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## An efficient and facile one-pot synthesis of cyanohydrin esters from carbonyl compounds catalyzed by iron(III) chloride

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Abstract—A variety of cyanohydrin esters were readily prepared from carbonyl compounds with trimethylsilyl cyanide and acid anhydride under the influence of a catalytic amount of iron(III) chloride in a convenient one-pot procedure. © 2005 Elsevier Ltd. All rights reserved.

O-Protected cyanohydrin derivatives constitute versatile intermediates in organic synthesis.<sup>1</sup> and several direct methods for their preparation have been reported so far. Cyanohydrin silyl ethers are prepared from carbonyl compounds with trialkylsilyl cyanide under the influence of Lewis acids,<sup>2</sup> Lewis bases,<sup>3</sup> or organocatalyst.<sup>4</sup> For cyanohydrin alkyl ethers, we recently demonstrated a convenient one-pot synthesis directly from aldehydes with trimethylsilyl cyanide (TMSCN) and alkoxytrimethylsilane catalyzed by iron(III) chloride.<sup>5,6</sup> On the other hand, O-acyl protected cyanohydrins also attract the interest of many organic chemists.<sup>7</sup> Sydnes et al. reported that reaction of acylals with trimethylsilyl cyanide in the presence of titanium(IV) chloride afforded the corresponding cyanohydrin esters.<sup>8</sup> Kagan et al. described a one-pot esterification of O-trimethylsilyl protected cyanohydrins using 2 equiv of acid anhydride or acid chloride catalyzed by scandium triflate.<sup>9</sup> Synthesis of cyanohydrin esters from carbonyl compounds using acyl cyanide<sup>10</sup> as a cyanating agent is a straightforward and promising method. Actually, by this methodology, O-acyl protected cyanohydrins are prepared from the parent aldehydes in the presence of a base.<sup>11</sup> Recently, we developed an efficient cyanobenzoylation of aldehydes with benzoyl cyanide in the absence of a catalyst in DMSO.<sup>12,13</sup> However, it is difficult to prepare various types of acylated cyanohydrins because commercially available acyl cyanides are limited and comparatively expensive.<sup>14</sup> Although cyanohydrin esters can be also

prepared directly from aldehydes with alkali metal cyanide and acid anhydride, excessive amounts (4 equiv) of an acylating agent, and metal cyanide are needed.<sup>15</sup> In addition, almost all examples of the preparation of *O*acyl cyanohydrins reported so far are restricted to acetate and benzoate.

Herein, we wish to report a novel and convenient onepot preparation of various cyanohydrin esters from carbonyl compounds with trimethylsilyl cyanide as a safer cyanating agent and readily available acid anhydride under the influence of a catalytic amount of iron(III) chloride.

First, we undertook to examine one-pot preparation of *O*-acyl protected cyanohydrin from the corresponding aldehyde catalyzed by iron(III) chloride via in situ-generated acylal (1,1-*gem*-diacetate). A mixture of benzaldehyde and 5 mol % of iron(III) chloride was treated with 2.0 equiv of acetic anhydride at 0 °C; after 10 min, 1.5 equiv of trimethylsilyl cyanide was added and stirred for additional 2 h at room temperature. The usual workup of the reaction mixture afforded the desired product,  $\alpha$ -(acetoxy)phenylacetonitrile, in 65% yield (Method A: Scheme 1). In contrast, when acetic anhydride was added to the reaction mixture of benzaldehyde and

PhCHO 
$$\xrightarrow{Ac_2O, FeCl_3}$$
  $\xrightarrow{TMSCN}$   $\xrightarrow{OAc}$   
CH<sub>3</sub>NO<sub>2</sub>  $rt, 2 h$   $Ph$  CN  
0 °C, 10 min  $65\%$ 

Scheme 1. One-pot preparation of cyanohydrin acetate (Method A). (Molar ratio of benzaldehyde/Ac<sub>2</sub>O/TMSCN/FeCl<sub>3</sub> = 1:2.0:1.5:0.05.)

*Keywords*: Cyanation; Cyanohydrin ester; Trimethylsilyl cyanide; Acid anhydride; Carbonyl compound; Iron(III) chloride.

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**Scheme 2.** One-pot preparation of cyanohydrin acetate (Method B). (Molar ratio of benzaldehyde/TMSCN/Ac<sub>2</sub>O/FeCl<sub>3</sub> = 1:1.5:2.0:0.05.)

trimethylsilyl cyanide, the yield was increased to 84% (Method B: Scheme 2).

After preliminary investigations using method B, we found that treatment with 1.2 equiv of trimethylsilyl cyanide at 0  $^{\circ}$ C for 30 min at the first step and employment of 1.5 equiv of acetic anhydride gave the best result as shown in Table 1 (entry 4). A screening of solvents revealed that nitromethane as a solvent gave the best result (Table 2, entry 1).

