Neodymium triflate as a recyclable catalyst for chemoselective thioacetalisation

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Neodymium triflate has been found to be an efficient and recyclable catalyst for the chemoselective protection of aldehydes.

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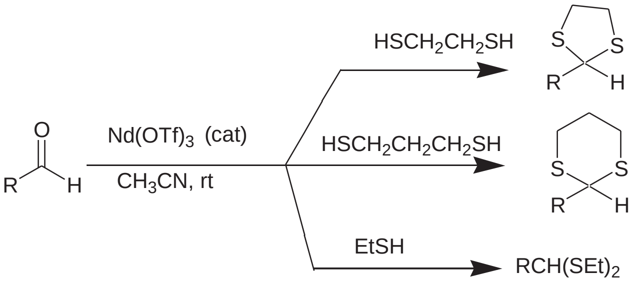
One of the most challenging problems during multistep syntheses is how to protect a carbonyl group from a specific nucleophilic attack until its electrophilic nature can be exploited. Among the different carbonyl protecting groups, 1,3-dithiolanes and 1,3-dithianes have long been used as protective groups[1] and acyl anion equivalents in carbon-carbon bond forming reactions.[2] There are many reports for the preparation of thioacetals from carbonyl compounds employing acid catalysts such as HCl,[3] $BF_3.OEt_2$,[4] PTSA,[5] $AlCl_3$,[6] $TiCl_4$,[7] TMSOTf,[8] i-Pr_3SiOTf,[9] and $InCl_3$.[10] Most recently, methods employing SO_2,[11] LiBr,[12] $LiBF_4$,[13] I_2,[14] $ZrCl_4$,[15] 5 M $LiClO_4$,[16] and $Sc(OTf)_3$[17] have been reported. However, many of these methods have some drawbacks such as low yields of the products, long reaction times,[15] harsh reaction condition, [3-5]difficulties in work-up,[6,7] the requirement for an inert atmosphere,[16] and the use of stoichiometric [4,11]or relatively expensive reagents.[8–10,15,16] Some of the methods mentioned above are incompatible with other protecting groups such as TBS ethers [4b,12b,13b,14b] and fail to protect deactivated aromatic aldehydes.[17] Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Interestingly, only a few of these methods have demonstrated the chemoselective protection of aldehydes in the presence of ketones. Therefore, the search continues for a better catalyst, one superior to the existing ones in terms of operational simplicity, reusability, economic viability, and greater selectivity.

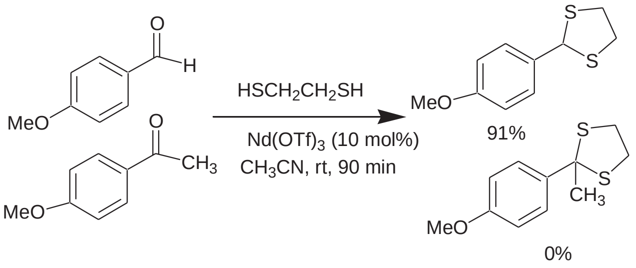
Recently, lanthanide triflates have been introduced as promising mild and selective reagents in organic synthesis.[18] The catalyst neodymium triflate is commercially available and can be used for the preparation of dithiolanes, dithianes, and diethyldithioactals from carbonyl compounds. While most conventional Lewis acids are decomposed in the presence of water, $Nd(OTf)_3$ is stable in water and does not decompose under aqueous work-up conditions. Thus, recyclisation is often possible. A catalytic amount of $Nd(OTf)_3$ is sufficient to obtain the desired compounds in excellent yield (Scheme 1).



Scheme 1

Thus, various aromatic, aliphatic, and heterocyclic aldehydes undergo the protection reactions using 1,2-ethanedithiol, 1, 3-propanedithiol, or ethanethiol to give the corresponding 1, 3-dithiolanes, 1,3-dithianes or ethyldithioacetals. Interestingly, the experimental procedure is very simple and does not need the use of dry solvents or an inert atmosphere. The results shown in the Table clearly indicate the scope and generality of the reaction with respect to different aromatic, aliphatic, and unsaturated aldehydes. Note that the conversion can be achieved in the presence of other protecting groups such as acetyl, benzyl, allyl, esters, and TBS ethers. Moreover, highly deactivated aromatic aldehydes can be protected as dithioacetals in good yields (entries 4, 11) with longer reaction times.

