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Journal of Fluorine Chemistry 128 (2007) 679–682
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Short communication

Facile protection of carbonyl compounds as oxathiolanes and transoxathioacetalization of oxyacetals promoted by iron(III) trifluoroacetate or trifluoromethanesulfonate as chemoselective and recyclable catalysts

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Received 7 March 2007; received in revised form 1 April 2007; accepted 3 April 2007
Available online 6 April 2007

Abstract

Oxathioacetalization of carbonyl compounds and transoxathioacetalization of *O*,*O*-acetals/ketals are reported under nearly neutral conditions promoted by iron(III) trifluoroacetate [$Fe(CF_3CO_2)_3$] or trifluoromethanesulfonate [$Fe(CF_3SO_3)_3$] as recyclable and highly efficient Lewis acid catalysts.

Keywords: Iron trifluoroacetate; Trifluoromethanesulfonate; Oxathiolanes; Carbonyl compounds; Protection

1. Introduction

One of the major challenging problems during multistep syntheses is to protect carbonyl functionality from nucleophilic attack until its electrophilic nature can be exploited. Among carbonyl protecting groups, 1,3-oxathiolanes are an important class of compounds for the following reasons. Firstly, they can be used as acyl carbanion equivalents [1] for carbon–carbon bond forming reactions. Secondly, the chiral 1,3-oxathiolanes are valuable synthons for enantioselective synthesis of α-hydroxyaldehydes, first demonstrated by Lynch and Eliel [2]. Later on, these compounds were further utilized by Utimoto et al. [3] for studying diastereoselective reactions. Thirdly, the use of *O*,*S*-acetals is more convenient than the corresponding *O*,*O*-acetals or *S*,*S*-acetals because they are comparatively more stable than *O*,*O*-acetals in acidic conditions and much easier to remove than *S*,*S*-acetals. Though a large number of methods have been developed for the protection and deprotection of carbonyl compounds as 1,3-dithiolanes, only a few methods are available for oxathioacetals [4]. A plethora of procedures are reported for their formation employing protic acids or Lewis acids such as HCl [5a], *p*-TsOH [5b], $BF_3 \cdot OEt_2$ [5c], TMSCl/NaI [5d], TMSOTf [5e], Bu_4NBr_3 [5f], $H_3PW_{12}O_{40}/SiO_2$ [5g], $In(OTf)_3$ [5h], NBS [5i], $Sc(OTf)_3$ [5j], $ZrCl_4$ [5k], $HClO_4$ [5l], $LiBF_4$ [5m], $ZnCl_2/Na_2SO_4$ [5n], SO_2 [5o], polystyryl diphenylphosphine–iodine complex [5p], natural kaolinitic clay [5q], $MoO_2(acac)_2$ [5r], Me_2S/Br_2 [5s], polyphosphoric acid/SiO_2 [5t], $HClO_4/SiO_2$ [5u], $Pr(OTf)_3$ [5v], $Yb(OTf)_3$/ionic liquid [5w], 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TABCO)/Br_2 [5x] and $TaCl_5/SiO_2$ [5y]. A number of these methods suffer from certain drawbacks such as low yields, relatively harsh reaction conditions and long reaction times, reflux temperatures, expensive reagents, inconvenient procedures, the use of stoichiometric amounts of catalyst, unwanted side reactions, poor chemoselectivity and the use of catalysts destroyed in the work-up procedure which cannot be recovered and used again. Additionally, handling of some of these catalysts is not easy in the laboratory apart from their hygroscopic nature due to strong tendency for hydrolysis. However, developments in this area demand further searches

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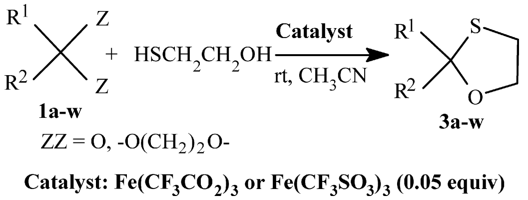
doi:10.1016/j.jfluchem.2007.04.002



Scheme 1. Conversion of carbonyl compounds to oxathiolanes and transoxathioacetalization of oxyacetals catalyzed by $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$.

for better catalysts that could be superior to the existing ones with regard to environmental compatibility, efficiency, chemoselectivity, operational simplicity, cost effectiveness, toxicity, handling and recyclability. In this respect, we are interested in introducing better catalysts to overcome these limitations.

