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Lutetium Triflate as an Efficient and Recyclable Catalyst for Chemoselective Thioacetalization of Aldehydes

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ABSTRACT

Lutetium triflate has been found to be an efficient and recyclable catalyst for chemoselective thioacetalization of aldehydes.

Key Words: Aldehydes; Chemoselectivity; Lutetium triflate; Thio-acetalization.

The protection of carbonyl compounds plays an important role during multistep syntheses in organic, medicinal, carbohydrate, and drug design chemistry. Among the different carbonyl protecting groups, 1,3-dithiolanes,

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1,3-dithianes, and diethyldithioacetals^[1] are important, as they are stable under both mildly acidic and basic conditions. In addition, these are utilized as masked acyl anions or masked methylene functions in carbon-carbon bond-forming reactions.^[2] In the literature, there are numerous methods reported for the preparation of thioacetals from carbonyl compounds employing PTSA,^[3] BF₃ · OEt₂,^[4] Zn(OTf)₂,^[5] SO₂,^[6] TMSOTf,^[7] AlCl₃,^[8] TiCl₄,^[9] Cu(OTf)₂,^[10] SOCl₂,^[11] ZrCl₄,^[12] InCl₃,^[13] I₂,^[14] LiBr,^[15] LiBF₄,^[16] Sc(OTf)₃,^[17] and 5 M LiClO₄.^[18] However, many of these methods have some drawbacks, such as low yields of the products, long reaction times,^[12] harsh reaction conditions,^[3,4] difficulties in workup,^[8,9] requirement for an inert atmosphere,^[18] and use of stoichiometric^[4,6] or relatively expensive reagents.^[7,9,12,15] Some methods mentioned above are incompatible with other protecting groups, such as tert-butyldimethylsilyl (TBS) ethers^[4b,15b,14b,16b] and fail to protect deactivated aromatic substrates.^[17] Moreover, the main disadvantage of all existing methods is that the catalysts are decomposed in the workup procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst, one superior to the existing ones with regard to recyclability, operational simplicity, economic viability, and greater selectivity.

Recently, lanthanide triflates have been introduced as promising mild and selective reagents in organic synthesis.^[19] The catalyst lutetium triflate is commercially available and can be used as catalyst in the preparation of dithiolanes, dithianes, and dithioacetals from carbonyl compounds. While most conventional Lewis acids decompose in the presence of water, $Lu(OTf)_3$ is stable in water and does not decompose under aqueous workup conditions. Thus, recyclization is often possible from aqueous workup (see the "Experimental" section). A catalytic amount of $Lu(OTf)_3$ is sufficient to obtain the desired compounds in excellent yield (Scheme 1). Thus, various aromatic, aliphatic, heterocyclic aldehydes undergo the protection reactions using 1,2-ethanedithiol, 1,3-propranedithiol or ethanethiol to give the corresponding 1,3-dithiolanes, 1,3-dithianes or diethyldithioacetals in good to excellent yield (Table 1). The experimental procedure for these reactions is simple and does not need the use of dry solvents or inert atmospheres. It is noteworthy that the



Scheme 1.

