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A One Pot Synthesis of β-Acetamido Ketones and Furans by Cobalt(II) Catalyzed Coupling of 1,3- or 1,4- Dicarbonyl Compounds and Aldehydes : A Remarkable Role of Dioxygen

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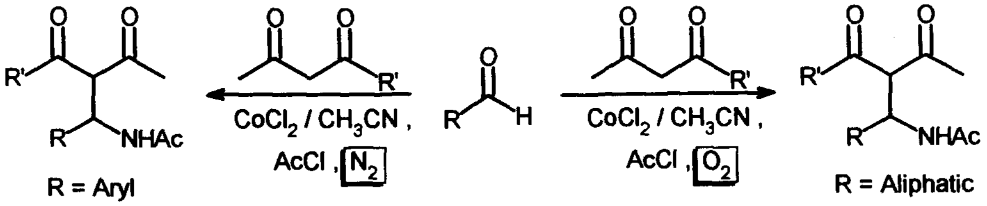
Abstract : Cobalt(II) catalyses the coupling of 1,3- and 1,4-dicarbonyl compounds with various aldehydes in the presence of acetonitrile to give β-acetamido ketones and furan amides respectively. The outcome of these reactions is controlled by the reaction atmosphere as aromatic aldehydes react to give β-ketoamide in the presence of nitrogen, whereas the reaction with aliphatic aldehydes gives the later product only in the presence of oxygen atmosphere.

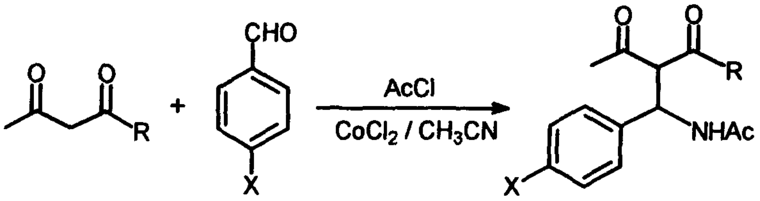
In a recent communication we have demonstrated[1,2] that cobalt(II) catalyses the reaction between various ketones and aldehydes in the presence of acetyl chloride and acetonitrile to give β-keto amides[3]. We now show that the outcome of these reactions is highly dependent upon the presence or absence of dioxygen which brings about a contrasting reactivity profile between aliphatic and aromatic aldehydes. Accordingly the reaction of aromatic aldehydes with 1,3-dicarbonyl compounds provides high yields of β-keto amides under nitrogen, whereas aliphatic aldehydes afford similar products only under oxygen atmosphere (Scheme 1). A brief account of these intriguing observations is presented below.



Scheme 1

In a typical experimental procedure, 1,3-dicarbonyl compound (5 mmol) and aromatic aldehyde (5 mmol) were taken in acetonitrile (30mL) and the mixture was heated in the presence of catalytic amount of cobalt(II) chloride and acetyl chloride (10 mmol) under nitrogen atmosphere to afford, after column chromatography, the corresponding β-keto amides in good yields (Table 1). According to this protocol the reaction of acetyl acetone with p-nitro and p-hydroxybenzaldehyde afforded a high yield of β-acetamido ketones (Table 1, entry 1 and 2). Similarly methyl acetoacetate reacted with p-nitro and p-chlorobenzaldehyde to afford

Table 1 : Cobalt (II) Catalyzed Reaction of p- Substituted Benzaldehyde with 1,3-Dicarbonyl Compounds in Acetonitrile.

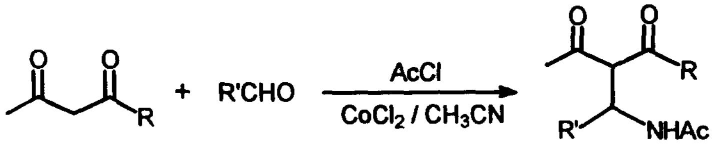


Entry	R	X	Reaction atmosphere	Yield (%)[a]
1	Me	NO_2	N_2	75
2		OH	N_2	63
3	OMe	NO_2	N_2	(73)[b]
4		Cl	N_2	(64)[b]
5		OH	O_2	(27)[c]

a) Isolated yield.
b) A mixture of syn : anti (1:3) diastereomers are obtained.
c) The major product of this reaction is the corresponding enone arising due to Knoevenagel condensation.

the corresponding β-acetamido ketones as a mixture of diastereomers in which the anti-isomer was found to be the major one in both the cases (Table 1,entry 3 and 4). *It is interesting to note that the reactions described in Table 1 afford the corresponding α,β-unsaturated compounds as the major product under an oxygen atmosphere; however, the corresponding amides were also present but only in minor amounts.* The reaction of 1,3-dicarbonyl compounds with aliphatic aldehydes is quite interesting as no β-keto amides were obtained under a nitrogen atmosphere. However, moderate to good yields of corresponding β-keto amides were obtained under an oxygen atmosphere (Table 2). Thus the reaction of acetyl acetone with n-butanal, isobutanal and cyclohexanecarboxaldehyde afforded the corresponding β-acetamido ketones in good yields under an oxygen atmosphere (Table 2, entry 1-3). Similarly, methyl acetoacetate and n-butanal afforded the corresponding β-acetamido esters in the presence of acetyl chloride, cobalt(II) chloride and acetonitrile (Table 2, entry 4). *It is important to note that no reaction was observed between the 1,3-dicarbonyl compound and the aliphatic aldehyde under a nitrogen atmosphere.* These results are in contrast with the reaction of aromatic aldehydes presented in Table 1.

