aqueous solutions of sodium fluoborate and the phosphonium halide. The phosphonium fluoborate which precipitates may be dried under vacuum and converted to the ylide in the usual way.[9]

(9) This work was supported by grants from the Sloan Foundation and the National Science Foundation (CHE 78-01769).

(10) Fellow of the Alfred P. Sloan Foundation (1978-1980).

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Selective Reduction via Enolate Protection

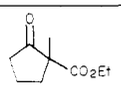
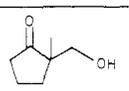
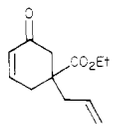
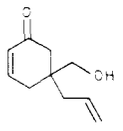
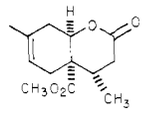
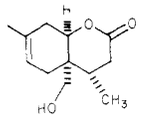
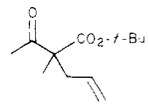
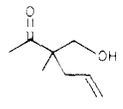
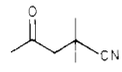
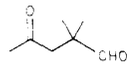
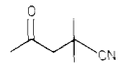
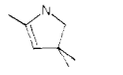
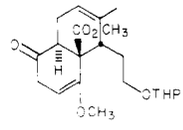
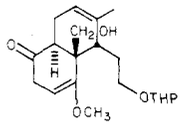
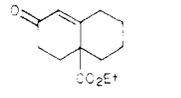
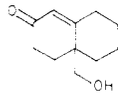
Summary: The use of enolate anions as protecting groups in order to effect the selective reduction of dicarbonyl compounds is studied.

Sir: Many procedures are available for the reduction of a ketone or aldehyde in the presence of an ester or lactone.[1] In order to achieve the complementary selectivity, a sequence involving protection, reduction, and deprotection must be employed. In addition to the obvious operational inconvenience, olefin isomerization and other acid-catalyzed rearrangements can occur during protection and deprotection. The concept of using selective enolate formation in combination with hydride reduction was first conceived by Barton[2] for the reduction of steroidal ketones. Both Schlessinger[3] and Goldsmith[4] have also used this method. However, aside from these interesting applications, no study of this reduction strategy has been reported. We now present an investigation of its scope and limitations.

Ketone deprotonation was effected with either lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide. These reagents are nonnucleophilic and capable of completely deprotonating ketones at low temperatures. The reducing agents employed included lithium aluminum hydride, diisobutylaluminum hydride, and lithium triethylborohydride. A variety of substituted dicarbonyl compounds was used. The results are illustrated in Table I.

This method is advantageous for the unambiguous synthesis of certain aldols, as evidenced by entries 1 and 4. Hirano and co-workers[5] have studied the acid-catalyzed aldol condensation between ketones and formaldehyde. Although the reaction of 2-methylcyclopentanone and formaldehyde affords a mixture of products, the major product is identical by NMR and IR with compound 1 prepared by our method. Reduction of the keto nitrile (entries 5 and 6) affords either a keto aldehyde or cyclic imine **2**, depending on the choice of reducing agents. The yields in both cases were somewhat reduced due to the volatility of the products. Imine **2** was identical by NMR with the compound produced by reduction of 4,4-dimethyl-5-nitro-2-pentanone.[6] The change in reaction conditions for entries 7 and 8 was necessitated by the extremely slow rate of reduction in tetrahydrofuran (incomplete after 48 h).

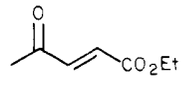
Table I. Selective Reductions

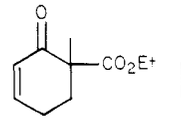
entry	reactant	reaction conditions	time, h	% yield	product[a]
1		A	1	76	 **1**
2		A	0.5	62	
3		A	0.5	65	
4		A	0.5	81	
5		B	2.0	46	
6		A	0.5	67	 **2**
7		C	8	95	
8		C	8	90	

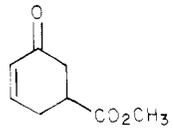
[a] All products exhibited satisfactory IR, ^{1}H NMR, ^{13}C NMR and mass spectral data and analytical analyses. See footnote 8 for experimental procedure.

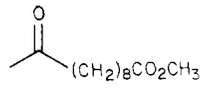
In contrast to the successful results in Table I, compounds I–IV failed to afford synthetically useful yields of the desired reduction products.

