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Conversion of α,β-epoxyketones to diosphenols using 6-methyl-2-pyridone anion as an hydroxide equivalent

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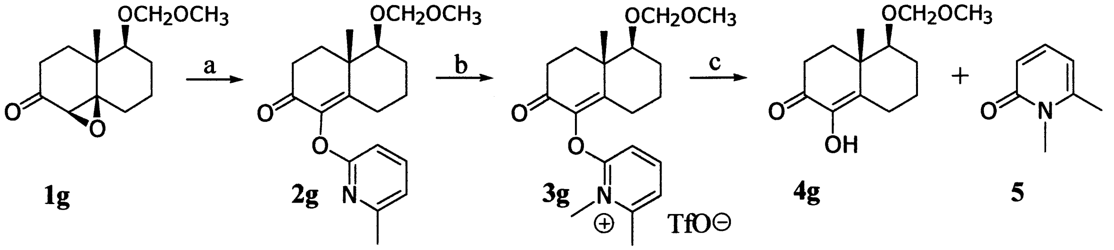
Abstract

Treatment of α,β-epoxyketones with 6-methyl-2-pyridone anion gives diosphenol (6-methyl-2-pyridyl) ethers that can be cleaved to diosphenols under mild basic conditions. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: diosphenols; α-diketones; diosphenol ethers; α,β-epoxyketones; 6-methyl-2-pyridone; 2-pyridones; hydroxide equivalent.

The diosphenol (enolized α-diketone) array is found in diverse natural products,[1–5] and has synthetic utility for Claisen rearrangements,[6] aldol and Michael additions,[7] Wittig reactions,[8] ring-cleavage reactions,[9] ring-contraction reactions,[10] and photochemical reactions.[11] α,β-Epoxyketones have been used as precursors of diosphenols via isomerization with strong acid in a hydroxylic solvent.[12] This procedure, however, gives variable results[13] and is incompatible with many functional groups. Treatment of α,β-epoxyketones with methoxide often gives acceptable yields of diosphenol methyl ethers,[14] but hydrolysis to the parent diosphenols requires harsh conditions.[15] The apparently simpler route, namely treatment of an α,β-epoxyketone with hydroxide ion,[16] is unsatisfactory since any diosphenol produced undergoes benzilic acid rearrangement.[17] We now report that treatment of α,β-epoxyketones with 6-methyl-2-pyridone



Scheme 1. (a) 2 Equiv. 6-methyl-2-pyridone, 0.1 equiv. KH, Bu_2O–HMPA 9:1, 140°C, 6 h (conditions 'A'), 66%; (b) MeOTf, CH_2Cl_2, 25°C, 3 h, 95%; (c) 1 M aq. Na_2CO_3–acetone 1:1, 25°C, 12 h, 88% (of **4**) Overall: 54% yield

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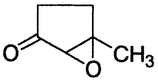
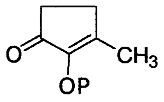
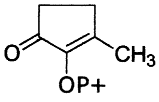
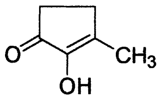
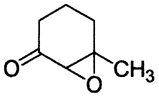
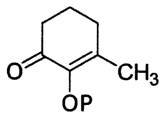
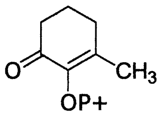
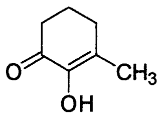
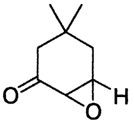
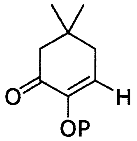
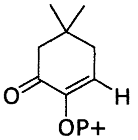
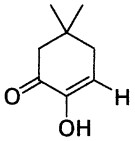
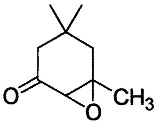
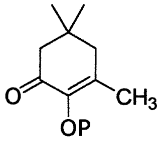
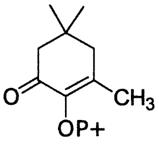
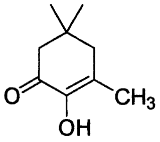
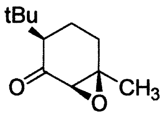
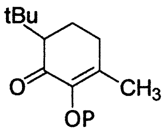
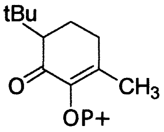
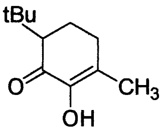
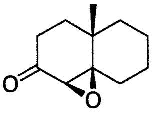
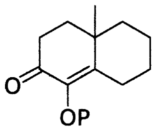
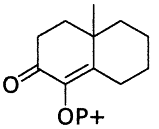
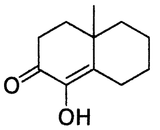
anion gives diosphenol (6-methyl-2-pyridyl) ethers that can be cleaved to diosphenols under mild basic conditions (Scheme 1).

