



Acylative Cleavage of Ethers with ZnCl₂

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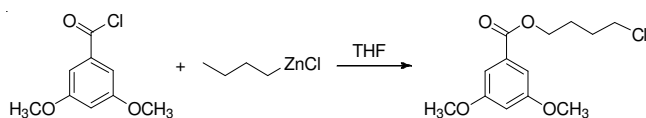
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Acylative cleavage of common ether solvents with ZnCl₂ was reported. Different substituted acyl chlorides were reacted with the common ether solvents in the presence of ZnCl₂ to obtain the corresponding substituted benzoate.

Key Words: Acylative cleavage, Ether, ZnCl₂

INTRODUCTION

Ethers have been widely used as good solvents in the reaction of organic metal due to their appropriate polarity and inertness¹⁻³. However, when we tried to prepare 1-(3,5-dimethoxyphenyl)pentan-1-one from 3,5-dimethoxybenzoyl chloride and butylzinc chloride (prepared with butylmagnesium chloride with ZnCl₂), 4-chlorobutyl 3,5-dimethoxybenzoate was surprisingly obtained (**Scheme-I**). It was finally found that this ester product came from the reaction of 3,5-dimethoxybenzoyl chloride and tetrahydrofuran under the catalysis of ZnCl₂. In fact, it is reported that ethers can be converted to the corresponding esters in the presence of acylating reagents in many literature⁴⁻⁸. Although ZnCl₂ had been reported earliest to achieve the synthesis of 4-chlorobutyl benzoate with benzoyl chloride and THF⁹, there was no detailed research about its scope to achieve acylative cleavage of ethers. Herein, acylative cleavage of common ether solvents with ZnCl₂ was reported.



Scheme-I

EXPERIMENTAL

The NMR spectra were recorded on Bruker Avance III 500 MHz and chemical shifts are expressed in ppm using TMS as an internal standard. Mass spectra are recorded on Varian 210-MS.

Synthesis of substituted benzoate with acyl chlorides and ethers: ZnCl₂ (3.75 mmol) was dissolved in ether (10

mL) and then acyl chloride (5 mmol) was added. The reactant was stirred for 12 h at room temperature. 10 % HCl solution was added and the mixture was extracted with EtOAc twice. Then the combined organic layer was washed with saturated NaHCO₃ and water successively and dried with MgSO₄. The solvent was removed and the residue was purified with column chromatography (V_{PE} : V_{EtOAc} = 8:1) to give the yellow oil liquid.

Ethyl 3,5-dimethoxybenzoate (1a): ¹H NMR (CDCl₃, 500 MHz): δ 7.20 (d, *J* = 2.35 Hz, 2H, Ar-H), 6.65 (t, *J* = 2.39 Hz, 1H, Ar-H), 4.38 (q, *J* = 7.17 Hz, 2H, CH₃CH₂), 3.84 (s, 6H, OCH₃), 1.39 (t, *J* = 7.09 Hz, 3H, CH₃CH₂); EI-MS: 210.0 [M]⁺.

Isopropyl 3,5-dimethoxybenzoate (1b): ¹H NMR (CDCl₃, 500 MHz): δ 7.20 (d, *J* = 2.31 Hz, 2H, Ar-H), 6.64 (t, *J* = 2.33 Hz, 1H, Ar-H), 5.27-5.22 (m, 1H, CH(CH₃)₂), 3.84 (s, 6H, OCH₃), 1.37 (d, *J* = 6.28 Hz, 6H, CH(CH₃)₂); EI-MS: 224.0 [M]⁺.

4-Chlorobutyl 3,5-dimethoxybenzoate (1c): ¹H NMR (CDCl₃, 500 MHz): δ 7.18 (d, *J* = 2.33 Hz, 2H, Ar-H), 6.65 (t, *J* = 2.35 Hz, 1H, Ar-H), 4.35 (t, *J* = 5.70 Hz, 2H, OCH₂), 3.83 (s, 6H, OCH₃), 3.62 (t, *J* = 6.01 Hz, 2H, CH₂Cl), 1.96-1.93 (m, 4H, OCH₂(CH₂)₂CH₂Cl); EI-MS: 272.0 [M]⁺.

