Notes

Palladium Catalyzed, Regioselective Reduction of 1,2-Epoxides by Ammonium Formate

Peter S. Dragovich,* Thomas J. Prins, and Ru Zhou

Agouron Pharmaceuticals Inc., 3565 General Atomics Court, San Diego, California 92121

Received February 6, 1995

The reduction of an epoxide to a saturated alcohol is a useful transformation in organic synthesis, and many methods have been developed which accomplish this conversion.[1] Of these, catalytic hydrogenolysis ranks among the simplest and has been utilized extensively in the past for the reduction of a variety of oxirane substrates.[2] More recently, several reagent combinations have been discovered which effect catalytic hydrogenolysis under mild conditions without the use of molecular hydrogen.[3] These transfer hydrogenation systems have been found to reduce a variety of organic functional groups, but have not, to the best of our knowledge, been employed for the conversion of 1,2-epoxides to alcohols.[3,4] Herein we report that 1,2-epoxides are regioselectively reduced at the least substituted end by ammonium formate in the presence of a palladium metal catalyst to provide the corresponding alcohols in high yield.

Stirring an ethanol suspension of 1,2-epoxydecane (**1**), palladium on activated carbon (10%, 0.040 g per mmol of epoxide), and ammonium formate (3 equiv) for 48 h at 23 °C provided 2-decanol (**2**) in 81% yield after filtration through Celite, concentration, and flash column chromatography (Table 1, entry 1). ^{1}H NMR analysis prior to chromatography indicated that less than 5% of the alternate reduction product, 1-decanol (**3**), was produced in the reaction. Heating the reaction medium (~50 °C) resulted in considerable sublimation of ammonium formate and did not significantly shorten the reduction time. In contrast, conventional hydrogenolysis of **1** employing molecular hydrogen (~1 atm) and the identical palladium catalyst proceeded at a much faster rate, but resulted in the formation of larger quantities of 1-decanol (entry 2). Addition of formic acid (3 equiv) to the conventional reduction medium further increased the amount of 1-decanol produced in agreement with literature precedent (entry 3).[5] Interestingly, conducting the ammonium formate-mediated reduction under a hydrogen atmosphere did not significantly alter the reaction time, yield, or selectivity (entry 4). The above experiments demonstrated the ability of the ammonium formate/Pd–C system to effect epoxide reduction, albeit at a slower rate than methods employing molecular hydrogen, and emphasized the importance of the neutral reaction conditions in obtaining the high levels of regioselectivity observed.

Table 1. Reductive Transformation of 1,2-Epoxydecane (1) to 2-Decanol (2) and 1-Decanol (3)

entry	reductant	time (h)	yield (%)	2:3[a]
1	HCO_2NH_4	48	81	97:3
2	H_2	2.5	85	86:14
3[b]	H_2	2	65	76:24
4	$HCO_2NH_4 + H_2$	48	85	96:4

[a]Determined by ^{1}H NMR. [b]3 equiv HCO_2H present.

Having completed the initial study described above, we then applied the ammonium formate/Pd–C reduction conditions to a variety of other 1,2-epoxides to better define the scope of the reaction. As indicated in Table 2, the time required to effect complete oxirane reduction was found to be substrate dependent and varied between 1 and 48 h. Of the epoxides examined, those containing polar functional groups were typically reduced more rapidly than simple, aliphatic compounds (entry 1 vs entry 2), although the presence of an aryl moiety in the substrate also appeared to accelerate the reaction rate (entries 3 and 8). Glycidic epoxides were reduced the most rapidly of all the compounds examined (entries 6, 7, and 9), and in such cases it was possible to effect oxirane reduction in the presence of a benzyl ether (entry 7). Importantly, the ester functional group, which may be destroyed by hydride-mediated reduction methods, was unaffected by the transfer hydrogenation reaction (entry 5). However, conversion of a primary, aliphatic bromide to the corresponding hydrocarbon was observed when utilizing the above conditions.[6] Since the success of surface-mediated transformations can be dependent on the precise nature of the heterogeneous catalyst employed, it was noteworthy that reaction times and product yields did not vary appreciably when the reductions were conducted utilizing palladium catalysts which differed in composition and surface area.[7] As with the reduction of 1,2-epoxydecane described above, the isolation of the product alcohols was extremely simple and involved filtration of the reaction mixtures through Celite, concentration, and purification of the residues by flash column chromatography. Regardless of reaction

(1) For leading references on the reductive transformation of epoxides to alcohols, see (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 505–508. (b) Bartók, M.; Láng, K. L. in *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues*; Patai, S., Ed.; John Wiley & Sons: New York, 1980; Vol. 2, pp 609–681. (c) Gorzynski Smith, J. *Synthesis* **1984**, 629.

