C. R. Chimie 14 (2011) 525–529

Contents lists available at ScienceDirect

Comptes Rendus Chimie

www.sciencedirect.com

Preliminary communication/Communication

Mild and efficient protection of diol and carbonyls as cyclic acetals catalysed by iron (III) chloride

Iyad Karamé [a,*], Mohamad Alamé [a], Ali Kanj [a], Ghinwa Nemra Baydoun [a], Hassan Hazimeh [a], Mirvat el Masri [a], Lorraine Christ [b]

[a] Department of chemistry and biochemistry, laboratory of organometallic catalysis and coordination chemistry, Lebanese University, faculty of sciences I, Haddath, Lebanon
[b] Institut de recherche sur la catalyse et l'environnement de Lyon, UMR 5256, 2, avenue Einstein, 69626 Villeurbanne cedex, France

ARTICLE INFO

Article history:
Received 27 August 2010
Accepted after revision 6 December 2010
Available online 3 February 2011

Keywords:
Cyclic acetal
Diol
Carbonyl
Iron
Protection

ABSTRACT

A friendly method for the protection of diols and carbonyls catalysed by hexahydrated iron (III) chloride has been developed. This method, which consists of the transformation of diols and carbonyls to cyclic acetals, functions in mild conditions and it is efficient for a wide range of diols.

RÉSUMÉ

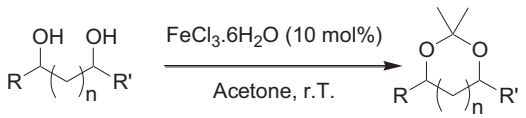
Une méthode simple pour la protection des diols et des carbonyls catalysée par le chlorure de fer (III) a été développée. Cette méthode qui consiste à la transformation des diols et des carbonyls en acétales cycliques, fonctionne dans des conditions douces et elle est efficace pour une variété large des diols.

Reactions which generate cyclic acetals are important for the protection of carbonyl groups in organic synthesis [1] as well as for the protection of alcohol groups in carbohydrates [2]. Cyclic acetals are equally important for the generation of chiral auxiliaries for asymmetric induction [3] and for the production of polymers, pharmaceuticals, cosmetics and fragrances [4–6]. The development of new methods and the modification of existing ones for making acetals are therefore considered as an important challenge. Recently, it has been described that cyclic acetals with five to eight membered rings can be obtained by reactions between alkynes and diols catalysed by cationic gold (I) catalyst [7]. Epoxides can be converted directly to cyclic acetals, with only five membered rings, called acetonides, in the presence of acetone and catalysed by a Lewis acid [8]. Classical methods to obtain cyclic acetals involve the reaction of an aldehyde or a ketone with an alcohol, catalysed by toluenesulfonic acid, with azeotropic removal of water or transacetalization reactions. When the ketone is not stable, this procedure involves a large excess of reactant and tedious work-up procedures [1,9]. More convenient and useful methods, under mild conditions, for the production of cyclic acetals of various carbonyls compounds in excellent yields were recently reported, some were using catalytic amounts of tetrabutylammonium tribromide [10] or $ZrCl_4$ [11] in the presence of trialkyl orthoformate, and others were using silylated alcohols with catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as Lewis acid [12].

Recently, it has been shown that $ZrCl_4$ is an efficient catalyst for one-pot protection/deprotection of diols, where 2,2-dimethoxypropane (DMP) is the protecting agent, forming cyclic acetals [13]. However, there is still a scope for further improvement in this field since there is no

* Corresponding author.
E-mail address: iyad.karameh@ul.edu.lb (I. Karamé).

1631-0748/$ – see front matter
doi:10.1016/j.crci.2010.12.001



Scheme 1. Iron (III) chloride catalyses the transformation of diols into acetonides.

