Chem. Pharm. Bull. **44**(1) 252—254 (1996)

SYNTHESIS OF KETONES BY RETRO-BENZOIN CONDENSATION CATALYZED BY POTASSIUM CYANIDE

Akira MIYASHITA,* Yumiko SUZUKI, Yoko OKUMURA, and Takeo HIGASHINO

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422, Japan

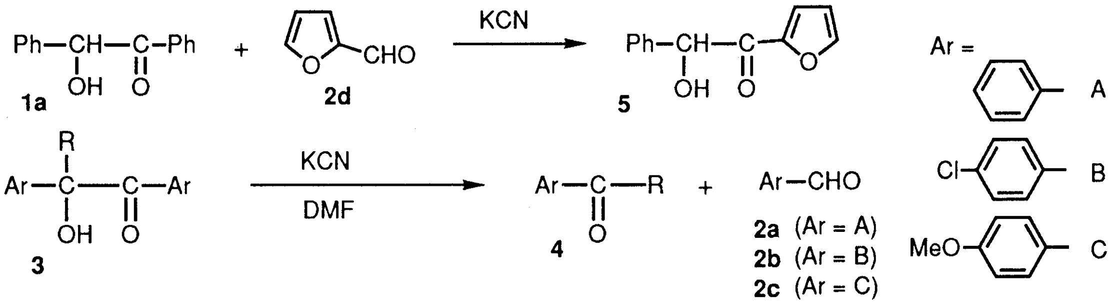
The treatment of 2-benzyl-1,2-diphenyl-2-hydroxyethanone (**3a**, benzylbenzoin) with potassium cyanide in DMF gave deoxybenzoin (**4a**). The formation of deoxybenzoin (**4a**) proceeds through retro-benzoin condensation by catalytic action of cyanide ion. Similarly, retro-benzoin condensation applied to several substituted benzoins **3** resulted in the formation of the corresponding ketones **4** in excellent yields.

KEY WORDS retro-benzoin condensation; cyanide ion; ketone; catalyst; benzoin; azolium ylide

In our continuous study of benzoin condensation and related reactions,[1] we have been interested in the catalytic action of cyanide ion and the electron-accepting effect of the cyano group for development of synthetic methods of organic compounds. We have so far found several reactions promoted by cyanide ion and the cyano group.[1]

Benzoin condensation is a characteristic reaction because it proceeds only by catalytic action of cyanide ion.[2] Furthermore, all of the reaction processes are reversible.[2a, 3] Indeed, 1-(2-furyl)-2-phenyl-2-hydroxyethanone (**5**, benzfuroin), which is a cross-benzoin product, is produced by treatment of benzoin (**1a**) with 2-furaldehyde (**2d**) in the presence of cyanide ion.[4] This result indicates that the most stable compound is finally given as the reaction product in benzoin condensation. In the presence of cyanide ion, self-condensation of benzaldehyde (**2a**) gives benzoin (**1a**), and cross-condensation between benzoin (**1a**) and 2-furaldehyde (**2d**) gives cross-benzoin product **5**. We considered that benzoin **1a** is the most stable compound among the former reaction products and cross-benzoin product **1d** is the most stable compound of the latter reaction products.

These results led us to synthesize ketones by retro-benzoin condensation. We considered that treatment of benzoin derivatives, such as benzylbenzoins (**3a-c**), with catalytic amounts of cyanide ion gives ketones (**4a-c**) and aldehyde (**2a-c**) by carbon-carbon bond cleavage. Among the reaction mixtures, ketone **4**, benzoin derivative **3**, and aromatic aldehyde **2**, ketone is the most stable product, because the cross-condensation between aromatic aldehydes and ketones cannot give the corresponding cross-benzoins **3** in the usual way.



