

Quantitative “On Water” Ring-Opening of Steroidal Epoxides Accelerated by Sand: A Green Procedure

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ABSTRACT: Dihydroxylated steroids have been prepared quantitatively by stirring a mixture of a very sparingly soluble high-melting-point (VSSHMP) steroidal epoxide, polytetrafluoroethylene (PTFE) sand, and aqueous H₂SO₄; no organic solvents or phase transfer catalysts were used. The sand and aqueous H₂SO₄ are highly recyclable. The promoting effects of the sand for these “on water” reactions have been demonstrated for the first time. This is a green, waste-free, mild, and operationally simple procedure. Various functional groups such as ketones, esters, ethers, ketals, epoxides on D-rings, and α,β -unsaturated ketones all survived these reaction conditions. This methodology is useful for using less organic solvents, reducing the cost of the products and protecting the environment.

KEYWORDS: polyhydroxysteroid, green reaction, ring-opening, steroidal epoxides, sand

■ INTRODUCTION

Polyhydroxysteroids and their derivatives are commonly found in food products from plants and in marine invertebrates.^{1,2} Oxysterols such as triols and epoxides form in foodstuffs due to the reactive oxygen species that are produced by heat treatment, contact with oxygen, or exposure to sunlight, and these oxysterols can be absorbed by humans when these foodstuffs are consumed.^{3–5} In addition, polyhydroxysteroids exhibit activities for certain diseases such as muscular dystrophy and cancer.^{6,7}

Polyhydroxysteroids can be synthesized through dihydroxylation reactions that start with naturally occurring and abundant Δ^5 -steroids. The *syn*-dihydroxylation of Δ^5 -steroids has been achieved using metal oxides such as OsO₄⁸ or RuO₄.⁹ Several methods for the *anti*-dihydroxylation of Δ^5 -steroids such as the use of NBS/acetic acid¹⁰ and H₂O₂/HCOOH¹¹ systems are well documented. The most often used procedures consist of the epoxidation of Δ^5 -steroids and the ring-opening of the epoxides. The epoxidation is usually achieved in excellent yields via peroxyacid oxidation routes.¹² The ring-opening reaction is often catalyzed by various acids in organic or aqueous organic media to give 24–100% yields.^{13–15} The acids employed include HClO₄,¹⁶ H₂SO₄,¹⁷ HIO₄,¹⁸ and Bi(OTf)₃,¹⁹ and the reaction media used include tetrahydrofuran,²⁰ acetone,²¹ dioxane,²² and aqueous systems of these solvents.^{23,24} The problems with these procedures include nonquantitative yields for most of the systems, the necessity of using organic solvents in the reactions and in the workup, and sometimes the need for chromatographic purifications.¹⁷ There have been no reports on ring-opening reactions of VSSHMP steroidal epoxides mediated by water that do not use organic solvents. Since organic solvents are volatile and pollute the environment, it would be ideal if these ring-opening reactions could be carried out in a system mediated solely by water.

There are reports of “in-water” reactions²⁵ of water-soluble substrates and “on-water” reactions^{26–28} of water insoluble substrates. Previously, we reported on a series of green

reactions performed by stirring a mixture of the substrate, the corresponding reagent(s), water, a catalytic amount of Aliquat 336, and sand.²⁹ Herein, quantitative “on water” ring-opening reactions of VSSHMP steroidal epoxides in the presence of PTFE sand with no organic solvents or Aliquat 336 are reported.

■ MATERIALS AND METHODS

General Experimental Information. All of the chemicals were obtained from commercial sources or prepared according to standard methods.¹² The ¹H and ¹³C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 and 100 MHz, respectively), using tetramethylsilane (TMS) as the internal standard ($\delta = 0$). IR spectra were obtained using a BIO-RAD FTS 3000 spectrometer, using potassium bromide disks, and the spectra were scanned from 400 to 4000 cm⁻¹. Melting points were recorded on an X-4 Micromelting Point Apparatus. Elemental analyses for C, H, and N were performed on a Yanaco CHNCORNER MF-3 elemental analyzer. MS (ESI, positive) analysis was carried out on a LCQ Advantage MAX liquid chromatograph mass spectrometer. The size of the PTFE sand was 70 pieces/g. The stirring rod was modified by inserting a 25-cm PTFE wire into the blades, which was used in all the following experiments unless specified.