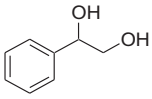
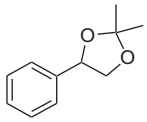
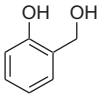
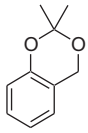
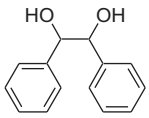
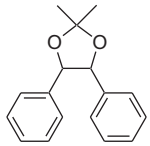
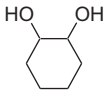
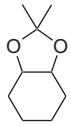
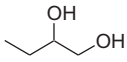
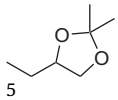
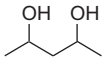
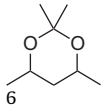
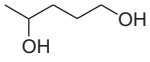
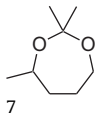
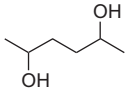
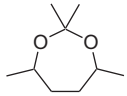
efficient method yet for the preparation of cyclic acetals directly from carbonyls and diols without the assistance of additives or co-catalysts.

We report here an efficient and easy method for the preparation of cyclic acetals from diols and carbonyls using hexahydrated Fe (III) trichloride as a catalyst (Scheme 1). This method is proved to be useful for a wide range of substrates. A few examples using anhydrous $FeCl_3$ as a catalyst have been reported in carbohydrate chemistry [14].

In a preliminary experiment, 1,2-butanediol **d5** (Table 1, entry five) was stirred with 10 mol% of hexahydrated $FeCl_3$ and acetone at room temperature for two hours and were subjected to the conditions of the reactions. The results are summarized in Table 1.

The conversion of 1,2-diol type **d1**-**d5**, α-aromatic substituted and aliphatic diols (Table 1, entries one to five) to the corresponding 1,3-dioxalanes was much faster than

Table 1
$FeCl_3.6H_2O$ catalyses conversion of diol to acetonides in acetone.

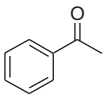
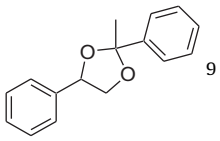
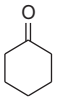
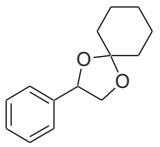
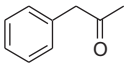
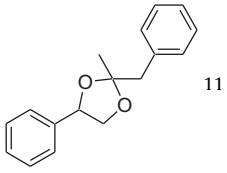
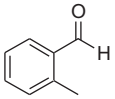
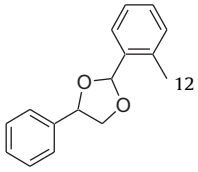
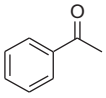
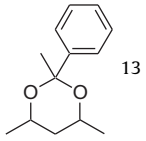
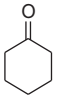
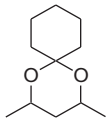
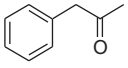
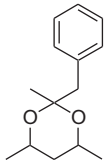
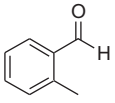
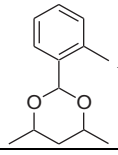
Entry	Substrate	Conversion (%)	Product	Isolated yield (%)
1	 d1	100[a]	 1	98
2	 d2	100	 2	98
3	 d3	100	 3	98
4	 d4	74 (100)[b]	 4	98
5	 d5	100	 5	98
6	 d6	100	 6	98
		65 (78)[b]		74
7	d7		7	
8	 d8	50	 8	50

[a] After 30 minutes.
[b] After 24 hours.

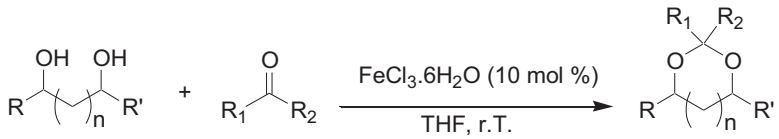
the conversion of 1,4-diols type **d7**-**d8** (Table 1, entries seven and eight). This is due to the chelation effect, where diols with closer hydroxyl functions can be coordinated more easily than diols with farther hydroxyl functions. However, the transformation of 1,3-diols such as 2,4-pentanediol was as easy as 1,2-diols type. A diastereomeric mixture of diols **d3**, **d4**, **d6** and **d8** yielded a diastereomeric mixture of acetonides in different ratios as observed by GC-MS and ^{1}H NMR of the reaction products.

