

Vanadyl triflate as an efficient and recyclable catalyst for chemoselective thioacetalization of aldehydes

Surya Kanta De*

*Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy,
Purdue Cancer Center, Purdue University, West Lafayette, IN 47907, USA*

Received 31 July 2004; received in revised form 26 September 2004; accepted 27 September 2004

Abstract

Vanadyl triflate has been found to be an efficient and recyclable catalyst for chemoselective protection of aldehydes. Some of the major advantages of this method are high chemoselectivity, ease of operation, short reaction times, high yields, and compatibility with protecting groups.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Vanadyl triflate; Aldehydes; 1,3-Dithiane; 1,3-Dithiolane; Recyclability

1. Introduction

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 the different carbonyl protecting groups, 1,3-dithianes, 1,3-oxathiolanes, 1,3-dithiolanes have long been used as protective groups, and as an acyl anion equivalent in carbon–carbon bond forming reactions [2]. They are generally obtained by protic acid or Lewis acid catalyzed condensation of carbonyl compounds with thiols or dithiols [1]. In the literature there is quite a plethora of procedures reported for the protection of carbonyl compounds as dithioacetals employing HCl [3], BF₃·OEt₂ [4], PTSA [5], SO₂ [6], LiBr [7], LiBF₄ [8], InCl₃ [9], Bu₄NBr₃ [10], I₂ [11], 5 M LiClO₄ [12], TiCl₄ [13], Sc(OTf)₃ [14], ZrCl₄ [15], TMSOTf [16], as catalysts or as stoichiometric reagents. However, many of these methods have some drawbacks such as low yields of the products [10] long reaction times [15], harsh reaction conditions [3–5], difficulties in work-up [13], the requirement for an

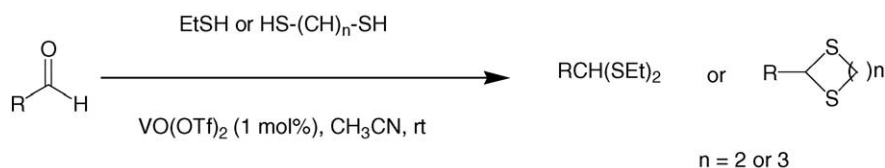
inert atmosphere [12], and use of stoichiometric reagents [4,6]. Some of methods mentioned above are incompatible with other protecting groups and fail to protect deactivated aromatic substrates [14]. Interestingly, only a few of these methods have demonstrated chemoselective protection of aldehydes in the presence of ketones [9,13–15]. 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. Therefore, there is further scope to explore mild and efficient methods for thioacetalization of carbonyl compounds.

2. Results and discussion

Recently, there has been considerable interest growing in the use of vanadyl triflate as a potential Lewis acid in various organic reactions because the catalyst is quite stable in water and reusable [17]. The catalyst vanadyl triflate is readily prepared using a reported method [18] and can be used for the preparation of dithiolanes, dithianes, and diethyldithioacetals from carbonyl compounds. While most conventional Lewis acids decompose in the presence of water, VO(OTf)₂ is stable in water and does not decompose under aqueous work-up.

* Tel.: +1 765 743 9702; fax: +1 765 494 1414.

E-mail address: skd125@pharmacy.purdue.edu.



Scheme 1.

Table 1

VO(OTf)₂ catalyzed protection of aldehydes as dithiolanes, dithianes or ethyldithioacetals at room temperature

Entry	Substrate	Reagent	Time (min)	Yield ^a (%)
1	Benzaldehyde	HSCH ₂ CH ₂ CH ₂ SH	15	93
2	4-Methoxybenzaldehyde	HSCH ₂ CH ₂ CH ₂ SH	20	90
3	Benzaldehyde	HSCH ₂ CH ₂ SH	20	95
4	4-Methoxybenzaldehyde	HSCH ₂ CH ₂ SH	20	92
5	4-Chlorobenzaldehyde	HSCH ₂ CH ₂ SH	2	91/84 ^b
6	4-Nitrobenzaldehyde	HSCH ₂ CH ₂ SH	45	79
7	Furfural	HSCH ₂ CH ₂ SH	15	88
8	4-Benzyloxybenzaldehyde	HSCH ₂ CH ₂ SH	30	86
9	Cinnamaldehyde	HSCH ₂ CH ₂ SH	20	83
10	2-Naphthaldehyde	HSCH ₂ CH ₂ SH	35	76
11	Thiophene 2-carboxaldehyde	HSCH ₂ CH ₂ SH	20	90/86 ^b
12	Piperonal	HSCH ₂ CH ₂ SH	30	87
13	2-Methoxybenzaldehyde	HSCH ₂ CH ₂ SH	30	79
14	4-Carbomethoxybenzaldehyde	HSCH ₂ CH ₂ SH	35	82
15	4-Allyloxybenzaldehyde	HSCH ₂ CH ₂ SH	30	92
16	Hexaldehyde	HSCH ₂ CH ₂ SH	40	77
17	1-Octanal	HSCH ₂ CH ₂ SH	45	76
18	Butyraldehyde	HSCH ₂ CH ₂ SH	35	72
19	Decyl aldehyde	HSCH ₂ CH ₂ SH	40	78
20	4-Acetyloxybenzaldehyde	HSCH ₂ CH ₂ SH	30	85
21	4-Benzoyloxybenzaldehyde	HSCH ₂ CH ₂ SH	40	87
22	4-Bromobenzaldehyde	HSCH ₂ CH ₂ SH	15	94
23	4-Chlorobenzaldehyde	EtSH	40	79
24	Benzaldehyde	EtSH	40	85