Recently, we reported that solvolytic and non-solvolytic ring-opening reactions of epoxides are facilitated in the presence of iron(III) trifluoroacetate [6]. Also, iron(III) triflate is a novel Lewis acid, which has attracted little attention as a catalyst [7]. Very recently, Oriyama and co-workers reported that iron(III) triflate catalyzes one-pot synthesis of acetal-type protected cyanohydrins from carbonyl compounds [8]. To the best of our knowledge, there is no report on the application of $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$ as Lewis acid catalysts for the preparation of oxathioacetals. In this paper, we wish to disclose an efficient method for oxathioacetalization of various aldehydes and ketones and transoxathioacetalization of *O*,*O*-acetals/ketals by reaction with 2-mercaptoethanol using catalytic amounts of iron(III) trifluoroacetate or trifluoromethanesulfonate as powerful, recyclable and non-hygroscopic Lewis acid catalysts under almost neutral conditions (Scheme 1).

2. Results and discussion

These reagents have several advantages over other conventional Lewis acids, for example, they are stable in water and therefore do not decompose under aqueous work-up conditions and also recycling of $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$ is often possible with no loss in their potency and makes the procedure environmentally acceptable by utilizing these properties. The highly stable and non-hygroscopic nature, high chemoselectivity, easy preparation, high yield, short reaction periods, easy handling and work-up are other advantages of the catalysts.

To choose the most appropriate medium in this heterocyclization reaction, we examined the protection of benzaldehyde **1a** as a model compound with 2-mercaptoethanol using $Fe(CF_3CO_2)_3$ in various solvents (Table 1). The solvents examined were dichloromethane, tetrahydrofuran, chloroform, *n*-hexane and acetonitrile. The reactions were carried out by stirring **1a** with $Fe(CF_3CO_2)_3$ (5 mol%) and 1.2 equiv of 2-mercaptoethanol at room temperature. The reaction of **1a** with 1.2 equiv of 2-mercaptoethanol in CH_2Cl_2 for 30 min afforded 2-phenyl-1,3-oxathiolane **2a** in 60% conversion (Table 1, entry 1). When the reaction was carried out in CH_3CN, the reaction took place rapidly and **2a** was obtained in 100% conversion (Table 1, entry 2), it turned out to be one of the best choices in view of high solubility of substrates within it. In the case of the other solvents such as $CHCl_3$, THF and *n*-hexane **2a** was obtained in lower conversions (Table 1, entries 3–5). Next, the effect of the amount of the $Fe(CF_3CO_2)_3$ was examined with **1a** (1 mmol) and 2-mercaptoethanol in acetonitrile. The optimum molar ratio of **1a** to 2-mercaptoethanol to $Fe(CF_3CO_2)_3$ (1:1.2:0.05) was found to be ideal for complete conversion. Similar reactions were carried out with $Fe(CF_3SO_3)_3$ as shown in Table 1. It should be noted that in the absence of catalyst no conversion of **1a** to **2a** occurred after 24 h (Table 1, entry 6).