In order to further explore the scope of the catalytic process presented here, we have studied a series of reactions involving different combinations of two selected diols with four different carbonyls (Table 2). The diol **d1** or **d6** was dissolved in THF with one equivalent of carbonyl

Table 2
$FeCl_3.6H_2O$ catalyses direct formation of cyclic acetals from diols and carbonyls.

Entry	Diol	Carbonyl	Conv.[a]	Product	Isolated yield (%)
1	d1		30	 9	30
2	d1		97	 10	95
3	d1		16(60)[b]	 11	60
4	d1		73	 12	70
5	d6		8	 13	6
6	d6		100	 14	98
7	d6		64	 15	60
8	d6		100	 16	99

[a] Conversion of carbonyl.
[b] After 24 hours.



d1: R= Ph, R'= H
d6: R=R'= Me

Scheme 2. Iron (III) catalyses the transformation of diols and carbonyls into cyclic acetals.

compound and 10 mol% of hexahydrated $FeCl_3$ and stirred at room temperature for two hours producing the corresponding cyclic acetal[1] (Scheme 2).

Reactions between cyclohexanone and **d1** as well as **d6** were almost completely done with a quantitative yield (> 95 %) (Table 2, entries two and six). However, when 2-phenylpropanone is used, yields were less important than those obtained with cyclohexanone (Table 2, entries three and seven) but much higher than the yields obtained with acetophenone (Table 2, entries one and five).

It seems that this reaction is easier with aliphatic ketones than benzylic and aromatic ones where the conversions were not completed. The reaction of *ortho*-methylbenzaldehyde with the diol **d1** (Table 2, entry four) leads to a good conversion, whereas, complete conversion was obtained with diol **d6** (Table 2, entry eight). The cyclic acetals (entries one, three, four, five, seven and eight) obtained in the examples shown in Table 2, exhibit new stereogenic centre except those with cyclohexanone. The use of optically pure diols may induce the stereochemistry of the formed stereogenic centre, this will constitute the object of a future study.

In conclusion, a new method for the preparation of acetonides and cyclic acetals was developed using $FeCl_3$, a very cheap and friendly catalyst. This method uses diols as substrates for the preparation of cyclic acetals of not only five membered rings (as with the use of epoxides) but also for cyclic acetals of six, seven and eight membered rings. Furthermore, this friendly procedure uses ketones, which are commercially available worldwide, and it can be also used for the protection of diols as well as of ketones and aldehydes.

Acknowledgments

We acknowledge Dr. Iman Saad, director of the department of chemistry and biochemistry, and Prof. Bassam Badran for their logistical support.

References

[1] T.W. Greene, P.G.M. Wuts, Protective group in organic synthesis, 4th ed., John Wiley and Sons, New Jersy, NI, 2007.
[2] M. Miljkovic, Cyclic acetals and ketals, in: Carbohydrates: synthesis mechanisms, and stereoelectronic effects, Springer, New York, 2009, p. 143–167.
[3] (a) J.K. Whitesell, Chem Rev 89 (1989) 1581 ;
(b) E.J. Corey, L.I. Wu, J Am Chem Soc 115 (1993) 9327 ;
(c) M. Tanaka, M. Oba, K. Tamai, H. Suemune, J Org Chem 66 (2001) 2667 ;
(d) A. Alexakis, P. Mangeney, Tetrahedron Asymmetry 1 (1990) 477.
[4] (a) R.C. Li, R.M. Broyer, H.D. Maynard, J Polym Sci A 44 (2006) 5004 ;
(b) Drysdale NE, Lewin LA, Barsotti RJ, Corcoran PH. US Pat. Appl. Publ. US 20060074198 A1 20060406, 2006
(c) S. Kaihara, S. Matsumura, J.P. Fisher, Macromolecules 40 (2007) 7625 ;
(d) Papisov M, PCT. Int. Appl. WO 9632419 A1 19961017, 1996.
[5] (a) M. Aepkers, B. Wünsch, Bioorg Med Chem 13 (2005) 6836 ;
(b) M. Schmidt, J. Ungvári, J. Glöde, B. Dobner, A. Langner, Bioorg Med Chem 15 (2007) 2283 ;

