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Influence of co-solvents in the highly efficient selective monohydrolysis of a symmetric diester

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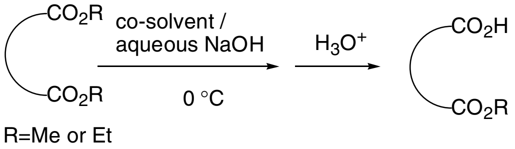
Abstract—The influence of the co-solvents in the selective monohydrolysis of a symmetric diester, in an aqueous NaOH medium at 0 °C, has been examined. The reactions were found to proceed through reaction media consisting of water with a small amount of a co-solvent and the starting symmetric diester. Slightly polar aprotic solvents that are slightly miscible with water, such as THF and acetonitrile, were found to be effective co-solvents.

Hydrolysis of an ester is one of the most commonly applied reactions in organic chemistry. Historically, one of the most widely used methods has been saponification with the use of base pellets such as NaOH or KOH, and an alcohol, which is a water-miscible solvent. This method has been generally useful for hydrolysis of a single ester into a carboxylic acid on a large scale at low cost.

By contrast, monohydrolysis of symmetric diesters without the use of enzymes has been a more challenging task. Limited examples have been reported for selective saponification of symmetric diesters,[1] but in most cases, complex mixtures of the starting diesters, half-esters, and diacids are formed even with the use of one equivalent of the base, making separation and purification difficult. However, we previously reported highly efficient selective monohydrolysis with the use of an aqueous NaOH solution in the THF–water media at around 0 °C (Scheme 1).[2] This reaction enables selective monohydrolysis of a series of symmetric diesters, yielding the corresponding half-esters in high to quantitative yields under these straightforward conditions. Because half-esters are important building blocks, this reaction is expected to have great synthetic versatility, and therefore we have been expanding the scope of this reaction from various points of view.



Scheme 1. Selective monohydrolysis of symmetric diesters.

One of the most remarkable differences between this monohydrolysis reaction and classical saponification is the reaction media. The use of the aqueous NaOH or KOH solution in the THF–water media at 0 °C instead of a solid base and an alcohol medium makes the reaction mixture quite clean in all the cases we have tried thus far, showing only spots of half-esters and dicarboxylic acids, if they exist, on thin layer chromatography plates after consumption of the starting diesters. Therefore, we have studied the influence of solvents by changing the proportion of THF as well as the type of co-solvent from THF to a variety of co-solvents. The symmetric diester applied in this study is dimethyl bicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylate, **1**, which afforded among the highest yields of the corresponding half-ester (>99%), **2**, with the highest selectivity as reported earlier.[2] Due to the high selectivity observed for this diester, we reasoned that the role of the solvent would become apparent.

Although some studies about effects of solvents in hydrolysis of single esters have been reported,[3] those

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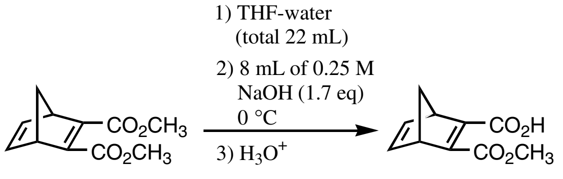
reporting such effects in hydrolysis of symmetric diesters are limited to discussion of simple linear diesters[4] or symmetric diesters applying enzymes.[5] Therefore it is anticipated that our study will provide some practical information about the role of the solvent and potentially provide insight into the mechanisms of this selective monohydrolysis.

First, we changed the proportion of the THF as the co-solvent, following the conditions we initially reported.[2,6] The total volume of the reaction mixture is consistent with that in the previous study.[2] The results are summarized in Table 1. The yields are the best isolated yields of half-ester **2** and recovered diester **1**. For the purpose of estimating the efficiency of the reactions, the reaction rate constants were measured with the reactions periodically monitored by ^{1}H NMR.[7]

