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# Synthesis of Mannich type products via a three-component coupling reaction

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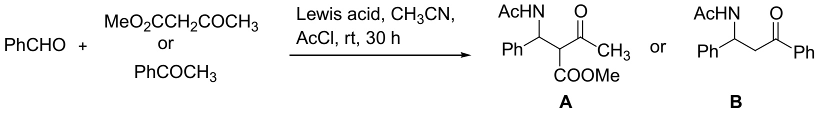
**Abstract**—The reactions of alkyl nitriles, acetyl chloride, aldehydes and β-ketoesters or simple ketones was studied for the one-pot synthesis of β-acetamido carbonyl compounds. It was observed that the reaction proceeds in the absence of Lewis acids. However, a Lewis acid catalyzes the reaction and several were tested. It was found that whereas $Cu(OTf)_2$ is suitable for the coupling of β-ketoesters with aldehydes, $Sc(OTf)_3$ is the best for ketones. A possible mechanism is proposed based on the isolation and characterization of an intermediate.

One-pot transformations, particularly multi-component reactions (MCR)[1] are of current interest to organic chemists. Since the first MCR reported in 1850 by Strecker,[2] this methodology has emerged as an efficient and powerful tool in modern synthetic organic chemistry allowing the facile creation of several new bonds in a one-pot transformation. Very recently, transition metal catalyzed MCR reactions of aldehydes, ketones and amines (Mannich reactions) were reported.[3] Recently, we reported cycloaddition reactions of aziridines and azetidines with nitriles, which were proposed to proceed in a Ritter fashion.[4] Based on this assumption, it can be

**Table 1.** Effect of Lewis acid on the three-component coupling to give β-acetamido-carbonyl compounds



| Entry | Lewis acid | Isolated yield (%) | |
|---|---|---|---|
| | | A | B |
| 1 | Nil | 15 | 30 |
| 2 | $Zn(OTf)_2$ (10 mol %) | 20 | 60 |
| 3 | $Bi(OTf)_3$ (10 mol %) | 44 | 69 |
| 4 | $Sn(OTf)_3$ (10 mol %) | 36 | 68 |
| 5 | $Sc(OTf)_3$ (10 mol %) | 47 | 82 |
| 6 | $Cu(OTf)_2$ (10 mol %) | 65 | 64 |
| 7 | $Yb(OTf)_3$ (10 mol %) | — | 75 |
| 8 | $BF_3{\cdot}OEt_2$ (100 mol %) | — | 78 |
| 9 | $BF_3{\cdot}OEt_2$ (10 mol %) | — | 48 |
| 10 | $CuCl_2$ (100 mol %) | — | 79 |
| 11 | $BiCl_3$ (100 mol %) | — | 77 |
| 12 | $LaCl_3$ (100 mol %) | — | 77 |
| 13 | $LiClO_4$ (100 mol %) | — | 59 |
| 14 | $InCl_3$ (100 mol %) | — | 19 |

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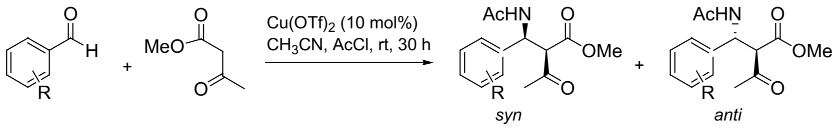
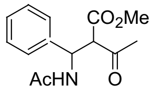
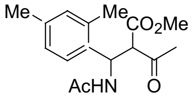
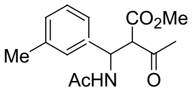
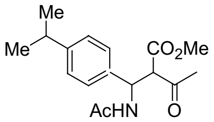
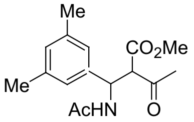
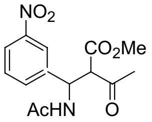
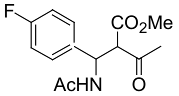
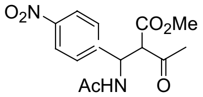
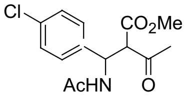
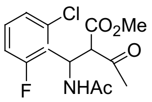
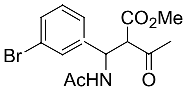
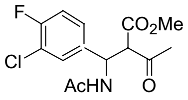
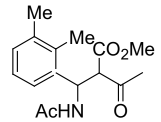
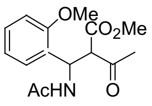
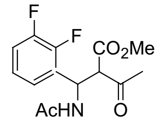
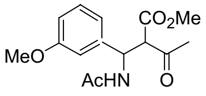
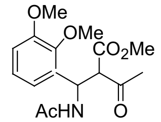
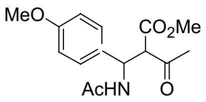
envisioned that Mannich-type products (retron: N–C–C–CO) can be obtained if the amine is replaced by an acetyl source (acetyl chloride or acetic anhydride) and the intermediate adds to the alkyl nitrile in a Ritter fashion. In this letter, we disclose our results based on the above concept.