[1] General procedure of the protection of diols with acetone: a 10 mL vial containing a Teflon®-coated stirring bar was charged with $FeCl_3$ (27 mg, 0.1 mmol), acetone (1 mL) and the diol (1 mmol). The resulting solution was stirred at room temperature for two hours. Acetone was removed with a rotary evaporator, and the product was purified on silica gel column chromatography (cyclohexane-AcOEt = 80:20). Its purity (> 98%) was determined by ^1H NMR. Conversions were determined by GC coupled with MS. All the final products were isolated and characterized by comparison of their ^1H NMR spectra with already reported data (1, [15] 2, [16] 3, [17] 4, [18] 5, [19] 6, [20]). We report here the ^1H and ^{13}C NMR for the new compounds: 7, ^1H NMR ($CDCl_3$, 300 MHz), d (ppm): 3.85 (m, 1H, O-CH), 3.35 (t, 2H, J = 6.8 Hz), 1.2–1.5 (m, 4H, CH_2), 1.25 (s, 6H, $O_2C(CH_3)_2$, 1.2 (d, 3H, J = 6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz), d (ppm): 108, 73, 67, 34, 27, 25, 21.7. 8 ^1H NMR ($CDCl_3$, 300 MHz), d (ppm): 3.85 (m, 2H, O-CH), 1.2–1.5 (m, 4H, CH_2), 1.25 (s, 6H, $O_2C(CH_3)_2$), 1.2 (d, 6H, J = 6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz), d (ppm): 105, 74, 32, 28, 22.procedure for the protection of diols/ketones: a 10 mL vial containing a Teflon®-coated stirring bar was charged with $FeCl_3$ (27 mg, 0.1 mmol), THF (1 mL), ketone (1mmol) and diol (1 mmol). The resulting solution was stirred at room temperature for two hours. Then THF was removed and the product was purified on silica gel column chromatography (cyclohexane-AcOEt = 80:20). Its purity (> 98%) was determined by ^1H NMR. Conversions were determined by GC-MS. All the final products were isolated and characterized by comparison of their ^{13}C and ^1H NMR spectra with already reported data (9, [21] 10, [22] 13, [7] 14, [23]). We report here the 1H and ^{13}C NMR for the new compounds: 11 (tow diastereomers): ^1H NMR ($CDCl_3$, 300 MHz), d (ppm): 7.1–7.3 (m, 20H, Ar), 4.95 (dd, 