Thin-layer chromatography of the enolate solution[7]


I


III


IV


II

before the addition of the hydride reagent indicated, in the cases that failed, that new products have already begun to form. Thus, the failure was due to enolate anion instability. Such instability could arise from intramolecular

(1) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; Chapter 2.

(2) Barton, D. H. R.; Hesse, R. H.; Wilshire, C.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1075.

(3) Kieczykowski, G. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 1938.

(4) Goldsmith, D. J.; Lewis, A. J.; Still, W. C. *Tetrahedron Lett.* **1973**, 4807.

(5) Hirano, F.; Wakabayashi, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2579.

(6) Sheiman, B. M.; Dymova, S. F.; Spiro, V. B.; Kustanovich, I. M.; Berezovski, V. M. *Khim. Geterotsikl. Soedin.* **1971**, *7*, 475.

(7) TLC of enolate solutions in reactions which were successful showed only starting material. Aliquots for TLC could be either first quenched and then chromatographed or simply chromatographed directly.

0022-3263/80/1945-4262$01.00/0

cyclizations or anion exchange followed by polymerization. Efforts to circumvent this limitation by forming the magnesium enolate with (diisopropylamino)magnesium bromide or by deprotonation *and* reduction at −78 °C were unsuccessful.

Acknowledgment. We thank the National Cancer Institute (Grant No. CA23663) for generous financial support.

(8) A: enolate formation with *i*-Pr_2NLi in THF at −78 °C; $LiAlH_4$ added at −78 °C and solution warmed slowly to −40 °C; quench by pouring into cold dilute HCl. B: enolate formation with *i*-Pr_2NLi in THF at −78 °C; DIBAL added at −78 °C and solution warmed slowly to −20 °C; quench by pouring into dilute acetic acid. C: enolate formation with *i*-Pr_2NLi in benzene–hexane at −20 °C; DIBAL added at −20 °C and solution warmed slowly to 0 °C; quench by stirring in two-phase system of cold acetic acid and chloroform.

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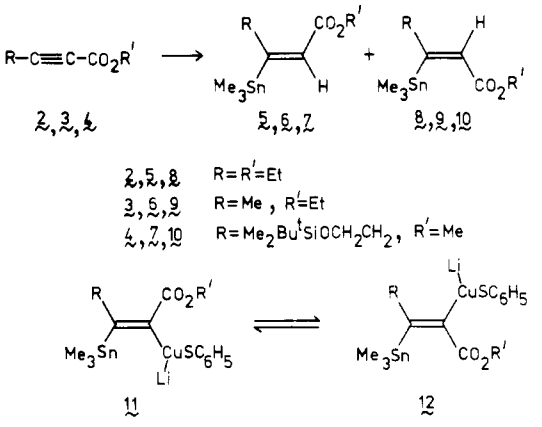
Stereoselective Conjugate Addition of Lithium (Phenylthio)(trimethylstannyl)cuprate to α,β-Acetylenic Esters. Preparation of (*E*)- and (*Z*)-4-Lithio-1,3-pentadienes and Their Reaction with Electrophiles

Summary: Depending on experimental conditions, reaction of lithium (phenylthio)(trimethylstannyl)cuprate (**1**) with α,β-acetylenic esters **2**–**4** affords, highly stereoselectively, either the (*E*)- (**5**–**7**) or the (*Z*)-β-trimethylstannyl (**8**–**10**) α,β-unsaturated esters. Two of the latter substances (**6** and **9**) were transformed into the geometrically isomeric 4-lithio-1,3-pentadienes (**16** and **20**, respectively), which react smoothly with electrophiles to afford products of general structures **21** and **22**.

Sir: Recently, we reported that lithium (phenylthio)(trimethylstannyl)cuprate [$C_6H_5S(Me_3Sn)CuLi$, **1**][1] is an excellent reagent for transferring, in a conjugate sense, the trimethylstannyl group to α,β-unsaturated carbonyl systems.[4] This reagent was shown to be particularly effective in converting β-iodo α,β-unsaturated ketones[5] into the corresponding β-trimethylstannyl enones, which, in principle, can serve as convenient precursors of β-acylvinyl anion equivalents.[6] We report herein (a) that the cuprate reagent **1** smoothly transfers one Me_3Sn group to α,β-acetylenic esters, (b) that the course of the reaction can be controlled experimentally so as to produce, *highly stereoselectively*, either the (*E*)- or the (*Z*)-β-trimethylstannyl α,β-unsaturated esters, and (c) that the products can be converted into functionalized 4-lithio-1,3-alkadienes, species which exhibit considerable promise as reagents in organic synthesis.