The generality of this protocol has been proved with a wide range of aromatic, aliphatic and heterocyclic aldehydes (Table 2, entries 1a–n) bearing Cl, OMe, NO_2, OH and Me groups whilst remaining strictly unchanged. It is worthy of note that the oxathioacetalization of cinnamaldehyde and piperonal as unsaturated and protected aldehydes proceeded successfully by this method to afford the corresponding oxathioacetals in high yields (Table 2, entries 1g, n). These reactions proceeded quite cleanly under almost neutral conditions and practically pure products were obtained after a simple work-up procedure without any requirement to the use of inert atmosphere. Moreover, neither the use of dehydrating agent nor the azeotropic removal of water is necessary in our procedure. Catalytic quantities of $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$ (5 mol%) were added to a stirred solution of the carbonyl compound and the required 2-mercaptoethanol in acetonitrile and then the mixture was stirred at room temperature. These catalysts have been recovered almost quantitatively from the aqueous layers and used again for the second runs and the yields of the second ones were comparable to those of the first runs (Table 2). Ketones were also oxathioacetalized to 1,3-oxathiolanes using $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$ (5 mol%) (Table 2, entries 1o–u)

Table 1
Oxathioacetalization of benzaldehyde **1a** with 2-mercaptoethanol catalyzed by $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$[a]

Entry	Solvent	Reaction conditions	Molar ratio	Time (min)	Conversion (%)[b]
1	CH_2Cl_2	Substrate/2-mercaptoethanol/$Fe(CF_3CO_2)_3$	1/1.2/0.05	30 (30)	60 (68)
2	CH_3CN	Substrate/2-mercaptoethanol/$Fe(CF_3CO_2)_3$	1/1.2/0.05	20 (15)	100 (99)
3	$CHCl_3$	Substrate/2-mercaptoethanol/$Fe(CF_3CO_2)_3$	1/1.2/0.05	30 (30)	70 (75)
4	THF	Substrate/2-mercaptoethanol/$Fe(CF_3CO_2)_3$	1/1.2/0.05	30 (30)	55 (60)
5	*n*-Hexane	Substrate/2-mercaptoethanol/$Fe(CF_3CO_2)_3$	1/1.2/0.05	30 (30)	50 (58)
6	CH_3CN	Substrate/2-mercaptoethanol	1/1	24 h	0 (0)

[a] The numbers in parenthesis are related to $Fe(CF_3SO_3)_3$.
[b] GC yield.

Table 2
Oxathioacetalization and transoxathioacetalization of carbonyl compounds catalyzed by $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$ at room temperature[a]

Entry	R^1	R^2	ZZ	Time (min)		Yield (%)[b]	
				$Fe(CF_3CO_2)_3$	$Fe(CF_3SO_3)_3$	$Fe(CF_3CO_2)_3$	$Fe(CF_3SO_3)_3$
1a	C_6H_5	H	O	20, 25[c]	10, 15[c]	90, 92[c]	90, 81[c]
1b	$4\text{-}O_2NC_6H_4$	H	O	45	40	87	91
1c	$4\text{-}MeC_6H_4$	H	O	20, 30[c]	10, 20[c]	92, 81[c]	94, 85[c]
1d	$4\text{-}MeOC_6H_4$	H	O	15	10	91	92
1e	$4\text{-}OH\text{-}3\text{-}MeOC_6H_3$	H	O	10	10	89	90
1f	$2\text{-}ClC_6H_4$	H	O	25	25	87	87
1g	PhCH=CH	H	O	20	15	91	89
1h	2-Naphthyl	H	O	15	15	89	93
1i	$3,4,5\text{-}(MeO)_3C_6H_2$	H	O	20	15	93	92
1j	$4\text{-}ClC_6H_4$	H	O	20	10	90	92
1k	2-Furyl	H	O	15	10	95	98
1l	$3,4\text{-}(MeO)_2C_6H_3$	H	O	10	10	91	91
1m	*n*-Hexanal	H	O	30	20	90	86
1n	Piperonal	H	O	25	25	87	93
1o	α-Tetralone		–	70	60	89	90
1p	Cyclopentanone		–	80	70	89	92
1q	Cyclohexanone		–	95	80	85	85
1r	4-Cholesten-3-one		–	180	180	90	90
1s	Ph	Me	O	190	180	82	81
1t	Ph	Ph	O	200	180	89	85
1u	Ethyl acetoacetate		–	75	70	88	90
1v	$4\text{-}MeC_6H_4$	H	$O(CH_2)_2O$	20	15	92	94
1w	C_6H_5	H	$O(CH_2)_2O$	15	15	89	88
1x	Cyclohexanone		$O(CH_2)_2O$	100	90	92	97
1y	$4\text{-}MeOC_6H_4$	H	$O(CH_2)_2O$	15	15	91	93

