$Pr(OTf)_3$ as an Efficient and Recyclable Catalyst for Chemoselective Thioacetalization of Aldehydes

Surya Kanta De*

Department of Chemistry, University of Washington, Seattle, WA 98195, USA
Fax +1(765)4941414; E-mail: skd125@yahoo.com

Received 13 May 2004; revised 5 August 2004

Abstract: Praseodymium triflate has been found to be an efficient and recyclable catalyst for chemoselective protection of aldehydes.

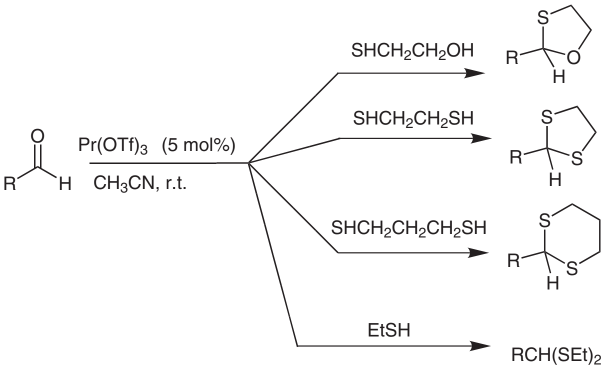
Key words: praseodymium triflate, aldehydes, 1,3-dithiolanes, 1,3-oxathiolanes, 1,3-dithianes, dithioacetals

The protection of carbonyl functionality as a dithioacetal[1] is important in the total synthesis of complex natural and non-natural products due to the group's inherent stability under both acidic and basic conditions. Among different carbonyl protecting groups, 1,3-dithianes, 1,3-oxathiolanes, 1,3-dithiolanes have long been used as protective groups, and an acyl anion equivalent in carbon-carbon bond forming reactions.[2] In the literature there is quite a plethora of procedures reported for the protection of carbonyl compounds as dithioacetals employing HCl,[3] $BF_3{\cdot}OEt_2$,[4] PTSA,[5] Bu_4NBr_3,[6] TMSOTf,[7] i-Pr_3SiOTf,[8] SO_2,[9] LiBr,[10] $LiBF_4$,[11] $InCl_3$,[12] $AlCl_3$,[13] $TiCl_4$,[14] 5 M $LiClO_4$,[15] $ZrCl_4$,[16] $Sc(OTf)_3$,[17] and I_2[18] as catalyst or as stoichiometric reagents. However, many of these methods have some drawbacks such as low yields of the products,[6] long reaction times,[16] harsh reaction conditions,[3–5] difficulties in work-up,[13,14] the requirement for an inert atmosphere,[15] and the use of stoichiometric[4,9] or relatively expensive reagents.[6–8,15,16] Interestingly, only a few of these methods have demonstrated chemoselective protection of aldehydes in the presence of ketones. Some of the methods mentioned above are incompatible with other protecting groups such as TBS ethers[4b,10b,11b,18b] and fail to protect deactivated aromatic aldehydes.[17] Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed[2–16,18] in the work-up procedure and cannot be recovered or reused. Therefore, there is still a need to search for a better catalyst that could be superior to the existing ones with regards to toxicity, handling, easy availability, economic viability, recyclability, greater selectivity, and operational simplicity.

Recently, there has been growing interest in the use of lanthanide triflates as potential Lewis acids in various organic reactions[19] because they are quite stable in water and are reusable. The catalyst praseodymium triflate [$Pr(OTf)_3$] is commercially available and can be used for preparation of oxathiolanes, dithiolanes, dithianes, and diethyldithioacetals from carbonyl compounds. While most conventional Lewis acids are decomposed or deactivated in the presence of water or protic solvent, $Pr(OTf)_3$ is stable in water and does not decompose under aqueous work-up conditions. Thus, recyclization is often possible. These unique properties of praseodymium triflate make this method eco-friendly, and environmentally acceptable.

In this letter, various types of aldehydes are reported to be rapidly converted to the corresponding cyclic or acyclic thioacetals under mild conditions in the presence of a catalytic amount of $Pr(OTf)_3$ at room temperature. Interestingly, the experimental procedure is very simple and does not require the use of anhydrous solvents or an inert atmosphere.

