31579-69-8; *trans*-**3a**, 31579-70-1; **3b** (isomer 1), 95798-60-0; **3b** (isomer 2), 95909-01-6; **3b** (isomer 3), 95909-02-7; **3b** (isomer 4), 95909-03-8; **3c** (isomer 1), 95798-61-1; **3c** (isomer 2), 95909-04-9; **3c** (isomer 3), 95909-05-0; **3c** (isomer 4), 95909-06-1; **4b**, 34908-52-6; **4c**, 95798-62-2; **5a**, 218-01-9; **5b**, 3697-24-3; **5c**, 54986-62-8; **6**, 22901-09-3; **7a**, 3487-44-3; **7b**, 1754-88-7; **7c**, 16666-78-7; **8a**, 95798-50-8; (*E*)-**8b**, 95798-51-9; (*Z*)-**8b**, 95798-52-0; (*E*)-**8c**, 95798-53-1; (*Z*)-**8c**, 95798-54-2; methyltriphenylphosphonium bromide, 1779-49-3; ethyltriphenylphosphonium bromide, 1530-32-1; propyltriphenylphosphonium bromide, 6228-47-3; 1,3-dihydrobenzo[*c*]thiophene *S*,*S*-dioxide, 2471-91-2.

Synthesis of Arylacetylenes by the Sodium Hydride Catalyzed Cleavage of 4-Aryl-2-methyl-3-butyn-2-ols

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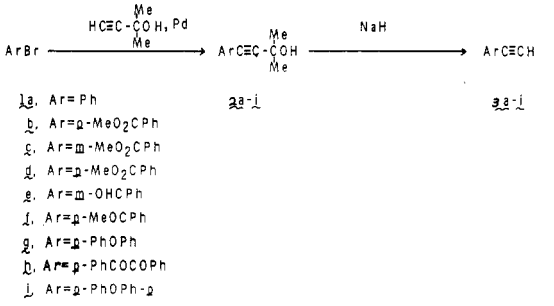
Recent advances in a two step synthesis of arylacetylenes have been reported.[1-4] The first step is displacement of an aromatic bromine or iodine atom by an acetylene adduct. The second step is removal of the protecting group to yield the arylacetylene.

Ethynyltrimethylsilane provides an excellent vehicle for the introduction of an acetylene group to an aromatic nucleus. Reaction of aryl halides (bromide or iodide) with ethynyltrimethylsilane in a secondary or tertiary amine solvent containing a small amount of palladium catalyst has given quantitative yields of (trimethylsilyl)ethynylaryls.[1,2a,b] The trimethylsilyl protecting group is easily removed by treatment with dilute potassium hydroxide[1] or under milder conditions by treatment with potassium carbonate.[2a,b] Yields of unpurified arylacetylenes are nearly quantitative. However, this method is expensive due to the high cost of ethynyltrimethylsilane.

The reaction of the relatively inexpensive reagent 2-methyl-3-butyn-2-ol with an aryl halide under conditions analogous with those employed with ethynyltrimethylsilane has given near quantitative yields of 4-aryl-2-methyl-3-butyn-2-ols (**2**).[3a,4a,b] Treatment with alkali-metal hydroxides at elevated temperatures is required for cleavage of the 2-hydroxypropyl group. In one case,[3a-d] **2** was heated at 120–140 °C under vacuum with powdered potassium hydroxide. Ester groups present were not affected under these conditions. In the other case,[4a,b] cleavage was effected by the slow distillation of a toluene solution of **2** containing a catalytic amount of sodium hydroxide. Acetone, the byproduct, must be removed by distillation to shift the equilibrium toward the arylacetylene (**3**).

Scheme I



We previously reported that the reaction of methyl 4-bromobenzoate with 2-methyl-3-butyn-2-ol at 90 °C in trimethylamine containing catalytic amounts of dichlorobis(triphenylphosphine)palladium, triphenylphosphine, and cuprous iodide provided 4-(4-(methoxycarbonyl)-phenyl)-2-methyl-3-butyn-2-ol (**2d**, Ar = MeO_2CPh-) in excellent yield.[5] Complete cleavage of the 2-hydroxypropyl group proved difficult. Treatment with sodium hydroxide in refluxing toluene combined with removal of acetone via distillation resulted in saponification of the ester. Only partial cleavage of the 2-hydroxypropyl group occurred even with distillation times of up to 10 h. Heating with a catalytic amount of potassium hydroxide at 120–140 °C under vacuum again resulted in only partial cleavage as both **2d** and the desired methyl 4-ethynylbenzoate sublimed from the reaction mixture under those conditions. No detectable saponification of the ester occurred. A weakly nucleophilic strong base may initiate the cleavage of the 2-hydroxypropyl group without affecting the ester group. This proved to be the case with sodium hydride. Distillation of a toluene solution of **2d** containing a catalytic amount of sodium hydride produced good yields of methyl 4-ethynylbenzoate. Herein, we report the results of the sodium hydride cleavage of various 4-aryl-2-methyl-3-butyn-2-ols, some containing base-sensitive groups (Scheme I).