Table 1. Effect of volume of THF in the monohydrolysis of **1**



1 (1.2 mmol) **2**

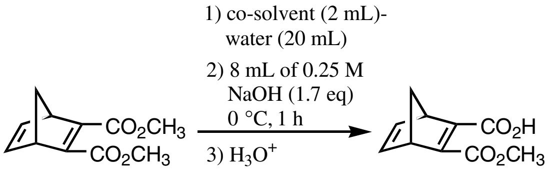
Volume (mL) of THF[a]	Time	Yield[b] (%)	Reaction rate constant (L mol^{-1} s^{-1})
22 (73%)	8 h	88 (0)	$3.26 \pm 0.02 \times 10^{-3}$
18 (60%)	6 h, 30 min	81 (1.2)	$6.06 \pm 0.12 \times 10^{-3}$
14 (47%)	5 h, 20 min	84 (0.4)	$1.10 \pm 0.02 \times 10^{-2}$
10 (33%)	3 h	90 (1.6)	$2.06 \pm 0.23 \times 10^{-2}$
6 (20%)	70 min	94 (1.2)	$2.56 \pm 0.06 \times 10^{-2}$
2 (7%)[c]	70 min	>99 (0)	$4.70 \pm 0.02 \times 10^{-2}$
1 (3%)	70 min	>99 (0)	$4.81 \pm 0.10 \times 10^{-2}$
0 (0%)	70 min	>99 (0)	$4.59 \pm 0.07 \times 10^{-2}$

[a] Percentage of THF (v/v) is shown in parenthesis.
[b] Isolated yield of **2**. Recovered **1** is shown in parenthesis.
[c] The same conditions reported in Ref. 2.

These results clearly indicate that decreasing the proportion of THF to below 7% does not influence the reaction rates significantly, but increasing the proportion of THF diminishes the rates tremendously. This tendency perhaps reflects the solubility of THF in water under these conditions. The increased proportion of THF is anticipated to decrease the exposure of the carbomethoxy group to the aqueous NaOH. The yields of the monohydrolysis reaction also decrease to some extent as the proportion of THF increases, although the yields remain extremely high even when no THF is used. These reduced yields may be attributed to the small amount of the corresponding diacid formed due to the prolonged reaction time and remained in the aqueous layer, or may be attributed to the difficulty of extracting the half-ester. When the initial proportion of THF is increased to 20% or greater, we often observed formation of hydrates in the reaction mixture, which constrained stirring and complicated the extraction of the product.[8] Therefore, it appears that the optimal proportion of the THF as a co-solvent is approximately the proportion reported previously.

Table 2 summarizes the results of changing a variety of co-solvents under the same conditions of the 7% of co-solvent and the reaction temperature.[2] All the co-solvents chosen here are easily volatile upon work-up.

Table 2. Effects of co-solvents in the monohydrolysis of **1**



1 (1.2 mmol) **2**

Co-solvent	Yield[a] (%)	Reaction rate constant (L mol^{-1} s^{-1})
THF[b]	>99 (0)	$4.70 \pm 0.02 \times 10^{-2}$
CH_3CN	>99 (0)	$4.85 \pm 0.40 \times 10^{-2}$
Methanol	90 (0.8)	$3.73 \pm 0.50 \times 10^{-2}$
Ethanol	86 (0)	$3.48 \pm 0.06 \times 10^{-2}$
2-Propanol	88 (0.8)	$3.29 \pm 0.02 \times 10^{-2}$
CH_2Cl_2	9 (89)	$8.60 \pm 0.27 \times 10^{-4}$
None	>99 (0)	$4.59 \pm 0.07 \times 10^{-2}$

[a] Isolated yield of **2**. Recovered **1** is shown in parenthesis.
[b] The same conditions reported in Ref. 2.

From these results, it is apparent that methylene chloride showed a tremendous decrease in reaction rate, but all other co-solvents or no co-solvent showed similar reaction rates. More specifically, methylene chloride, which has little miscibility with water, decreases the reaction rate significantly due to the reduced exposure of the carboalkoxy group to the aqueous NaOH. This result is similar to the cases in which large percentages of THF are applied as shown in Table 1. On the other hand, other solvents that are water-miscible to a small or large extent do not change the reaction rate significantly. The isolated yields of half-ester **2** appear to be the highest when THF, acetonitrile, or no co-solvent is used, and slightly decrease when an alcohol is used as a co-solvent. These results indicate that the decreased yields may be due to the formation of the small amount of the corresponding diacid, and/or to the difficulty of extracting the product. Overall, THF or acetonitrile appears to be the best co-solvent among the solvents tested in this study for this selective monohydrolysis reaction.

