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# $CeCl_3·7H_2O$-Promoted highly chemoselective hydrolysis of 1,3-oxathio- and dithioacetals

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**Abstract**—A highly selective hydrolysis of the 1,3-oxathio- and 1,3-dithioacetals has been achieved in high yields using $CeCl_3·7H_2O$–NaI in acetonitrile at reflux temperature under neutral conditions. This method is mild and compatible with a wide range of functional groups such as TBDPS, THP, PMB, MOM, allyl, propargyl, prenyl, benzyl ethers, carbamates and acetate, etc., present in the substrate. © 2002 Elsevier Science Ltd. All rights reserved.

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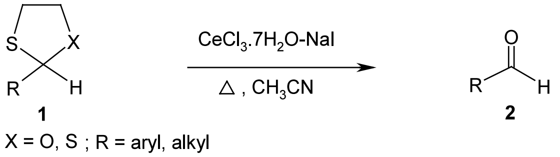
Protection and deprotection of carbonyl groups remain crucial challenges to organic chemists.[1] Among the carbonyl protecting groups, 1,3-oxathio- and dithioacetals are versatile[2] due to their ease of installation and also to their stability under basic or mildly acidic conditions. In addition to carbonyl protection, they are very useful as masked acyl anions[3] or masked methylene functions in carbon–carbon bond forming reactions.[4] However, the final stage of the chemical process frequently requires their cleavage so as to regenerate the parent carbonyl compounds. In consequence, a variety of procedures have been developed for the cleavage of 1,3-oxathio- and dithioacetals under both hydrolytic[5,6] and oxidative conditions.[7,8] Many of these methods require strongly acidic or oxidizing conditions that limit their efficiency. Furthermore, most of these methods often involve the use of corrosive or toxic reagents[9] such as mercury salts and other heavy metal salts, harsh conditions, incompatibility with other functional groups thus limiting their usage in a synthetic sequence of reactions especially on large scale. Therefore, there is a need to develop a mild and high yielding protocol for the chemoselective hydrolysis of dithio- and oxathioacetals under neutral conditions.

Lanthanide halides are unique Lewis acids[10] that are currently of great research interest. Among these catalysts, cerium halides[11] are relatively non-toxic, readily available at low cost and are fairly stable to water. In addition, the combination of cerium trichloride heptahydrate and sodium iodide has been successfully employed for the deprotection of various protecting groups such as *t*-butyl esters, dioxolanes, trialkylsilyl ethers, PMB ethers, trityl ethers, prenyl esters, and alkyl aryl ethers.[12]

We wish to report that cerium(III) chloride–NaI is an efficient reagent system for the selective hydrolysis of 1,3-oxathio- and dithioacetals under neutral conditions (Scheme 1).

The cleavage was effected using an equimolar ratio of $CeCl_3·7H_2O$–NaI in acetonitrile at reflux temperature. The deprotection proceeded efficiently in high yields with high chemoselectivity. The combination of cerium(III) chloride with NaI selectively cleaved an oxathioacetal group leaving other functional groups including olefins, ethers and esters, intact. This method is highly chemoselective allowing deprotection of oxathio- and dithioacetal groups without affecting other hydroxyl protecting groups such as *p*-methoxybenzyl, prenyl, allyl, propargyl ethers and methoxymethyl ethers. The major advantage of this cleavage is in the selective hydrolysis of the thioacetal moiety in the presence of highly acid sensitive THP and TBDPS ethers, which do not survive either with NBS



**Scheme 1.**

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*Keywords*: cerium reagents; dithioacetals; oxathioacetals; carbonyl compounds.