General Procedures for the Ring-Opening Reaction of Steroidal Epoxides. A mixture of steroidal epoxide (1c–1o, 1.25 mmol; Table 1, entries 1–13), PTFE sand (5 g), and aqueous H₂SO₄ (5 mL) was mechanically stirred. After TLC (thin layer chromatography) indicated the completion of the reaction, the suspension on the water was filtered and washed with water (5 mL) to give a quantitative yield of the corresponding dihydroxylated steroid. The sand remained on the bottom of the flask and was easily recovered. The reaction times and temperatures and the concentrations of H₂SO₄ are listed in Table 1. Products 2a,¹⁹ 2b,¹⁹ 2c,¹⁹ 2e,¹⁹ 2f,³⁰ 2g,³⁰ 2i,¹⁹ 2m,³¹ 2o,³² and 2n¹⁶ are previously reported compounds. Products 2d, 2j, and 2k are new compounds.

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Table 1. Aqueous Quantitative Ring-Opening of VSSHMP Steroidal Epoxides^a

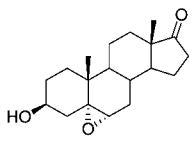
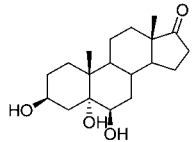
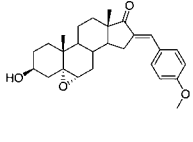
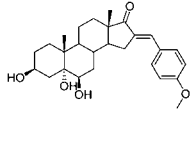
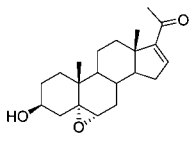
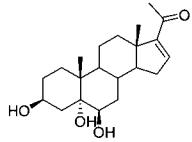
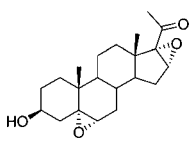
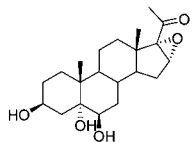
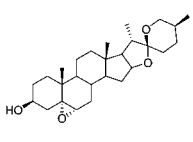
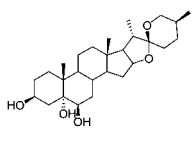
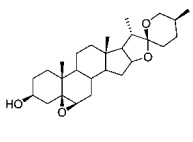
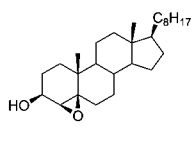
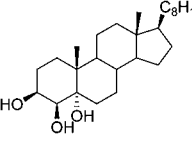
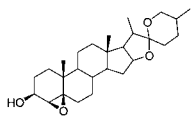
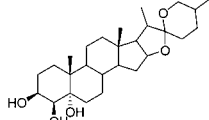
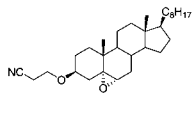
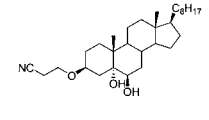
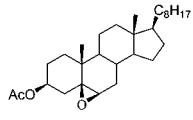
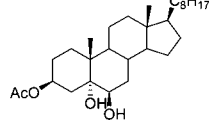
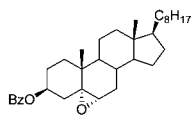
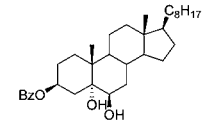
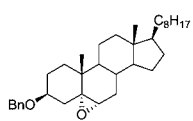
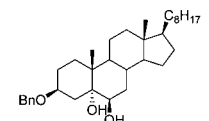
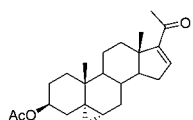
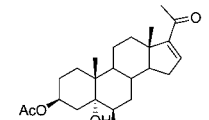
Entry	Substrate	S ^b (mol/L)	Mp (°C)	Product	T (°C)	H ₂ SO ₄ (mol/L)	Time (h)
1	 1c	1.0x10 ⁻³	227-230	 2c	25	0.127	14
2	 1d	3.8x10 ⁻⁶	256-258	 2d	25	0.510	46
3	 1e	1.9x10 ⁻⁴	201-203	 2e	25	0.127	17
4	 1f	3.5x10 ⁻⁴	203-205	 2f	25	0.510	16
5	 1g	2.1x10 ⁻⁵	218-220	 2g	25	0.127	22.5
6	 1h	2.1x10 ⁻⁵	202-204	2g	25	0.127	31
7	 1i	3.1x10 ⁻⁷	95-96	 2i	50	0.127	8

