCl_3$) δ: 4.07 (2H, s, CH_2), 6.46—6.58 (1H, m, aromatic H), 7.03—7.42 (6H, m, aromatic H), 7.48—7.54 (1H, m, aromatic H).

4′-Methyldeoxybenzoin (**4e**, 4-methoxybenzyl phenyl ketone): The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 1) gave **4e** in 99% yield (624 mg). Colorless scales (acetone–*n*-hexane), mp 95—96 °C (lit.,[10d] mp 95 °C). IR (KBr) cm^{-1}: 1690 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s, Me), 4.17 (2H, s, CH_2), 6.92—8.07 (9H, m, aromatic H).

3-Benzoylpropionitrile (**4f**): The fraction eluted with *n*-hexane–AcOEt (10 : 1) gave **4f** in 94% yield (450 mg). Colorless plates (*n*-hexane–CH_2Cl_2), mp 75—76 °C (lit.,[10e] mp 76 °C). IR (neat) cm^{-1}: 1680 (CO), 2250 (CN). ^{1}H-NMR ($CDCl_3$) δ: 2.75 (2H, t, J=7 Hz, CH_2), 3.49 (2H, t, J=7 Hz, CH_2), 7.34—7.70 (2H, m, aromatic H), 7.85—8.08 (2H, m, aromatic H).

3-(4-Chlorobenzoyl)propionitrile (**4g**): The fraction eluted with *n*-hexane–AcOEt (5 : 1) gave **4g** in 87% yield (501 mg). Colorless scales (*n*-hexane–acetone), mp 68—70 °C (lit.,[10e] mp 73 °C). IR (KBr) cm^{-1}: 1673 (CO), 2250 (CN). ^{1}H-NMR ($CDCl_3$) δ: 2.75 (2H, t, J=7 Hz, CH_2), 3.35 (2H, t, J=7 Hz, CH_2), 7.42 (2H, d, J=9 Hz, aromatic H), 7.85 (2H, d, J=9 Hz, aromatic H).

3-(4-Methoxybenzoyl)propionitrile (**4h**): The fraction eluted with *n*-hexane–AcOEt (10 : 1) gave **4h** in 99% yield (561 mg). Colorless needles (*n*-hexane–acetone), mp 95—96 °C (lit.,[10f] mp 95—96 °C). IR (KBr) cm^{-1}: 1675 (CO), 2250 (CN). ^{1}H-NMR ($CDCl_3$) δ: 2.71 (2H, t, J=7 Hz, CH_2), 3.32 (2H, t, J=7 Hz, CH_2), 3.84 (3H, s, OMe), 6.87 (2H, d, J=9 Hz, aromatic H), 7.84 (2H, d, J=9 Hz, aromatic H).

3-(4-Chlorobenzoyl)-2-methylpropionitrile (**4i**): The fraction eluted with *n*-hexane–AcOEt (10 : 1) gave **4i** in 97% yield (604 mg). Colorless oil (lit.,[10e] mp 60 °C). MS m/z: 207 (M^+). IR (neat) cm^{-1}: 1688 (CO), 2255 (CN). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=7 Hz, Me), 2.65 (2H, d, J=8 Hz, CH_2), 3.43—4.10 (1H, m, CH), 7.44 (2H, d, J=9 Hz, aromatic H), 7.87 (2H, d, J=9 Hz, aromatic H).

Ethyl 3-(4-chlorobenzoyl)propionate (**4j**): The fraction eluted with *n*-hexane–AcOEt (10 : 1) gave **4j** in 98% yield (708 mg). Colorless scales (*n*-hexane–CH_2Cl_2), mp 58—59 °C (lit.,[10f] mp 58—59 °C). IR (KBr) cm^{-1}: 1668, 1728 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $OCH_2\underline{CH}_3$), 2.76 (2H, t, J=7 Hz, CH_2), 3.28 (2H, t, J=7 Hz, CH_2), 4.16 (2H, q, J=7 Hz, $OCH_2\underline{CH}_3$), 7.44 (2H, d, J=9 Hz, aromatic H), 7.93 (2H, d, J=9 Hz, aromatic H).