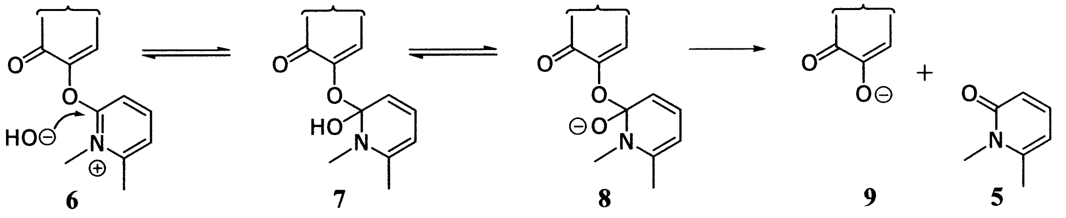
Other N-hindered[18] 2-hydroxyazaarenes such as 2-hydroxyquinoline and 6-phenyl-2-pyridone may be used in this sequence but, save crystallinity of the diosphenol ether, offer no advantage over the readily-available[19] 6-methyl-2-pyridone. Table 1 shows results for the transformation of six racemic α,β-epoxyketones into diosphenols.[20] Vigorous epoxide opening conditions 'A' (Bu_2O–HMPA, 140°C)[21] are required for some substrates; for **1a**–**c**, conditions 'B' (2 equiv. 6-methyl-2-pyridone, 1 equiv. NaOH, s-BuOH, 100°C, 4–12 h) suffice. Complete experimental details (including spectral data) for the preparation of **4d** from **1d** are provided as a footnote.[22]

Table 1

Step synthesis of diosphenols. P = 6-methyl-2-pyridyl; P+ = N,6-dimethyl-2-pyridinium

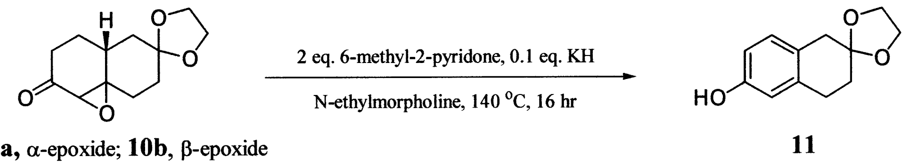
α,β-epoxyketone	6-Me-2-pyridyl ether	N-Me pyridinium salt	diosphenol	yield
 **1a**	 **2a** (78%, B)	 **3a** (95%)	 **4a** (90%)	67%
 **1b**	 **2b** (72%, B)	 **3b** (91%)	 **4b** (87%)	57%
 **1c**	 **2c** (68%, B)	 **3c** (90%)	 **4c** (85%, enols)	52%
 **1d**	 **2d** (70%, A)	 **3d** (91%)	 **4d** (86%)	55%
 **1e**	 **2e** (30%, A)	 **3e** (89%)	 **4e** (78%)	21%
 **1f**	 **2f** (68%, A)	 **3f** (88%)	 **4f** (92%)	55%

The ability of 2-pyridolates to function as hydroxide equivalents requires pyridine-oxygen fission during hydrolysis of the quaternized ethers, presumably via decomposition of the tetrahedral intermediate **8** (Scheme 2).



Scheme 2.

Our reaction sequence fails in the case of either **10a** or **10b**, when the major product is **11** (Scheme 3).



10a, α-epoxide; **10b**, β-epoxide

11

Scheme 3.

6-Methyl-2-pyridone and related compounds may be used in the Mitsunobu reaction to invert alcohols (including those sensitive to acid and/or strong base). We will give details of this procedure shortly.

