Reaction of Esters with Thionyl Chloride Catalyzed by Zinc Halides

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Abstract. The ability of esters of primary and secondary alcohols butyl acetate and L-menthyl acetate (2-isopropyl-5-methylcyclohexyl acetate) to interact with thionyl chloride in the presence of zinc halides (chloride or bromide) was studied. 1-chlorobutane with a minor admixture of 2-chlorobutane (less than 3.6 %) was the main product of the reactions of butyl acetate. For L-menthyl acetate, the main product was 2-chloro-1-isopropyl-4-methylcyclohexane with minor impurities mainly represented by 1-isopropyl-4-methylcyclohexene and other six-membered unsaturated hydrocarbons. When $ZnBr_2$ used as a catalyst, impurities of bromo-substituted hydrocarbons were found in the reaction products, which demonstrates the possibility of halogen atoms exchange between zinc halide and the resulting organic products of the reaction.

Keywords: esters, thionyl chloride, haloalkanes, zinc, catalyst.

Взаимодействие сложных эфиров
с хлористым тионилом,
катализируемое галогенидами цинка

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Аннотация. Исследована способность сложных эфиров первичного и вторичного спиртов – бутилацетата и L-ментилацетата (2-изопропил-5-метилциклогексилацетата), взаимодействовать с тионилхлоридом в присутствии галогенидов (хлорида или бромида) цинка. В качестве основного продукта реакции бутилацетата идентифицирован 1-хлорбутан, с минорной примесью (не превышающей 3.6 %) 2-хлорбутана. Для L-ментилацетата основным продуктом являлся 2-хлор-1-изопропил-4-метилциклогексан; минорные примеси в основном представляли собой 4-метил-1-изопропилциклогексен и другие непредельные углеводороды с шестичленным циклом. При использовании в качестве катализатора $ZnBr_2$ в продуктах реакции обнаружены примеси бромзамещенных углеводородов, что показывает возможность обмена атомами галогенов между галогенидом цинка и образующимися органическими продуктами реакции.

Ключевые слова: сложные эфиры, тионилхлорид, алкилгалогениды, цинк, катализатор.

Introduction

Thionyl chloride is widely used for the synthesis of alkyl and acyl chlorides from alcohols [1] and carboxylic acids [2], respectively. In addition, it is known that they are able to react with benzyl alcohol esters [3] as well as tertiary alcohols [4], and in the latest studies the authors note the absence of interaction between $SOCl_2$ and primary and secondary alcohols. However, a particular reaction for obtaining 4-chlorobutyryl chloride from γ-butyrolactone in the presence of zinc chloride is known [5]. It was also found that placing a mixture of thionyl chloride with ethyl acetate in a zinc container after some time results in an exothermic uncontrolled reaction with extensive emission of gas and with the formation of ethyl chloride, sulfur dioxide, acetyl chloride, and elemental sulfur [6]. This allowed to

suggest that zinc compounds are able to catalyze the reaction of thionyl chloride with a wider range of esters than only benzyl and tertiary esters. A previous study [7] showed that treatment of a chloroform solution of poly-3-hydroxybutyrate with thionyl chloride in the presence of zinc chloride resulted in the oligomerization of this polyester associated with formation of chloroalkyl and chloroacyl groups at the ends of the polymer chain. Meanwhile, the reaction rate under the specified conditions was quite low that allowed to obtain only oligomers with a minimum weight-average molecular weight of 16.7 kDa. In this study, the ability of primary and secondary alcohol esters (butyl acetate and L-menthyl acetate) to react with thionyl chloride in the presence of zinc halides (chloride and bromide) was studied. Since the proposed reaction affects the carbon backbone of the alcohol, but not that of the acid, it was decided to focus on studying the behavior of the alcohol part of the ester in the course of the reaction. As the compounds of interest, we chose acetates as they represent esters with the least complex acid residue. Butyl acetate was chosen as an ester of a relatively simple primary alcohol allowing feasible rearrangements of the carbon backbone. L-menthyl acetate was chosen as a derivative of the relatively complex secondary alcohol L-menthol to assess the feasibility of the reaction proceeding through the elimination mechanism, including migration of unsaturated bonds. Taking into account previous study and the identified relatively low reaction rate under these conditions, the experiments were carried out over 4 days.

