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Cyanobenzoylation and Hydrocyanation of Aldehydes with Benzoyl Cyanide Using No Catalyst

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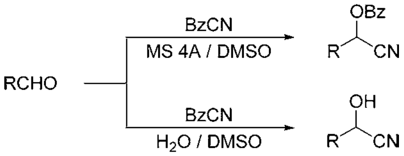
ABSTRACT



In the presence of MS 4Å in DMSO, cyanobenzoylation of various aldehydes with benzoyl cyanide proceeded very smoothly to give the corresponding cyanohydrin benzoates in high to excellent yields without an acid or a base. On the other hand, reaction of aldehydes with BzCN in DMSO–H_2O also occurred readily to afford the corresponding free cyanohydrins exclusively.

Hydrocyanation and cyanosilylation of aldehydes are important carbon−carbon bond-forming reactions, because they give versatile intermediates such as cyanohydrins and cyanohydrin silyl ethers.[1] Among various cyanide ion sources, trimethylsilyl cyanide is a safer and easily handled reagent compared to hydrogen cyanide, and various cyanosilylations of aldehydes catalyzed by Lewis acids have been already developed.[2] Recently, the direct preparation of cyanohydrin esters by the reaction of aldehydes with acyl cyanides has been also reported.[3] Acyl cyanides are also safer and commercially available reagents.[4] Although these reactions are very efficient methods to give cyanohydrin derivatives, base catalysts such as potassium carbonate,[5] 1,4-diazabicyclo[2.2.2]octane (DABCO)[6] are required to promote the cyanobenzoylation.

In contrast, very recently, we have shown that the silylation of alcohols with trialkylsilyl chloride in DMSO−hexane proceeds very smoothly at room temperature without a catalyst.[7] This reaction presumably occurs via an activation of the trialkylsilyl chloride by coordination of the DMSO oxygen atom to the silicon atom. Therefore, we envisioned that if an acyl cyanide was activated by DMSO in a similar way, cyanobenzoylation of aldehyde with acyl cyanide would take place efficiently to afford the corresponding cyanohydrin ester without a base catalyst. From the viewpoint of green chemistry, a noncatalytic process is very significant and attractive for synthetic organic chemistry. However, efficient cyanobenzoylation or hydrocyanation without a catalyst has not been reported so far. Herein, we wish to report efficient and convenient methods to produce cyanohydrin benzoate (**2**) or cyanohydrin (**3**) selectively from various aldehydes (**1**) with benzoyl cyanide under catalyst-free conditions (Scheme 1).

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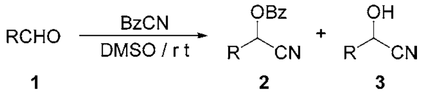
Scheme 1. Cyanobenzoylation or Hydrocyanation of Aldehyde with Benzoyl Cyanide



Initially, we undertook to examine the solvent effect for the cyanobenzoylation of 3-phenylpropanal (Table 1). The reaction of 3-phenylpropanal (**1a**) with 1.2 equiv of benzoyl cyanide in CH_2Cl_2 at room temperature for 6 h scarcely afforded the corresponding cyanohydrin products (**2a** and **3a**, run 1). On the other hand, when MeCN or THF was used as a solvent, combined yields of cyanohydrin benzoates (**2a**) and free cyanohydrins (**3a**) were moderate (runs 2 and 3). In the cases of using DMF or DMSO, the reactions were carried out smoothly (runs 4 and 5). As expected, DMSO turned out to be the most effective solvent and to activate benzoyl cyanide efficiently.

Table 1. Effect of Solvent for Cyanobenzoylation of 3-Phenylpropanal (**1a**)[a]

run	solvent	yield[b] of **2a** [%]	yield[b] of **3a** [%]
1	CH_2Cl_2	3	4
2	MeCN	38	27
3	THF	15	55
4	DMF	64	26
5	DMSO	53	39

[a] All reactions were carried out using aldehyde **1a** (0.3 mmol) and BzCN (0.36 mmol) at rt for 6 h. [b] Yields of isolated products.

