Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 5881–5883

Catalyst-free DMSO-promoted synthesis of cyanohydrin carbonates from aldehydes

Katsuyuki Iwanami, Yumi Hinakubo and Takeshi Oriyama*

Faculty of Science, Ibaraki University, 2-1-1 Bunkyo, Mito 310-8512, Japan

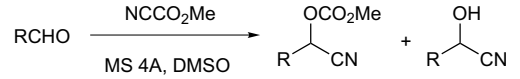
Received 4 June 2005; revised 22 June 2005; accepted 23 June 2005
Available online 14 July 2005

Abstract—A variety of cyanohydrin carbonates were readily prepared from aldehydes with cyanoformate in DMSO using no catalyst in a convenient one-pot procedure.

Cyanohydrins are known as a most versatile synthetic intermediate.[1] *O*-protected cyanohydrin derivatives have also attracted the interest of organic chemists and several synthetic methods for their preparation have been reported.[2–4] Quite recently, we demonstrated a convenient one-pot synthesis of cyanohydrin alkyl ethers directly from aldehydes with trimethylsilyl cyanide and alkoxytrimethylsilane under the influence of a catalytic amount of iron(III) chloride.[5] For cyanation of aldehydes, cyanotrimethylsilane (TMSCN) is a commonly used reagent, because it is safer and easier to handle than hydrogen cyanide. Alkyl cyanoformate is another candidate as cyanating agent of aldehydes for preparation of cyanohydrin carbonates.[6–8] Generally, carbonates are less susceptible to hydrolysis than esters because of the resonance effect of the second oxygen, and they have useful tunability of the cleaving procedure by the properties of the second alkyl substituent moiety.[9] Although cyanation with cyanoformate is a very efficient method to yield cyanohydrin carbonates, base catalysts such as potassium carbonate,[6a] diisopropylamine,[6b] 1,4-diazabicyclo[2.2.2]octane[6c] or tributyltin cyanide[7] are required as an activator. On the other hand, our previous investigations documented the silylation of alcohols with trialkylsilyl chloride in DMSO-hexane without a catalyst[10] and the cyanobenzoylation of aldehydes with benzoyl cyanide in DMSO using no catalyst.[11] These reactions proceed via activation of the agents by coordination of the DMSO oxygen atom to the silicon atom of trialkyl silyl chloride or the carbonyl carbon atom of acyl cyanide. On the basis of this background, herein, we wish to report cyanation of aldehydes using alkyl cyanoformates in DMSO without a catalyst.

In the first place, we undertook to examine the preparation of cyanohydrin carbonates from aldehydes in DMSO. A mixture of benzaldehyde and methyl cyanoformate in DMSO was stirred at room temperature for 3 h, and the desired product **1**, α-(methoxycarboxy)phenylacetonitrile, was obtained in 43% yield (Table 1, Run

Table 1. The effect of dehydrating agents[a]



1 **2**

Run	RCHO	Dehydrating agents	Yield of **1**[b] (%)	Yield of **2**[b] (%)
1	PhCHO	None	43	17
2		MS 4A (150 mg)	73	0
3		MS 3A (150 mg)	72	0
4		MS 5A (150 mg)	41	6
5		$MgSO_4$ (150 mg)	44	4
6		MS 4A (30 mg)	70	0
7		MS 4A (10 mg)	77	0
8		MS 4A (5 mg)	43	0
9	$PhCH_2CH_2CHO$	None	63	34
10		MS 4A (150 mg)	80	0
11		MS 4A (120 mg)	96	0
12		MS 4A (60 mg)	91	3

[a] All reactions were performed using aldehyde (0.3 mmol) and methyl cyanoformate (0.36 mmol) at rt for 3 h.
[b] Isolated yield of purified product.

Keywords: Cyanation; Cyanohydrin carbonate; Cyanoformate; Aldehyde; DMSO.
* Corresponding author. Tel.: +81 29 228 8368; fax: +81 29 228 8403; e-mail: tor@mx.ibaraki.ac.jp

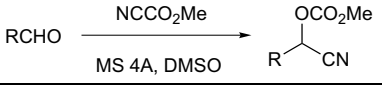
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.128

1). However, free cyanohydrin **2** was also obtained in 17% yield simultaneously, because the intermediate cyanohydrin alkoxide anion might be hydrolyzed by a trace amount of water in the reaction mixture. Therefore, to prevent the hydrolysis of the cyanation intermediate, the reaction was carried out in the presence of a dehydrating agent. When the reaction (0.3 mmol scale) was performed in the presence of 150 mg of molecular sieves (MS) 4A, cyanation was achieved efficiently and the formation of **2** was not observed (Run 2). Although using MS 3A also yields the desired **1** (Run 3), MS 5A and $MgSO_4$ were not effective for this transformation (Runs 4 and 5), and a small amount of free cyanohydrin **2** was detected as a side product. Finally, we found that using 10 mg of MS 4A for benzaldehyde (Run 6), and using 120 mg of MS 4A for 3-phenylpropionaldehyde gave the best result (Run 11).

