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Zinc oxide as an economical and efficient catalyst for the one-pot preparation of β-acetamido ketones via a four-component condensation reaction

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Abstract—A new, efficient, one-pot, four-component condensation of benzaldehyde derivatives, acetophenone derivatives, acetyl chloride and acetonitrile in the presence of zinc oxide as catalyst is described for the synthesis of β-acetamido ketones.

1. Introduction

Multicomponent reactions (MCRs) are important for the achievement of high levels of diversity, as they allow more than two building blocks to be combined in practical, time-saving one-pot operations, giving rise to complex structures by simultaneous formation of two or more bonds, according to the domino principle.[1] MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Researchers have transformed this powerful technology into one of the most efficient and economic tools for combinatorial and parallel synthesis.[1,2] Due to their inherent simple experimental procedures and their one-pot character, they are perfectly suited for automated synthesis. Thus, MCRs have attracted considerable interest owing to their exceptional synthetic efficiency.[1–3]

Acetamido- or amino-ketone derivatives are important for their biological and pharmaceutical properties,[4] and in the preparation of antibiotic drugs such as nikkomycine or neopolyoxines.[5] The best known route for the synthesis of this class of compounds is the Dakin–West reaction,[6a] the condensation of an α-amino acid with acetic anhydride in the presence of a base provides the α-acetamido ketones via an azalactone intermediate.[6b] Recently, other synthetic methods have been used for the formation of β-acetamido ketones through the multicomponent condensation of aryl aldehydes, enolizable ketones and acetyl chlorides in acetonitrile in the presence of Lewis or Brønsted acid catalysts such as $CoCl_2$,[7,8] Montmorillonite K-10 clay,[9] silica sulfuric acid,[10] $BiCl_3$ generated from BiOCl,[11] $ZrOCl_2{\cdot}8H_2O$,[12] heteropoly acid,[13] sulfuric acid absorbed on silica gel,[14] $Sc(OTf)_3$[15] and silica supported $H_3PW_{12}O_4$.[16]

In recent years, zinc oxide (ZnO) has gained much interest in the synthesis of nitriles from aldoximes,[17] the Beckmann rearrangement,[18] Friedel–Crafts acylation[19] and the acylation of alcohols, phenols and amines.[20] Herein, we describe a new, simple, mild and effective procedure for the one-pot synthesis of β-acetamido ketones via a four-component condensation reaction between aldehydes, enolizable ketones, acetyl chloride and acetonitrile in the presence of zinc oxide as catalyst (Scheme 1). The MCRs for the preparation of β-acetamido ketones were carried out under reflux at 80 °C.

First, we prepared *N*-(3-oxo-1,3-diphenylpropyl)acetamide from the reaction of benzaldehyde, acetophenone, acetyl chloride and acetonitrile (reactant as well

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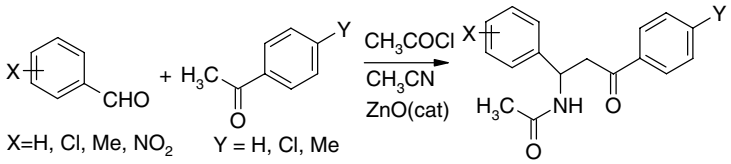


Scheme 1.

as solvent) in the presence of different metal oxides including CuO, Fe_2O_3, CdO, TiO_2, Th_2O_3, neutral Al_2O_3 and ZnO (Table 1).

The results in Table 1 show that amongst these catalysts, ZnO was the catalyst of choice in terms of yield. Furthermore, it is moisture stable, non-toxic and easy to handle; it is also an inexpensive and commercially available inorganic solid Lewis acid.

Next, we optimized the amount of zinc oxide in the reaction between benzaldehyde, acetophenone, acetyl chloride and acetonitrile (Table 2). The optimum amount of ZnO was found to be 50 mol %.

Thus, we prepared a range of β-acetamido ketones under the optimized reaction conditions: aldehyde (1 equiv), enolizable ketone (1 equiv), acetyl chloride (2 equiv) and acetonitrile (reactant as well as solvent, 4 mL) in the presence of ZnO (50 mol %) (Table 3).

As shown in Table 3, aromatic aldehydes or acetophenones with both electron-withdrawing or -donating substituents produced β-acetamido ketones without the formation of any side products, in high to excellent yields at reflux (Table 3, entries 1–23).