Table 1. continued

Entry	Substrate	S ^b (mol/L)	Mp (°C)	Product	T (°C)	H ₂ SO ₄ (mol/L)	Time (h)
8		1.5x10 ⁻⁵	168-171		25	0.127	13
	1j			2j			
9		1.2x10 ⁻¹²	87-89		25	0.510	16
	1k			2k			
10		5.3x10 ⁻⁸	95-97		80	1.019	2.5
	1l			2b			
11		1.7x10 ⁻⁹	148-151		80	1.019	2.2
	1m			2m			
12		7.0x10 ⁻⁹	102-103		80	0.510	6
	1n			2n			
13		2.5x10 ⁻⁵	174-176		80	1.019	1
	1o			2o			

^aAll conversions are 100%, and all isolated yields are >99%. ^bS, solubility; **1c**, **1e–1j**, and **1k–1o**, data from Sci Finder; **1d** and **1k**, data calculated using Software Wskow.³³ Reaction conditions: **1c–1o** (1.25 mmol), aqueous H₂SO₄ (5 mL), and PTFE sand (5 g).

16-(4-Methoxy-benzylidene)-17-oxo-androstan-3 β ,5 α ,6 β -triol (2d). Yellow solid; mp 204–207 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.91 (3H, s, 18-CH₃), 1.19 (3H, s, 19-CH₃), 3.54 (1H, s, 6 α -H), 3.80 (3H, s, OCH₃), 4.03–4.20 (1H, m, 3 α -H), 6.89 (2H, d, *J* = 6.9 Hz, Ar-H), 7.32 (1H, s, ArCH), 7.45 (2H, d, *J* = 6.9 Hz, Ar-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 214.62, 165.15, 138.79, 137.00, 136.73, 132.99, 118.99, 99.99, 80.23, 79.71, 71.53, 60.11, 54.02, 52.32, 50.28, 45.74, 43.29, 38.46, 37.09, 36.60, 35.79, 34.49, 34.03, 25.19, 21.37, 19.41; IR (KBr, cm⁻¹) ν 3417, 2935, 1702, 1600, 1512, 1254, 1176, 1074, 1035, 830; MS (ESI, positive) *m/z* 441.5 ([M + H]⁺), 463.4

([M + Na]⁺), 903.3 ([2 M + Na]⁺). Anal. Calcd. for C₂₇H₃₆O₅: C%, 73.61; H%, 8.24; O%, 18.16. Found: C%, 73.52; H%, 8.18.

(25R)-Spirostan-22 α -O-3 β ,4 β ,5 α -triol (2j). White solid; mp 254–257 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.78 (3H, s, 18-CH₃), 0.80 (3H, d, *J* = 6.2 Hz, 21-CH₃), 0.98 (3H, d, *J* = 6.8 Hz, 27-CH₃), 1.18 (3H, s, 19-CH₃), 3.38 (1H, t, *J* = 10.9 Hz, 26 α -H), 3.47–3.50 (1H, m, 26 β -H), 3.54 (1H, s, 4 α -H), 4.10–4.20 (1H, m, 3 α -H), 4.41 (1H, dd, *J* = 7.1, 7.4 Hz, 16-H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 111.39, 108.79, 80.75, 77.98, 74.42, 67.36, 66.38, 62.41, 56.20, 46.03, 41.56, 40.69, 39.41, 38.41, 34.50, 31.87, 31.39, 31.25, 30.28, 28.97, 26.52, 26.07, 20.37, 17.52, 16.72, 15.93, 15.06; IR (KBr, cm⁻¹) ν 3412, 2950,

