1i, 2050-47-7; **2a**, 1719-19-3; **2b**, 33577-96-7; **2c**, 33577-97-8; **2d**, 33577-98-9; **2e**, 95785-27-6; **2f**, 95785-28-7; **2g**, 17541-02-5; **2h**, 95785-29-8; **2i**, 17541-14-9; **3a**, 536-74-3; **3b**, 33577-99-0; **3c**, 10602-06-9; **3d**, 3034-86-4; **3f**, 42472-69-5; **3g**, 4200-06-0; **3i**, 21368-80-9; $HC{\equiv}CC(CH_3)_2OH$, 115-19-5; NaH, 7646-69-7.

Improved Method for the Conversion of Enol Lactones to Cyclic α,β-Unsaturated Ketones

Paul A. Aristoff

Lipids Research, The Upjohn Company, Kalamazoo, Michigan 49007

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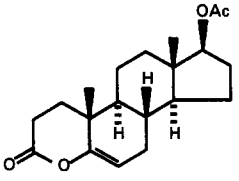
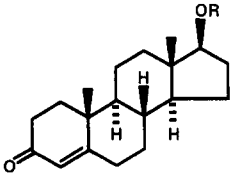
During the course of developing an improved synthesis of the benzindene prostaglandins, potent stable prostacyclin analogues,[1] we had occasion to investigate the direct conversion of an enol lactone to a cyclic α,β-unsaturated ketone. One of the most promising methods to accomplish this transformation, published a number of years ago by a Syntex group, is illustrated (along with the proposed mechanism) in Scheme I.[2] Treatment of enol lactone **a** with 1 equiv of the phosphonate anion **b** at low temperature results in lactone cleavage to give the ketone enolate **c**. Subsequent proton transfer affords the β-ketophosphonate anion **d** which is then set up to undergo an intramolecular Wadsworth–Emmons reaction to give the desired enone **e**.[2]

Despite the obvious potential of such a convergent procedure, this method appears to have been only sparingly employed since the original communication. The few times this reaction has been used in a synthesis the yields have been poor (25–48%).[3] We decided to reexamine the reaction in several steroid examples.

Treatment of enol lactone **1**[2] with 1 equiv of lithium dimethyl methylphosphonate[4] at −78 °C in tetrahydrofuran (THF) followed by slow warming to 25 °C and then either stirring at room temperature for 17 h or heating at 55 °C for 4 h gave a 27% yield of testosterone acetate (**2**) along with about a 30% yield of a closely eluting dimeric product.[5,6] Treatment of **1** with 2 equiv of lithium dimethyl methylphosphonate under similar conditions afforded a 22% yield of **2** and a 7% yield of **3**.