(2) For leading references on the hydrogenolysis of epoxides, see (a) Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; pp 478–483. (b) Rylander, P. N. *Hydrogenation Methods*, Academic Press: London, 1985; pp 137–139.

(3) (a) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567. (b) Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev.* **1985**, *85*, 129. (c) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91.

(4) The reduction of α,β-epoxy ketones utilizing transfer hydrogenation methods has been reported: Torii, S.; Okumoto, H.; Nakayasu, S.; Kotani, T. *Chem. Lett.* **1989**, 1975.

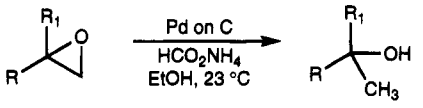
(5) (a) Newman, M. S.; Underwood, G.; Renoll, M. *J. Am. Chem. Soc.* **1949**, *71*, 3362. (b) McQuillin, F. J.; Ord, W. O. *J. Chem. Soc.* **1959**, 3169.

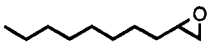
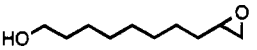
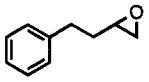
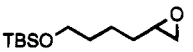
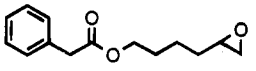
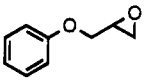
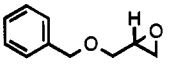
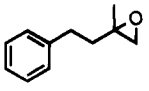
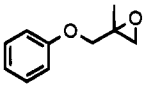
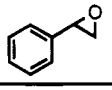
(6) Dragovich, P. S.; Prins, T. J.; Zhou, R. Unpublished results.

(7) For example, reductions of 1,2-epoxy-3-phenoxypropane employing 10% palladium on activated carbon purchased from Aldrich (dry, 1600–1800 m^2/g), Lancaster (dry, 1000 m^2/g), and Degussa (type E101 NE/W, wet, 1000 m^2/g) were each complete within 1 h and afforded 1-phenoxy-2-propanol in 91, 85, and 89% yields, respectively.

0022-3263/95/1960-4922$09.00/0

Table 2. Reduction of 1,2-Epoxides by Ammonium Formate/Pd–C



entry	substrate	time (h)	yield[a] (%)
1		48	81
2		10	95
3		3.5	85
4		48	92
5		6	97
6		1	91
7		0.75	80
8		5	90
9		3	95
10		1.5	58[b]

[a]Isolated yields. [b]Phenethyl alcohol. TBS = t-Bu(CH_3)$_2$Si

time, the purified alcohols were isolated in excellent yields, and all contained less than 5% of the corresponding less-substituted reduction products as determined by ^{1}H NMR analysis. The only exception observed was styrene oxide which provided phenethyl alcohol in lieu of α-methylbenzyl alcohol when subjected to the reduction conditions (entry 10). As expected, reduction of benzyl (*R*)-(−)-glycidyl ether afforded (*R*)-1-(phenylmethoxy)-2-propanol with little or no loss of optical activity (entry 7).

In summary, a simple transfer hydrogenation method employing ammonium formate and a heterogeneous palladium metal catalyst has been shown to regioselectively reduce 1,2-epoxides at the least substituted end to produce alcohols in high yield. Although the mechanistic details of this reduction remain to be determined, the described transformation should prove useful in organic synthesis.

Experimental Section

All reductions were performed in septum-sealed flasks under a slight positive pressure of argon. All commercial reagents were used as received from their respective suppliers. 1,2-Epoxydecane, 1,2-epoxy-3-phenoxypropane, benzyl (*R*)-(−)-glycidyl ether, and styrene oxide were purchased from Aldrich. The remaining epoxide substrates were prepared from olefin precursors by peracid oxidation.[8] For entries 2, 3, and 9, the olefins were purchased from Aldrich, while the olefins required for substrate entries 4,[9] 5,[10] and 8[11] were synthesized according to literature methods or standard protocols. Palladium on activated carbon (dry, 10% Pd) was purchased from either Aldrich, Fluka, Lancaster, or Janssen. Flash column chromatography[12] was performed using silica gel 60 (Merck Art 9385). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, utilizing a Varian UNITY*plus* 300 spectrometer. Chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane. Infrared absorption spectra were recorded using a Perkin-Elmer 1600 series FTIR. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

