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Facile synthesis of *β*-amino ketones *via* direct Mannich-type reaction catalysed by Zirconium oxychloride

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ABSTRACT

Zirconium oxychloride($ZrOCl_2{\cdot}8H_2O$) in ethanol at room temperature is proven to act as a very efficient catalyst for a one-pot synthesis of β-amino ketones from the condensation of aromatic ketones, aromatic aldehydes and aromatic amines in short reaction time. The present environmentally benign procedure for the synthesis of β-amino ketones is suitable for library synthesis and it will find application in the synthesis of potent biologically active molecules. The process presented here is operationally simple, environmentally benign and has excellent yield. Furthermore, the catalyst can be recovered conveniently and reused efficiently.

Keywords: Zirconium oxychloride; One-pot synthesis; Mannich reaction; *β*-aminocarbonyl compound

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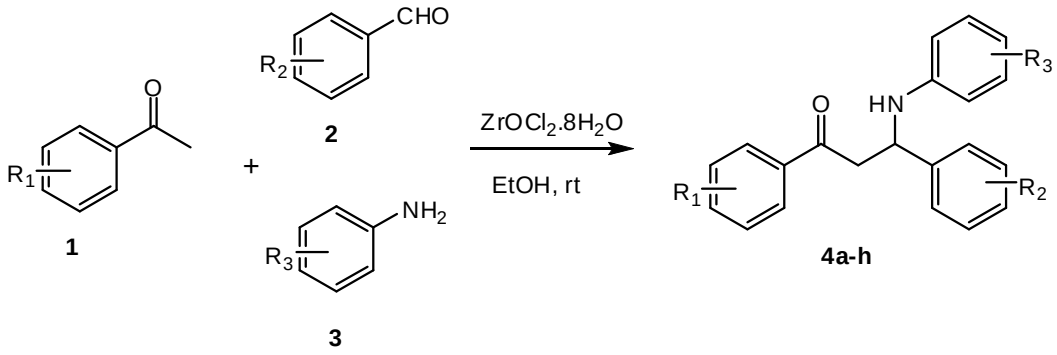
INTRODUCTION

Multicomponent reactions (MCRs) are special types of synthetically useful organic reactions in which three or more different starting materials react to a final product in a one pot procedure. Such reactions are atom-efficient processes by incorporating the essential parts of the starting materials into the final product. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high throughput generation of organic compounds. MCRs comply with the principles of green chemistry in terms of economy of steps as well as many of the stringent criteria of an ideal organic synthesis. These reactions are effective in building highly functionalized small organic molecules from readily available starting materials in a single step with inherent flexibility for creating molecular complexity and diversity coupled with minimization of time, labour, cost and waste production [1]. Hence, the development of multi-component reaction protocols for the synthesis of heterocyclic compounds has attracted significant interest in modern organic synthesis and medicinal chemistry.

Mannich reactions are focused on the condensation of enolizable ketones with formaldehyde and amines. They are among the most important carbon-carbon bond forming reactions in organic synthesis and provide *β*-amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals and natural products. Therefore, the development of new synthetic methods leading to *β*-amino carbonyl compounds or their derivatives have attracted much attention [2,3]. In recent years, much attention has been drawn to the development of new synthetic methods to prepare one-pot Mannich reactions using a variety of acidic catalysts [4-15].

As a continuing interest in the development of new carbon-carbon bond formation reactions [16-17],we found Zirconium oxychloride($ZrOCl_2{\cdot}8H_2O$)as an inexpensive and commercially available catalyst and can efficiently catalyze through one-pot condensation of aromatic ketones, aromatic aldehydes and aromatic amines in short reaction time (Scheme 1). After the reaction, $ZrOCl_2{\cdot}8H_2O$ could be easily recovered by simple phase separation and could be reused many times without loss of its catalytic activity. Application of such catalysts will lead to minimal pollution and waste material. Literature study reveal that, direct Mannich type reaction catalyzed by $ZrOCl_2{\cdot}8H_2O$has not been reported.



Scheme 1 Synthesis of *β*-amino carbonyl compounds from aromatic ketones, aromatic aldehydes and aromatic amines using $ZrOCl_2{\cdot}8H_2O$

MATERIALS AND METHODS

Apparatus and analysis

All chemicals were purchased from merck and Aldrich chemical companies. Analytical thin-layer chromatography was performed with E.merck silica gel 60F glass plates. Visualization of the developed chromatogram was performed on silica gel 90, 200-300 mesh. ^{1}H NMR (300MHz) and. ^{13}C NMR (75MHz) spectra were obtained using a Bruker DRX-500 Avance at ambient temperature, using TMS as an internal standard.Mass spectra were determined on a Varian-Saturn instrument. FT-IR spectra were obtained as KBr pellets on shimadzu spectrometer.