Table 1. Preparation of β-acetamido ketones from benzaldehyde and acetophenone in the presence of acetyl chloride and acetonitrile catalyzed using a variety of metal oxides under reflux at 80 °C

Entry	Metal oxide[a]	Time (h)	Yield[b] (%)
1	CuO	20	40
2	Fe_2O_3	20	65
3	CdO	18	35
4	TiO_2	18	20
5	Th_2O_3	45	—
6	Neutral Al_2O_3	45	—
7	ZnO	6	90

[a] 50 mol % used for each reaction.
[b] Isolated yield.

Table 2. Preparation of β-acetamido ketones from benzaldehyde and acetophenone in the presence of acetyl chloride and acetonitrile catalyzed using ZnO under reflux at 80 °C

Entry	Metal oxide (mol %)	Time (h)	Yield[a] (%)
1	10	48	70
2	20	24	75
3	30	12	87
4	40	9	89
5	50	6	90
6	60	5.5	90
7	70	5.2	91

[a] Isolated yield.

The proposed mechanism for the ZnO catalyzed transformation is shown in Scheme 2. Although it is not clear how ZnO acts as a catalyst for the reaction, on the basis of previously reported mechanism for applying of ZnO for the preparation of acylium ion in Friedel–Crafts acylation reaction[19] and also acylation of alcohols, phenols and amines[20] it is suggested that the aldehyde is first acylated to an intermediate **I** which then reacts with the enol form of acetophenone derivative to produce **III** after exchange of H^+ from **II**. Next, acetonitrile attacks **III** with elimination of acetate to give **IV**. Generated HCl could be trapped by ZnO which is converted to $ZnCl_2$.[21] Hydrolysis of **IV** accompanied by tautomerization gave the desired β-acetamido ketone. Furthermore, the reaction was also performed in the presence of $ZnCl_2$ as catalyst which also led to the one-pot synthesis of the β-acetamido ketone.

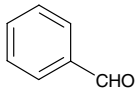
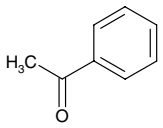
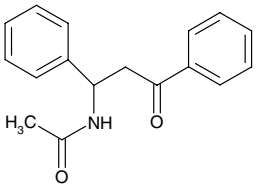
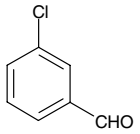
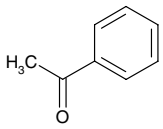
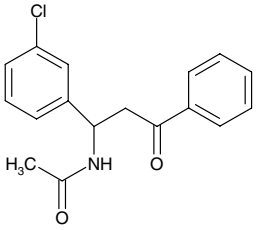
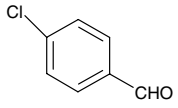
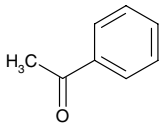
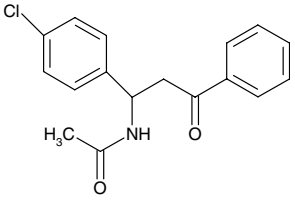
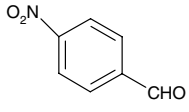
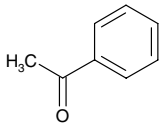
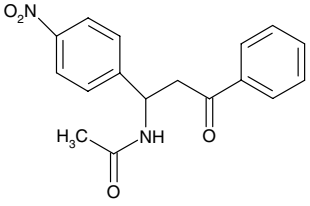
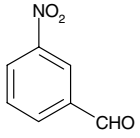
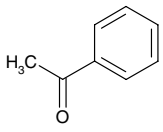
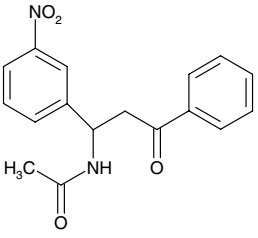
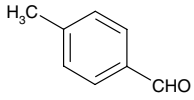
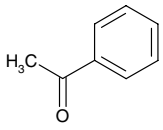
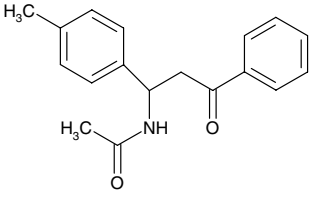
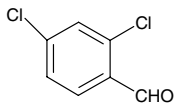
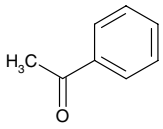
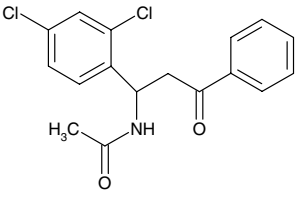
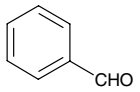
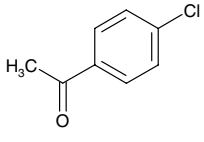
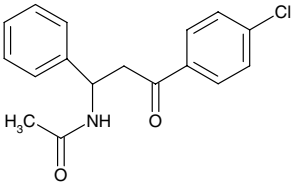
In summary, we have demonstrated ZnO as a cheap, commercially available, reusable and non-corrosive catalyst for the synthesis of β-acetamido ketones in excellent yields under mild reaction conditions. The simple experimental procedure combined with the easy work-up and excellent yields of products are salient features of the presented method.