General Reduction Procedure. Ammonium formate (3.0 equiv) was added to a suspension of the epoxide substrate (1–3 mmol, ~0.5 M) and palladium on activated carbon (dry, 10% Pd, approximately 0.040 g per mmol of epoxide) in absolute ethanol at 23 °C. The reaction mixture was vigorously stirred at 23 °C until thin layer chromatographic analysis indicated that reduction was complete (1–48 h) and then was filtered through Celite. The filtrate was concentrated and the residue was purified by flash column chromatography (eluting with EtOAc in hexanes) to provide the alcohol product.

2-Decanol: R_f = 0.58 (30% EtOAc in hexanes); IR (film) 3347 (br) cm^{-1}; ^{1}H NMR δ 0.88 (t, 3 H, J = 6.7 Hz), 1.19 (d, 3 H, J = 6.5 Hz), 1.21–1.61 (m, 14 H), 3.74–3.82 (m, 1 H); ^{13}C NMR δ 14.0, 22.6, 23.4, 25.7, 29.2, 29.5, 29.6, 31.8, 39.3, 68.0. Anal. Calcd for $C_{10}H_{22}O$ C: 75.88, H: 14.01. Found C: 75.77, H: 13.93.

1,9-Decanediol: R_f = 0.26 (50% EtOAc in hexanes); IR (film) 3340 (br) cm^{-1}; ^{1}H NMR δ 1.19 (d, 3 H, J = 6.2 Hz), 1.24–1.59 (m, 14 H), 3.64 (t, 2 H, J = 6.5 Hz), 3.76–3.82 (m, 1 H); ^{13}C NMR δ 23.3, 25.7, 29.3, 29.5, 32.6, 39.2, 62.7, 68.0. Anal. Calcd for $C_{10}H_{22}O_2$ C: 68.92, H: 12.72. Found C: 68.81, H: 12.63.

4-Phenyl-2-butanol: R_f = 0.22 (12.5% acetone in hexanes); IR (film) 3355 (br) cm^{-1}; ^{1}H NMR δ 1.23 (d, 3 H, J = 6.2 Hz), 1.31–1.38 (m, 1 H), 1.73–1.82 (m, 2 H), 2.62–2.82 (m, 2 H), 3.77–3.90 (m, 1 H), 7.16–7.23 (m, 3 H), 7.25–7.32 (m, 2 H); ^{13}C NMR δ 23.6, 32.1, 40.8, 67.5, 125.8, 128.4, 142.0. Anal. Calcd for $C_{10}H_{14}O$ C: 79.96, H: 9.39. Found C: 79.91, H: 9.36.

6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-hexanol: R_f = 0.33 (20% EtOAc in hexanes); IR (film) 3354 (br) cm^{-1}; ^{1}H NMR δ 0.05 (s, 6 H); 0.89 (s, 9 H), 1.19 (d, 3 H, J = 6.2 Hz), 1.38 (d, 1 H, J = 4.5 Hz); 1.40–1.57 (m, 6 H), 3.62 (t, 2 H, J = 6.4 Hz); 3.75–3.84 (m, 1 H); ^{13}C NMR δ −5.4, 18.3, 21.9, 23.3, 25.9, 32.6, 38.9, 63.0, 67.8. Anal. Calcd for $C_{12}H_{28}O_2Si$ C: 62.01, H: 12.14. Found C: 61.94, H: 12.06.

Phenylacetic Acid 5-Hydroxyhexyl Ester: R_f = 0.13 (20% EtOAc in hexanes); IR (film) 3403 (br), 1732 cm^{-1}; ^{1}H NMR δ 1.17 (d, 3 H, J = 5.9 Hz), 1.21–1.45 (m, 4 H), 1.59–1.69 (m, 3 H); 3.62 (s, 2 H); 3.64–3.77 (m, 1 H), 4.10 (t, 2 H, J = 6.5 Hz); 7.23–7.36 (m, 5 H); ^{13}C NMR δ 21.9, 23.3, 28.4, 38.5, 41.3, 64.7, 67.5, 126.9, 128.4, 129.1, 134.0, 171.6. Anal. Calcd for $C_{14}H_{20}O_3$ C: 71.16, H: 8.53. Found C: 71.27, H: 8.61.

