J. Braz. Chem. Soc., Vol. 21, No. 2, 371-374, 2010.
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0103 - 5053 $6.00+0.00

Short Report

The Use of Anhydrous $CeCl_3$ as a Recyclable and Selective Catalyst for the Acetalization of Aldehydes and Ketones

Claudio C. Silveira,*[a] Samuel R. Mendes,[a] Francieli I. Ziembowicz,[a] Eder J. Lenardão[b] and Gelson Perin[b]

[a]*Departamento de Química, Universidade Federal de Santa Maria, CP 5001, 97105-970 Santa Maria-RS, Brazil*

[b]*Instituto de Química e Geociências, LASOL, Universidade Federal de Pelotas, CP 354, 96010-900 Pelotas-RS, Brazil*

Um método eficiente, limpo, quimiosseletivo e sem a utilização de solventes para a síntese de dimetil acetais de aldeídos e cetonas foi desenvolvido usando ortoformiato de trimetila e $CeCl_3$ anidro como catalisador. O método é geral e, sob condições reacionais brandas, fornece compostos carbonílicos protegidos em bons rendimentos, incluindo aril e alquil cetonas e aldeídos. O catalisador pode ser reutilizado diretamente, três vezes, sem perda significativa da atividade.

An efficient, clean, chemoselective and solvent-free method for the synthesis of ketone and aldehyde dimethyl acetals was developed using trimethyl orthoformate and commercially available anhydrous $CeCl_3$ as a recyclable catalyst. The method is general and affords the protected carbonyl compounds in good yields and under mild conditions, including aryl and alkyl ketones and activated aldehydes. The catalyst could be utilised directly for 3 cycles, without significant loss of activity.

Keywords: cerium(III) chloride, acetals, trimethyl orthoformate, aldehydes, ketones

Introduction

Acetalization of aldehydes and ketones is the most frequently used strategy for protection of carbonyl groups against nucleophilic reagents.[1] Besides being very useful derivatives in total synthesis, acetals can be easily transformed into several utile functional groups.[2] Because of the versatility and usefulness of acetals in organic synthesis, several methods for the protection[3-20] and the selective, mild deprotection[21] of aldehydes and ketones have been described. The classical procedure for protection involves the Lewis[3-15] or protic acid-catalyzed[16-20] reaction of a carbonyl compound with a large excess of an alcohol in the presence of a water scavenger. Among the employed Lewis acids are metal triflates,[3-8] lanthanoid chlorides,[9,10] $SnCl_4$,[11] $FeCl_3$,[12] $LiBF_4$,[13] $ZnCl_2$[14] and pyridinium ions[15] while HCl,[16] *p*-TsOH,[17] HBF_4,[18] 2,6-pyridinedicarboxylic acid[19] and silica-supported $HClO_4$[20] have been used as protic acids. Despite the advocated advantages of several recently described methods for the acetalization reaction, they have some drawbacks, such as the use of toxic, strong and corrosive acids, non-recyclable catalysts, volatile organic solvents (VOCs) and, in some cases, non-commercially available catalysts. A greener, atom efficient approach to acetals is the use of trialkyl orthoesters instead of alcohols, because they provide both alkoxy groups while scavenging the water produced in the reaction.[3,4,9,10,13,14]

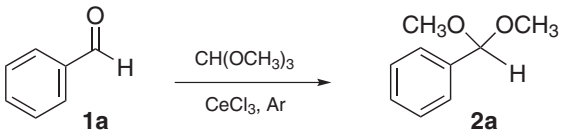
In view of our interest in the development of new, cleaner methods for classical reactions[22] and new applications of cerium(III) in organic synthesis,[23] we decide to study the reaction of carbonyl compounds **1** with trimethyl orthoformate to obtain dimethyl acetals **2** (Tables 1 and 2).[24]

Results and Discussion

Initially, we chose benzaldehyde **1a** (2.0 mmol) and trimethyl orthoformate (2.2 mmol) as standard starting materials to establish the best conditions for the reaction under solvent-free media. We examined the temperature, amount of anhydrous $CeCl_3$[25] and the reaction time (Table 1).