Experimental

Materials

Reagents of the following manufacturers were used: Natural L-menthyl acetate ((1R,2S,5R)-5-Methyl-2-(propan-2-yl)cyclohexyl acetate, ≥98 %, FCC, FG) – Sigma-Aldrich, Saint Louis, MO, USA; butyl acetate (chemically pure, 99.5 %), chloroform (extra pure, 99.8 %), hexane (extra pure, 99.5 %), 1,4-dioxane (chemically pure, 99.5 %) – EKOS-1, Russia; thionyl chloride (reagent grade, 97 %), anhydrous zinc chloride (reagent grade, ≥98 %), anhydrous zinc bromide (reagent grade, ≥98 %) – Acros Organics, India; pyridine (p.a. 99 %) – Chemsolute.

The experiment in a chloroform solution

0.005 mol (1.08 ml or approx. 0.992 g) of L-menthyl acetate (MA) (198.3 g/mol, 0.92 g/cm^3) was placed in a 50 ml Erlenmeyer flask and 20 ml of chloroform, 0.0005 mol of anhydrous zinc chloride (68.1 mg; 136.3 g/mol) or zinc bromide (112.6 mg; 225.2 g/mol), and 0.02 mol of thionyl chloride (1.45 ml, 119.0 g/mol, 1.64 g/cm^3) were added. Thus, the MA: SOCl$_2$: catalyst ratio was 10:40:1. The resulting mixture was stirred on a magnetic stirrer at 45–55 °C for four days. In the control no catalyst was added and the sample was stirred under the same conditions. Afterwards, the solvent, the remaining thionyl chloride and acetyl chloride were distilled off on a rotary evaporator at 40 °C and 100 mbar pressure. The resulting residue was redissolved in 10 ml of hexane, filtered through PTFE filters with a pore size of 0.45 μm, and evaporation was repeated in the same conditions.

The experiment in pure thionyl chloride

The experiment in pure thionyl chloride was carried out with butyl acetate (BA) and L-menthyl acetate with a higher content of thionyl chloride and catalyst (ester: SOCl$_2$: catalyst ratio was 10:50:2) using 30 ml vials and without stirring. The following were added to the vials: 1 mmol of catalyst (136.2

mg of $ZnCl_2$ or 225.2 mg of $ZnBr_2$); 5 mmol of BA (658 µl; 116.2 g/mol, 0.882 g/cm^3) or MA (1.08 ml); 25 mmol (1.81 ml) of thionyl chloride. The catalysts were added in a dry form or as a 2 ml of dioxane solution (0.5 mmol/ml). To prepare dioxane solution, 10 mmol of $ZnCl_2$ (1.362 g) or $ZnBr_2$ (2.252 g) were dissolved in 20 ml of dioxane at 80 °C. Additional 20 µl of pyridine were supplemented to half of the vials. Mixtures of esters with thionyl chloride without addition of a catalyst served as control samples. However, as for the experimental samples, some control samples were also supplemented with 2 ml of dioxane, 20 µl of pyridine, or dioxane and pyridine together. After the end of the experiment, 10 ml of hexane was added to each sample. The resulting mixtures were filtered through PTFE syringe filters with a 0.45 µm pore size and concentrated by evaporation of hexane, thionyl chloride, acetyl chloride, and dioxane using rotary evaporator at 45 °C and a 100 mbar pressure.