Ethyl 4-methoxybenzoate (2a): ¹H NMR (CDCl₃, 500 MHz): δ 8.01 (d, *J* = 8.95 Hz, 2H, Ar-H), 6.92 (d, *J* = 8.93 Hz, 2H, Ar-H), 4.35 (q, *J* = 7.19 Hz, 2H, CH₃CH₂), 3.86 (s, 6H, OCH₃), 1.38 (t, *J* = 7.21 Hz, 3H, CH₃CH₂); EI-MS: 180.0 [M]⁺.

Isopropyl 4-methoxybenzoate (2b): ¹H NMR (CDCl₃, 500 MHz): δ 8.00 (d, *J* = 8.82 Hz, 2H, Ar-H), 6.92 (d, *J* = 8.82 Hz, 2H, Ar-H), 5.26-5.21 (m, 1H, CH(CH₃)₂), 3.87 (s, 6H, OCH₃), 1.36 (d, *J* = 6.29 Hz, 6H, CH(CH₃)₂); EI-MS: 194.0 [M]⁺.

4-Chlorobutyl 4-methoxybenzoate (2c): ¹H NMR (CDCl₃, 500 MHz): δ 8.00 (d, *J* = 8.82 Hz, 2H, Ar-H), 6.93 (t, *J* = 8.89

Hz, 1H, Ar-H), 4.34 (t, $J = 5.88$ Hz, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 3.63 (t, $J = 6.13$ Hz, 2H, CH_2Cl), 1.95-1.94 (m, 4H, $\text{OCH}_2(\text{CH}_2)_2\text{CH}_2\text{Cl}$); EI-MS: 242.1 $[\text{M}]^+$.

Ethyl 2-methoxybenzoate (3a): $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.78 (d, $J = 7.80$ Hz, 1H, Ar-H), 7.44 (t, $J = 8.94$ Hz, 1H, Ar-H), 6.98-6.95 (m, 2H, Ar-H), 4.35 (q, $J = 7.17$ Hz, 2H, OCH_2CH_3), 3.89 (s, 3H, OCH_3), 1.36 (t, $J = 7.08$ Hz, 3H, OCH_2CH_3); EI-MS: 180.8 $[\text{M}]^+$.

Ethyl 2-ethoxybenzoate (4a): $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.77 (d, $J = 7.65$ Hz, 1H, Ar-H), 7.43-7.40 (m, 1H, Ar-H), 6.94 (t, $J = 8.70$ Hz, 2H, Ar-H), 4.36 (q, $J = 7.20$ Hz, 2H, $\text{COOCH}_2\text{CH}_3$), 4.10 (q, $J = 6.98$ Hz, 2H, $\text{ArOCH}_2\text{CH}_3$), 1.44 (t, $J = 6.93$ Hz, 3H, $\text{ArOCH}_2\text{CH}_3$), 1.37 (t, $J = 7.18$ Hz, 3H, $\text{COOCH}_2\text{CH}_3$); EI-MS: 194.7 $[\text{M}]^+$.

Ethyl benzoate (5a): $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 8.07 (d, $J = 7.23$ Hz, 2H, Ar-H), 7.55 (t, $J = 8.55$ Hz, 1H, Ar-H), 7.44 (t, $J = 7.60$ Hz, 2H, Ar-H), 4.40 (q, $J = 7.11$ Hz, 2H, OCH_2CH_3), 1.40 (t, $J = 7.18$ Hz, 3H, OCH_2CH_3); EI-MS: 150.2 $[\text{M}]^+$.

Ethyl 2-chlorobenzoate (6a): $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.80 (d, $J = 8.35$ Hz, 1H, Ar-H), 7.44-7.37 (m, 2H, Ar-H), 7.30 (t, $J = 7.64$ Hz, 1H, Ar-H), 4.39 (q, $J = 7.15$ Hz, 2H, OCH_2CH_3), 1.38 (t, $J = 7.11$ Hz, 3H, OCH_2CH_3); EI-MS: 184.2 $[\text{M}]^+$.

Ethyl 4-chlorobenzoate (7a): $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.98 (d, $J = 8.52$ Hz, 2H, Ar-H), 7.40 (d, $J = 8.53$ Hz, 2H, Ar-H), 4.38 (q, $J = 7.17$ Hz, 2H, OCH_2CH_3), 1.39 (t, $J = 7.13$ Hz, 3H, OCH_2CH_3); EI-MS: 184.0 $[\text{M}]^+$.