We observed that when a mixture of an enolizable ketone (a β-ketoester or a simple aryl alkyl ketone), aldehyde and acetyl chloride were stirred at room temperature in acetonitrile for 30 h, β-acetamido carbonyl compounds were obtained in 15–30% yields. The reaction was more efficient in the presence of a Lewis acid. Thus, a variety of Lewis acids were screened and the results are summarized in Table 1. It was observed that where $Cu(OTf)_2$ returned a high yield for the coupling of an aldehyde with a β-ketoester, acetophenone was coupled more efficiently with similar aldehydes

**Table 2.** Three-component coupling route to (β-acetamido ketoesters in the presence of $Cu(OTf)_2$



| Entry | β-Acetamido ketoester | Yield[a,b] (%) | *syn*/*anti*[c] | Entry | β-Acetamido ketoester | Yield[a,b] (%) | *syn*/*anti*[c] |
|---|---|---|---|---|---|---|---|
| 1 |  | 65 | 44/56 | 10 |  | 54 | 67/33 |
| 2 |  | 73 | 49/51 | 11 |  | 60 | 50/50 |
| 3 |  | 70 | 60/40 | 12 |  | 49 | 18/82 |
| 4 |  | 70 | 47/53 | 13 |  | 43 | 47/53 |
| 5 |  | 68 | 14/86 | 14 |  | 30 | 35/65 |
| 6 |  | 72 | 48/52 | 15 |  | 62 | 49/51 |
| 7 |  | 63 | 33/67 | 16 |  | 33 | 52/48 |
| 8 |  | 55 | 60/40 | 17 |  | 58 | 50/50 |
| 9 |  | 68 | 62/38 | 18 |  | 35 | 45/55 |

[a] Yields are reported after aqueous work-up.

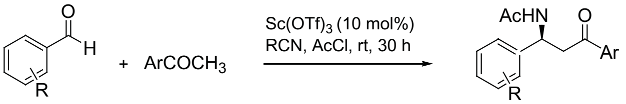
[b] The product was obtained as a mixture of diastereomers.

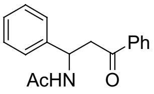
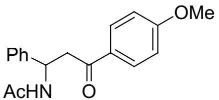
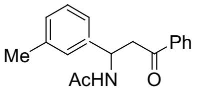
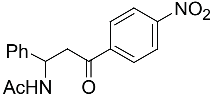
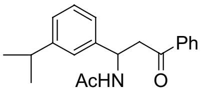
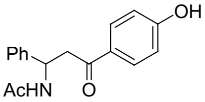
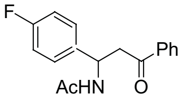
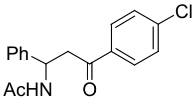
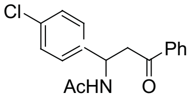
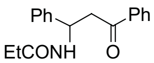
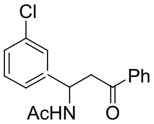
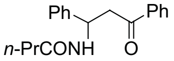
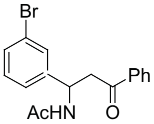
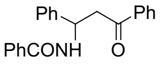
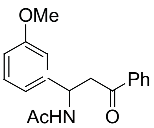
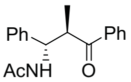
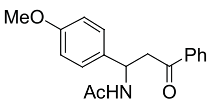
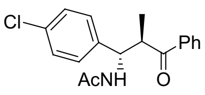
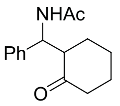
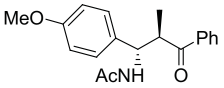
[c] Ratio obtained from $^1H$ NMR of the crude reaction mixture.

using $Sc(OTf)_3$. When compared to the literature procedure,[5] that is, harsh reaction conditions (high temperature) and long reaction times (5 d) with $CoCl_2$ as a catalyst, our procedure appeared to be simple and efficient.[6] The reaction was extended to a variety of aldehydes with β-ketoesters using $Cu(OTf)_2$ as catalyst and the results are summarized in Table 2. In all cases mixtures of *syn*- and *anti*-diastereomers were obtained,[7] whilst the diastereoselectivity depended upon the nature of the reactants. For example, 4-chlorobenzaldehyde and 3-nitrobenzaldehyde gave products where the *syn*/*anti* ratio was reasonably good (Table 2, entries 5 and 12) whereas other aldehydes gave poor diastereoselectivity.