2. General experimental procedure for the one-pot preparation of β-acetamido ketones

A solution of the aryl aldehyde (2 equiv), aryl ketone (2 equiv), acetyl chloride (4 equiv), acetonitrile (4 mL) and ZnO (1 equiv) was heated at 80 °C under reflux. The reaction mixture was stirred for the appropriate time (Table 3). The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled and poured into 50 mL of ice-water. The solid residue was separated and dissolved in dichloromethane. The solution was filtered and zinc oxide was isolated and could be reused. The organic phase was absorbed on silica gel and purified by column chromatography petroleum ether (60–80 °C)/ethyl acetate (9/1). All the products were identified by comparison of their ^{1}H NMR and IR data with those of authentic samples.[7–16] The spectral data of some representative β-acetamido ketones are given below.

β-Acetamido-β-(phenyl)propiophenone (Table 3, entry 1). Mp: 102–104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.03 (s, 3H), 3.45 (dd, $J = 6.0$ and 16.9 Hz, 1H), 3.77 (dd, $J = 5.2$ and 16.9 Hz, 1H), 5.58 (dd, $J = 5.6$ and

Table 3. Preparation of β-acetamido ketones from aldehydes and enolizable ketones in the presence of acetyl chloride and acetonitrile catalyzed using 50 mol % zinc oxide

Entry	Aldehyde	Ketone	Product	Time (h)	Yield[a] (%)
1				6	90
2				5.5	93
3				5.5	92
4				5.5	88
5				5	90
6				5.5	89
7				5	93
8				6	89

(*continued on next page*)

Table 3 (*continued*)