1-Phenyl-1,4-pentanedione (**4k**): The fraction eluted with *n*-hexane–AcOEt (10 : 1) gave **4k** in 94% yield (497 mg). Colorless oil (lit.,[10g] mp 28—29 °C). MS m/z: 176 (M^+). IR (KBr) cm^{-1}: 1680, 1712 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s, Me), 2.82 (2H, d, J=6 Hz, CH_2), 3.22 (2H, d, J=6 Hz, CH_2), 7.40—7.64 (3H, m, aromatic H), 7.70—8.01 (2H, m, aromatic H).

1-(4-Chlorophenyl)-1,4-pentanedione (**4l**): The fraction eluted with $CHCl_3$ gave **4l** in 98% yield (621 mg). Colorless scales (*n*-hexane–CH_2Cl_2), mp 75.5—76 °C (lit.,[10g] mp 76 °C). IR (KBr) cm^{-1}: 1672, 1709 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s, Me), 2.89 (2H, d, J=6 Hz, CH_2), 3.24 (2H, d, J=6 Hz, CH_2), 7.44 (2H, d, J=9 Hz, aromatic H), 7.92 (2H, d, J=9 Hz, aromatic H).

Benzophenone (**4m**): The fraction eluted with *n*-hexane–$CHCl_3$ (3 : 1) gave **4m** in 63% yield (548 mg).

4-Chlorophenyl Phenyl Ketone (**4n**): The fraction eluted with *n*-hexane–$CHCl_3$ (3 : 1) gave **4n** in 69% yield (447 mg).

Synthesis of Ketones (4) by Retro-Benzoin Condensation of α-Substituted Benzoins (3) Catalyzed by Tetrabutylammonium Cyanide (6, Bu_4NCN, Method b) General Procedure: A mixture of α-substituted benzoin (**3**, 3.0 mmol) and Bu_4NCN (**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_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and AcOEt.

The structures of the reaction products were determined by comparison of the spectral data and the melting points with those of authentic samples.

Preparation of Azolium Salts (7) 1,3-Dimethylimidazolium iodide (**7a**),[11a] 1,3-dimethylbenzimidazolium iodide (**7b**),[11b] 1,4-dimethyl-1,2,4-triazolium iodide (**7c**),[11c] 2-methylimidazo[1,5-*a*]pyridinium iodide (**7d**),[11d] pyrido[1′,2′ : 3,4]imidazo[1,5-*a*]pyridinium iodide (**7f**),[11d] and 3,4,5-trimethylthiazolium iodide (**7g**),[11e–g] were synthesized by reported procedures.

2-Methyl-1,2,4-triazolo[4,3-*a*]pyridinium iodide (**7e**): A solution of 1,2,4-triazolo[4,3-*c*]pyridine[11g] (10 g, 0.084 mol) and MeI (14 g, 0.1 mol) in MeOH (30 ml) was refluxed for 3 h. The reaction mixture was concentrated, and a small portion of ether was added to the residue. The separated crystalline solid was collected, washed with a small portion of ether, and dried to give a mixture of **6e** and 1-methylimidazo[1,5-*a*]pyridinium iodide (18 g, 82%). Fractional recrystallization with MeOH gave **6e** in 20% (4.4 g) yield. Slightly brown needles (MeOH), mp 228—231 °C. *Anal.* Calcd for $C_7H_8IN_3$: C, 32.21; H, 3.09; N, 16.10. Found: C, 32.15; H, 2.89; N, 16.01. ^{1}H-NMR (DMSO-d_6) δ: 4.40 (3H, s, NMe), 7.51 (1H, t, J=7 Hz, C^6-H), 7.87—7.93 (1H, m, C^7-H), 8.08 (1H, d, J=9 Hz, C^8-H), 8.96 (1H, d, J=7 Hz, C^5-H), 10.74 (1H, s, C^3-H).

Synthesis of Ketones (4) by Retro-Benzoin Condensation of α-Substituted Benzoins (3) Catalyzed by Azolium Salts (7) (Method c) General Procedure: Sodium hydride (60% in oil, 120 mg, 3.0 mmol) or sodium amide (117 mg, 3.0 mmol) was added to a mixture of α-substituted benzoin (**3**, 3.0 mmol) and an azolium salt (**7**, 1.0 mmol) in DMF (20 ml), and the mixture was stirred (reaction conditions are shown in Table 3). The reaction mixture was poured into ice–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and AcOEt.

