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A simple method for the alkaline hydrolysis of esters

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Abstract—A very mild and rapid procedure for the efficient alkaline hydrolysis of esters in non-aqueous conditions has been developed, by the use of dichloromethane/methanol (9:1) as solvent. This method conveniently provides both carboxylic acids and alcohols from the corresponding esters and sodium hydroxide in a few minutes at room temperature. A plausible reaction mechanism is proposed.

Synthesis and structure determination, two of the major concerns of the organic chemist, usually involve the conversion of functional groups. Among other transformations, the saponification of esters to carboxylic acids is a very common organic transformation and one of the most extensively studied reactions in chemistry.[1,2]

Ester derivatives are widely present in many drugs, natural products and synthetic compounds. Furthermore, they are frequently used for the protection of carboxylic acids and alcohols, which, as synthons, are unmasked late in the synthesis.

Saponification processes typically involve the use of aqueous solutions, combining water and other water miscible organic solvents, such as methanol, ethanol, tetrahydrofuran, dioxane and dimethoxyethane in order to dissolve both, esters and hydroxides (KOH, NaOH, LiOH). The reaction temperature varies from room temperature to the boiling point of the mixture, while the length of the reaction time varies from 30 min to 24 h, or more. A relatively large excess of hydroxide is normally used, with a concentration chosen to be, usually, between 0.1 N and 2 N.

The rate of a saponification reaction is altered by steric and electronic effects,[3] as well as by the solvent,[4] due to specific interactions of solvent molecules with the reactants. Hydroxylic solvents interact strongly with anions and increase the energy barrier for reactions that involve the approach of a negative charge to a neutral system. A direct HO^-/ester nucleophilic collision in an aqueous environment must involve a great amount of desolvation energy, since the hydroxide ion is strongly solvated by water molecules.[5]

Changing the traditional protic solvents of saponification reactions to other solvents that do not stabilize the reactants, seems to be a rather good modification, since in less polar aprotic solvents the reaction goes faster.

In a recent study[6] on the selective enrichment of the β-COOH of Ac-Arg(Tos)-Gly-Asp(OBn)-Resin with oxygen-17, during solid phase peptide synthesis (SPPS), it has been established that the solvent system dichloromethane/methanol, compatible with SPPS, in a ratio of about 6:1–9:1, was optimal for successful saponification of the side chain of the peptide with $Na^{17}OH$. Methanol was used in order to dissolve sodium hydroxide. Methanolysis was, also, observed to some extent in the presence of higher-levels of methanol.

This interesting observation encouraged us to study and develop an efficient and practical saponification process

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in non-aqueous conditions that would be applied to a variety of esters (Eq. 1).

$$\mathrm{RCOOR'} \xrightarrow[2.\ H_3O^+]{1.\ NaOH,\ rt \atop (CH_2Cl_2\ /\ CH_3OH\ \sim 9:1)} \mathrm{RCOOH + R'OH} \qquad (1)$$

To the best of our knowledge, there are only a few reports[7] on non-aqueous saponification conditions. Among the various approaches, $(CH_3)_3COK$ in DMSO, or in dry Et_2O with the presence of 1 equiv of water, has been reported for the hydrolysis of hindered esters,[7a,b] while $Ba(OH)_2{\cdot}8H_2O$ in methanol has been used to deprotect simple alkyl esters,[7c] under conditions suitable for parallel synthesis. Recently, sodium trimethylsilanolate (TMSONa)[7d] has been utilized for the selective removal of methyl esters on the chain of Glu or Asp on solid support. More recently, the use of hydroxide ion-exchange resin has been investigated for ester hydrolysis[7e] in various organic solvents, but the proposed procedure was time consuming. A microwave-enhanced hydrolysis of esters,[7f] using $KF–Al_2O_3$ under solvent free conditions has also been described.

Procedures allowing simple, efficient and reliable ester hydrolysis, without racemizations or other undesirable side reactions would be advantageous and very helpful to the broad scientific community. In order to establish a gentle, time and temperature effective methodology, without large excess of alkali or high concentrations of reactants, avoiding undesirable by-products, we sought to perform saponification experiments on several types of esters using CH_2Cl_2 as the reaction solvent, containing methanol in a ratio CH_2Cl_2/CH_3OH ~9:1.

A range of several carboxylic esters was saponified quantitatively in dichloromethane using NaOH (dissolved in MeOH) with a final normality of 0.1–0.5 N, for a short time at rt (Table 1). The aprotic solvents Et_2O, THF and dioxane demonstrated comparable efficiency, however, CH_2Cl_2 was the best choice, since the reaction was apparently faster and the work-up easier.

From the results summarized in Table 1, it is obvious that the proposed hydrolysis protocol[8] works efficiently in all cases. Minor differentiations could be observed depending on the substrate structure. As expected, the reaction rate depends on the concentration and the ratio of the reactants, as well as on steric and electronic effects.

