6, 75 (1977).

(3) For a general survey of literature, see R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf, "Total Synthesis of Steroids", Academic Press, New York, N.Y., 1974, Chapter 1.

(4) G. H. Douglas, G. C. Buzby, Jr., C. R. Walk, and H. Smith, *Tetrahedron*, **22**, 1019 (1966).

(5) H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wendt, G. C. Buzby, Jr., R. A.

Edgren, J. Fisher, T. Foell, B. Gadsby, D. Hartley, D. Herbst, A. B. A. Jansen, K. Ledig, B. J. McLoughlin, J. McMenamin, T. W. Pattison, P. C. Phillips, R. Rees, J. Sidall, J. Siuda, L. L. Smith, J. Tokolics, and H. P. Watson, *J. Chem. Soc.*, 4472 (1964).

(6) P. N. Rao, *Steroids*, **23**, 173 (1974).

(7) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

Reduction of Aryl Diethyl Phosphates with Titanium Metal: A Method for Deoxygenation of Phenols

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An exceedingly simple method for the deoxygenation of phenols by reduction of the corresponding aryl diethyl phosphates with freshly prepared, highly activated titanium metal in tetrahydrofuran is presented.

The deoxygenation of phenols is often times an important and necessary synthetic objective. This goal can be achieved by catalytic hydrogenation as well as dissolving metal reduction methods. Among the catalytic hydrogenation techniques are the reduction of tosylate esters,[1,2] mesylate esters,[3] potassium arylsulfonates,[4] phenyl ethers,[5] methyl ethers,[6] 1-phenyl-5-tetrazolyl ethers,[7] O-arylisoureas,[8] and phenylurethanes.[9] The use of dissolving metal methods includes alkali metal in liquid ammonia reduction of mesylate esters;[10] 2,4-diaminophenyl ethers;[11] and diethyl phosphate esters.[10,12] By far the best of the dissolving metal reductions is the latter in which aryl diethyl phosphate esters are reduced with lithium metal in liquid ammonia. The esters are easily formed [HPO(OEt)₂, CCl₄, Et₃N or NaH, THF, ClPO(OEt)₂] in high yields (70 to 100%). Reported reductions of the corresponding aryl diethyl phosphates with lithium, sodium, or potassium metal in liquid ammonia proceeds in 2 to 96% yield. This method was found to be compatible with isolated carbon–carbon double bonds (alkenes).

We recently reported a new method for the reduction of enol phosphates to alkenes in high yields with titanium metal.[13] We now wish to report herein an alternative procedure for reducing aryl diethyl phosphate esters to aromatic hydrocarbons in high yield under aprotic conditions utilizing freshly prepared titanium metal.[14]

Highly activated titanium metal can be freshly prepared from anhydrous titanium(III) chloride by reduction with either magnesium[15] or potassium[16] metals in anhydrous tetrahydrofuran. The optimum stoichiometry for this reaction in Figure 1 utilizes 3 equiv of aryl diethyl phosphate (prepared by treatment of 3 equiv of the phenol with 3.3 equiv of sodium hydride in anhydrous tetrahydrofuran in the presence of 3 equiv of diethyl phosphorochloridate) with 2 equiv of freshly prepared, highly activated titanium metal in tetrahydrofuran. Titanium metal is prepared by treatment of 2 equiv of anhydrous titanium(III) chloride with 6 to 6.6 equiv of potassium metal. The reduction reaction is allowed to reflux for 6 to 16

h, then quenched with absolute methanol at 5 °C, filtered through a column of silica gel:celite (1:4, respectively), concentrated in vacuo, and either distilled or crystallized to afford the respective aromatic hydrocarbon in high yield.

Table I lists the starting phenols, yields of the aryl diethyl phosphates, yields of the aromatic hydrocarbon products, and the time for each of the reductions. This new reduction method is exceedingly simple and it appears to be quite general for phenols with isolated ester functional groups, ethers, alcohols, and alkenes present in the structure. Reduction of the diethyl phosphate ester derived from methyl podocarpate with titanium metal in refluxing tetrahydrofuran for 17 h affords desoxymethyl podocarpate in 80% yield with no observed reduction of the ester moiety. Similarly, reduction of estradiol 3-(diethyl phosphate) produces estra-1,3,5(10)-trien-17β-ol in 86% yield. Styrene double bonds, aryl aldehydes, aryl ketones, aryl esters, and aryl chlorides were found not to be compatible with this new reduction technique.

