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COBALT(II) CHLORIDE CATALYSED CONDENSATION OF ACETOACETATE WITH ENOLISABLE ALDEHYDES

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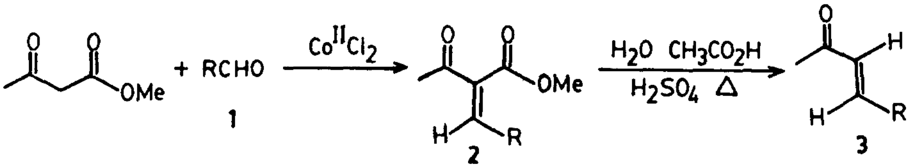
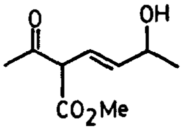
Summary : Enolisable aldehydes and methyl acetoacetate react in the presence of cobalt(II) chloride (catalytic) to give the corresponding α, β -unsaturated carbonyl compound in excellent yields. Non enolisable aldehydes do not react under these conditions. A catalytic cycle for these reactions has been proposed by involving the intermediacy of a cobalt(III) enol complex of aldehyde.

Knoevenagal condensation is now a very well established method[1] for the synthesis of α,β -unsaturated carbonyl compounds. This reaction is usually carried out in the presence of a base with non-enolisable aldehydes or ketones. However, in Lehnert's modification[2] of this method, which requires $TiCl_4$ and a base, aldehydes with an enolisable hydrogen can be condensed to give α , β -unsaturated carbonyl compounds in excellent yields. Lehnert's method requires one equivalent of $TiCl_4$ and base which severely limits the scope of this method on a large scale preparation. While exploring an alternative route to this method, we discovered that cobalt(II) chloride efficiently catalysed[3] the condensation of methyl acetoacetate with enolisable aldehydes and surprisingly non-enolisable aldehydes do not react under these conditions. A preliminary account of these findings is given below :

Aldehydes (10 mmol) and acetoacetate (10 mmol) are added to a stirred solution of dry cobalt(II) chloride (≃ 20 mg) and acetic anhydride (0.05 mmol) in dry acetonitrile (50 mL), and the resulting mixture is stirred at 25°C for 6-8 hours. Acetonitrile is removed under vacuum and the residue is taken into ether and the ether is washed with a saturated solution of sodium bicarbonate and water. Drying ($MgSO_4$) and evaporation of ether gives a gum which is purified by column chromatography (SiO_2) to give compound 2 in excellent yields (Scheme 1). These reactions are quite facile with enolisable aldehydes and no reaction was observed with benzaldehyde, p-methoxybenzaldehyde, o-hydroxybenzaldehyde, cinnamaldehyde, pivaldehyde and acrolein. Reaction with crotonaldehyde is quite interesting as it takes a longer time (20 hours) for the condensation and besides giving the usual dienes **2h** it also gives alcohol 4 in 40% yield. The α,β-unsaturated carbonyl compounds 2 are formed in a highly stereoselective manner and they can be converted to (E)-enones on acid hydrolysis (H_2SO_4-AcOH). The (E)-enones are formed predominantly although in few cases they are contaminated with a trace of (Z)-enones. These reactions are facilitated by a catalytic quantity of acetic anhydride[4] as it is observed that the absence of acetic anhydride results in the formation of oligomeric materials (10-15%) along with the expected product.



a) R=C_2H_5	a) 85%	a) 48%
b) R=$C_3^nH_7$	b) 88%	b) 58%
c) R=$C_4^nH_9$	c) 80%	c) 52%
d) R=C_5H_{11}	d) 78%	d) 52%
e) R=C_6H_{13}	e) 83%	--
f) R=$C_6H_5CH_2$	f) 68%	--
g) R=cyclo-C_6H_{11}	g) 82%	--
h) R=CH_3-CH=CH	h) 72%	--