Isopropyl 4-chlorobenzoate (7b): $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ 7.98 (d, $J = 8.55$ Hz, 2H, Ar-H), 7.40 (δ , $J = 8.51$ Hz, 2H, Ar-H), 5.28-5.23 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.37 (d, $J = 6.30$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$); EI-MS: 198.1 $[\text{M}]^+$.

RESULTS AND DISCUSSION

To begin with, the reaction of 3,5-dimethoxybenzoyl chloride with ethyl ether was selected to be a model reaction to survey the reaction condition. Besides ZnCl_2 , other common Lewis acid, FeCl_3 , AlCl_3 , SnCl_4 and MgCl_2 were used to catalyze this transformation. It has been shown that the better yield 67.4 % was obtained under the catalysis of ZnCl_2 when compared with other common Lewis acids. Considering the liability to hydrolyzation of acyl chloride, ZnCl_2 , FeCl_3 and AlCl_3 were dried with refluxing SOCl_2 and compared with those without dryness. ZnCl_2 and FeCl_3 without pretreatment almost provided no ester product while AlCl_3 without pretreatment gave better yield than anhydrous AlCl_3 (Table-1, Entry 1-7). When the reactant ratio of acyl chloride to ether was increased to 1:30 or reduced to 1:10, it was unhelpful to the yield (Table-1, entry 9-10). Moreover, the ZnCl_2 amount was tried to be reduced. The results showed that the reaction did not happen in the absence of ZnCl_2 . The yield was improved with the increase of the amount of ZnCl_2 and the best yield was obtained when 0.75 equivalents ZnCl_2 was employed (Table-1, entry 11-14). Therefore, optimized conditions involved reaction of 3,5-dimethoxybenzoyl chloride with ethyl ether (20 equiv) under the catalysis of ZnCl_2 (0.75 equiv) at 25 °C, which gave ethyl 3,5-dimethoxybenzoate in yield 68 %.

To investigate the scope of acylative cleavage of ether solvents with ZnCl_2 , the common ether solvents were selected

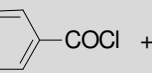
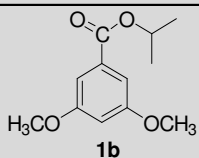
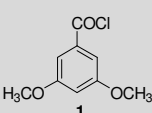
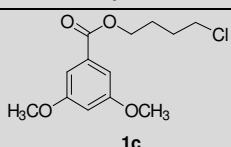
to react with different substituted acyl chloride and the results were listed in Table-2. The acyclic ethers, ethyl ether and *iso*-propyl ether, gave the common ester while the cyclic ether tetrahydrofuran formed the chloroester. As we can see, the common ether, *iso*-propyl ether and tetrahydrofuran are all able to react with different substituted acyl chloride, which means the corresponding ester will be the inevitable byproduct in the reaction of acyl chloride in the presence of ZnCl_2 and ether solvent. Moreover, the results indicated that the electron-donating group methoxy group on benzene group was unfavourable to the acylative cleavage of ether and the reaction yields with compound **2** were better than those with compound **1**. This is in accord with the reaction mechanism that ZnCl_2 deprives the chloride ion from acyl chloride to form the active acyl cation which attacks the oxygen group of ether to obtain the product.

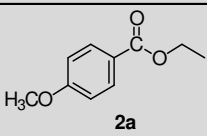
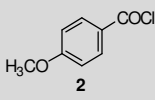
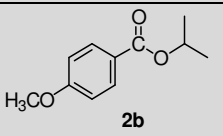
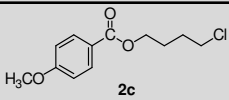
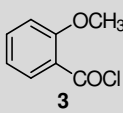
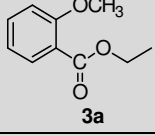
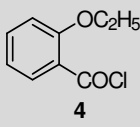
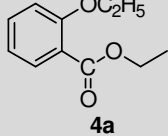
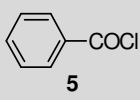
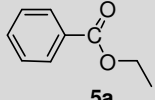
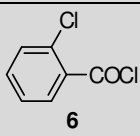
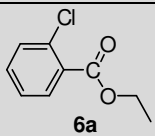
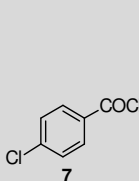
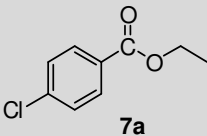
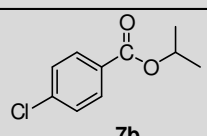
TABLE-1
SYNTHESIS OF ETHYL 3,5-DIMETHOXYBENZOATE **1a**^a

