Olefin-Insertion Reaction between the Carbonyls of Benzils; Formation of 1,4-Diketones by Michael Additon Catalyzed by Cyanide Ion

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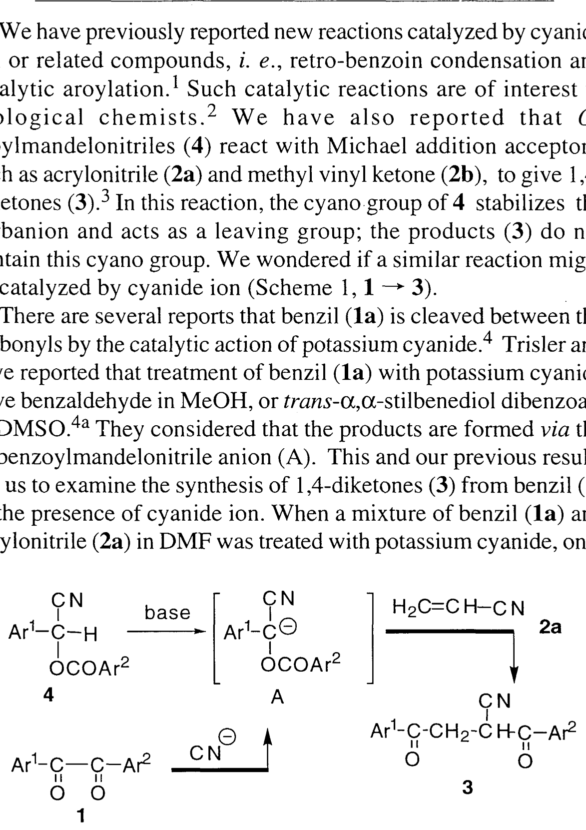
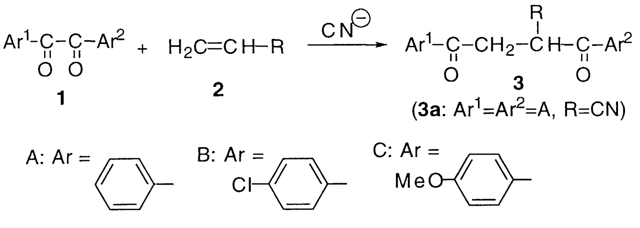
Benzils (**1**) react with Michael addition acceptors (**2**) in the presence of cyanide ion as a catalyst to give 1,4-diketones (**3**), which are products of ethylene group insertion between the carbonyls of the benzils. The 1,4-diketones (**3**) are produced through the formation of the *O*-aroylmandelonitrile anion, followed by Michael addition and rearrangement of the aroyl group with decyanation.

We have previously reported new reactions catalyzed by cyanide ion or related compounds, *i. e.*, retro-benzoin condensation and catalytic aroylation.[1] Such catalytic reactions are of interest to biological chemists.[2] We have also reported that *O*-aroylmandelonitriles (**4**) react with Michael addition acceptors, such as acrylonitrile (**2a**) and methyl vinyl ketone (**2b**), to give 1,4-diketones (**3**).[3] In this reaction, the cyano group of **4** stabilizes the carbanion and acts as a leaving group; the products (**3**) do not contain this cyano group. We wondered if a similar reaction might be catalyzed by cyanide ion (Scheme 1, **1** → **3**).

There are several reports that benzil (**1a**) is cleaved between the carbonyls by the catalytic action of potassium cyanide.[4] Trisler and Frye reported that treatment of benzil (**1a**) with potassium cyanide gave benzaldehyde in MeOH, or *trans*-α,α-stilbenediol dibenzoate in DMSO.[4a] They considered that the products are formed *via* the *O*-benzoylmandelonitrile anion (A). This and our previous results led us to examine the synthesis of 1,4-diketones (**3**) from benzil (**1**) in the presence of cyanide ion. When a mixture of benzil (**1a**) and acrylonitrile (**2a**) in DMF was treated with potassium cyanide, only the starting benzil (**1a**) was recovered. We considered that under this reaction condition, the cyanide ion could not add to the carbonyl carbon of benzil because of insufficient nucleophilicity. Thus, in the formation of **3a** by reaction of **1a** with **2a**, several compounds that provide cyanide ion were tried. As shown in Table 1, when tetrabutylammonium cyanide (Bu_4NCN), and potassium cyanide (KCN) and crown ether (18-crown-6) were used, the expected 1,4-diketone (**3a**) was obtained. Further, the use of TMSCN and tetrabutylammonium fluoride (Bu_4NF) also gave **3a**. This reaction proceeds through *in situ* formation of tetrabutylammmonium cyanide (Bu_4NCN). Since tetrabutylammonium cyanide cannot be easily handled because of its hygroscopicity, this procedure is very convenient.



