

(0.1 g) for 3.5 h followed by evaporation, acidification, and dissolution in CHCl_3 . Evaporation produced a yellow syrup (15 mL) of the trimethyl ether of anthraquinone 17: IR (CHCl_3) 1715, 1670, 1590 cm^{-1} ; NMR (CDCl_3) 2.47-2.83 (2 H, m, $\text{CH}_2\text{CO}_2\text{CH}_3$), 2.90-3.47 (3 H, m, Ar CH_2 , CHCO_2CH_3), 3.88 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 7.17-8.13 (6 H, m, Ar H, CO_2H).

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Registry No. 4, 481-72-1; 7, 72036-12-5; 8, 72036-13-6; 8, free acid, 72036-14-7; 9, 72036-15-8; 10, 72036-16-9; 11, 72036-17-0; 11 dimethyl ester, 72036-18-1; 12, 72036-19-2; 15, 72036-20-5; 15 dimethyl ether, 72036-21-6; 15 methyl ester dimethyl ether, 72036-22-7; 16, 72036-23-8; 16 dimethyl ether methyl ester, 72036-24-9; 17, 72036-25-0; 17 dimethyl ester, 72036-26-1; 17 trimethyl ether, 72036-27-2; 17 trimethyl ether dimethyl ester, 72036-28-3; diethyl 2-carbethoxy-succinate, 7459-46-3.

Synthesis of Alkyl 4-Hydroxy-2-alkynoates

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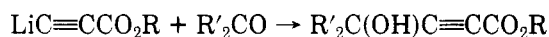
The lithium acetylide anion of ethyl or methyl propiolate is readily prepared by the addition of *n*-butyllithium to ethyl or methyl propiolate at low temperature. The anion rapidly adds to a variety of aldehydes or ketones to give ethyl or methyl 4-hydroxy-2-alkynoates in high yield.

We recently required a variety of alkyl 4-hydroxy-2-alkynoates and the corresponding 4-keto compounds for our studies on asymmetric reducing agents.² At the time of the initiation of this project there were no general procedures for preparing this class of compounds. Herein we report that the lithium anion of methyl or ethyl propiolate rapidly adds to a variety of aldehydes or ketones to give the corresponding alkyl 4-hydroxy-2-alkynoates in high yield.

Sodium or potassium salts of alkyl propiolates are reported to give low yields of addition product to ketones.³ Grignard reagents react in a complex manner with esters of propiolic acid and do not appear to cleanly form the desired acetylenic anion.⁴ It has been reported that the lithium anions of propiolic esters may be added to aldehydes although no details are given and the generality of the reaction was not demonstrated.⁵

We have found that the lithium acetylide salt of methyl or ethyl propiolate may be readily prepared at low temperature by the reaction of the propiolate ester with *n*-butyllithium.⁶ The acetylenic anion rapidly adds to a variety of aldehydes and ketones to give the methyl or

ethyl 4-hydroxy-2-alkynoates upon workup. The results are presented in Table I.



The lithium anions are relatively stable when kept at low temperature. The ethyl ester appears to be easier to handle than the methyl ester and may be prepared and used at -78°C (dry ice/acetone bath). On the other hand to achieve good results with the methyl ester, one must maintain the reaction at $<-100^\circ\text{C}$ (4:1:1 tetrahydrofuran-ether-pentane solvent; 4:1:1 low-boiling petroleum ether-acetone-isopropyl alcohol in liquid nitrogen slush bath). Either lithium compound decomposes to a black solution if warmed to 0°C and gives very little addition product upon subsequent reaction with an aldehyde or ketone.

The addition of the anion to aldehyde or ketones appears to be rapid and quantitative. Only in the reaction with acetophenone were appreciable amounts of ketone recovered. Workup is facilitated by protonation with acetic acid or saturated ammonium chloride at low temperature. The reaction may also be quenched by the addition of trimethylsilyl chloride. The trimethylsilyl group is then removed in the acidic aqueous workup. If the reaction mixture is allowed to warm to room temperature before quenching, there is a severe loss of product.

