$Zn(OTf)_2.6H_2O$ catalysed acylation of aldehydes: preparation of 1,1-diacetates and α-chloroalkyl esters

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1,1-Diacetates (acylals) and α-chloroalkyl esters were prepared from carbonyl compounds with acylating reagents in the presence of 5% mol hexaaqua zinc triflate [$Zn(OTf)_2.6H_2O$] with good yields under mild reaction conditions.

Keywords: hexaaqua zinc triflate [$Zn(OTf)_2.6H_2O$]; 1,1-diacetateacylal; α-chloroalkyl esters

Acylals, being stable in neutral and basic conditions,[1] are synthetically useful protecting groups for carbonyl compounds. Geminal diacetates of α,β-unsaturated aldehydes can serve as precursors for the Diels–Alder reactions.[2-3] α-Chloroalkyl esters are also interesting bifunctional derivatives containing two leaving groups. Hence, the preparations of 1,1-diacetates and α-chloroalkylesters have received considerable attention.

Since Knoevenagel[4] and Claussner[5] found that aldehydes could be converted into 1,1-diacetates with acetic anhydride in the presence of catalytic sulfuric acid about one century ago, many methods of protection for aldehydes have been reported (Scheme 1). In general, the preparation of 1,1-diacetates can be achieved using protic acids,[6-8] Lewis acids,[9-15] H_2NSO_3H,[16] NBS,[17] I_2[18] and other reagents.[19,21] Recently, a zirconium complex[22], bismuth nitrate[23] and indium triflate[24] have been shown to be good catalysts for the preparation of acylals. However, many of these methods require high temperatures, longer reaction times, highly toxic catalysts, or employ strongly acidic or oxidising conditions.

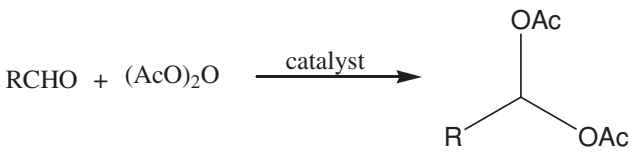
Similarly, α-chloroalkyl esters are synthesised by acylation of carbonyl compounds using acid chlorides and a Lewis acid catalyst[25-28] (Scheme 2), such as zinc chloride or aluminum chloride. Ishino *et al*. reported a convenient approach to the preparation of α-haloalkyl esters using a Zn/TMSCl system,[29] but usually 6 mol equiv. of the zinc metal were needed.

Thus, methods of preparation of 1,1-diacetates and α-chloroalkyl esters under mild reaction conditions, in good yields, and using simple experimental procedures are still of interest.

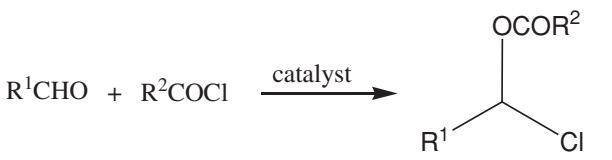
We have found that $Zn(OTf)_2.6H_2O$[30] is an efficient catalyst for the preparation of acylals and α-chloroalkyl esters. Herein, we report the results of our study.

Results and discussion

Various 1,1-diacetates have been prepared from aldehydes and ketones with acetic anhydride using 5% mol of $Zn(OTf)_2.6H_2O$



Scheme 1



Scheme 2

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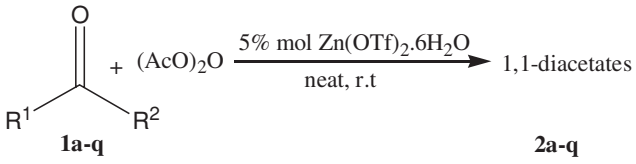


Scheme 3

(Scheme 3), as shown in Table 1. Reactions were carried out at room temperature and without solvent. Aromatic aldehydes reacted with acetic anhydride to give the corresponding 1,1-diacetates in high yield (entries 1–8).

