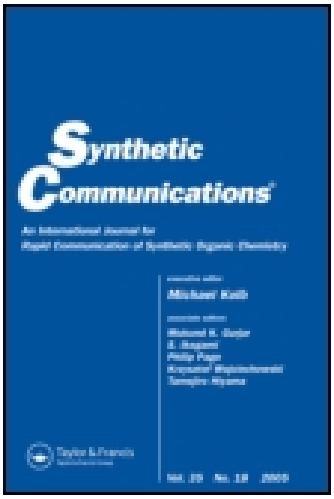

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# Simple and New Method for the Synthesis of β-Acetamido Ketones on a Solid Surface

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# SIMPLE AND NEW METHOD FOR THE SYNTHESIS OF β-ACETAMIDO KETONES ON A SOLID SURFACE

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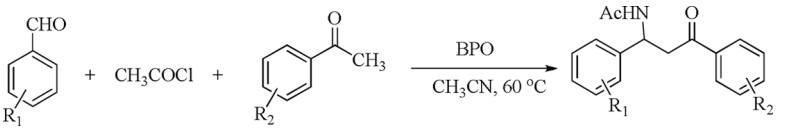
## GRAPHICAL ABSTRACT




**Abstract** *Borax/$POCl_3$(BPO) was found to be an efficient reagent for the preparation of various β-acetamido ketones by a one-pot reaction of aryl aldehydes, enolisable ketones, acetyl chloride, and acetonitrile in a solvent-free medium. The present methodology offers several advantages, such as a cheaper process, good to excellent yields, simple procedure, short reaction times, and easy workup.*

**Keywords** β-Acetamido ketones; borax; Dakin–West; multicomponent reactions; solid surface



## INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[1–3] The strategies of MCRs offer significant advantages over conventional linear-type syntheses for their high degree of atom economy, convergence, ease of execution, and broad application. MCRs are particularly useful to generate diverse chemical libraries of "druglike" molecules for biological screening.[4,5] In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. As one of the mostly studied MCRs, discovered in 1912, the Mannich reaction is an aminoalkylation reaction of aldehyde (Fig. 1)[6] and is a very useful method for the preparation of β-amino compounds.

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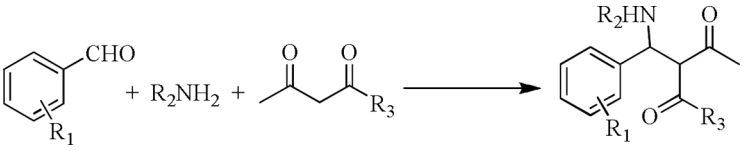



**Figure 1.**

β-Acetamido ketones are versatile intermediates, in that their skeletons exist in a number of biologically or pharmacologically active compounds.[7,8] They could easily be converted to 1,3-amino alcohols,[9] which are utilized for the synthesis of several antibiotics.[10] β-Acetamido ketones are usually prepared through acylation of β-aminoketones,[11] Michael addition to α,β-unsaturated ketones,[12] or photoisomerization of phthalimides.[13] Dakin et al. first reported the preparation of this kind of compound by the Dakin–West reaction in 1928, which is the condensation between an α-amino acid and acetic anhydride in the presence of a base, providing acetamido ketones.[14]

Some catalysts, including montmorillonite K10 Clay,[15] $SiO_2$–$H_2SO_4$,[16] triflate salts,[17] zeolite,[18] iodine,[19] $BiCl_3$ generated in situ from BiOCl and acetyl chloride,[20] $ZrOCl_2 \cdot 8H_2O$,[21] iron(III) chloride,[22] $CeCl_3 \cdot 7H_2O$,[23] heteropolyacids,[24,25] ZnO,[26] polianiline salts,[27] selectfluor,[28] and TMSCl,[29] have been employed for the synthesis of β-acetamido carbonyl compounds. While offering some advantages, all of these methods suffer from different drawbacks such as the use of expensive reagents, long reaction times, harsh reaction conditions, and tedious workup procedures.

Surface-mediated solid-phase reactions are of growing interest,[30] because of their ease of setup and workup, mild reaction conditions, rate of the reaction, selectivity, good yields, lack of solvent, and the low cost of the reactions in comparison with their homogeneous counterparts.

This article describes a facile synthesis of β-acetamido ketones. It was found that borax (anhydrous)–supported $POCl_3$ can catalyze the preparation of β-acetamido ketones by a one-pot reaction of aryl aldehydes, enolisable ketones, acetyl chloride, and acetonitrile in solvent-free conditions (Fig. 2). It is interesting to note that the reaction was not observed in the presence of $POCl_3$ and borax separately.