The reaction was conducted under the optimal conditions<sup>16</sup> with various aromatic and aliphatic aldehydes and ketones. The successful results are summarized in Table 3. In the case of benzaldehyde having an electron-donating group such as tolualdehydes, the corresponding cyanohydrin acetate could be obtained in good to high yields (entries 2–4). Especially, a sterically

Table 1. Optimization of the reaction conditions<sup>a</sup>

		TMSC	N	Ac <sub>2</sub> O	OA	C
	There -	FeCl CH <sub>3</sub> N	3 D <sub>2</sub>	rt, 2 h	Ph	CN
Entry	Temperat the first s	ture of tep/°C	Time of first step	the p/min	Equivalent of Ac <sub>2</sub> O	Yield <sup>b</sup> /%
1	0		0		1.5	52
2	0		10		1.5	52
3	0		20		1.5	90
4	0		30		1.5	92
5	0		30		1.2	86
6	rt		30		1.5	88
$7^{c}$	0		30		1.5	83

<sup>a</sup> Molar ratio of benzaldehyde/TMSCN/FeCl<sub>3</sub> = 1:1.2:0.05.

<sup>b</sup> Isolated yield of purified product.

<sup>c</sup> 1.5 equiv of acetyl chloride was used instead of acetic anhydride.

Table 2. Effect of solvents<sup>a</sup>

		TMSCN	Ac <sub>2</sub> O	0/	Ac
		FeCl <sub>3</sub>	rt	Ph	`CN
	0	°C, 30 min			
Entry	Solvent	Time o	f the second	step/h	Yield <sup>b</sup> /%
1	CH <sub>3</sub> NO	2 3			94
2	$CH_2Cl_2$	12			81
3	CH <sub>3</sub> CN	12			38
4	DMF	12			29
5	Toluene	12			27
6	THF	12			0

<sup>a</sup> Molar ratio of benzaldehyde/TMSCN/Ac<sub>2</sub>O/FeCl<sub>3</sub> = 1:1.2:1.5:0.05. <sup>b</sup> Isolated yield of purified product. 
 Table 3. Synthesis of various cyanohydrin acetates from carbonyl compounds<sup>a</sup>

0 	TMSCN	Ac <sub>2</sub> O	NCOAc
R <sup>M</sup> R'	FeCl <sub>3</sub>	rt	R R'
	CH <sub>3</sub> NO <sub>2</sub> , 0 °C, 30 min		

Entres	Carbonal comment	Time of the	V:-14b/0/
Entry	Carbonyl compound	second step/h	rield /%
1	PhCHO	3	94
2	2-MeC <sub>6</sub> H <sub>4</sub> CHO	3	82
3	3-MeC <sub>6</sub> H <sub>4</sub> CHO	3	80
4	4-MeC <sub>6</sub> H <sub>4</sub> CHO	3	91
5	2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> CHO	6	91
6 <sup>°</sup>	4-MeOC <sub>6</sub> H <sub>4</sub> CHO	9	56
7	4-BrC <sub>6</sub> H <sub>4</sub> CHO	6	95
8	4-AcC <sub>6</sub> H <sub>4</sub> CHO	6	73
9	4-MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> CHO	12	93
10	1-Naphthaldehyde	5	85
11	2-Naphthaldehyde	4	89
12 <sup>d</sup>	PhCH <sub>2</sub> CH <sub>2</sub> CHO	3	89
13	cyclo-C <sub>6</sub> H <sub>11</sub> CHO	4	91
14	t-BuCHO	3	62
15 <sup>e</sup>	Acetophenone	12	79
16	Benzylacetone	3	80
17	Cyclopentanone	3	91
18	Cyclohexanone	5	90

<sup>a</sup> Molar ratio of carbonyl compound/TMSCN/Ac<sub>2</sub>O/FeCl<sub>3</sub> = 1:1.2:1.5:0.05.

<sup>b</sup> Isolated yield of purified product.

<sup>c</sup>CH<sub>3</sub>CN was used as a solvent.

<sup>d</sup> The reaction of the second step was performed at 60 °C.

<sup>e</sup> 2.5 equiv of Ac<sub>2</sub>O was used.

hindered aldehyde, mesitaldehyde, gave the corresponding O-acetyl cyanohydrin in 91% yield (entry 5), but with *p*-anisaldehyde, the desired product was obtained in 56% yield (entry 6) because of the messiness of the reaction mixture. As regards benzaldehyde having an electron-withdrawing group, the corresponding acetate was also obtained in good to excellent yields (entries 7–9), and the ester function is tolerated under these reaction conditions (entry 9). Starting from 1- and 2-naphthaldehyde, the desired products were obtained in 85% and 89% yield, respectively (entries 10 and 11). Similarly, aliphatic aldehydes, 3-phenylpropionaldehyde and cyclohexanecarbaldehyde afforded cyanohydrin acetate in high yields (entries 12 and 13). Even in the case of sterically hindered pivalaldehyde, the desired product was obtained in 62% yield (entry 14). Furthermore, we have found that this reaction is similarly effective for aromatic, aliphatic, and alicyclic ketones (entries 15-18) to yield the corresponding O-acetyl protected cyanohydrins in good to high yields.

