

AN IMPROVED PROCEDURE FOR THE TWO CARBON HOMOLOGATION OF
ESTERS TO α,β -UNSATURATED ESTERS

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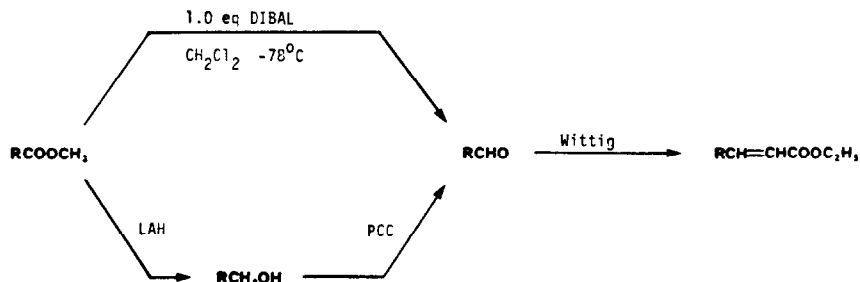
ABSTRACT: Treatment of esters with diisobutylaluminum hydride (DIBAL) in the presence of lithio-trialkylphosphonoacetate results in improved yields of the homologated α,β -unsaturated esters. The problematic overreduction, which has previously been observed in the half reduction of esters using DIBAL, is minimal (<3%) under these conditions.

In recent years the condensations of aldehydes with weak carbon nucleophiles, often under the influence of Lewis acid catalysis, have been widely exploited as practical means of controlling relative stereochemistry in acyclic systems.¹ The application of these methods toward efficient carbocyclization procedures are relatively limited. The development of these intramolecular strategies would be facilitated by new methodologies for the *in situ* generation of aldehydes from stable precursors under neutral or Lewis acidic conditions. Toward this end we have investigated the half-reduction of esters carried out in the presence of carbon nucleophiles derived from trialkylphosphonoacetates.² Our results provide an improved procedure for the two-carbon homologation of esters to α,β -unsaturated esters.

The homologation of esters to α,β -unsaturated esters is a very common functional group interconversion encountered in the course of organic synthesis. The transformation is usually performed by half reduction of the ester to the aldehyde followed by subsequent Wittig olefination. Diisobutylaluminum hydride (DIBAL) is typically the reducing agent employed. While DIBAL is quite efficient for the half reduction of 5- and 6-membered ring lactones, competing overreduction is often observed when simple alkyl esters or medium ring lactones are employed as the substrate. For example, slow addition of a cooled solution of DIBAL (50 mmol) to a cooled solution of caprolactone (50 mmol) in methylene chloride gave upon work-up only a 60% yield of the desired lactol contaminated with 20% each of the 1,6-hexanediol and recovered starting lactone.

This overreduction is usually minimized through the use of nonpolar solvents at very low temperatures (-100°C) or by the use of special ester groups, for which breakdown of the tetrahedral intermediate obtained upon initial reduction is relatively slow.³ Alternatively, a two-step procedure involving complete reduction to the primary alcohol followed by re-oxidation to the aldehyde is frequently employed (Figure I).

Figure I





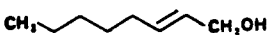
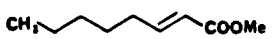
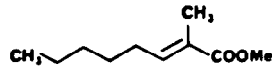
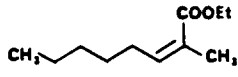
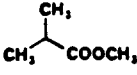
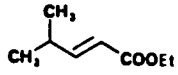
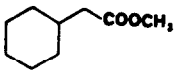
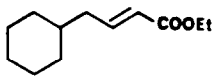
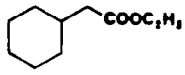
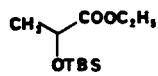
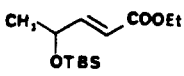

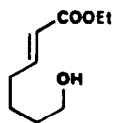
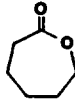
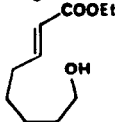
The DIBAL reduction (THF -78°C) of saturated esters and lactones in the presence of phosphonate anions leads to good yields (60-80%) of the homologous esters with little or no overreduction of either the starting or the product esters. For example, caprolactone is smoothly transformed under the conditions of this one-pot procedure to the corresponding unsaturated hydroxy ester (eq 1). Careful analysis of the crude reaction mixture shows less than 3% of the overreduction products, 1,6-hexanediol and 1,8-oct-2-enediol. The product, ethyl 8-hydroxy-2-octenate, is isolated in 62% yield with $> 95\%$ E stereochemistry.