1454, 1343, 1243, 1177, 1152, 1053, 981, 952; MS (ESI, positive) m/z 449.7 ($[M + H]^+$), 471.6 ($[M + Na]^+$), 919.5 ($[2M + Na]^+$). Anal. Calcd. for $C_{27}H_{44}O_5$: C%, 72.28; H%, 9.89; O%, 17.83. Found: C%, 72.37; H%, 9.81.

β -(2-Cyanoethoxy)-5 α ,6 β -cholestandiol (2k). White solid; mp 157–160 °C; 1H NMR (400 MHz, $CDCl_3$) δ 0.69 (3H, s, 18- CH_3), 0.88 (6H, d, J = 6.6 Hz, 26- CH_3 and 27- CH_3), 0.92 (3H, d, J = 6.4 Hz, 21- CH_3), 1.19 (3H, s, 19- CH_3), 2.60 (2H, t, J = 6.4 Hz, $NCCCH_2CH_2O$), 3.56 (1H, s, 6 α -H), 3.66–3.86 (3H, m, $NCCH_2CH_2O$ and 3 α -H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.23, 75.94, 75.90, 62.88, 56.28, 55.94, 45.87, 42.74, 39.94, 39.49, 38.47, 37.59, 36.16, 35.79, 34.48, 32.11, 30.17, 28.22, 27.99, 27.29, 24.13, 23.88, 22.82, 22.57, 21.16, 19.42, 18.67, 16.81, 12.16; IR (KBr, cm^{-1}) ν 3511, 2938, 2253, 1468, 1372, 1244, 1112, 1170, 1044, 957; MS (ESI, positive) m/z 491.4 ($[M + H_2O]^+$), 496.4 ($[M + Na]^+$), 969.2 ($[2M + Na]^+$). Anal. Calcd. for $C_{30}H_{51}NO_3$: C%, 76.06; H%, 10.85; N%, 2.96; O%, 10.13. Found: C%, 75.97; H%, 10.78; N%, 2.91.

Recycling Procedure for the Ring-Opening Reaction of 1a. A mixture of **1a** (1.000 g), aqueous H_2SO_4 (0.127 mol/L, 15 mL), and PTFE sand (5 g) was mechanically stirred at 25 °C for 6.2 h. After TLC indicated the completion of the reaction, the suspension on water was filtered to give **2a** quantitatively, leaving the PTFE sand on the bottom of the flask. Then, a new sample of **1a** (1.000 g) and the filtrate were added to the flask used in the first reaction and treated as described above to yield **2a** quantitatively. The reaction was repeated in this manner 10 times. The reaction times (6.2–7 h) and yields (>99%) remained almost the same for all cycles.

Table 2. Effects of PTFE Sand on the Reaction Rates

entry	amount of 1c	time, conversion ^a (sand, 5 g)	time, conversion ^a (sand, 1 g)	time, conversion ^a (sand, 0 g)
1	100 mg	2.5 h, 100%	2.5 h, 100%	2.5 h, 47.8%
2	500 mg	3.0 h, 100%	3.0 h, 93.9%	3.0 h, 69.4%
			3.5 h, 100%	
3	5000 mg	4.0 h, 100%	4.0 h, 79.4%	4.0 h, 58.8%
			6.0 h, 100%	

^aDetermined by 1H NMR. Reaction conditions: **1c** (100 mg, 500 mg, or 5000 mg), aqueous H_2SO_4 (0.127 mol/L; 2 mL for the 100 mg scale reaction; 5 mL for the 500 mg scale reaction; 20 mL for the 5000 mg scale reaction), and PTFE sand at 40 °C.