The described methodology provides an efficient laboratory procedure for ester hydrolysis and the possibility of

Table 1. Reaction conditions for the alkaline hydrolysis of esters to carboxylic acids

Entry	Ester	RCOOR′/NaOH	NaOH (N)	Time[a]	RCOOH[b]	
					Mp (°C)	$[\alpha]_D^{20}$
1	Ac–Pro–OMe[c]	1:1.1	0.1	50 min	116–118 (115–117)[10b]	−167° (−171), *c* 1 in $CHCl_3$[12a]
		1:5	0.2	15 min		
2	Boc–Tyr(2,6-di-Cl–Bzl)–OMe[c]	1:1.1	0.1	1 h 20 min	103–104 (105)[e]	+20.2° (+20), *c* 2 in EtOH[e]
		1:2	0.1	45 min		
		1:4	0.1	30 min		
3	Boc–Glu(OAll)–OH	1:2	0.1	15 min		−14.1° (−14.5), *c* 1 in MeOH[e]
		1:3	0.1	10 min		
4	Boc–Asp(OBzl)–OH	1:3	0.1	10 min		−4.8° (−5.0), *c* 1 in MeOH[e]
5	Fmoc–Asp(OMe)–OH[d]	1:3	0.1	10 min	—	
6	$CH_2{=}C(CH_3)–COOMe$	1:1.5	0.5	15 min	—	
7	$CH_3CH{=}CHCOOEt$	1:1.5	0.3	15 min	70–72 (70–72)[e]	
8	$PhCH{=}CHCOOEt$	1:1.5	0.2	55 min	130–132 (133)[e]	
9	PhCOOMe	1:1.5	0.2	1 h 20 min	120–122 (122–123)[e]	
10	$n\text{-}C_4H_9CH{=}CHCH_2COOEt$	1:2	0.2	30 min	—	
11	$n\text{-}C_5H_{11}CH{=}CHCH_2COOMe$	1:2	0.2	30 min	—	
12	$RCH(COOEt)_2$					
	(a, R = H)	1:1.1	0.5	35 min	130–133 (134–135)[e]	
	(b, R = Me)			45 min	128–131 (129–132)	
	(c, R = *n*-Bu)			1 h 50 min	100–101 (102)[12c]	
	(d, R = Bzl)			2 h	110–114 (117–120)[e]	
13	Methyl (3,5-dibenzyloxy)benzoate	1:8	0.5	4 h	208–209 (210-1)[12d]	
14	Isopropyl myristate	1:2	0.2	~2 h	55–57 (57–58)[12e]	
15	Tripalmitin	1:2	0.2	~2.5 h	62–64 (65)[12f]	
16	CH_3COOPh	1:1.5	0.3	5 min	—	
17	$CH_3COOCH_2CH{=}C(CH_3)_2$	1:1.5	0.2	15 min	—	
18	Geranyl phenylacetate	1:2	0.2	~4 h	75–77 (77–78)[e]	
19	Benzyl pivalate	1:2	0.2	~10 h	—	
20	2-Phenylethyl pivalate	1:2	0.2	~12 h	—	

[a] Monitored by TLC until the starting material was exhausted.
[b] The literature melting points and specific rotations are given in parentheses.
[c] The methyl esters of these amino acids were prepared from the corresponding protected amino acids with diazomethane.
[d] With simultaneous Fmoc-deprotection.
[e] These values have been derived from the pure products supplier (Fluka Laboratory Chemicals).

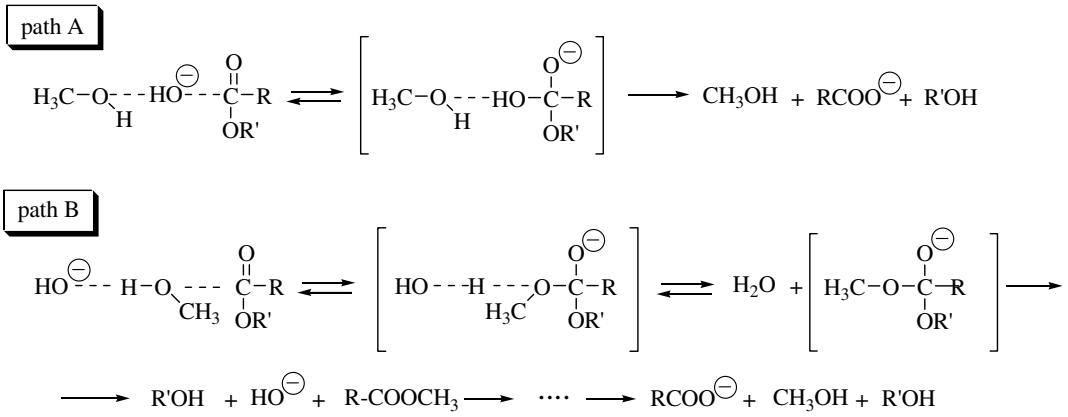

Figure 1. Suggested mechanism for the saponification of esters in CH_2Cl_2/MeOH ~9:1 (path A: direct, path B: through methanolysis).

isolating both products,[8,9] acids (entries 1–15, 18) and/or alcohols (entries 16–20).

