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A PRACTICAL SYNTHESIS OF (Z)-3-ALKENOATES

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Summary: Deconjugative protonation of (E)-2-alkenoate with bulky alkoxy group using potsssium disilazide as the base gives (Z)-3-alkenoate selectively.

In connection with other projects we have seeking a general route to alkyl (Z)-3-alkenoates with high stereoselectivities. Among several synthetic routes available, the α,β-unsaturated ester is an especially attractive synthetic intermediate for several reasons including accessibility from a simple aldehyde via Wittig reaction. Two recent publications[1] described that deprotonation of ethyl (E)-2-alkenoates with LDA in THF-HMPA yields after protonation the double bond migrated Z-3-isomer as major products. Thus, "electrophilic discharge of the Li dienoate from the ester of an (E)-2-alkenoate leads stereospecifically the (Z)-3-alkenoate ester unless the C-4 carbon bears a substituent larger than CH_3 beyond which the reaction becomes increasingly stereorandom."[1b] This communication describes a simple and yet useful solution to this problem for effecting such transformation with high stereoselectivities.

Deconjugative alkylation of the enolate anion derived from ethyl crotonate was first reported independently by Rathke and Schlessinger.[2] A major experimental concern in generating crotonic enolates was the possibility that the base employed for these reactions might also act as a nucleophile. An essentially non-nucleophilic form of lithium diisopropylamide was realized by the formation of 1:1 complex with HMPA and no Michael addition to ethyl crotonate was observed with this base mixture. Under standard reaction conditions an ester of dodecenoic acid was added to a slight excess of LDA in THF-HMPA at -78°C. The enolate thus obtained was quenched after 30 min with water. After usual workup the product was analyzed by GC in which the new double bond stereochemistry was approximately 85:15 Z/E.

A variety of likely amides were explored with every bulky amines. We now discovered a much more effective non-nucleophilic base for this transformations. Thus, in the case of ethyl (E)-2-dodecenoate, chosen as representative long chain ester, reaction with a few of the bases provides the Z/E ratios shown in Table 1. Clearly potassium disilazide in the absence of HMPA gave the most satisfactory results for the above transforamtions. Furthermore, the ratio is significantly enhanced as the size of the alcohol group increases, and in praticular, the use of 2,4-dimethyl-3-pentanol ester leads to the almost exclusive formation of Z-esters (Z:E = 97:3). These findings are general for a variety of simple α,β-unsaturated esters and obviously has great synthetic utility. A typical experimental procedure follows.

2,4-dimethyl-3-pentyl (E)-2-dodecenoate (1). To a solution of LDA (75 mmol) in dry THF (100 ml) and HMPA (13 ml) was added phosphonoacetate **2**[3] (22.1 g, 75 mmol) dropwise at 0°C under nitrogen. The resulting solution was stirred at 0°C for 15 min and decanal (14 ml, 75 mmol) was added dropwise at 0°C. Whole mixture was stirred 30 min at 0°C, and 30 min at room tempeature. After usual workup, the product was purified by column chromatography to give the E-ester **1** as a colorless oil (18.3 g, 84%).

Isomerization of the E-ester **1**. Potassium (391 mg, 10 mmol) was added to a solution of naphthalene (1.28 g, 10 mmol) in dry THF (6 ml) at room temperature under nitrogen, and the resulting deep-green solution was stirred 1 h. The solution was cooled to 0°C and treated with hexamethyldisilazane (3.2 ml, 15 mmol) to generate a solution of $KN(SiMe_3)_2$. To a stirred solution of 2,4-dimethyl-3-pentyl (E)-2-dodecenoate (163 mg, 0.55 mmol) in dry THF (4 ml) was added the above solution of $KN(SiMe_3)_2$ (0.8 ml, 0.8 mmol) at -78°C. The resulting dark red solution was stirred 2 h at -78°C to complete the isomerization. The reaction was quenched with saturated NH_4Cl at -78°C and the product was extracted with ether. Chromatographic purification affords the desired 2,4-dimethyl-3-pentyl (Z)-3-dodecenoate (**3**) as a colorless liquid (105 mg, 64%).

1 3 (Z / E = 97:3)

Table 1. Base catalyzed isomerization of (E)-2-dodecenoate[a]

Entry	1	Reaction Conditions				3	
	R-	Base	HMPA	Solvent	Temp.(°C)	Yield(%)	Z/E[b]
1	Et	LDA	3 equiv	THF	-78	85	84:16
2	Et	$KN(SiMe_3)_2$	1 equiv	THF	-78	84	85:15
3	Et	$KN(SiMe_3)_2$	———	THF	-78	75	90:10
4	Et	$KN(SiMe_3)_2$	———	DME	-78	84	88:12
5	Et	$KN(SiMe_3)_2$	———	Diglyme	-78	49	93: 7
6	$CH(^iPr)_2$	LDA	3 equiv	THF	-78	85	84:16
7	$CH(^iPr)_2$	$KN(SiMe_3)_2$	1 equiv	THF	-78	80	94: 6
8	$CH(^iPr)_2$	$KN(SiMe_3)_2$	———	THF	-78	64	97: 3
9	$CH(^iPr)_2$	$KN(SiMe_3)_2$	———	DME	-40	94	89:11
10	$CH(^iPr)_2$	$KN(SiMe_3)_2$	———	DME	-60	79	92: 8
11	$CH(^iPr)_2$	$KN(SiMe_3)_2$	———	Diglyme	-60	81	90:10
12	$CH(^iPr)_2$	$KN(SiMe_3)_2$	———	THF	-100	c	———

[a] Unless otherwise specified all the reaction was conducted on 0.5-1 mmole scale as described in text. [b] Z/E ratio was determined by GC on a 25-m PEG-HT capillary column. [c] Low conversion and the starting material was recovered.

References and Notes

1. (a) E.-P. Krebs, Helv. Chimica. Acta, **94**, 1023 (1981); (b) A. S. Kende and B. H. Toder, J. Org. Chem., **47**, 163 (1982).
2. M. W. Rathke and D. Sullivan, Tetrahedron Lett., 4249 (1972); J. L. Herrmann, G. P. Kieczykowski, and R. H. Schlessinger, ibid., 2433 (1973).
3. Prepared from $P(OEt)_3$ and 2,4-dimethyl-3-pentyl bromoacetate (87%).

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