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Communications

Cleavage of Esters under Nearly Neutral Conditions at High Pressure. Chemo- and Regioselective Hydrolysis in Organic Solvents

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Summary: Hydrolysis of esters proceeded at room temperature under high pressures in the presence of iPr_2NEt or *N*-methylmorpholine using CH_3CN-H_2O (60:1) as the solvent. This very mild procedure enables the smooth hydrolysis of biologically important compounds such as amino esters, aliphatic unsaturated fatty esters, and β-hydroxy esters; no racemization, no isomerization, and no side reactions take place.

Hydrolysis of esters is one of the most essential transformations in organic synthesis. Normally, a basic or acidic aqueous solution is used for ester hydrolysis. However, the hydrolysis of biologically related molecules such as amino esters, peptides, or unsaturated fatty esters under such conditions is accompanied by side reactions, loss of chirality, or isomerization.[1] We report an entirely new approach to this problem via high-pressure induced hydrolysis (eq 1). Hydrolysis is carried out at room temperature under >8 kbar in CH_3CN-H_2O.

$$RCO_2R^1 \xrightarrow[\substack{CH_3CN-H_2O\ (60:1)\\ N\text{-methylmorpholine}\\ \text{or } iPr_2NEt}]{>8\ \text{kbar},\ 30\ ^\circ C} RCO_2H + R^1OH \qquad (1)$$

The results are summarized in Table I. Normally, the hydrolysis of β-hydroxy esters is accompanied by retroaldol reaction, and the hydrolysis of β,γ-unsaturated esters is accompanied by isomerization of the double bond. The ester **1** or **3** has a β,γ-olefinic moiety in addition to a β-hydroxy group. In the event, the ordinary aqueous hydrolysis of **3** gave a number of products. The high-pressure induced hydrolysis afforded the desired hydroxy acid **2** as a single product (entry 1). Ethyl arachidonate **4** gave **5** in high yield (entry 2); no side reactions took place. Regioselectivity may be observed in the high-pressure systems. The diester **6** could be converted to **7** selectively at high pressure (entry 3), whereas the aqueous NaOH hydrolysis at 1 bar gave **8** and **9** as major products: **7**, 20%, **8**, 65%, **9**, 15%. Similarly, discrimination between the two ester groups in **10** was possible at high pressure; the high-pressure hydrolysis gave **11** in 100% yield, whereas the ordinary hydrolysis produced a mixture of **11**, **8**, and **9**. Hydrolysis of amino acid derivatives also proceeded very smoothly without racemization. Especially notworthy is the hydroysis of **12** (entry 4). Standard aqueous hydrolysis is inefficient since **13** is very water soluble. The high-pressure induced hydrolysis requires normally 3–4 equiv of H_2O, and thus isolation of water soluble products is simplified. Needless to say, the hydrolysis under the same conditions at 1 bar did not occur. The high-pressure hydrolysis of **14**, **16**, and **18** also proceeded smoothly, giving **15**, **17**, and **19**, respectively. Selective alcohol exchange enables the selective hydrolysis of **20** and **6** (entries 5 and 6). The ordinary aqueous procedure produced many products. In conclusion, the high-pressure induced hy-

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[1] (a) Aqueous alkali carbonates or bicarbonates: Kaestle, K. L.; Anwer, M. K.; Audhya, T. K.; Goldstein, G. *Tetrahedron Lett.* **1991**, *32*, 327. (b) $AlCl_3$–alkyl sulfides: Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *46*, 1991. Tsuji, T.; Kataoka, T.; Yoshioka, M.; Sendo, Y.; Nishitani, Y.; Harai, S.; Maeda, T.; Nagata, W. *Tetrahedron Lett.* **1976**, 2795. (c) Sodium benzeneselenoate: Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605. (d) Nitrosonium tetrafluoroborate: Ho, T.-L.; Olah, G. A. *Synthesis* **1977**, 418. (e) Lithium methylmercaptide: Corey, E. J.; Brennan, T. M.; Carney, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 7316. Shekhani, M. S.; Grubler, G.; Echner, H.; Voelter, W. *Tetrahedron Lett.* **1990**, 339. (f) Potassium *tert*-butoxide: Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918. (g) Iodotrimethylsilane: Ho, T.-L.; Olah, G. A. *Synthesis* **1977**, 917. (h) Alkali metal carbonates: Martinez, J.; Laur, J.; Castro, B. *Tetrahedron Lett.* **1983**, 5219. Amblard, M.; Rodriguez, M.; Martinez, J. *Tetrahedron* **1988**, *44*, 5101. Zaugg, H. E. *J. Org. Chem.* **1976**, *41*, 3419. (i) Catalytic hydrogenation: Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 929; *Tetrahedron Lett.* **1981**, 4369.

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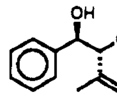
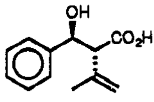
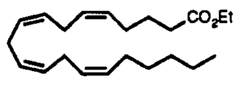
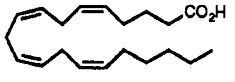
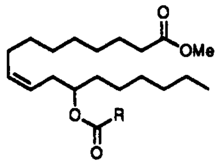
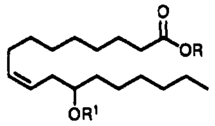
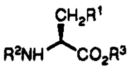
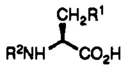
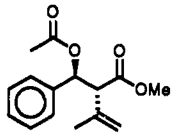
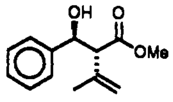
Table I. High-Pressure Induced Hydrolysis[a]