Note that the protocol can also be extended for chemoselective protection of an aldehyde in the presence of a ketone. For example, when an equimolar mixture of 4-methoxybenzaldehyde and 4-methoxyacetophenone was allowed to react with 1,2-ethanedithiol in the presence of catalytic amount of $Nd(OTf)_3$, only dithiolane derivative of 4-methoxybenzaldehyde was obtained (Scheme 2).



Scheme 2

In conclusion, I have demonstrated a very simple and convenient protocol for the protection of various aldehydes as dithioacetals in the presence of a wide range of other protecting groups by using a catalytic amount of $Nd(OTf)_3$. Further, the catalyst can be readily recovered and reused, thus making the procedure more environmentally acceptable.

Experimental

Most of the products are known compounds and were checked by comparison of their spectral data (^{1}H NMR) and physical properties (bp or mp) with an authentic sample. For entries 12, 13 and 19 the product 1H NMR was consistent with the proposed structures. For entry 20 characterisation is more tentative based on the other examples. Entries 4 and 15 give characterised novel confounds. The reaction was monitored by thin layer chromatography.

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 $Nd(OTf)_3$ (295 mg, 10 mol%) at room temperature. The resulting mixture was stirred for 1.5 h, then diluted with ethyl acetate (200 ml), washed with water (50 ml), dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel, eluted with 10% ethyl acetate in hexane to afford pure 2-(4-methoxyphenyl)-1,3-dithiolane. The aqueous layer containing the catalyst can be evaporated under reduced pressure to give a white solid which was reused for the next thioacetalisation reaction (Table 1).

Product characterisation data: (Compounds are numbered as the entries – Table 1)

1: b.p. 157–159 ˚C/3 torr; lit.[19] 160 ˚C/3 torr. **2**: b.p. 140–142 ˚C/4 torr; lit.[19]140 ˚C/4 torr. **3**: m.p. 117–118 ˚C; lit.[19] 119 ˚C. **4**: m.p. 75–76 ˚C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.5 Hz, 2 H), 7.67

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

Entry	Substrate	Reagent	Time/h	Yield ^{a}/%
1	Benzaldehyde	HSCH$_2$CH$_2$SH	2	82
2	4-Methoxybenzaldehyde	HSCH$_2$CH$_2$SH	1.5	91
3	4-Chlorobenzaldehyde	HSCH$_2$CH$_2$SH	2	84/78^b
4	4-Nitrobenzaldehyde	HSCH$_2$CH$_2$SH	8	74
5	Furfural	HSCH$_2$CH$_2$SH	1	82
6	4-Benzyloxybenzaldehyde	HSCH$_2$CH$_2$SH	1.5	82
7	Cinnamaldehyde	HSCH$_2$CH$_2$SH	1	82
8	2-Naphthaldehyde	HSCH$_2$CH$_2$SH	7	72
9	Thiophene 2-Carboxaldehyde	HSCH$_2$CH$_2$SH	2	83/80^b
10	Piperonal	HSCH$_2$CH$_2$SH	4	81
11	2-Methoxybenzaldehyde	HSCH$_2$CH$_2$SH	9	72
12	4-Carbomethoxybenzaldehyde	HSCH$_2$CH$_2$SH	2	82
13	4-Allyloxybenzaldehyde	HSCH$_2$CH$_2$SH	1.5	90
14	Hexaldehyde	HSCH$_2$CH$_2$SH	5	78
15	4-TBSO-benzaldehyde	HSCH$_2$CH$_2$SH	2	82
16	1-Octanal	HSCH$_2$CH$_2$SH	4	72
17	Butyraldehyde	HSCH$_2$CH$_2$SH	2	71
18	Decyl aldehyde	HSCH$_2$CH$_2$SH	2	70
19	4-Acetyloxybenzaldehyde	HSCH$_2$CH$_2$SH	3	82
20	4-Benzoyloxybenzaldehyde	HSCH$_2$CH$_2$SH	3	88
21	4-Bromobenzaldehyde	HSCH$_2$CH$_2$SH	2	84
22	Benzaldehyde	HSCH$_2$CH$_2$CH$_2$SH	2	82
23	4-Methoxybenzaldehyde	HSCH$_2$CH$_2$CH$_2$SH	2	90
24	4-Chlorobenzaldehyde	HSCH$_2$CH$_3$	4	77
25	2-Naphthaldehyde	HSCH$_2$CH$_3$	12	70

