

Solid Lithium Perchlorate, a Highly Efficient and Chemoselective Catalyst for the Acetalization of Aldehydes

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Abstract

A simple, efficient, and general method has been developed for the chemoselective acetalization of aldehydes with 1,3-propanediol, 1,2-ethanediol and trimethyl orthoformate in the presence of solid lithium perchlorate under solvent-free conditions. Both cyclic and acyclic acetals of aldehydes were obtained under environmentally benign conditions in good to excellent yields.

Keywords: Acetalization; Aldehyde; 1,3-Propanediol; 1,2-Ethanediol; Trimethyl orthoformate; Lithium perchlorate

Introduction

The acetal group is one of the most widely used protecting groups for the carbonyl compounds [1-4]. The protection of aldehyde as acetal requires an efficient method under mild conditions with reagents compatible with different functional groups, specially in the total synthesis of natural products [5,6]. In general, the reaction is usually performed in the presence of acids. Many Lewis acids, which catalyzed acetalization under aprotic conditions, have been reported in the literature [7-29]. There are shortcomings to use acids in the acetalization reaction of aldehydes, such as long reaction time, reflux condition, unwanted side reaction and nonselectivity.

Results and Discussion

In recent years, concentrated solution of lithium perchlorate in diethyl ether (LPDE) has been used in various organic transformations [30-36]. The LPDE is a

convenient medium to carry out many different reactions under neutral condition. On the other hand, due to the current challenge for developing solvent-free and environmentally benign synthetic systems and in continuation with our interest on the applications of lithium perchlorate for various organic transformations, herein, we describe the scope of a simple, general and efficient protocol for the protection of aldehydes using solid LiClO_4 under the first solvent-free conditions. Lithium perchlorate is a very mild and remarkable catalyst for the protection of aldehyde with 1,3-propanediol and 1,2-ethanediol, which allows survival of the other functional groups including α,β -unsaturated aldehydes. We have found that various aldehydes can be converted to their corresponding acetals upon treatment with 1,3-propanediol and 1,2-ethanediol in the presence of solid lithium perchlorate. Aliphatic and aromatic aldehydes can be converted to their corresponding acetals with a very short reaction time (*ca.* 10-20 min), Scheme 1. Aromatic aldehydes with both electron-donating and -withdrawing groups at the para and meta

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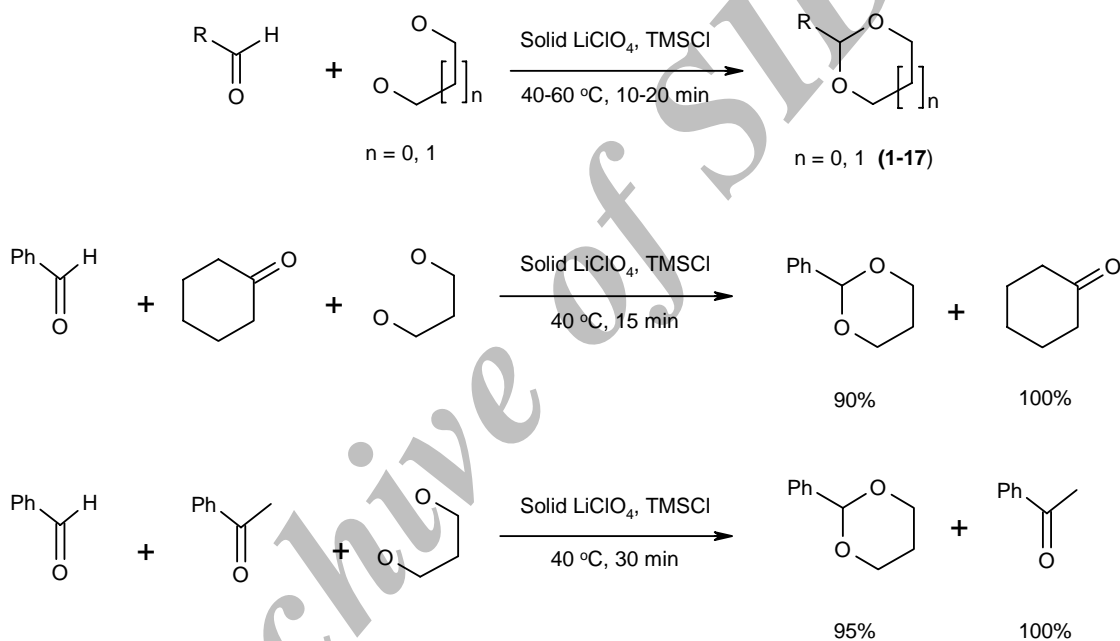
positions, produce the corresponding acetals in good to excellent yields. For aldehyde with electron-donating group, the reaction was carried out at higher temperature (*ca.* 80°C, Table 1, Entry 12).