Preparation of α-Substituted Benzoins (3): Alkylation of Benzoins (5) General Procedure: A solution of sodium hydroxide (1.05 g in 50 ml of H_2O) was added to a solution of benzoin (**5**, 25 mmol) in dimethyl sulfoxide (DMSO) (100 ml), and then alkyl halide [benzyl bromide (**9a**), 4.3 g (25.2 mmol) or *p*-methylbenzyl chloride (**9b**), 3.54 g (25.2 mmol)] was added to the resulting solution. After the green color of the reaction solution turned to yellow, the reaction mixture was poured into 10% brine and extracted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$, and/or recrystallization to give α-substituted benzoins (**3a—e**).

α-Benzylbenzoin (**3a**, α-benzyl-α-hydroxybenzyl phenyl ketone): Yield 79%, colorless columns (MeOH), mp 114—116 °C (lit.[7b] 118—121 °C).

IR (KBr) cm^{-1}: 1668 (CO), 3520 (OH). ^{1}H-NMR ($CDCl_3$) δ: 3.60 (1H, d, J=14 Hz, a proton signal of CH_2), 3.96 (1H, d, J=14 Hz, a proton signal of CH_2), 3.95 (1H, s, OH), 6.81—7.77 (15H, m, aromatic H).

α-Benzyl-4,4′-dichlorobenzoin (**3b**, α-benzyl-α-hydroxy-4-chlorobenzyl 4-chlorophenyl ketone): Yield 99%, colorless needles (MeOH), mp 137—138 °C. *Anal.* Calcd for $C_{21}H_{16}Cl_2O_2$: C, 67.94; H, 4.34. Found: C, 68.24; H, 4.08. IR (KBr) cm^{-1}: 1657 (CO), 3420 (OH). ^{1}H-NMR ($CDCl_3$) δ: 3.34 (1H, d, J=14 Hz, a proton signal of CH_2), 3.83 (1H, d, J=14 Hz, a proton signal of CH_2), 3.45 (1H, s, OH), 6.94—7.74 (13H, m, aromatic H).

α-Benzyl-4,4′-dimethoxybenzoin (**3c**, α-benzyl-α-hydroxy-4-methoxybenzyl 4-methoxyphenyl ketone): Yield 72%, yellow needles (MeOH), mp 103—105 °C (lit.,[7a] 119 °C). IR (KBr) cm^{-1}: 1659 (CO), 3440 (OH). ^{1}H-NMR ($CDCl_3$) δ: 3.45 (1H, d, J=14 Hz, a proton signal of CH_2), 3.73 (1H, d, J=14 Hz, a proton signal of CH_2), 3.74 (3H, s, OMe), 3.82 (3H, s, OMe), 4.22 (1H, s, OH), 6.58—8.03 (15H, m, aromatic H).

α-Benzylfuroin [**3d**, 1,2-di(2-furyl)-2-hydroxyethanone]: The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 1) gave **3d**. Yield 51%, colorless prisms (acetone–*n*-hexane), mp 87—88 °C. *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.33; H, 4.95. IR (KBr) cm^{-1}: 1670 (CO), 3450 (OH). ^{1}H-NMR ($CDCl_3$) δ: 3.50 (1H, d, J=14 Hz, a proton signal of CH_2), 3.95 (1H, d, J=14 Hz, a proton signal of CH_2), 4.43 (1H, s, OH), 6.25—7.52 (11H, m, aromatic H).

α-(4-Methylbenzyl)benzoin [**3e**, α-(4-methylbenzyl)-α-hydroxybenzyl phenyl ketone]: The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 1) gave **3e**. Yield 61%, colorless prisms (acetone–*n*-hexane), mp 120—121 °C. *Anal.* Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.63; H, 6.57. IR (KBr) cm^{-1}: 1665 (CO), 3420 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s, Me), 3.40 (1H, d, J=14 Hz, a proton signal of CH_2), 3.73 (1H, d, J=14 Hz, a proton signal of CH_2), 3.88 (1H, s, OH), 6.65—7.72 (14H, m, aromatic H).