*e-mail: silveira@quimica.ufsm.br

Table 1. Acetalization[a] of benzaldehyde using $CeCl_3$



Entry	$CeCl_3$ / (mol%)[b]	Solvent	Temperature / °C	time / h	Yield / (%)
1	10	-	r.t.	6	83
2	10	-	0	1	85
3	10	-	-20	3	70
4	10	-	-78	5	22
5	5	-	0	1	95
6	1	-	0	6	77
7	2	-	0	6	87
8	10	CH_3NO_2	r.t.	10	50
9	10	CH_3CN	r.t.	24	45
10	10	CH_3OH	r.t.	6	75
11	10	CH_3OH	0	5	65

[a]Reaction conditions: trimethyl orthoformate (2.2 mmol); benzaldehyde **1a** (2.0 mmol) and solvent (2 mL) when mentioned. [b]Anhydrous cerium (III) chloride.[25]

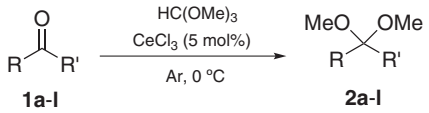
It was found that using 10 mol% of dry $CeCl_3$ the acetal **2a** was obtained in 83% yield after stirring at room temperature for 6 h (Table 1, entry 1). The reaction time was reduced to 1 h when the mixture was stirred at 0 °C, affording the same result (Table 1, entry 2). By stirring at lower temperatures, such as −20 and −78 °C, the product was obtained only in modest yields (entries 3 and 4). The effect of the amount of the catalyst was also evaluated. When 5 mol% of $CeCl_3$ was used, **2a** was obtained in excellent yield (95%) after stirring at 0 °C for 1 h (Table 1, entry 5). The use of lower amounts of $CeCl_3$ did not presented satisfactory results (entries 6 and 7). We also tested the effect of the solvent in the reaction, such as CH_3CN, CH_3NO_2 and CH_3OH (entries 8-11). When CH_3OH (2 mL) was used, **2a** was obtained in 75% yield after stirring for 6 h at room temperature (entry 10) and in 65% yield after 5 h at 0 °C (entry 11). The lower yields observed in these cases are probably due to the reduction of the catalytic activity of $CeCl_3$ in view of a competition between the heteroatom of the solvent and the carbonyl group of the aldehyde for the cerium metal centre.[3]

Since the best conditions were established, the protocol was extended to other aromatic and aliphatic aldehydes and ketones (Table 2).

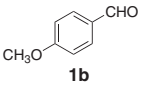
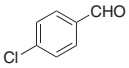
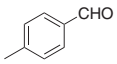
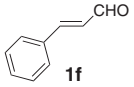
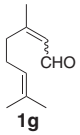
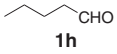
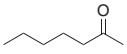
The dimethyl acetals **2** were obtained in good to excellent yields under solvent-free conditions after stirring at 0 °C for 1-4 h in all but three tested examples. In the case of solid *p*-chlorobenzaldehyde (entry 4) and the less reactive ketones acetophenone and heptan-2-one (entries 11 and 12), it was necessary the use of methanol (2 mL) as solvent under reflux. Besides, a longer reaction time (8-10 h) was required to obtain satisfactory yields from ketones. The chemoselectivity of the reaction was also investigated. Thus, when an equimolar mixture of benzaldehyde **1a**, cyclohexanone **1h** and trimethylorthoformate was subjected to acetalization reaction in presence of $CeCl_3$, only the acetal of benzaldehyde **2a** was isolated after stirring for 4 h, while the cyclohexanone was completely recovered, along with a small amount of **1a**. This result shows the high selectivity of our method. In addition, citral **1g**, which is a mixture of *trans*- and *cis*-3,7-dimethylocta-2,6-dienal (*Z:E* = 40:60), was selectively converted to the respective dimethyl acetal in 78% yield after 4 h without any isomerization of the double bonds (*Z:E* = 40:60; entry 7). To extend the scope of $CeCl_3$-catalyzed acetalization of carbonyl compounds we sought to explore the use of triethyl orthoformate for the synthesis of diethyl acetals, under the same conditions employed to methyl acetals. In this way, the reaction was performed with benzaldehyde and cyclohexanone, and the corresponding diethyl acetals were obtained in 93 and 86% isolated yield, respectively.