In order to show the chemoselectivity with this method, we studied competitive reaction for the acetalization of aldehydes. A mixture of an aldehyde and a ketone in 1 to 1 ratio was treated with a diol (1,3-propanediol or 1,2-ethanediol) in the presence of solid lithium perchlorate at 40-60°C. By monitoring with TLC and ¹H NMR techniques, exclusively the acetal of the aldehyde was observed in the presence of the ketone, (Scheme 1). All the acetals derived from parent aldehydes are known, and their spectral data have been

reported in the literature [3].

We also found that the reaction of an aldehyde with trimethyl orthoformate in the presence of solid lithium perchlorate is a convenient method for the synthesis of dimethyl acetals in excellent yields with high chemoselectivity. The results are shown in Scheme 2.

In conclusion, we found that solid lithium perchlorate is a remarkable catalyst for the chemoselective acetalization of aldehydes in the presence of ketones. The reaction condition is very general, simple, mild and chemoselective for aldehydes. Although lithium perchlorate is a low cost reagent in compare with many Lewis acids, it is easy to recover and reuse it for other reactions.



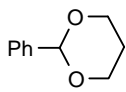
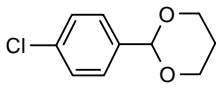
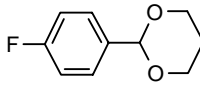
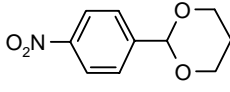
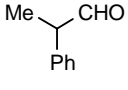
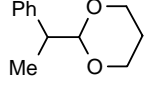
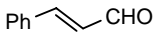
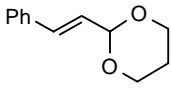
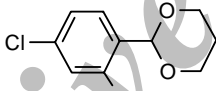
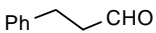
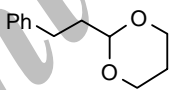
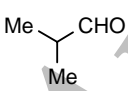
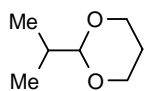
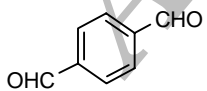
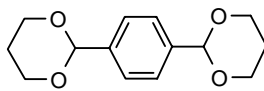
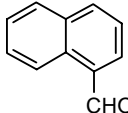
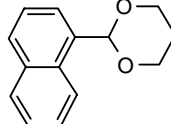
Scheme 1

Aldehyde	Time (min)	Yield (%)	Reaction
PhCHO, 18	8	95	$\text{R or Ar}-\text{CHO} + \text{CH}(\text{OMe})_3 \xrightarrow[\text{TMSCl, 40-60 } ^\circ\text{C}]{\text{Solid LiClO}_4, \text{ MeOH}} \text{R or Ar}-\text{CH}(\text{OMe})_2$
4-O ₂ NC ₆ H ₄ CHO, 19	15	97	
3-O ₂ NC ₆ H ₄ CHO, 20	15	89	
2,4-Cl ₂ C ₆ H ₃ CHO, 21	8	91	
PhCH ₂ CH ₂ CHO, 22	20	86	

(18-22)

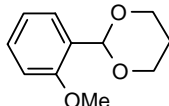
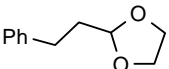
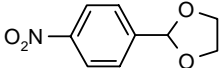
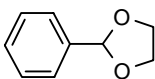
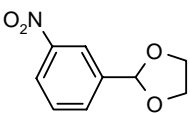
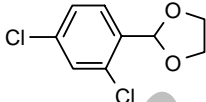
Scheme 2

Table 1. Acetalization of aldehydes mediated by solid LiClO₄ under solvent-free conditions

