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Iron(III) triflate-catalyzed one-pot synthesis of acetal-type protected cyanohydrins from carbonyl compounds

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Abstract—A variety of cyanohydrin THP ethers were readily prepared from carbonyl compounds with trimethylsilyl cyanide and tetrahydropyran-2-yl acetate under the influence of a catalytic amount of iron(III) triflate in a convenient one-pot procedure. This method was also effective to prepare *O*-protected cyanohydrins by various acetal-type protective groups.

Cyanohydrins are well-known as one of the most important synthetic intermediates.[1] *O*-protected cyanohydrin derivatives have also attracted the interest of organic chemists, and several straightforward methods for their preparation from carbonyl compounds have been reported so far.[2–5] Acetal-type protective groups of a hydroxyl function such as tetrahydropyran-2-yl (THP) ether and methoxymethyl (MOM) ether are widely used in organic synthesis, because they have a unique property of being stable in alkaline conditions and are deprotected in acidic conditions, which are in inverse relation to esters.[6] However, to the best of our knowledge, a simple one-pot procedure for the synthesis of cyanohydrins protected by THP or MOM ether has never been reported.

On the other hand, in the course of our study for the convenient synthesis of a variety of *O*-protected cyanohydrins, very recently, we developed an efficient and general one-pot synthetic method of cyanohydrin alkyl ethers[7] and cyanohydrin esters[8] directly from carbonyl compounds under the influence of a catalytic amount of iron(III) chloride.[9] Moreover, our previous investigations documented catalyst-free synthesis of cyanohydrin benzoates[10] and cyanohydrin carbonates[11] in DMSO. Next, we attempted to prepare another type of *O*-protected cyanohydrins directly from carbonyl compounds. Herein, we wish to report the first example to prepare *O*-protected cyanohydrin derivatives by an acetal-type protective group in a convenient one-pot procedure catalyzed by iron(III) triflate.

First, we undertook to examine the one-pot preparation of cyanohydrin THP ethers from aldehydes via in situ generated cyanohydrin TMS ether.[8] A mixture of 3-phenylpropionaldehyde in the presence of 5 mol % of iron(III) chloride in acetonitrile was treated with 1.2 equiv of trimethylsilyl cyanide (TMSCN) at 0 °C for 30 min, and then 1.2 equiv of tetrahydropyran-2-yl acetate (THPOAc)[12] was added, and stirred for additional 3 h at room temperature. The usual work-up of the reaction mixture afforded the desired product, 2-(tetrahydropyran-2-yloxy)-4-phenylbutyronitrile, in 56% yield (Table 1, run 1). Dihydropyran (DHP) was not a suitable reagent for this purpose (run 2). Although the yield was improved up to 74% at −20 °C in the second step (run 4), the desired product was not obtained at −78 °C (run 6), because no reaction occurred in the second step. In contrast, when iron(III) triflate[13] was used as a catalyst, the expected reaction proceeded very smoothly at −78 °C and the desired product was obtained in 88% yield (run 9). A screening of solvents revealed that propionitrile as a solvent gave the best result (runs 9–13). In addition, other representative Lewis acids gave unsatisfactory results (runs 14–16).

The reaction was carried out under optimal conditions (Table 1, run 9) with various aromatic and aliphatic aldehydes and ketones, and the successful results are summarized in Table 2.[14] For aliphatic aldehyde,

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Keywords: Iron(III) triflate; Cyanation; Cyanohydrin THP ether; Acetal-type protective group; Trimethylsilyl cyanide; Carbonyl compounds.

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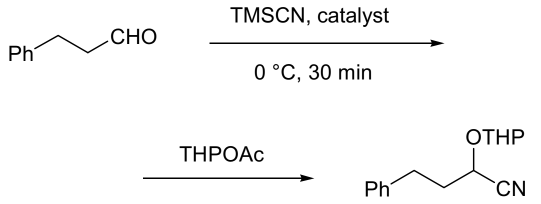
Table 1. Optimization of the reaction conditions[a]



Run	Catalyst	Solvent	Temperature of the 2nd step/°C	Time of the 2nd step/h	Yield[b]/%
1	$FeCl_3$	MeCN	rt	3	56
2[c]	$FeCl_3$	MeCN	rt	6	0
3	$FeCl_3$	MeCN	0	1	48
4	$FeCl_3$	MeCN	−20	1	74
5	$FeCl_3$	EtCN	−40	1	27
6	$FeCl_3$	EtCN	−78	3	0
7	$Fe(OTf)_3$	MeCN	−20	1	35[d]
8	$Fe(OTf)_3$	EtCN	−40	1	54[d]
9	$Fe(OTf)_3$	EtCN	−78	3	88
10[e]	$Fe(OTf)_3$	EtCN	−78	3	61
11	$Fe(OTf)_3$	*n*-PrCN	−78	3	70
12	$Fe(OTf)_3$	CH_2Cl_2	−78	3	83
13	$Fe(OTf)_3$	Toluene	−78	3	41
14	$Fe(OTf)_2$	EtCN	−78	3	48
15	$Sc(OTf)_3$	EtCN	−78	3	61
16	$Yb(OTf)_3$	EtCN	−78	3	0

[a] Molar ratio of 3-phenylpropionaldehyde:catalyst:TMSCN:THPOAc = 1:0.05:1.2:1.2.