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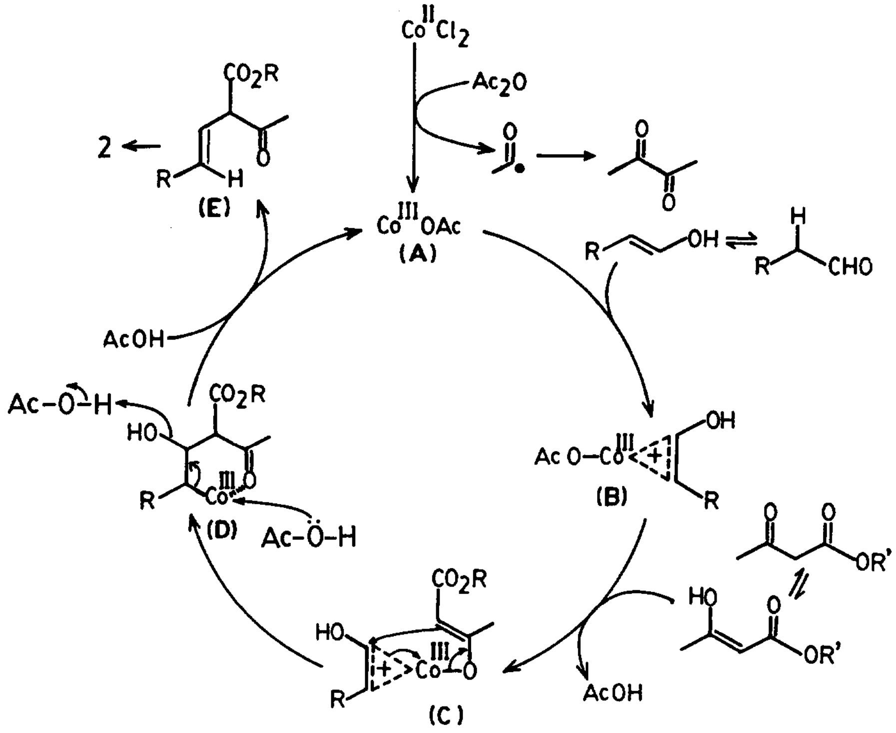
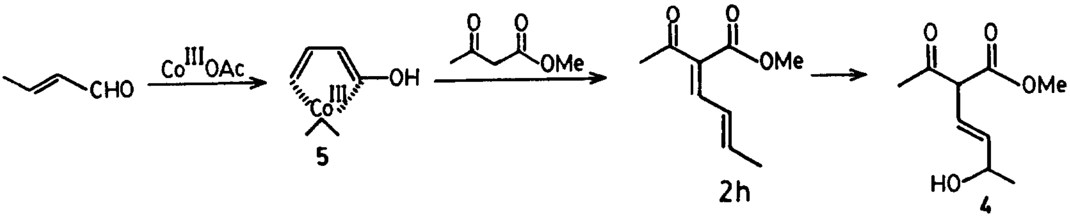
Scheme 1

The mechanism of these reactions has a very strong resemblence with that of the vinyl ether-acetoacetate reactions[3]. Since these reactions take place only with enolisable aldehydes, it is conceivable that the enol form of the aldehyde may be the reactive species. The transition metal complexes are known to stabilise the enol form of acetaldehyde as shown in case of iron[5] and platinum complexes[6] of vinyl alcohol. In analogy with the cobalt(III) complexes of enol ethers[7], the reaction of enolisable aldehydes may be proceeding via similar enol complexes of aldehydes. Thus a cobalt(II) complex will transfer an electron to acetic anhydride to generate[8] a cobalt(III) species (**A**) which forms a π-complex (B) with the enol of an aldehyde (Scheme 2). The complex (B) may react with the enol form of acetoacetate to yield a cobalt(III) enolate-π-complex (C) which will undergo the carbon-carbon bond formation to give a cobalt-σ-complex (D). The α, β-unsaturated carbonyl compound 2 can be obtained from (D) on protonation and the cobalt(III) complex (**A**) will be regenerated to complete the catalytic cycle. The formation of a π or σ-complex of cobalt(III) from enol ethers has already been speculated by Dolphin and coworkers[7]. Cobalt is acting as a templete in bringing the



Scheme 2

acetoacetate and aldehyde together for a bond formation and this template effect prohibits other side reactions of aldehydes under these conditions. In light of this mechanism it is clear that crotonaldehyde is reacting via the cobalt-dienol complex 5 which reacts with acetoacetate to yield the alkene **2h** and alcohol 4 and the later may be obtained via the addition of water on 2h. The iron complexes similar to 5 are known to exist as stable entities[9].



Scheme 3

In conclusion, the chemospecifity and very high (E)-stereoselectivity of this reaction will make it extremely useful in organic synthesis.

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