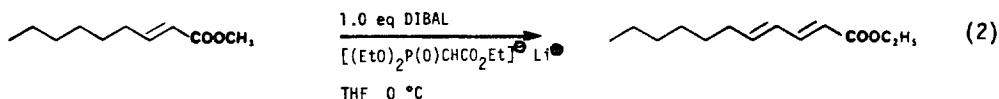
We have examined a number of substrates and these reaction conditions appear to be quite generally applicable (Table I). The observed E/Z olefin ratios are comparable to those that can be obtained by starting with the corresponding isolated aldehyde. Olefin isomer ratios are usually slightly higher when triethyl- rather than trimethylphosphonoacetate is employed (entries A and C). Often the isomer ratio is markedly dependent upon the metal counterion used with the phosphonate anion. In general, lithio anions are the preferred reagents. Using excess (3.2 eq) of DIBAL, under otherwise identical conditions, the corresponding allylic alcohol can be prepared directly from the ester (entry B). The procedure is compatible with methodologies developed for the selective formation of E - and Z -trisubstituted olefins (entries D and E).⁴ Alkyl substituents α or β to the ester moiety are tolerated as is an α -silyloxy substituent (entries F-I). Ethyl esters and lactones react with equal facility relative to methyl esters.

Observations in our laboratories suggest that α,β -unsaturated esters are reduced by DIBAL only slowly at -78°C , a fact which we believe in part accounts for the success of this chemistry.⁵ In contrast to the results summarized in Table I, methyl benzoate gives a poor

Table I. Two-Carbon Homologation of Esters and Lactones to α,β -Unsaturated Esters.

| ENTRY | SUBSTRATE | PHOSPHONATE | BASE | PRODUCT | YIELD | E:Z |
|-------|---|--|----------------|--|-------|-------|
| A |  | $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ | n-BuLi |  | 86 | 90:10 |
| B | " | $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ | n-BuLi |  | 70 | 90:10 |
| C | " | $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$ | n-BuLi |  | 81 | 85:15 |
| D | " | $(\text{EtO})_2\text{P}(\text{O})\text{CH}(\text{CH}_3)\text{CO}_2\text{Et}$ | NaH |  | 77 | 82:18 |
| E | " | $(\text{EtO})_2\text{P}(\text{O})\text{CH}(\text{CH}_3)\text{CO}_2\text{Et}$ | KH/Crown ether |  | 63 | 9:91 |
| F |  | $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ | n-BuLi |  | 72 | 92:8 |
| G |  | " | " |  | 75 | 91:9 |
| H |  | " | " | " | 81 | 91:9 |
| I |  | " | " |  | 72 | 90:10 |
| J |  | " | " |  | 71 | 95:5 |
| K |  | " | " |  | 62 | 95:5 |

yield of methyl cinnamate under our standard reaction conditions and significant amounts of overreduction products are obtained. Under similar conditions (THF -78°C) the reduction/olefination of methyl 2-octenate gives only a poor yield of conjugated diene. However, this methodology is not limited to saturated esters as simply running the reaction at 0°C , under otherwise identical conditions, leads to formation of these conjugated diene ester in 70% yield.



The intramolecular Wittig olefination provides an efficient macrocyclization procedure, however, the aldehyde substrates are often difficult to prepare.⁶ This present methodology permits the more readily accessible ester to be used in place of an aldehyde. This reduction/olefination of the readily prepared phosphonate diesters should yield the macrocyclic unsaturated lactone. Further studies on the applications of this chemistry are in progress.



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Sample Procedure: Preparation of E-ethyl 8-hydroxy-2-octenate. To a cooled (-78°C) solution of 12.8 g (57.5 mmol) of triethylphosphonoacetate in 300 mL of THF was added 23 mL (59.8 mmol) of a 2.6 M solution of n-butyl lithium in hexanes. To the resulting solution was added 6.18 g (54.1 mmol) of caprolactone. The solution was equilibrated at -78°C then 36 mL (54 mmol) of a 1.5 M solution of Dibal in toluene was added at the rate of 1 mL/min. The resulting mixture was slowly warmed to room temperature (8h) then quenched with excess $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$. The mixture was filtered, dried, concentrated *in vacuo*, and chromatographed on silica to yield 6.2 g (62%) of E-ethyl 8-hydroxy-2-octenate as a colorless liquid.

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