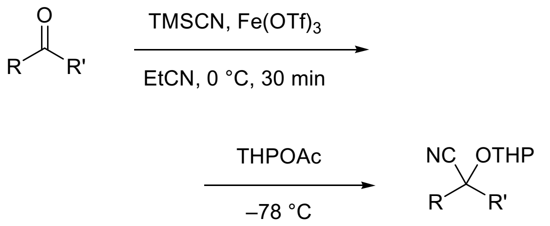
[b] Isolated yield of purified product.

[c] DHP was used instead of THPOAc.

[d] The lower yield was due to a complicated reaction mixture.

[e] Nitromethane was used as a solvent in the 1st step.

Table 2. Synthesis of various cyanohydrin THP ethers[a]



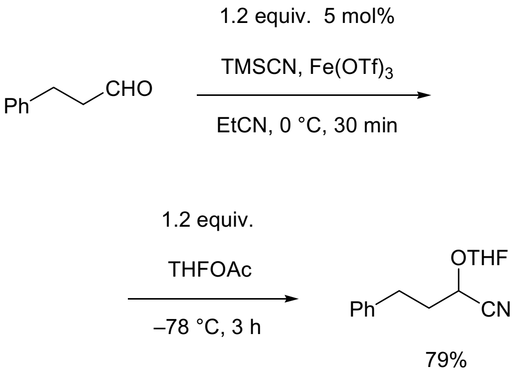
Run	Carbonyl compound	Time of the 2nd step/h	Yield[b]/%
1	$PhCH_2CH_2CHO$	3	88
2	$PhCH_2CH(CH_3)CHO$	3	78
3	*t*-BuCHO	3	80
4	(*E*)-PhCH=CHCHO	3	85
5	PhCHO	1	95
6	4-MeC_6H_4CHO	2	73
7[c]	4-MeC_6H_4CHO	1	90
8[c]	3-MeC_6H_4CHO	1	75
9[c]	2-MeC_6H_4CHO	1	86
10[c]	$2,4,6\text{-Me}_3C_6H_2CHO$	5	90
11[c]	4-MeOC_6H_4CHO	2	93
12	4-BrC_6H_4CHO	2	74
13[c]	4-BrC_6H_4CHO	1	86
14[c]	$4\text{-MeO}_2CC_6H_4CHO$	3	90
15[c]	1-Naphthaldehyde	2	94
16[c]	2-Naphthaldehyde	2	92
17[d]	Benzylacetone	3	74
18[d]	Benzalacetone	3	79
19[d]	Cyclopentanone	3	88
20[d]	Cyclohexanone	4	88

[a] Molar ratio of carbonyl compound:$Fe(OTf)_3$:TMSCN:THPOAc = 1:0.05:1.2:1.2, unless otherwise noted.

[b] Isolated yield of purified product.

[c] Nitromethane was used as a solvent in the 1st step.

[d] 1.5 equiv of TMSCN and 1.5 equiv of THPOAc were used.



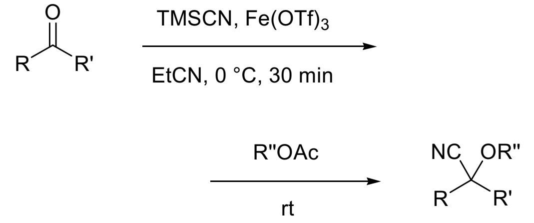
Scheme 1. Synthesis of cyanohydrin THF ether from 3-phenylpropionaldehyde.

α-branched 2-methyl-3-phenylpropionaldehyde, sterically hindered pivalaldehyde, and α,β-unsaturated aldehyde, the corresponding cyanohydrin THP ethers were obtained in good yields (runs 2–4). Similarly, benzaldehyde afforded the desired product in 95% yield (run 5). In the case of substituted aromatic aldehyde, the corresponding cyanohydrin THP ethers were obtained in good to high yields using nitromethane as a solvent in the first step (runs 7–11, 13, and 14). Especially, sterically hindered mesitaldehyde gave the corresponding THP ethers in 90% yield (run 10), and the ester function was tolerated under these reaction conditions (run 14). Starting from 1- and 2-naphthaldehyde, the desired products were obtained in high yields (runs 15 and 16). Furthermore, we found that this reaction was similarly effective for various ketones to yield the corresponding *O*-THP protected cyanohydrins in good to high yields (runs 17–20).