Moreover, we ascertained the most suitable solvent for this cyanohydrin carbonate synthesis to be DMSO. DMF and CH_3CN gave lower yield (57% and 40%, respectively), and CH_2Cl_2 and toluene gave none of the desired cyanohydrin carbonate.

The reaction was carried out under optimal reaction conditions with various aromatic and aliphatic aldehydes as shown in Table 2.[12] Substituted benzaldehyde with an electron-donating group, tolualdehydes, the corresponding cyanohydrin carbonates could be obtained in good yields (Runs 2–4). In the case of substituted benzaldehyde with an electron-withdrawing group, 4-bromobenzaldehyde and 4-methoxycarbonylbenzaldehyde also gave the corresponding carbonates in 88% and 77% yield, respectively (Runs 5 and 6), and the ester function is tolerated under these reaction conditions (Run 6). Starting from 1- and 2-naphthaldehyde, the desired products were obtained quantitatively. Similarly, aliphatic aldehydes afforded the desired products in good to high yields (Runs 9–13). Especially, sterically hindered pivalaldehyde gave successfully the corresponding product in 83% yield (Run 13).

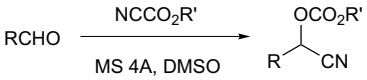
Table 2. Synthesis of cyanohydrin carbonates from various aldehydes[a]



Run	RCHO	Temp	Time (h)	Yield[b] (%)
1	PhCHO	rt	6	80
2	2-MeC_6H_4CHO	60 °C	9	83
3	3-MeC_6H_4CHO	60 °C	5	62
4	4-MeC_6H_4CHO	60 °C	12	71
5	4-BrC_6H_4CHO	rt	3	88
6	4-$MeO_2CC_6H_4CHO$	rt	2	77
7	1-Naphthaldehyde	rt	120	97
8	2-Naphthaldehyde	rt	2	97
9	$PhCH_2CH_2CHO$	rt	1	96
10	*n*-BuCHO	rt	1	80
11	$PhCH(CH_3)CHO$	60 °C	19	87
12	*cyclo*-$C_6H_{11}CHO$	rt	1	90
13	*t*-BuCHO	rt	3	83

[a] All reactions were performed using aldehyde (0.3 mmol) and methyl cyanoformate (0.36 mmol) in the presence of 10 mg of MS 4A for aromatic aldehydes (Runs 1–8) and 120 mg for aliphatic aldehydes (Runs 9–13).
[b] Isolated yield of purified product.

Table 3. Synthesis of cyanohydrin carbonates from various cyanoformates[a]

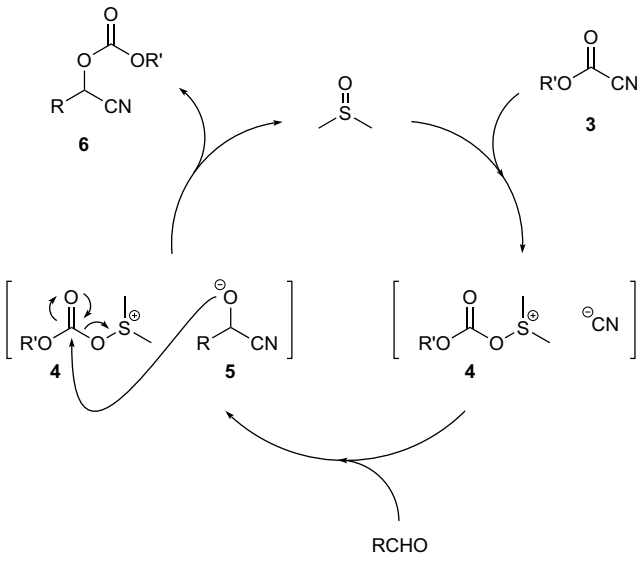


Run	RCHO	$NCCO_2R'$	Time (h)	Yield[b] (%)
1	PhCHO	$NCCO_2Bn$	12	91
2		$NCCO_2CH_2CH{=}CH_2$	3	100
3		$NCCO_2CH_2CCl_3$	3	0[c]
4	$PhCH_2CH_2CHO$	$NCCO_2Bn$	1	73
5		$NCCO_2CH_2CH{=}CH_2$	2	98
6		$NCCO_2CH_2CCl_3$	3	61[d]

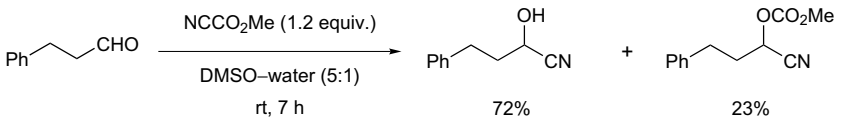
[a] All reactions were performed using aldehyde (0.3 mmol) and cyanoformate (0.36 mmol) at rt in the presence of 10 mg of MS 4A for benzaldehyde (Runs 1–3) and 120 mg for 3-phenylpropionaldehyde (Runs 4–6).
[b] Isolated yield of purified product.
[c] No reaction was occurred.
[d] 39% of free cyanohydrin was obtained.

Furthermore, this reaction was similarly effective for various cyanoformates[13] to give the corresponding carbonates as illustrated in Table 3. Particularly, allyl cyanoformate gave the corresponding allyloxycarbonyl derivative quantitatively (Runs 2 and 5).