A catalytic amount of praseodymium triflate (5 mol%) is sufficient to obtain the desired carbonyl derivatives in excellent yields (Scheme 1). The method has the ability to tolerate a variety of other protecting groups such as benzyloxy, allyloxy, methoxy, ester, TBS ether. As shown in Table 1, various activated and deactivated aromatic aldehydes, heterocyclic aldehydes and aliphatic aldehydes undergo the protection reactions using 2-mercaptoethanol, 1,2-ethanedithol, 1,3-propanedithiol or ethanethiol in the presence of catalytic amount of $Pr(OTf)_3$ in MeCN at room temperature to afford the corresponding 1,3-oxathiolanes, 1,3-dithiolanes, 1,3-dithianes or diethyldithioacetals in good to excellent yields.



Scheme 1

It is interesting to note that ketones did not produce the corresponding thioacetals under the same reaction conditions. With this objective, a set of competitive protection reactions was conducted between aldehydes and ketones, the results of which are shown in Scheme 2. These results

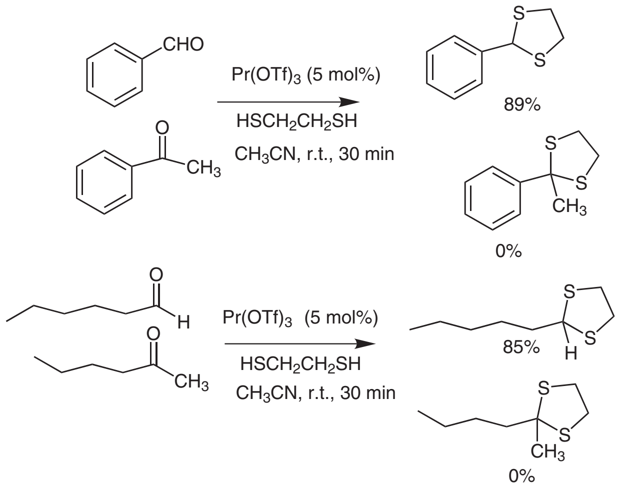
SYNTHESIS 2004, No. 17, pp 2837–2840
Advanced online publication: 07.10.2004
DOI: 10.1055/s-2004-834858; Art ID: M03504SS

indicate that the presented protocol is potentially applicable for the chemoselective protection of aldehydes to the corresponding dithioacetals in the presence of ketone functions in multi-functional compounds. The aldehyde functionality of a keto-aldehyde was protected chemoselectively under identical condition (Scheme 3).

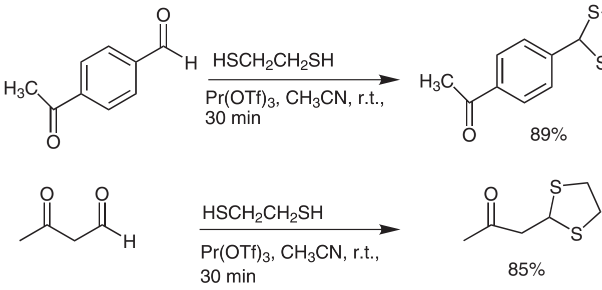
Most recently, I reported the thioacetalization of aldehydes using $ScCl_3$,[20] $CoCl_2$,[21] $Y(OTf)_3$[22] as catalysts and $RuCl_3$[23] as a catalyst for acetalization of alcohols. Metal halides such as $CoCl_2$, $ScCl_3$, $RuCl_3$ or other are generally decomposed during work-up and could not reused. Metal triflates are stable in water and do not decompose under aqueous work-up conditions. In this context, $Sc(OTf)_3$ and $Y(OTf)_3$ work well for thioacetalization of aldehydes. The catalyst $Sc(OTf)_3$ is five times more expensive than $Pr(OTf)_3$ and it did not work well with deactivated aromatic aldehydes.[17] The reused catalytic activity of $Pr(OTf)_3$ is better than that of $Y(OTf)_3$ and is identical to that of $Sc(OTf)_3$. The activity of recovered catalyst, $Y(OTf)_3$, decreases after two runs whereas $Pr(OTf)_3$ can be used five times without any loss of catalytic activity (Table 2). These results indicate that $Pr(OTf)_3$ is superior to the other metal triflates with regards to recyclability and economic viability.

