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Practical selective monohydrolysis of bulky symmetric diesters

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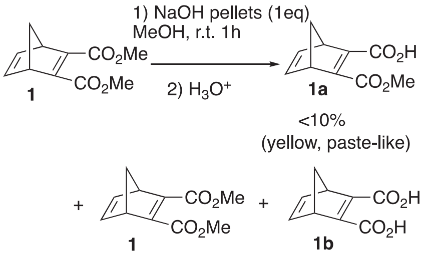
ABSTRACT

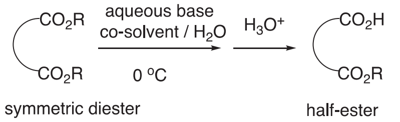
The highly efficient selective monohydrolysis reaction we previously reported has been applied to monohydrolysis of several bulkyl symmetric diesters, including diethyl esters, dipropyl esters, and dibutyl esters. A greater proportion of a polar aprotic co-solvent, DMSO, and aqueous KOH appear to help improve the reactivity of bulky diesters compared to the corresponding dimethyl esters. The procedure is mild and practical, yielding the corresponding half-esters in high yields under simple conditions.

Half-esters are among the most important building blocks for organic synthesis of a variety of compounds including natural products, drugs, polymers, and dendrimers.[1] Most typically, they are prepared by monohydrolysis of symmetric diesters. However, the classical monosaponification of symmetric diesters tends to produce complex mixtures consisting of starting diesters, half-esters, and diacids in which both the ester groups are hydrolyzed, and a small percentage of the corresponding half-esters, typically as yellowish material. For example, in our experiments, monosaponification of dimethyl bicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylate, **1**, resulted in a complex mixture, and less than 10% of the half-ester was obtained as a yellowish paste-like solid (Scheme 1).[2] Enzymatic monohydrolysis of symmetric diesters requires random screening, as it provides no basis for prediction of the reactivity.

Earlier, we reported highly efficient selective monohydrolysis of symmetric diesters.[3] This reaction selectively monohydrolyzes a series of symmetric diesters under mild and practical conditions with high yields. The reaction mixtures are clean, and only the half-esters, and diacids as well as the starting diesters, if they exist, are observable, unlike the monosaponification reactions. In many cases, the yields are near quantitative (Scheme 2).



Scheme 1. Classical monosaponification of a symmetric diester.



Scheme 2. Selective monohydrolysis of symmetric diesters.

However, when the starting diesters have relatively bulky ester groups, the reactions sometimes require an extended period of time or greater amounts of a base for completion of the reactions within a shorter reaction time. The amount of base and the reaction time tend to increase as the bulkiness of the ester group increases depending on the starting diesters.[4] For example, while the dimethyl ester, **1**, is monohydrolyzed in about one hour with about 2 equivalents of a base, monohydrolysis of the corresponding diethyl ester, **2**, needs about three to four times the equivalent of the base or a longer reaction time,[3] and the same monohydrolysis of diisopropyl ester, **3**, requires about 19 h (Scheme 3).[5]

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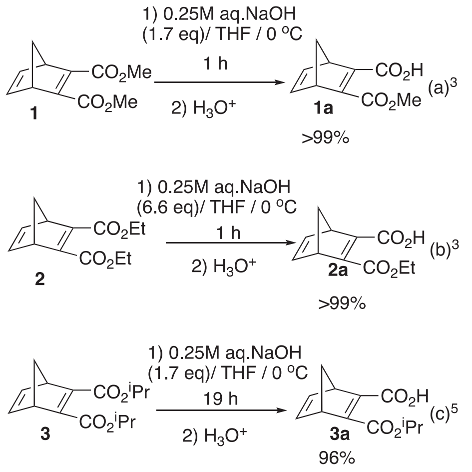


Scheme 3. Examples of selective monohydrolysis.

This trend is consistent with our observation reported before that the monohydrolysis occurs at the interface between the aqueous face and the diester, hence reflecting the reduced contact of the more hydrophobic ester groups with the aqueous phase. The drawback in this trend is occasional decrease of the yields of half-esters due to the prolonged reaction time. A long reaction time while maintaining 0 °C may also be difficult. Therefore, here we attempted to improve the selectivity of monohydrolysis of bulky symmetric diesters.