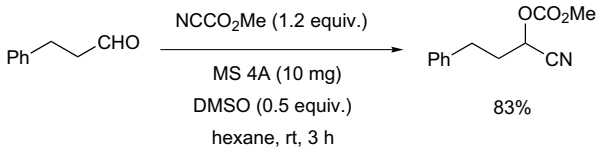
A proposed mechanism of the present reaction is illustrated in Scheme 1. In the first step, DMSO would coordinate to the carbonyl carbon atom of cyanoformate **3** to form a cationic species **4** and a cyanide anion. Next, an aldehyde would be cyanated to afford a cyanohydrin alkoxide anion **5**. And then, attack of an anion **5** to the carbonyl carbon of **4** would lead to the formation of the desired cyanohydrin carbonate **6** and the regeneration of



Scheme 1. Proposed reaction mechanism.



Scheme 2. Cyanation performed in the presence of water.



Scheme 3. Cyanation using 0.5 equiv of DMSO.

DMSO. In contrast, when the reaction was performed without a dehydrating agent, an alkoxide **4** would be hydrolyzed to form a free cyanohydrin (Table 1, Runs 1 and 9). When the reaction was performed in DMSO–water (5:1), the corresponding free cyanohydrin was produced in 72% yield (Scheme 2). In addition, to clarify the regeneration of DMSO, we examined the reaction of 3-phenylpropionaldehyde with methyl cyanoformate in the presence of 0.5 equiv of DMSO in hexane. And the expected product was obtained in 83% yield, as shown in Scheme 3.

In conclusion, we have developed an efficient and convenient method for the synthesis of cyanohydrin carbonate starting from a variety of aldehydes in DMSO. This reaction has the following synthetic advantages: (1) in contrast to the known cyanation of aldehydes using cyanoformate, the present procedure needs neither a base nor a metal catalyst, (2) various carbonate types of a protecting group for the hydroxyl function are obtained by using the corresponding cyanoformate, (3) the atom economy is extremely high as almost all of the reagent is consumed, (4) extremely mild reaction conditions, and (5) experimental convenience. Further investigations to broaden the scope and synthetic applications of this efficient and convenient cyanation are under way in our laboratory.

References and notes

1. (a) Gregory, R. J. H. *Chem. Rev.* **1999**, 3649; (b) Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752; (c) Chen, F.-X.; Feng, X. *Synlett* **2005**, 892.
2. Cyanohydrin silyl ethers: (a) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55; (b) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, *49*, 4929; (c) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537; (d) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 541; (e) Golinski, M.; Brock, C. P.; Watt, D. S. *J. Org. Chem.* **1993**, *58*, 159; (f) Yang, Y.; Wang, D. *Synlett* **1997**, 1379; (g) Saravanan, P.; Anand, R. V.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 3823; (h) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett.* **2001**, *42*, 3041; (i) Azizi, V.; Saidi, M. R. *Phosphorus Sulfur Silicon Relat. Elem.* **2003**, *178*, 2111; (j) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900; (k) Zhou, H.; Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G. *Synlett* **2004**, 1077.
3. Cyanohydrin esters: Hoffmann, H. M. R.; Ismail, Z. M.; Hollweg, R.; Zein, A. R. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1807.
4. Cyanohydrin alkyl ether from acetal: Mukaiyama, T.; Soga, T.; Takenoshita, H. *Chem. Lett.* **1989**, 997.
5. Iwanami, K.; Oriyama, T. *Chem. Lett.* **2004**, *33*, 1324.
6. (a) Okimoto, M.; Chiba, T. *Synthesis* **1996**, 1188; (b) Poirier, D.; Berthiaume, D.; Boivin, R. P. *Synlett* **1999**, 1423; (c) Deardorff, D. R.; Taniguchi, C. M.; Tafti, S. A.; Kim, H. Y.; Choi, S. Y.; Downey, K. J.; Nguyen, T. V. *J. Org. Chem.* **2001**, *66*, 7191.
7. Scholl, M.; Lim, C.-K.; Fu, G. C. *J. Org. Chem.* **1995**, *60*, 6229.
8. (a) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195; (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636; (c) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197.
9. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999, p 179.
10. Watahiki, T.; Matsuzaki, M.; Oriyama, T. *Green Chem.* **2003**, *5*, 82.
11. Watahiki, T.; Ohba, S.; Oriyama, T. *Org. Lett.* **2003**, *5*, 2679.
12. Typical procedure: To a solution of 3-phenylpropionaldehyde (40.3 mg, 0.30 mmol) in DMSO (2.0 mL) was added methyl cyanoformate (29 μL, 0.36 mmol) in the presence of MS 4A (120 mg) under argon atmosphere. The reaction mixture was stirred for 1 h at room temperature and quenched with a phosphate buffer (pH 7). The organic materials were extracted with Et_2O and dried over anhydrous magnesium sulfate. 2-Methoxycarboxy-4-phenylbutanenitrile (63.4 mg, 96%) was isolated by thin-layer chromatography on silica gel.
13. Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486.