Lutetium Triflate as Catalyst

Entry	Substrate	Reagent	Time (h)	Yield ^a (%)
2	4-Methoxybenzaldehyde	HSCH ₂ CH ₂ SH	4	89
3	4-Chlorobenzaldehyde	HSCH ₂ CH ₂ SH	5	85/79 ^b
4	4-Nitrobenzaldehyde	HSCH ₂ CH ₂ SH	10	72
5	Furfural	HSCH ₂ CH ₂ SH	3	86
6	4-Benzyloxybenzaldehyde	HSCH ₂ CH ₂ SH	5	80
7	Cinnamaldehyde	HSCH ₂ CH ₂ SH	2	91
8	2-Naphthaldehyde	HSCH ₂ CH ₂ SH	12	70
9	Thiophene 2-carboxaldehyde	HSCH ₂ CH ₂ SH	3	$85/81^{b}$
10	Piperonal	HSCH ₂ CH ₂ SH	8	83
11	2-Methoxybenzaldehyde	HSCH ₂ CH ₂ SH	7	80
12	4-Carbomethoxybenzaldehyde	HSCH ₂ CH ₂ SH	7	85
13	4-Allyloxybenzaldehyde	HSCH ₂ CH ₂ SH	4	91
14	Hexaldehyde	HSCH ₂ CH ₂ SH	6	83
15	4-TBSO-benzaldehyde	HSCH ₂ CH ₂ SH	3	88
16	1-Octanal	HSCH ₂ CH ₂ SH	6	72
17	Butyraldehyde	HSCH ₂ CH ₂ SH	7	78
18	Decyl aldehyde	HSCH ₂ CH ₂ SH	6	70
19	4-Acetyloxybenzaldehyde	HSCH ₂ CH ₂ SH	6	82
20	4-Benzoyloxybenzaldehyde	HSCH ₂ CH ₂ SH	5	85
21	4-Bromobenzaldehyde	HSCH ₂ CH ₂ SH	5	91
22	Benzaldehyde	HSCH ₂ CH ₂ CH ₂ SH	5	88
23	4-Methoxybenzaldehyde	HSCH ₂ CH ₂ CH ₂ SH	4	90
24	4-Chlorobenzaldehyde	HSCH ₂ CH ₃	6	73
25	2-Naphthaldehyde	HSCH ₂ CH ₃	12	68

Table 1. $Lu(OTf)_3$ catalyzed protection of aldehydes as dithiolanes, dithianes, or ethyldithioacetals at room temperature.

 a Yields refer to pure isolated products, characterized by 1 H NMR and mass spectrometry (MS).

^bIsolated yields with reused catalyst.

conversion can be achieved in the presence of other protecting groups such as benzyl, acetyl, allyl, esters, and TBS ethers. Moreover, highly deactivated aromatic aldehydes can be protected as dithioacetals in good yield.

Also, note that the protocol can be extended for the chemoselective protection of an aldehyde in the presence of a ketone. For instance, when an equimolar mixture of 4-methoxybenzaldehyde and 4-methoxyacetophenone was allowed to react with 1,2-ethanedithiol in the presence of a catalytic amount



Scheme 2.

of Lu(OTf)₃, only the dithiolane derivative of 4-methoxybenzaldehyde was obtained in 89% yield after 2 h (Scheme 2).

In summary, a simple and efficient method has been developed by using a catalytic amount of $Lu(OTf)_3$ for protection of aldehydes as dithioacetals in the presence of a wide range of other protecting groups. Further, the catalyst can be readily recovered and reused, thus making the procedure environmentally friendly and acceptable.

EXPERIMENTAL

Most of the products are known compounds and were identified by their spectral data (¹H NMR) and physical properties compared with those of authentic samples. The progress of reaction was monitored by thin-layer chromatography (TLC) on silica gel. All yields refer to isolated products.

A Typical Procedure

To a stirred mixture of 4-methoxybenzaldehyde (680 mg, 5 mmol) and 1,2-ethanedithiol (564 mg, 6 mmol) in acetonitrile (30 mL) was added $Lu(OTf)_3$ (312 mg, 10 mol%) at room temperature. The resulting mixture was stirred for 1.5 h, then diluted with ethyl acetate (150 mL), washed with water (60 mL), dried (MgSO₄), and concentrated. The residue was chromatographed over silica gel, eluted 15% ethyl acetate in hexane to afford pure 2-(4-methoxyphenyl)-1,3-dithiolane. The aqueous layer containing the catalyst can

Lutetium Triflate as Catalyst

Product Characterization Data

(Compounds are Numbered as the Entries—Table 1)

Compound 1: Bp 157–159°C/3 torr; lit.^[20] 160°C/3 torr.

Compound 2: Bp 140–142°C/4 torr; lit.^[20] 140°C/4 torr.

Compound 3: Mp 117–118°C; lit.^[20] 119°C.