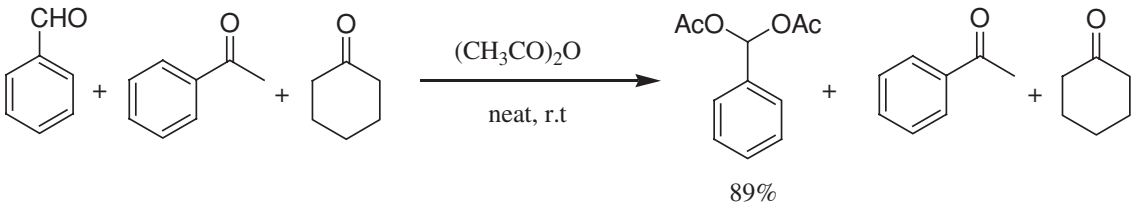
The use of cinnamaldehyde afforded the corresponding product in 84% yield (entry 9). The reactions of aliphatic aldehydes with acetic anhydride also gave the corresponding products in good yields after 6 h (entries 10, 11). The reaction was also performed in some organic solvents but afforded lower yields (entry 1). Unfortunately, ketones proved resistant to 1,1-diacetate synthesis with acetic anhydride. Poor yields of the desired products were found even after long reaction times (entries 12–17).

Thus, a separate experiment was carried out with 1 mmol of benzaldehyde, 1 mmol of acetophenone, 1 mmol of cyclohexanone and 1.2 mmol of acetic anhydride in the presence of 5% mol of $Zn(OTf)_2.6H_2O$ (Scheme 4). As expected, the dominant product was the 1,1-diacetate of benzaldehyde, with only traces of the 1,1-diacetate of ketones being detected. So the above method represented a selective preparation of 1,1-diacetates of aldehydes in the presence of ketones.

Table 1 Preparation of 1,1–diacetates (2) catalysed by 5% mol $Zn(OTf)_2.6H_2O$ without organic solvent[a]

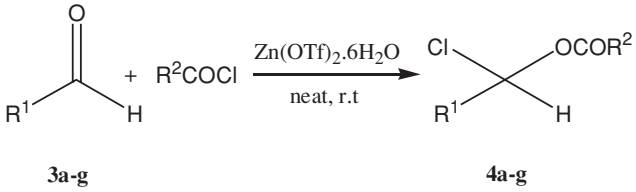
Entry	Substrate	Time/h	Yield[b]/%
1	C_6H_5CHO **1a**	1	91 (41[c], 51[d], 67[e])
2	*p*–ClC_6H_4CHO **1b**	1	91
3	*p*–$CH_3OC_6H_4CHO$ **1c**	1	90
4	*p*–$CH_3C_6H_4CHO$ **1d**	1	91
5	*p*–$NO_2C_6H_4CHO$ **1e**	1	94
6	*m*–$NO_2C_6H_4CHO$ **1f**	1	93
7	2–Thiophene aldehyde **1g**	1	90.5
8	2–Furan aldehyde **1h**	1	89
9	$C_6H_5CHCHCHO$ **1i**	2	84
10	*n*–$C_9H_{19}CHO$ **1j**	6	71
11	*n*–C_3H_7CHO **1k**	6	68
12	$C_6H_5COCH_2CH_3$ **1l**	8	16
13	$C_6H_5COCH_3$ **1m**	8	15
14	2–Acetothiophene **1n**	8	15
15	Cyclohexanone **1o**	8	14
16	Pentan–2–one **1p**	8	14
17	Octan–2–one **1q**	8	11

[a]2 mol equiv. acetic anhydride was used.
[b]Isolated yields.
[c]The reaction was performed in chloroform.
[d]The reaction was performed in nitromethane.
[e]The reaction was performed in acetonitrile.



Scheme 4

Next, we examined the reaction of aldehydes with acid chlorides (Scheme 5). It is interesting that aldehydes could be converted into α-chloroalkyl esters quickly and our results are summarised in Table 2. Acetyl chloride and benzoyl chloride were used as representative acid chlorides in the reactions. Both of the acid chlorides reacted with the substrates smoothly and quickly. Aromatic aldehydes were easily converted into α-chloroalkyl esters using 1.5 equiv. of the acid chloride in the presence of 5% mol $Zn(OTf)_2.6H_2O$ and without solvent.



Scheme 5

Conclusion

In conclusion, $Zn(OTf)_2.6H_2O$ is an efficient catalyst for the preparation of corresponding 1,1-diacetates and α-chloroalkyl esters from aldehydes. The advantages offered are the simplicity of the operation, good yields, mild reaction conditions, short reaction times and high selectivity.

Experimental

All products were analysed by ^{1}H NMR, being recorded on a Varian-400 MHz instrument using $CDCl_3$ as the solvent with TMS as an internal standard. IR spectra were recorded on a AVATAR-370 Infrared Spectrophotometer. Microanalysis was carried out on a Carlo-Erba 1106 instrument. Melting points were determined on a Digital Melting Point Apparatus WRS-1B and are uncorrected. $Zn(OTf)_2.6H_2O$ was prepared according to the literature.[30]

Preparation of 1,1-diacetates: a mixture of aldehyde (2 mmol) and $Zn(OTf)_2.6H_2O$ (0.1 mmol, 0.036g) was treated with acetic anhydride (4 mmol) for the given time. The resulting pink mixture was treated with 20 ml saturated Na_2CO_3 and then extracted with chloroform (10 ml × 3). The combined organic phases were dried over anhydrous $MgSO_4$, and filtered. After concentration in vacuum, the desired product was obtained by TLC (hexane/ethyl acetate = 6:1).