entry	substrates	conditions	conversion (%)	products (isolated yield, %)
1	 1, R = Me 3, R = Et	10 kbar, iPr$_2$NEt/CH$_3$CN-H$_2$O 30 °C, 4 d	100	 2, 91
2	 4	10 kbar, Et$_3$N/CH$_3$CN-H$_2$O 30 °C, 4 d	78	 5, 100
3	 6, R = Me 10, R = Ph	10 kbar, 30 °C, 2.5 d iPr$_2$NEt/CH$_3$CN-H$_2$O	25	 7, R = H, R^1 = Ac; 94.5 8, R = Me, R^1 = H; 3.9 9, R = H, R^1 = H; 1.6 11, R = H, R^1 = PhCO
4	 >99%ee 12, R^1 = OH, R^2 = Cbz, R^3 = CH$_2$Ph 14, R^1 = H, R^2 = Boc, R^3 = Me 16, R^1 = CO$_2$CH$_2$Ph, R^2 = Cbz, R^3 = CH$_2$Ph 18, R^1 = H, R^2 = Cbz, R^3 = CH$_2$Ph	10 kbar, 30 °C, 4 d NMM/CH$_3$CN-H$_2$O	100	 >99%ee ~100% 13, R^1 = OH, R^2 = Cbz 15, R^1 = H, R^2 = Boc 17, R^1 = CO$_2$CH$_2$Ph, R$_2$ = Cbz 19, R^1 = H, R^2 = Cbz
5	 20	10 kbar, 30 °C, 4 d iPr$_2$NEt-MeOH	85	 1, 100
6	6	10 kbar, 30 °C, 4 h iPr$_2$NEt-MeOH	99	8; 100

[a] NMM; N-methylmorpholine. CH$_3$CN-H$_2$O (60:1) or MeOH was used as a solvent. The aqueous hydrolysis at 1 bar was carried out with 1.2 equiv of 1 N NaOH in MeOH. [b] The mechanical loss during isolation led to ~90%. No byproducts were detected.

drolysis opens a new door to ester cleavage reactions.[2,3] Side reactions are minimized, and no isomerization or racemization were observed in the hydrolysis of the previously difficult systems.

Hydrolysis of **18** is representative. In a Teflon capsule were placed **18** (377 mg, 1.2 mmol), acetonitrile (3 mL), water (0.2 mL), and NMM (0.13 mL, 1.2 mmol). The capsule was placed in a high pressure apparatus. The hydrolysis was carried out at 10 kbar for 2 days. The pressure was released, and 1 N aqueous HCl was added to the reaction mixture. Extraction with CHCl$_3$, drying over anhydrous MgSO$_4$, and removal of the solvents gave 268 mg of **19** (100%, white prisms recrystallized from hexane, mp 73–74 °C). Instead of NMM, Et$_3$N (0.167 mL, 1.2 mmol) can be utilized. The high-pressure apparatus was purchased from Hikari High Press Inc.[4]

Supplementary Material Available: Synthetic methods and physical data for **1**–**20** (3 pages). Ordering information is given on any current masthead page.

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(2) Neutral hydrolysis: (a) Kahne, D.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 7529. (b) Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1987**, *109*, 3145. (c) Chin, J.; Zou, X. *J. Am. Chem. Soc.* **1984**, *106*, 3687. (d) Chin, J.; Banaszczyk, M. *J. Am. Chem. Soc.* **1989**, *111*, 2724; *Ibid.* **1989**, *111*, 4103. Hydrolysis of amino esters: (e) Prestidge, R. L.; Harding, D. R. K.; Battersby, J. E.; Hancock, W. S. *J. Org. Chem.* **1975**, *40*, 3288. (f) Huffmann, W. F.; Hall, R. F.; Grant, J. A.; Holden, K. G. *J. Med. Chem.* **1978**, *21*, 413. Hydrolysis of erythronolide: (g) Sakan, K.; Babirad, S. A.; Smith, D. A.; Houk, K. N. *Tetrahedron Lett.* **1990**, *31*, 3687. Hydrolysis with DBU or imidazole: (h) Parish, E. J.; Miles, D. H. *J. Org. Chem.* **1973**, *38*, 1223. (i) Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 833.

(3) Mechanistic studies on high-pressure induced hydrolysis: (a) Isaacs, N. S.; Najem, T. S. *Can. J. Chem.* **1986**, *64*, 1140. (b) Kurz, J. L.; Lu, J. Y. W. *J. Phys. Chem.* **1983**, *87*, 1444. (c) Tonnet, M. L.; Whalley, E. *Can. J. Chem.* **1975**, *53*, 3414. (d) Brower, K. R. *J. Am. Chem. Soc.* **1972**, *94*, 5747. (e) Andersen, B.; Grønlund, F.; Olsen, J. *Acta Chem. Scand.* **1969**, *23*, 2458.

(4) For recent reviews on high-pressure reactions: (a) Uyehara, T.; Saito, K.; Yamamoto, Y. *Yuki Gosei Kagaku Kyokaishi* **1989**, *47*, 321; *Chem. Abstr.* **1989**, *111*, 6484*t*. (b) Jurczak, J., Baranowski, B., Eds. *High Pressure Chemical Synthesis*; Elsevier: Amsterdam, 1989. (c) Isaacs, N. S.; George, A. V. *Chem. Brit.* **1987**, *23*, 47. (d) Sasaki, M.; Osugi, J. *Yuki Gosei Kagaku Kyokaishi* **1983**, *41*, 692; *Chem. Abstr.* **1983**, *99*, 157440*k*. (e) *Organic Synthesis at High Pressure*; Matsumoto, K., Acheson, R. M. Eds.; John Wiley: New York, 1991.