Results and Discussion

Yields of arylacetylenes were generally good as shown in Table I, although some polymeric residue was a byproduct of the cleavage of the 2-hydroxypropyl group with sodium hydride. Removal of this group from **2a** was readily achieved but isolation of phenylacetylene (**3a**) from the toluene solution was not possible due to the tendency of phenylacetylene to codistill with toluene. HPLC analysis of the solution was used to determine yield in this case. Attempts to scale up the cleavage procedure met with some difficulty. Cleavage of the 2-hydroxypropyl group from **2d** on a larger scale (1.5 mol) required an extended distillation period (6–8 h) for an approximate 50% conversion. This prolonged heating was obviously leading to decomposition of the desired material. Several attempts to remove the 2-hydroxypropyl groups from **2e** and **2h**, compounds containing an aldehyde group and a 1,2-diketone group, respectively, failed. Only starting material was recovered. The precise reasons for these failures are unknown, but it has been reported that reaction of *p*-nitrobenzaldehyde with several equivalents of sodium hydride gives a mixture of *p*-nitrobenzoic acid and *p*-

(1) Takahashi, S.; Koroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

(2) (a) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280. (b) Lau, K. S. Y., Kelleghan, W. J.; Boschan, R. H.; Bilow, N. *J. Polym. Sci., Polym. Chem. Ed.* **1983**, *21*, 3009.

(3) (a) Shvartsberg, M. S.; Moroz, A. A.; Kotlyarevskii, I. L. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1972**, 981. (b) Shvartsberg, M. S.; Kotlyarevskii, I. L.; Kozhevikova, A. N.; Andrievskii, V. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1970**, 1144. (c) Shvartsberg, M. S.; Moroz, A. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1971**, 1582. (d) Shvartsberg, M. S.; Kozhevnikova, A. N.; Moroz, A. A.; Vasilevskii, S. F.; Bizhan, L. N.; Kotlyarevskii, I. L. *Dokl. Vses. Konf. Khim. Atsetilena, 4th* **1972**, (Pub. 1972), *2*, 52.

(4) (a) Sabourin, E. T. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1979**, *24*, 233. (b) Sabourin, E. T.; Onopchenko, A. *J. Org. Chem.* **1983**, *48*, 5135.

(5) Havens, S. J.; Hergenrother, P. M. *J. Polym. Sci., Poly. Chem. Ed.* **1984**, *22*, 3011.

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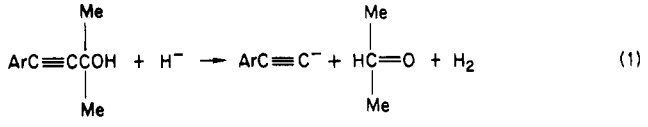
Table I. Summary of Physical Constants and Yields

compd	mp, °C	bp, °C (mm Hg)	yield,[a] % (purificatn method)	IR, cm^{-1} C≡C	IR, cm^{-1} C≡CH	NMR ($CDCl_3$), δ C≡CH
2a	48.5–50.5	82–85 (0.5) [lit.[b] 84–90 (0.6)]	67 (vacuum distd)	2230		
2b		132–135 (0.5) [lit.[c] 137–138 (0.5)]	62 (vacuum distd)	2235		
2c[d]		160–164 (0.35)	71 (vacuum distd)			
2d	83.5–84.5 [lit.[c] 83.5–84]		70 (recryst EtOH/H_2O)			
2e[d]		120–123 (0.3)	66 (vacuum distd)			
2f[d]		139–140 (0.4)	67 (vacuum distd)	2238		
2g	44–48 [lit.[e] 46.5–47.5]		55 (recryst hexane)	2230		
2h[d]	78.5–80.5		71 (recryst hexane)	2220		
2i	139–140 [lit.[e] 141.5–142.5]		74 (recryst EtOH/H_2O)	2220		
3a			62[f]			
3b		63–70 (0.3) [lit.[c] 80–81 (0.50)]	70 (vacuum distd)	2105	3285	3.40
3c	53.5–55 [lit.[g] 48–50]		72 [subl, 45 °C (65 Pa)]	2103	3255	3.95
3d	91–93 [lit.[g] 92.5–93.5]		69 [subl, 60 °C (15 Pa)]	2105	3245	3.25
3e[h]			0			
3f	67–68.5 [lit.[i] 69–70]		51 [subl, 50 °C (7 Pa)]	2095	3208	3.31
3g		95–97 (0.25) [lit. 92–94[j] (1.0)]	63 (vacuum distd)	2115	3295	3.00
3h[h]			0			
3i	74.5–76 [lit.[k] 72–73]		70 (recryst hexane)		3282	3.03