Under the above conditions, the aldehyde was transformed into the cyanohydrin benzoate as well as the free cyanohydrin simultaneously because benzoyl cyanide is hydrolyzed by a trace amount of water in the reaction mixture and hydrogen cyanide is generated. Therefore, to prevent the hydrolysis of the benzoyl cyanide, the reaction was carried out in the presence of various dehydrating agents.

When cyanobenzoylation of aldehyde was performed with 40 mg of molecular sieves (MS) 4Å, the yield of desired **2a** could be greatly improved and the formation of **3a** was suppressed (Table 2, run 1). MS 3Å and $MgSO_4$ were also effective as dehydrating agents (runs 2 and 4). Additionally, by increasing the loading of MS 4Å, **2a** could be synthesized exclusively in excellent yield (92%) and no **3a** was obtained (run 6).

Representative and successful examples for the synthesis of various cyanohydrin benzoates from aliphatic and aromatic aldehydes are collected in Table 3. Open-chain and cyclic aliphatic aldehydes were cyanobenzoylated in high to excellent yields under the optimal reaction conditions (runs 1−5). Especially, it should be noted that the sterically hindered trimethylacetaldehyde (**1e**), which branched at the α-position to the carbonyl group, was transformed into the corresponding cyanohydrin benzoate in 97% yield (run 5). On the other hand, cyanobenzoylation of aromatic aldehydes needed a slightly higher reaction temperature (60 °C) (runs 6−8).

Table 2. Effect of Additive for Cyanobenzoylation of 3-Phenylpropanal (**1a**)[a]

run	additive	yield[b] of **2a** [%]	yield[b] of **3a** [%]
1	MS 4Å (40 mg)	92	7
2	MS 3Å (40 mg)	90	8
3	MS 5Å (40 mg)	72	20
4	$MgSO_4$ (40 mg)	91	7
5	MS 4Å (100 mg)	90	tr
6	MS 4Å (150 mg)	92	0

[a] All reactions were carried out in DMSO using aldehyde **1a** (0.3 mmol) and BzCN (0.36 mmol) at rt for 6 h. [b] Yields of isolated products.

Table 3. Synthesis of Various Cyanohydrin Benzoates (**2a**−**h**) from Various Aldehydes (**1a**−**h**)[a]

run	RCHO (**1**)	time [h]	yield[b] [%]
1	$Ph(CH_2)_2CHO$ (**1a**)	6	92
2	$CH_3(CH_2)_5CHO$ (**1b**)	6	81
3	*c*-$C_6H_{11}CHO$ (**1c**)	6	90
4	$PhCH(CH_3)CHO$ (**1d**)	1	80
5	*t*-BuCHO (**1e**)	24	97
6[c]	PhCHO (**1f**)	3	89
7[c]	*p*-BrC_6H_4CHO (**1g**)	3	89
8[c]	2-NaphCHO (**1h**)	3	84

[a] All reactions were carried out in DMSO using aldehyde **1** (0.3 mmol) and BzCN (0.36 mmol) in the presence of MS 4Å (150 mg) at rt, unless otherside stated. [b] Yields of isolated products. [c] Reactions were carried out at 60 °C.

Next, to compare the reactivity of reagents, we attempted the preparation of cyanohydrin derivatives from 3-phenylpropanal with various acyl cyanides and trimethylsilyl cyanide (Table 4). By using *p*-toluoyl cyanide,[8] the corresponding cyanohydrin *p*-methylbenzoate (**2i**) was similarly formed in 91% yield (run 2). In contrast, the reaction of aldehyde with acetyl cyanide gave the corresponding cyanohydrin acetate (**2j**) in only 16% yield (run 3). This result can be considered to be caused by easy hydrolysis or lower reactivity of the acetyl cyanide compared to that of the benzoyl cyanide. Additionally, in the case of trimethylsilyl cyanide, the cyanohydrin (**3a**) could be isolated in 75% yield by treatment of 1 N HCl solution for desilylation after cyanosilylation (run 4). From these control experiments, it is clear that benzoyl cyanide is the most promising cyanation agent under these reaction conditions.