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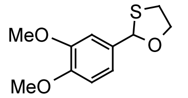
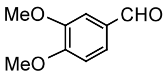
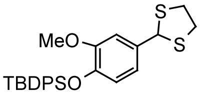
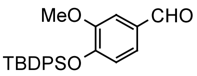
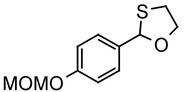
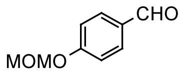
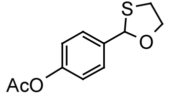
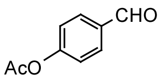
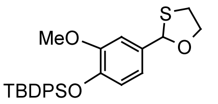
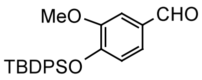
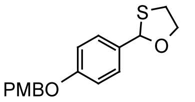
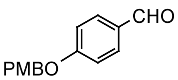
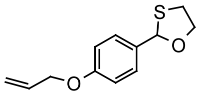
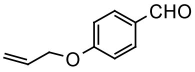
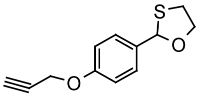
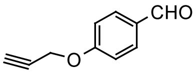
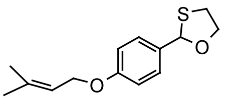
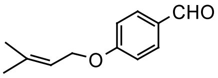
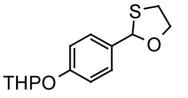
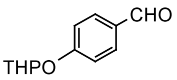
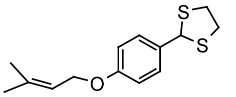
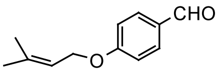
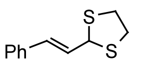
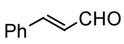
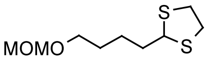
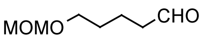
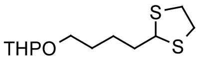
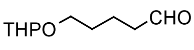
or TMSOTf. In terms of selectivity and efficiency, this procedure is superior to reported methods where oxidants as well as strong acids are used. Due to the mild reaction conditions, a number of functional groups, albeit being capable of reacting with $CeCl_3 \cdot 7H_2O$, remain intact. In addition, this method does not require the use of expensive reagents or anhydrous solvents and no precautions need to be taken to exclude moisture from the reaction system. Thus, the present method is efficient and mild enough to tolerate a wide range of

**Table 1.** Selective hydrolysis of 1,3 oxathio- and thioacetals by $CeCl_3 \cdot 7H_2O$–NaI

| Entry | Thioacetal **1** | Aldehyde[a] **2** | Reaction time (h) | Yield[b] (%) |
|---|---|---|---|---|
| a |  |  | 3.0 | 90 |
| b |  |  | 5.0 | 83 |
| c |  |  | 4.0 | 88 |
| d |  |  | 3.5 | 85 |
| e |  |  | 3.0 | 82 |
| f |  |  | 3.0 | 87 |
| g |  |  | 3.5 | 90 |
| h |  |  | 4.0 | 92 |
| i |  |  | 3.0 | 85 |
| j |  |  | 3.5 | 81 |
| k |  |  | 3.0 | 90 |
| l |  |  | 3.5 | 93 |
| m |  |  | 4.5 | 85 |
| n |  |  | 3.5 | 88 |

[a] All products were characterized by $^1H$ NMR, IR and mass spectroscopy.

[b] Isolated and unoptimized yields

functional groups. As is evident from Table 1 the acid sensitive protecting groups are compatible with $CeCl_3 \cdot 7H_2O$–NaI in acetonitrile at ambient temperature. The cleavage proceeds smoothly and rapidly in commercial grade acetonitrile containing 1.5% of water which promotes the hydrolysis of thioacetals. Finally, we have examined the possibility of $CeCl_3 \cdot 7H_2O$ functioning catalytically or at least, in less than stoichiometric amounts. However, the best results were obtained using an equimolar ratio of $CeCl_3 \cdot 7H_2O$–NaI. In the absence of NaI, the deprotection by $CeCl_3$ alone in acetonitrile at ambient temperature took longer to achieve complete conversion. This clearly indicates that the addition of 1 equiv. of NaI is crucial in the deprotection to obtain high yields of products.[13]

In summary, this paper describes a method for the selective hydrolysis of 1,3-oxathio- and dithioacetals using a cheap and readily available reagent system that operates under neutral conditions thereby leaving acid- and base-labile protecting groups intact. The high levels of chemoselectivity in this process combined with the simple methodology, high yields and ready availability of reagents will facilitate a wider use of oxathio- and dithioacetal protecting groups in organic synthesis.

