Short communication

Single-Pot Conversion of an Acid to the Corresponding 4-Chlorobutyl Ester

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Abstract

A single pot conversion of carboxylic acids into the corresponding 4-chlorobutyl esters has been achieved by a novel procedure. The intermediate acid chlorides are not isolated. The double bond and aromatic methoxy group survive the mild reaction conditions. In almost all the examples studied the products are purified by simple flash chromatography.

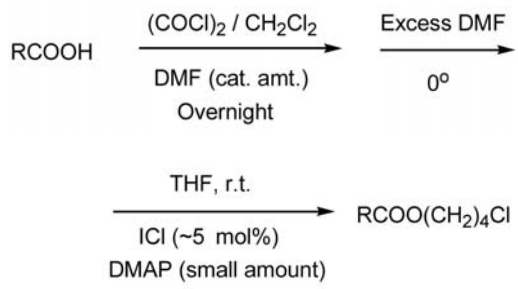
Keywords: 4-Chlorobutyl esters, acylative cleavage, esterification, ring opening, iodine monochloride

1. Introduction

Tetrahydrofuran (THF) ring opening with acid chloride is a useful method to prepare 4-chlorobutyl esters. However, the reaction is very slow and therefore various catalysts and techniques are employed to accelerate it. Anhydrous $ZnCl_2$[1,2], $FeCl_3$[3] YCl_3,[4] $InBr_3$,[5] $Bi(NO_3)_3$,[6] $Co_2(CO)_8$,[7] zinc dust under ultrasonication,[8] iodine,[9,10] some group 5 and group 6 metals ($MoCl_5$, WCl_6, $NbCl_5$ and $TaCl_5$),[11] and BCl_3[12] are some notable substances used for this purpose. 4-Iodobutyl esters can also be prepared by THF ring cleavage using acid chloride (or anhydride) in the presence of sodium iodide[13] or samarium triiodide.[14] However, these require the preparation and isolation of acid chlorides which are difficult to handle and purify. THF ring cleavage leading to 4-bromobutyl esters can be carried out with the help of acyloxyphosphonium bromides that are generated *in situ* from the salts of acids and $Ph_3P.Br_2$. These reactions are catalysed by $ZnBr_2$[15] or allyl samarium bromide.[16] In the present communication we report direct and convenient method for the preparation of 4-chlorobutyl esters from the acids by THF ring cleavage.

2. Results and Discussion

In our method the acid was first converted into the acid chloride using oxalyl chloride and a catalytic amount of dimethyl formamide (DMF) in dichloromethane. After 24 hours the excess oxalyl chloride was decomposed at low temperature by slow addition of excess DMF. This way the THF ring cleavage by oxalyl chloride itself was avoided. Thereafter tetrahydrofuran, 5 mol % iodine monochloride (Wijs solution) and a small amount of 4-dimethylaminopyridine (DMAP) was added in succession. The second stage required some 8 to 24 hours for completion, depending on the initial reactant acid. The sequence of operations is presented in Scheme 1.



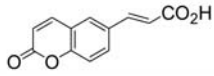
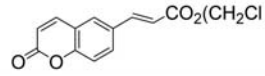
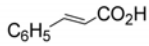
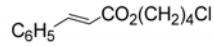
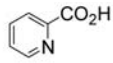
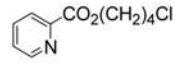
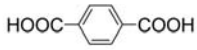
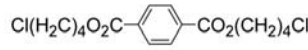
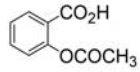
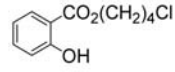
Scheme 1. The conversion of an acid into the 4-chlorobutyl ester

Initially we employed anhydrous $ZnCl_2$ as a catalyst in the second stage. This resulted in a considerable amount of side products that were difficult to separate by chromatography. Therefore, we used a soft acid, i.e., NBS and iodine[9] as catalyst in separate experiments. However, conversions in these cases were low even after long reac-

tion times. The use of iodine monochloride along with a little DMAP accelerated the reaction without formation of undesirable side products. The general procedure is given in the experimental section.

