

**A HIGHLY SELECTIVE METHOD FOR THE SYNTHESIS OF
(E)- α -METHYL- α , β -UNSATURATED ALDEHYDES**

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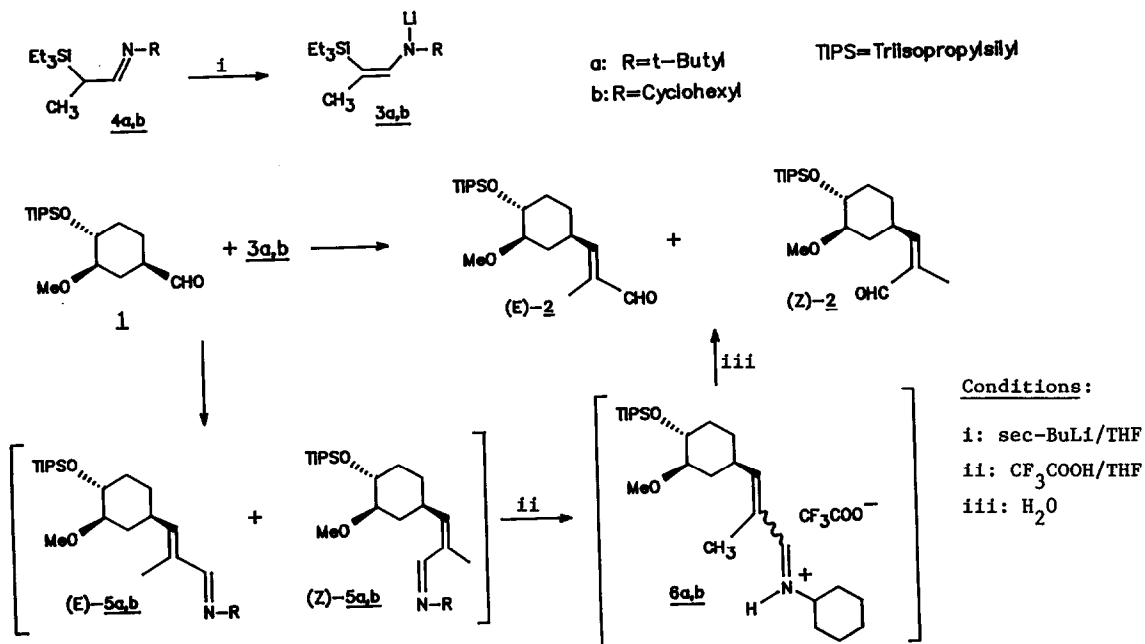
Summary: Anhydrous acidic treatment of E,Z mixtures of α -methyl- α , β -unsaturated imines followed by hydrolysis gives the corresponding aldehydes with $\geq 100:1$ E:Z ratios.

In conjunction with studies on the synthesis of the novel and potent immunoregulant FK-506¹ we required the efficient conversion of the aldehyde 1 to (E)-2.² After several unsuccessful attempts,³ we turned our attention to the procedure of Corey and coworkers⁴ as modified by Schlessinger et al.,^{5,6} which employed the α -lithio-silylimine 3. However, effective purification of the silylimine 4 was difficult and utilization of impure material usually returned 7-15% of the starting aldehyde, which was difficult to separate from the product aldehydes. A second and more serious concern was that the ratio of (E) and (Z)-2 varied from 2:1 to 10:1.⁷ Our investigation of these issues has resulted in the development of a simple variant of the literature procedure which provides good yields and exceptional selectivity for the (E)-enal (>100:1) for a variety of aldehyde substrates.

Although the 2-(triethylsilyl)-t-butylimine (4a)⁵ could be readily obtained, ¹H NMR analysis indicated the presence of significant amounts of triethylsilyl-containing contaminants, which were not removed by repeated fractional distillation. Since this material gave erratic results in the condensation reaction, we decided to replace the t-butyl group with a higher molecular weight moiety, in the hope of simplifying purification. The cyclohexylimine 4b, after a single distillation, provided good, reproducible yields in the aldehyde addition step.