Experiments in Table 2 to Determine the Function of PTFE Sand. A mixture of epoxide **1c**, PTFE sand, and aqueous H_2SO_4 (0.127 mol/L) was mechanically stirred at 40 °C. The reaction times were indicated by TLC, and the conversions were determined by 1H NMR analysis of the products after filtration. The amounts of **1c**, PTFE sand, and aqueous H_2SO_4 and the reaction times and conversions are listed in Table 2.

RESULTS AND DISCUSSION

Optimization of the Ring-Opening Conditions for VSSHMP Epoxides 1a and 1b. A mixture of 5 α ,6 α -epoxycholestan-3 β -ol (**1a**, 500 mg, 1.24 mmol, mp, 143–144 °C, solubility, 4.2×10^{-7} mol/L; Table 3, entry 1), PTFE sand (5 g, 70 pieces/g), and aqueous H_2SO_4 (5 mL, 0.184 mol/L) was stirred mechanically at 60 °C for 3 h to give cholestan-3 β ,5 α ,6 β -triol (**2a**) quantitatively after filtration. The addition of Aliquat 336 to the reaction (Table 3, entry 2) did not change the reaction time or the yield, although it did in our previous work.²⁹ When the reaction was agitated using a standard stirring rod and no PTFE sand (Table 3, entry 3), the conversion was only 71% in 6 h. The reaction rate is sensitive to reaction temperature (25 °C, 4 h; 80 °C, 1 h; Table 3, entries 5 and 6) and to the concentration of H_2SO_4 (0.184 mol/L, 25

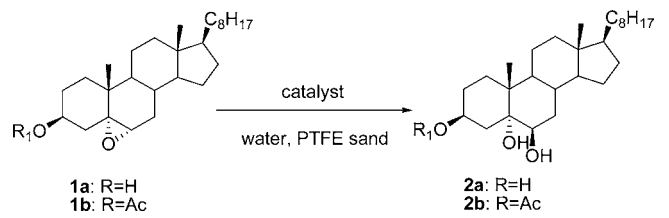
°C, 4 h; 0.127 mol/L, 25 °C, 6 h; Table 3, entries 5 and 4). Other catalysts such as $HClO_4$, $TfOH$, HCl , $TsOH$, $AcOH$, and $NaOH$ were tested and did not give better results than H_2SO_4 . Therefore, based on performance and price, H_2SO_4 was chosen as the catalyst. The optimized conditions for **1a** (1.24 mmol) were aqueous H_2SO_4 (5 mL, 0.127 mol/L) and PTFE sand at 25 °C (5 g) (Table 3, entry 4).

However, these optimized conditions (Table 3, entry 4) did not work well for cholesteryl acetate (**1b**). For **1b**, the hydrolysis of the ester group and the epoxide ring-opening took place simultaneously when the concentration of H_2SO_4 was 0.127–1.019 mol/L, and the reaction temperature was 25–80 °C. This is probably because of the prolonged reaction times (9–48 h; Table 3, entries 12–15). After raising the concentration of H_2SO_4 to 0.510 mol/L and the reaction temperature to 80 °C, the reaction time was shortened to 7 h, and the conversion was 100% (Table 3, entry 16). Further increasing the concentration of H_2SO_4 to 1.019 mol/L afforded **2b** in quantitative yield in 1.5 h (Table 3, entry 17). The optimized conditions for **1b** (1.25 mmol) were aqueous H_2SO_4 (5 mL, 1.019 mol/L) and PTFE sand (5 g) at 80 °C (Table 3, entry 17).