Entry	Reactant ratio ^b	Catalyst	Catalyst amount (equiv)	Yield (%)
1	1:20	ZnCl_2	1	67
2	1:20	FeCl_3	1	Trace
3	1:20	FeCl_3^c	1	56
4	1:20	AlCl_3	1	17
5	1:20	AlCl_3^c	1	Trace
6	1:20	SnCl_4	1	47
7	1:20	MgCl_2	1	Trace
8	1:10	ZnCl_2	1	51
9	1:30	ZnCl_2	1	57
10	1:20	ZnCl_2	0	n.d. ^d
11	1:20	ZnCl_2	0.1	10
12	1:20	ZnCl_2	0.3	43
13	1:20	ZnCl_2	0.5	55.4
14	1:20	ZnCl_2	0.75	68

^aReaction condition: 3,5-dimethoxybenzoyl chloride(5 mmol) with ethyl ether was stirred at 25°C for 12 h; ^bReactant ratio: 3,5-dimethoxybenzoyl chloride: ethyl ether; ^cDried by refluxing with SOCl_2 ; ^dNot detected

TABLE-2
SYNTHESIS OF SUBSTITUTED BENZOATES FROM ACYL CHLORIDES AND ETHERS

Entry	Acyl chloride	Ether	Product	Yield (%)
1		(<i>i</i> -Pr) ₂ O		50
2		THF		46

Entry	Acyl chloride	Ether	Product	Yield (%)
3		Ether		70
4		(<i>iso</i> -Pr) ₂ O		83
5		THF		58
6		Ether		70
7		Ether		70
8		Ether		71
9		Ether		65
10		Ether		80
11		(<i>iso</i> -Pr) ₂ O		68

Conclusion

ZnCl₂ was proved to successfully catalyze the acylative cleavage of common ether solvents. Different substituted acyl chlorides were reacted with the common ether solvents in the presence of ZnCl₂ to obtain the corresponding substituted benzoate. The acyclic ethers gave the common ester while the cyclic ether tetrahydrofuran formed the chloroester.

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REFERENCES

1. Q. Chen, L. Iies, N. Yoshikai and E. Nakamura, *Org. Lett.*, **13**, 3232 (2011).
2. A. Graces, L.F. Sanchez-Barba, C. Alonso-Moreno, M. Fajardo, J. Fernandez-Baeza, A. Otero, A. Lara-Sanchez, I. Lopez-Solera and A.M. Rodriguez, *Inorg. Chem.*, **49**, 2859 (2010).
3. M.H. Xie, C.Y. Feng, J.T. Zhang, C.Q. Liu, K. Fang, G.Y. Shu and W.S. Zuo, *J. Organomet. Chem.*, **696**, 3397 (2011).
4. V. Suresh, N. Suryakiran, K. Rajesh, J.J.P. Selvam, M. Srinivasulu and Y. Venkateswarlu, *Synth. Comm.*, **38**, 92 (2008).
5. V. Suresh, N. Suryakiran and Y. Venkateswarlu, *Can. J. Chem.*, **85**, 1037 (2007).
6. J.S. Yadav, B.V.S. Reddy, P.M.K. Reddy, U. Dash and M.K. Gupta, *J. Mol. Catal. A: Chem.*, **271**, 266 (2007).
7. M.A. Pasha and Y.Y. Myint, *Ultrason. Sonochem.*, **13**, 175 (2006).
8. S.J. Coles, J.F. Costello, W.N. Draffin, M.B. Hursthouse and S.P. Paver, *Tetrahedron*, **61**, 4447 (2005).
9. M.E. Synerhole, *Org. Synth.*, **29**, 30 (1949).