Highly Efficient Selective Monohydrolysis of Symmetric Diesters

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Ester hydrolysis is one of the most fundamental reactions in organic chemistry. Alkaline hydrolysis or saponification using a base such as NaOH in aqueous alcohol is a well-known method.

However, for monohydrolysis of symmetric diesters, almost no efficient way has been reported to hydrolyze one of the ester groups selectively. Half-esters, which are produced by such selective monohydrolysis of diesters, are very versatile building blocks in organic synthesis. However, the only effective monohydrolysis hitherto reported utilizes enzymes, a process which provides no basis for predictions for the yield and enantioselectivity. For cases where racemic or achiral monoesters are desired, no systematic studies have been reported for monohydrolysis of symmetric diesters. Classical alkaline hydrolysis usually does not afford easily manageable results: Usually, it gives slurry complex mixtures of di- and monocarboxylic acids and the starting diesters, and it also often requires many hours. Furthermore, the separation of the reaction mixture is very difficult. Only a limited number of examples of selective hydrolysis using malonic diesters have been reported,[1] and most of them do not enable purification at the stage of monohydrolysis; therefore crude half-esters are used for further steps without purification. In contrast, ring-opening reactions of cyclic anhydrides with alkoxides are rather common for obtaining half-esters in both asymmetric[2] and nonasymmetric versions.[3,1a]

The method described here presents highly efficient and practical ester monohydrolysis using THF−water media as follows (Scheme 1).

When several symmetric diesters were submitted to ester hydrolysis reactions in a mixture of THF and 10 times the volume of diluted aqueous NaOH solution at 0 °C, the corresponding monocarboxylic acids were obtained in very high yields, up to near-quantitative yields. In addition, the reactions appeared to be completed rapidly and were worked up within 30−60 min for all of the cases reported here. Furthermore, the reaction mixtures were quite clean; after consumption of the starting diesters, only the spots of half-esters and small amounts of dicarboxylic acids, if they existed, were observed on thin-layer chromatography plates,[4] and therefore, the isolation and purification of the resultant half-esters after routine single silica gel column chromatography was quite straightforward.

Table 1 summarizes the representative results using nine symmetric dimethyl and diethyl esters. All of the reactions were conducted at least twice, and therefore

Scheme 1

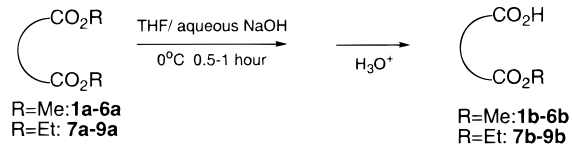
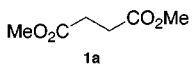
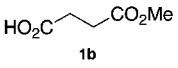
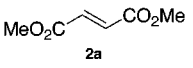
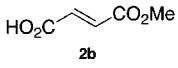
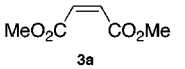
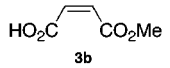
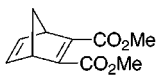
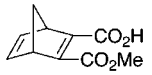
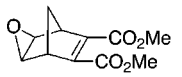
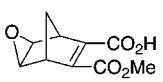
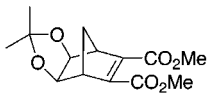
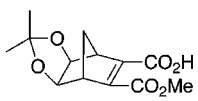
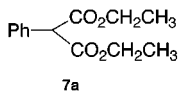
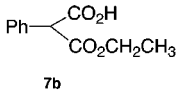
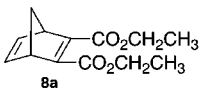
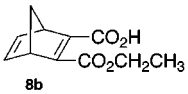
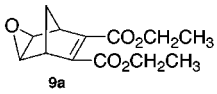
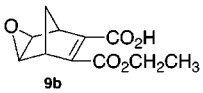


Table 1. Mononydrolysis of Symmetric Diesters in the Two-Phase Reaction

entry	diester	product	yield (%)[a]
1	 1a	 1b	70%
2	 2a	 2b	79%
3	 3a	 3b	95%[b]
4	 4a	 4b	>99%
5	 5a	 5b	>99%
6	 6a	 6b	>99%
7	 7a	 7b	87%[c]
8	 8a	 8b	>99%
9	 9a	 9b	>99%

[a] Yields are isolated yields from silica gel column chromatography based on the amounts of the diesters submitted to the reaction. [b] The yield was diminished due to the slight volatility of **3b**. [c] Approximately 11% of **7a** was recovered.

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(2) (a) Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1717. (b) Hiratake, J. Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1053. (c) Kawakami, Y.; Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1984**, 779. (d) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142. (e) Albers, T.; Biagini, S. C. G.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A.; North, M.; Uriarte, E.; Zagotto, G. *Synthesis* **1996**, 393. (f) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1 and references therein. (g) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett.* **1999**, 195 and references therein.