We initially applied ultrasound in order to accelerate the reaction rate,[6] because ultrasound-assisted reactions are known to enhance rates of many two-phase reactions.[7] However, ultrasound-assisted conditions did not improve the selectivity or reactivity of the diisopropyl ester, **3**. At the best result, the half-ester was obtained only in 60% yield with the use of 6 equivalents of aqueous KOH after 3 h with recovery of 12% of the starting diester, **3**.[6]

We next tried to adjust reaction conditions without a special device. According to our hypothesis, once one of the two ester groups is monohydrolyzed, the intermediary monocarboxylates form micellar aggregates in which the remaining hydrophobic portions point inside and the hydrophilic carboxylate groups point outside, prohibiting further hydrolysis and keeping the remaining ester group intact. Consistent with this hypothesis, we observed that a water–miscible polar aprotic co-solvent such as THF and CH_3CN increases the reaction rate and selectivity while a protic co-solvent such as an alcohol decreases the selectivity, perhaps by dissociating the micellar aggregates.[8] We also previously reported that use of DMSO improved *exo*-selectivity of various dialkyl bicycle[2.2.1]heptane-2,3-carboxylates by accelerating the monohydrolysis of the sterically less hindered *exo*-ester groups.[9,10]

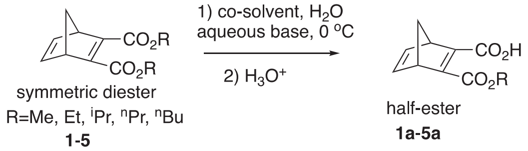
Furthermore, we found that KOH often improves selectivity and reactivity compared to NaOH, which is perhaps due to stronger affinity of K^+ with carbonyl oxygen, leading to the enhanced electrophilic character of the starting ester group.[11] We reported that aqueous KOH improved selectivity in various diesters including dialkyl malonates.[11–13]

Here we report various selective monohydrolysis of symmetric bulky diesters by tuning the reaction conditions based on our previous findings and mechanistic hypothesis.

We first screened the selective monohydrolysis of dialkyl bicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylates.[14] All these diesters were synthesized in high yields by simple Diels-Alder reactions of cyclopentadiene and the corresponding dialkyl acetylenedicarboxylates.[15] The results are summarized in Table 1.

As for the dimethyl ester, **1**, the reaction is known to proceed quite efficiently regardless of the kinds of base or co-solvent.[3,8,11] Therefore, in all the cases, the reaction produced near-quantitative yields of the corresponding half-ester, **1a**, although we noticed, judging from the reaction time, that DMSO and KOH somewhat enhanced the reaction rate, which is consistent with our previous observation. The volume percentage of the co-solvent is the same

Table 1
Selective monohydrolysis of dialkyl bicycle[2.2.1]hept-2,5-diene-2,3-dicarboxylates.



1-5
(1.2 mmol)

1a-5a

Run	R	Co-solvent	Co-solvent (v/v):H₂O (mL)	Aqueous base	Reaction time	Yield (%)
1	**1**: Me	THF	2 mL (7%):20 mL	0.25 M NaOH 8 mL	45 min	>99
2		DMSO	2 mL (7%):20 mL	0.25 M NaOH 8 mL	40 min	>99
3		DMSO	2 mL (7%):20 mL	0.25 M KOH 8 mL	30 min	>99
4	**2**: Et	THF	4 mL (13%):24 mL	0.5 M KOH 4 mL	5 h 30 min	95
5		THF	16 mL (44%):16 mL	0.5 M KOH 4 mL	3 h	93
6		THF	24 mL (67%):8 mL	0.5 M KOH 4 mL	1 h 50 min	95
7		DMSO	4 mL (13%):24 mL	0.5 M KOH 4 mL	3 h	84
8		DMSO	16 mL (44%):16 mL	0.5 M KOH 4 mL	2 h	92
9		DMSO	24 mL (67%):8 mL	0.5 M KOH 4 mL	1 h 30 min	>99
10	**3**: ^{i}Pr	THF	22 mL (73%):4 mL	0.5 M KOH 4 mL	12 h	71
11		DMSO	24 mL (67%):8 mL	0.5 M KOH 4 mL	4 h 30 min	87
12		DMSO	22 mL (73%):4 mL	0.5 M KOH 4 mL	3 h	93
13	**4**: ^{n}Pr	THF	22 mL (73%):4 mL	0.5 M KOH 4 mL	12 h	78
14		DMSO	24 mL (67%):8 mL	0.5 M KOH 4 mL	4 h	91
15		DMSO	22 mL (73%):4 mL	0.5 M KOH 4 mL	3 h	96
16	**5**: ^{n}Bu	THF	32 mL (84%):2 mL	0.5 M KOH 4 mL	18 h	63
17		DMSO	32 mL (84%):2 mL	0.5 M KOH 4 mL	6 h	84