

A mild hydrolysis of esters mediated by lithium salts

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Abstract—When treated with amine bases such as triethylamine and various lithium salts in wet solvents, esters are efficiently hydrolyzed to the corresponding acids in good yields. Esters incorporating an α - or β -heteroatom with respect to the ester carbonyl group are hydrolyzed rapidly even at room temperature. To further demonstrate the usefulness of this method, one example is provided where hydrolysis of acetylated camphorsultam is mediated by LiBr.

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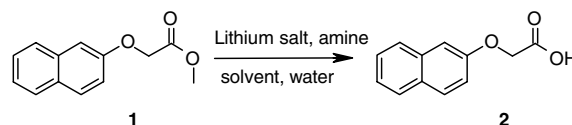
Hydrolysis of esters is one of the most frequently used transformations in organic synthetic chemistry. Most of these hydrolyses employ reagents such as NaOH or LiOH. However, the high basicity and nucleophilicity of such hydroxides make them unsuitable as reagents when sensitive substrates such as esters prone to epimerization or those incorporating other unstable moieties are reacted. Trimethyltin hydroxide has successfully been used as a mild and efficient reagent when such labile esters are hydrolyzed.¹ Mild cleavage of esters can also be achieved through treatment with various nucleophiles such as LiS-n-Pr² and LiI³ or electrophiles such as TMSI.⁴

Despite the fact that mild methods already exist for the cleavage of esters we wanted to develop a new, mild and general approach that could be applied safely on a large scale using simple and environmentally friendly reagents at room temperature. We also wanted to avoid the use of reagents that produce reactive and hazardous intermediates such as stannanes and alkyl halides. To our knowledge, no such method has been reported. Herein, we communicate our preliminary results on such a hydrolysis method which utilizes simple amines and lithium salts as reagents.

It is known that certain esters and carbonates are slowly hydrolyzed when treated with amine bases in wet solvents.⁵ In order to achieve a useful and generally

accepted hydrolysis method our plan was to speed-up this type of reaction by adding various Lewis acids. Lithium chloride is a frequently used additive in various types of organic transformations and there are many examples where the presence of this salt increases the rate of reaction.⁶ Initially we chose ester **1** (Scheme 1) as test-substrate for our study. In wet acetonitrile and in the presence of triethylamine (5 equiv) this ester was not hydrolyzed (Table 1, entry 1). However, we were delighted to find that in the presence of LiCl as an additive, the hydrolysis of **1** proceeded smoothly furnishing acid **2** as a single product (Table 1, entry 2). Encouraged by this observation we decided to study this reaction further by varying parameters such as solvent, amine and Lewis acid. Various amine bases, solvents and lithium sources such as LiBr, LiCl, LiBF₄, LiCF₃CO₂, Li₂SO₄, LiNO₃ and LiCF₃SO₃ were examined using ester **1** as test-substrate (Scheme 1). Also, the effect on the rate by varying the amount of amine, lithium source and added water was investigated.

Table 1 summarizes some of the most significant results where the effect of using different lithium salts and solvents on the conversion was studied. Our experiments showed that among the different lithium sources tested LiCl, LiBr, LiBF₄ and LiCF₃SO₃ resulted in the fastest



Scheme 1. In the presence of an amine base in a wet solvent, the hydrolysis of ester **1** is mediated by various lithium salts.

Keywords: Mild hydrolysis; Selective hydrolysis; Ester hydrolysis; Lithium salts; Triethylamine.

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Table 1. Conversion of ester **1** to acid **2** from using various lithium salts and solvents^a

Entry	Lithium salt	Solvent	Conversion (%)
1	—	CH ₃ CN	0
2	LiCl	CH ₃ CN	74
3	LiCl	MeOH	38
4	LiCl	CH ₃ NO ₂	2
5	LiCl	THF	94
6	LiCl	DMF	13
7	LiCl	DMSO	3
8	CF ₃ SO ₃ Li	CH ₃ CN	90
9	LiBr	CH ₃ CN	100
10	LiNO ₃	CH ₃ CN	80
11	LiBF ₄	CH ₃ CN	91
12	Li ₂ SO ₄	CH ₃ CN	3
13	C ₇ H ₇ SO ₃ Li	CH ₃ CN	23
14	CF ₃ CO ₂ Li	CH ₃ CN	68
15	CF ₃ SO ₃ Li	THF	35
16	LiBr	THF	100
17	LiNO ₃	THF	43
18	LiBF ₄	THF	39
19	Li ₂ SO ₄	THF	3
20	C ₇ H ₇ SO ₃ Li	THF	18
21	CF ₃ CO ₂ Li	THF	25

^a Conditions: Ester **1** (100 mg, 0.46 mmol) was dissolved in the specified solvent (1 ml) containing 6 vol % of water. Triethylamine (0.32 ml, 2.3 mmol) was added followed by the lithium salt (2.3 mmol). The mixture was stirred vigorously at room temperature for 7.5 h after which the reaction was quenched by the addition of AcOH (0.13 ml, 2.3 mmol). The specified conversion was determined through LC analysis of the crude mixture.

reactions. Acetonitrile and THF turned out to be the solvents of choice.