Scheme 1.



1a: Ar^1=A, Ar^2=A, **1b**: Ar^1=B, Ar^2=B, **1c**: Ar^1=C, Ar^2=C, **1d**: Ar^1=A, Ar^2=C, **1d**: Ar^1=B, Ar^2=A
2a: R=CN, **2b**: R=COMe, **2c**: R=COOMe, **2d**: R=COOEt

Scheme 2.

Table 1. Cyanide ion–donating effect under several conditions for the reaction of benzil (**1a**) with acrylonitrile (**2a**)

Donors of cyanide ion	Solvent	**3a**, Yield /%
Bu_4NCN	THF	60
TMSCN + Bu_4NF	THF	80
KCN + 18–crown–6	CH_3CN	30
KCN	DMF	– (100)[a]
KCN + Bu_4NBr	THF	– (100)[a]

[a] Recovery of starting **1a**.

Several 1,4-diketones (**3**) could be synthesized by this approach (Methods I and II), as shown in Table 2.[5] Namely, in the presence of Bu_4NCN (Method I), benzils (**1**) reacted with Michael addition acceptors (**2**) to give the corresponding 1,4-diketones (**3**) in moderate to good yields. The *in situ* formation of Bu_4NCN (Method II) from TMSCN and Bu_4NF was also effective. However, 4,4'-dimethoxybenzil (**1c**) did not give the 1,4-diketones (**3g** and **3h**). We considered that addition of cyanide ion could not proceed

Table 2. Formation of 1,4-diketones (**3**) by reaction of benzils (**1**) with Michael addition acceptors (**2**) catalyzed by cyanide ion

	Substrates			Product; 1,4-diketone 3				
Entry	**1**	**2**	Method[a]		Ar^1	Ar^2	R	Yield /%
1	**1a**	**2b**	Method I	**3b**	A	A	COMe	54
2	**1a**	**2b**	Method II	**3b**	A	A	COMe	67
3	**1a**	**2c**	Method I	**3c**	A	A	COOMe	60
4	**1a**	**2d**	Method I	**3d**	A	A	COOEt	87
5	**1b**	**2a**	Method I	**3e**	B	B	CN	50
6	**1b**	**2b**	Method I	**3f**	B	B	COMe	37
7	**1b**	**2a**	Method II	**3e**	B	B	CN	89
8	**1b**	**2b**	Method II	**3f**	B	B	COMe	64
9	**1c**	**2a**	Method I	**3g**	C	C	CN	–
10	**1c**	**2b**	Method I	**3h**	C	C	COMe	–
11	**1d**	**2a**	Method I	**3i**	A	C	CN	60
12	**1e**	**2a**	Method I	**3j**	B	A	CN	93

[a] Method I; Bu_4NCN and Method II; *in situ* formation of Bu_4NCN from TMSCN and Bu_4NF.

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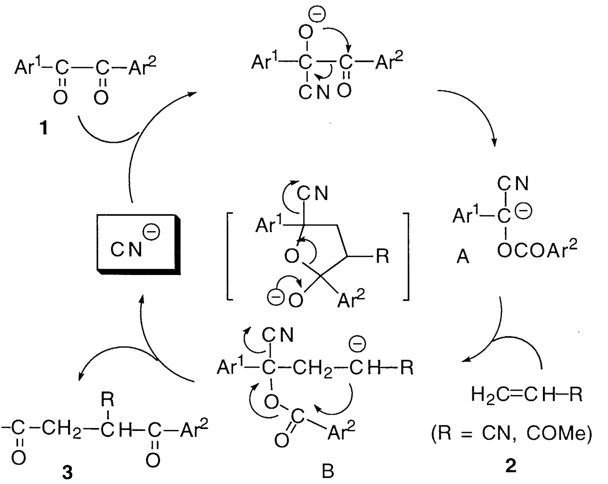
because of the low electrophilicity of the carbonyl groups of benzil (**1c**) owing to the electron-donating effect of the methoxy groups. The fact that the starting benzil (**1c**) was recovered supports this idea.

Unsymmetrical benzils (**1d** and **1e**) were also examined (Entries 11 and 12). Namely, 4-methoxybenzil (**1d**) reacted with acrylonitrile (**2a**) to give the 1,4-diketone (**3i**). This result indicates that cyanide ion adds to the carbonyl carbon of lower electron density. Similarly, treatment of 4-chlorobenzil (**1e**) with acrylonitrile (**2a**) catalyzed by Bu_4NCN furnished the 1,4-diketone (**3j**). This result further supports the above proposal.