[a] Yields are those of the various compounds after purification by the method indicated. [b] Klein, J.; Zitrien, S. *J. Org. Chem.* **1970**, *35*, 666. [c] From ref 3c. [d] Elemental analyses (±0.2% for C, H) or mass spectra consistent with structure were obtained for compounds **2c,e,f,h**. [e] Shvartsberg, M. S.; Kotlyarevskii, I. L.; Volgina, G. I.; Trotsenko, Z. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 905. [f] Average yield as determined from HPLC analysis of the reaction mixture. [g] From ref 2a. [h] The sodium hydride cleavage of the 2-hydroxypropyl group failed. [i] Kotlyarevskii, I. L.; Shvartsberg, M. S.; Volgina, G. I.; Vasilevskii, S. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1965**, 1705. [k] Ratto, J. J.; Dynes, P. J.; Hamermesh, C. L. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 1035.

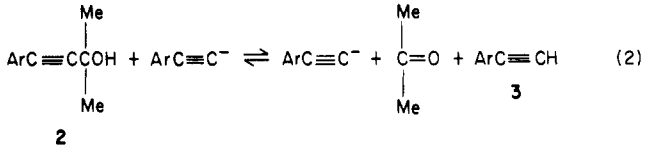
nitrobenzyl alcohol.[6] The apparent resolution of this problem is the employment of a base-resistant protecting group (possibly ketal or thioketal) at the aryl bromide stage.

Sodium hydride cleavage of the 2-hydroxypropyl group is probably initiated by abstraction of the hydroxy proton, followed by loss of acetone and formation of the substituted arylacetylide (eq 1). The arylacetylide, in turn,



(1)

2



(2)

2

abstracts a hydroxy proton from another 2-hydroxypropyl group in a reversible step, which is driven forward by removal of acetone (eq 2). This step yields the arylacetylene, acetone, and another arylacetylide, which can propagate the cleavage. According to this scheme, the substituted arylacetylide is sufficient to affect cleavage. To test this hypothesis sodium phenylacetylide was prepared (reaction of phenylacetylene with sodium) and used in place of sodium hydride for the cleavage of the 2-hydroxypropyl group from **2a**. The desired phenylacetylene was obtained as before.

Experimental Section

General Methods. Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer Model 297 spectrophotometer (liquids, neat; solids, KBr). Proton nuclear magnetic resonance (^{1}H NMR) spectra were taken on a Varian EM 360A spectrometer with tetramethylsilane as internal standard. HPLC was performed on a Waters Associates ALC/GPC 244 liquid chromatograph using a μ-Porasil column with (1:9) dichloromethane/isooctane as the mobile phase. Elemental analysis was performed by Galbraith Laboratories, Inc., Knoxville, TN.

Starting Materials. Aryl bromides **1a,e–g** were obtained from Aldrich Chemical Co. and used without further purification. Methyl bromobenzoates (**1b–d**) were prepared by refluxing the appropriate bromobenzoic acid with an excess of methanol containing a catalytic amount of sulfuric acid. (4-Bromophenyl)-phenylethanedione (**1h**) (4-bromobenzil) was prepared by the Friedel–Crafts acylation of benzene with (4-bromophenyl)acetyl chloride, followed by selenium dioxide oxidation of the resulting 2-(4-bromophenyl)-1-phenylethanone. 4,4′-Dibromodiphenyl oxide (**1i**) was prepared by bromination of diphenyl oxide in carbon tetrachloride. 2-Methyl-3-butyn-2-ol was purchased from Aldrich Chemical Co. Dichlorobis(triphenylphosphine)palladium was purchased from Strem Chemical, Inc. Triethylamine was distilled before use.