As mentioned above, we also wanted to investigate the effect of using various amines and the amount of amine required. Also, we were interested in studying the effect of using different amounts of added water and lithium salts. A summary of the results is as follows (for details, see [Supplementary data](#)): a low water content increased the rate of the hydrolysis. As expected, the rate was directly correlated to the pK_b of the amine used as *N*-methylmorpholine gave a low conversion to the carboxylic acid even after a prolonged reaction time while the use of DBN gave full conversion within a few minutes. However, the hydrolysis can be performed with *N*-methylmorpholine as base with good results if the reaction is performed at reflux. Remarkably, the amount of amine used was not as crucial as expected. High amine loading only gave a slightly faster reaction compared with the reactions with a low loading. However, using a large excess of the lithium salt gave a much higher rate than in those reactions performed with low loading. At room temperature, no reaction occurred when either the lithium salt or the amine was excluded.

From these results we decided to choose two general hydrolysis methods, one of which eventually should be applied to various types of esters to assess the reliability of the method. The first method includes the following reagents and relative amounts: Triethylamine (3 equiv) in CH₃CN containing 2 vol % of water, 10 equiv of LiBr and the substrate (1 equiv, ~0.2 mmol/ml CH₃CN). The

second method includes triethylamine (3 equiv) in THF containing 2 vol % of water, 10 equiv of LiCl and the substrate (1 equiv, ~0.2 mmol/ml THF). Because the first method resulted in much faster hydrolysis, it was chosen for further studies on various types of esters. [Figure 1](#) summarizes the yields and reaction times for the hydrolysis of selected esters using the LiBr-mediated method.

As shown in [Figure 1](#), the LiBr-mediated hydrolysis can be applied to various types of esters with good results.