General procedure for the synthesis of mannich base derivatives

A mixture aromatic ketone **1** (11 mmol) aromatic aldehyde **2** (10 mmol), aromaticlamine**3** (10 mmol), and $ZrOCl_2{\cdot}8H_2O$(10 mol%) was stirred in EtOH (10 ml) at room temperature. The progress of reaction was monitored by TLC. The reaction mixture was placed at room temperature, then 60ml hot CH_2Cl_2 was added to dissolve the solid product. The catalyst was removed by hot filtration and dried for next use. The organic layer was washed twice saturated $NaHCO_3$ solution (10 ml), dried (Na_2SO_4), and evaporated to yield the crude product. The crude product was purified *via* recrystalisation from ethanol or ethanol / acetone (v/v = 3:2) to give the corresponding compounds.

Spectral data for selected compounds

1-(4-nitrophenyl)-3-phenyl-3-(phenylamino)propan-1-one ***(4b)***

IR (KBr, cm 1): 3405 (N-H), 3054 (C-H), 1687 (C=O), 1596 (C=C), 1340 (C-C); ^{1}HNMR(300 MHz, DMSO-d_6) (δ ppm): 6.45–7.97 (m, 14H, Ar-H), 6.25 (d, 1H, NCH), 5.01 (s, 1H, NH), 3.68-3.77 (dd, 2H, $COCH_2$).^{13}C NMR(75 MHz, DMSO-d_6) (δppm): 47.5, 53.2, 113.3, 116.4, 122.2, 123.5, 124.6, 125.5, 126.4, 127.2, 128.8, 129.1, 129.4, 141.8, 142.7, 144.2, 150.2, 197.0. MS (ESI): m/z 346. Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.76; H, 5.19; N, 8.02%.

3-(4-hydroxyphenyl)-1-(4-nitrophenyl)-3-((4-nitrophenyl)amino)propan-1-one ***(4h)***

IR (KBr, cm 1): 3409 (N-H), 3101 (C-H), 1689(C=O), 1697(C=C), 1342 (C-C); ^{1}HNMR (300 MHz, DMSO-d_6) (δ ppm):9.67 (s, 1H, OH), 6.77–8.35 (m, 12H, Ar-H), 6.60 (d, 1H, NCH), 5.01 (s, 1H, NH), 3.32-3.40 (dd, 2H, $COCH_2$).^{13}C NMR (75 MHz, DMSO-d_6) (δppm): 47.5, 53.2, 112.2, 121.9, 122.2, 123.5, 124.6, 125.5, 126.4, 127.2, 128.8, 130.0, 131.9, 136.0, 142.7, 144.9, 148.0, 156.1, 190.3. MS (ESI): m/z 407. Anal. Calcd for $C_{21}H_{17}N_3O_6$: C, 61.91; H, 4.21; N, 10.31. Found: C, 61.95; H, 4.11; N, 10.28%.

RESULTS AND DISCUSSION

To obtain the optimum condition for the synthesis of β-aminocarbonyl compounds, the reaction of acetophenone, benzaldehyde and aniline was chosen as a model reaction. Initially, a systematic study was carried out for catalytic evaluation of $ZrOCl_2{\cdot}8H_2O$for the preparation of β-aminocarbonyl compounds at room temperature in ethanol. Our studies showed that in the absence of catalyst in ethanol no product was formed (Table 1, entry 1). The model reaction was conducted in the presence of various catalysts (Table 1, entries 2–8). Among the various catalysts, $ZrOCl_2{\cdot}8H_2O$proved to be the best (Table 1, entry 8). Lower yield was obtained when the same reaction carried out with lower amount of the catalyst (Table 1, entries9-11). Further, an increase in the amount of the catalyst no improvement could be observed in the yield of the product (Table 1, entry 12).

Using the optimized reaction conditions, a range of *β*-aminocarbonyl compounds were synthesized. Various substituted aromatic ketones, aromatic aldehydes, and aromatic amines undergo the reaction in the presence of catalytic amount of $ZrOCl_2{\cdot}8H_2O$(10mol%) in ethanol at room temperature to furnish the corresponding*β*-aminocarbonyl compounds (Scheme 1). The results of this study are summarized in Table 2. It was indicated that both electron deficient and electron rich aromatic compounds worked well, giving high yield of the product.