Reduction of the diethyl phosphate ester derived from carvacrol with titanium metal in refluxing tetrahydrofuran for 8 to 16 h followed by quenching with deuterium oxide does not incorporate deuterium. Reduction of the diethyl phosphate ester derived from eugenol under similar conditions followed by quenching with methanol at 5 °C produces the expected product 3-(3-methoxyphenyl)propene (B) in only 4.7% yield along with alkylated product 3-(3-methoxyphenyl)-1-pentene (A) in 74% yield. Reduction of eugenol diethyl phosphate under identical conditions to the latter experiment in the presence of 1 equiv of 100% ethanol gives compounds A, B, C, and D in a ratio of 5:88:2:5 in 82% combined yield. This series of experiments indicates that the reduction is probably producing a carbanionic species (aryl anion) which in the absence of a proton source (ROH or H₂O) most likely cleaves tetrahydrofuran over a period of 6 to 16 h at reflux. Eugenol diethyl phosphate is reduced in the presence of a proton source (EtOH) to afford the expected product B in 72% yield;
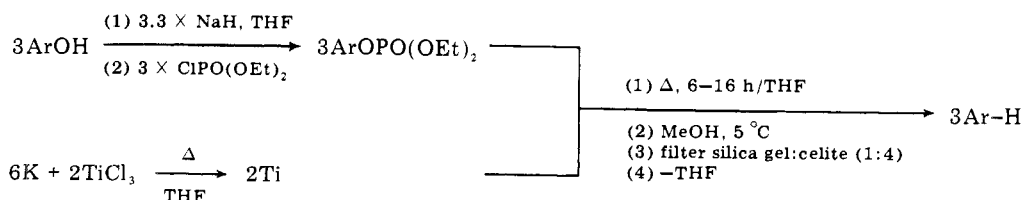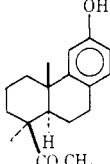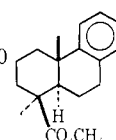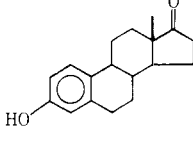

(1) 3.3 × NaH, THF
3ArOH ————————————→ 3ArOPO(OEt)₂
(2) 3 × ClPO(OEt)₂

Δ
6K + 2TiCl₃ ————→ 2Ti
THF

(1) Δ, 6–16 h/THF
————————————————→ 3Ar–H
(2) MeOH, 5 °C
(3) filter silica gel:celite (1:4)
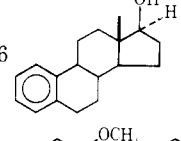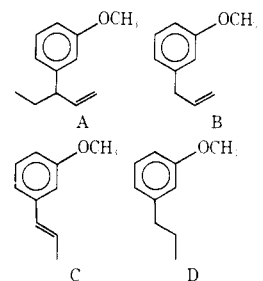(4) –THF

Figure 1.

Table I

phenol	registry no.	isolated yield, % (aryl phosphate)	registry no.	isolated yield, % (aromatic hydrocarbon)	registry no.	reduction time, h	ref (yield, %)
1-naphthol	90-15-3	91	33650-14-5	74 (naphthalene)	91-20-3	6	10 (71)[a] 10 (57)[b] 12 (22)[c]
2-naphthol	135-19-3	92	16519-26-9	77 (naphthalene)		6	10 (88)[a] 10 (95)[b] 12 (47)[d]
thymol	89-83-8	97	67951-84-2	92 (p-cymene)	99-87-6	8–16	
carvacrol	499-75-2	98	67951-85-3	93 (p-cymene)		8–16	
4-(2-propyl)phenol	99-89-8	98	16462-76-3	84 (isopropylbenzene)	98-82-8	8–16	
2-(2-propyl)phenol	88-69-7	96	16498-19-4	82 (isopropylbenzene)		8–16	
4-nonylphenol	104-40-5	99	67951-86-4	93 (nonylbenzene)	1081-77-2	6	
2,5-dimethylphenol	95-87-4	97	53336-83-7	81 (p-xylene	106-42-3	6–16	
3,5-dimethylphenol	108-68-9	98	5336-82-6	83 (m-xylene)	108-38-3	6	10 (63)[a] 10 (58)[b]
2,6-dimethoxyphenol	91-10-1	98	67951-87-5	89 (1,3-dimethoxybenzene)	151-10-0	6	
2,4,6-trimethylphenol	527-60-6	99	67951-88-6	89 (2,4,6-trimethylbenzene)	108-67-8	6–16	
hexylresorcinol	136-77-6	95	67951-89-7	83 hexylbenzene	1077-16-3	16	
	55029-03-3	97	38041-52-0	80	2651-34-5	17	18 (57)[e]
	53-16-7	98[f]	2626-19-9	86	2529-64-8	18	12 (78)[a]
eugenol	97-53-0	94	67951-90-0	79[g] ratio 94:6 (A–B) 82[h] ratio 5:88:2:5 (A–B–C–D)		8–16	

