# Cobalt-catalysed Three-component Coupling involving Ketones or Ketoesters, Aldehydes and Acetonitrile: a Novel One-pot Synthesis of β-Acetamido Ketones

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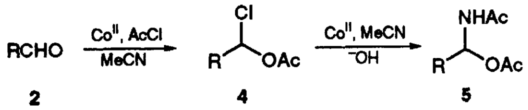
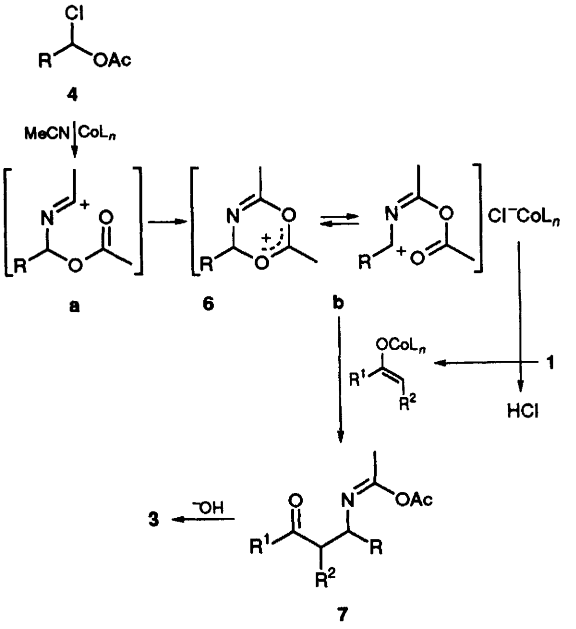
Cobalt(II) chloride catalyses one-pot coupling of ketones or ketoesters, aldehydes and acetonitrile in the presence of acetyl chloride to give β-acetamido ketones **3** in good yields.

The selective formation of a carbon–carbon bond *via* aldol condensation constitutes a fundamentally important organic transformation. The classical version of this reaction requires a hydroxide base which mediates the bond formation between carbonyl compounds, although, this protocol allows very little control in selectivity during the formation of an aldol derived from the reaction between two different enolisable carbonyl compounds. However, with the advent of directed aldol condensation the bond formation[1] between two different enolisable carbonyl compounds may be conducted in a controlled and precise manner to achieve the synthesis of the desired aldol product. Metal-catalysed coupling between enolisable ketones and aldehydes has seldom been used to achieve the formation of aldols or related products, although the reaction between silyl enol ethers and aldehydes or the corresponding acetal is known to proceed[2] readily under the influence of a metal catalyst. We have observed recently that aldehydes react with acetyl chloride in acetonitrile under the influence of a catalytic amount of cobalt(II) chloride to afford α-acetoxy amides in quantitative yields. Interestingly, if the latter reaction is performed in the presence of an enolisable ketone **1** then the corresponding β-acetamido ketones **3** are obtained[3] as the major products. A preliminary account of our finding on this interesting transformation is presented below.

A mixture of enolisable ketone **1** (5 mmol), aldehyde **2** (5 mmol) and acetyl chloride (10 mmol) is heated (70–80 °C) in acetonitrile (50 ml) in the presence of a catalytic quantity of dry cobalt(II) chloride for 8–12 h. The aqueous base work-up followed by column chromatography over silica gel (ethyl acetate–light petroleum) afforded β-acetamido ketones **3** as solids (Table 1). Thus acetophenone **1a** and propiophenone **1b** reacted with various 4-substituted benzaldehyde or butanal **2** to give good yields of **3** (Table 1, entries 1–5). The reaction with propiophenone **1b** is highly stereoselective as one of the diastereoisomers† is obtained as the major product (Table 1, entries 4 and 5). Similarly the reaction of acetyl acetone **1c** or methyl acetoacetate **1d** with aldehydes **2** leads to the formation of β-acetamido ketones **3** in moderate to good yields (Table 1, entries 6–11), however, these carbonyl compounds required longer times to react as compared to the corresponding ketones **1a** and **1b**. Methyl acetoacetate