Compound 4: Mp 75–76°C, ¹H NMR (500 MHz, CDCl₃) δ 8.16 (*d*, J = 8.5 Hz, 2H), 7.67 (*d*, J = 8.5 Hz, 2H), 5.65 (*s*, 1H), 3.56–3.45 (*m*, 2H), 3.43–3.36 (*m*, 2H). MS m/z 228 (M + H)⁺ Anal. Calcd. for C₉H₉NO₂S₂: C, 47.56; H, 3.99; N, 6.16. Found: C, 47.52; H, 4.01; N, 6.14%.

Compound 5: Bp 110–111°C/5 torr; lit.^[20] 110°C/5 torr.

- **Compound 6**: Mp 86–87°C; ¹H NMR (500 MHz, CDCl₃) δ 7.48–7.30 (*m*, 7H), 6.90 (*d*, J = 8.5 Hz, 2H), 5.63 (*s*, 1H), 5.05 (*s*, 2H), 3.51–3.45 (*m*, 2H), 3.36–3.30 (*m*, 2H).
- **Compound 7**: Mp 65–66°C; lit.^[20] 67°C.
- **Compound 8**: Mp 148–150°C; lit.^[21] 149°C.
- Compound 9: Oil; lit.^[20] oil (identical NMR data).
- **Compound 10**: Mp 45–47°C; lit.^[22] 44°C.
- Compound 11: Bp 138–139°C/0.6 torr; lit.^[23] 140°C/0.6 torr.
- **Compound 12**: Mp 110–111°C, ¹H NMR (500 MHz, CDCl₃) δ 7.98 (*d*, J = 8 Hz, 2H), 7.57 (*d*, J = 8 Hz, 2H), 5.64 (*s*, 1H), 3.90 (*s*, 3H), 3.54–3.46 (*m*, 2H), 3.39–3.35 (*m*, 2H).
- **Compound 13**: Oil, ¹H NMR (500 MHz, CDCl₃) δ 7.44 (*d*, *J* = 8 Hz, 2H), 6.85 (*d*, *J* = 8.5 Hz, 2H). 6.10–5.90 (*m*, 1H), 5.63 (*s*, 1H), 5.41–5.26 (*m*, 2H), 4.52 (*d*, *J* = 4 Hz, 2H), 3.52–3.45 (*m*, 2H), 3.38–3.32 (*m*, 2H).

Compound 14: Bp 120–122°C/16 torr; lit.^[8] 125°C/16 torr.

Compound 15: Oil, ¹H NMR (500 MHz, CDCl₃) δ 7.38 (*d*, *J* = 8.5 Hz, 2H), 6.76 (*d*, *J* = 8.5 Hz, 2H), 5.62 (*s*, 1H), 3.52–3.40 (*m*, 2H), 3.35–

3.26 (*m*, 2H), 0.97 (*s*, 9H), 0.19 (*s*, 6H). MS m/z 313 (M + H)⁺ Anal. Calcd. for C₁₅H₂₄OS₂Si: C, 57.64; H, 7.74. Found: C, 57.66; H, 7.78%.

Compound 16: Bp 287°C/760 torr; lit.^[20] 289°C/760 torr.

Compound 17: Bp 64–66°C/3 torr; lit.^[20] 65°C/3 torr.

Compound 18: Bp 320°C/760 torr; lit.^[23] 322°C.

Compound 19: Mp 95–96°C, ¹H NMR (500 MHz, CDCl₃) δ 7.53 (*d*, J = 6.5 Hz, 2H), 7.03 (*d*, J = 6.5 Hz, 2H), 5.63 (*s*, 1H), 3.49–3.40 (*m*, 2H), 3.35–3.32 (*m*, 2H), 2.29 (*s*, 3H).

Compound 20: Bp 180°C/5 torr; lit.^[23] 188°C/5 torr.

Compound 21: Mp 61–62°C; lit.^[23] 61°C.

Compound 22: Mp 74–75°C; lit.^[20] 75°C.

Compound 23: Mp 114–115°C; lit.^[20] 115°C.

Compound 24: Bp 120°C/5 torr; lit.^[20] 125/5 torr.

Compound 25: Bp 150–152°C; lit.^[23] 150°C.

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