[a] Li, NH₃ [b] Na, NH₃. [c] K, NH₃. [d] Na, NH₃, THF. [e] Li, NH₃, THF. [f] NaH, ClPO(OET)₂, THF followed by NaBH₄, EtOH. [g] Ti, THF, Δ. [h] Ti, THF, 1 × EtOH, Δ. [i] Registry no.—A, 67951-91-1; B, 24743-14-4; C, 20112-91-8; D, 62103-69-9.

however, in the absence of a proton source (other than THF) the intermediate aryl anion ($pK_a \approx 37$–43, estimated) abstracts the more acidic benzylic–allylic proton of compound B ($pK_a \approx 33$–35, estimated) to generate a resonance stabilized carbanion which is then probably alkylated with diethyl phosphate anion to give product A.

In conclusion, this new reduction technique appears to be quite general for the deoxygenation of phenols (in the presence of methyl ethers, as well as isolated esters, alcohols, and alkenes) to aromatic hydrocarbons in high yields (74 to 93%) under aprotic conditions without the necessity of an aqueous extraction type of workup.

Experimental Section

Materials and Techniques. Melting points were determined on a Büchi melting point apparatus. All melting points and boiling points are uncorrected and are reported in °C. Analytical gas phase chromatography (GC) was performed on a Varian Aerograph Model 1400, equipped with a flame ionization detector with helium as the carrier gas using either a 6 ft, stainless steel, 1/8-in. diameter column, packed with 3% SE-30 on Varaport 30, 100/120 mesh with a flow rate of 15 mL/min at ambient temperature or a 6 ft, stainless steel, 1/8-in. column,

packed with 5% OV-17 on Varaport 30, 80/100 mesh with a flow rate of 15 mL/min at ambient temperature. Silica gel PF 254 + 336 (E. Merck No. 7748) and silica gel "Baker Analyzed" reagent (60–200 mesh) were used for thin layer and column chromatography, respectively. Silica gel 60 (230–400 mesh, E. Merck No. 9385) was used for medium pressure liquid chromatography. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 237B grating infrared spectrophotometer. Samples were taken as 10% solutions in spectroquality carbon tetrachloride or chloroform using balanced 0.1-mm sodium chloride cells or were taken as thin films between sodium chloride plates. Nuclear magnetic resonance (NMR) spectra were measured on Varian Associates Model T-60 spectrometer in the solvent indicated. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride immediately before use in all reactions. All reactions were performed under an atmosphere of dry nitrogen or argon using an apparatus designed by Johnson and Schnieder.[17] All equipment was dried in an oven at 120 °C for several hours prior to use then allowed to cool in a desiccator over Drierite. Titanium(III) chloride (Alfa No. 77116) was transferred in an atmosphere of dry nitrogen within a drybox.

General Method for the Formation of Aryl Diethyl Phosphate Esters. Carvacrol Diethyl Phosphate Ester. Sodium hydride (50% in oil, 0.525 g, 11.0 mmol) was washed (3 × 10 mL) and finally covered with THF (5 mL) under nitrogen. Carvacrol (1.50 g, 1.54 mL, 10.0 mmol) was then added and the mixture was allowed to stir for 0.5 h.

Diethyl phosphorochloridate (1.72 g, 1.44 mL, 10.0 mmol) was added and stirring was continued for 22 h. The mixture was diluted with ether (100 mL) and washed with 10% NaOH (3 × 50 mL) and the combined ethereal extracts were dried (MgSO₄), filtered through MgSO₄, and concentrated in vacuo. The residual oil, 2.981 g, was chromatographed on silica gel to give 2.802 g (98%) of a colorless oil, the desired ester: IR (thin film) 1525 (aromatic C=C stretch), 1270 (P=O stretch), 1240, 900 (POC aromatic stretch), 1060, 960 cm⁻¹ (doublet POC ethyl stretch); NMR (CCl₄) δ 1.20 (d, 6 H, CH (CH₃)₂), 1.30 (t, 6 H, **CH₃CH₂O**), 2.25 (s, 3 H, CH₃), 2.85 (septet, 1 H, CH(CH₃)₂), 4.15 (m, 4 H, CH₃CH₂O), 6.95 (m, 3 H, aromatic).