GC–MS analysis

10 µL of each sample was dissolved in 990 µL of chemical grade hexane. The analysis was carried out using Agilent 6890N gas chromatograph with Agilent 5975C mass spectrometer and with Agilent VF-200ms polytrifluoropropylmethylsiloxane column (length 60 m, internal diameter 250 µm, sorbing layer thickness 0.10 µm). Helium was used as a carrier gas at a flow rate of 1.2 $ml×min^{-1}$ and sample injection was carried out with a 30:1 flow split. The inlet and transfer line temperatures were set to 220 °C and 230 °C, respectively. Temperature profile of the oven was the following: 55 °C for 3 minutes, then heating to 310 °C at a 10 $°C×min^{-1}$ rate, holding the temperature for 5 minutes. The solvent delay was preliminarily determined experimentally as time of the release of the most of hexane (5.50 min). Electron impact (70 eV) was used for samples ionization. The results were processed in MSD Chemstation ver. E.02.02.1431.

Results and Discussion

The ability of esters to react with thionyl chloride in the presence of zinc halides was firstly assessed in chloroform solution using L-menthyl acetate. There was no visible dissolution of the catalysts. During the experiment, a black precipitate gradually accumulated in the experimental flasks. In the control experiment, 857 mg of a transparent yellowish liquid was obtained which constituted approx. 86 % of the mass of the original MA. In experiments with $ZnCl_2$ and $ZnBr_2$, 550 mg and 792 mg of dark liquid were respectively obtained that constituted approx. 55 and 80 % of the mass of the original MA.

The original MA corresponded to the reagent grade (≥98 % purity) and, according to GC–MS, contained 1.84 % of cis- and trans- isomers of 4-tert-butylcyclohexyl acetate. The predominant component in both cases was the original MA. The reaction products amounted to approx. 29 and 26 % from the original MA when $ZnCl_2$ and $ZnBr_2$ used as catalysts, respectively. 2-chloromenthane (2-chloro-1-isopropyl-4-methylcyclohexane) predominated in the mixture of the products amounting to 61.6 and 47.1 %, respectively (Table 1). In the case of $ZnCl_2$, a significant amount (17.2 %) of 1-isopropyl-4-methylcyclohexene was also observed. The remaining products were mainly unsaturated derivatives of substituted cyclohexane, and their content ranged from 0.5 to 6.7 %. The exceptions were a trace of p-cymene (0.65 and 2.27 %, respectively), apparently formed as a result of the side process of aromatization, and 1-dichloromethyl-2-(1-methylethenyl)-benzene (7.4 and 7.3 %, respectively), probably resulted from the interaction of intermediates of the side aromatization reaction

with chloroform. In addition, for the sample with $ZnBr_2$, 2-bromomenthane was also detected, which amounted to 2.34 % of the total products, indicating the inclusion of bromine atoms from the catalyst.

The following experiment was carried out with BA and L-menthyl acetate in pure thionyl chloride. 1 mmol of $ZnCl_2$ or $ZnBr_2$ (as a dry-form or in the form of dioxane solution), 5 mmol of BA or L-menthyl acetate, and 25 mmol of thionyl chloride were added to the vials. Dioxane was studied as a potential solvent for zinc halides. In addition, 20 µl of pyridine were added to some of the vials as a potential reaction modifier (which is characteristic for reactions with alcohols [1]). No catalysts were added to the control samples, but dioxane and/or pyridine were added to some of them.

When the esters were added, the dry-form catalysts dissolved in them. The formation of a crystalline precipitate was observed in the samples with dioxane solution of catalysts. In the samples where dry-form catalysts were added, precipitation was also observed after pyridine supplementation. After adding thionyl chloride, release of gas and a change in the color of the solutions from almost colorless to bright yellow were observed. Loosely closed vials with samples were incubated in a sand bath at approx. 50 °C (the temperature fluctuated from 45 to 55 °C during the experiment). The experiment lasted for four days. By the end of the experiment, the contents in the vials with catalysts darkened to a dark brown color. In vials with menthyl acetate and dry-form catalysts, a black precipitate insoluble in hexane was formed.