In conclusion, a very simple and convenient protocol for the protection of various aldehydes as dithioacetals using a catalytic amount of praseodymium triflate has been demonstrated. Further, the catalyst can be readily recovered and reused, thus making this method eco-friendly and environmentally acceptable. Moreover, highly deactivated aromatic aldehydes can be converted to the corresponding dithioacetals without any difficulty. A high degree of chemoselectivity, high product yields, and reusability are the main advantages of this new method, which will make it a useful and important addition to the present methodologies.

^1H NMR spectra were recorded on a Bruker 500 MHz spectrometer in $CDCl_3$ as the solvent and TMS as internal standard. Mass spectra were recorded with a Bruker ion trap spectrometer. All products are known and were determined using comparison of their physical and spectral data with those reported in the literature (see refs[20,24–29]).



Scheme 2



Scheme 3

2-(4-Methoxyphenyl)-1,3-dithiane; Typical Procedure

To a stirred mixture of 4-methoxybenzaldehyde (681 mg, 5 mmol) and 1,3-propanedithiol (649 mg, 6 mmol) in MeCN (25 mL) was added $Pr(OTf)_3$ (146 mg, 5 mol%) at r.t. The resulting mixture was stirred at r.t. for 30 min, then diluted with EtOAc (150 mL), washed with water (60 mL), dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel, eluted with 10% EtOAc in hexane to afford pure 2-(4-methoxyphenyl)-1,3-dithiane. The aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid. The IR spectrum of the recovered catalyst was identical to that of the commercially available catalyst (Aldrich), which could be reused for the next thioacetalization reaction, without losing any significant activity (Table 2, entries 2, 3, and 17).

Table 1 $Pr(OTf)_3$ Catalyzed Protection of Aldehydes as Dithianes, Dithiolanes, Oxathiolanes or Diethyldithioacetals at Room Temperature

Entry	Catalysts	1st,a	2nd	3rd	4th	5th	Average
1	$Pr(OTf)_3$	89	87	90	88	93	89.4
2	$Y(OTf)_3$	90	84	70	65	60	73.8
3	$Sc(OTf)_3$	92	87	92	82	91	88.8
4	$CoCl_2$	90	52	–	–	–	28.4
5	$ScCl_3$	86	50	–	–	–	27.2

[a] Isolated yield (for first run only), and conversion of starting material (for other runs, based on ^1H NMR).

Table 2 The Thioacetalization of Benzaldehyde with 1,3-Dithiolane in the Presence of Catalysts and Recycled Catalysts

Entry	Substrate	Reagent	Time (h)	Yield[a] (%)
1	Benzaldehyde	$HSCH_2CH_2CH_2SH$	0.5	89
2	4-Methoxybenzaldehyde	$HSCH_2CH_2CH_2SH$	0.5	91/85[b]
3	4-Chlorobenzaldehyde	$HSCH_2CH_2CH_2SH$	1	89/86[b]
4	4-Nitrobenzaldehyde	$HSCH_2CH_2CH_2SH$	3	84
5	Furfural	$HSCH_2CH_2CH_2SH$	1	86
6	4-Benzyloxybenzaldehyde	$HSCH_2CH_2SH$	1	88
7	Cinnamaldehyde	$HSCH_2CH_2SH$	0.5	87
8	Thiophene-2-carboxaldehyde	$HSCH_2CH_2SH$	1	91
9	4-Hydroxybenzaldehyde	$HSCH_2CH_2SH$	5	78
10	Butyraldehyde	$HSCH_2CH_2SH$	1	82
11	4-Allyloxybenzaldehyde	$HSCH_2CH_2SH$	1	83
12	Hexaldehyde	$HSCH_2CH_2SH$	0.5	85
13	4-TBSO-benzaldehyde	$HSCH_2CH_2SH$	1	83
14	4-Carbomethoxybenzaldehyde	$HSCH_2CH_2SH$	1	91
15	4-Methylbenzaldehyde	$HSCH_2CH_2SH$	1	92
16	4-Nitrobenzaldehyde	$HSCH_2CH_2SH$	4	80
17	Benzaldehyde	$HSCH_2CH_2SH$	0.5	89/82[b]
18	4-Methoxybenzaldehyde	$HSCH_2CH_2SH$	1	93
19	4-Bromobenzaldehyde	$HSCH_2CH_2SH$	1	89
20	Decylaldehyde	$HSCH_2CH_2SH$	1	80
21	Benzaldehyde	$HSCH_2CH_2OH$	2	79
22	4-Methoxybenzaldehyde	$HSCH_2CH_2OH$	2	81
23	Hexaldehyde	$HSCH_2CH_2OH$	3	79
24	Benzaldehyde	CH_3CH_2SH	6	89
25	4-Chlorobenzaldehyde	CH_3CH_2SH	5	91
26	4-Methoxybenzaldehyde	CH_3CH_2SH	5	85
27	Butyraldehyde	CH_3CH_2SH	6	79

[a] Yields refer to pure isolated products, characterized by IR, ^{1}H NMR and MS.