1H, J_{HH} = 6.7 and 8.9 Hz) 4.7 (dd, 1H, J_{HH} = 3.5 and 8.2 Hz), 4.61 (dd, 1H, J_{HH} = 6.7 and 8.4 Hz), 4.13 (dd, 1H, J_{HH} = 0.8 and 6.15 Hz), 4.1 (dd, 1H, J_{HH} = 0.87 and 6.2 Hz), 3.32 (dd, 1H, J_{HH} = 7.9 and 8.8 Hz), 3.02 (s, 2H, CH_2-Ar), 2.95 (s, 2H, CH_2-Ar), 1.4 (s, 3H, CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz), d (ppm): 138, 137, 131, 130.6, 128.5, 128, 127, 126.7, 110, 77, 72, 46, 25. 12 (two diastereomers): ^1H NMR ($CDCl_3$, 300 MHz), d (ppm): 7.65 (m, 1H, Ar), 7.59 (m, 1H, Ar), 7.15–7.45 (m, 14H, Ar), 6.3 (s, 1H, -(O)$_2$-CH-Ar), 6.13 (s, 1H, -(O)$_2$-CH-Ar), 5.18 (dd, 2H, J_{HH} = 7.4 and 6.8 Hz), 4.5 (dd, 1H, J_{HH} = 8.3 and 6.33 Hz), 4.0 (dt, 1H, J_{HH} = 7.6 Hz), 3.9 (dt, 1H, J_{HH} = 7 and 0.6 Hz), 3.75 (dt, 1H, JHH = 7.5 Hz), 2.45 (s, 3H, CH_3-Ar), 2.44 (s, 3H, CH_3-Ar). ^{13}C NMR ($CDCl_3$, 75.5 MHz), d (ppm): 137, 136.6, 135, 130, 128.5, 128, 127, 126.7, 126, 125.7, 103, 79, 72, 17. 15 (tow diastereomers): ^1H NMR ($CDCl_3$, 300 MHz), d (ppm): 7–7.4 (m, 10H, Ar), 3.85 (m, 4H, -CH-), 3.07 (s, 2H, -CH_2-Ar), 2.82 (s, 2H, -CH_2-Ar), 1.05–1.26 (m, 4H, -CH_2-), 1.2 (s,3H, CH_3), 1.13 (d, 3H, CH_3, JHH = 5.8 Hz), 1.1 (s, 3H, CH_3), 1 (d, 3H, CH_3, JHH = 5.6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz), d (ppm): 139, 128, 127, 126, 101, 73, 45, 40, 25, 22. 16 (two diastereomers): for one diastereomer ^1H NMR ($CDCl_3$, 300 MHz), d (ppm): 7.6 (m, 1H, Ar), 7.22 (m, 2H, Ar), 7.12 (m, 1H, Ar), 5.97 (s, 1H, CH-Ar), 4.5 (m, 1H, OCH-), 4.2 (m, 1H, OCH-), 2.4 (CH_3-Ar), 1.65 (m, 1H, -HCH-), 1.51 (d, 3H, -CH_3, J_{HH} = 6.5 Hz), 1.46 (m, 1H, -HCH-), 1.29 (d, 3H, -CH_3, J_{HH} = 6.5 Hz). For other diastereomer ^1H NMR ($CDCl_3$, 300 MHz), d (ppm): 7.6 (m, 1H, Ar), 7.22 (m, 2H, Ar), 7.12 (m, 1H, Ar), 5.62 (s, 1H, CH-Ar), 9.96 (m, 2H, OCH_2-), 2.4 (CH_3-Ar), 1.6 (m, 1H, -HCH-), 1.4–1.42 (m, 1H, -HCH-), 1.30 (d, 3H, -CH_3, J_{HH} = 6.5 Hz). ^3C NMR ($CDCl_3$, 75.5 MHz), d (ppm): 137, 135, 130, 128, 126, 125.7, 99, 73, 40.5, 21.6, 17.