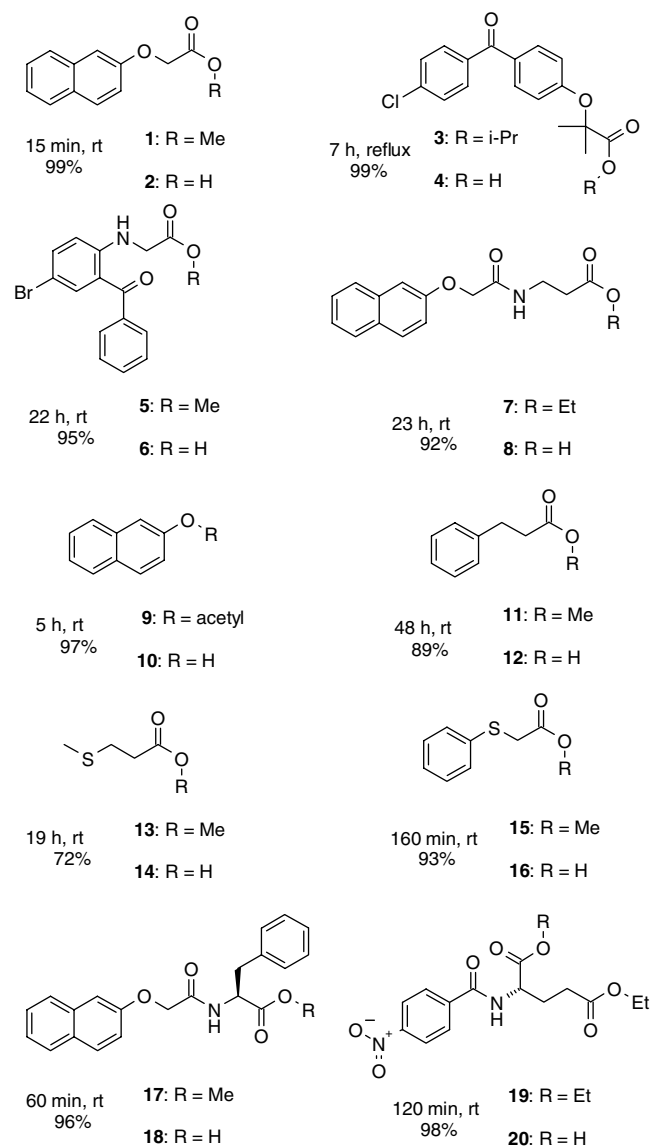


Figure 1. Hydrolysis of selected esters (isolated yields given) using the following procedure: the ester (typically 0.5–1 g) was dissolved in CH₃CN (10 ml/g of ester) containing 2 vol % of water. Triethylamine (3 equiv) was added followed by the addition of LiBr (10 equiv). The mixture was stirred vigorously at room temperature, except in one case, in which the reaction was performed at reflux (compound **3–4**). When full conversion was achieved, as judged by LC analysis of the crude mixtures, the acids (or alcohol **10**) were isolated after a simple work-up procedure. Alternatively, the acids were isolated after purification by preparative HPLC.

Although the fastest rates in general were observed when esters incorporating an α -heteroatom were reacted (e.g., esters **1**, **15** and **17**) the method can also be applied to esters incorporating a β -heteroatom (e.g., esters **7** and **13**). Unless not activated (as in the case of ester **9**), those esters lacking a heteroatom in both these positions reacted very slowly (e.g., ester **11**). This selectivity can be an advantage in some cases. For example, diester **19** gave only monoacid **20** (structure confirmed by HMQC) and no hydrolysis occurred at the other ester moiety. We also wanted to investigate if this method was suitable for the cleavage of chiral auxiliary derivatives such as oxazolidinones and camphorsultams. Thus, in two separate experiments the method described above was applied on acetylated camphorsultam **21** and acetylated oxazolidinone **23**, respectively (Scheme 2). Whereas the cleavage of the oxazolidinone derivative partly failed due to the formation of byproduct **25**, camphorsultam **22** was successfully isolated from amide **21** in 90% yield after 5 h of stirring at room temperature.

The explanation for the rate-increase in the lithium-mediated hydrolyses might be due to the coordination of lithium to the ester carbonyl group and to the heteroatom at the α or β position, resulting in a five- or six-membered chelate, respectively (Fig. 2). Such a coordination would make the ester carbonyl group more reactive towards the attack of the hydroxide ion. This would explain why esters lacking heteroatoms in the α or β positions with respect to the ester carbonyl group, react more slowly.

In conclusion, a mild, simple and selective hydrolysis method has been developed that can be applied to esters, which either are activated (e.g., phenyl esters) or incorporate an α - or β -heteroatom with respect to the ester carbonyl group. Provided that the reaction is run in either aqueous CH_3CN or THF and depending on the sensitivity of the substrate, various lithium salts and

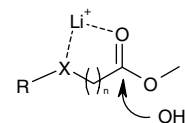


Figure 2. Proposed reaction intermediate for the lithium-mediated hydrolyses. X = heteroatom, $n = 1$ or 2 .

amine bases can be used. Preliminary results also indicate that the method is useful for the cleavage of chiral auxiliary derivatives (e.g., camphorsultam amides).

Acknowledgements

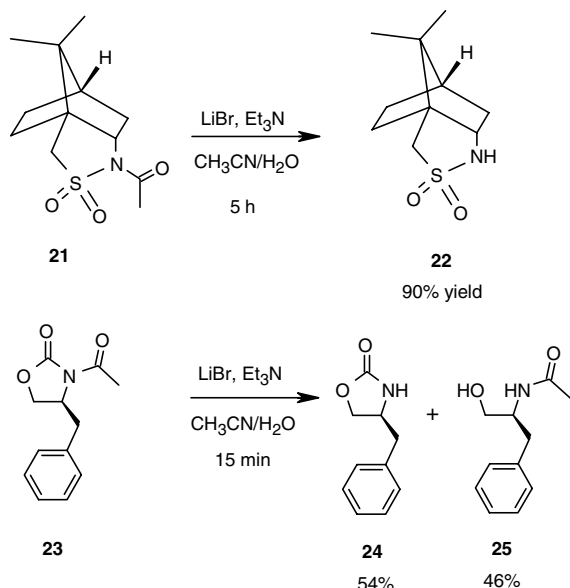
We thank Clas Landersjö for performing the HMQC experiments and Johan Gottfries for computer assisted elucidation of the experiments.

Supplementary data

Additional experiments where the effect of using different lithium salts, amines and solvents in the hydrolysis of esters **1** and **17** are investigated. Detailed experimental procedures and full characterization of all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.029.

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Scheme 2. Hydrolysis of acetylated camphorsultam **21** and acetylated (*S*)-4-benzyl-2-oxazolidinone **23**.