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STEREOSELECTIVE SYNTHESES OF BOTH Z- AND E-β-ACYLOXY-α,β-UNSATURATED ESTERS AND THEIR STEREOSPECIFIC CONVERSION TO β-ALKYL-α,β-UNSATURATED ESTERS

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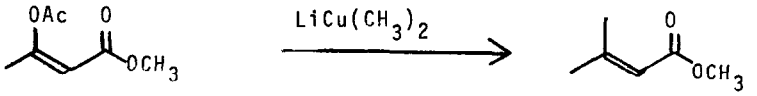
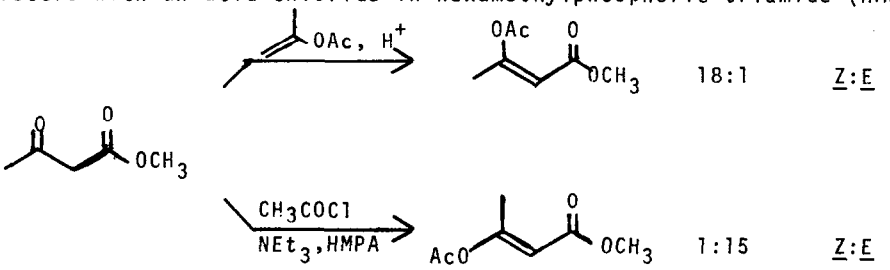
The reaction of lithium diorganocuprates with β-acetoxy-α,β-unsaturated carbonyl compounds gives substituted α,β-unsaturated carbonyl compounds in high yields and moderate stereospecificity.[1]



We now describe highly stereoselective syntheses of both Z- and E-β-acyloxy-α,β-unsaturated esters and an improved, more highly stereospecific procedure for the reaction of these enol esters with lithium diorganocuprates. The combination of these reactions allows the stereoselective conversion of β-ketoesters into either the Z or E isomer of β-dialkyl-α,β-unsaturated esters.

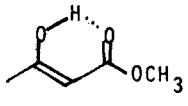
The Z isomer of β-acetoxy-α,β-unsaturated esters is formed almost exclusively in the acid catalyzed reaction of β-keto esters with isopropenyl acetate.[2] In contrast, the E isomer is formed in the triethylamine promoted reaction of β-keto esters with an acid chloride in hexamethylphosphoric triamide (HMPA).



Both the acid and base catalyzed procedures gave enol esters in moderate to excellent yields and with greater than 93% stereoselectivity (Table I). Benzoyl chloride and pivaloyl chloride gave higher yields of enol esters than did acetyl chloride in the base catalyzed procedure. The lower yields obtained with acetyl chloride may be due to the competing formation of ketene[3] which is known to react with acetoacetic esters to give predominantly C-acylated products.[4] For synthetic purposes, the E enol benzoates are the preferred intermediates since they can be prepared in high yield and since their reactions with cuprates proceed in high yield and with high stereospecificity.

The following experiment provides details of a typical preparation on an E enol ester. Benzoyl chloride (17 g, 0.12 mol) was added dropwise over 30 minutes to a stirred solution of methyl acetoacetate (11 g, 0.095 mol) and triethylamine (12 g, 0.12 mol) in 20 ml HMPA maintained below 0° by an ice-salt bath. The reaction mixture was stirred at room temperature for 2.5 hours and worked up by the addition of 50 ml of water and 50 ml ether, separation, and extraction of the water layer with two 50 ml portions of ether. The combined ether layers were washed with water and with saturated aqueous sodium chloride, dried ($MgSO_4$), and distilled to give methyl (E)-3-benzoyloxy-2-butenoate [19.3 g; 92.5%; 19:1 E:Z by gas chromatography; bp 109-111° (0.4 mm)].

The dramatic differences in the ratio of isomeric enol acetates obtained in these two procedures can be explained in terms of the stereochemistry of the different reactive forms of methyl acetoacetate in acidic and basic media. Under acidic conditions the reactive form of methyl acetoacetate is probably the internally hydrogen bonded Z enol 1. In contrast, the reactive form of methyl acetoacetate in HMPA containing triethylamine is probably the solvent separated ion 2. The E conformation of 2 would be preferred since the oxygen atoms bearing negative charge are maximally separated.