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## References

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.
2. (a) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943; (b) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097; (c) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075.
3. (a) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937; (b) Seebach, D. *Synthesis* **1969**, 17; (c) Bulman-Page, P. C.; Van-Niel, M. B.; Prodger, J. *Tetrahedron* **1989**, *45*, 7643.
4. Pettit, G. W.; Van Tamelen, E. E. *Org. React.* **1962**, *12*, 356.
5. (a) Oishi, T.; Kamemoto, K.; Ban, Y. *Tetrahedron Lett.* **1972**, *12*, 1085; (b) Hirano, M.; Ukawa, K.; Yakabe, S.; Clark, J. H.; Morimoto, T. *Synthesis* **1997**, 858; (c) Schmittel, M.; Levis, M. *Synlett* **1996**, 315.
6. (a) Ravindranathan, T.; Chavan, S. P.; Dantale, S. W. *Tetrahedron Lett.* **1995**, *36*, 2285; (b) Chavan, S. P.; Soni, P.; Kamat, S. K. *Synlett* **2001**, 1251.
7. (a) Fuji, K.; Ichikawa, K.; Fujitha, E. *Tetrahedron Lett.* **1978**, *18*, 3561; (b) Emerson, D. W.; Winberg, H. *Tetrahedron Lett.* **1971**, *11*, 3445; (c) Mehta, G.; Uma, R. *Tetrahedron Lett.* **1996**, *37*, 1897; (d) Karimi, B.; Seradj, H.; Tabae, M. H. *Synlett* **2000**, 1798.
8. (a) Mandai, T.; Takeshita, M.; Kawada, M.; Otera, J. *Chem. Lett.* **1984**, 1259; (b) Nishide, K.; Yokota, K.; Nakamura, D.; Sumiya, T.; Node, M. *Tetrahedron Lett.* **1993**, *34*, 3425.
9. (a) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553; (b) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366; (c) Ho, T. L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791.
10. (a) Kobayashi, S. *Synlett* **1994**, 689; (b) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15.
11. (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209; (b) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Cappa, A.; Marcantoni, E.; Sambri, L.; Orregiani, E. *J. Org. Chem.* **1999**, *64*, 5696; (c) Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183.
12. (a) Marcantoni, E.; Massaccesi, M.; Torregiani, E.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2001**, *66*, 4430; (b) Yadav, J. S.; Reddy, B. V. S. *Synlett* **2000**, 1275; (c) Yadav, J. S.; Reddy, B. V. S.; Madan, Ch.; Riaz Hashim, S. *Chem. Lett.* **2000**, 738; (d) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Chand, P. K.; Prasad, A. R. *Synlett* **2002**, 137.
13. **Experimental procedure**: A mixture of oxathio- or dithioacetal (5 mmol), $CeCl_3 \cdot 7H_2O$ (5 mmol) and sodium iodide (5 mmol) in acetonitrile (10 mL) was stirred at reflux temperature for an appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo, and the resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the parent carbonyl compound. Spectroscopic data **1e**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.18 (s, 9H), 3.20 (m, 2H), 3.60 (s, 3H), 3. 85 (m, 1H), 4.45 (m, 1H), 5.85 (s, 1H), 6.60 (d, 1H, $J=8.0$ Hz), 6.78 (dd, 1H, $J=2.7$, 8.0 Hz), 6.90 (d, 1H, $J=2.7$ Hz), 7.28–7.42 (m, 6H), 7.65–7.78 (m, 4H). **2e**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.18 (s, 9H), 3.60 (s, 3H), 6.60 (d, 1H, $J=8.0$ Hz), 7.18 (dd, 1H, $J=2.7$, 8.0 Hz), 7.24 (d, 1H, $J=2.7$ Hz), 7.30–7.41 (m, 6H), 7.65–7.78 (m, 4H), 9.78 (s, 1H). **1k**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.75 (s, 3H), 1.80 (s, 3H), 3.30 (m, 2H), 3.50 (m, 2H), 4.45 (dd, 2H, $J=1.8$, 10.3 Hz), 5.45 (m, 1H), 5.60 (s, 1H), 6.80 (d, 2H, $J=8.0$ Hz), 7.40 (d, 2H, $J=8.0$ Hz). **2k**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.75 (s, 3H), 1.80 (s, 3H), 4.45 (dd, 2H, $J=1.8$, 10.3 Hz), 5.45 (m, 1H), 6.90 (d, 2H, $J=8.0$ Hz), 7.80 (d, 2H, $J=8.0$ Hz), 9.85 (s, 1H).