3	Ar	R	Reaction conditions Temp. (°C)	 Time (min)	4	Yield (%)
3a	A	$PhCH_2$	80	60	**4a**	98
3b	B	$PhCH_2$	80	60	**4b**	96
3c	C	$PhCH_2$	80	60	**4c**	95
3d	A	$NCCH_2CH_2$	80	60	**4d**	94
3e	B	$NCCH_2CH_2$	80	60	**4e**	87
3f	C	$NCCH_2CH_2$	80	60	**4f**	99
3g	B	$EtOOCCH_2CH_2$	80	15	**4g**	98
3h	B	$NCCH_2(CH_3)CH$	r.t.	30	**4h**	97
3i	A	$H_3CCOCH_2CH_2$	r.t.	30	**4i**	94
3j	B	$H_3CCOCH_2CH_2$	r.t.	30	**4j**	98

Chart 1

---

* To whom correspondence should be addressed.

When 2-benzyl-1,2-diphenyl-2-hydroxyethanone (**3a**) was treated with a catalytic amount of potassium cyanide in DMF at 80 °C for 1 h, deoxybenzoin (**4a**) was given in 98% yield together with benzaldehyde in 20% yield.[5] As expected, deoxybenzoin (**4a**) was produced by retro-benzoin condensation. Similarly, other benzylbenzoins such as 2-benzyl-1,2-bis(*p*-methoxyphenyl)-2-hydroxyethanone (**3b**) and 2-benzyl-1,2-bis(*p*-chlorophenyl)-2-hydroxyethanone (**3c**) afforded the corresponding deoxybenzoins such as 1-(*p*-methoxyphenyl)-2-phenylethanone (**4b**) and 1-(*p*-chlorophenyl)-2-phenylethanone (**4c**) in good yields.

Similar results were obtained in other benzoin derivatives **3**. When the compounds **3d-j**, which are Michael-addition products of benzoins, were treated with catalytic amount of potassium cyanide in DMF, the corresponding ketones **4d-j** were given in excellent yields. These results are shown in Chart 1.

Based on the mechanism of benzoin condensation, the formation of the ketones can be illustrated as shown in Chart 2. Since the ketone is the most stable compound among the sequential products, the reaction proceeds to the formation of ketone by carbon-carbon bond cleavage.

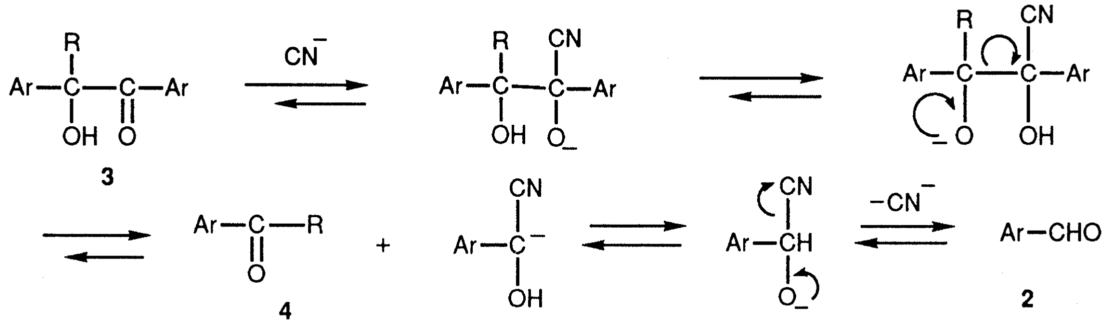
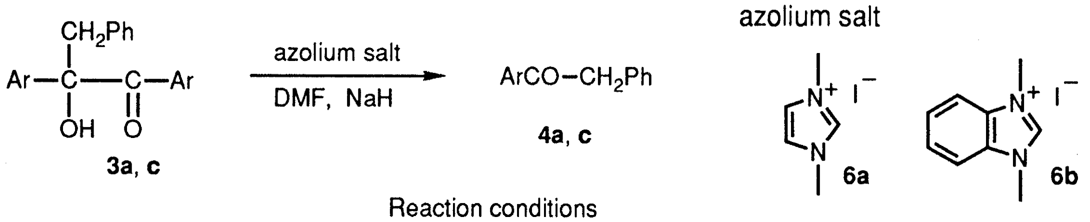