4-Aryl-2-methyl-3-butyn-2-ols (2). All of these compounds were prepared by using a procedure similar to one reported in the literature.[4a,b] Physical constants and yields are shown in Table I.

Arylacetylenes (3). The synthesis of methyl 4-ethynylbenzoate (**3d**) will serve as an example for the cleavage of the 2-hydroxypropyl group using sodium hydride. To a solution of **2d** (21.83 g, 0.10 mol) in anhydrous toluene (200 mL) was added sodium hydride (0.32 g) as a 60% dispersion in oil. The stirred suspension was slowly distilled until the boiling point of the distillate reached 110 °C (ca. 100 mL of distillate collected). The residue was cooled and filtered and the filtrate evaporated under reduced pressure. The solid was dissolved in dichloromethane, and the solution was washed with 5% sodium bicarbonate solution and with water. After being dried ($MgSO_4$), the solution was filtered and the filtrate evaporated under reduced pressure to leave **3d** as a crude solid. Sublimation at 60 °C (15–45 Pa) provided methyl 4-ethynylbenzoate **3d** (11.1 g, 69%) as a white solid: mp 91–93 °C (lit.[2a] 92.5–93.5 °C); IR (KBr) 3245 (vs, sharp, C≡CH), 2105 (w, sharp, C≡C), 1702 (vs, sharp, ester C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25 (s, 1 H, C≡CH), 3.93 (s, 3 H, CO_2CH_3), 7.75 (q, 4 H, J_{ab} = 8 Hz, Ar).

Acknowledgment. We thank Mrs. Alice Chang for HPLC analyses. The use of sodium hydride was suggested by Dr. James Wolfe, Chemistry Department, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061.

Registry No. **1a**, 108-86-1; **1b**, 610-94-6; **1c**, 618-89-3; **1d**, 619-42-1; **1e**, 3132-99-8; **1f**, 99-90-1; **1g**, 101-55-3; **1h**, 39229-12-4;

(6) Lewis, G. E. *J. Org. Chem.* **1965**, *30*, 2433.

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

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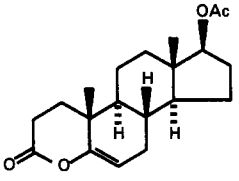
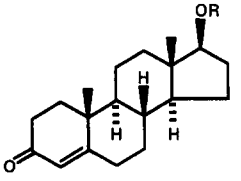
During the course of developing an improved synthesis of the benzindene prostaglandins, potent stable prostacyclin analogues,[1] we had occasion to investigate the direct conversion of an enol lactone to a cyclic α,β-unsaturated ketone. One of the most promising methods to accomplish this transformation, 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

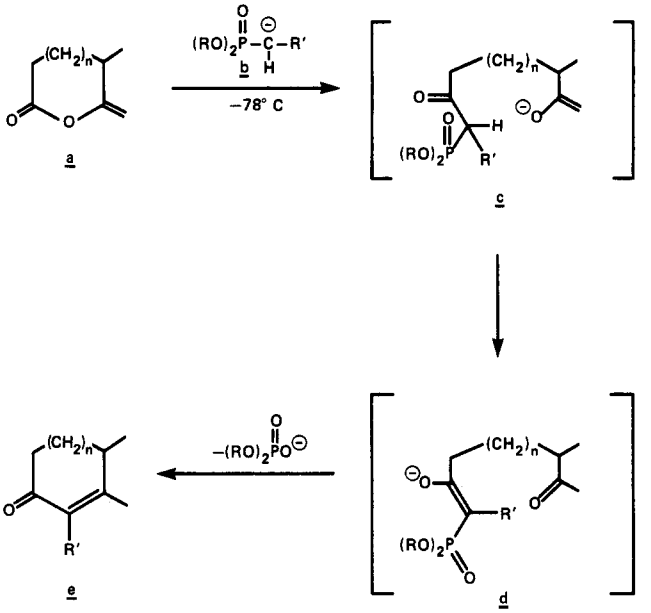


2 R=$COCH_3$

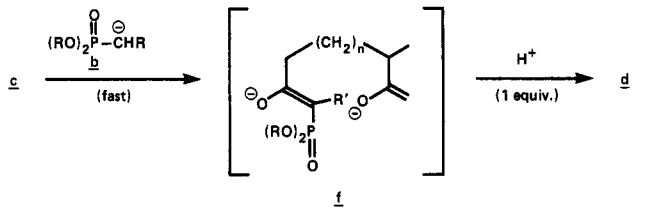
3 R=H

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.

0022-3263/85/1950-1765$01.50/0