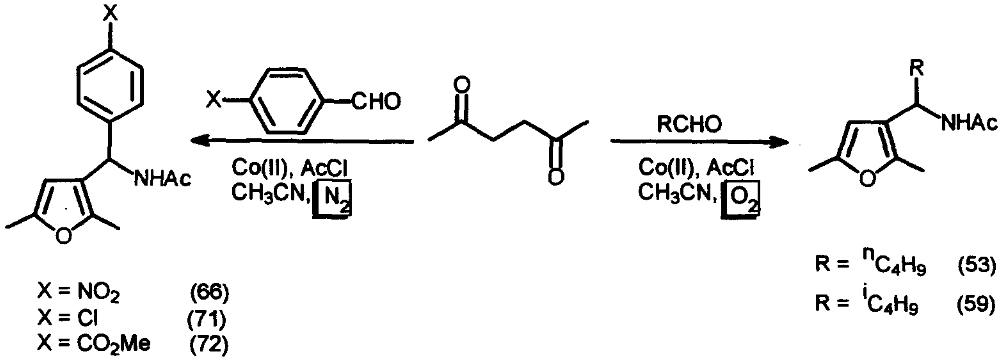
Table 2 : Cobalt (II) Catalyzed Reaction of Aliphatic Aldehyde with 1,3-Dicarbonyl Compounds in Acetonitrile.



Entry	R	R'	Reaction atmosphere	Yield (%)[a]
1	Me	$^{n}C_3H_7$	O_2	26
2		$^{i}C_3H_7$	O_2	76
3		$^{c}C_6H_{11}$	O_2	59
4	OMe	$^{n}C_3H_7$	O_2	(21)[b]
5			N_2	0

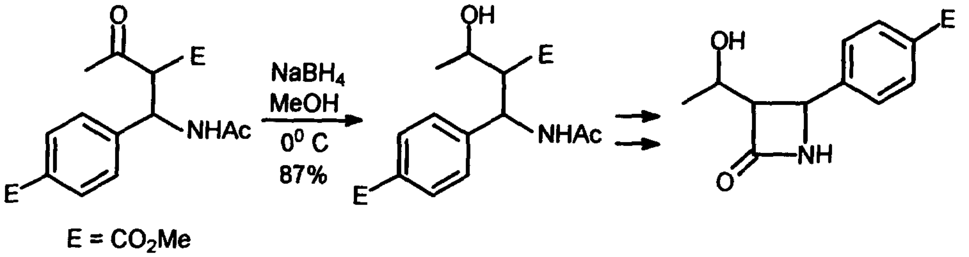
a) Isolated yield.
b) A mixture of diastereomers are obtained.

The reaction of an aldehyde with hexane-2,5-dione also exhibits a similar reactivity profile as observed for 1,3-dicarbonyl compounds. Thus the reaction of hexane-2,5-dione with p-substituted benzaldehydes under a nitrogen atmosphere afforded the furan amide as the only product, whereas the same reaction under an oxygen atmosphere did not yield any amide. Interestingly the reaction with aliphatic aldehyde and hexane-2,5-dione under an oxygen atmosphere also exhibits a similar contrasting behaviour with respect to aromatic aldehydes as observed for 1,3-dicarbonyl compounds. Accordingly, the reaction of n-butanal and hexane-2,5-dione under an oxygen atmosphere provides the furan amide as the only product, whereas unidentifiable products were obtained under a nitrogen atmosphere. A similar reaction with 2-methylpropanal under these conditions afforded the corresponding furan amide in good yields (Scheme 2).



Scheme 2

The amides derived from methyl acetoacetate and aldehydes are good precursors for the synthesis of β-lactams as the latter may be accessed from the hydroxy amide which can be easily obtained on sodium borohydride reduction of β-acetamido esters as demonstrated in Scheme 3. Cobalt(II) catalyzed alkylations of pentane-2,4-dione have been studied extensively by Moreno-Manas et al[4], who have shown that these reactions are proceeding via non-carbon chain reactions initiated by cobalt(II). In light of their observation it is conceivable that the aromatic aldehydes may be reacting by an ionic process, whereas the requirement for oxygen in the reactions with aliphatic aldehydes indicates that the latter reactions are more likely proceeding via a radical mechanism. However, the role of the oxygen atmosphere in these reactions is not clear at the moment and we are currently undertaking a study to understand the diverse reactivity profile exhibited by aliphatic and aromatic aldehydes.



Scheme 3

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