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GENERATION OF ESTER ENOLATES BY REDUCTIVE α-DEACETOXYLATION

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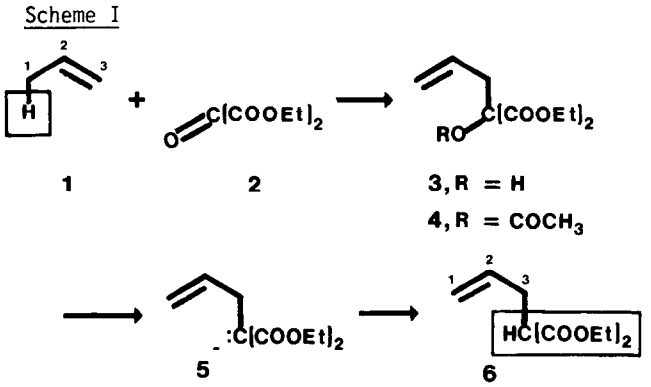
Diethyl allylmalonates or 2-arylalkanoic esters are prepared in good yield by reductive α-deoxygenation of the corresponding α-acetoxy or α-alkoxy esters. Since the intermediate ester enolates are generated under aprotic conditions, a one pot reductive-alkylation is also possible. One application of this procedure allows diethyl oxomalonate to serve as a conjunctive reagent for stitching together an alkene and an alkyl halide with a malonyl group as linchpin.

Ene reactions of diethyl oxomalonate[1] (DEOM) replace allylic hydrogen with an α-hydroxymalonyl group (scheme I) by a pericyclic mechanism requiring allylic rearrangement. The consequent

Scheme I

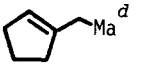
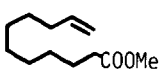
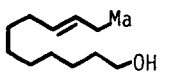
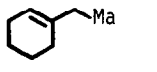
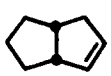
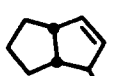
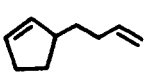
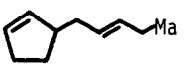
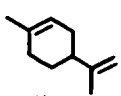
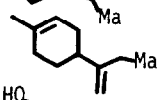
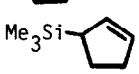
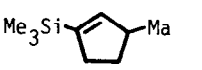
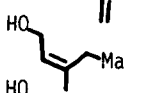
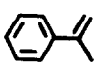
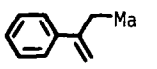
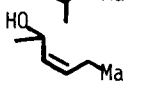


prospect of a novel regiocontrolled synthesis of diethyl allylmalonates 6 from alkenes 1 and DEOM (2) prompted us to seek a method for reductive conversion of a α-hydroxymalonates 3 into malonate anions 5. Thus, although ester enolates are generally prepared by deprotonation of the corresponding esters[2] or reductive cleavage of α-haloesters,[3] analogy with ketones[4] suggested that generation of the synthetically useful ester enolate intermediates by reductive α-deoxygenation might be feasible. A crucial step in the method developed (*vide infra*) is

conversion of the 3° alcohols 3 into the corresponding acetates 4. Although acetic anhydride in pyridine is ineffective for these difficult acylations, 4-(N,N-dimethylamino)pyridine catalyzes rapid, high yield acetylation.[5]

Reductive α-deoxygenation of hydroxy or acetoxy ketones can be accomplished by various dissolving metal and related reactions. However, both 3 and 4 are recovered unreduced after treatment with zinc in acetic acid,[6] chromous chloride in aqueous acid-acetone,[7] or aluminum amalgam in aqueous ethanol.[8] Although a poor yield of an allylmalonate was obtained by reductive deoxygenation of an α-hydroxymalonate 3 with lithium in liquid ammonia, the α-acetoxy derivatives 4 are deacetoxylated in good yields with this reagent[3,4] (Table I). Even better yields are ob-

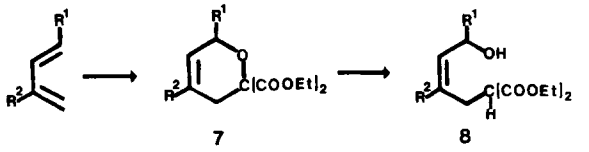
Table I: Diethyl Allylmalonates from Alkenes and 1,3-Dienes

Entry	Olefin	Reduction Product[a]	Method[b]	Yield[c] (%)	Entry	Olefin	Reduction Product[a]	Method[b]	Yield[c] (%)
		 Ma[d]	A B	77 66		 COOMe	 Ma OH	B	43
		 Ma	A	73				A	95
		 Ma	A	93			 Ma Ma	A	72
	 Me_3Si	 Me_3Si Ma	A B	86 73			 HO Ma	A	75
		 Ma	A	78			 HO Ma	A	70

[a] *Ene adducts 3 (entries 1-8) are prepared in 50-90% yields according to reference 1 and acetylated in near quantitative yields according to reference 5; Diels-Alder adducts 7 entries 9,10) are prepared according to reference 11 in 75-80% yields;* [b] *For reduction reaction conditions see footnote 10;* [c] *From acetoxy malonate 4 or alkoxy malonate 7;* [d] $Ma=CH(COOEt)_2$

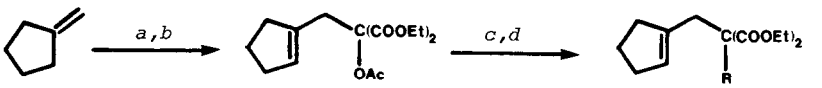
tained by adding a solution of sodium α-(N,N-dimethylamino)naphthalenide[9] in hexamethylphosphoramide to a solution of the acetylated ene adduct 4 in benzene (see entries 1 and 4). The dark green color of the naphthalenide anion is discharged rapidly, and the reduction can be done as a titration.[10] This procedure permits selective deoxygenation of the acylated ene adduct of DEOM with α-methylstyrene (entry 5). Use of excess reducing agent in this case results in reduction of the C=C bond which is conjugated with an aromatic ring. However, we were unable to avoid reduction of an isolated carbomethoxyl group (as in entry 6) by titration with a naphthalenide solution.