Aqueous Quantitative Ring-Opening of VSSHMP Steroidal Epoxides. The optimized conditions for **1a** (Table 3, entry 4) were applied to a series of VSSHMP epoxides (**1c–1k**) (mp: 87–258 °C, solubilities: 1.0×10^{-3} – 1.2×10^{-12} mol/L; Table 1, entries 1–9), and quantitative yields of dihydroxylated steroids were obtained. For **1d**, **1f**, **1i**, and **1k**, the optimized conditions had to be slightly modified. The possible reason the epoxide on the D-ring of **1f** is stable toward hydrolysis is that the oxygen of the ketone and the epoxide complex with H^+ form a five-membered ring. The steric hindrance of this ring hinders the attack of nucleophilic water on C_{16} . For **1i**, the reaction temperature was raised to 50 °C, and for **1d**, **1f** and **1k**, the concentration of H_2SO_4 was increased to 0.510 mol/L in order to get reasonable reaction rates. The ring-openings of VSSHMP epoxides **1l–1o** (mp: 95–176 °C, solubilities: 2.5×10^{-5} – 7.0×10^{-9} mol/L; Table 1, entries 10–13) were achieved in quantitative yields using the optimized conditions for **1b** (Table 3, entry 17). For **1n**, the concentration of H_2SO_4 was reduced to 0.510 mol/L to avoid the hydrolysis of the ether bond. At the end of all these reactions, the crystalline products were suspended on water, and the sand remained on the bottom of the flasks. The products were easily collected by filtration. Sand, water, and H_2SO_4 are highly recyclable. In the ring-opening reaction of **1a**, sand, water, and H_2SO_4 were reused for 10 cycles, and the reaction times and yields remained almost the same. Ketone, ester, ether, ketal, epoxide on D-rings, and α,β -unsaturated ketone functional groups all tolerate these conditions.

No relationships between the reaction rates and the melting points of the substrates could be found from the data in Table 1. This is probably because all the reaction temperatures are lower than the melting points of the substrates. The data in Table 1 suggest that the reaction rates are mainly determined by the concentration of H_2SO_4 , the reaction temperature, the position and configuration of the epoxide rings, the solubility of the substrates, and the number of oxygen atoms on the substrates. The ring-opening reactions for the 5 α ,6 α -epoxides are faster than those for the 5 β ,6 β -epoxides (**1g** vs **1h**; **1b** vs **1k**). This is due to the steric hindrance at the C-5 position of the 5 β ,6 β -epoxides,³⁴ which hinders the attack of the nucleophilic water on the protonated epoxide rings. A higher

Table 3. Optimization of the Ring-Opening Conditions for VSSHMP Epoxides 1a and 1b



entry	substrate	catalyst	CC ^a (mol/L)	T (°C)	time (h)	product	C ^a (%)	yield ^b (%)
1	1a ^c	H ₂ SO ₄	0.184	60	3	2a	100	>99
2 ^d	1a	H ₂ SO ₄	0.184	60	2.8	2a	100	>99
3 ^e	1a	H ₂ SO ₄	0.184	60	6	2a	71 ^f	NI ^a
4	1a	H ₂ SO ₄	0.127	25	6	2a	100	>99
5	1a	H ₂ SO ₄	0.184	25	4	2a	100	>99
6	1a	H ₂ SO ₄	0.184	80	1	2a	100	>99
7	1a	HClO ₄	0.180	25	6.5	2a	100	>99
8	1a	TfOH ^g	0.188	25	4	2a	100	>99
9	1a	HCl	0.182	25	7	2a	83 ^f	NI ^a
10	1a	TsOH ^g	0.188	25	3.5	2a	100	>99
11	1a	NaOH	0.330	80	5	NR ^a	0	0
12	1b ^c	H ₂ SO ₄	0.127	25	48	1a, 2a, 2b	h	h
13	1b	H ₂ SO ₄	0.204	25	48	1a, 2a, 2b	h	h
14	1b	H ₂ SO ₄	0.510	25	48	1a, 2a, 2b	h	h
15	1b	H ₂ SO ₄	1.019	50	9	1a, 2a, 2b	h	h
16	1b	H ₂ SO ₄	0.510	80	7	2a, 2b	100	82
17	1b	H ₂ SO ₄	1.019	80	1.5	2b	100	>99

