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A CONVENIENT ROUTE TO α,β-UNSATURATED METHYL KETONES APPLICATION TO RETINAL ANALOGUE SYNTHESIS

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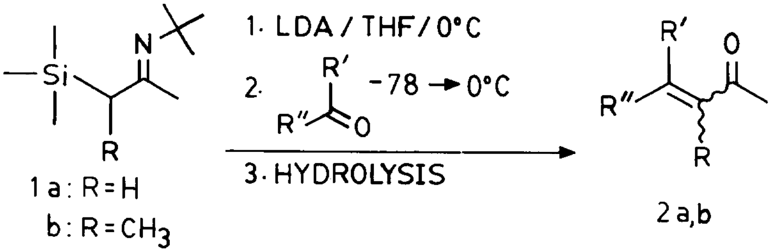
Abstract: Deprotonated ketimines 1a,b add to aldehydes and ketones to provide tri- and tetra-substituted α,β-unsaturated methyl ketones 2a,b with substantial percentage of Z-geometry which are not readily accessible by other methods.

Although numerous methods are currently available to effect a formal condensation of acetone or methyl ethyl ketone with aldehydes to form α,β-unsaturated methyl ketones, we have found no one step procedure which will give a substantial amount of Z isomer when applied to retinal synthesis. Futhermore, multistep procedures[1] to condense methyl ethyl ketone with retinoid polyenones gave very little of the desired E or Z tetra-substituted methyl ketones. Since α-silyl aldimines[2] and esters[3,4] reliably provide a good percentage of Z-adducts with aldehydes as well as ketones in condensation reactions, we investigated the use of α-silyl ketimines 1a,b as methyl ketone aldol equivalents as indicated in the Scheme.



Silyl ketimine 1a[5] was prepared from acetone t-butyl imine[6] according to the basic procedure described by Corey et al.[2] for the preparation of silyl aldimines. Deprotonation of 1a with LDA in THF at 0°C occurred exclusively α to the silyl group as ascertained by methyl iodide quenching to give 1b only.[7] Reaction of 1a with various aldehydes and ketones according to the Scheme gave a modest yield of the desired products. The results in the Table demonstrate entry into both isomeric series, with the Z-isomer predominating in some cases. Hydrolysis was readily achieved with wet silica gel, this feature being highly desirable for acid labile compounds (e.g., retinoids).

The results with 1b are variable and moreover, the intermediate imines resisted wet silica gel hydrolysis thus necessitating an oxalic acid workup.[2] However this procedure is still more effective than other multistep procedures.[1] For example, the condensation of 1b with β-ionone (entry 1) gives the tetra-substituted methyl ketone (83% Z, 52% overall). Attempts by us to prepare this compound by multistep procedures involving Wittig reagents, aldol type condensations or variants of the McMurry[8] coupling reaction failed.

A typical experimental procedure involves the addition of 1.05 eq. of 1a or 1b to 1.10 eq. of LDA at 0°C and stirring for one hour. The reaction mixture is cooled to -78°C and the aldehyde or ketone is added. After stirring 15 min., the reaction is allowed to warm to 0°C, then transferred to a wet silica gel slurry.[9] If 1b was used, 400 mg oxalic acid per 1.5 mmol. 1b is then added to the slurry. The slurry is stirred for one hour, packed into a short chromatography column and eluted. Products are isolated by silica gel chromatography.

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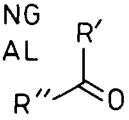
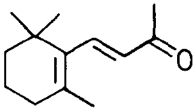
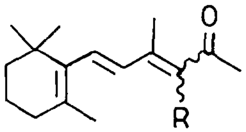
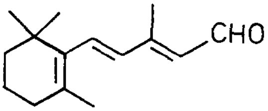
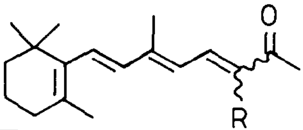
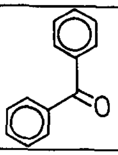
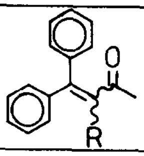
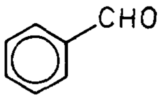
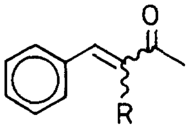
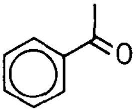
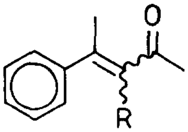
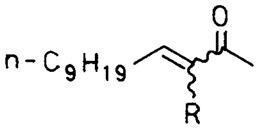
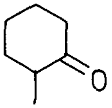
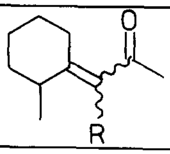
Table

ENTRY	STARTING MATERIAL 	PRODUCTS 2a,b	R	E / Z	YIELD %[a.]
1			H CH_3	47/53 17/83	59 (82) 52
2			H CH_3	62/38 41/59	65 53
3			H CH_3	——— ———	86 56
4			H CH_3	43/57 68/32	81 40
5			H CH_3	59/41	58 (70) < 10
6	n-$C_9H_{19}CHO$		H CH_3	52/48 46/54	64 50
7			H CH_3	60/40	62

a.) Based on isolated products, yield in parenthesis based on recovered starting aldehyde or ketone

References and Notes

1. A typical procedure involves the addition of methyllithium to the appropriate aldehyde. If the α double bond is tetra-substituted this reaction often gives a low yield and thermally labile products. Oxidation with manganese dioxide completes the sequence and is an unreliable reaction with secondary allylic alcohols.
2. E.J. Corey, D. Enders and M.G.Bock, Tetrahedron Lett., 1976, 7.
3. M.W. Rathke and D.F. Sullivan, Syn. Comm., 1973, 3, 67.
4. K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto and H. Nozaki, J. Am. Chem. Soc., 1974, 96, 1620.
5. 1a is purified by fractional distillation, B.P.: 33-34°C/0.1mm Hg, Yield: 42%. Silyl aldimines and ketimines can be stored at -60°C for at least one year. Storage at -20°C leads to noticeable decomposition after one month.

6a. Acetone *t*-butyl imine was prepared by a modified procedure of Weingarten *et al.*[6b] Titanium tetrachloride (13 ml, 0.12 mole) in 75 ml pentane is added over 30 minutes to *t*-butylamine (80 ml, 0.76 mole) in 250 ml diethyl ether with mechanical stirring and ice bath cooling. Acetone (18 ml, 0.25 mole) is then added over 30 min. The reaction mixture is filtered after stirring an additional 15 min. with cooling. The filtrate is concentrated *in vacuo* and fractionally distilled, B.P.: 44-47°C/65 mm Hg, yield: 44%. Stored at -60°C.

b. H. Weingarten, J.P. Chupp and W.A. White, J. Org. Chem., 1976, 32 ,3246.

7. 1a is added to 1.05 eq. of 1 *M* LDA in THF at 0°C and stirred for one hour. The reaction mixture is cooled to -78°C, quenched with 1.2 eq. methyl iodide, allowed to warm to 0°C, then partitioned between pentane and water. The pentane layer is concentrated *in vacuo* and 1b is isolated by fractional distillation,[5] B.P.: 39-42°C/0.1 mm Hg, Yield: 83%
8. J.E. McMurry, M.P. Fleming, K.L. Kees and L.R. Krepski, J. Org. Chem., 1978, 43, 3255.
9. The wet silica gel hydrolysis consists of 3 g silica gel, 8 ml benzene and 1.2 ml water stirred into an even suspension for every 1.5 mmol of H^+ or H_2O required.

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