(3) (a) Sabitha, G.; Srividya, R.; Yadav, J. S. *Tetrahedron* **1999**, *55*, 4015. (b) Bolm, C.; Dinter, C. L.; Seger, A.; Höcker, H.; Brozio, J. *J. Org. Chem.* **1999**, *64*, 5730.

(4) In most cases, the dicarboxylic acids, which may form in the reaction, stayed in the aqueous layer after extraction with ethyl acetates.

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the results were reproducible. The yields indicated in the table are all isolated yields as pure products from silica gel column chromatography based on the amount of the starting diesters submitted to the reaction. All of the half-esters obtained in this way showed satisfactory ^{1}H and ^{13}C NMR with no peaks of impurities, and elemental analysis or mass spectrum data. Melting points were all matched to reported values, when available. Therefore, the whole reaction procedure is quite straightforward.

The solvent effect is remarkable in contrast to classical alkaline hydrolysis or saponification using alcohols, which are more water-soluble solvents. These conditions have been reported to require at least room temperature and often reflux, and frequently take more than 10 h. However, the reactions that apply in the THF−water medium are completed immediately at 0 °C. In the case of diethylesters, almost three times the volume of NaOH solution was needed to accelerate the completion of the reaction, although the yields were still high.

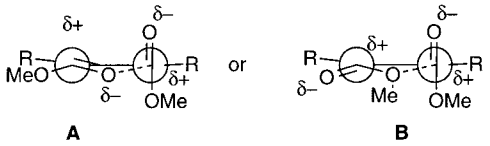
The reason for the solvent effect is unclear; however, THF is less miscible than alcohols but contains water to a considerable extent, especially at the interface between THF and water, forming semi-two phases at a low temperature (0 °C). Since carboalkoxy groups are the most hydrophilic parts and therefore are expected to be facing the interface between THF and water, the monohydrolysis may be occurring at this interface selectively, while the hydrophobic parts of the molecules are protected within the THF-enriched medium.[5] Once one of the carboalkoxy groups is converted to a carboxylate anion, it may have stronger interference with the remaining carboalkoxy groups, which may prohibit further hydrolysis. Relative resistance toward the hydrolysis observed for diethylesters may also be attributed to this more hydrophobic character of the carboethoxy group.

It seems that the geometry of the diester is an important factor. The diesters that afforded the corresponding half-esters in high yields all possess two carboalkoxy groups in "cis" or "geminal" orientation. This trend is well-illustrated in the comparison of the results of diesters **2a** and **3a**. It should be noted that all of the diesters of such types, **3a**−**9a**, afforded the corresponding half-esters in near-quantitative yields.

The reason for the steric trend of the starting diesters remains to be resolved. However, there may be some conformational bias[6] as in **A** or **B** due to electrostatic interactions between two closely located carboalkoxy groups in these diesters, which might facilitate the hydrolysis of a carboalkoxy group from one particular direction. This conformational restriction would be more evident in the nonpolar aprotic organic phase (THF) especially at low temperatures (0 °C) as applied in these experiments[7] (Scheme 2).

It would also be expected that the nucleophilic character of one of the carbonyl groups would be more

Scheme 2



A **B**

enhanced in this conformation, which might explain the efficiency in applying the nonpolar organic solvent described above.

The saturated linear symmetric diester, **1a**, and the *trans*-symmetric diester, **2a**, were also tried for the same reactions. The yields of the half-esters, **1b** and **2b**, dropped slightly to ~70% for these cases, which might be due to the lack of the geometrical demand. However, the reaction products can be separated quite easily from the starting diesters, and if the reactions are stopped before the starting diesters are consumed, the starting diesters can be resubmitted and the monocarboxylic acids can be obtained in higher yields.

The cold reaction temperature (0 °C) is important in order to obtain high yields and a clean reaction mixture. When allowed to warm to room temperature, the reaction mixture thickened, and the thin-layer chromatography was smeared. In addition, a crude half-ester was obtained in a low yield after silica gel column chromatography.

It should also be noted that the labile functional groups, epoxy groups in **5a** and **9a**, remained intact in these reactions. Earlier, we observed that the carboxylates of these half-esters **5b** and **9b**, generated by pig liver esterase monohydrolysis in a slightly basic buffer solution (pH = 8), underwent skeletal conversion to afford 6-formyl-1-(alkoxycarbonyl)bicyclo[3.1.0]hex-2-ene-2-carboxylic acids in quantitative yields.[8] However, upon hydrolysis of these epoxy diesters, only a trace to small amount (<1% for monohydrolysis of **4a** and <5% for monohydrolysis of **8a** by ^{1}H NMR analysis) of the rearranged products was detected.