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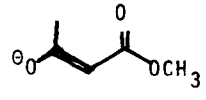

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In tetrahydrofuran, a solvent less likely to support solvent-separated ion

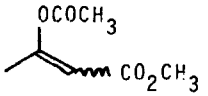
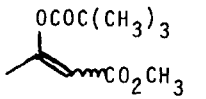
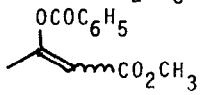
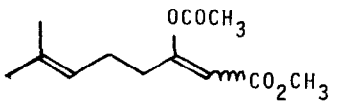
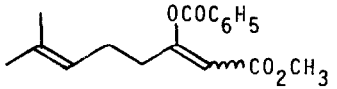
pairs than HMPA, the reaction of methyl acetoacetate, acetyl chloride, and triethylamine leads to a 56% yield of methyl 3-acetoxy-2-butenoate with a reduced 1.65:1 E:Z preference.[5]

Previously we reported[1] that the reaction of methyl (Z)-3-acetoxy-2-butenoate with 1.2 equivalents of lithium diethylcuprate in ether at -78° gives a 1:1 ratio of methyl (Z)- and (E)-3-methyl-2-pentenoate in 52% yield. We have now been able to optimize the yield and stereospecificity of the reaction. A 5:1 ratio of methyl (Z)- and (E)-3-methyl-2-pentenoate can be obtained in 97% yield using 4-5 equivalents of $(CH_3CH_2)_2CuLi \cdot PBu_3$[7] at -100° followed by addition of excess ethyl iodide[8] at -100°. High yields and stereospecificities have also been obtained in the cuprate reactions listed in Table I.

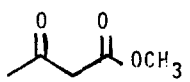
Acknowledgement. We wish to thank Eli Lilly Company for generous support of this research.

1. C.P. Casey, D. F.Marten and R. A. Boggs, Tetrahedron Lett., 2071 (1973).
2. R. Filler and S. M. Nagui, Tetrahedron, 19, 879 (1963). Although the isomer ratio was not reported, we found the reaction to be very stereoselective (see Table).
3. M. W. Rathke and D. F. Sullivan, Tetrahedron Lett., 1297 (1973).
4. H. Eck and H. Prigge, Liebigs Ann. Chem., 731, 12 (1970).
5. M. Suama, Y. Murato, K. Ichikawa, Nippon Kasaku Zasshi, 91, 162 (1970); C.A., 73, 24604h (1970). This work reports the reaction of ethyl acetoacetate with benzoyl chloride and acetyl chloride in pyridine. Benzoyl chloride gives a 11:89 ratio of Z:E isomers while acetyl chloride gives a 26:74 ratio.
6. C. P. Casey and D. F. Marten, Synth. Commun., 3, 321 (1973).
7. Prepared from 2 eq ethyllithium in benzene (Foote Mineral Co.) and 1 eq. $CuI \cdot PBu_3$ at -100° in ether.
8. If ethyl iodide is not added as much as 30% methyl crotonate is formed under these conditions.

TABLE I. Synthesis of Enol Esters and Their Reactions with $LiCuR_2$

β-Keto Ester	Acylation Conditions	Enol Ester[i]	Z:E	% Yield[c]	$LiCuR_2$ R=	Temp °C	Product[i]	Z:E[d]	% Yield[b]
3	$CH_3(OAc)C{=}CH_2$ TsOH		18:1[d]	79	C_2H_5[a]	-100	5	4.9:1	97
3	CH_3COCl NEt_3,HMPA	"	1:15[d]	56	C_2H_5[a]	-100	5	1:7.6	81
3	$(CH_3)_3CCOCl$ NEt_3,HMPA		1:20[d]	92	C_2H_5[a]	-100	5	1:6.1	63
3	C_6H_5COCl NEt_3, HMPA		1:19[d]	93	C_2H_5[a]	-100	5	1:8.1	72
3	"	"	1:19[d]	93	CH_3[g]	-78	6	----	100
4	$CH_3(OAc)C{=}CH_2$ TsOH		>20:1[e]	90	CH_3[g]	-78	7	1:10.3	84[d,f]
4	CH_3COCl NEt_3,HMPA	"	1:12[e]	55	CH_3[g]	-50	7	7.1:1	86
4	C_6H_5COCl NEt_3,HMPA		<1:20[e]	86	CH_3[h]	-64	7	5.8:1	100

a. Procedure involves 4-5 equivalents of $LiCuEt_2{\cdot}PBu_3$ at -100° for 10-15 min followed by excess ethyl iodide at -100° for 10 min. b. Yield determined by G.C. c. Yield of isolated products. d. Isomer ratio determined by G.C. and NMR. e. Isomer ratio estimated by NMR. f. See Ref. 6. g. 2.0 equivlaents $LiCuMe_2$ were used. h. 2.7 equivalents $LiCuMe_2$ were used. i. The ir, nmr and high resolution mass spectra were in agreement with the assigned structures of all compounds reported.



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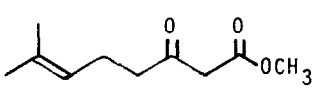

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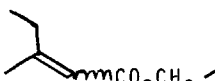

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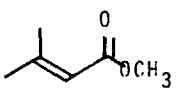

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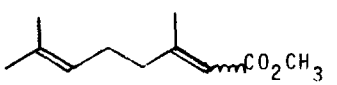

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