Next, to clarify the generalization of this useful transformation, we investigated other acid anhydrides instead of acetic anhydride, as illustrated in Table 4. Reaction with propionic anhydride, isobutyric anhydride, or crotonic anhydride gave the corresponding cyanohydrin esters in high yields (entries 1–3). On the other hand, when pivalic anhydride or benzoic anhydride was used as an acylating agent, though the reaction of the second step needed higher temperature or longer reaction time, the

Table 4. Synthesis of various cyanohydrin esters from carbonyl compounds<sup>a</sup>

		O II	TMSCN (R"CO) <sub>2</sub> O NC	OCOR"	
		R <sup></sup> R'	FeCl <sub>3</sub>	< R'	
		CH <sub>3</sub> NC	D <sub>2</sub> , 0 °C, 30 min		
Entry	Carbonyl compound	R″	Temperatures of the second step/°C	Time of the second step/h	Yield <sup>b</sup> /%
1	PhCHO	Et	rt	3	95
2	PhCHO	<i>i</i> -Pr	rt	3	94
3	PhCHO	CH <sub>3</sub> CH=CH	rt	3	89
4	PhCHO	t-Bu	60	2	89
5°	PhCHO	Ph	60	12	77
6	PhCH <sub>2</sub> CH <sub>2</sub> CHO	t-Bu	60	3	83
7	PhCH <sub>2</sub> CH <sub>2</sub> CHO	Ph	60	3	82
8	Cyclopentanone	<i>t</i> -Bu	rt	12	87
9 <sup>c</sup>	Cyclopentanone	Ph	rt	9	68

<sup>a</sup> Molar ratio of carbonyl compound/TMSCN/acid anhydride/FeCl<sub>3</sub> = 1:1.2:1.5:0.05.

<sup>b</sup> Isolated yield of purified product.

<sup>c</sup> 1.1 equiv of Bz<sub>2</sub>O was used.



Scheme 3. Cyanosilylation of benzaldehyde catalyzed by iron(III) chloride.



**Scheme 4.** Direct *O*-acetylation of cyanohydrin TMS ether catalyzed by iron(III) chloride.

corresponding cyanohydrin pivaloates or benzoates were also obtained in good to high yields (entries 4–9).

Concerning the reaction mechanism, when the reaction of entry 1 in Table 3 was quenched after the completion of the first step, the corresponding trimethylsilyl ether,  $\alpha$ -(trimethylsiloxy)phenylacetonitrile, was detected by <sup>1</sup>H NMR analysis,<sup>17</sup> as shown in Scheme 3. On the other hand, when the isolated cyanohydrin TMS ether<sup>18</sup> was treated with 1.5 equiv of acetic anhydride in the presence of 5 mol% of iron(III) chloride, the corresponding acetate,  $\alpha$ -(acetoxy)phenylacetonitrile, was obtained readily in 98% yield (Scheme 4). These experimental results suggest that the present cyanoacylation proceeds via cyanohydrin trimethylsilyl ether as an intermediate.

In conclusion, we have developed an efficient one-pot synthesis of *O*-acyl protected cyanohydrins starting from a variety of parent carbonyl compounds. The present reaction has the following synthetic advantages: (1) a catalytic amount of iron(III) chloride promotes both cyanation and *O*-acylation, in contrast to the known cyanation of carbonyl compounds, (2) various ester types of a protecting group for the hydroxyl function are obtained by using readily available acid anhydride, (3) a broad range of aldehydes and ketones can be applied, (4) mild reaction conditions, and (5) experimental convenience. Further investigations to broaden the scope and synthetic applications of this efficient cyanation are under way in our laboratory.

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- 16. Typical procedure: To a suspension of anhydrous iron(III) chloride (2.5 mg, 0.015 mmol) and benzaldehyde ( $30 \mu L$ , 0.30 mmol) in nitromethane (2 mL) was added trimethylsilyl cyanide ( $48 \mu L$ , 0.36 mmol) and stirred at 0 °C under an argon atmosphere. After 30 min, acetic anhydride ( $42 \mu L$ , 0.45 mmol) was added and stirred for 3 h at room temperature. The reaction mixture was quenched with a phosphate buffer (pH 7), and the organic materials ware extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>.  $\alpha$ -(Acetoxy)phenylacetonitrile (48.7 mg, 94%) was isolated by thin-layer chromatography on silica gel.
- 17. The yield was determined by <sup>1</sup>H NMR analysis (400 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.
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