Finally, we investigated hydrocyanation of aldehydes by adding water instead of MS 4Å (Table 5). We presumed that if water is added intentionally in a reaction mixture, benzoyl cyanide would be hydrolyzed and hydrocyanation would occur by hydrogen cyanide. The reaction of 3-phenylpropanal

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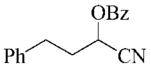
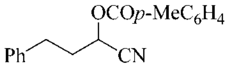
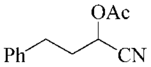
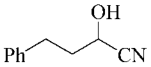
[8] For some reports of synthesis of the substituted acyl cyanides, see: (a) Olah, G. A.; Arvanaghi, M.; Prakash, G. K. S. *Synthesis* **1983**, 636. (b) Murahashi, S.; Naota, T.; Nakajima, N. *Tetrahedron Lett.* **1985**, *26*, 925. (c) Murahashi, S.; Naota, T. *Synthesis* **1993**, 433.

Table 4. Synthesis of Various Cyanohydrin Derivatives from 3-Phenylpropanal (**1a**) Using Various Cyanating Reagents[a]

run	RCN	product	yield[b] [%]
1	BzCN	 (**2a**)	92
2	p-MeC_6H_4COCN	 (**2i**)	91
3	AcCN	 (**2j**)	16[c]
4[d]	TMSCN	 (**3a**)	75

[a] All reactions were carried out in DMSO using aldehyde **1a** (0.3 mmol) and RCN (0.36 mmol) in the presence of MS 4Å (150 mg) at rt for 6 h. [b] Yields of isolated products. [c] The corresponding cyanohydrin (**3a**) was obained in 53% yield. [d] After reaction, 1 N HCl/rt/0.5 h.

Table 5. Synthesis of Various Cyanohydrins (**3a−f**) from Various Aldehydes (**1a−f**)[a]

run	RCHO (**1**)	time [h]	yield[b] [%]
1	$Ph(CH_2)_2CHO$ (**1a**)	6	91
2	$CH_3(CH_2)_5CHO$ (**1b**)	6	82
3	c-$C_6H_{11}CHO$ (**1c**)	24	100
4	$PhCH(CH_3)CHO$ (**1d**)	6	93
5	t-BuCHO (**1e**)	3	74
6	PhCHO (**1f**)	6	60

[a] All reactions were carried out in DMSO−hexane (5:1) using aldehyde **1** (0.3 mmol), BzCN (0.36 mmol) at rt. [b] Yields of isolated products.

with benzoyl cyanide in DMSO−H_2O (5:1) was performed smoothly to afford the corresponding free cyanohydrin exclusively in high yield (run 1). Furthermore, this method could be applied to selective syntheses of various cyanohydrins. Hydrocyanation proceeded efficiently both with sterically hindered aldehydes as well as with open-chain ones in high to excellent yields (runs 2−5). However, hydrocyanation of an aromatic aldehyde occurred more slowly than those of aliphatic aldehydes, and the corresponding cyanohydrin was obtained in moderate yield (run 6).

In summary, we have presented highly efficient and convenient methods for the cyanobenzoylation or hydrocyanation of various aldehydes with benzoyl cyanide in DMSO. These reactions proceeded smoothly under mild reaction conditions, and various cyanohydrin benzoates or cyanohydrins were obtained in high to excellent yields. It is possible to obtain cyanohydrin benzoate or free cyanohydrin by adding MS 4A or water, respectively. This is the first example for the synthesis of cyanohidrin derivatives using no catalyst. Accordingly, these reactions are very attractive from the standpoints of green chemistry, because the atom economy is extremely high to consume almost all of the reagent in the case of cyanobenzoylation. Further research addressing the scope and elucidation of the reaction mechanism is under way in our laboratory.

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Supporting Information Available: Experimental procedures and ^1H NMR, ^{13}C NMR, and IR spectra for compounds **2a−j** and **3a−f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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