Reusability of the catalyst:

The reusability of the catalyst is one of the most important benefits and makes it useful for commercial applications. Thus the recovery and reusability of $ZrOCl_2{\cdot}8H_2O$were investigated. The reusability of the catalyst was checked by separating the $ZrOCl_2{\cdot}8H_2O$ from the reaction mixture and drying in a vaccum oven at 60^oC for 4 h prior to reuse in subsequent reaction. The recovered catalyst one be reused at least three additional times in subsequent reactions without significant loss in product yield (Fig 1)

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Table 1The direct mannich reaction: effect of catalyst[a]

Entry	Catalyst	Amount of catalyst (mol %)	Time(h)	Yield(%)[b]
1	None	-	8	0
2	$FeCl_3$	10	6	21
3	$InCl_3$	10	4	32
4	$La(OTf)_3$	10	4	52
5	$Nd(OTf)_3$	10	4	68
6	$Yb(OTf)_3$	10	5	82
7	$Al(CH_3SO_3)_3.4H_2O$	10	4	84
8	$ZrOCl_2{\cdot}8H_2O$	10	3	92
9	$ZrOCl_2{\cdot}8H_2O$	8	3	88
10	$ZrOCl_2{\cdot}8H_2O$	5	3	76
11	$ZrOCl_2{\cdot}8H_2O$	3	3	68
12	$ZrOCl_2{\cdot}8H_2O$	15	3	92

[a]*Reaction Conditions: benzaldehyde (10 mmol), aniline (10 mmol), acetophenone(11 mmol) stirring in ethanol.*
[b]*Isolated Yields*

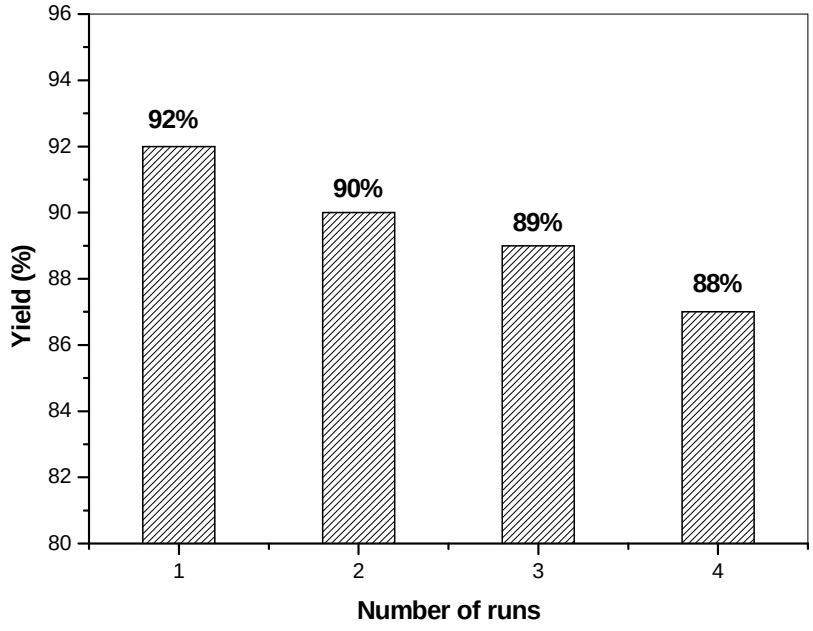

Figure 1 Reusability of catalyst

Table 2 The direct mannich reaction of various aromatic ketone, aromatic aldehyde, aromatic amine[a]

Entry	R_1	R_2	R_3	Product	Time (h)	Yield (%)[b]
1	H	H	H	**4a**	3.0	92
2	4- NO_2	H	H	**4b**	3.0	89
3	H	H	4-Cl	**4c**	3.0	80
4	H	4-OH	4-NO_2	**4d**	2.5	92
5	H	4-Cl	4-NO_2	**4e**	2.5	87
6	4-NO_2	4-CH_3	H	**4f**	3.0	88
7	H	4-CH_3	H	**4g**	3.0	90
8	4-NO_2	4-OH	4-NO_2	**4h**	3.0	86

[a]*Reaction conditions: aromatic ketons (11 mmol), aromatic aldehyde (10 mmol), aromatic amine (10 mmol) and ethanol at room temperature.*
[b]*Isolated Yields.*

CONCLUSION

An economic, rapid, and environmentally benign procedure has been developed for one-pot synthesis of *β*-aminocarbonyl compounds at room temperature in ethanol by three-component reaction of aromatic aldehydes, aromatic ketones and aromatic amines with $ZrOCl_2{\cdot}8H_2O$as catalyst. The method has several advantages, including short reaction times, high yields, and facile workup, which makes it a useful and attractive procedure for synthesis of these compounds.

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