Preparation of α-chloroalkyl esters: 3 mmol of acid chloride was added dropwise into the mixture of aldehyde (2 mmol) and $Zn(OTf)_2.6H_2O$(0.1 mmol, 0.036g). After the given time, the brown reaction mixture was treated with 20 ml water and extracted with ether (10 ml × 3). The combined organic phases were dried with anhydrous $MgSO_4$, and the corresponding product purified by TLC (hexane/ethyl acetate = 8:1).

2a: M.p. 40–43 °C (Lit.[6], 41–41.5 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 7.69 (^{1}H, s), 7.50–7.53 (2H, m), 7.40–7.43 (3H, m), 2.12 (6H, s); IR (cm^{-1}): 1752 (C=O).

2b: M.p. 78–80 °C (Lit.[6], 79–80 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 7.64 (1H, s), 7.46 (2H, d, *J*=8.4 Hz), 7.37 (2H, d, *J*=8.4 Hz), 2.13 (6H, s); IR (cm^{-1}): 1750 (C=O).

2c: M.p. 62–63 °C (Lit.[6], 64–65 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 7.63 (1H, s), 7.47 (2H, d, *J*=8.8 Hz), 6.93 (2H, d, *J*=8.8 Hz), 3.82 (3H, s), 2.12 (6H, s); IR (cm^{-1}): 1750 (C=O).

2d: M.p. 80–81 °C (Lit.[6], 81–82 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 7.62 (1H, s), 7.28–7.33 (4H, m), 2.36 (3H, s), 2.10 (6H, s); IR (cm^{-1}): 1755 (C=O).

2e: M.p. 123–125 °C (Lit.[6], 124–125 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 8.26–8.29 (2H, m), 7.68–7.72 (3H, m), 2.15 (6H, s); IR (cm^{-1}): 1761 (C=O).

2f: M.p. 63–65 °C (Lit.[6], 63–64 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 8.40 (1H, s), 8.28 (1H, dd, *J*=1.2, 8.0 Hz), 7.86 (1H, d, *J*=7.8 Hz), 7.75 (1H, s), 7.62 (1H, t, *J*=8.0 Hz), 2.18 (6H, s); IR (cm^{-1}): 1760 (C=O).

2g: M.p. 65–67 °C (Lit.[6], 66–67 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 7.72 (1H, s), 7.17–7.20 (1H, m), 6.75–6.80 (1H, m), 6.71–6.74 (1H, m), 2.12 (6H, s); IR (cm^{-1}): 1765 (C=O).

Table 2 $Zn(OTf)_2.6H_2O$ (5% mol) catalysed reaction of acid chlorides with aldehydes[a] (3)

Entry	R^1	R^2	Time/min.	Yield[b] /%
1	C_6H_5 **3a**	CH_3	40	94
2	*p*–ClC_6H_4 **3b**	CH_3	40	93
3	*m*–$CH_3OC_6H_4$ **3c**	CH_3	40	91
4	*p*–$NO_2C_6H_4$ **3d**	CH_3	40	89
5	*m*–$NO_2C_6H_4$ **3e**	Ph	60	91
6	*p*–$CH_3OC_6H_4$ **3f**	Ph	60	92
7	C_6H_5 **3g**	Ph	60	90

[a]1.5 mol of acid chloride was used.
[b]Isolated yields.

2h: M.p. 51–52 °C (Lit.[6], 50–51 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 7.73 (1H, s), 7.46 (1H, s), 6.54 (1H, d, *J*=3.4 Hz), 6.39–6.4 (1H, m), 2.14 (6H, s); IR (cm^{-1}): 1763 (C=O).

2i: M.p. 83–85 °C (Lit.[24], 84–85 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 7.41–7.43 (2H, m), 7.27–7.38 (4H, m), 6.88 (1H, d, *J*=15.8 Hz), 6.21 (1H, dd, *J*=6.5, 15.8 Hz), 2.14 (6H, s); IR (cm^{-1}): 1762 (C=O).