^a Yields refer to pure isolated products.

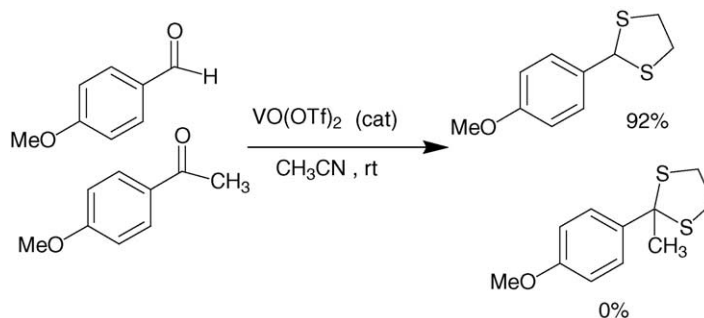
^b Isolated yields with reused catalyst.

Thus, recyclization is often possible (four times used without significant loss of activity). A catalytic amount (1 mol%) of VO(OTf)₂ is sufficient to get the desired compounds in excellent yield (Scheme 1). Thus, various aromatic, aliphatic,

and heterocyclic aldehydes undergo the protection reaction using 1,2-ethanedithiol, 1,3-propanedithiol 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 Table 1, clearly indicate the scope and generality of the reaction with respect to various aromatic, aliphatic, and unsaturated aldehydes. It is noteworthy that the conversion can be achieved in the presence of other protecting groups such as acetyl, benzyl, allyl, and esters. Furthermore, highly deactivated aromatic aldehydes can be protected as dithioacetals in good yields.

It is noteworthy that the method can also 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 reaction with 1,2-ethanedithiol in the presence of a catalytic amount VO(OTf)₂, only the dithiolane derivative of 4-methoxybenzaldehyde was obtained (Scheme 2).

For a successful vanadyl triflate-catalyzed thioacetalization reaction, one would expect generation of triflic acid in the reaction medium. In order to neutralize the triflic acid, a reaction in the presence of 2,6-di-*tert*-butylpyridine (a highly hindered organic base which does not interact with the metal catalyst) resulted a low yield (10%) of product. This result indicates the formation of triflic acid, which is actual catalyst for the thioacetalization. However, a reaction in the presence of triflic acid gave in low yield of the product. It is well known that acetalizations and deacetalizations are reversible reactions. Precise control of the acidity in a small-scale reaction with corrosive triflic acid or any other strong acid is extremely difficult. Considering the reversible nature of these processes, this low yield with strong acid is expected.



Scheme 2.

3. Conclusion

In conclusion, a simple and efficient method has been developed for thioacetalization of aldehydes in the presence of a wide range of other protecting groups using a catalytic amount of VO(OTf)₂. Further, the catalyst can be readily recovered and reused, thus making the procedure more environmentally acceptable. The method has advantages in terms of high yields of products, short reaction times, operational simplicity, and chemoselectivity.

4. Experimental

All of the products are known compounds and were identified of their spectral data (¹H NMR) and physical properties with those of authentic samples [2–20]. The progress of reaction was monitored by thin layer chromatography on silica gel. All yields refer to isolated products. Unless otherwise indicated, all anhydrous solvents were commercially obtained and stored in sure-seal bottles under nitrogen. All other reagents and solvents were purchased as the highest grade available and used without further purification.