After filtration and evaporation, from 430 to 493 mg of liquid was collected from the vials with butyl acetate, which amounted to 74–85 % of the weight of the original BA (Table 1). Similar values for vials with MA ranged from 548 to 891 mg and 55 to 90 %, respectively. Meanwhile, the smallest amount of liquid fraction was collected from vials with dry-form catalysts, where the formation of precipitate was observed.

In the absence of zinc halides, there was practically no reaction between the components of the mixture (Table 1): in the control BA sample no products were detected (Fig. 1a). In the presence of catalysts, even in the best conditions, less than half of the butyl acetate reacted: its maximum amount reacted with thionyl chloride was observed for samples with dry-form $ZnCl_2$ and with and without pyridine supplement, amounting to 47.6 and 42.8 % (Fig. 1b) of the original amount, respectively. For $ZnBr_2$, the corresponding values were 13.8 and 12.7 %; for the rest of the samples they did not exceed 3 %. The predominant product was 1-chlorobutane, accounting for at least 90 % (typically approx. 96 %) of the total compounds formed (Fig. 2a). When dry-form catalysts had been used, the presence of 2-chlorobutane admixture was observed, that amounted to up to 3.6 %. When dioxane had been presented in the medium, 2-chlorobutane was not detected. In samples where $ZnBr_2$ had been used as a catalyst, 1-bromobutane admixture was detected with the maximum concentration of 6.3 % for the sample with pyridine.

For MA, the reaction proceeded more fully (Table 1). In the control MA sample 0.44 % of 2-chloromenthane was observed (Fig. 1c). In the sample with dry-form $ZnBr_2$ without pyridine supplement, residual MA in the medium was not detected. For $ZnCl_2$ (Fig. 1d), as well as for both catalysts with pyridine supplement, the corresponding values ranged from 93 % to 98 %. The main product of the reaction was 2-chloromenthane (Fig. 2b), which for all the experimental samples amounted to at least half of the total compounds formed. The highest content of 2-chloromenthane in the liquid fraction was found when $ZnCl_2$ was used as a catalyst, amounting to approx. 91 % for the reaction in a pure solvent and from 69 to 78 % in the presence of dioxane, depending on

Table 1. Resulting products of butyl acetate and L-menthyl acetate treatment with thionyl chloride in the presence of zinc halides.