The three-component coupling reaction was extended to ketones and the results are summarized in Table 3. In most cases, high yields of product were obtained. The reaction was not clean with aliphatic aldehydes. Similarly, acyclic aliphatic ketones gave unsatisfactory

**Table 3.** Three-component coupling route to β-acetamido ketones in the presence of $Sc(OTf)_3$[a]



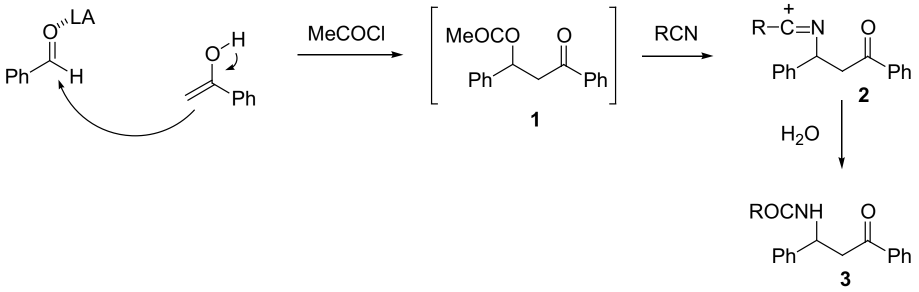
| Entry | β-Acetamido ketone | Isolated yield (%) | Entry | β-Acetamido ketone | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 |  | 82 | 11 |  | 98 |
| 2 |  | 80 | 12 |  | 95 |
| 3 |  | 85 | 13 |  | 86 |
| 4 |  | 76 | 14 |  | 90 |
| 5 |  | 84 | 15 |  | 93 |
| 6 |  | 90 | 16 |  | 60 |
| 7 |  | 67 | 17 |  | 74 |
| 8 |  | 82 | 18 |  | 87[b] |
| 9 |  | 85 | 19 |  | 85[c] |
| 10 |  | 32 | 20 |  | 75[d] |

[a] RCN was used as solvent; for entries 1–14 and for entries 18–20, MeCN was used; for entry 15, *n*-propionitrile was used; for entry 16, *n*-butyronitrile was used; benzoyl nitrite was used for entry 17.

[b] The major compound was shown to be *anti* with a ratio of 32:68.

[c] The major compound was shown to be *anti* with a ratio of 10:90.

[d] The major compound was shown to be *anti* with a ratio of 35:65.



**Scheme 1.** Proposed reaction mechanism.

results, however, cyclohexanone gave a 32% yield of the product (Table 3, entry 10). The reaction proceeded well with nitriles such as propionitrile (entry 15), butyronitrile (entry 16) and phenyl nitrile (entry 17). The reactions of propiophenone proceeded in good yield and good diastereoselectivity (Table 3, entries 18–20).

The mechanism may involve the enolic form of the ketone which attacks the activated aldehyde to provide a β-acetoxy ketone **1** (Scheme 1). The acetate group of **1** is displaced by the nucleophilic nitrogen of the nitrile to provide a stable carbocation **2** that reacts in a Ritter fashion with water to provide the Mannich type product **3**. The intermediacy of **1** was confirmed by its isolation and characterization ($^1$H and $^{13}$C NMR). In a separate experiment, the acetate **1** could be converted to the final product by treatment with acetonitrile.

In conclusion, we have reported an efficient and improved three-component coupling reaction for the synthesis of β-acetamide carbonyl compounds (Mannich-type products). The method offers several advantages such as high yields, short reaction times and tolerance to a wide variety of reactants.

## Acknowledgements

V.K.S. thanks the Department of Science and Technology, India for a research grant. G.P., A.G. and R.P.S. thank CSIR for research fellowships.

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6. *General experimental procedure*: To a stirred suspension of Cu(OTf)$_2$ in dry alkyl or phenyl nitrile (5 mL) were added an aldehyde (1 mmol), methylacetoacetate/ketone (1 mmol) and acetyl chloride (1.1 mmol). The reaction mixture was stirred at ambient temperature for 30 h. The solvent was removed under reduced pressure to afford a residue which was taken into ethyl acetate, washed with water, saturated sodium bicarbonate solution, and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and filtered. The filtrate was evaporated under reduced pressure and the residue was purified over silica gel to afford the β-acetamido ketones (Tables 2 and 3).
7. The ratio of *syn*/*anti* diastereomers was determined by $^1$H NMR based on the coupling constants between the methine protons.