It was observed that the $CeCl_3$ can be successfully reused up to 2 times without any treatment, with good results. Thus, for example, after the completion of the acetalization of benzaldehyde **1a** (in 10.0 mmol scale), the crude product **2a** was simply separated by decantation from the insoluble catalyst and a small amount of $CeCl_3$ (0.05 mmol; 0.5 mol % each time) was added each time before repeating the reaction. Under these conditions, **2a** was obtained with similar yield (2 runs, 93 and 94% yield

Table 2. Acetalization of aldehydes and ketones using $CeCl_3$



1a-l **2a-l**

Entry	Substrate **1**	Product **2**[a]	time / h	Yield / (%)[b]
1	 **1a**	**2a**	1	95
2	 **1b**	**2b**	2	90
3	 **1c**	**2c**	3	88
4	 **1d**	**2d**	2.5	95[c]
5	 **1e**	**2e**	1.5	93
6	 **1f**	**2f**	4	91
7	 **1g**	**2g**	4	78[d]
8	 **1h**	**2h**	3	95
9	 **1i**	**2i**	3	82
10	 **1j**	**2j**	4	85
11	 **1k**	**2k**	10	86[c]
12	 **1l**	**2l**	8	77[c]

[a]The products were identified by ^1H and ^{13}C NMR and compared with literature data.[3-20] [b]Yields of pure products isolated. [c]The reaction was carried out in the presence of methanol (2 mL) under reflux. [d]*Z*:*E* = 40:60.

after 1 h reaction). Without adding this extra amount of $CeCl_3$, the yield was reduced to 89 and 75% on runs 2 and 3, respectively.

Conclusions

In summary, anhydrous $CeCl_3$ has proved to be an effective, robust and recyclable catalyst for the acetalization of aryl and alkyl carbonyl compounds. The method is simple, clean and general and the catalyst can be reused directly for 2 times without loss of activity. For almost all the examples studied, this new, green methodology eliminates completely the necessity of using organic solvents in the reaction.

Acknowledgments

This project is funded by MCT/CNPq, CAPES and FAPERGS.

References

1. Wuts, P. G. M.; Greene, T. W. In *Greene's Protective Groups in Organic Synthesis,* 4th ed.; Wiley: New York, 2007, ch. 4; Kocienski, P. J. In *Protective Groups,* 3rd ed.; Thieme: New York, 2004, ch. 2.
2. Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N.; *Org. Lett.* **2005**, *7*, 3697; Lemiègre, L.; Stevens, R. L.; Combret, J.-C.; Maddaluno, J.; *Org. Biomol. Chem.* **2005**, *3*, 1308; Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T.; *Org. Biomol. Chem.* **2006**, *4*, 2337; Li, L.-S.; Das, S.; Sinha, S. C.; *Org. Lett.* **2004**, *6*, 127.
3. Williams, D. B. G.; Lawton, M. C.; *Green Chem.* **2008**, *10*, 914.
4. Leonard, N. M.; Oswald, M. C.; Freiberg, D. A.; Nattier, B. A.; Smith, R. C.; Mohan, R. S.; *J. Org. Chem.* **2002**, *67*, 5202.
5. Smith, B. M.; Graham, A. E.; *Tetrahedron Lett.* **2006**, *47*, 9317.
6. Borujeni, K. P.; Massah, A. R.; *React. Funct. Polym.* **2006**, *66*, 1126.
7. Tsunoda, T.; Suzuki, M.; Noyori, R.; *Tetrahedron Lett.* **1980**, *21*, 1357.
8. Ono, F.; Inatomi,Y.; Tada, Y.; Mori, M.; Sato, T.; *Chem. Lett.***2009**, *38*, 96.
9. Luche, J.-L.; Gemal, A. L.; *J. Chem. Soc., Chem. Commun.* **1978**, 976.
10. Gemal, A. L.; Luche, J.-L.; *J. Org. Chem.* **1979**, *44*, 4187.
11. Anderson, S. H.; Uh, H.-S.; *Synth. Commun.* **1973**, *3*, 125.
12. Bornstein, J.; Bedell, S. F.; Drummond, P. E.; Kopsloski, C. L.; *J. Am. Chem. Soc.* **1956**, *78*, 83.
13. Hamada, N.; Kazahaya, K.; Shimizu, H.; Sato, T.; *Synlett* **2004**, 1074.
14. Roy, A.; Rahman, M.; Das, S.; Kundu, D.; Kundu, S. K.; Majee, A.; Hajra, A.; *Synth. Commun*. **2009**, *39*, 590.
15. Procuranti, B.; Connon, S. J.; *Org. Lett.* **2008**, *10*, 4935.
16. Cameron, A. F. B.; Hunt, J. S.; Oughton, J. F.; Wilkinson, P. A.; Wilson, B. M.; *J. Chem. Soc.* **1953**, 3864.