To find the optimal conditions, the synthesis of β-acetamido-β-phenyl propiophenone was used as a model reaction. A mixture of benzaldehyde (3 mmol), acetophenone (3 mmol), acetyl chloride (0.6 ml), and acetonitrile (10 ml) was stirred under various reaction conditions at 80 °C (Table 1). In the absence of the catalyst, β-acetamido-β-phenyl propiophenone was obtained in a trace amount after 10 h,

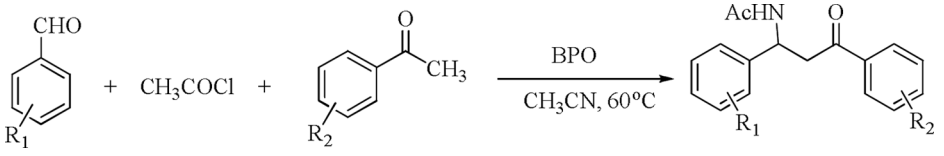



**Figure 2.**

**Table 1.** Preparation of β-acetamido-β-phenyl propiophenone from benzaldehyde (3 mmol) and acetophenone (3 mmol) in the presence of acetyl chloride (0.6 mL) and acetonitrile (10 mL) in various conditions at 80 °C

| Entry | Catalyst (g) | Time (h) | Yield[a] (%) |
|---|---|---|---|
| 1 | No catalyst | 10 | Trace |
| 2 | Borax (0.3) | 5 | 25 |
| 3 | $POCl_3$ (0.3) | 5 | 5 |
| 4 | BPO (0.05) | 3 | 45 |
| 5 | BPO (0.1) | 0.5 | 89 |
| 6 | BPO (0.2) | 0.5 | 88 |
| 7 | BPO (0.3) | 0.5 | 90 |

[a]Isolated yields.

**Table 2.** Preparation of β-acetamido-β-phenyl propiophenone from benzaldehyde (3 mmol) and acetophenone (3 mmol) in the presence of acetyl chloride (0.6 mL), acetonitrile (10 mL), and BPO (0.1 g) at different temperatures

| Entry | Temperature (°C) | Time (h) | Yield[a] (%) |
|---|---|---|---|
| 1 | 25 | 5 | 45 |
| 2 | 45 | 1.5 | 67 |
| 3 | 60 | 0.5 | 88 |
| 4 | 80 | 0.5 | 89 |

[a]Isolated yields.



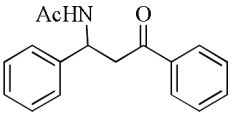
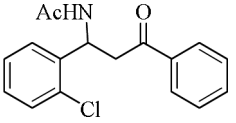
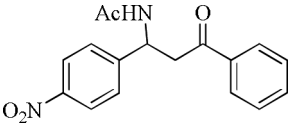
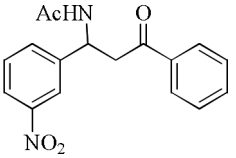
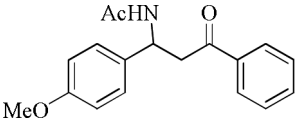
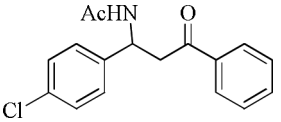
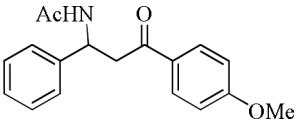
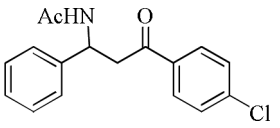
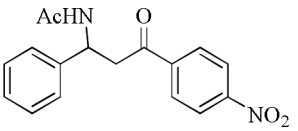
while good results were obtained in the presence of BPO after 0.5 h (Table 1, entries 5–7). Using an optimized amount of catalyst, we found that 0.1 g of BPO could effectively catalyze the model reaction at 80 °C. With inclusion of 0.05 g BPO, the reaction took a longer time. No significant impact on the yield was observed when the amount of BPO was increased to 0.3 g. (Table 1, entries 6 and 7). The effect of temperature was studied by carrying out the model reaction in the presence of BPO (0.1 g) at room temperature (25 °C), 45 °C, 60 °C, and 80 °C. It was observed (Table 2, entries 1–3) that the yield was increased as the reaction temperature was raised, but above 60 °C temperature has no effect on the yield and time of the reaction.

To evaluate the efficiency of this methodology, we used several other aromatic aldehydes and acetophenone derivatives having electron-donating as well as electron-withdrawing substituents to obtain the corresponding β-acetamido ketones under the optimized reaction conditions (Table 3). In general, electron-donating substituents furnished faster reaction rates, affording β-acetamido ketones in good yields (Table 3, entries 5, 7, and 17). On the other hand, electron-withdrawing substituents decreased the rate of the reaction, and moderate yields of β-acetamido ketones were obtained (Table 3, entries 11–15).