Reaction of Benzoins (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 benzoin (**5**, 5.0 mmol) and a Michael acceptor (**10**, 7.5 mmol) in DMF (20 ml). After the green color of the reaction solution turned to yellow, the reaction mixture was poured into 10% brine and extracted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and AcOEt to give α-substituted benzoins (**3f**—**l**).

α-(2-Cyanoethyl)benzoin [**3f**, α-(2-cyanoethyl)-α-hydroxybenzyl phenyl ketone]: The fraction eluted with *n*-hexane–AcOEt (5 : 1) gave **3f**. Yield 90%, colorless needles (*n*-hexane–CH_2Cl_2), mp 99—100 °C. *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.17; H, 5.63; N, 5.05. IR (KBr) cm^{-1}: 1664 (CO), 2240 (CN), 3420 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.09—2.93 (4H, m, CH_2CH_2), 4.35 (1H, s, OH), 7.25—7.84 (10H, m, aromatic H).

α-(2-Cyanoethyl)-4,4′-dichlorobenzoin [**3g**, 4-chlorophenyl α-(2-cyanoethyl)-α-hydroxy-4-chlorobenzyl ketone]: The fraction eluted with *n*-hexane–AcOEt (5 : 1) gave **3g**. Yield 86%, colorless needles (*n*-hexane–CH_2Cl_2), mp 112—123 °C. *Anal.* Calcd for $C_{17}H_{13}Cl_2NO_2$: C, 61.10; H, 3.92; N, 4.19. Found: C, 61.11; H, 3.71; N, 4.08. IR (KBr) cm^{-1}: 1664 (CO), 2250 (CN), 3450 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.18—2.44 (4H, m, CH_2), 2.52—2.71 (2H, m, CH_2), 4.10 (1H, s, OH), 7.29—7.42 (6H, m, aromatic H), 7.70 (2H, d, J=8 Hz, aromatic H).

α-(2-Cyanoethyl)-4,4′-dimethoxybenzoin [**3h**, α-(2-cyanoethyl)-α-hydroxy-4-methoxybenzyl 4-methoxyphenyl ketone]: The fraction eluted with *n*-hexane–AcOEt (5 : 1) gave **3h**. Yield 87%, colorless columns (*n*-hexane–$CHCl_3$), mp 88—89 °C. *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.24; H, 5.85; N, 4.20. IR (KBr) cm^{-1}: 1648 (CO), 2249 (CN), 3425 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.06—2.18 (1H, m, CH_2), 2.45—2.82 (3H, m, CH_2), 3.81 (3H, s, OMe), 3.82 (3H, s, OMe), 4.68 (1H, s, OH), 6.79 (2H, d, J=9 Hz, aromatic H), 6.90 (2H, d, J=9 Hz, aromatic H), 7.32 (2H, d, J=9 Hz, aromatic H), 7.73 (2H, d, J=9 Hz, aromatic H).

α-(2-Cyano-1-methylethyl)-4,4′-dichlorobenzoin [**3i**, 4-chlorophenyl α-(2-cyano-1-methylethyl)-α-hydroxy-4-chlorobenzyl ketone]: The fraction eluted with *n*-hexane–AcOEt (10 : 1) gave **3i**. Yield 50%, colorless oil. MS *m/z*: 347 (M^+).

α-(2-Ethoxycarbonylethyl)-4,4′-dichlorobenzoin [**3j**, α-(2-ethoxycarbonylethyl)-α-hydroxy-4-chlorobenzyl 4-chlorophenyl ketone]: The fraction eluted with *n*-hexane–AcOEt (10 : 1) gave **3j**. Yield 66%, colorless columns (*n*-hexane–$CHCl_3$), mp 115—116 °C. *Anal.* Calcd for $C_{19}H_{18}Cl_2O_4$: C, 59.86; H, 4.76. Found: C, 59.94; H, 4.62. IR (KBr) cm^{-1}: 1674 (CO), 1718 (CO), 3540 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, $OCH_2\underline{CH}_3$), 2.17—2.31 (1H, m, CH_2), 2.41—2.63 (3H, m, CH_2), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.32 (1H, s, OH), 7.27 (2H, d, J=9 Hz, aromatic H), 7.34 (2H, d, J=9 Hz, aromatic H), 7.44 (2H, d, J=9 Hz, aromatic H), 7.80 (2H, d, J=9 Hz, aromatic H).