2j: Oil (Lit.[24]) ^{1}H NMR ($CDCl_3$) ppm δ: 6.78 (1H, t, *J*=5.6 Hz), 2.09 (6H, s), 1.71–1.78 (2H, m), 1.25–1.32 (14H, m), 0.86–0.89 (3H, m); IR (cm^{-1}): 1760 (C=O).

2k: Oil (Lit.[31]) ^{1}H NMR ($CDCl_3$) ppm δ: 6.51 (1H, t, *J*=5.4 Hz), 2.08 (6H, s), 1.80–1.84 (2H, m), 1.24–1.29 (2H, m), 0.90–0.94 (3H, t, *J*=4.4 Hz); IR (cm^{-1}): 1764 (C=O).

2l: M.p. 51–53 °C ^{1}H NMR ($CDCl_3$) ppm δ: 7.51–7.53 (2H, m), 7.40–7.43 (3H, m), 2.17 (2H, m), 2.13 (6H, s), 1.09 (3H, m); IR (cm^{-1}): 1760 (C=O); Anal. calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.12; H, 6.87.

2m: M.p. 49–52 °C (Lit.[19]) ^{1}H NMR ($CDCl_3$) ppm δ: 7.51–7.54 (2H, m), 7.40–7.44 (3H, m), 2.15 (3H, s), 2.13 (6H, s); IR (cm^{-1}): 1758 (C=O).

2n: M.p. 69–70 °C ^{1}H NMR ($CDCl_3$) ppm δ: 7.17–7.21 (1H, m), 6.74–6.78 (1H, m), 6.71–6.73 (1H, m), 2.20 (3H, s), 2.12 (6H, s); IR (cm^{-1}): 1761 (C=O); Anal. calcd. for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30. Found: C, 52.66; H, 5.35.

2o: Oil (Lit.[19]) ^{1}H NMR ($CDCl_3$) ppm δ: 1.36–1.40 (6H, m), 1.78–1.82 (4H, m), 2.14 (6H, s); IR (cm^{-1}): 1750 (C=O).

2p: Oil ^{1}H NMR ($CDCl_3$) ppm δ: 2.11 (6H, s), 1.79 (3H, s), 1.68–1.73 (2H, m), 1.30–1.35 (2H, m), 1.03 (3H, t, *J*=4.4 Hz); IR (cm^{-1}): 1768 (C=O).

2q: Oil ^{1}H NMR ($CDCl_3$) ppm δ: 2.12 (6H, s), 1.81 (3H, s), 1.70–1.73 (2H, m), 1.29–1.38 (8H, m), 1.01 (3H, m); IR (cm^{-1}): 1758 (C=O).

4a: Oil (Lit.[25]) ^{1}H NMR ($CDCl_3$) ppm δ: 7.48–7.50 (2H, m), 7.41–7.43 (3H, m), 7.36 (1H, s), 2.09 (3H, s); IR (cm^{-1}): 1760 (C=O).

4b: Oil (Lit.[25], 29–30 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 7.43 (1H, s), 7.42 (2H, d, *J*=8.0 Hz), 7.35 (2H, d, *J*=8.0 Hz), 2.10 (3H, s); IR (cm^{-1}): 1760 (C=O).

4c: Oil ^{1}H NMR ($CDCl_3$) ppm δ: 7.37 (1H, s), 7.26–7.31 (1H, m), 7.02–7.07 (2H, m), 6.86–6.92 (1H, m), 3.79 (3H, s), 2.09 (3H, s); IR (cm^{-1}): 1764 (C=O); calcd. for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17. Found: C, 56.01; H, 5.20.

4d: M.p. 94–95 °C (Lit.[25], 95–96 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 8.26–8.28 (2H, m), 7.77–7.79 (2H, m), 7.47 (1H, s), 2.18 (3H, s); IR (cm^{-1}): 1761 (C=O).

4e: M.p. 64–65 °C ^{1}H NMR ($CDCl_3$) ppm δ: 8.27–8.30 (1H, m), 8.10–8.14 (2H, m), 7.97–8.00 (1H, m), 7.73 (1H, s), 7.62–7.68 (2H, m), 7.46–7.54 (3H, m); IR (cm^{-1}): 1753 (C=O); calcd. for $C_{14}H_{10}ClNO_4$: C, 57.65; H, 3.46; N, 4.80. Found: C, 57.69; H, 3.50; N, 4.83.

4f: M.p. 76–78 °C ^{1}H NMR ($CDCl_3$) ppm δ: 8.11–8.14 (2H, m), 7.46–7.64 (8H, m), 3.64 (3H, s); IR (cm^{-1}): 1755 (C=O); calcd. for C15H13ClO3: C, 65.11; H, 4.74; Found: C, 65.07; H, 4.71.