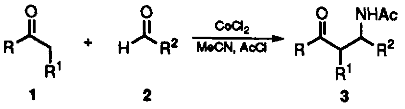


Scheme 1



Scheme 2

**Table 1** Cobalt(II) chloride catalysed one pot synthesis of β-acetamido ketones from ketones and aldehydes



| Entry | Carbonyl compound | | | Aldehyde | Reaction | Product | Yield[a] |
|---|---|---|---|---|---|---|---|
| | R | R$^1$ | | R$^2$ | time/h | | (%) |
| 1 | Ph | H | **1a** | 4-$NO_2C_6H_4$ **2a** | 4 | **3a** | 56 |
| 2 | | | | 4-$CO_2MeC_6H_4$ **2b** | 4 | **3b** | 59 |
| 3 | | | | Pr$^n$ **2c** | 10 | **3c** | 34 |
| 4 | Ph | Me | **1b** | 4-$ClC_6H_4$ **2d** | 3 | **3d** | 78$^{b-d}$ |
| 5 | | | | **2b** | 4 | **3e** | 64$^{b-d}$ |
| 6 | Me | COMe | **1c** | **2b** | 8 | **3f** | 62 |
| 7 | | | | **2c** | 10 | **3g** | 26 |
| 8 | | | | **2d** | 8 | **3h** | 53 |
| 9 | | | | Pr$^i$ **2e** | 10 | **3i** | 47 |
| 10 | Me | $CO_2Me$ | **1d** | **2b** | 14 | **3j** | 44$^{b,d}$ |
| 11 | | | | **2d** | 12 | **3k** | 41$^{b,d}$ |

[a] Yield of the isolated product by column chromatography. [b] Yield of the mixture of diastereoisomers. [c] *Anti*-diastereoisomer was obtained as the major product (*anti*:*syn* = 3:1). [d] The ratio of the diastereoisomers were determined by the coupling constants between methine protons in the $^1H$ NMR spectrum of the crude reaction mixture.

exhibited poor selectivity as nearly an equal mixture of diastereoisomers was obtained in its reaction with aromatic or aliphatic aldehydes (Table 1, entries 10 and 11). The yield of ketone **3** is high with aromatic aldehydes having an electron-withdrawing group in 4-position whereas the reaction with benzaldehyde, 4-methyl- and 4-methoxy-benzaldehyde afforded low yields of **3** along with some eliminated product. The reaction with aliphatic aldehydes also can be performed *via* their $\alpha$-chloroacetate to give **3** in comparable yields.

A preliminary mechanistic investigation (Scheme 1) reveals that this reaction is proceeding *via* the initial cobalt(II) catalysed formation of $\alpha$-chloroacetate **4** from aldehyde and acetyl chloride. Complexes **4** from aliphatic aldehydes may be isolated as stable compounds whereas for the aromatic aldehydes this compound eludes separation and instead the corresponding $\alpha$-acetoxyamides **5** are obtained in quantitative yields (Scheme 2). We have observed that **4** on further reaction with acetonitrile in the presence of cobalt(II) chloride affords, after an aqueous base work-up, the corresponding $\alpha$-acetoxy amides. Thus the cobalt-catalysed reaction of acetonitrile with chloroacetate may give a stabilised cationic species **6** which will react with the cobalt enolate of the ketone to afford the imidate ester **7** and the later on treatment with base during the work-up will yield the amide **3**. Our recent studies have indicated[5] that cobalt enolates are formed during reaction of enolisable ketones with aldehydes or allyl acetates. The high reactivity of ketones as compared with 1,3-dicarbonyl compounds also indicates that the reaction is proceeding *via* the metal enolate as the stabilised enolates from the latter are likely to be less reactive than the corresponding enolates derived from ketones.

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## Footnote

† We have assigned *anti*-stereochemistry to the major product **3d** based on the coupling constant between the methine protons. **3d**-*syn*: $\delta$ 4.1 (dq, $J$ 7.5 and 8 Hz, 1H), 5.25 (dd, $J$ 7.3 and 8 Hz, 1H). **3d**-*anti*: 4.15 (dq, $J$ 7 and 10 Hz, 1H), 5.20 (dd, $J$ 7 and 10 Hz, 1H). These $J$ values are in agreement with $J$ values of a similar compound reported recently.[4]

## References

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