1

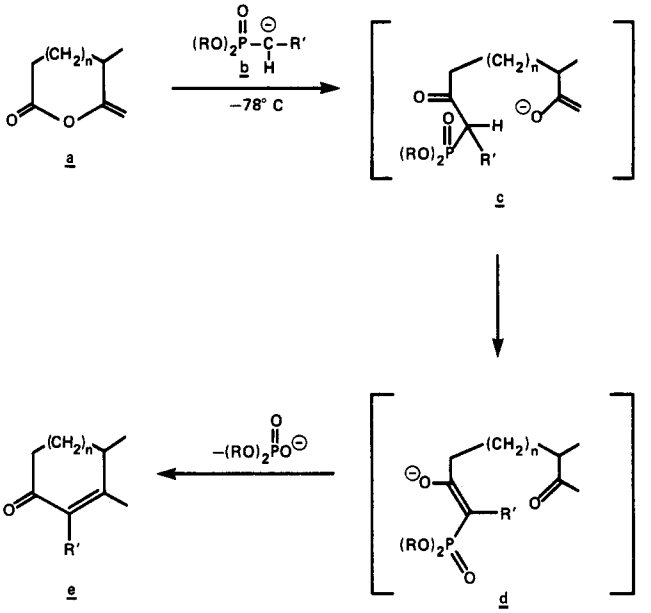


2 R=$COCH_3$

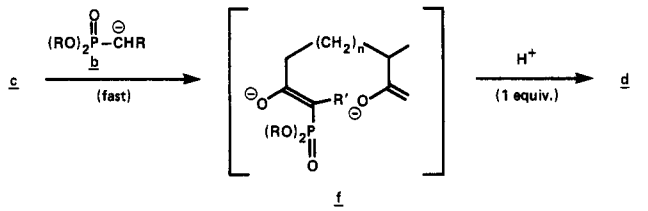
3 R=H

The observation that in this and other examples[3] it was possible to recover nearly all the unreacted phosphonate suggested a slightly different mechanism than the one originally proposed. We suggest that the reaction is actually proceeding through a dianion intermediate as shown in Scheme II. Rather than proton transfer taking place to convert **c** to **d** directly (Scheme I), the phosphonate anion **b** rapidly deprotonates **c** to form the dianion **f**. An external proton source, possible enol lactone **a**, then converts **f** to **d**. Apparently, even at low temperature, intermediate **c** is converted to **f** as fast as it is formed.

Scheme I



Scheme II



Support for this mechanism comes from the fact that when enol lactone **1** was treated with 2 equiv of lithium dimethyl methylphosphonate at −78 °C and then slowly warmed to −20 °C, treated with 1 equiv of acetic acid, and then heated at 55 °C for 3 h,[7] a 40% yield of testosterone acetate (**2**) was obtained along with a 52% yield of testosterone (**3**). On large scale it was simpler just to treat the crude reaction mixture with aqueous potassium carbonate in methanol. In this manner an overall 85% yield (from **1**) of analytically pure testosterone was achieved. Thus deliberate formation of dianion **f** using 2 equiv of phosphonate anion followed by back titration to the monoanion **d** with 1 equiv of acid gave a much better overall yield of product.

Another example using a more complex phosphonate also illustrates this point. Treatment of phosphonate **4**[8] (2 equiv) at −78 °C in THF with *n*-butyllithium (2 equiv) and then after 1 h at −78 °C with enol lactone **6**[9] (1 equiv), followed by slow warming to −25 °C, treatment with acetic (1 equiv), and subsequent heating at 55 °C, afforded the

(1) Aristoff, P. A.; Harrison, A. W. *Tetrahedron Lett.* **1982**, *23*, 2067.
(2) Henrick, C. A.; Böhme, E.; Edwards, J. A.; Fried, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 5926. See also: Fried, J. H. U.S. Patent 3 639 428, 1972 and Fried, J. H. German Patent 1 812 124, 1969; *Chem. Abstr.* **1969**, *71*, 123725.
(3) Crowe, D. F.; Christie, P. H.; DeGraw, J. I.; Fujiwara, A. N.; Grange, E.; Lim, P.; Tanabe, M.; Cairns, T.; Skelly, G. *Tetrahedron* **1983**, *39*, 3083. See also: Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 4597.
(4) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654.
(5) Henrick et al.[2] report at 50% yield for this same reaction.
(6) The dimeric product appears to arise from the addition of the enolate of **2** to starting enol lactone **1**.
(7) The reaction at this point could instead be stirred for 17 h at room temperature to achieve the same results.
(8) Sturtz, G. *Bull. Soc. Chim. Fr.* **1964**, 2340.
(9) Enol lactone **6** was prepared in 54% yield from lactone **5**[10] by reduction with sodium borohydride in glyme at 0 °C followed by silylation with *tert*-butyldimethylsilyl chloride and imidazole in THF. We thank Dr. Joel Huber of the Upjohn Co. for a generous supply of compound **5**.
(10) Komeno, T.; Ishihara, S.; Itani, H. *Tetrahedron* **1972**, *28*, 4719.

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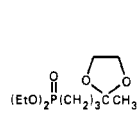
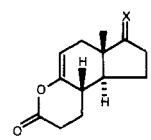
desired enone 7 in 70% yield. Only a 26% yield of 7 was obtained when 1 equiv of phosphonate 4 (and no acid) was used.[11]

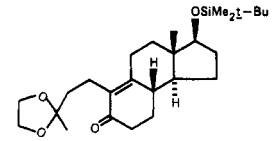


4



5 X = O

6 X = α-H, β-OSiMe$_2$t-Bu



7

It is hoped that this improved modification of the enol lactone to cyclic α,β-unsaturated ketone reaction will result in its wider use in synthesis.