The secondary alcohols are readily oxidized to the alkyl 4-oxo-2-alkynoates with Jones reagent. Attempts to prepare the ketones directly by the reaction of the acetylide anion with an acid chloride⁷ gave poor yields of keto product.

This process provides a rapid, high-yield synthesis of a variety of alkyl 4-hydroxy-2-alkynoates. Such compounds are useful in the synthesis of lactones and other natural products.⁵ The observation that the corresponding ketones

(1) Fellow of the Alfred P. Sloan Foundation.

(2) Asymmetric reduction of the 4-keto compounds gives the hydroxy compounds in 77-100% enantiomeric purity. Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A., *J. Am. Chem. Soc.* in press.

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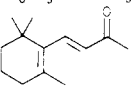
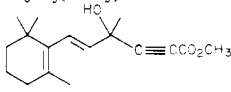

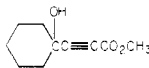

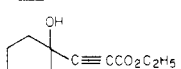
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(6) Suzuki reports that lithium diisopropylamide must be used as a base to avoid addition of *n*-butyllithium to the ester. (Yamada, K.; Miyaura, N.; Itoh, M.; Suzuki, A. *Synthesis* 1977, 679). We have found no interference by the ester group. In fact lithium salts of propargyl acetates may be prepared under similar conditions with no interference by the acetate (Midland, M. M. *J. Org. Chem.* 1977, 42, 2650).

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Table I. Preparation of Alkyl 4-Hydroxy-2-alkynoates from Lithium Acetylide Salts of Alkyl Propiolic Esters

alkyl group in ester	ketone or aldehyde	product ^a	% yield ^b
CH ₃	(CH ₃) ₂ CO	(CH ₃) ₂ COHC≡CCO ₂ CH ₃	91
C ₂ H ₅	C ₆ H ₅ COCH ₃	C ₆ H ₅ (CH ₃)COHC≡CCO ₂ C ₂ H ₅	63
CH ₃			74
CH ₃			74
C ₂ H ₅			85
C ₂ H ₅	CH ₃ CHO	CH ₃ CHOHC≡CCO ₂ C ₂ H ₅	59
C ₂ H ₅	<i>n</i> -C ₅ H ₁₁ CHO	<i>n</i> -C ₅ H ₁₁ CHOHC≡CCO ₂ C ₂ H ₅	73
CH ₃	C ₆ H ₅ CHO	C ₆ H ₅ CHOHC≡CCO ₂ CH ₃	71
C ₂ H ₅	C ₆ H ₅ CHO	C ₆ H ₅ CHOHC≡CCO ₂ C ₂ H ₅	84

^a All products exhibited satisfactory spectra in accord with the assigned structure. ^b Isolated yield.

may be reduced to chiral alcohols of high enantiomeric purity² further enhances the value of these compounds in synthesis.

Experimental Section

All reactions were run in dry apparatus under a nitrogen atmosphere by using syringe techniques.⁸ Tetrahydrofuran was distilled from potassium-benzophenone and stored under nitrogen. *n*-Butyllithium in hexane (Aldrich) was standardized by the method of Watson and Eastham.⁹ All ketones and aldehydes were obtained commercially. Aldehydes were distilled under nitrogen prior to use. Methyl and ethyl propiolate were obtained from Aldrich and Farchan and were used directly.

Methyl 4-Hydroxy-4-methyl-2-pentynoate. A dry 50-mL flask equipped with a magnetic stirring bar and septum-capped inlet was connected to a mercury bubbler and flushed with nitrogen. The flask was charged with 10 mL of a 4:1:1 mixture of tetrahydrofuran, ethyl ether, and pentane and 5 mmol of methyl propiolate. The flask was cooled to approximately -120 °C by using a 4:1:1 mixture of low boiling petroleum ether, acetone, and isopropyl alcohol with liquid nitrogen. A 5-mmol sample of *n*-butyllithium (3.13 mL of a 1.60 M solution) was then added dropwise. The solution was stirred for 5 min, and then 5 mmol of acetone was added. The mixture was stirred for 5 min, and then the cooling bath was removed. The flask was allowed to warm slightly, and 2 mL of a saturated ammonium chloride solution was added. After warming to room temperature, the organic phase was dried with potassium carbonate and the solvent removed on a rotary evaporator. The residue was distilled in a Kugelrohr apparatus [pot temperature 135 °C (30 mm)] to give 0.65 g of product (91%).

