Iron(III) Fluoride: A Highly Efficient and Versatile Catalyst for the Protection of Carbonyl Compounds under Solvent-Free Conditions

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Carbonyl compounds are successfully converted into oxathioacetals and dithioacetals with 2-mercaptoethanol and ethane-1,2-dithiol using a catalytic amount of iron(III) fluoride under solvent-free conditions. The catalysts were recovered and reused in various runs without affecting the efficiency of the process.

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During multi-step synthesis, the protection of carbonyl groups is widely achieved by the formation of oxathioacetals and dithioacetals.^[1] These substrates are also important because of their application as precursors for acyl anions and their masked methylene functions.^[2] Numerous methods have been reported for the preparation of oxathioacetals and thioacetals from carbonyl compounds, including the use of BF₃·EtO,^[3] Mg(OTf)₂,^[4] AlCl₃,^[5] TiCl₄,^[6] Sc(OTf)₃,^[7] LiBr,^[8] InCl₃,^[9] LiBF₄,^[10] TMSCl/NaI,^[11] TMSOTf,^[12] LaCl₃,^[13] SiCl₄,^[14] Cu(OTf)₂/SiO₂,^[15] ZrCl₂/SiO₂,^[16] WCl₆,^[17] 5 M LiClO₄/Et₂O,^[18] TaCl₅/SiO₂,^[19] Bi(OTf)₃,^[20] $MoO_2(acac)_2$,^[21] Y(OTf)₃,^[22] Bi(NO₃)₃,^[23] and ionic liquids.^[24] However, many of these methods require harsh reaction conditions, long reaction times, expensive reagents that are inconvenient to handle, and result in low yields. Hence, there is scope to explore mild and efficient methods for the protection of carbonyl compounds of oxathioacetals and dithioacetals.

Lewis acid-catalyzed reactions have been of recent interest in organic synthesis because of their reactivities and selectivities under mild conditions.^[25] While many kinds of Lewis acid-promoted reactions have been developed and applied in industry, these reactions must be carried out anhydrously. Small amounts of water stop the reaction because most Lewis acids immediately react with water, rather than with the substrates, and decompose or deactivate. This fact has restricted the use of Lewis acids. Further, restraint on the use of organic solvents, in particular halogenated solvents, is desired from an environmental aspect. Recently, the use of metal triflates as catalysts has increased. However, the high cost, commercial non-availability, and susceptibility to moisture impede triflate use for large-scale synthetic applications. The strong Lewis acidic characteristic of metal triflates may cause competitive side reactions such as rearrangement and dehydration due to the formation of triflic acid. Iron(III) fluoride is a better



Scheme 1.

alternative in this regard, as it is a mild catalyst. In a previous report we demonstrated that iron(III) fluoride is an excellent water-tolerant Lewis acid and is a highly efficient catalyst for the chemoselective addition of trimethylsilyl cyanide (TMSCN) to aldehydes in water.^[26] In this report, we have synthesized oxathiocetals and dithioacetals using iron(III) fluoride under solvent-free conditions for the first time, as this is one of the most useful synthetic transformations with varied applications. The experimental procedure is simple and does not require an inert atmosphere. Moreover, the catalyst can be recovered and reused at least twice without appreciable loss of activity. Preliminary results on the synthesis of oxathioacetals and dithioacetals in the presence of 5 mol% iron(III) fluoride are presented (Scheme 1).