In most of the cases studied so far a single product was formed. Only a flash chromatography was needed to purify it. All products ecept (I and IV) from 3-[coumarin-6-yl]prop-2-enoic acid (1) and from 3,5-dinitrobenzoic

Table 1. Reaction condition and yield with various substrates

Starting acid (Structure No.)	Product esters (Structure No.)	Time in the second step, hours	Yield, %
			
(1)	(I)	20	72
			
(2)	(II)	20	75
			
(3)	(III)	12	95
$3,5\text{-}(NO_2)_2C_6H_3COOH$	$3,5\text{-}(NO_2)_2C_6H_3CO_2(CH_2)_4Cl$		
(4)	(IV)	12	92
$4\text{-}NO_2C_6H_4COOH$	$4\text{-}NO_2C_6H_4CO_2(CH_2)_4Cl$		
(5)	(V)	8	90
C_6H_5COOH	$C_6H_5CO_2(CH_2)_4Cl$		
(6)	(VJ)	24	66
			
(7)	(VII)	24	74
$4\text{-}CH_3C_6H_4COOH$	$4\text{-}CH_3C_6H_4CO_2(CH_2)_4Cl$		
(8)	(VIII)	24	65
$4\text{-}CH_3OC_6H_4COOH$	$4\text{-}CH_3OC_6H_4CO_2(CH_2)_4Cl$		
(9)	(IX)	24	48
			
(10)	(X)	24	52
$C_6H_5CH_2COOH$	$C_6H_5CH_2CO(CH_2)_4Cl$		
(11)	(XI)	24	78
$CH_3(CH_2)_{10}CO_2H$	$CH_3(CH_2)_{10}CO_2(CH_2)_4Cl$		
(12)	(XII)	24	72
$HO_2C[CH_2]_2CO_2H$	$Cl(CH_2)_4O_2C[CH_2]CO_2(CH_2)_4Cl$		
(13)	(XIII)	24	74
$4\text{-}CH_3C_6H_4SO_2OH$	$4\text{-}CH_3C_6H_4SO_3(CH_2)_4Cl$		
(14)	(XIV)	48	52

[a] This is a new acid prepared in our laboratory.

acid (4) are colorless liquids. It is noteworthy that phenolic ether in 4-methoxybenzoic acid (9) survived the reaction conditions. However, the acetoxy group *ortho* to the acid function in 4-acetoxybenzoic acid (aspirin 10) did not survive, and at the same time the yield of deacetylated 4-chlorobutyl ester (X) was somewhat low. Dibasic acids (7 and 13) were converted into the corresponding diesters (VII and XIII respectively) using three equivalents of oxalyl chloride. The procedure was quite successful with α,β-unsaturated acids (1 and 2); the double bond remained unaffected under the mild reaction conditions. The method worked well with aromatic acids having electron releasing as well as electron donating substituents. The time to reach the equilibrium however varied for different substrates; longer times were needed for aromatic acids having electron releasing substituents. The reaction conditions and yields for different reactants are summarized in Table 1.

All the products were characterized spectroscopically. Physical and spectral data are presented in the experimental section.

3. Experimental

3. 1. Preparation of 3-[Coumarin-6-yl]prop-2-enoic acid (1)

This was prepared by condensation of coumarin-6-carbaldehyde (348 mg, 2 mmol) with malonic acid (312 mg, 3 mmol) in dry pyridine (10 ml) using catalytic amounts of piperidine and β-alanine. After 12 hours at room temperature the reaction mixture was refluxed for 4 hours. Then the mixture was treated with conc. HCl. When all the pyridine was neutralised the product precipitated out as a pure compound. Yield: 395 mg (91%). M.p. = 327 °C. LCMS: *m/z* 216.9 (M^+ +1). ^{1}H NMR (300 MHz, d_6-DMSO): δ 12.457 (1H, br. s, -COOH); 8.020–7.905 (3H, H-7,8 of coumaryl group and H-4); 7.604 (1H, d, *J* = 16 Hz, H-3); 7.395 (1H, d, *J* = 2.7 Hz, H-5 of coumaryl group), and 6.570–6.505 (2H, H-3 of coumaryl group and H-2). Anal. Calcd. for $C_{12}H_8O_4$ (M.W. 216.19): C 66.67, H 3.70. Found C 66.81, H 3.62.