4g: M.p. 50–52 °C (Lit.[32], 51–52 °C) ^{1}H NMR ($CDCl_3$) ppm δ: 7.61–7.67 (2H, m), 7.46–7.56 (6H, m), 7.38–7.43 (3H, m); IR (cm^{-1}): 1750 (C=O).

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References

1 H.W. Pinnick, K.S. Kochhar, B.S. Bal, R.P. Deshpande and S.N. Radhakrishna, *J. Org. Chem*., 1983, 48, 1765.
2 B.B. Snider and S.G. Amin, *Synth. Commun*., 1978, 117.
3 P. Kummar, V.R. Hedge and T.P. Kumar, *Tetrahedron Lett*., 1995, 36, 601.
4 F. Knoevenagel, J. Liebigs Ann. *Chem*., 1905, 111.
5 P. Claussner, Ber. Dtsch. *Chem. Ges*., 1905, 38, 2860.
6 F. Freeman and E.M. Karchetski, *J. Chem. Eng. Data*, 1977, 22, 355.
7 S.M. Lieberman and R. Connor, *Org. Synth*., 1951, Coll. Vol. 2, 441–443.
8 M.J. Gregory, *J. Chem. Soc*., B 1970, 1201.
9 J.K. Michie and J.A. Miller, *Synthesis*, 1981, 824.
10 K.S. Kochhar, B.S. Bal, R.P. Deshpande, S.N. Rajadhyaksha and H.W. Pinnick, *J. Org. Chem*., 1983, 48, 1765.
11 I. Scribine, Bull. *Soc. Chem*. Fr., 1961, 1194.
12 Y.Q. Li, *Synth. Commun*., 2000, 30, 3913.
13 V.K. Agarwal, S. Fonquerna and G.P. Vennall, *Synlett*, 1998, 849.
14 K.L. Chandra, P. Saravanan and V.K. Singh, *Synlett*, 2000, 359.
15 M.D. Carrigan, K.J. Eash, M.C. Oswald and R.S. Mohan, *Tetrahedron Lett*., 2001, 42, 8133.
16 T.S. Jin, G. Sun, Y.W. Li and T.S. Li, *Green Chem*., 2002, 4, 255.
17 B. Karimi, H. Seradj and R.G. Ebrahimian, *Synlett*, 2000, 623.
18 N. Deka, D.J. Kalita, R. Borah and J.C. Sarma, *J. Org. Chem*., 1997, 62, 1563.
19 M. Curini, F. Epifano, M.C. Marcotullio, O. Rosati and M. Nocchetti, *Tetrahedron Lett*., 2002, 43, 2709.
20 G.P. Romanelli, H.J. Thomas, G.T. Baronettic and J.C. Autinoa, *Tetrahedron Lett*., 2003, 44, 1301.
21 M.V. Joshi, C.S. Narasimhan and D. Mukesh, *Zeolites*, 1995, 15, 597;
22 G. Smitha and C.S. Reddy, *Tetrahedron*, 2003, 59, 9571.
23 D.H. Aggen, J.N. Arnold, P.D. Hayes, N.J. Smoter and R. S. Mohan, *Tetrahedron*, 2004, 60, 3675.
24 R. Ghosh, S. Maiti, A. Chakraborty and R. Halder, *J. Mol. Catal. A: Chem*., 2004, 215, 49.
25 M. Neuenschwnder, P. Bigler, K. Christen, R. Iseli and R. Kyburz, *Helv. Chim. Acta*, 1978, 61, 2047.
26 P. Bigler, S. Schonholzer and M. Neuenschwnder, *Helv. Chim. Acta*, 1978, 61, 2059.
27 P. Bigler, H. Muhle and M. Neuenschwnder, *Synthesis*, 1978, 593;
28 T. S. Chou and P. Knochel, *J. Org. Chem*., 1990, 55, 4791.
29 Y. Ishino, M. Mihara, T. Takeuchia and M. Takemoto, *Tetrahedron Lett*., 2004, 45, 3503.
30 C. Nguyen-Trung, J.C. Bryan and D.A. Palmer, *Struct. Chem*., 2004, 15, 89.
31 B.C. Ranu, J.D. Dutta and A. Das, *Chem. Lett*., 2003, 32, 366.
32 P.R. Jones, C.J. Jarboe and R. Nadeau, *J. Organometallic. Chem*., 1967, 8, 361.