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A SIMPLE SYNTHESIS OF α-METHYLENE-β-HYDROXYALKANONES

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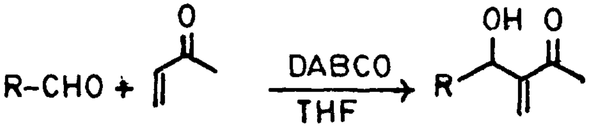
Summary: Reaction of methyl vinyl ketone with a variety of aldehydes, catalyzed by 1,4-diazabicyclo (2.2.2)octane (DABCO) in tetrahydrofuran, conveniently provides the corresponding α-methylene-β-hydroxyalkanones in good yields.

The α-alkoxyalkylation of α,β-unsaturated ketones provides multifunctional molecules for possible use in the synthesis of natural products of biological importance. Several methods are reported in literature for the introduction of an organic group at α-position of α,β-unsaturated ketones. Recently Leonard and Livinghouse have used 9-(phenylseleno)-9-borabicyclononane for effective formal aldol condensation at α-carbon of α,β-unsaturated ketones.[1] Noyori *et al.*[2] reported another method for synthesis of this kind of molecules via conjugate addition of phenyl silyl selenide to α,β-unsaturated ketones and the aldol type of reaction of enol silyl ethers catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) followed by β-elimination of selenoxides. Most of these methods, however, suffer from low yields or use expensive chemicals. Herein we report a straightforward and simple synthesis of α-methylene-β-hydroxyalkanones via the reaction of methyl vinyl ketone with representative aldehydes catalyzed by DABCO in THF as solvent.

In 1972 Hillman and Baylis in their patent reported that bicyclic tertiary amines can be effective catalysts for the coupling of acrylic acid derivatives to certain aldehydes.[3] Later on Drewes *et al.*[4] and Hoffmann *et al.*[5,6,7] used this method in their synthesis of necic acids. Perlmutter and Teo recently reported the coupling of ethyl acrylate to N-(para-toluenesulfonyl)imines of aromatic aldehydes.[8]

It appeared to us that coupling reaction of methyl vinyl ketone to aldehydes catalyzed by DABCO would be an effective method for synthesis of α-methylene-β-hydroxyalkanones. Accordingly, we carried out the reaction of methyl vinyl ketone with decanal under neat conditions. This reaction was not clean. The best results were obtained when this reaction was carried out in THF (2M solution) (eq.1, $R={}^{n}C_9H_{19}$) though the reaction takes more time. Representative examples (1-7) of the α-methylene-β-hydroxyalkanones are prepared from various aldehydes andmethyl vinyl ketone (Table 1).



(1)

It was found that propionaldehyde,[9] and 2-furaldehyde did not give clean products under these conditions. It appears that the rate of reaction decreases as the number of carbon atoms increases in the alkyl chain of the aliphatic aldehyde. The first step in this catalytic cycle may involve the conjugate addition of DABCO to methyl vinyl ketone, consistent with the fact that 2-cyclohexenone fails to react with hexanal even under neat conditions. The following procedure for the synthesis of 4-hydroxy-3-methylenetridecan-2-one (4) is representative. A solution of decyl aldehyde (3.12 g, 20 mmol), methyl vinyl ketone (1.4 g, 20 mmol) and DABCO (0.33 g, 3 mmol) in 5 mL of THF was allowed to stand at room temperature for ten days. The reaction mixture was taken up in ether (25 mL) and washed with 2N hydrochloric acid, sodium bicarbonate solution and dried over Na_2SO_4. After removal of the solvent the product was purified by column chromatography (5% ethyl acetate, 95% hexane) and then distilled to obtain 4 (bp 117-120/0.5 mm) in 62% yield (2.8 g). IR (neat): 3450, 1665 cm^{-1}. ^1H NMR ($CDCl_3/SiMe_4$): 0.87 (distorted t,3H); 1.28(m,16H), 2.35(s,3H), 3.04(b,1H,D_2O washable), 4.43(m,1H), 6.0(s,1H), 6.08(s,1H). ^{13}C NMR ($CDCl_3/SiMe_4$): 13.85, 22.48, 25.65, 26.18, 29.12, 29.41, 31.70, 36.40 (alkyl C), 70.19 (<u>C</u>-OH), 124.87, 150.88 (C=C), 200.08 (C=O). Anal. calcd. for $C_{14}H_{26}O_2$: C, 74.283, H, 11.578; Found C, 74.50, H, 11.576.

Table 1: Preparation of α-methylene-β-hydroxyalkanones from methyl vinyl ketone and aldehydes (eq.1) catalyzed by DABCO in THF as solvent.[a,b]

R-CHO	Product	Reaction time	bp/mm	Yield (%)[c]
$^nC_5H_{11}CHO$	1	72 h	74-77/0.5	65
$^nC_6H_{13}CHO$	2	80 h	80-85/0.5	73
$^nC_7H_{15}CHO$	3	100 h	119-122/3	63
$^nC_9H_{19}CHO$	4	10 days	117-120/0.5	62
$^nC_{15}H_{31}CHO$[d]	5	15 days	146-148/0.3	51[d]
C_6H_5CHO	6	9 days	118-120/1	51
$C_6H_5CH_2CH_2CHO$[e]	7	85 h	136-138/1.2	65

C_6H_5 = Phenyl; a) All reactions were carried out on 20 mmol scale in 2 M THF solution; b) All the products are identified spectroscopically by IR, ^1H NMR and ^{13}C NMR; c) Yields of the pure products after purifying by column chromatography followed by distillation; d) Only 70% reaction was complete. Percentage yield was calculated accordingly; e) This reaction was carried out on 10 mmol scale.

This procedure represents a simple, one-pot synthesis of α-methylene-β-hydroxyalkanones. The use of optically active amines in place of DABCO to achieve optical induction will be the subject of our future reports.

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9. This reaction was also carried out under neat condition as well as in dilute solution (1M THF) and found that the reaction was not clean.

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