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12. Reaction conditions are very important. Isophorone oxide, for example, gives moderate yields of 2-hydroxyisophorone when treated with (a) 2% aq. sulfuric acid (Langin-Lanteri, M. T.; Huet, J. *Synthesis* **1976**, 541) or with (b) 37% aq. HCl (Ref. 9d) but only a 3% yield of diosphenol when treated with (c) $BF_3{\cdot}Et_2O$ in benzene (in this non-basic solvent the major products result from ring-contraction—House, H. O.; Wasson, R. L. *J. Am. Chem. Soc.* **1959**, *79*, 1488).
13. The isomerization involves regiospecific epoxide fission to generate partial positive charge at the β-carbon atom. Thus, it is not surprising that β-*unsubstituted*-α,β-epoxyketones (such as **1c**) give poor yields of diosphenols and that verbenone oxide or 2,3-epoxy-3-*t*-butylcycloalkanones give mainly skeletally-rearranged products: (a) Ponaras, A. A. unpublished. Acid treatment of 4β,5β-epoxy-3-ketosteroids gives mainly 2α-hydroxy-3-keto-Δ^4 steroids, probably via the alternative regiochemical sense of epoxide fission: (b) Camerino, B.; Patelli, B.; Vercellone, A. *J. Am. Chem. Soc.* **1956**, *78*, 3540. (c) Burnett, R. L.; Kirk, D. N. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1830.
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18. 2-Pyridone itself is unsatisfactory because its anion shows greater reactivity at nitrogen than at oxygen.
19. Commercially available from Acros, Alfa Aesar, ICN, Kingchem, Lancaster, Pfaltz and Bauer, and Sigma-Aldrich.
20. All new substances were characterized by IR, NMR, MS and elemental analysis or HRMS.
21. Epoxide opening in boiling *N*-methyl- or *N*-ethylmorpholine (no added HMPA) is also satisfactory. Reaction in THF–HMPA at 67°C (cf. Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 2150) requires many days, confirming that 2-pyridolates are less nucleophilic than phenolates.
22. Two drops of 30% KH oil suspension were added, under N_2, to a stirred solution of 2.20 g (20 mmol) of 6-methyl-2-pyridone in 1.3 mL of dry HMPA and 10 mL of dry Bu_2O. Then a solution of 1.54 g (10 mmol) of

isophorone oxide in 2 mL Bu_2O was added rapidly, the mixture was heated at reflux for 6 h, cooled, diluted with 100 mL of ether and washed successively with 3×50 mL of water and 50 mL of brine. Evaporation of the $MgSO_4$-dried extract, followed by evacuation at the oil pump gave 4.5 g of a residue which was chromatographed on 180 g of silica gel (Davison, 235–400 mesh) packed in cyclohexane/EtOAc (4:1) to afford 1.72 g (70%) of **2d**. IR 1680, 1599 cm^{-1}; 60 MHz NMR δ 1.05 (s, 6H), 1.85 (s, 3H), 2.3–2.5 (m, 7H), 6.49 (d, $J=4.5$ Hz, 1H), 6.61 (d, $J=4.5$ Hz, 1H), 7.35 (t, $J=4.5$ Hz, 1H). Anal. calcd for $C_{15}H_{19}NO_2$: C, 73.04; H, 7.08. Found: C, 72.79; H, 7.18. A 2.45 g (10 mmol) portion of **2d** was added at 0°C, under N_2, to a stirred solution of 1.5 mL (11 mmol) of methyl triflate in 10 mL of dry CH_2Cl_2 and kept at this temperature for 0.5 h and then at room temperature for 2.5 h. The solvent was evaporated, then 10 mL of tetrachloroethylene was added and evaporated, ultimately at the oil pump, giving 3.74 g (91%) of **3d** as a solid. IR 1685, 1636, 1586, 1497 cm^{-1}; 60 MHz NMR δ 1.14 (s, 6H), 1.98 (s, 3H), 2.35 (s, 2H), 2.55 (s, 2H), 2.70 (s, 3H), 4.05 (s, 3H), 7.00 (d, $J=8$ Hz, 1H), 7.30 (d, $J=8$ Hz, 1H), 8.00 (t, $J=8$ Hz, 1H). This solid was added to a mixture of 5 mL of a 1 M aq. Na_2CO_3 solution and 5 mL of acetone and stirred overnight. The solvent was evaporated and the residue was suspended in 50 mL of ether and extracted with 3×50 mL of an ice-cold 1 M NaOH solution in MeOH/water 1:1. The comb. aq. methanolic extracts were neutralized with ice-cold 3 M aq. HCl (about 50 mL) and extracted with 3×50 mL of CH_2Cl_2. The comb. organic extracts were washed successively with a 50 mL satd $NaHCO_3$ solution and 50 mL of brine. The $MgSO_4$-dried extract was evaporated to give 1.3 g of crude product which, after filtration in 5 mL of CH_2Cl_2 through a 1 g plug of silica gel, concentration and crystallization from hexane, gave 1.21 g (86%) of **4d**, mp 91–92°C, mp, mixed mp and spectra identical to an authentic sample prepared according to Ref. 9d. Triflate salt **3d** could be converted to the highly-crystalline hexafluorophosphate by adding a 0.411 g (1 mmol) portion of it to a stirred solution of 1.0 g of $NaPF_6$ in 5 mL of MeOH, then evaporating. The residue was suspended in 50 mL of CH_2Cl_2 and washed with 3×25 mL of water. Evaporation of the $MgSO_4$-dried extract gave a solid which was crystallized from abs. EtOH, to give 0.36 g (90%) of white plates, mp 168–170°C. Anal. calcd for $C_{16}H_{22}F_6NO_2P$: C, 47.40; H, 5.50. Found: C, 47.20; H, 5.54.