Chart 2

In the previous paper, we reported that azolium salts such as 1,3-dimethylimidazolium iodide (**6a**) and 1,3-dimethylbenzimidazolium iodide (**6b**) can be used as effective catalysts for benzoin condensation. The catalytic action is similar to that of cyanide ion.[1] Namely, aromatic aldehydes underwent self-condensation by catalytic action of the azolium ylides, resulting in the formation of benzoins. These results indicated that the azolium salts can be employed as effective catalysts for this retro-benzoin condensation. As expected, benzylbenzoins **3a** and **3c** cleaved into the corresponding deoxybenzoins **4a** and **4c** by catalytic action of the azolium salts. However, the yields were low, because purification of the produced deoxybenzoins from the reaction mixture was not easy. It could be observed that the azolium salts **6a** and **6b** catalyze the retro-benzoin condensation effectively (Chart 3).

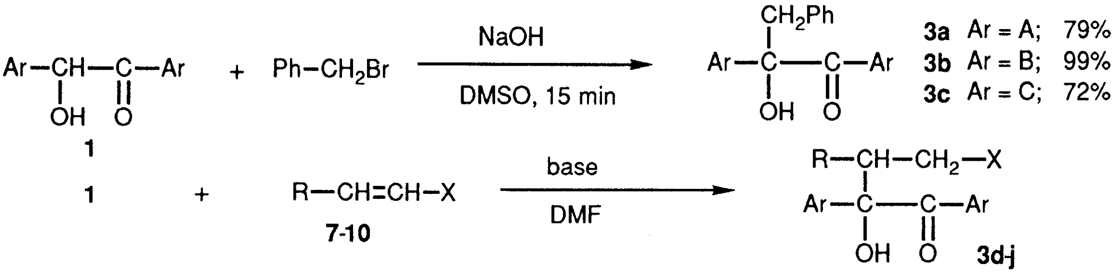


	Ar	Azolium salt	Reaction conditions			Yield (%)
			Temp. (°C)	Time (min)		
3a	A	**6a**	80	60	**4a**	87
3c	C	**6a**	80	60	**4c**	53
3a	A	**6b**	80	60	**4a**	18
3c	C	**6b**	80	60	**4c**	43

Chart 3

The benzoin derivatives used in this paper were prepared by alkylation of benzoins. Benzylation of the benzoins **1** gave benzylbenzoins **3a-c**.[6] Moreover, Michael-addition of the anion derived from benzoin (**1a**) with acrylonitrile (**7**) gave 4,5-diphenyl-4-hydroxy-5-oxopentanonitrile (**3d**).[7] Similarly, the benzoin derivatives (**3e-j**) were obtained by Michael-addition of the benzoins **1a-c** with acrylonitrile (**7**), ethyl acrylate (**8**), methyl vinyl ketone (**9**), and 2-butenonitrile (**10**). These results are shown in Chart 4.

Stetter and co-workers reported a method of preparing ketones from aldehydes and Michael-addition acceptors by catalytic action of cyanide ion. This reaction proceeds through the formation of the active aldehydes derived from aldehydes and cyanide ion. But the reaction is not so easy as to yield the ketones efficiently.[8] In contrast, this synthesizing of ketones by retro-benzoin condensation is easy and certain.



1	Ar		R	X	Reaction conditions Temp. (°C)	 Time (min)		Yield (%)
1a	A	**7**	H	CN	r.t.	15	**3d**	90
1b	B	**7**	H	CN	r.t.	15	**3e**	86
1c	C	**7**	H	CN	r.t.	15	**3f**	87
1b	B	**8**	H	COOEt	r.t.	20	**3g**	66
1b	B	**10**	Me	CN	60	30	**3h**	50
1a	A	**9**	H	$COCH_3$	60	30	**3i**	34
1b	B	**9**	H	$COCH_3$	r.t.	90	**3j**	59

Chart 4

We found a new method of synthesizing ketones by retro-benzoin condensation from benzoin derivatives. In organic synthesis, this is the first example for producing ketones by retro-benzoin condensation. Cyanide ion is an effective catalyst in this reaction.