^{a}Yields refer to pure isolated products.
^{b}Isolated yields with reused catalyst

(d, *J* = 8.5 Hz, 2 H), 5.65 (s, 1 H), 3.56–3.45 (m, 2 H), 3.43–3.36 (m, 2 H). MS *m/z* 228 (M+H)$^+$ Anal. Calcd for C$_9$H$_9$NO$_2$S$_2$: C, 47.56; H, 3.99; N, 6.16. Found C, 47.52; H, 4.01; N, 6.14%. **5**: bp 110–111˚C/5 torr; lit.[19] 110 ˚C/5 torr. **6**: m.p. 86–87 ˚C; ^{1}H NMR (500 MHz, CDCl$_3$) δ7.48–7.30 (m, 7 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 5.63 (s, 1 H), 5.05 (s, 2 H), 3.51–3.45 (m, 2 H), 3.36–3.30 (m, 2 H). **7**: m.p. 65–66 ˚C; lit.[20] 67 ˚C. **8**: m.p. 148–150 ˚C; lit.[21] 149 ˚C. **9**: oil; lit.[19] oil (identical NMR data). **10**: m.p. 45–47 ˚C; lit.[22] 44 ˚C. **11**: b.p. 138–139 ˚C/0.6 torr; lit.[23] 140 ˚C/0.6 torr. **12**: m.p. 110–111 ˚C, ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, *J* = 8 Hz, 2 H), 7.57 (d, *J* = 8 Hz, 2 H), 5.64 (s, 1 H), 3.90 (s, 3 H), 3.54–3.46 (m, 2 H), 3.39–3.35 (m, 2 H). **13**: oil, ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 (d, *J* = 8 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 6.10–5.90 (m, 1 H), 5.63 (s, 1 H), 5.41–5.26 (m, 2 H), 4.52 (d, *J* = 4 Hz, 2 H), 3.52–3.45 (m, 2 H), 3.38–3.32 (m, 2 H). **14**: b.p. 120–122 ˚C/16 torr; lit.[6] 125 ˚C/16 torr. **15**: oil, ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38 (d, *J* = 8.5 Hz, 2 H), 6.76 (d, *J* = 8.5 Hz, 2 H), 5.62 (s, 1 H), 3.52–3.40 (m, 2 H), 3.35–3.26 (m, 2 H), 0.97 (s, 9 H), 0.19 (s, 6 H). MS *m/z* 313 (M+H)$^+$ Anal Calcd for C$_{15}$H$_{24}$OS$_2$Si: C, 57.64; H, 7.74. Found C 57.66, H 7.78% . **16**: b.p. 287 ˚C/760 torr; lit.[19] 289 ˚C/760 torr. **17**: b.p. 64–66 ˚C/ 3 torr; lit.[24] 65 ˚C/3 torr. **18**: b.p. 320 ˚C/760 torr; lit.[25] 322 ˚C. **19**: m.p. 95–96 ˚C, ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.53 (d, *J* = 6.5 Hz, 2 H), 7.03 (d, *J* = 6.5 Hz, 2 H), 5.63 (s, 1 H), 3.49–3.40 (m, 2 H), 3.35–3.32 (m, 2 H), 2.29 (s, 3 H). **20**: oil; lit.[26] oil. **21**: m.p. 61–62 ˚C; lit.[23] 61 ˚C. **22**: m.p. 74–75 ˚C; lit.[19] 75 ˚C. **23**: m.p. 114–115 ˚C; lit.[27] 115 ˚C. **24**: oil; lit.[19] oil (identical NMR data). **25**: oil; lit.[28] oil (identical NMR data)

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