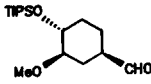

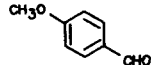


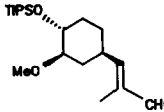
We investigated the source of the product ratio variability by examining the individual steps in the formation of the unsaturated aldehyde. Quenching the reaction with water did not lead to any appreciable hydrolysis of the intermediate imines (E)-5 and (Z)-5, which could be easily quantitated by ¹H NMR ($\text{CH}=\text{N}$ for (E)-5a at 7.78 ppm; for (Z)-5a at 8.31 ppm). The ratios of these compounds varied between 1:1 and 5:1, depending on reaction conditions.

Hydrolysis under the usual aqueous oxalic acid conditions led to ratios of product aldehydes (E)-2 and (Z)-2 which were similar to those observed for the corresponding imines. However, enhancements of the aldehyde ratios relative to the imine ratios in favor of the E isomer were seen on several occasions. It seemed possible that the unsaturated imines were undergoing isomerization in competition with hydrolysis under these conditions.⁸ Indeed, treatment of the crude mixture of imines with anhydrous trifluoroacetic acid in tetrahydrofuran (THF) at room temperature led within 30 minutes to an imine mixture which possessed an E:Z ratio of ca. 120:1. Addition of water then effected hydrolysis to the enals (E)-2 and (Z)-2, in a ratio of >100:1.



We have examined this isomerization procedure on a variety of substrates and found that, when coupled with the use of the N-cyclohexylimine 3b, reproducibly good yields of (E)- α -methyl- α,β -unsaturated aldehydes can be obtained, with excellent selectivities (Table).⁹ Although other methods to isomerize unsaturated carbonyl compounds are known, this protocol has the particular advantage that the species being equilibrated are (presumably) the bulky protonated imines 6, which possess a greater steric bias than the parent aldehydes. In addition, we have observed that the Z aldehyde 2 can be transformed into the imines (E)-5 and (Z)-5 under standard dehydrating conditions, and application of the usual isomerization conditions then produces a high ratio of E to Z product.

Table The Reaction of α -Lithiosilylimine **3b** with Various Aldehydes

RCHO	Crude E:Z Isomer Ratio ^b ; (Yield) ^c	
	Method ^a	Method ^a
	A	B
	100:1 (84%)	2:1 (85%)
	>100:1 (85%) ^{d*}	11:1 (-)
	>100:1 (87%)	1.3:1 (91%)
	>100:1 (91%) [*]	2:1 (-)
	>100:1 (82%)	6:1 (83%)
	>100:1 (68%)	2:1 (-)

a) Method A: Anhydrous isomerization with trifluoroacetic acid followed by aqueous hydrolysis; Method B: hydrolysis with aqueous oxalic acid.⁴ b) Determined by ¹H NMR at 300 MHz. c) Yields for method A are for the chromatographed E isomer; yields for method B are for combined E and Z isomers. Yields with asterisks were determined by quantitative HPLC analysis (25 cm Zorbax SIL column, 35°C, eluant 94:6 hexane:ethyl acetate at 2 mL/min; detection at 230 nm). d) Reaction performed with the lithio-*t*-butylimine **3a**.

EXPERIMENTAL:

Silylimine 4b Propionaldehyde *N*-cyclohexylimine¹⁰ was silylated according to the procedure of Schlessinger⁵. The crude product **4b** was fractionally distilled under vacuum (b.p. 84–86°C at 0.1 mmHg; 88% yield) to give material whose ¹H NMR was consistent with the desired product. A small amount of an unidentified impurity (d at 5.95 ppm) was also observed but did not interfere with the subsequent reaction. ¹H NMR (300 MHz, CDCl₃, Me₄Si) δ 7.65 (d, 1H, *J*=6.7), 2.87 (tt, 1H, *J*=10.6, 4.1), 2.03 (pentet, 1H, *J*=7.0), 1.82–1.20 (m, 10H), 1.16 (d, 3H, *J*=7.0), 0.96 (t, 9H, *J*=7.8), 0.60 (q, 6H, *J*=7.9).