The saponification of several discrete classes of natural products, such as, triglycerides, terpenoids and amino acid derivatives, received more attention and a detailed monitoring of the optimum conditions of time and reagents concentration at rt has been performed.

The hydrolysis conversion was quantitative for all the compounds studied, as shown in Table 1. The yields of recovered pure products were ~80–90%, except for entries 1, 3 and 4, where the yields were about 70–75%, due to the high solubility of products in both water and organic solvents. For cases 5, 12a, 16 and 17 yields were not determined, as the reaction products were, also, very soluble in water and without special interest.

Importantly, the saponification of the methyl esters of orthogonally protected amino acids (entries 1 and 2) was carried out without racemization, as evidenced by their observed specific rotations $[\alpha]_D$. In the case of side-chain ester derivatives of amino acids (entries 3–5), one more equivalent of NaOH was required, due to the α-COOH group. It is, also, of interest that the saponification of β,γ-unsaturated esters (entries 10 and 11) was accomplished without any isomerization to the corresponding α,β-unsaturated acids, as shown by their ^{1}H NMR spectra, compared with those of authentic samples. The saponification of diethyl malonates[3c] to malonic acids, was found to proceed relatively rapidly, depending on the substituent R, without any decarboxylation. On the other hand, longer reaction times, or more harsh reaction conditions were required for the sterically hindered esters, especially for entries 13 and 18–20, while the esters of fatty acids (14 and 15) reacted at a moderate rate (Table 1).

The ^{1}H NMR data of all the isolated products, without further purification, were identical to those of the expected pure compounds.

Conversion reactions for entries 1, 2, 9 and 12a were, also, performed with equivalent amounts of MeONa and $H_2^{17}O$, instead of NaOH, in order to produce $Na^{17}OH$ for the selective enrichment of the COOH group.[10]

The method appears to be fairly general, allowing quantitative hydrolysis of both alkyl and aryl esters. Moreover, it can be applied in cases where aqueous work-up must be avoided, since the sodium salt RCOONa can be isolated pure,[9] while the alcohol can be extracted. It is well known that triglycerides in olive oil samples,[11a] cinnamates,[3,11b] prolinates,[11c] other amino acids,[11d] malonates,[12b,c] etc., are saponified under relatively more vigorous reaction conditions, compared with these of the present work.

A plausible mechanistic process, very similar to the widely accepted classical mechanism[2] and consistent with our results, can be proposed (Fig. 1). The formation of a tetrahedral intermediate would be achieved via a nucleophilic attack on the carbonyl carbon by the HO^- with assistance by a methanol molecule (path A). Moreover, a parallel process, where nucleophilic interaction of a methanol molecule, assisted by a hydroxide ion, could be responsible for the observed methyl ester,[6] which is, subsequently saponified (path B). In the less polar solvent CH_2Cl_2, used in this work, the HO^-/ester nucleophilic attack is favored, and the reaction accelerated, due to extensive desolvation of the hydroxide ions.

In summary, a simple, rapid and gentle saponification method has been established, which involves the use of CH_2Cl_2 as the reaction solvent, containing about one-tenth its volume of methanol, and low concentrations of the hydroxide at room temperature. This methodology constitutes an advantageous alternative protocol, compared to the existing methods, for the alkaline hydrolysis of esters.

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8. *General experimental procedure for the saponification reaction*: To a solution of the ester (1 equiv), in a CH_2Cl_2/CH_3OH (~9:1, v/v) mixture, was added a methanolic solution of NaOH 2–3 N (1–4 equiv), with the final concentration of the alkali being about 0.1–0.2 N. After 2–3 min of stirring, the solution became cloudy and the sodium salt of the carboxylic acid started to precipitate. The mixture was stirred until all the ester was consumed to give a large amount of white precipitate. The reaction was monitored by TLC for the disappearance of the starting ester (Table 1). The solvents were then removed under vacuum, the residue was diluted with water and the aqueous solution was extracted with diethyl ether in order to isolate the water insoluble alcohol (16–20), or/and to remove any negligible amount of unreacted ester. The aqueous phase was then cooled, acidified to pH 2–3 with dilute HCl or $NaHSO_4$ and extracted with AcOEt or Et_2O or CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was removed to afford the acid (1–15 and 18).
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