Entry	Aldehyde	Product	Aldehyde/Diol Ratio ^a	Time ^b (min)	Yield ^c (%)	
1	PhCHO		1	1:1.5	10	96
2	4-ClC ₆ H ₄ CHO		2	1:1.5	15	93
3	4-FC ₆ H ₄ CHO		3	1:1.5	13	85
4	3-O ₂ NC ₆ H ₄ CHO		4	1:1.5	10	96
5			5	1:1.5	10	91
6			6	1:1.5	20	63
7	2,4-Cl ₂ C ₆ H ₃ CHO		7	1:1.5	15	97
8			8	1:1.5	10	90
9			9	1:1.5	10	93
10			10	1:3	15	97
11			11	1:1.5	25	45

^aIn all cases one equivalent of sodium hydroxide and 1.5 equivalent solid LiClO₄ were used^bReactions were performed at about 50°C^cIsolated yields^dReaction was performed at about 80°C

Table 1. Continued

Entry	Aldehyde	Product	Aldehyde/Diol Ratio ^a	Time ^b (min)	Yield ^c (%)	
12	2-MeOC ₆ H ₄ CHO		12	1:1.5	30	87 ^d
13	Ph-CH ₂ -CH ₂ -CHO		13	1:1.5	15	92
14	4-O ₂ NC ₆ H ₄ CHO		14	1:1.5	10	95
15	C ₆ H ₅ CHO		15	1:1.5	15	93
16	3-O ₂ NC ₆ H ₄ CHO		16	1:1.5	10	94
17	2,4-Cl ₂ C ₆ H ₃ CHO		17	1:1.5	15	93

Experimental

General

All reactions were carried out under an atmosphere of argon. NMR spectra were recorded on a Bruker ACF 500 using chloroform-*d* as solvent. Infrared spectra (IR) were measured on a Perkin Elmer 1600 FT-IR spectrometer. Column chromatography was performed on silica gel, Merck grade 60. CH₂Cl₂ was distilled before use. Lithium perchlorate was purchased from Across. All the reactions were performed under argon.

The General Procedure for Acetalization of Aldehydes Mediated by Solid LiClO₄

Lithium perchlorate (3.0 mmol, 0.32 g), an aldehyde (2 mmol) and 1,3-propanediol (or 1,2-ethanediol) (3 mmol) were added to a flask. Then trimethylsilyl chloride, TMSCl, (0.8 mmol, 0.1 mL) was added and the mixture stirred for 10 to 20 min at about 50°C. The reaction monitored by TLC and quenched at room temperature by adding dichloromethane (20 mL). The

solid lithium perchlorate was filtered off. Due to stability of LiClO₄ in water, it is possible to recover it, and use it again after reactivating by heating it in vacuum at 160°C. The organic layer was washed with water three times and dried over Na₂SO₄. The solvent removed using a rotary evaporator. Although in most cases almost pure products were obtained, further purification was carried out by microdistillation or by recrystallization.

The General Procedure for Acetalization of Aldehydes with Trimethyl Orthoformate Mediated by Solid LiClO₄

Lithium perchlorate (3 mmol, 0.32 g), an aldehyde (2 mmol), trimethyl orthoformate (5 mmol) and methanol (0.3 mL) were added to a flask. Then TMSCl (0.8 mmol, 0.1 mL) was added and the mixture stirred for 10 to 15 min at about 40-60°C. The reaction was monitored by TLC and quenched at room temperature by adding dichloromethane (20 mL). The solid lithium perchlorate was filtered off. The organic layer was washed with water three times and dried over Na₂SO₄. The solvent

was removed using a rotary evaporator.

Caution: Although we did not have any accident while using LiClO_4 , it is advisable to dry lithium perchlorate in a fume hood using a suitable lab-shield.