(c) G. Marucci, P. Angeli, L. Brasili, M. Buccioni, D. Giardina, U. Gulini, A. Piergentili, G. Sagratini, Med Chem Res 14 (2005) 274 ;
(d) H. Kamogawa, Y. Haramoto, M. Nanasawa, Bull Chem Soc Jpn 52 (1979) 846 ;
(e) A.C. Lima-Leite, K.P. Da Silva, I.A. de Souza, J. Magali de Araujo, D.C. Brondani, Eur J Med Chem (2004) 1059.

[6] (a) M.J. Climent, A. Velty, A. Corma, Green Chem 4 (2002) 565 ;
(b) M.J. Climent, A. Corma, A. Velty, M. Susarte, J Catal 196 (2000) 345 ;
(c) Suffis R, Morton LB, Ishida K, Sawano K, Van Loveren AG, Tetsuo N, Green CB, Reitz GA, Kang RKL, Sato T. US Patent 5,626,852, 1997.
(d) K. Bauer, D. Garbe, H. Surburg, Common fragrances and flavours materials, 2nd ed., VCH, New York, 1990 ;
(e) Dilk E. PCT. Int. Appl. WO 2005009984 A1 20050203, 2005 ;
(f) Lenselink W. US Patent 4,211,674, 1980.

[7] L.L. Santos, V.R. Ruiz, M.J. Sabater, A. Corma, Tetrahedron 64 (2008) 7902.

[8] S. Saha, S.K. Mandal, S.C. Roy, Tetrahedron Lett 49 (2008) 5928.

[9] (a) J. March, Advanced organic chemistry, 4th ed., John Wiley and Sons, New York, 1992, p. 889 ;
(b) J.-C. Cintrat, V. Leat-Crest, J.-L. Parrain, E.L. Grognec, I. Beaudet, J.P. Quintard, J Org Chem (2004) 4251.

[10] R. Gopinath, Sk.J. Haque, B.K. Patel, J Org Chem 67 (2002) 5842.

[11] H. Firouzabadi, N. Iranpoor, B. Karimi, Synlett (1999) 321.

[12] (a) M. Kurihara, W. Hakamata, J Org Chem 68 (2003) 3413 ;
(b) B. Karimi, B. Golshani, Synthesis (2002) 784.

[13] S. Singh, C.D. Duffy, S.T.A. Shah, P.J. Guiry, J Org Chem 73 (2008) 6429.

[14] (a) R. Bisaz, dipl Chem ETH Diss Nr (1975) 5500 ;
(b) P.P. Singh, M.M. Gharia, F. Dasgupta, H.C. Srivastava, Tetrahedron Lett 5 (1977) 439 ;
(c) R.H. Furneaux, G.J. Gainsford, G.P. Lynch, S.C. Yorke, Tetrahedron 49 (1993) 9605.

[15] (a) H. Firouzabadi, N. Iranpoor, H.R. Shaterian, Bull Chem Soc Jpn 75 (2002) 2195 ;
(b) A. Procopio, R. Dalpozzo, A. De Nino, L. Maiuolo, M. Nardi, B. Russo, Adv Synth Catal 347 (2005) 1447.

[16] P.K. Choudhury, J. Almena, F. Foubelo, M. Yus, Tetrahedron 53 (1997) 17373.

[17] (a) S.H. Lee, J.C. Lee, N.S. Kim, Bull Korean Chem Soc 26 (2005) 221 ;
(b) D.H.R. Barton, P.D. Magnus, G. Smith, G. Strecket, D.J. Zurr, J Chem Soc Perkin Trans 1 (1972) 542 ;
(c) E.J. Enholm, J.P. Schulte, J Org Chem 64 (1999) 2610 ;
(d) C. Rosini, S. Scammzzi, M.P. Focati, P. Salvadori, J Org Chem 60 (1995) 8289.

[18] (a) R.U. Lemieux, J.W. Lown, Can J Chem 42 (1964) 893 ;
(b) J.E. McMurry, J.G. Rico, Tetrahedron Lett 30 (1989) 1169.

[19] U. Schmidt, J. Talbiersky, F. Bartkowiak, J. Wild, Angew Chem Int Ed Engl 19 (1980) 198.

[20] H.-S. Dang, B.P. Roberts, D.A. Tocher, J Chem Soc Perkin Trans 1 (2001) 2452.

[21] M. Masui, T. Kawaguchi, S. Ozaki, J Chem Soc Chem Commun 21 (1985) 1484.

[22] T. Fujisaka, M. Miura, M. Nojima, S. Kusabayash, J Chem Soc Perkin Trans 1 (1989) 1031.

[23] T. Sugimura, M. Yoshikawa, T. Futagawa, A. Tai, Tetrahedron 46 (1990) 5955.