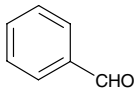
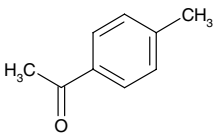
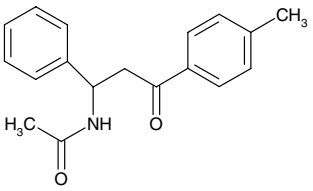
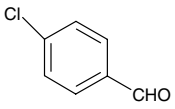
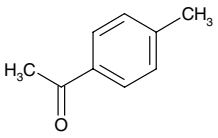
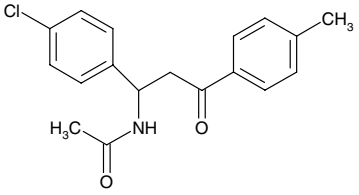
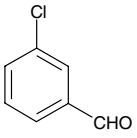
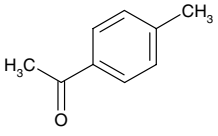
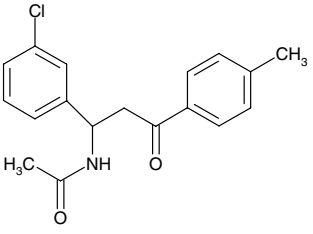
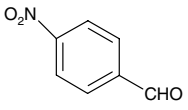
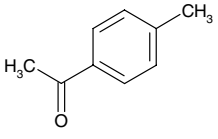
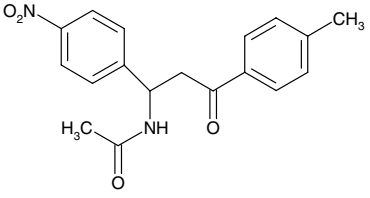
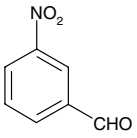
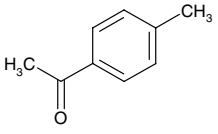
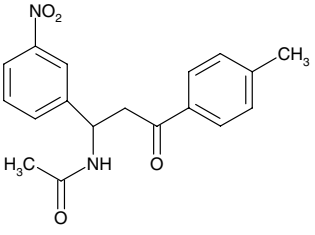
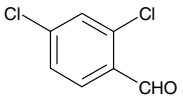
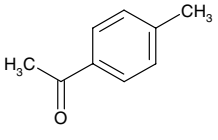
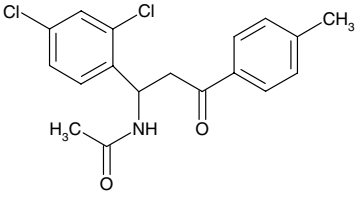
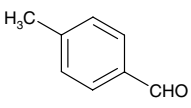
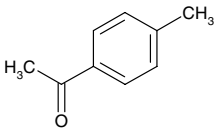
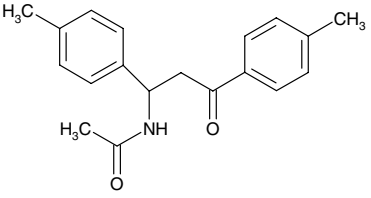
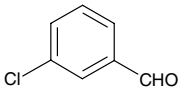
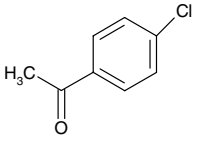
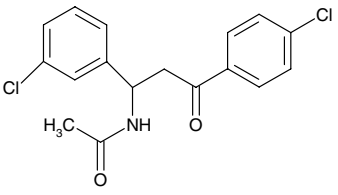
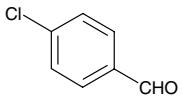
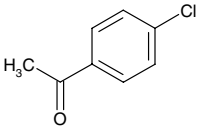
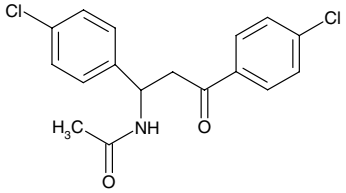
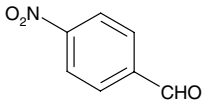
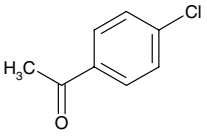
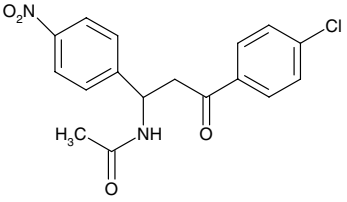
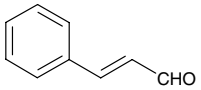
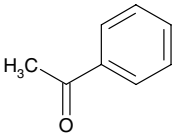
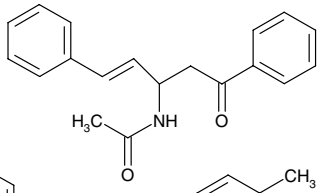
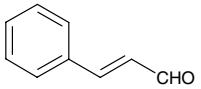
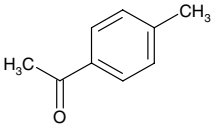
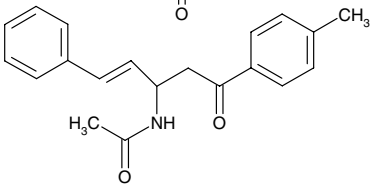
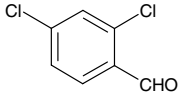
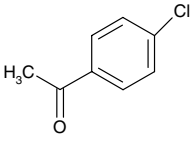
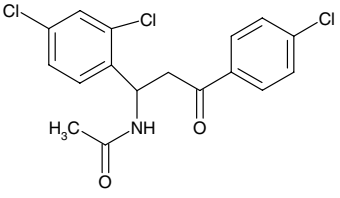
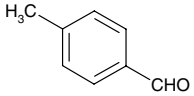
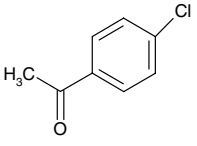
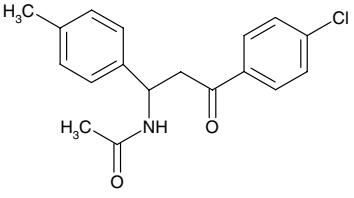
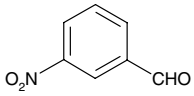
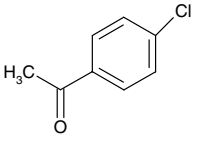
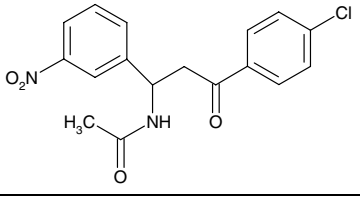
Entry	Aldehyde	Ketone	Product	Time (h)	Yield[a] (%)
9				5	92
10				6	87
11				6	88
12				5.5	87
13				5	86
14				5	91
15				5.5	93
16				5	89