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References

- Greene T.W. and Wuts P.G.M. *Protective Groups in Organic Synthesis*. 3rd Ed., John Wiley and Sons, New York (1999).
- Loewenthal H.J.E. In: McOmie J.F.W. (Ed.), *Protective Groups in Organic Chemistry*, Plenum Press, London, Chapter 9 (1973).
- Hanson J.R. *Protecting Groups in Organic Synthesis*. 1st Ed.; Blackwell Science, Inc, Malden, Mass. (1999).
- Kocienski P.J. In: Enders R., Noyori R., and Trost B.M. (Eds.), *Protective Groups*. Thieme, Stuttgart, Chapter 4 (1994).
- Bergstrom R.G. *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogous*. Supplement E; Patai S., Wiley, New York, Part 2, Chapter 20 (1980).
- Hwu J.R., Leu L.C., Robl J.A., Anderson D.A., and Wetzel J.M. *J. Org. Chem.*, **52**: 188-191 (1987).
- Bornstein J., Bedell, S.F., Drummond P.E., and Kopsloski C.L. *J. Am. Chem. Soc.*, **78**: 83-86 (1956).
- Hassner A., Wiederkehr R., and Kascheres A.J. *J. Org. Chem.*, **35**: 1962-1964 (1970).
- Anderson S.H. and Uh H-S. *Synth. Commun.*, **3**: 125-131 (1973).
- Gemal A.L. and Luche J.-L. *J. Org. Chem.*, **44**: 4187-4189 (1979).
- Tsunoda T., Suzuki M., and Noyori R. *Tetrahedron Lett.*, **21**: 1357-1358 (1980).
- Ott J., Ramos Tombo G.M., Schmid B., Venzani, G., Wang L.M., and Ward T.R. *Tetrahedron Lett.*, **30**: 6151-6154 (1989).
- Jun-ichi T., Horiuchi H., and Uemura S. *J. Org. Chem.*, **60**: 4039-4043 (1995).
- Clerici A., Pastori. N., and Porta O. *Tetrahedron*, **54**: 15679-15690 (1998).
- Karimi B. and Ashtiani A.M. *Chem. Lett.*, 1199-1200 (1999).
- Karimi B., Seradj H., and Ebrahimian G.-R. *Synlett*, 1456-1458 (1999).
- Firouzabadi H., Iranpoor N., and Karimi B. *Synlett*, 321-323 (1999).
- Laskar D.D., Prajapati D., and Sandhu J.S. *Ibid.*, 1283-1284 (1999).
- Leonard N.M., Oswald M.C., Freiberg D.A., Nattier B.A., Smith R.C., and Mohan R.S. *J. Org. Chem.*, **67**: 5202-5207 (2002).
- Gopinath R., Jiaul Haque S.K., and Patel B.K. *Ibid.*, **67**: 5842-5845 (2002).
- Curini M., Epifano F., Marcotullio M.C., Rosati O., and Nocchetti M. *Tetrahedron Lett.*, **43**: 2709-2711 (2002).
- Romanelli G.P., Thomas H.J., Baronetti G.T., and Autino J.C. *Ibid.*, **44**: 1301-1303 (2003).
- Srivastava N., Dasgupta S.K., and Banik B.K. *Ibid.*, **44**: 1191-1194 (2003).
- Firouzabadi H., Iranpoor N., Nowrouzi F., and Amani K. *Ibid.*, **44**: 3951-3954 (2003).
- Smitha G. Reddy Ch.S. *Tetrahedron*, **59**: 9571-9576 (2003).
- Srivastava N., Dasgupta S.K., and Banik B.K. *Tetrahedron Lett.*, **44**: 1191-1193 (2003).
- Ishino Y., Mihara M., Takeuchi T., and Takemoto M. *Ibid.*, **45**: 3503-3506 (2004).
- Aggen D.H., Arnold J.N., Hayes P.D., Smoter N., and Mohan R.S. *Tetrahedron*, **60**: 3675-3679 (2004).
- Rajabi F. and Saidi M.R. *J. Sciences, I.R.I.*, **15**: 333-337 (2004).
- Sankararaman S. and Nesakumar J.E. *Eur. J. Org. Chem.*, 2003-2011 (2000).
- Saidi M.R., Azizi N., and Zali-Boinee H. *Tetrahedron*, **57**: 6829-6832 (2001).
- Saidi M.R., Azizi N. and Naimi-Jamal M.R. *Tetrahedron Lett.*, **42**: 8111-8113 (2001).
- Azizi N. and Saidi M.R. *Ibid.*, **43**: 4305-4308 (2002).
- Saidi M.R. and Azizi N. *Synlett*, 1347-1349 (2002).
- Saidi M.R. and Azizi N. *Tetrahedron: Asymmetry*, **14**: 389-392 (2003).
- Azizi N. and Saidi M.R. *Organometallics*, **23**: 1457-1456 (2004).