E	Cat.	Py	S	PF, %	ΣPP, %	MP, %	Other relevant products	FMP, %
MA	–	–	C	86.4	0.0	0.0	–	0.0
MA	ZnCl$_2$	–	C	55.4	28.8	61.6	17.2 % – 1-isopropyl-4-methylcyclohexene; 0.65 % – p-cymene	9.8
MA	ZnBr$_2$	–	C	79.9	26.0	47.1	2.3 % – 1-isopropyl-4-methylcyclohexene; 2.3 % – 2-bromomenthane; 2.3 % – p-cymene	9.8
BA	–	–	–	84.9	0.0	0.0	–	0.0
BA	ZnCl$_2$	–	–	74.0	42.8	96.9	3.1 % – 2-chlorobutane	30.7
BA	ZnBr$_2$	–	–	79.7	13.8	95.9	2.9 % – 1-bromobutane; 1.2 % – 2-chlorobutane	10.5
BA	–	+	–	83.6	0.0	0.0	–	0.0
BA	ZnCl$_2$	+	–	74.3	47.6	96.4	3.6 % – 2-chlorobutane	34.1
BA	ZnBr$_2$	+	–	80.9	12.7	90.8	6.3 % – 1-bromobutane; 2.9 % – 2-chlorobutane	9.3
BA	–	–	D	84.3	0.4	100.0	–	0.3
BA	ZnCl$_2$	–	D	80.8	2.3	100.0	–	1.9
BA	ZnBr$_2$	–	D	82.4	2.7	96.5	3.5 % – 1-bromobutane	2.1
BA	–	+	D	83.9	0.1	100.0	–	0.1
BA	ZnCl$_2$	+	D	80.1	2.2	100.0	–	1.8
BA	ZnBr$_2$	+	D	79.9	1.9	98.2	1.8 % – 1-bromobutane	1.5
MA	–	–	–	89.9	0.4	100.0	–	0.4
MA	ZnCl$_2$	–	–	57.4	93.0	90.7	1.2 % – 1-isopropyl-4-methylcyclohexene	48.4
MA	ZnBr$_2$	–	–	66.5	100.0	52.8	0.27 % – 2-bromomenthane	35.1
MA	–	+	–	88.8	0.6	52.5	47.5 % – 1-isopropyl-4-methylcyclohexene	0.3
MA	ZnCl$_2$	+	–	55.3	98.0	91.5	1.3 % – 1-isopropyl-4-methylcyclohexene	49.6
MA	ZnBr$_2$	+	–	61.5	96.6	49.9	0.84 % – 2-bromomenthane	29.6
MA	–	–	D	89.2	0.4	78.1	22.0 % – 1-isopropyl-4-methylcyclohexene	0.3
MA	ZnCl$_2$	–	D	83.5	69.0	69.3	11.5 % – 1-isopropyl-4-methylcyclohexene; 1.15 % – p-cymene	39.9
MA	ZnBr$_2$	–	D	84.9	11.9	50.6	33.0 % – 1-isopropyl-4-methylcyclohexene; 2.46 % – 2-bromomenthane	5.1
MA	–	+	D	89.1	0.0	0.0	–	0.0
MA	ZnCl$_2$	+	D	85.8	18.7	78.0	14.9 % – 1-isopropyl-4-methylcyclohexene	12.5
MA	ZnBr$_2$	+	D	83.0	10.3	53.2	23.9 % – 1-isopropyl-4-methylcyclohexene; 0.95 % – 2-bromomenthane	4.5

E – ester: BA – butyl acetate, MA – L-menthyl acetate; Cat. – catalyst; Py – pyridine supplement; S – presence of solvent in the media: C – chloroform; D – dioxane; PF – purified liquid fraction, in wt% of the original ester; ΣPP – content of reaction products in PF; MP – the content of main product (1-chloroheptane for BA and 2-chloromenthane for MA) in PF; FMP – final yield of main product.
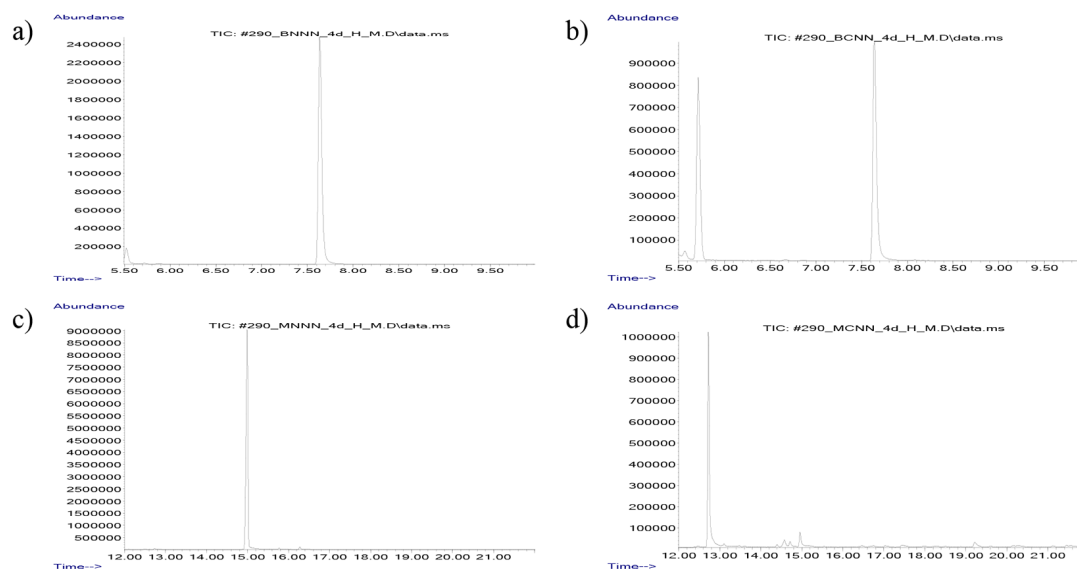
Fig. 1. Chromatograms of products obtained by treatment of esters with thionyl chloride: a) butyl acetate, without catalyst; b) butyl acetate, ZnCl₂; c) L-menthyl acetate, without catalyst; d) L-menthyl acetate, ZnCl₂. Retention times (min): 5.7 – butyl acetate; 7.6–1-chlorobutane; 12.7–2-chloromenthane; 15.0 – L-menthyl acetate