4.1. Preparation of vanadyl triflate, VO(OTf)₂

To a solution of vanadyl sulfate trihydrate (172 mg, 1.05 mmol) in methanol (2 mL) was added barium triflate (436 mg, 1 mmol) at ambient temperature. The reaction mixture was stirred for 1 h, the barium sulfate precipitate was then removed by filtration over a short pad of celite. The filtrate was concentrated and dried at 110 °C to give vanadyl triflate (81%) as faint blue solid, which was used directly for the thioacetalization reactions

4.2. A typical procedure for thioacetalization of aldehyde

To a stirred mixture of 4-methoxybenzaldehyde (680 mg, 5 mmol) and 1,2-ethanedithiol (564 mg, 6 mmol) in dry acetonitrile (10 mL) was added VO(OTf)₂ (18 mg, 1 mol%) at room temperature under argon atmosphere. The resulting mixture was stirred for 20 min, then diluted with ethyl acetate (50 mL), washed with water (20 mL), dried (MgSO₄) and concentrated. The residue was chromatographed over silica gel and eluting with 15% 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 (40 °C, 30 mmHg pressure) to give a white solid, which reused for the next thioacetalization reaction (Table 1).

4.3. A typical procedure for chemoselective protection of aldehyde in the presence of ketones

To a stirred mixture of 4-methoxybenzaldehyde (1 mmol), 4-methoxyacetophenone (1 mmol), 1,2-ethanedithiol (2.2 mmol) in dry acetonitrile (4 mL) was added vanadyl triflate (1 mol%) at room temperature under argon atmosphere. The resulting mixture was stirred for 20 min then diluted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL), dried (MgSO₄), and concentrated. The ¹H NMR of crude mixture indicates the primarily the dithiolane derivative of 4-methoxybenzaldehyde. Finally, the crude product was purified over silica gel column (15% ethyl acetate in hexane).

References

- [1] T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, third ed., Wiley, New York, 1999, p. 329.
- [2] (a) D. Seebach, Angew. Chem., Int. Ed. Engl. 8 (1969) 639; (b) B.T. Grobel, D. Seebach, Synthesis (1977) 357; (c) P.C. Bulman Page, M.B. Van Niel, J.C. Proddger, Tetrahedron 45 (1989) 7643; (d) G.R. Pettit, E.E. Van Tamelen, Org. Recat. 12 (1962) 356.
- [3] J.W. Ralls, R.M. Dobson, B. Reigel, J. Am. Chem. Soc. 71 (1949) 3320.
- [4] (a) L.F. Fieser, J. Am. Chem. Soc. 76 (1954) 1954; (b) T. Nakata, S. Nagao, S. Mori, T. Oishi, Tetrahedron Lett. 26 (1985) 6461.
- [5] C. Djerassi, M. Gorman, J. Am. Chem. Soc. 75 (1953) 3704.
- [6] B. Burezyk, Z. Kortylewicz, Synthesis (1982) 831.
- [7] H. Firouzabadi, N. Iranpoor, B. Karimi, Synthesis (1999) 58.
- [8] J.S. Jadav, B.S. Reddy, S.K. Pandey, Synth. Lett. (2001) 238.
- [9] S. Madhuswamy, S. Arulananda Babu, C. Gunanathan, Tetrahedron Lett. 42 (2001) 359.
- [10] E. Mondal, P.R. Sahu, G. Bose, A.T. Khan, Tetrahedron Lett. 43 (2002) 2843.
- [11] S. Samajdar, M.K. Basu, F.F. Becker, B. Banik, Tetrahedron Lett. 42 (2001) 4425.
- [12] V.G. Saraswathy, V. Geetha, S. Sankaranan, J. Org. Chem. 39 (1994) 4665.
- [13] B.S. Ong, Tetrahedron Lett. 21 (1980) 4225.
- [14] A. Kamal, G. Chouhan, Tetrahedron Lett. 43 (2002) 1347.
- [15] B. Karimi, H. Seradj, Synlett (2000) 805.
- [16] T. Ravindranathan, S.P. Chavan, S.W. Dante, Tetrahedron Lett. 36 (1995) 2285.
- [17] For a general review on V(IV), see: T. Hirao, Chem. Rev. 97 (1997) 2707.
- [18] For catalyst preparation, see: C.T. Chen, J.H. Kuo, C.H. Li, N.B. Barhate, S. Hon, T.W. Li, S.D. Chao, C.C. Liu, Y.C. Li, I.H. Chang, J.S. Lin, C.J. Liu, Y.C. Chou, Org. Lett. 3 (2001) 3729. Also available from Bestgen Bio Tech, Taiwan.
- [19] S.K. De, Synthesis (2004) 828.
- [20] Y. Kamitori, M. Hojo, R. Masuda, T. Kimura, T. Yoshida, J. Org. Chem. 51 (1986) 1427.