General Method for Reduction of Aryl Diethyl Phosphate Esters. *p*-Cymene. Anhydrous titanium(III) chloride (0.467 g, 3.03 mmol) was stirred in dry THF (20 mL) and potassium metal (cut in small pieces, 0.359 g, 9.21 mg-atoms) was added under argon. This slurry was then stirred at reflux for 1 h until no trace of potassium metal was visible. The diethyl aryl phosphate ester derived from carvacrol (1.264 g, 4.42 mmol) was added and the mixture was stirred at reflux for 8 h. The reaction mixture was then cooled to 5 °C in an ice bath and quenched with methanol (2 mL), filtered through a short plug of celite:silica gel (4:1 w/w) concentrated in vacuo and distilled to give 0.550 g (93%) of *p*-cymene: bp 175–177 °C; IR (thin film) 1515 (aromatic C=C stretch), 815 cm⁻¹ (out of plane C–H bend); NMR (CDCl₃) δ 1.11 (d, 6 H, CH(CH₃)₂), 2.27 (s, 3 H, CH₃), 2.85 (septet, 1 H, **CH**(CH₃)₂), 7.10 (s, 4 H, aromatic).

Synthesis of Estra-1,3,5(10)-triene-17β-ol from Estrone. Sodium hydride (0.0525 g 50% in oil, 1.10 mmol) was washed (3 × 10 mL) and then covered with dry THF (2 mL) under nitrogen. Estrone (0.2701 g, 1.0 mmol) was added in dry THF (1 mL) and allowed to stir for 30 min. Diethyl phosphorochloridate (0.172 g, 0.144 mL, 1.0 mmol) was added and stirring was continued for 24 h. The reaction mixture was diluted with ether and washed with 10% NaOH, dried (MgSO₄), filtered through MgSO₄, and concentrated in vacuo giving a viscous oil (0.411 g) which crystallized on standing: mp 66.0–67.5 °C [lit.¹²ᵈ mp 67.0–68.0 °C]; IR (CHCl₃) 1725 (C=O), 1600 (C=C aromatic), 1270, 1035, 960 cm⁻¹ (PO(OR)₃); NMR (CCl₄) δ 0.85 (s, 3 H, CH₃), 2.51-1.18 (m, 21 H, –CH₂– and **CH₃CH₂O**), 2.81 (m, 3 H, benzylic), 4.10 (m, 4 H, **CH₃CH₂O**). 6.85 (m, 3 H, aromatic).

This material (estrone 3-(diethyl phosphate), 0.411 g, 1.0 mmol) was dissolved in 100% ethanol (2.5 mL) and cooled in an ice bath. Sodium borohydride (0.251 g, 6.50 mmol) in a solution of 100% ethanol (1.5 mL) and water (1.0 mL) was added and the mixture stirred vigorously. After 5 min, the reaction mixture was poured into ether and extracted three times with water and the ethereal solution was dried (MgSO₄) and concentrated in vacuo. Recrystallization from ether-pentane gave 0.400 g (98%) of estradiol 3-(diethyl phosphate): mp 112.5–114.0 °C [lit.¹²ᵈ mp 113.5–115.5 °C]; IR (CHCl₃) 3600, 3400 (OH), 1600 (aromatic), 1270, 1035, 960 cm⁻¹ (PO(OR)₃); NMR (CDCl₃) δ 0.80 (s, 3 H, CH₃), 2.50–1.20 (m, 21 H, –CH₂– and **CH₃CH₂O**), 2.81 (m, 3 H, benzylic), 3.42 (s, 1 H, OH), 3.71 (m, 1 H, CHOH), 4.10 (m, 4 H, CH₃CH₂O), 7.05 (m, 4 H, aromatic). This aryl phosphate ester was then reduced with freshly prepared, highly activated, titanium metal as in the above procedure for 18 h to afford 0.215 g (85.6%) of estra-1,3,5(10)-triene-17β-ol: mp 115–117 °C [lit.¹²ᵈ mp 117–118.5 °C]; IR (CHCl₃) 3600, 3460 (OH), 900 cm⁻¹ (aromatic); NMR (CDCl₃) δ 0.79 (s, 3 H, CH₃), 2.50–1.15 (m, 15 H, –CH₂–), 2.80 (m, 3 H, benzylic), 3.60 (m, 1 H,**OH**), 3.65 (m, 1 H, CHOH), 7.00 (m, 4 H, aromatic).