1-[2-(Carboethoxy)ethynyl]cyclopentanol. The reaction flask was charged with 10 mL of tetrahydrofuran and 5 mmol of ethyl propiolate. The solution was cooled to -78 °C, and 5 mmol of *n*-butyllithium was added. The solution was stirred for 10 min, and then 5 mmol of cyclopentanone was added. The mixture was stirred for 10 min, and then the bath was removed and the mixture allowed to warm slightly. Acetic acid, 1 mL, was added and the solution warmed to room temperature. Ethyl ether was added and the mixture washed with saturated sodium bicarbonate. The ether layer was dried with potassium carbonate and the ether removed on a rotary evaporator. The residue was distilled in a

Kugelrohr apparatus [pot temperature 110 °C (1 mm)] to give 0.77 g of product (85%).

Ethyl 4-Hydroxy-2-nonynoate. A 150-mL flask was charged with 70 mL of the tetrahydrofuran-ether-pentane solvent and 50 mmol of ethyl propiolate. The solution was cooled to -120 °C and 50 mmol of *n*-butyllithium added dropwise over 15 min. After an additional 10 min, 50 mmol of hexanal (6.0 mL) was added. The solution was stirred at -120 °C for 20 min, and then 75 mmol of trimethylsilyl chloride (9.25 mL) was added. The solution was warmed to room temperature and 50 mL of ethyl ether added. The mixture was washed with 100 mL of water. The organic layer was dried over magnesium sulfate and concentrated. The residue was distilled through a short-path distillation head; bp 112 °C (0.15 mm), yield 7.17 g (73%).

Ethyl 4-Oxo-2-nonynoate. The above alcohol (6.95 g, 35 mmol) was dissolved in 70 mL of acetone and cooled in an ice bath. Jones reagent,¹⁰ 23 mL, was added over 10 min. A 10-mL sample of ethanol was then added to destroy excess Jones reagent. The solution was stirred for 5 min and then diluted with 100 mL of water. The water was extracted with ether (2 × 30 mL). The ether extracts were washed with water, dried over magnesium sulfate, and concentrated. The product was distilled in a Kugelrohr apparatus [pot 100 °C (0.12 mm)] to give 5.2 g of product (76% yield).

Acknowledgment. We wish to thank the National Institutes of Health and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. Methyl propiolate lithium acetylide salt, 72036-29-4; ethyl propiolate lithium acetylide salt, 72036-30-7; acetone, 67-64-1; 1-phenylethanone, 98-86-2; 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one, 14901-07-6; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; acetaldehyde, 75-07-0; hexanal, 66-25-1; benzaldehyde, 100-52-7; methyl 4-hydroxy-4-methyl-2-pentynoate, 25294-59-1; ethyl 4-hydroxy-4-phenyl-2-pentynoate, 72036-31-8; 6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-hydroxy-4-methylhex-5-en-2-ynoate methyl ester, 72036-32-9; 1-[2-(carboethoxy)ethynyl]cyclohexanol, 72036-33-0; 1-[2-(carboethoxy)ethynyl]cyclopentanol, 72036-34-1; ethyl 4-hydroxypent-2-ynoate, 72036-35-2; ethyl 4-hydroxy-2-nonynoate, 72036-36-3; methyl 4-hydroxy-4-phenyl-2-butynoate, 33553-90-1; ethyl 4-hydroxy-4-phenyl-2-butynoate, 72036-37-4; methyl propiolate, 922-67-8; ethyl propiolate, 623-47-2; ethyl 4-oxo-2-nonynoate, 72036-38-5.

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