1-Phenoxy-2-propanol: R_f = 0.44 (30% EtOAc in hexanes); IR (film) 3389 (br) cm^{-1}; ^{1}H NMR δ 1.29 (d, 3 H, J = 6.2 Hz), 2.37 (d, 1 H, J = 3.7 Hz), 3.80 (dd, 1 H, J = 9.2, 7.6 Hz), 3.95 (dd, 1 H, J = 9.2, 3.3 Hz), 4.17–4.23 (m 1 H); 6.89–7.00 (m, 3 H), 7.25–7.32 (m, 2 H); ^{13}C NMR δ 18.7, 66.1, 73.1, 114.5, 121.0, 129.4, 158.5. Anal. Calcd for $C_9H_{12}O_2$ C: 71.03, H: 7.95. Found C: 70.95, H: 7.96.

(8) (a) Brown, H. C.; Ikegami, S.; Kawakami, J. H. *J. Org. Chem.* **1970**, *35*, 3243. (b) Brown, H. C.; Kawakami, J. H.; Ikegami, S. *J. Am. Chem. Soc.* **1970**, *92*, 6914.

(9) Kinney, W. A.; Crouse, G. D.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4986.

(10) 5-Hexene-1-ol was treated with phenylacetyl chloride (1 equiv), triethylamine (1.2 equiv), and 4-(dimethylamino)pyridine (0.02 equiv) in CH_2Cl_2 at 23 °C to provide the corresponding ester in 75% yield.

(11) Charlton, J. L.; Williams, G. J.; Lypka, G. N. *Can. J. Chem.* **1980**, *58*, 1271.

(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(*R*)-1-(Phenylmethoxy)-2-propanol: $R_f = 0.31$ (1% acetone in CH_2Cl_2); IR (film) 3416 (br) cm^{-1}; ^1H NMR δ 1.14 (d, 3 H, J = 6.5 Hz), 2.88 (s, br, 1 H), 3.28 (dd, 1 H, J = 9.3, 8.1 Hz), 3.46 (dd, 1 H, J = 9.3, 3.1 Hz), 3.99 (ddq, 1 H, J = 8.1, 6.5, 3.1 Hz), 4.55 (s, 2 H), 7.25–7.35 (m, 5 H); ^{13}C NMR δ 18.6, 66.3, 73.1, 75.7, 76.6, 127.6, 128.3, 137.8. Anal. Calcd for $C_{10}H_{14}O_2$ C: 72.26, H: 8.49. Found C: 72.31, H: 8.46; $[\alpha]^{26}_D = -14.9$ (c = 2, $CHCl_3$).[13]

2-Methyl-4-phenyl-2-butanol: R_f = 0.21 (20% EtOAc in hexanes); IR 3381 (br) cm^{-1}; ^1H NMR δ 1.25 (s, 1 H), 1.29 (s, 6 H), 1.83–1.77 (m, 2 H), 2.27–2.68 (m, 2 H), 7.72–7.16 (m, 5 H); ^{13}C NMR δ 29.1, 30.6, 45.6, 70.6, 125.5, 128.1, 128.2, 142.4. Anal. Calcd for $C_{11}H_{16}O$ C: 80.44, H: 9.82. Found C: 80.30, H: 9.91.

2-Methyl-1-phenoxy-2-propanol: $R_f = 0.18$ (20% EtOAc in hexanes); IR (film) 3398 (br) cm^{-1}; ^1H NMR δ 1.37 (s, 6 H), 2.27 (s, 1 H), 3.82 (s, 2 H), 6.99–6.93 (m, 3 H), 7.34–7.29 (m, 2 H); ^{13}C NMR δ 26.0, 70.0, 75.8, 114.5, 120.9, 129.4, 158.6. Anal. Calcd for $C_{10}H_{14}O_2$ C: 72.26, H: 8.49. Found C: 72.37, H: 8.46.

JO950229A

(13) Optical rotation of (a) neat (*R*)-1-(phenylmethoxy)-2-propanol: Sugawara, F.; Nakayama, H.; Ogawa, T. *Carbohydr. Res.* **1983**, *123*, C25; $[\alpha]_D = -29.1$. (b) (*S*)-1-(phenylmethoxy)-2-propanol (90% ee) in $CHCl_3$ solution: Manzocchi, A.; Fiecchi, A.; Santaniello, E. *Synthesis* **1987**, 1007; $[\alpha]^{25}_D = +11.0$ (c = 2, $CHCl_3$).