When a mixture of benzaldehyde, 2-mercaptoethanol, and 5 mol% iron(III) fluoride under solvent-free conditions was stirred at room temperature, the corresponding oxathioacetal was obtained at 95% yield after direct distillation of the resulting odorless mixture. Similarly, various aldehydes were selectively converted into the corresponding oxathioacetals and dithioacetals in high yields. Results are summarized in Table 1. Both activated and deactivated aromatic aldehydes were converted to oxathioacetals and dithioacetals. The tolerance of various functional groups under the present reaction conditions have been examined by reacting substrates with methoxy, nitro, chloro, methylenedioxy, phenoxy,

Entry	Substrate	Thiol	Time [min]	Yield [%] ^{A,B}
1	Benzaldehyde	HSCH ₂ CH ₂ OH	5	95
2	4-Methylbenzaldehyde	HSCH ₂ CH ₂ OH	10	94
3	4-Nitrobenzaldehyde	HSCH ₂ CH ₂ OH	20	92
4	4-Chlorobenzaldehyde	HSCH ₂ CH ₂ OH	25	90
5	3,4-Methylenedioxybenzaldehyde	HSCH ₂ CH ₂ OH	15	93
6	3-Phenoxybenzaldehyde	HSCH ₂ CH ₂ OH	20	90
7	2-Napthaldehyde	HSCH ₂ CH ₂ OH	30	88
8	Cinnamaldehyde	HSCH ₂ CH ₂ OH	30	89
9	Pentanal	HSCH ₂ CH ₂ OH	10	90
10	Hexanal	HSCH ₂ CH ₂ OH	10	95
11	Furfuraldehyde	HSCH ₂ CH ₂ OH	15	90
12	Thiophene-2-carboxaldehyde	HSCH ₂ CH ₂ OH	15	92
13	Cyclohexanone	HSCH ₂ CH ₂ OH	45	89
14	Cyclopentanone	HSCH ₂ CH ₂ OH	45	91
15	2-Hepanone	HSCH ₂ CH ₂ OH	120	85
16	Benzaldehyde	HSCH ₂ CH ₂ SH	10	92
17	4-Methylbenzaldehyde	HSCH ₂ CH ₂ SH	15	94
18	4-Methoxybenzaldehyde	HSCH ₂ CH ₂ SH	20	96
19	4-Chlorobenzaldehyde	HSCH ₂ CH ₂ SH	35	92
20	3,4-Methylenedioxybenzaldehyde	HSCH ₂ CH ₂ SH	25	90
21	2,3-Dichlorobenzaldehyde	HSCH ₂ CH ₂ SH	35	98
22	4-Cyanobenzaldehyde	HSCH ₂ CH ₂ SH	30	95
23	4-Bromobenzaldehyde	HSCH ₂ CH ₂ SH	35	98
24	Cinnamaldehyde	HSCH ₂ CH ₂ SH	25	90
25	Hexanal	HSCH ₂ CH ₂ SH	10	98
26	Cyclopentanone	HSCH ₂ CH ₂ SH	50	96
27	2-Hexanone	HSCH ₂ CH ₂ SH	100	85
28	Benzophenone	HSCH ₂ CH ₂ SH	220	83

Table 1. FeF₃-catalyzed formation of oxathioacetals and dithioacetals under solvent-free conditions

^A Yields are of pure isolated products. ^B Products were characterized by physical data and spectroscopy.

Aldehyde	Product	Thiol	Time [min]	Yield [%] ^{A,B}
тнро Сно	2a	HSCH ₂ CH ₂ OH	7	93
тврмостосно	2b	HSCH ₂ CH ₂ OH	8	92
4-TBDMSO-CHO	2c	HSCH ₂ CH ₂ SH	10	94
4-EtOOC	2d	HSCH ₂ CH ₂ OH	12	94
4-H ₃ CCHN CHO	2e	HSCH ₂ CH ₂ OH	15	92
4-РМВО-СНО	2f	HSCH ₂ CH ₂ SH	10	95
4-МОМО-СНО	2g	HSCH ₂ CH ₂ SH	10	95

Table 2. Conversion of aldehydes bearing protecting groups to thioacetals

^A Yields are of pure isolated products. ^B Products characterized by physical data and spectroscopy.

olefinic, methyl, cyano, and bromo groups, and the reaction conditions are compatible with these functional groups. Acidsensitive substrates such as furfuraldehyde are also protected as oxathioacetal in good yield without formation of such by-products normally encountered in acidic conditions. This method was then applied to protect different types of cyclic (entries 13, 14, 26), aliphatic (entries 15, 27), and aromatic ketones (entry 28) at room temperature. The 1,3-oxathiolanes and 1,3-dithiolanes were formed in good yields, although the time required for the completion of the reaction was longer compared with aldehydes.