In conclusion, a highly efficient semi-two-phase reaction using THF-aqueous NaOH at 0 °C was found to produce pure half-esters from symmetric diesters in high yields. The mechanisms, such as solvent effects and geometrical effects, are to be resolved; however, this reaction is quite straightforward and clean as opposed to classical methods, and its synthetic versatility is expected. Further expansion using more complex systems remains to be pursued.

Experimental Section

General Procedures. All of the melting points are uncorrected. ^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz spectra were measured as solutions in $CDCl_3$ or acetone-d_6 using TMS as an internal standard. The IR spectra were recorded on an FTIR instrument.

General Procedure for Monohydrolysis of Symmetric Dimethyl Esters. Diester (1.2 mmol) was dissolved in 2 mL of THF, and 20 mL of water was added. The reaction mixture was immersed in an ice−water bath and cooled to 0 °C. To this

(5) Similarly, selective partial monohydrolysis of (−)-dimenthyl esters was reported using tetrabutylammonium hydroxide, which generates naked OH^- under dry conditions. Hasegawa, T.; Yamamoto, H. *Synlett.* **1999**, 84.

(6) This "conformational lock" due to electrostatic interaction between carboalkoxy groups and other functional groups to explain diastereoselectivity has been reported. For example, see: (a) Yamamoto, Y.; Nemoto, H.; Kikuchi, R.; Komatsu, H.; Suzuki, I. *J. Am. Chem. Soc.* **1990**, *112*, 8598. (b) Yamamoto, Y.; Taniguchi, K.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1429. (c) Yamamoto, Y.; Chounan, Y, Nishii, S.; Ibuka, T.; Kitabara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652.

(7) A similar destruction of molecular symmetry in the solid state has been reported for **6a**,[7a] as well as for other symmetric diesters.[7b,c] (a) Niwayama, S.; Inouye, Y.; Eastman, M. *Tetrahedron Lett.* **1999**, *40*, 5961. (b) Battiste, M. A.; Griggs, B. G.; Sackett, D.; Coxon, J. M.; Steel, P. J. *J. Organomet. Chem.* **1987**, *330*, 437. (c) Dahl, L. F.; Wei, C. H. *Inorg. Chem.* **1963**, *4*, 71

(8) (a) Niwayama, S.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1994**, *116*, 3290. (b) Niwayama, S.; Noguchi, H.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1993**, *34*, 665. (c) Niwayama, S.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1988**, *29*, 6313.

reaction mixture, 8 mL of 0.25 N NaOH was added in small portions with stirring until the consumption of the starting diester was detected by thin-layer chromatography. The reaction was stirred at the same temperature for about 30 min to 1 h, and the reaction mixture was acidified with 1 N HCl at 0 °C, saturated with NaCl, extracted with ethyl acetate three to four times, and dried with sodium sulfate. This extract was evaporated in vacuo and purified by silica gel column chromatography to afford the desirable half-esters. The typical eluent for column chromatography was ethyl acetate to elute the pure half-ester.

Half-Ester ***1b***. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.6−2.7 (4H, m), 3.62 (3H, s), 9.9 (1H, br.s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.54, 28.86, 51.91, 172.64, 178.34; IR (neat, cm^{-1}) 1710, 1729, 2600−3990; mp 55−56 °C.[9] Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.61; H, 6.05.

Half-Ester ***2b.*** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.80 (3H, s), 6.81 (1H, d, J = 18.0 Hz), 6.90 (1H, d, J = 18.0 Hz), 11.2 (1H, br.s); ^{13}C NMR (75 MHz, acetone-d_6) δ = 52.6, 134.0, 134.7, 165.9, 166.1; IR (neat, cm^{-1}) 1720, 1710, 2940−3000; mp 141−141.5 °C (lit. 141−141.5 °C).[10] Anal. Calcd for $C_5H_6O_4$: C, 46.16; H, 4.65. Found: C, 45.82; H, 4.73.

Half-Ester ***3b.*** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.92 (3H, s), 6.39 (1H, d, J = 12.6 Hz), 6.49 (1H, d, J = 12.6 Hz), 9.8 (1H, br.s (−COOH)); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 53.35, 129.51, 135.01, 165.57, 167.74; IR (neat, cm^{-1}) 1720, 1740, 2940−3060. HRMS Calcd for $C_5H_{16}O_4N(M+NH_4)^+$: 148.0610. Found: 148.0607.