whether pyridine was supplemented in the medium. When $ZnBr_2$ was used as a catalyst, up to 2.5 % 2-bromomenthane was formed as well as a large number of by-products in small concentrations, mainly identified as unsaturated derivatives of substituted cyclohexanes containing double bonds both in the cyclohexane ring and in pendant groups. In the presence of dioxane, the reaction proceeded much more slowly and products yield ranged from 10 to 69 % of the amount of MA in the reaction mixture; a significant amount of 1-isopropyl-4-methylcyclohexene was detected, ranging from 11 to 33 % of the total products. Along with lower concentrations of reagents, the low yield could be because of the partial precipitation of catalysts observed in dioxane samples. Also, in the presence of solvents (both chloroform and dioxane), small amounts of p-cymene (up to 2.3 %) were observed, indicating the possibility of a side mechanism of aromatization of the cyclohexane ring.

Thus, for all the experimental samples studied, in the ternary system "ester – thionyl chloride – zinc halide" the reaction between the ester and thionyl chloride occurred with the formation of the corresponding chloroalkanes (Fig. 2). Accordingly, the interaction of aliphatic esters with thionyl chloride in the presence of zinc halides, leading to the formation of acid halide and haloalkyl groups at the site of bond breakage, can be considered as a universal reaction for esters of primary and secondary alcohols. Although, it should be noted that corresponding reaction proceeds at a relatively low rate, and in the case of secondary alcohols, followed by the formation of a large number of by-products due to elimination and rearrangement reactions. A low reaction rate was previously observed for benzyl alcohol esters [3], but in this case it proceeded without catalysts.

When $ZnBr_2$ used as a catalyst, the presence of the corresponding bromoalkanes in the reaction products is observed, which indicates the inclusion of bromide ions from the catalyst. A previously proposed mechanism [3] involves a nucleophilic attack of the carbonyl oxygen atom on the sulfur atom of thionyl chloride, with the formation of the first intermediate presented as an ionic structure

having a full positive charge on the carbonyl atom and a free chlorine anion. Further, the alkyl chloride leaves, and then the second intermediate formed undergoes rearrangement with the elimination of SO_2 and the formation of an acyl chloride molecule. It can be assumed that the decomposition of the first intermediate occurs with the separation of the "alcohol" alkyl group represented by a relatively stable carbocation (benzylic or tert-butyl, as in another [4] study), which then interacts with the chloride anion. For esters, the "alcohol" alkyl group of which does not form sufficiently stable carbocations, this separation is difficult. In this case, the zinc halide can act as a halogen donor for the alkyl group, allowing its detachment from the acid part along with the concomitant transfer of a chlorine atom from the chlorosulfite group to the zinc and the subsequent decomposition of the intermediate into acyl chloride, alkyl halide, ZnHal2 and SO2 (Fig. 2). It is obvious that this particular step is irreversible, since in the absence of a catalyst no intermediate products were found.