Experimental Section[12]

Testosterone (3). A solution of 0.43 mL (4.0 mmol) of dimethyl methylphosphonate in 60 mL of THF at −78 °C was treated dropwise with 2.6 mL (4.08 mmol) of 1.57 M *n*-butyllithium in hexane. The resulting solution was stirred for 55 min at −78 °C and then treated dropwise with a solution of 659 mg (1.98 mmol) of enol lactone 1[2] in 8 mL of THF. The resulting gray suspension was stirred for 30 min at −78 °C, allowed to warm over 2.5 h to −20 °C, and then treated dropwise with 0.11 mL (1.92 mmol) of glacial acetic acid. The resulting solution was heated at 55 °C for 3 h, cooled to 0 °C, neutralized with 1 M aqueous hydrochloric acid, partitioned between ethyl acetate and brine, and dried ($MgSO_4$). The solvents were concentrated in vacuo to give 0.8 g of a yellow oil (TLC indicated about 1:1 testosterone to testosterone acetate) which was dissolved in 80 mL of methanol and 20 mL of water. The resulting solution was treated with 5.0 g of anhydrous potassium carbonate, stirred for 18 h at ambient temperature, treated with 10 mL of 1 M aqueous hydrochloric acid, and partitioned between brine and ethyl acetate. The organic extracts were dried (Na_2SO_4), and the solvents were removed under reduced pressure to give 570 mg (100%) of **3** as an off-white solid. Recrystallization of **3** from hot ethyl acetate and hexane gave 487 mg (85%) of pure testosterone (**3**) as a white solid: mp 153–154 °C (mixed melting point with authentic testosterone 153–154 °C); R_f 0.22 in 50% ethyl acetate in hexane (identical with authentic testosterone); NMR δ 0.80 (s, 3 H), 0.85–2.7 (m including 3 H s at δ 1.21, 23 H), 3.5–3.9 (m, 1 H), 5.78 (s, 1 H); ^{13}C NMR δ 11.07, 17.45, 20.71, 23.38, 30.46, 31.62, 32.83, 33.96, 35.77, 36.51, 38.70, 42.86, 50.57, 54.00, 81.55, 123.87, 171.12, 199.2; IR (mull) 3530, 3385, 1665, 1655, 1645, 1610, 1465, 1455, 1445, 1380, 1235, 1065, 1055, 870 cm^{-1}; mass spectrum, calcd for $C_{22}H_{36}O_2Si$ (M^+ for the trimethylsilyl derivative) *m/e* 360.2484, found *m/e* 360.2490. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.11; H, 9.91.

[3a*S*-(3aα,9aα,9bβ)]-3β-((*tert*-Butyldimethylsilyl)oxy)-3aβ-methyl-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1,2,3,3a,4,5,8,9,9a,9b-decahydro-7*H*-benz[*e*]inden-7-one (7). A solution of 385 mg (1.45 mmol) of diethyl (4-(cycloethylenedioxy)pentyl)phosphonate (**4**)[8] in 22 mL of THF at −78 °C was treated with 0.94 mL (1.49 mmol) of 1.58 M *n*-butyllithium in hexane, stirred 1 h at −78 °C, treated dropwise with 242 mg (0.72 mmol) of enol lactone 6[9] in 3 mL of THF, stirred for 1 h at −78 °C, warmed to −25 °C over 2 h, treated with 0.04 mL (0.70 mmol) of glacial acetic acid, heated at 60 °C for 6 h, cooled to 0 °C, neutralized with aqueous hydrochloric acid, and partitioned between brine and ethyl acetate. The organic extracts were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was chromatographed on silica gel eluted with 20% ethyl acetate in hexane to give 227 mg (70%) of enone **7** as a colorless oil: R_f 0.25 in 20% ethyl acetate in hexane; NMR δ 0.03 (s, 6 H), 0.9 (s, 12 H), 1.0–3.1 (m including 3 H s at δ 1.39, 21 H), 3.4–3.8 (m, 1 H), 3.98 (s, 4 H); ^{13}C NMR δ −3.25, −2.89, 10.63, 18.05, 20.13, 23.51, 23.60, 25.81, 26.62, 26.83, 30.95, 36.55, 37.07, 38.11, 39.04, 42.85, 50.52, 64.60, 81.19, 109.82, 134.16, 159.14, 198,42; IR (film) 1675, 1615, 1465, 1380, 1365, 1280, 1255, 1215, 1140, 1105, 1065, 905, 890, 850, 845, 775 cm^{-1}; mass spectrum, calcd for $C_{26}H_{44}O_4Si$ *m/e* 448.3009, found *m/e* 448.3019. Anal. Calcd for $C_{26}H_{44}O_4Si$: C, 69.59; H, 9.88. Found: C, 69.88; H, 10.01.