Half-Ester ***4b.*** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.14 (1H, d, J = 10.2 Hz), 2.25 (1H, d, J = 10.2 Hz), 3.96 (3H, s), 4.12 (1H, s), 4.25 (1H, s), 6.92 (2H, m);^{13}C NMR (75 MHz, $CDCl_3$) δ = 53.31, 53.69, 54.64, 72.62, 141.71, 142.58, 150.99, 162.25, 162.49, 168.11; IR (neat, cm^{-1}) 1711, 1730, 2650−3980; mp 107 °C (lit. 108−109 °C).[11] HRMS Calcd for $C_{10}H_{11}O_4(M+H)^+$: 195.0657. Found: 195.0657.

Half-Ester ***5b.*** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.56 (1H, d, J = 12 Hz), 1.79 (1H, d, J = 12 Hz), 3.50 (1H, br.s), 3.6 (2H, m), 3.69 (1H, br.s), 3.95 (3H, s), 9.7 (1H, br.s (−COOH)); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 38.48, 47.07, 47.95, 53.99, 57.68, 57.71, 148.11, 158.49, 162.23, 167.71; IR(cm^{-1}) 1713, 1725, 2650−3980. HRMS calcd for $C_{10}H_{11}O_5(M+H)^+$: 211.0606. Found: 211.0596.

Half-Ester ***6b.*** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.35 (3H, s), 1.51 (3H, s), 1.90 (1H, br.d, J = 10.0), 2.07 (1H, d, J = 10.0 Hz), 3.67 (1H, br.s), 3.53(1H, br.s), 3.94 (3H, s), 4.39 (2H, br.s); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 24.38, 25.79, 41.15, 49.35, 50.41, 53.99, 79.44, 79.64, 114.70, 142.84, 153.51, 161.54, 167.53; IR (neat, cm^{-1}) 1720, 1730, 2670−3000; mp 140 °C (optically active **6b** obtained by pig liver esterase is reported to be 140−141.5 °C).[12] Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.00; H, 5.83.

General Procedure for Monohydrolysis of Symmetric Diethyl Esters. Diester (0.9 mmol) was dissolved in 2 mL of THF, and 20 mL of water was added. The reaction mixture was immersed in an ice−water bath and cooled to 0 °C. To this reaction mixture, 24 mL of 0.25 N NaOH was added in small portions with stirring until the consumption of the starting diester was detected by thin-layer chromatography. The reaction was stirred at the same temperature for about 30 min to 1 h, and the reaction mixture was acidified with 1 N HCl at 0 °C, saturated with NaCl, extracted with ethyl acetate three to four times, and dried with sodium sulfate. This extract was evaporated in vacuo and purified by silica gel column chromatography to afford the desirable half-esters. The typical eluent for column chromatography ethyl acetate to elute the pure half-ester.

Half-Ester ***7b.*** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.25 (3H, t, J = 7.2 Hz), 4.2 (2H, m), 4.66 (1H, s), 7.3 (5H, m), 10.9 (1H, br.s (−COOH)); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.82, 57.50, 62.11, 128.39, 128.63, 129.13, 132.02, 167.97, 173.75; IR (neat, cm^{-1}) 1711, 1739, 2660−2990; mp 77 °C (lit. 76−77 °C).[1a] Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.16; H, 5.66.

Half-Ester ***8b.*** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.50 (3H, t, J = 7.2 Hz), 2.19 (1H, d, J = 10.0 Hz), 2.30 (1H, d, J = 10.0 Hz), 4.16 (1H, br.s), 4.28 (1H, br.s), 4.4 (2H, m), 6.9 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.88, 53.34, 54.68, 63.31, 72.63, 141.71, 142.67, 151.37, 162.10, 162.64, 167.73; IR (neat, cm^{-1}) 1710, 1729, 2650−2980. HRMS Calcd for $C_{11}H_{12}O_4(M^+)$: 208.0735. Found: 208.0736.

Half-Ester ***9b.*** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.48 (3H, t, J = 7.2 Hz), 1.57 (1H, d, J = 11.2 Hz), 1.78 (1H, d, J = 11.2 Hz), 3.53 (1H, br.s), 3.6 (2H, m), 3.74 (1H, br.s), 4.4 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.90, 38.51, 47.15, 48.08, 57.80, 57.80, 63.78, 148.40, 158.78, 162.23, 167.40; IR (neat, cm^{-1}) 1710, 1728, 2650−2980. HRMS calcd for $C_{11}H_{16}O_5N(M+NH_4)^+$: 242.1029. Found: 242.1029.

Acknowledgment. The author thanks Oklahoma State University, College of Arts and Sciences for financial support (start-up funds).

Supporting Information Available: Copies of ^{13}C NMR spectra of **3b**−**5b**, **8b**, and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Half-ester **1b** is a known compound, but the melting point was not found.

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