Deoxymethyl Podocarpate. Sodium hydride (0.191 g 50% oil, 4.0 mmol) was washed (3 × 10 mL) and finally covered with dry THF (5 mL) under dry nitrogen. Methyl podocarpate (1.05 g, 3.65 mmol) was added in dry THF (1 mL) and the mixture was allowed to stir for 30 min. Diethyl phosphorochloridate (0.688 g, 0.576 mL, 4.0 mmol) was added and the mixture stirred for 24 h at room temperature. The reaction mixture was then diluted with ether and washed with 1 NaOH. The ethereal solution was dried (MgSO₄), filtered through MgSO₄, and concentrated in vacuo giving a yellowish syrup (1.631 g). Chromatography on silica gel afforded the desired phosphate ester as a crystalline solid: 1.501 g (97%); mp 49–50 °C; IR (CHCl₃) 1720 (C=O ester), 1600 (aromatic), 1270, 1025, and 960 cm⁻¹ (OP(OR)₃); NMR (CCl₄) δ 0.99 (s, 3 H, CH₃), 2.40–1.10 (m, 18 H, –CH₂– and **CH₃CH₂O**), 2.75 (m, 2 H, benzylic), 3.55 (s, 3 H, CH₃–O), 4.10 (m, 4 H, CH₃CH₂O), 6.87 (m, 3 H, aromatic). This aryl phosphate ester was reduced as in the above procedure with freshly prepared, highly activated, titanium metal to afford 0.767 g (79.6%) of white crystals: mp 139–141 °C [lit.¹⁸ mp 140–141 °C]; IR (CHc₃) 1720 (C=O), 1600 (C=C aromatic); NMR (CDCl₃) δ 1.01 (s, 3 H, CH₃), 2.40–1.10 (m, 12 H, aliphatic), 2.80 (m, 2 H, benzylic), 3.70 (s, 3 H, OCH₃), 6.82 (m, 4 H, aromatic).

References and Notes

(1) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, S178 (1949).
(2) H. Rottendorf and S. Sternhell, *Aust. J. Chem.*, **16**, 647 (1963).
(3) K. Clauss and A. Jensen, *Angew. Chem., Int. Ed. Engl.*, **12**, 918 (1973).
(4) W. Lonsky, H. Traitler, and K. Kratzyl, *J. Chem. Soc., Perkin Trans. 1*, 169 (1975).
(5) Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron*, **15**, 144, 154 (1961).
(6) G. S. Chandler and W. H. F. Sasse, *Aust. J. Chem.*, **16**, 20 (1963).
(7) W. J. Musliner and J. W. Gates, Jr., *Org. Synth.*, **51**, 82 (1971); *J. Am. Chem. Soc.*, **88**, 4271 (1966).
(8) E. Vowinkel and C. Wolf, *Chem. Ber.*, **107**, 907 (1974).
(9) J. D. Weaver and E. J. Eisenbraun, *Chem. Ind. (London)*, **No. 16**, 187 (1973).
(10) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).
(11) W. H. Pirkle and J. L. Zabriske, *J. Org. Chem.*, **29**, 3124 (1964).
(12) (a) S. W. Pelletier and D. M. Locke, *J. Org. Chem.*, **23**, 131 (1958); (b) R. A. Rossi and J. F. Bunnet, *ibid.*, **38**, 2314 (1974); (c) S. J. Dominianni, C. W. Ryan, and C. W. DeArmitt, *ibid.*, **42**, 345 (1977); (d) A. H. Goldkamp, W. H. Hoehn, R. A. Mikulec, E. F. Nutting, and D. L. Cook, *J. Med. Chem.*, **8**, 409 (1965).
(13) S. C. Welch and M. E. Walters, *J. Org. Chem.*, **43**, 2715 (1978).
(14) For an excellent review of "The Chemistry of Low Valent Titanium", see: J. E. McMurry, *Acc. Chem. Res.*, **7**, 281 (1974).
(15) S. Tyrlik and I. Wolochowicz, *Bull. Soc. Chim. Fr.*, 2147 (1973); *J. Chem. Soc., Chem. Commun.* 781 (1975); T. R. Nelson and J. J Tufaniello, *J. Org. Chem.*, **40**, 3159 (1975).
(16) J. E. McMurry and M. P. Fleming, *J. Org. Chem.*, **41**, 896 (1976); J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *ibid.*, **43**, 3255 (1978).
(17) W. S. Johnson and W. P. Schneider, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132.
(18) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80**, 217 (1958).