Conversion was achieved in the presence of several acid-sensitive protecting groups such as tetrahydro-2*H*-pyran-2-yl, *tert*-butyl dimethylsilyl, ester, amide, *para*-methoxybenzyl, and methoxymethyl ethers under the present reaction conditions. Results are presented in Table 2.



As aldehydes are converted faster than ketones, this procedure affords chemoselective protection of aldehydes in the presence of ketones (Scheme 2).

Further, we studied the catalytic ability of other iron salts such as FeCl₃, FeBr₃, and FeI₃ for the synthesis of oxathioacetals. By using 5 mol% of FeCl₃, FeBr₃, and FeI₃, benzaldehyde was converted into the corresponding oxathioacetal in 58%, 40%, and 35% yield, respectively, when the reaction mixture was stirred for 30 min. This result shows FeF₃ is a stronger catalyst than FeCl₃, FeBr₃, and FeI₃.

Iron(III) fluoride obtained as a white solid (97%) after distillation was used directly for the next reaction. The first run in the reaction of benzaldehyde with 1,2-mercaptoethanol gave 90% yield and the second run gave 87% yield of the corresponding oxathioacetal. This result indicates that iron(III) fluoride is expected to solve some severe environmental problems induced by Lewis acid-promoted reactions in industry. As compared with methods that require stoichiometric amounts of reagent,^[11,27] the present method required a catalytic amount of iron(III) fluoride (0.05 mmol) for the reaction to proceed cleanly. Moreover, neither use of dehydrating agent, [11,27c,27e,28] nor the azeotropic removal of water,^[27d,29] are necessary for the present method. Although various methods have been reported for this conversion, most of them require long reaction times^[3,5,6,8,10,14] and reflux temperatures,^[20] and reagents are expensive, not readily available and need to be prepared, [7,15,16,19-23] and some reagents are destroyed in the work-up procedure and cannot be recovered and reused.^[5,6,8,10,11,14,18,20,22] There are few methods for chemoselective protection of aldehydes^[8,15,18–24] in the presence of ketones. Thus, our study shows iron(III) fluoride is superior as a catalyst for the protection of carbonyl compounds as oxathioacetals and dithioacetals, with regard to toxicity, handling, selectivity, and recyclability. The superiority of this procedure is illustrated by the use of entirely solvent-free conditions and is applicable to distillable compounds. Although the synthesis of oxathioacetals and dithioacetals under solvent-free conditions has been reported,^[8,30] organic solvents were used in the work-up process.

In summary, the present procedure demonstrates the conversion of aldehydes into oxathioacetals and dithioacetals using iron(III) fluoride (0.05 mmol) under solvent-free conditions as an alternative to existing methods. Important features of the present method are chemoselective protection of aldehydes in the presence of ketones, high yields, operational simplicity, and mild reaction conditions.

Experimental

Iron(III) fluoride was purchased from Acros Organics and used without further purification. All reactions were carried out in oven-dried flasks. All chemicals were of analytical grade. IR spectra were recorded on a Bomem MB 104 FT-IR spectrometer and ¹H NMR spectra were recorded on an AC 300 F spectrometer (300 MHz). Mass spectra were recorded on a Bruker ion trap spectrometer.

In a typical procedure, a mixture of benzaldehyde (10 mmol), 1,2mercaptoethanol (10 mmol), and iron(III) fluoride (0.05 mmol) was stirred at room temperature for 5 min. After completion of the reaction, as indicated by TLC, the odorless mixture was directly distillated under reduced pressure of 0.5 mmHg at an oven temperature of 170–190°C to furnish 2-phenyl-1,3-oxathioacetal (95%). The iron(III) fluoride remained in the distilling flask as a white solid (97%) and was used directly for the next reaction without further purification.

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