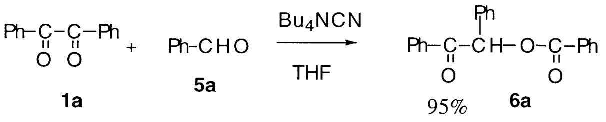
A plausible reaction pathway is shown in Scheme 3. Cyanide ion attacks benzil (**1**) at the carbonyl carbon of lower electron density and then rearrangement of the aroyl group results in the formation of the *O*-aroylmandelonitrile anion (A). Michael addition proceeds between the *O*-aroylmandelonitrile anion (A) and the acceptor (**2**) to give the *C*-anion (B). Intramolecular rearrangement of the aroyl group and decyanation furnish the 1,4-diketone (**3**). In this scheme, cyanide ion acts as a catalyst. The introduced cyano group stabilizes the carbanion and provides a good leaving group, cyanide ion, to promote this reaction. The aroyl group rearranges readily because the *C*–anion (B) can form a transition state having a five-membered ring system, and the cyano group can be easily released as cyanide ion.



Scheme 3.

This is a new method of synthesizing 1,4-diketones (**3**) by the reaction of a benzil (**1**) with a Michael addition acceptor (**2**) catalyzed by cyanide ion. The products (**3**) are convenient starting compounds for the synthesis of five-membered heteroarenes, *i. e.*, furans and pyrroles. This is an olefin-insertion reaction between the carbonyls of the benzils (**1**), and the 1,4-diketones (**3**)[6] are formed by double rearrangement of the aroyl group.

By analogy with the above reaction pathway, we speculated that the *O*-aroylmandelonitrile anion (A) might add to aldehyde to give an anion intermediate, which might form a transition state having a five-membered ring system. As expected, the treatment of benzil (**1a**) with benzaldehyde (**5a**) catalyzed by Bu_4NCN gave *O*-benzoylbenzoin (**6a**) in 95% yield (Scheme 4). This is a C–O group-insertion reaction between the carbonyls of benzil (**1a**).



Scheme 4.

In conclusion, we have found a new Michael addition–type olefin-insertion reaction between the carbonyls of benzils (**1**) to afford 1,4-diketones (**3**). Cyanide ion is required as the catalyst, and Bu_4NCN is an effective cyanide ion-donating compound. In a similar manner, benzaldehyde (**5a**) undergoes a C–O group-insertion reaction with benzil (**1a**) to give *O*–benzoylbenzoin (**6a**).

References and Notes

1 *a*) A. Miyashita, Y. Suzuki, Y. Okumura, and T. Higashino, *Chem. Pharm. Bull.*, **44**, 252 (1996); *b*) A. Miyashita, H. Matsuda, C. Iijima, and T. Higashino, *Chem. Pharm. Bull.*, **38**, 1147 (1990).

2 M. I. Page, "The Chemistry of Enzyme Action," Elsevier Science Publishers, Amsterdam, 1984.

3 A. Miyashita, Y. Matsuoka, A. Numata, and T. Higashino, *Chem. Pharm. Bull.*, **44**, 448 (1996).

4 *a*) J. C. Trisler and J. L. Frye, *J. Org. Chem.*, **30**, 306 (1965); *b*) J. C. Trisler, B. F. Freasier, and S-M. Wu, *Tetrahedron Lett.*, **1974**, 687; *c*) M. B. Rubin, A. L. Gutman, and S. Inbar, *Tetrahedron Lett.*, **1979**, 889; *d*) W. C. Reardon, J. E. Wilson, and J. C. Trisler, *J. Org. Chem.*, **39**, 1596 (1974); *e*) J. P. Kuebrich and R. L. Schowen, *J. Am. Chem. Soc.*, **93**, 1220 (1971).

5 A typical procedure is as follows. Method I: Tetrabutylammonium cyanide (Bu_4NCN, 161 mg, 0.6 mmol) was added to a solution of benzil (**1a**, 420 mg, 2.0 mmol) and acrylonitrile (**2a**, 106 mg, 2.0 mmol) in 10 ml of THF, and the resulting mixture was stirred at room temperature for 2 h under an argon atmosphere. 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 *n*-hexane and AcOEt. The fraction eluted with *n*-hexane-AcOEt (10:1) gave the 1,4-diketone (**3a**).
Method II: A solution of Bu_4NF-THF (1.0 mol/l, 1.2 mmol) in THF (5 ml) was added to a solution of **1a** (420 mg, 2.0 mmol), **2a** (106 mg, 2.0 mmol), and TMSCN (119 mg, 1.2 mmol) in 5 ml of THF, and whole was stirred for 2 h at room temperature under an argon atmosphere. Work-up as described for Method I gave **3a**.

6 The structures of the 1,4-diketones (**3**) were supported by comparison of the analytical data with those of authentic samples.