Formation of acetyl chloride was not evaluated in the scope of this study. Meanwhile, the progress of the reaction was evaluated only by the formation of haloalkanes (or their unsaturated derivatives) and by their quantitative ratio to the original esters. Although acetyl chloride was always present
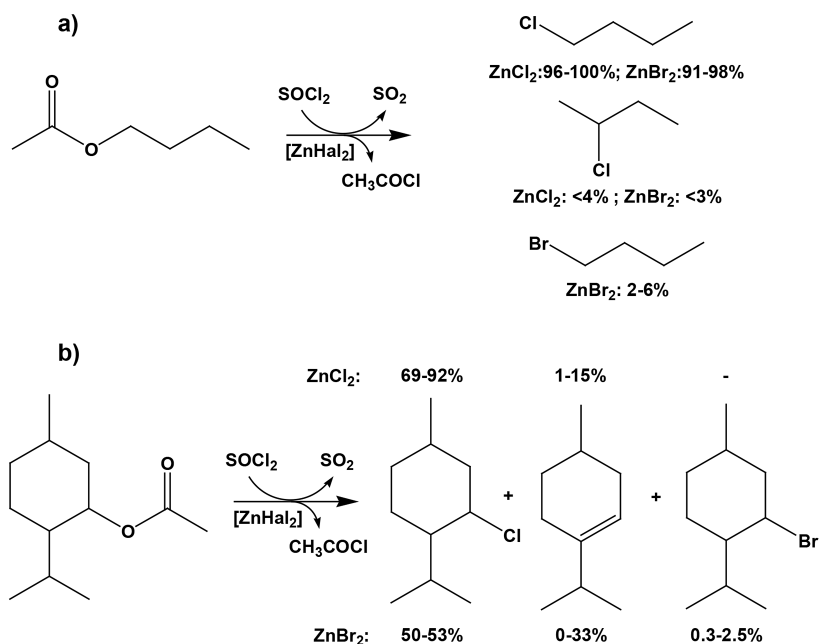

Fig. 2. The reaction of esters with thionyl chloride, and the main reaction products
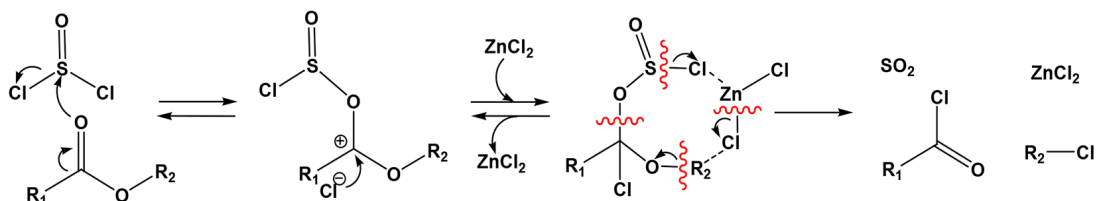

Fig. 3. Proposed mechanism for the reaction of esters with thionyl chloride, catalyzed by zinc chloride. The dotted line represents formation of new bonds, and the transverse wavy lines show the breakage of existing bonds

among reaction products, it was evaporated along with unreacted thionyl chloride and solvents, which made its quantitative evaluation unfeasible. As the mechanisms of this reaction will be further studied, the use of larger amounts of reagents will make it feasible to evaluate the amount of acyl chlorides formed.

Conclusions

So, the ability of esters of primary and secondary alcohols to interact with thionyl chloride in the presence of zinc halides (chloride or bromide) was shown. Although the rate of the described reaction is quite slow, it can be used to obtain alkyl chlorides directly from esters in a single step. Its further optimization for increase in yield and reduction of by-products may include altering the ratios of reagents and catalysts as well as reaction time and temperature. Taking into account the importance and prevalence of esters and thionyl chloride as a reagent, the studied reaction may be crucial for various technological processes. Although this method of preparing haloalkanes and acyl halides is generally more complex than commonly used methods (particularly those using alcohols and carboxylic acids, respectively), it can be useful in cases when the source material is only available in ester form (which is relevant for some natural compounds).

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