REFERENCES AND NOTES

1) *a*) Miyashita A., Suzuki Y., Iwamoto K., Higashino T., *Chem. Pharm. Bull.*, **42**, 2633 (1994); *b*) Miyashita A., Matsuda H., Suzuki Y., Iwamoto K., Higashino T., *ibid*, **42**, 2017 (1994); *c*) Miyashita A., Matsuda H., Higashino T., *ibid*, **40**, 2627 (1992); *d*) Miyashita A., Matsuda H., Iijima C., Higashino T., *ibid*, **40**, 43 (1992); *e*) *idem*, *ibid*, **38**, 1147 (1990); *f*) Miyashita A., Matsuoka Y., Iwamoto K., Higashino T., *ibid*, **42**, 1960 (1994).

2) *a*) Ide W. S., Buck J. S., *Org. React.*, **4**, 269 (1948); *b*) Kuebrick J. P., Schowen R. L., Wang M., Lupes M. E., *J. Am. Chem. Soc.*, **93**, 1214 (1971).

3) *a*) Lapworth A., *J. Chem. Soc.*, **83**, 995 (1903); *b*) *idem*, *ibid*, **85**, 1206 (1904).

4) *a*) K. Brass, E. Willig, R. Hanssen, *Chem. Ber.*, **63**, 2613 (1930); *b*) Buck J. S., Ide W. S., *J. Am. Chem. Soc.*, **53**, 2350 (1931); *c*) *idem*, *ibid*, **53**, 2784 (1931).

5) A typical procedure: A mixture of benzylbenzoin (**3a**, 906 mg, 3 mmol) and potassium cyanide (39 mg, 0.6 mmol) in DMF (30 ml) was stirred at 80 °C for 1 h and poured into H_2O. The mixture was neutralized with AcOH and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on SiO_2 with hexane-AcOEt (7:1). The first fraction gave benzaldehyde (**2a**) in 20% (64 mg) yield. The second fraction gave deoxybenzoin (**4a**, 588 mg, 98%), colorless needles (hexane), mp 56-57 °C.
The yield of **2a** was low, because further reactions proceeded in the presence of cyanide ion. Indeed, anisoin (**1c**, 5%), together with **4f** (99%) and *p*-anisaldehyde (**2c**, 50%), was obtained by retro-benzoin condensation of **3f**.

6) Hase T., *Synthesis*, **1980**, 36.

7) A typical procedure: To a mixture of benzoin (**1a**, 1.06 g, 5 mmol) and acrylonitrile (**7**, 398 mg, 7.5 mmol) in 20 ml of DMF was added 0.5 ml of DBU, and the mixture was stirred at room temperature for 15 min. After the green of the reaction mixture turned to yellow, the reaction mixture was poured into H_2O and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on SiO_2 with hexane-AcOEt (5:1). The first fraction gave alkylated benzoin (**3d**, 1.19 g, 90%). **3d**: Colorless needles (hexane-methylene chloride), 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}: 3420 (OH), 2240 (CN), 1664 (CO). ^1H-NMR ($CDCl_3$) δ (ppm): 7.84-7.25 (10H, m, aromatic H), 4.35 (1H, OH), 2.93-2.09 (4H, m, CH_2CH_2)

8) Stetter H., *Angew. Chem.*, **88**, 695 (1976), and references cited therein.
In this paper, Stetter reported that a 39% yield of **3f** was obtained, whereas this retro-benzoin condensation gave **3f** in 86% overall yield from anisoin (**1c**). To produce the ketones, Stetter reaction requires highly controlled conditions.

(Received September 18, 1995; accepted November 22, 1995)