^aCC, the concentration of the catalyst; NI, not isolated; C, conversion; and NR, no reaction. ^bIsolated yield. ^c1a: mp, 143–144 °C; solubility, 4.2 × 10⁻⁷ mol/L. 1b: mp, 98–99 °C, data from Sci Finder; solubility, 5.3 × 10⁻⁸ mol/L. ^dAliquat 336 (0.1 equiv) was added. ^eA standard stirring rod was used, without PTFE sand. ^fDetermined by ¹H NMR. ^gTsOH, *p*-toluenesulfonic acid; TfOH, triflic acid. ^hTLC indicates a mixture of 1a, 2a, and 2b. Reaction conditions: 1a or 1b (1.25 mmol), an aqueous solution of catalyst (5 mL), and PTFE sand (5 g).

solubility resulted in a higher ring-opening reaction rate (1c vs 1d; 1c vs 1e). For epoxides 1d and 1k, the solubilities are lower, so higher concentrations of H₂SO₄ were required to catalyze these reactions. More oxygen atoms on the substrates resulted in lower reaction rates (1e vs 1f; 1a vs 1f; 1a vs 1g). The probable reason is that the other oxygen atoms compete with the epoxide oxygen for the catalytic proton in the solid phase.

There are two competing factors in these reactions: an increase in the solubility of the substrate accelerates the reaction rates, and an increase in the number of oxygen atoms in the substrate reduces the reaction rates. In these situations, the acceleration of the reaction due to a higher solubility is the less important factor. For example, 1g and 1h have more oxygen atoms and better solubilities than 1a, and the reaction rates for 1g and 1h are lower than that for 1a. The ring-opening reactions of the esters and ethers of the steroidal epoxides (1i–1o) had to be carried out at higher concentrations of H₂SO₄ and at higher reaction temperatures because they have lower solubilities and more oxygen atoms.

Effects of PTFE Sand on the Reaction Rates. In our previously reported aqueous reactions of VSSHMP substrates, Aliquat 336 and sand were essential.²⁹ In this “on water” ring-opening reaction of VSSHMP steroidal epoxides, Aliquat 336 is not necessary, but sand is required. The ratio of the substrate to PTFE sand and its effects on the reactions were investigated, and the results are summarized in Table 2. When 100, 500, or 5000 mg of epoxide 1c were stirred in the presence of aqueous H₂SO₄ (0.127 mol/L) and 5 g of PTFE sand at 40 °C, the reactants were 100% converted in 2.5, 3.0, and 4.0 h, respectively. With no sand, the conversions were 47.8%,

69.4%, and 58.8%, and with 1 g of sand, the conversions were 100%, 93.9%, and 79.4%. Reducing the amount of sand to 1 g did not change the reaction rate (2.5 h) for the 100-mg scale reaction (100% conversion). However, the reaction rates for the 500- and 5000-mg scale reactions were reduced to 3.5 and 6.0 h, respectively (100% conversion). These data indicate that the reaction rates remain acceptable for a wide range of substrate to sand ratios (substrate/sand = 1:1–1:50). The reason that sand accelerates this “on water” reaction is that the steroidal epoxides are solids and are very sparingly soluble in water, and the catalyst, H₂SO₄, is in the aqueous phase. When the sand is agitated by the modified stirring rod, it promotes more efficient collisions between the epoxides and H₂SO₄. This is probably through the smashing of the solid epoxide and the epoxide and dihydroxylated steroid mixture. Other materials such as polystyrene, SiO₂, Al₂O₃, and TiO₂ tend to become pulverized under mechanical stirring and are not recyclable.

In summary, “on water” ring-opening reactions of steroidal epoxides have been achieved, leading to quantitative polyhydroxysteroids. The reaction does not require any organic solvents or phase transfer catalysts. The remarkable accelerating effects of PTFE sand in the “on water” reactions have been demonstrated for the first time. This methodology will be useful in the fields of heterogeneous reactions, green chemistry, and food chemistry.

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Notes

The authors declare no competing financial interest.

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