A Novel One-pot Synthesis of Cyanohydrin Alkyl Ethers from Aldehydes Catalyzed by Iron(III) Chloride

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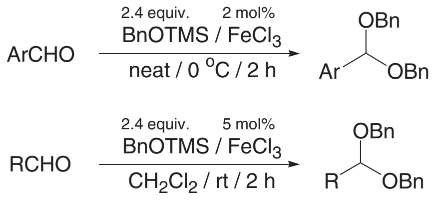
A variety of cyanohydrin alkyl ethers were readily prepared from aldehydes with trimethylsilyl cyanide and alkoxy-trimethylsilane under the influence of a catalytic amount of iron(III) chloride in a convenient one-pot procedure.

O-Protected cyanohydrins are known as versatile synthetic intermediates in organic synthesis,[1] and several straightforward methods have been reported so far. Cyanohydrin silyl ethers are obtained conveniently from the parent carbonyl compounds with trialkylsilyl cyanide under the influence of Lewis acids,[2] Lewis bases,[3] or organo-catalysts.[4] Cyanohydrin esters are prepared from aldehydes with acyl cyanide[5] in the presence of a base such as potassium carbonate[6a] and 1,4-diazabicyclo[2.2.2]octane.[6b] Recently, we also developed cyanobenzoylation of aldehydes with benzoyl cyanide without a catalyst.[7] On the other hand, cyanohydrin alkyl ethers can be prepared directly from acetals instead of from aldehydes.[8] However, methyl or ethyl ethers of cyanohydrins which are formed from dimethyl or diethyl acetals do not function appropriately as a protecting group, due to difficulty of their ether bond-cleavage.

Herein we wish to report a novel one-pot preparation of various cyanohydrin alkyl ethers, namely, *O*-alkyl protected cyanohydrins, including benzyl ether which is one of the most important and popular protecting groups for the hydroxy function.[9]

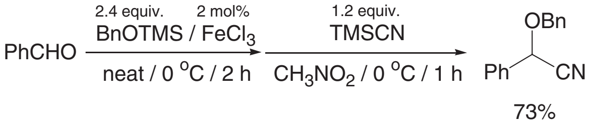
In the course of our exploration of the usefulness of the reactions promoted by iron(III) chloride,[10,11] we discovered a general and facile synthesis of dibenzyl acetals from aldehydes using benzyloxytrimethylsilane catalyzed by iron(III) chloride (Scheme 1).[11]



Scheme 1. Dibenzyl acetalizaion of aldehydes.

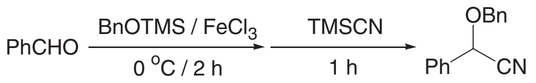
In the first place, we undertook to examine one-pot preparation of *O*-benzyl cyanohydrin via dibenzyl acetal in situ-formed from the corresponding aldehydes. A mixture of benzaldehyde and 2 mol % amount of iron(III) chloride was treated with 2.4 equiv. of benzyloxytrimethylsilane (BnOTMS) at 0 °C, after 2 h, 1.2 equiv. of trimethylsilyl cyanide (TMSCN) in nitromethane was added and stirred for additional 1 h at the same temperature. The usual work-up of the reaction mixture afforded the desired product, α-(benzyloxy)phenylacetonitrile in 73% yield (Scheme 2). To the best of our knowledge, this is the first example in which *O*-benzyl-protected cyanohydrin was obtained directly from aldehyde in a convenient one-pot procedure.

After the preliminary investigations, for aromatic aldehydes, we found that employment of 2.4 equiv. of benzyloxytrimethyl-



Scheme 2. One-pot synthesis of cyanohydrin benzyl ether.

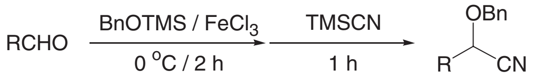
Table 1. Optimization of the reaction conditions of the second step for aromatic aldehyde[a]



Run	Solvent	Temp	Equiv. of TMSCN	Yield/%[b]
1	CH_3NO_2	0 °C	1.2	73
2	neat	0 °C	1.2	89
3[c]	neat	0 °C	1.2	70
4	neat	0 °C	1.5	93
5	neat	rt	1.5	98
6[d]	neat	rt	1.5	57

[a] Molar ratio of PhCHO:BnOTMS:$FeCl_3$ = 1:2.4:0.02.
[b] Isolated yield of purified product.
[c] TMSCN was added immediately after adding PhCHO.
[d] 1.2 equiv. of BnOTMS were used.