The small differences in the reaction rates observed in the kinetic data may be explained by similar tendencies reported earlier by the enhancement of hydrolysis with the use of DMSO over ethanol, as DMSO is also an aprotic solvent.[3c] Namely, DMSO effectively solvates the transition state of hydrolysis of an ester and poorly solvates the hydroxide ion, and hence activates the hydroxide ion. As THF and acetonitrile are aprotic solvents, the slightly enhanced reaction rates with these solvents compared to those with water or alcohols, protic solvents, may be attributed to such cumulative effects.

Therefore, we conclude that in the reaction mixture, the small amount of THF or acetonitrile is dissolved in a larger amount of water, making one aqueous phase, and that the diester participates in the reaction as the second phase, and the monohydrolysis occurs at the interface between the aqueous phase and the diester. The major role of THF or acetonitrile as a co-solvent is likely that of dispersing the starting diesters more smoothly to the reaction medium. This role is particularly advantageous when the starting diester is a solid as in many examples previously reported,[2] while the conditions free from an organic solvent are also anticipated to offer another practical advantage as a green reaction, especially on a large scale.

From a technical point of view, alcohols are miscible in water, and therefore extraction efficiency of the half-ester is expected to decrease due to the hydrophilic nature of the carboxyl group and the co-solvent. It should also be noted that when these alcohols were used as a co-solvent, turbidity was observed before the addition of the aqueous NaOH solution, and the reaction mixture thickened to some extent, but when THF or acetonitrile was used, the diesters existed as separate oil droplets, moving smoothly in the aqueous phase. Upon acidifying, precipitation of the half-ester from the reaction mixture was also most effective when THF or acetonitrile instead of an alcohol was used, perhaps due to the relatively non-polar aprotic nature and reduced solubility of these solvents in water.

In summary, we found that this highly efficient selective monohydrolysis of symmetric diesters is most effective when a small amount of an aprotic solvent with a small degree of miscibility with water was applied as a co-solvent at a low temperature (~0 °C). The reaction appears to occur at the interface between the symmetric diester and the aqueous phase that may contain the co-solvent. Such solvent effects may play an important role in the higher selectivity in our monohydrolysis reaction over that of classical saponification.

Recently, water-mediated reactions have become important as environmentally friendly reactions in green chemistry. To our knowledge, the reaction described here is among the first examples of water-mediated reactions being applied to desymmetrization.[9] We are investigating further mechanistic studies such as steric effects of the starting symmetric diester and other physicochemical behavior of the reaction intermediates, and the results will be reported in due course.

Acknowledgments

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6. Standard conditions are as follows: The starting symmetric diester (1.2 mmol) was dissolved in 2 mL of a co-solvent and was diluted with 20 mL of water prior to the addition of 8 mL of the aqueous NaOH (0.25 M) solution at 0 °C. The reaction mixture was acidified with 1 M HCl, saturated with NaCl, extracted with ethyl acetate three or four times, and dried with sodium sulfate.
7. The kinetic data were obtained from 12.5 mg (0.06 mmol) of diester **1** delivered to each test tube, as well as water, a co-solvent, and 0.25 M aqueous NaOH solution added proportionally at 0 °C in an ice-water bath in a cold room. The reaction mixture was periodically quenched with HCl and extracted with ethyl acetate, and the ethyl acetate extract was concentrated under a vacuum for ^{1}H NMR analysis. The reaction rates were calculated from the rate equation for second order kinetics, $\ln\{b(a-x)/a/(b-x)\} = (a-b)kt$, where a and b represent the initial concentrations of the diester and NaOH, respectively, and k, t, and x represent the reaction rate constant (L mol^{-1} s^{-1}), time (s), and the concentration of the consumed diester (M). All kinetic studies were repeated at least twice and confirmed to be reproducible.
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