Registry No. 1, 1458-92-0; 2, 1045-69-8; 3, 58-22-0; 4, 1213-29-2; 5, 96038-39-0; 6, 95935-95-8; 7, 95935-96-9; dimethyl methylphosphonate, 756-79-6; *tert*-butyldimethylsilyl chloride, 18162-48-6.

(11) Attempts to effect reaction using 1 equiv of phosphonate reagent and 2 equiv of base (e.g., lithium diisopropylamide) followed by treatment with 1 equiv of the enol lactone at low temperature, warming to about 0 °C, addition of 1 equiv of glacial acetic acid, and heating at 55 °C only gave low yields of the desired product. When 2 equiv of an expensive phosphonate reagent are used, it is usually simple to recover chromatographically the excess phosphonate since it is generally much more polar than any of the reaction products.

(12) All melting points are uncorrected. Combustion analysis, IR, and mass spectra were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co., with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (crystalline samples). Mass spectra were recorded at high resolution for derivatized (Me_3Si) or underivatized compounds at 70 eV. The ^1H NMR spectra of chloroform-*d* solutions were obtained on a Varian EM-390 spectrometer operating at 90 MHz. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. ^{13}C NMR spectra were obtained of chloroform-*d* solutions on a Varian CFT-20 spectrometer operating at 20 MHz. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. Brine refers to a saturated aqueous solution of NaCl. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reactions were done under an inert atmosphere. Thin-layer chromatography (TLC) was conducted with Analtech (Uniplates) precoated with silica gel (E. Merck, 70–230 mesh).

Hexacyanoferrate-Catalyzed Oxidation of Trimethoxybenzenes to Dimethoxy-*p*-benzoquinones with Hydrogen Peroxide

Masakatsu Matsumoto* and Hisako Kobayashi

Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

Yasushi Hotta*

Research & Development Center, Daikyo Oil Co., Ltd., Inaba-cho 9-16, Yokkaichi, Mie 510, Japan

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Hydrogen peroxide generates OH radical by the catalysis of iron salts, and their combination [Fe(II)/H_2O_2] is typically known as Fenton's reagent, which can oxidize a wide variety of organic substrates including arenes.[1,2] The reaction with arenes, however, frequently leads to results too complex for use in organic synthesis. The main reason is the high reactivity of the primary products (hydroxylated arenes) which are more easily oxidized than the starting arenes. In addition, the character of the iron salts might significantly affect the reaction; in most cases known so far, the iron salts used were those which can complex with phenols. This trend probably causes oxidation of arenes by H_2O_2/Fe salts to be all the more complicated. We report here a successful oxidation of arenes by H_2O_2 in the presence of potassium hexacyanoferrate, which has little ability to complex with ligands other than CN ion.[3]

(1) For reviews, see: (a) Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125. (b) Sheldon, R. A., Kochi, J. K., Eds. Metal-catalyzed Oxidation of Organic Compounds; Academic Press: New York, 1981.

(2) Fe(III)/H_2O_2 system is also known as Ruff's reagent, which is especially effective for oxidation of sugars; for a review, see: "The Action of Hydrogen Peroxide on Carbohydrates and Related Compounds"; Moody, G. J. In "Advances in Carbohydrate Chemistry"; Wolfrom, M. L., Ed.; Academic Press: New York, 1964; Vol. 19, p 149.

(3) Ferryl ion (FeO^{2+}) and singlet oxygen were recently reported to participate in a $Fe^{II}ClO_4/H_2O_2$ system especially in nonaqueous medium: Sugimoto, H.; Sawyer, D. T. *J. Am. Chem. Soc.* **1984**, *106*, 4283. These species might, however, be scarcely generated in hexacyanoferrate system because all the six CN ligands are little exchangeable with others.

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