Reductive cleavage is also effective for the α-alkoxymalonate products 7 from Diels-Alder reaction of DEOM with 1,3-dienes (entries 9,10).[11] Again, impressive control of the site of C-C bond formation is achieved, in these cases owing to the high structural specificity of the Diels-Alder reactions. The overall transformation achieves 1,4 carbohydroxylation of 1,3-dienes affording diethyl Z-(4-hydroxy-alk-2-enyl)propanedioates 8 stereoselectively.



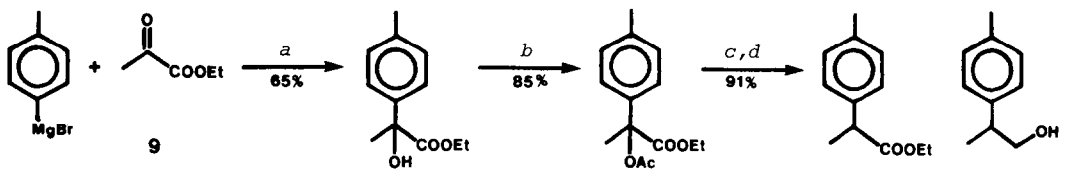
7 8

An additional useful aspect of naphthalenide reductions of acetylated DEOM ene adducts 4 is the possibility of *in situ* alkylation of the intermediate malonyl carbanions 5 (see scheme I). This allows net replacement of allylic hydrogen by a variety of diethyl alkylmalonyl groups. The versatility of the method is illustrated for methylenecyclopentane.[12]



a) DEOM; b) Ac_2O/Et_3N/DMAP; c) Na^+α-(Me_2N)-Naphthalenide$^-$; d) RX (yield): i-PrI (91%); EtI (81%); MeI (73%); allyl bromide (81%).

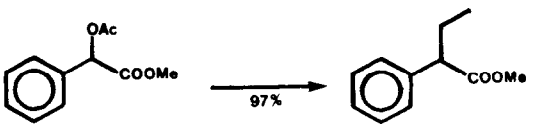
Generation of ester enolates by reductive α-deoxygenation is not limited to malonic esters. Thus, hydroxy ester 10, available[13] from ethyl pyruvate (9), affords 12 upon Li/NH_3 reduction



9 10 11 12 13

a) -78°C/Et_2O; b) Ac_2O/Et_3N/DMAP; c) Li/NH_3; d) NH_4Cl

of the derived acetate 11. A solution of 11 in ether is added dropwise to a solution of Li in liquid NH_3 until the blue color is just discharged, and then NH_4Cl is added to quench any strong base. If NH_4Cl is added in the presence of excess Li, 12 is reduced further to 13. Reductive alkylation[12] of acetate 14, prepared from methyl mandelate, affords 15 in excellent yield. Further studies on applications of α-deoxygenation for ester enolate generation are in progress.



14 15

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10. Except with sensitive substrates (e.g., Table I entry 5), a slight excess of reducing agent was used. Representative experimental procedures follow. Method A: A stock solution of reducing agent is prepared under dry nitrogen by stirring a mixture of sodium (24 mmol), α-(N,N-dimethylamino)naphthalene (20 mmol) and hexamethylphosphoramide (20 mL) for 15 hr. This solution can be stored for at least a week at room temperature without appreciable decomposition. Similar solutions in tetrahydrofuran or 1,2-dimethoxyethane are less stable. Reducing reagent solution is added dropwise (1-2 mL is required) with a syringe under dry nitrogen to a solution of acetate (0.5 mmol) in dry benzene (2 mL) until the green color persists for 20-30 sec. The product is isolated by quenching the reaction mixture with cold 10% HCl (20 mL) and extracting with ether (3 x 20 mL) followed by preparative TLC or Kügelrohr distillation of the crude product. Method B: A solution of the acetate (3 mmol) in anhydrous ether (6 mL) is added dropwise to a stirred solution of Li (16 mmol) in liquid NH_3 (40 mL). After stirring for 3 hr., the reaction mixture is quenched with excess granular NH_4Cl. Evaporation of the NH_3 and acidification with 10% HCl followed by extraction with ether affords crude product which is distilled under reduced pressure.

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12. Procedure identical with Method A above[10] except that excess alkyl halide (1.1 equiv) is added and the resulting mixture stirred for 30 min. before aqueous acidic quenching.

13. Addition of the organometallic in ether to a solution of 9 at -78°C gave double the yield obtained previously by addition of the ketoester to the organometallic without cooling: Lapkin, I.; Golovkova, A.I. J. Gen. Chem. USSR 1948, 18, 485-94.

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