When ethyl 2-pentynoate (**2**) was allowed to react with 2.5 equiv of **1** at −100 °C (THF, argon atmosphere) for 6 h and the resultant solution was treated with methanol,

Scheme I



the two geometric isomers **5** and **8** were obtained (Scheme I) in a ratio of approximately 97:3 (81%).[7,8] The reaction could be carried out in a shorter time and with an even higher stereoselectivity by adding a THF solution of **2** *containing 1.7 equiv of methanol* to a solution (THF) of 2.0 equiv of the cuprate reagent **1** (−100 °C, 15 min; −78 °C, 3 h).[9] Under these conditions the conjugate addition product consisted of essentially pure *E* isomer **5** (79% yield, <1% **7**). On the other hand, reaction of **2** with 1.2 equiv of **1** at −78 °C for 15 min and at −48 °C for 4 h, followed by protonation (methanol) and workup, afforded (76%) the two isomers **5** and **8** in a ratio of 2:98, respectively. In similar fashion, ethyl 2-butynoate (**3**) could be converted into either ethyl (*E*)-3-(trimethylstannyl)-2-butenoate (**6**) (78% yield, >99% stereoselectivity) or the corresponding *Z* isomer **9** (76% yield, 98% stereoselectivity), and methyl 5-(*tert*-butyldimethylsiloxy)-2-pentynoate (**4**)[10] was transformed into either of the two isomers **7** (82% yield, 96% stereoselectivity) or **10** (81% yield, 96% stereoselectivity).[11]

It is clear from the above results that the *E* isomers (**5**–**7**) are the products of kinetic control, while the *Z* isomers (**8**–**10**) are produced under thermodynamically controlled conditions. Apparently, at low temperatures (e.g., −100 °C) the "kinetic" intermediate (cf. **11**) is reasonably stable and isomerizes only very slowly. At somewhat higher temperatures (e.g., −78 °C), isomerization of **11** into **12** does occur, but this transformation can be minimized by the presence of a proton source such as methanol (protonation of **11** faster than isomerization). If the reaction mixtures are allowed to warm to −48 °C in the absence of methanol, equilibration (**11** ⇌ **12**) takes place, with the equilibrium largely favoring intermediate **12**. Subsequent protonation results in the formation of the nearly pure *Z* isomers (**8**–**10**). These observations parallel to some extent those

(1) A dark red solution of this reagent is prepared simply by addition of 1 equiv of solid (phenylthio)copper[2] to a cold (−20 °C) solution of (trimethylstannyl)lithium[3] in THF.
(2) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662.
(3) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836.
(4) Piers, E.; Morton, H. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1033.
(5) Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *5*, 193.
(6) Piers, E.; Morton, H. E. *J. Org. Chem.* **1979**, *44*, 3437.

(7) The product ratios reported herein were determined by gas–liquid chromatography, employing a column ($^1/_8$ in. × 6 ft) packed with 3% OV-17 on Chromosorb W(HP) (80–100 mesh).
(8) All new compounds reported herein exhibited spectral data in full accord with assigned structures and gave satisfactory elemental analyses and/or high-resolution mass spectrometric measurements.
(9) If the reaction was allowed to proceed at −78 °C (3 h) in the absence of methanol, subsequent protonation produced a considerable amount of the *Z* isomer (**5**/**8** ratio of ~68:32).
(10) We are very grateful to Professor L. Weiler and Dr. P. E. Sum for a sample of the tetrahydropyranyl ether of methyl 5-hydroxypentynoate, which was readily transformed into compound **4**.
(11) The ^1H NMR spectra of the conjugate addition products fully corroborated the stereochemical assignments. For example, the vinyl methyl group of the *E* isomer **6** (methyl group cis to the CO_2Et group) gives rise to a doublet ($J \approx 2$ Hz) at δ 2.34. The corresponding signal derived from the *Z* isomer **9** (Me and CO_2Et in a trans relationship) is found, as expected, at higher field (δ 2.12, d, $J \approx 2$ Hz). Analogous differences are found in the other pairs of addition products (**5**, **8** and **7**, **10**).

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