[a] Substrate/2-mercaptoethanol/catalyst (1/1.2/0.05).

[b] Isolated yield.

[c] Catalyst was recycled and reused for the second runs.

but considerably more slowly compared to aldehydes. Protection of α-tetralone and cholestenone as cyclic and steroidal ketones was catalyzed with $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$ under similar experimental conditions to afford the respective oxathioacetal (Table 2, entries 1o, r). Interestingly, ethyl acetoacetate also exhibited splendid selectivity towards the acetyl moiety as an example of β-ketoester and was smoothly protected in 88 and 90% yields under the above conditions without formation of a transesterification product (Table 2, entry 1u). To examine transoxathioacetalization, a mixture of the *O*,*O*-acetal **1v** and 2-mercaptoethanol was allowed to react in the presence of $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$ (5 mol%) at room temperature. The reaction mixture was worked up and purification of the crude product afforded the oxathioacetal **2v** in 92 and 94% yields (Table 2, entry 1v).

3. Experimental

3.1. Catalysts and general remarks

Iron(III) trifluoroacetate [6] and iron(III) trifluoromethanesulfonate [7] were prepared according to reported procedures. Yields refer to isolated products after purification. The products were characterized by comparing their spectral and physical data (TLC, MS, melting point, combustion elemental analysis and ^1H NMR) with those of authentic samples reported in the literature.

3.2. General procedure for oxathioacetalization and transoxathioacetalization of carbonyl compounds catalyzed by $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$

To a solution of carbonyl compound or an *O*,*O*-acetal/ketal (1 mmol) and 2-mercaptoethanol (1.2 mmol) in dry acetonitrile (5 ml) was added 5 mol% of $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$. The reaction mixture was stirred at room temperature and monitored by TLC until the disappearance of starting material. After the appropriate period (Table 2), the solvent was evaporated and the residue was diluted with dichloromethane (10 ml) and water (15 ml). The organic phase was separated and the aqueous layer was washed with dichloromethane (10 ml). Concentration of the combined organic layer under reduced pressure afforded the crude product, which was purified by neutral silica gel column chromatography to afford the corresponding oxathioacetal. The aqueous layer containing $Fe(CF_3CO_2)_3$ in the above work-up procedure was separated and evaporated under reduced pressure to afford the crude catalyst. The resulting solid residue was dried at 70 °C for 2 h to give the pure $Fe(CF_3CO_2)_3$ in 90% recovery. Work-up procedure for recovery of $Fe(CF_3SO_3)_3$ is similar to the former. The recycled catalysts were reused for the second runs (Table 2).

4. Conclusion

In conclusion, iron(III) trifluoroacetate and trifluoromethanesulfonate which are stable and non-hygroscopic Fe^{3+} compounds, can be considered as bench-top reagents for efficient oxathioacetalization and transoxathioacetalization of carbonyl compounds and high chemoselectivity of the reaction should be useful for selective protection of carbonyl group in the presence of other carbonyl moieties. In addition, we have developed catalysts as interesting alternatives to liquid, hygroscopic and expensive reagents as mentioned in Section 1. Moreover, nearly neutral conditions, short reaction times, high yields of the products, easy work-up, compatibility with various functional groups, and the environmentally friendly nature of the our procedure should make the presented protocol useful and important in addition to the known methodologies.

Acknowledgement

We gratefully acknowledge the Kermanshah University of Medical Sciences Research Council for financial support.

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