[b] Isolated yields with the reused catalyst.

References

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3 rd ed.; John Wiley and Sons: New York, **1999**, 329–344.

(2) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639.
(b) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357.
(c) Bulman Page, P. C.; Van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643. (d) Pettit, G. R.; Van Tamelen, E. E. *Org. React.* **1962**, *12*, 356.

(3) Ralls, J. W.; Dobson, R. M.; Reigel, B. *J. Am. Chem. Soc.* **1949**, *71*, 3320.

(4) (a) Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945.
(b) Nakata, T.; Nagao, S.; Mori, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6461.

(5) Djerassi, C.; Gorman, M. *J. Am. Chem. Soc.* **1953**, *75*, 3704.

(6) Mondal, E.; Sahu, P. R.; Bose, G.; Khan, T. *Tetrahedron Lett.* **2002**, *43*, 2843.

(7) Ravindranathan, T.; Chavan, S. P.; Dante, S. W. *Tetrahedron Lett.* **1995**, *36*, 2285.

(8) Streinz, L.; Koutek, B.; Saman, D. *Collect. Czech. Chem. Commun.* **1977**, *62*, 665.

(9) Burezyk, B.; Kortylewicz, Z. *Synthesis* **1982**, 831.

(10) (a) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58. (b) Tandon, M.; Begley, T. P. *Synth. Commun.* **1997**, *27*, 2953.

(11) (a) Jadav, J. S.; Reddy, B. S.; Pandey, S. K. *Synlett* **2001**, 238. (b) Metcalf, B. W.; Burkhart, J. P.; Jund, K. *Tetrahedron Lett.* **1980**, *21*, 35.

(12) Madhuswamy, S.; Arulananda Babu, S.; Gunanathan, C. *Tetrahedron Lett.* **2001**, *42*, 359.

(13) Ong, B. S. *Tetrahedron Lett.* **1980**, *21*, 4225.

(14) Kumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, *24*, 1289.

(15) Saraswathy, V. G.; Geetha, V.; Sankaranan, S. *J. Org. Chem.* **1994**, *52*, 4665.

(16) Karimi, B.; Seradj, H. *Synlett* **2000**, 805.

(17) Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2002**, *43*, 1347.

(18) (a) Samajdar, S.; Basu, M. K.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2001**, *42*, 4425. (b) Vaino, A. R.; Szarek, W. A. *J. Chem. Soc., Chem. Commun.* **1996**, 2351.

(19) (a) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15. (b) Kobayashi, S. *Synlett* **1994**, 689. (c) Kobayashi, S.; Tomaaki, H.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165. (d) Hamada, T.; Manabe, K.; Nagayama, S.; Shiro, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989.

(20) De, S. K. *Synthesis* **2004**, 828.

(21) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 1035.

(22) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 2339.

(23) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 2919.

(24) Robbe, Y.; Fernandez, J. P.; Dubiel, R.; Chapat, J. P.; Senteac, H.; Fatome, M.; Denis, J. *Eur. J. Med. Chem.* **1982**, *17*, 235.

(25) Prabhat, A.; Samson, C.; Lesage, M.; Goiller, D. *J. Org. Chem.* **1990**, *55*, 648.

(26) Kamitori, Y.; Hojo, M.; Mashuda, R.; Kimura, T.; Yoshida, T. *J. Org. Chem.* **1986**, *51*, 1427.

(27) Toshikazu, H.; Ohshiro, S.; Agawa, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1569.

(28) Degani, S.; Regondi, R. *Synthesis* **1981**, 51.

(29) Gonnella, N. C.; Lakshmikantham, M. V.; Cava, M. P. *Synth. Commun.* **1997**, *9*, 17.