Unsaturated Aldehyde 2 To a -78°C solution of 0.366g (1.44 mmol) of the imine **4b** in 2 mL of THF under nitrogen was added 1.02 mL (1.33 mmol) of a 1.3M *sec*-butyllithium/cyclohexane solution dropwise. The reaction was stirred at

-78°C for 30 min and then was treated with 0.349 g (1.11 mmol) of the aldehyde 1 in 1 mL of THF. The mixture was warmed to -20°C and was stirred for 1 h. The reaction was quenched with 2 mL of water, and the resulting mixture was extracted with 2x20 mL of ethyl acetate. The combined organic extracts were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was dissolved in 5 mL of THF and the solution was treated at 0°C with 0.10 mL (1.33 mmol) of trifluoroacetic acid dropwise under nitrogen. After one hour at 0°C 2 mL of water were added, and the mixture was stirred at 0°C for 12 hours. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution and was extracted with 25 mL of ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography with 7% ethyl acetate/hexanes to give 0.329 g (84%) of the unsaturated aldehyde (E)-2.^{7,11}

References and Notes

1. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M. J. Am. Chem. Soc. 1987, 109, 503
2. Askin, D.; Volante, R.P.; Reamer, R.A.; Ryan, K.M.; Shinkai, I. Tetrahedron Lett. 1988, 29, 277; Mills, S.; Desmond, R.; Reamer, R.A.; Volante, R.P.; Shinkai, I. Tetrahedron Lett. 1988, 29, 281⁵
3. The phosphorane **i**, gave only small amounts of (E)-2 on reaction with 1. The anion of the phosphonate **ii** gave very unpromising ratios of the E and Z unsaturated esters in model studies with 3-cyclohexene-1-carboxaldehyde.

$$\text{i } \text{Ph}_3\text{P}=\text{C}(\text{CH}_3)\text{CHO} \quad \text{ii } (\text{EtO})_2\text{P}(\text{O})\text{CH}(\text{CH}_3)\text{CO}_2\text{Et}$$
4. Corey, E.J.; Enders, D.; Bock, M.G. Tetrahedron Lett. 1976, 7:
5. Schlessinger, R.H.; Poss, M.A.; Richardson, S.; Lin, P. Tetrahedron Lett. 1985, 26, 2391.
6. Recent uses of Corey's silylimine with aldehydes: Meyers, A.I.; Lawson, J.P.; Walker, D.G.; Linderman, R.J. J. Org. Chem. 1986, 54, 5111; DeWit, P.P.; van Schaik, T.A.M.; van der Gen, A. Rec. Trav. Chim. 1984, 103, 369; Takahashi, T.; Kitamura, K.; Tsuji, J. Tetrahedron Lett. 1983, 24, 4695; Derguini, F.; Caldwell, C.G.; Motto, M.G.; Balogh-Nair, V.; Nakanishi, K. J. Am. Chem. Soc. 1983, 105, 646. These latter workers carried out the equilibration of a mixture of tetraenamine iminium isomers to the all-trans form under anhydrous conditions.
7. The structures of (E)-2 and (Z)-2 were initially assigned by nuclear Overhauser effect experiments as well as a COSY study. We thank Mr. Robert Reamer for this work. Subsequent comparison of 2 (after desilylation) with the reported⁶ degradation product established its identity. Other compounds in this study were assigned by comparison of ¹H NMR data to that of 2 and 5. In addition, all compounds were characterized by IR and mass spectroscopy.
8. Control experiments with a 1:1 mixture of (E)-2 and (Z)-2 in aqueous oxalic acid at 0°C for 3 hours indicated no change in ratio.
9. Not surprisingly, isomerization of the unsaturated imines derived from acetophenone proceeded quite slowly and gave only a 4:1 ratio of isomers.
10. Prepared according to the procedure of Cambell, K.; Sommers, A.; Cambell, B. J. Am. Chem. Soc. 1944, 66, 82.
11. Alternatively, an in-situ isomerization may be employed: after the reaction is complete, 0.26 mL of trifluoroacetic acid (3 equiv) is added at -20°C, the mixture is stirred at 0°C for one h, 2 mL of water is added, and the mixture is stirred at 0°C for 12 hours, to give a ca. 50:1 ratio of E and Z isomers, and an isolated yield of (E)-2 of 79%.

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