## EXPERIMENTAL

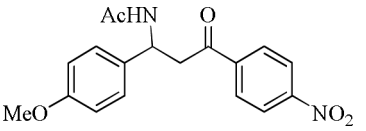
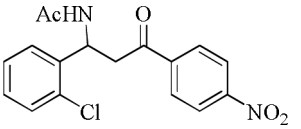
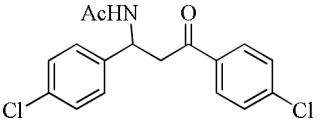
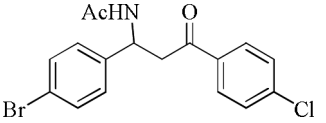
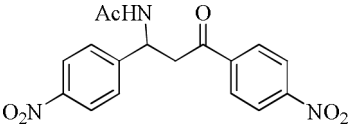
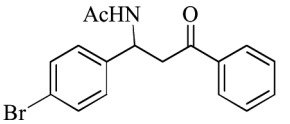
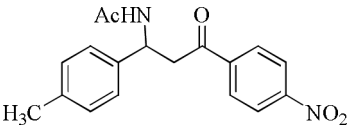
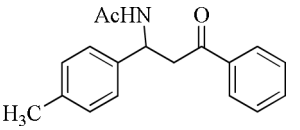
All compounds were known, and their physical and spectroscopic data were compared with those of authentic samples and found to be identical.

**Table 3.** One-pot condensation of aryl aldehydes, aryl ketones, acetyl chloride, and acetonitrile to give the corresponding β-acetamido ketones catalyzed by BPO

| Entry | R1 | R2 | Product | Time (min) | Yield[a] (%) | Mp Found | Mp Reported |
|---|---|---|---|---|---|---|---|
| 1 | H | H |  | 30 | 88 | 102–103 | 103–105[29] |
| 2 | 2-Cl | H |  | 40 | 85 | 134–136 | 135–137[29] |
| 3 | 4-$NO_2$ | H |  | 65 | 80 | 146–147 | 148–149[15] |
| 4 | 3-$NO_2$ | H |  | 70 | 87 | 112–114 | 112–115[15] |
| 5 | 4-OMe | H |  | 30 | 90 | 109–112 | 110–112[29] |
| 6 | 4-Cl | H |  | 40 | 78 | 143–145 | 146–148[29] |
| 7 | H | 4-OMe |  | 25 | 86 | 128–131 | 130[21] |
| 8 | H | 4-Cl |  | 30 | 75 | 178–180 | 177–178[31] |
| 9 | H | 4-$NO_2$ |  | 40 | 82 | 99–101 | 101–103[32] |

(*Continued*)

**Table 3.** Continued

| Entry | R1 | R2 | Product | Time (min) | Yield[a] (%) | Mp Found | Mp Reported |
|---|---|---|---|---|---|---|---|
| 10 | 4-OM | 4-$NO_2$ |  | 45 | 77 | 86–88 | 87–89[15] |
| 11 | 4-Cl | 4-$NO_2$ |  | 40 | 82 | 193–196 | 192–195[32] |
| 12 | 4-Cl | 4-Cl |  | 50 | 77 | 140–142 | 141–143[16] |
| 13 | 4-Br | 4-Cl |  | 50 | 74 | 137–139 | 137–138[31] |
| 14 | 4-$NO_2$ | 4-$NO_2$ |  | 60 | 78 | 186–188 | 187–188[13] |
| 15 | 4-Br | H |  | 45 | 81 | 147–148 | 147–149[29] |
| 16 | 4-$CH_3$ | 4-$NO_2$ |  | 40 | 86 | 83–84 | 83–85[15] |
| 17 | 4-$CH_3$ | H |  | 30 | 78 | 111–113 | 112–114[29] |

[a]Isolated yields.

## Preparation of BPO

A mixture of $POCl_3$ (3 g) and anhydrous borax (2 g) were combined in a mortar and pestle by grinding them together until a fine, homogeneous powder was obtained (15–20 min).

**Table 4.** Comparison of the results for the preparation of β-acetamido ketones (Table 2, entry 1) using multicomponent reactions with some other catalysts

| Catalyst | Time (h) | Temperature (°C) | Yield (%) [Ref.] |
|---|---|---|---|
| BPO | 0.5 | 60 | 88 [Table 3] |
| Montmorillonite K-10 | 7 | 70 | 80[15] |
| Silica sulfuric acid | 1.08 | 80 | 91[16] |
| $Sc(OTf)_3$ | 30 | r.t | 82[17] |
| $ZrOCl_2 \cdot 8H_2O$ | 5 | r.t | 90[21] |
| ZnO | 6 | 80 | 90[33] |
| $BF_3 \cdot OEt_2$ | 30 | r.t | 78[17] |

### Synthesis of β-Acetamido Ketone: General Procedure

A mixture of ketone (3 mmol), aldehyde (3 mmol), and acetyl chloride (0.6 mL) in acetonitrile (10 mL) in the presence of BPO (0.1 g) was heated at 60 °C. The progress of reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was filtered to separate the catalyst, and then the solvent was evaporated to dryness under reduced pressure. The pure products could be obtained by recrystallization from a mixture of ethanol and water.

## CONCLUSION

In conclusion, we have developed a simple methodology for the one-pot synthesis of β-acetamido ketones by coupling four components (viz. benzaldehydes, acetophenones, acetyl chloride, and acetonitrile), catalyzed by BPO. The major advantages of the present protocol over existing methods can be seen by comparing our results with those of some recently reported procedures, as shown in Table 4. Good yields of the products, short reaction times, mild reaction conditions, and the ease of workup procedure make this protocol complementary to the existing methods. Studies for the application of this method as catalyst for several reactions are under investigation in our laboratory.

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