Next, to clarify the generalization of this useful transformation, we investigated other acetates instead of THPOAc. Reaction with tetrahydrofuran-2-yl acetate (THFOAc)[12] gave the corresponding cyanohydrin tetrahydrofuran-2-yl ethers in 79% yield (Scheme 1). Similarly, when methoxymethyl acetate (MOMOAc), 2-methoxyethoxymethyl acetate (MEMOAc), and benzyloxymethyl acetate (BOMOAc) were used,[15] the corresponding cyanohydrin MOM, MEM, and BOM ethers were also obtained, respectively, in moderate to good yields (Table 3).

Finally, we examined some transformations starting from cyanohydrin THP ether. A nitrile group was successfully reduced by lithium aluminum hydride to form an *O*-THP protected β-aminoalcohol derivative in 84% yield without loss of the THP group (Scheme 2). Additionally, the corresponding amide was obtained in 80%

Table 3. Synthesis of various *O*-protected cyanohydrins[a]

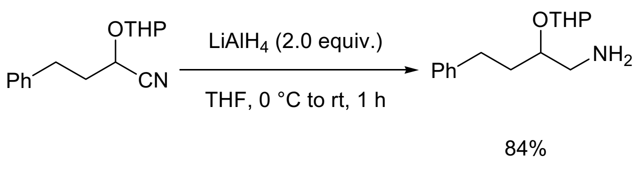


Run	Carbonyl compound	R″OAc (equiv)	Time of the 2nd step/h	Yield[b]/%
1[c]	$PhCH_2CH_2CHO$	MOMOAc (2.2)	5	34
2[d]		MOMOAc (2.2)	0.5	74
3		MOMOAc (2.2)	0.5	78
4		MEMOAc (1.2)	3	64
5		BOMOAc (1.2)	3	70
6[e]	PhCHO	MOMOAc (2.2)	1	84
7[e]		MEMOAc (1.2)	3	77
8[e]		BOMOAc (1.5)	3	79
9	Cyclopentanone	MOMOAc (2.1)	3	64
10		MEMOAc (1.5)	3	65
11		BOMOAc (1.5)	3	68

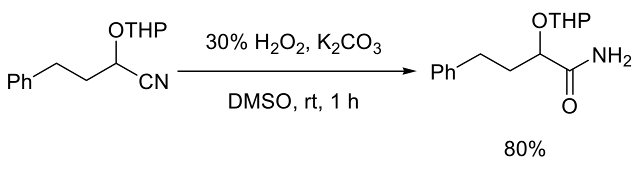
[a] Molar ratio of carbonyl compound:$Fe(OTf)_3$:TMSCN = 1:0.05:1.2.
[b] Isolated yield of purified product.
[c] Temperature of the 2nd step was -78 °C.
[d] Temperature of the 2nd step was 0 °C.
[e] Nitromethane was used as a solvent.

yield by treatment with basic hydrogen peroxide in DMSO (Scheme 3).[16]

In conclusion, the present efficient transformation has the following synthetic advantages: (1) a catalytic amount of iron(III) triflate promotes both cyanation and *O*-protection, in contrast to the known cyanation of carbonyl compounds, (2) various acetal-types of a protecting group for the hydroxyl function such as THP and MOM ether are obtained by using the corresponding acetate, (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 valuable cyanation are under way in our laboratory.



Scheme 2. Conversion of nitrile to amine.



Scheme 3. Conversion of nitrile to amide.

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14. Typical procedure: To a suspension of iron(III) triflate (7.4 mg, 0.015 mmol) and 3-phenylpropionaldehyde (40 μL, 0.30 mmol) in propionitrile (1 mL) was added trimethylsilyl cyanide (48 μL, 0.36 mmol) and stirred at 0 °C under an argon atmosphere. After 30 min, tetrahydropyran-2-yl acetate (52.8 mg, 0.36 mmol) in propionitrile (1 mL) was added and stirred for 3 h at −78 °C. The reaction mixture was quenched with a phosphate buffer (pH 7), and the organic materials were extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. 2-(Tetrahydropyran-2-yloxy)-4-phenylbutyronitrile (65.5 mg, 88%) was isolated by thin-layer chromatography on silica gel.
15. Preparation of MOMOAc: To a solution of acetic acid (3.43 g, 57 mmol) in CH_2Cl_2 (5 mL), Et_3N (6.39 g, 63 mmol) in CH_2Cl_2 (5 mL) and MOMCl (5.52 g, 69 mmol) in CH_2Cl_2 (5 mL) were added at 0 °C under an argon atmosphere, and stirred for 18 h at room temperature. The reaction mixture was quenched with a phosphate buffer (pH 7), and the organic materials were extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After removal of solvent, MOMOAc (3.33 g, 56%) was obtained by vacuum distillation. Starting from MEMCl and BOMCl, the corresponding MEMOAc and BOMOAc were obtained in 31% and 45% yield, respectively.
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