Table 2. Synthesis of cyanohydrin benzyl ethers from aromatic aldehydes[a]

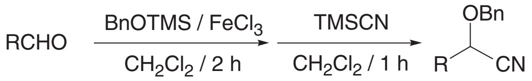


Run	RCHO	Temp	Yield/%[b]
1	PhCHO	rt	98
2	2-MeC_6H_4CHO	rt	96
3	3-MeC_6H_4CHO	rt	70
4	4-MeC_6H_4CHO	0 °C	95
5	2,4,6-$Me_3C_6H_2CHO$	0 °C	88
6	4-$MeOC_6H_4CHO$	rt	83
7	4-BrC_6H_4CHO	0 °C	87
8[c]	4-$MeO_2CC_6H_4CHO$	rt	51[d]
9	2-Naphthaldehyde	0 °C	70
10	(*E*)-PhCH=CHCHO	rt	87

[a] Molar ratio of aldehyde:BnOTMS:$FeCl_3$:TMSCN = 1:2.4:0.02:1.5.
[b] Isolated yield of purified product.
[c] Nitromethane was used as a solvent.
[d] 34% of dibenzyl acetal was recovered.

silane and 1.5 equiv. of trimethylsilyl cyanide without solvent gave the best result as shown in Table 1 (Run 5). The reaction was conducted with various aromatic aldehydes,[12] and the successful results are summarized in Table 2. In the case of substituted benzaldehyde with an electron-donating group such as tolualdehydes and *p*-anisaldehyde, the corresponding cyanohydrin benzyl ethers could be obtained in good to excellent yields (Runs 2–6). Especially, a sterically hindered aldehyde, mesitaldehyde, gave the corresponding cyanohydrin benzyl ether in 88% yield (Run 5). As regards benzaldehyde having an electron-withdrawing group, 4-bromobenzaldehyde also gave the corresponding ether in 87% yield (Run 7), but for 4-methoxycarbonylbenzaldehyde, the desired product was obtained in 51% yield (Run 8). Similarly, 2-naphthaldehyde and cinnamaldehyde afforded benzylated cyanohydrin in 70% and 87% yield, respectively (Runs 9 and 10).

Table 3. Synthesis of cyanohydrin benzyl ethers from aliphatic aldehydes[a]



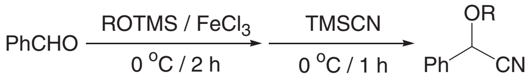
Run	RCHO	Temp	Yield/%[b]
1	$PhCH_2CH_2CHO$	rt	24
2[c]	$PhCH_2CH_2CHO$	0 °C	22
3	$PhCH_2CH_2CHO$	−20 °C	73
4	*n*-BuCHO	−20 °C	80
5	*cyclo*-$C_6H_{11}CHO$	−20 °C	74
6	*t*-BuCHO	−20 °C	47

[a] Molar ratio of aldehyde:BnOTMS:$FeCl_3$:TMSCN = 1:2.4:0.05:1.5.
[b] Isolated yield of purified product.
[c] 2 mol % of $FeCl_3$ was used and the reaction was performed in no solvent.

Next, for aliphatic aldehydes, 3-phenylpropanal was selected as a test compound, and we tentatively chose the reaction temperature of −20 °C (Table 3, Run 3). *n*-Pentanal and cyclohexanecarbaldehyde were transformed into the corresponding cyanohydrin benzyl ethers in good yields (Runs 4 and 5). Even in the case of sterically hindered pivalaldehyde, the desired product was obtained in 47% yield (Run 6).

Furthermore, this reaction was similarly effective for various trimethylsilyl ethers of alcohols as illustrated in Table 4. Reaction with allyloxytrimethylsilane gave the corresponding cyanohydrin allyl ether in 95% yield (Run 1). On the other hand, using *p*-methoxybenzyloxytrimethylsilane as an alkyl silyl ether, no reaction occurred (Run 2). Silyl ethers of primary and cyclic secondary alcohols gave the corresponding alkyl ethers of cyanohydrin in good yields (Runs 3–5).

Table 4. Synthesis of various cyanohydrin alkyl ethers[a]



Run	ROTMS	Yield/%[b]
1	$CH_2{=}CHCH_2OTMS$	95
2	PMBOTMS	0
3	$PhCH_2CH_2CH_2OTMS$	66
4	*n*-BuOTMS	91
5	*cyclo*-$C_6H_{11}OTMS$	77

[a] Molar ratio of PhCHO:ROTMS:$FeCl_3$:TMSCN = 1:2.4:0.02:1.5.
[b] Isolated yield of purified product.

In conclusion, we have developed a novel one-pot synthesis of *O*-alkyl protected cyanohydrins starting from a variety of parent aldehydes. This reaction has the following synthetic advantages: 1) in contrast to the known cyanations of aldehyde, this novel one-pot procedure promotes both cyanation and *O*-alkylation, 2) various alkyl-ether types of a protecting group for the hydroxyl function are obtained by using the corresponding alkoxytrimethylsilane, 3) extremely mild reaction conditions, 4) experimental convenience. Further investigations to broaden the scope and synthetic applications of this efficient cyanoalkylation are under way in our laboratory.

References and Notes

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12 Typical procedure: To a suspension of anhydrous iron(III) chloride (1.8 mg, 0.011 mmol) and benzyloxytrimethylsilane (292 µL, 1.48 mmol), was added benzaldehyde (63 µL, 0.62 mmol) and stirred at 0 °C under argon atmosphere. After 2 h, trimethylsilyl cyanide (124 µL, 0.93 mmol) was added and stirred for 1 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and quenched with a phosphate buffer (pH 7). The organic materials were extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. α-(Benzyloxy)-phenylacetonitrile (135.2 mg, 98%) was isolated by thin-layer chromatography on silica gel.