Table 3 (*continued*)

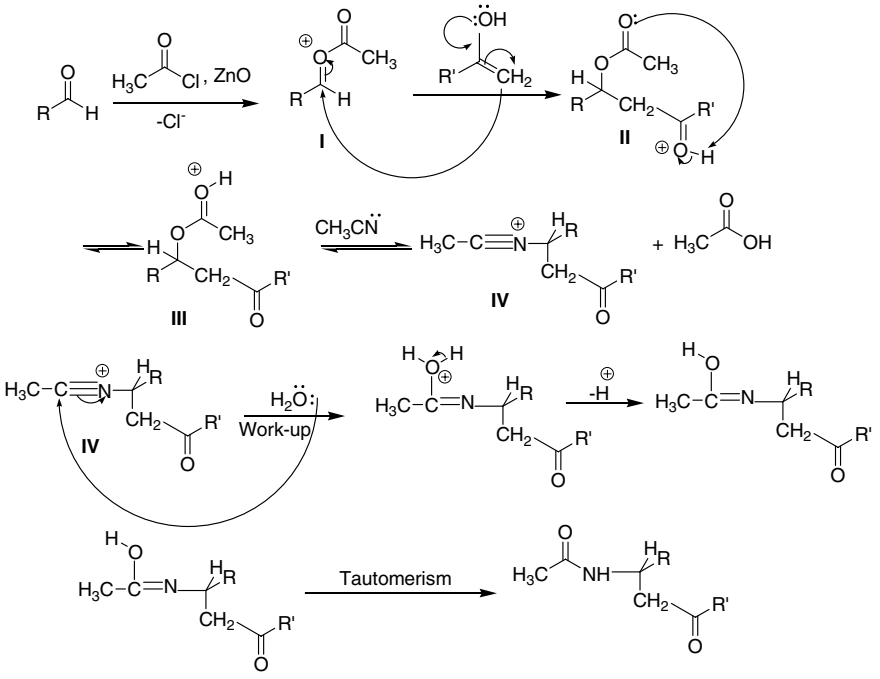
Entry	Aldehyde	Ketone	Product	Time (h)	Yield[a] (%)
17				6	92
18				6	88
19				2	89
20				2	87
21				5	94
22				5	91
23				6	87

[a] Isolated yield and all of the products were identified by comparing their ^{1}H NMR and IR data with those for authentic samples.[7–16]

13.1 Hz, 1H), 6.90 (d, $J = 6.3$ Hz, 1H), 7.24–7.60 (m, 8H), 7.91 (d, $J = 7.5$ Hz, 2H) ppm; IR (KBr, cm^{-1}) 3423, 1772, 1659, 1500, 1374, 1295, 1188, 1023, 704, 585.

β-Acetamido-β-(3-chlorophenyl)-4-chloropropiophenone (Table 3, entry 16). Mp: 111–113 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.07 (s, 3H), 3.42 (dd, $J = 5.9$ and 17.3 Hz, 1H), 3.75 (dd, $J = 5.4$ and 17.5 Hz, 1H), 5.54 (dd, $J = 5.6$ and 13.5 Hz, 1H), 7.17–7.24 (m, 4H), 7.34 (s, 1H), 7.42 (d, $J = 8.6$ Hz, 2H), 7.85 (d, $J = 8.6$ Hz, 2H); IR (KBr, cm^{-1}) 3300, 3135, 1687, 1638, 1584, 1532, 1394, 1361, 1086, 989, 817, 782, 698.

β-Acetamido-β-(2,4-dichlorophenyl)-4-chloropropiophenone (Table 3, entry 21). Mp: 163–165 °C, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.08 (s, 3H), 3.42 (dd, $J = 5.4$ and



Scheme 2.

17.2 Hz, 1H), 3.77 (dd, $J = 6.0$ and 17.2 Hz, 1H), 5.79 (dd, $J = 5.8$ and 13.5 Hz, 1H), 7.22 (dd, $J = 2.0$ and 8.4 Hz, 1H), 7.36 (d, $J = 2.0$ Hz, 1H), 7.41–7.47 (m, 4H), 7.84 (d, 8.5 Hz, 2H); IR (KBr, cm^{-1}) 3285, 3130, 2985, 1682, 1650, 1586, 1547, 1469, 1399, 1093, 990, 815.

Acknowledgement

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