3. 2. General Procedure for the Preparation of 4-chlobutyl esters (I – XIV)

The starting acid (1 mmol) was dissolved/suspended in 10 ml of dry dichloromethane to which oxalyl chloride (1.5 mmol for monobasic acid; 3 mmol for dibasic acid) in 5 ml dry dichloromethane was added dropwise at 0 C with constant stirring. A capillary drop of DMF was added and the reaction mixture kept overnight at room temperature. Thereafter, the excess oxalyl chloride was decomposed by adding excess DMF. Approximately 2–3 mmol of THF was added followed by 0.05 mmol ICl and 5 mg of DMAP. After attainment of equilibrium (TLC monitoring) the reaction mixture was poured into water and unreacted acid was neutralized with $NaHCO_3$ solution. The product was then extracted with dichloromethane and extract dried over anhydrous Na_2SO_4. This dried extract was concentrated and finally purified by chromatography over silica gel (60–120 mesh size). The products were eluted in 5–15% ethyl acetate in petroleum ether (60–80°). The product (I) from 3-[coumarin-6-yl]prop-2-enoic acid (1) and the product (IV) were solids with melting points 126 °C and 46 °C respectively. All other products were colorless oils.

Spectral Data of the 4-Chlorobutyl esters: All products were characterized by spectral studies; some of them are reported here for the first time. The spectral data of the new compounds and some other selected compounds (whose spectral data are unavailable in the literature) are only presented here. IR spectra were recorded in KBr discs with a Shimadzu spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Bruker FT NMR spectrometer (Model AV-500) using TMS as an internal standard.

4'-Chlorobutyl 3-[coumarin-6-yl]prop-2-en-1-oate (I): LCMS: *m/z* 306.9 (M^+ + 1) and 308.9 (M^+ + 3) in the intensity ratio of 3:1. IR (KBr): ν_{max} 3020 (CH-arom.), 2960 (CH-aliph.), 1727 (CO-ester), 1711 (CO-lactone), 1627 (C=C), 1260 (C-O), 1019 cm^{-1} (CH-*trans*-olefin). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.709 (1H, dd, *J* = 8 and 1.6 Hz, H-7 of coumaryl group), 7.726 (1H, d, *J* = 9.5 Hz, H-4 of coumaryl group), 7.696 (1H, d, *J* = 16 Hz, H-3), 7.627 (1H, d, *J* = 1.6 Hz, H-5 of coumaryl group), 7.354 (1H, d, *J* = 8 Hz, H-8 of coumaryl group), 6.467 (1H, d, *J* = 9.5, H-2 of coumaryl group), 6.448 (1H, d, *J* = 16 Hz, H-2), 4.226 (2H, t, *J* = 6 Hz, H-1'), 3.611 (2H, t, *J* = 6.2 Hz, H-4'), 1.907 (4H, m, H-2',3'). ^{13}C NMR (100 MHz, $CDCl_3$): 166.532, 160.096, 155.033, 142.983, 142.769, 130.930, 130.845, 127.762, 119.127, 118.854, 117.688, 117.532, 63.917, 44.511, 29.196, and 29.146. Anal. Calcd. for $C_{16}H_{15}ClO_4$ (M.W. 306.75): C 62.65, H 4.93. Found C 62.50, H 5.07.

4'-Chlorobutyl pyridine-2-carboxylate (III): LCMS: *m/z* 241.1 (M^+ + 1) and 216.1 (M^+ + 3) in the intensity ratio of 3:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.764 (1H, d, *J* = 4.5 Hz, H-6), 8.122 (1H, d, *J* = 8 Hz, H-3), 7.845 (1H, m, H-4), 7.480 (1H, m, H-5), 4.508 (t, *J* = 6.2 Hz, 2H), 3.639 (t, *J* = 6 Hz, 2H), 2.036 (m, 2H), 1.950 (4H, m, H-2',3').

