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A SIMPLE AND HIGHLY EFFECTIVE ROUTE TO α,β-UNSATURATED ALDEHYDES

E. J. Corey*, Dieter Enders and Mark G. Bock

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

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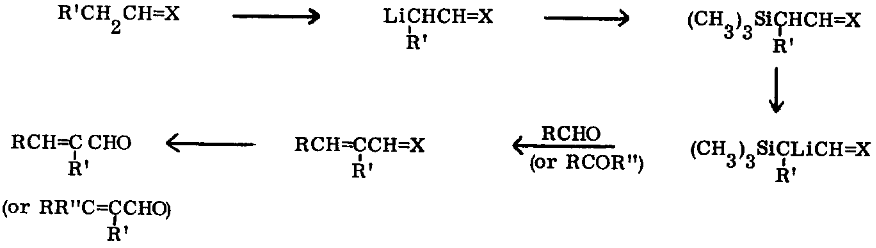
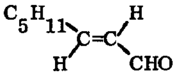
The formal "crossed-aldol" coupling of two aldehydes RCHO and $R'CH_2CHO$ to form an α,β-unsaturated aldehyde RCH=C(R')CHO is a highly useful synthetic operation in organic synthesis, especially in the area of natural products. A number of reagents and processes are currently available for effecting such a chain extension. These include (1) "directed aldol" condensation using an α-lithio or magnesio aldimine followed by acidic hydrolysis and dehydration,[1] (2) Wittig condensations with reagents such as $Ph_3P{=}CHCHO$,[2] $(RO)_2PO\bar{C}HCH{=}NR$,[3] and $Ph_3P{=}CHCH(OR)_2$,[4] (3) Lewis-acid-catalyzed acetal-vinyl ether condensation,[5] and (4) acetylide[6,7] or vinylmetallic[8] addition followed by carbinol rearrangement. Despite the availability of this array of approaches, our experience has been that there are numerous situations in which none of the known processes is really satisfactory. We describe herein a new method for the synthesis of α,β-unsaturated aldehydes which appears to offer special advantages in dealing with complex, polyfunctional substrates, including high efficiency, procedural simplicity and mildness of reaction conditions. Two modifications have been studied, one involving silyl aldimines[9] and the other silyl aldehyde dimethylhydrazones (DMH's)[11], as expressed by scheme A.



$X = N\text{-}\underline{t}\text{-}Bu$ or $NN(CH_3)_2$

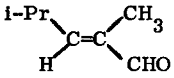
Scheme A

Using the t-butylimine modification, aldehydes **1** - **5** were prepared in the yields (after isolation) indicated.

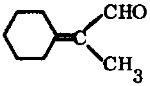


1 (94%)

2 (90%)



3 (88%)



4 (90%)

$C_6H_5CH{=}C(CH_3)CHO$

5 (90%, 1:1 E + Z)

The conversion of RR"CO to the coupled aldehyde RR"C=C(R')CHO can be accomplished essentially in one synthetic step as detailed in the following representative procedure.

Experimental Illustration

Silylation of Propionaldehyde t-Butylimine. To a stirred solution of lithium diisopropylamide (LDA, 66.0 mmole) in 100 ml of tetrahydrofuran (THF) was added propionaldehyde t-butylimine[9] (7.23 ml, 63.8 mmole) at 0° under argon. The solution was treated with a solution of trimethylchlorosilane (8.12 ml, 64.0 mmole) in THF with stirring and cooling. The reaction mixture was warmed to 0° over a 3.5 hr period, then poured into water (150 ml) and extracted with ether. The combined organic extracts were washed with brine, dried (K_2CO_3) and concentrated. The residual liquid was distilled at 175-178° to afford 8.5 g (73%) of clear, colorless product.[10]

Direct Synthesis of Cyclohexylidene Propionaldehyde (4). To a solution of lithium diisopropylamide (LDA, 2.60 mmole) in 9 ml of THF stirred magnetically at 0° (ice bath) was added the above described silylated propionaldehyde imine (0.493 g, 2.50 mmole) over a 5 min period under argon. The reaction mixture was stirred for 15 min more, cooled to -78° and treated with cyclohexanone. The resulting mixture was warmed to -20° over a 2.5 hr period and then quenched with water (3 ml). Solid oxalic acid was added to bring the pH to 4.5 and stirring was continued for 30 min more. The reaction mixture was poured into brine (10 ml) and extracted with ether. The combined organic extracts were washed with sodium bicarbonate solution, then dried (K_2CO_3) and concentrated under reduced pressure to remove solvent and hexamethyldisiloxane. Short path distillation at 80-85° (bath) (0.07 mm) afforded 310 mg (90%) of the pure α,β-unsaturated aldehyde **4**; ir, C=O stretch at 1675 cm^{-1} (CCl_4); nmr, no olefinic H, CH_3 and CH_2 protons at 1.69 ppm (downfield from tetramethylsilane), γ-CH_2 protons at 2.37 and 2.64 ppm, CHO proton at 10.10 ppm.

The N, N-dimethylhydrazone modification of the aldehyde synthesis according to Scheme A afforded the following aldehydes in the indicated yield: cinnamaldehyde (90%), **1** (90%), **2** (75%) and sorbaldehyde (75% from crotonaldehyde). Metallation of the α-trimethylsilyl aldehyde DMH was carried out with lithium diethylamide at -20° for 1 hr[11], the reaction mixture was cooled to -78° and the appropriate free aldehyde or ketone (1 equiv) was added. Warming to -20° over 1 hr and isolation afforded the DMH of the α,β-unsaturated aldehyde in yields of 85-95%. Hydrolysis to free α,β-unsaturated aldehyde was effected by conversion to the methiodide and stirring with a mixture of 5% hydrochloric acid and ether at 25° for 10 min.

It is expected that this method for aldehyde synthesis by chain extension will prove of value in more complex cases as it already has in these Laboratories.[12-14]

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