α-(3-Oxobutyl)benzoin [**3k**, phenyl α-(3-oxobutyl)-α-hydroxybenzyl ketone]: The fraction eluted with *n*-hexane–AcOEt (10 : 1) gave **3k**. Yield 34%, colorless prisms (*n*-hexane–CH_2Cl_2), mp 95—97 °C. *Anal.* Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.66; H, 6.38. IR (KBr) cm^{-1}: 1677 (CO), 1684 (CO), 3160 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.46—3.45 (7H, m, CH_2CH_2 and Me), 5.13 (s, OH), 7.23—7.54 (8H, m, aromatic H), 7.75—7.96 (2H, m, aromatic H).

α-(3-Oxobutyl)-4,4′-dichlorobenzoin [**3l**, 4-chlorophenyl α-(3-oxobutyl)-α-hydroxy-4-chlorobenzyl ketone]: The fraction eluted with *n*-hexane–AcOEt (10 : 1) gave **3l**. Yield 59%, colorless prisms (*n*-hexane–CH_2Cl_2), mp 84.5—85 °C. *Anal.* Calcd for $C_{18}H_{16}Cl_2O_3$: C, 51.55; H, 4.59. Found: C, 61.53; H, 4.39. IR (KBr) cm^{-1}: 1678 (CO), 3360 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.48—3.44 (7H, m, CH_2CH_2 and Me), 5.37 (s, OH), 7.26—7.44 (6H, m, aromatic H), 7.78—7.92 (2H, m, aromatic H).

Reaction of Benzils (8) with Grignard Reagents (11) General Procedure: A Grignard reagent (**11**, 15.0 mmol in 15 ml of Et_2O) was added to a solution of benzil (**8**, 10 mmol) in THF (40 ml), and the mixture was refluxed for 1 h with stirring, then poured into NH_4Cl–NH_3 solution and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and CH_2Cl_2.

α-Benzylbenzoin (**3a**): Yield 93%.

α-Benzyl-4,4′-dichlorobenzoin (**3b**): Yield 76%.

α-Phenylbenzoin (**3m**, α-hydroxy-α-phenylbenzyl phenyl ketone): Yield 60%, colorless prisms (acetone–*n*-hexane), mp 175—176 °C. *Anal.* Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.52; H, 5.45. IR (KBr) cm^{-1}: 1667 (CO), 3470 (OH). ^{1}H-NMR ($CDCl_3$) δ: 4.40 (1H, s, OH), 7.15—7.35 (15H, m, aromatic H).

α-Phenyl-4,4′-dichlorobenzoin (**3n**, 4-chlorophenyl α-hydroxy-α-phenyl-4-chlorobenzyl ketone): Yield 63%, colorless granules (acetone–*n*-hexane), mp 163—165 °C. *Anal.* Calcd for $C_{20}H_{14}Cl_2O_2$: C, 67.24; H, 3.95. Found: C, 67.14; H, 4.00. IR (KBr) cm^{-1}: 1698 (CO), 3540 (OH). ^{1}H-NMR ($CDCl_3$) δ: 3.03 (1H, s, OH), 7.16—7.35 (13H, m, aromatic H).

7-Hydroxy-7-phenyl-6-dodecanone (**3o**): Yield 84%, colorless oil (bp 155—165 °C/7 mmHg). *Anal.* Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.21; H, 10.27. IR (KBr) cm^{-1}: 1701 (CO), 3450 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.72—2.51 (22H, m, aliphatic H), 2.53 (1H, s, OH), 7.16—7.56 (5H, m, aromatic H). Compound **3o** was similarly prepared from 6,7-dodecadione.[12]

One-Pot Synthesis of Ketones (4) by Alkylation of Benzoins (5) Followed by Retro-Benzoin Condensation General Procedure: Sodium hydride [60% in oil, 156 mg (3.9 mmol) for reaction with benzyl bromide (**9**) or 24 mg (0.6 mmol) for Michael addition] was added to a solution of benzoin (**5a**, 3.0 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 mg, 0.6 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 H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and AcOEt.

The structures of the products, deoxybenzoin (**4a**), 4′-methyldeoxybenzoin (**4e**), and 3-benzoylpropionitrile (**4f**), were determined by comparison of the spectral data and the melting points with those of authentic samples.

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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).

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