17. Wenkert, E.; Goodwin, T. E.; *Synth. Commun*. **1977**, *7*, 409.
18. Kumar, D.; Kumar, R.; Chakraborti, A. K.; *Synthesis* **2008**, 1249.
19. Zhou, W.; Xu, L.-W.; Yang, L.; Zhao, P.-Q.; Xia, C.-G.; *J. Mol. Catal. A: Chem.* **2006**, *249*, 129.
20. Kumar, R.; Kumar, D.; Chakraborti, A. K.; *Synthesis* **2007**, 299.
21. Kantam, M. L.; Neeraja, V.; Sreekanth, P.; *Catal. Commun.* **2001**, *2*, 301; Bailey, A. D.; Cherney, S. M.; Anzalone, P. W.; Anderson E. D.; Ernat, J. J.; Mohan, R. S.; *Synlett* **2006**, 215; Krishnaveni, N. S.; Surendra, K.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R.; *J. Org.. Chem.* **2003**, *68*, 2018; Bailey, A. D.; Baru, A. R.; Tasche, K. K.; Mohan, R. S. *Tetrahedron Lett*. **2008**, *49*, 691.
22. Lenardão, E. J.; Trecha, D. O.; Ferreira, P. C.; Jacob, R. G.; Perin, G. *J. Braz. Chem. Soc*. **2009**, *20*, 93; Perin, G.; Jacob, R. G.; Dutra, L. G.; Azambuja, F.; Santos, G. F. F.; Lenardão, E. J.; *Tetrahedron Lett*. **2006**, *47*, 935; Lenardão, E. J.; Dutra, L. G.; Saraiva, M. T.; Jacob, R. G.; Perin, G.; *Tetrahedron Lett*. **2007**, *48*, 8011; Lenardão, E. J.; Mendes, S. R.; Ferreira, P. C.; Perin, G.; Silveira, C. C.; Jacob, R. G.; *Tetrahedron Lett.* **2006**, *47*, 7439.
23. Silveira, C. C.; Mendes, S. R.; *Tetrahedron Lett*. **2007**, *48*, 7469.
24. *Typical procedure for the synthesis of dimethyl acetals* ***2***. To a mixture of trimethyl orthoformate (0.254 g, 2.2 mmol) and anhydrous $CeCl_3$ (0.025 g, 0.1 mmol) at 0 °C under argon, was added benzaldehyde **1a** (0.212 g, 2.0 mmol). The reaction progress was followed by TLC, and after stirring at 0 °C for 1.0 h (see Table 2) the starting materials were completely consumed. The resulting reaction mixture was quenched with saturated aqueous sodium bicarbonate solution followed by extraction with ethyl acetate (3 × 5 mL). After drying the organic phase over anhydrous $MgSO_4$, the solvent was removed under reduced pressure to give the pure acetal **2a** as a colorless oil (0.323g, 95%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45-7.43 (m, 2H), 7.36-7.29 (m, 3H), 5.38 (s, 1H), 3.31 (s, 6H).^{31} ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.56, 103.09, 126.60, 128.08, 128.34, 137.99. When necessary, the residue was purified by column chromatography (ethyl acetate/hexanes 5/95).
25. Cerium chloride was dried according to: Dimitrov, V.; Kostova, K.; Genov, M.; *Tetrahedron Lett.* **1996**, *37*, 6787.

Received: July 3, 2009
Web Release Date: November 26, 2009