4'-Chlorobutyl 3,5-dinitrobenzoate (IV): LCMS: *m/z* 303 (M^+ + 1) and 305 (M^+ + 3) in the intensity ratio of 3:1. IR (thin film): ν_{max} 3010 (H-Ar), 2928 and 2856 (H-aliph.), 1739 (CO-ester), 1609, 1462 (NO_2), 1233 (C-O, ester), 1057 cm^{-1}(C-O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.237, (1H, t, *J* = 2.1 Hz, H-4), 9.158 (2H, d, *J* = 2.1 Hz, H-2,6), 4.459 (2H, t, *J* = 6 Hz, H-1'), 3.606 (2H, t, *J* = 6 Hz, H-4'), 1.948 (4H, m, H-2',3').

4'-Chlorobutyl 4-methoxybenzoate (IX): LCMS: *m/z* 243 ($M^+ + 1$) and 245 ($M^+ + 3$) in the intensity ratio of 3:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.992 (2H, d, *J* = 8.5 Hz, H-2,6), 6.923 (2H, d, *J* = 8.5 Hz, H-3,5), 4.333 (2H, t, *J* = 6 Hz, H-1'), 3.865 (3H, s, OCH_3), 3.612 (2H, t, *J* = 6 Hz, H-4'), 1.946 (4H, m, H-2',3').

4'-Chlorobutyl 2-hydroxybenzoate (X): ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.779 (1H, s, OH), 7.826 (1H, dd, *J* = 8 and 2.4 Hz, H-6), 7.450 (1H, dt, *J* = 8 and 2.4 Hz, H-4), 7.001–6.838 (2H, m, H-3,5), 4.364 (2H, t, *J* = 6 Hz, H-1'), 3.615 (2H, t, *J* = 6 Hz, H-4'), 1.954 (4H, m, H-2',3').

4'-Chlorobutyl dodecanoate (XII): ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.105 (2H, t, *J* = 6 Hz, H-1'), 3.575 (2H, t, *J* = 6 Hz, H-4'), 2.296, (2H, t, *J* = 7 Hz, H-2), 1.609 (2H, m, H-3), 1.290 (16H, m, H-4,5,6,7,8,9,10,11), 0.882 (3H, t, *J* = 7 Hz, H-12).

Bis-[4-chlorobutyl] butan-1,4-dioate (XIII): ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.132 (4H, t, *J* = 6 Hz, H-1', 1"), 3.570 (4H, t, *J* = 6 Hz, H-4',4"), 2.625, (4H, s, H-2,3), 1.826 (8H, m, H-2',2",3',3").

4'-Chlorobutyl 4-methylbenzenesulfonate (XIV): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.790 (2H, d, *J* = 8.5 Hz, H-2,6), 7.353 (2H, d, *J* = 8.5 Hz, H-3,5), 4.336 (2H, t, *J* = 6 Hz, H-1'), 3.602 (2H, t, *J* = 6 Hz, H-4'), 2.456 (3H, s, CH_3), 1.902 (4H, m, H-2',3').

4. Conclusions

We have developed a new one-pot methodology for transforming carboxylic and sulfonic acids into their 4-chlorobutyl esters in moderate to high yield using a new combination of reagent (oxalyl chloride) and catalyst (iodine monochloride).

5. Acknowledgement

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6. References

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Povzetek

Avtorji v prispevku poročajo o novi enostavni enostopenjski pretvorbi karboksilnih kislin v ustrezne 4-klorobutil estre. Vmesno nastali kislinski kloridi niso bili izolirani. Uporabljeni reakcijski pogoji so dovolj mili, da ostaneta dvojna vez na stranski verigi in aromatska metoksi skupina nespremenjeni. V večini primerov so bili produkti čiščeni z enostavno kolonsko kromatografijo.