

Short communication

Silzic ($\text{ZnCl}_2/\text{SiO}_2$) as a New and Recyclable Zinc (II) Catalyst for One-pot Three-component Syntheses of β -aminocarbonyl Compounds under Solvent-free Conditions

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Abstract

Silzic ($\text{ZnCl}_2/\text{SiO}_2$) is an efficient and recyclable catalyst for one-pot three-component coupling reaction of aldehydes, amines and ketones to produce the corresponding β -aminocarbonyl compounds in high yields under solvent-free conditions. The advantages of this protocol are high yields, mild reaction conditions, simple work-up and less environmental pollution. In addition, the preparation of silzic is simple and has higher activity than homogeneous ZnCl_2 .

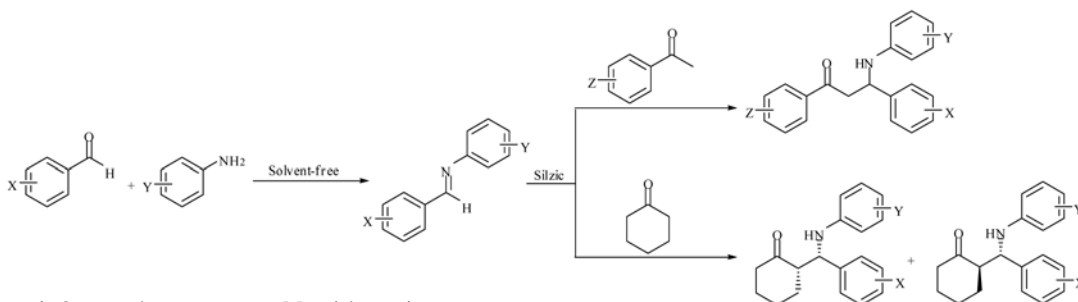
Keywords: Silzic, ZnCl_2 , mannich reaction, β -aminocarbonyl compounds, solvent-free.

1. Introduction

Multi-component reactions (MCRs) performed either in the solid phase or in solution,¹ have emerged as powerful tools in combinatorial chemistry for the generation of small-molecule libraries. The goal is to find new leads for drug development and optimization of processes or to identify novel biologically active substrates.

Mannich reaction is one of the most important multi-component reactions in organic synthesis. It provides β -amino carbonyl compounds, which are useful as building blocks for the synthesis of various pharmaceutically important compounds and natural products.² The increasing

popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen containing compounds in drugs, natural products, and have found wide application in organic synthesis.³ The classical Mannich reaction has some limitations, such as requirements for harsh reaction conditions and long reaction times. In addition, indirect-type⁴ Mannich reactions using preformed electrophiles such as imines and stable nucleophiles such as enolates or enol ethers suffer from the drawback of the necessity for the isolation and purification of the preformed intermediates. Therefore, a modified and improved methodology, known as the direct-type and using directly carbonyl compounds as nucleophiles was introduced.^{5–8} Although these methodologies are useful, most of the methods still en-



Scheme 1: One-pot three-component Mannich reactions

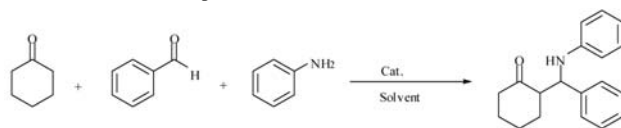
counter some limitations, such as requirements for expensive and non-recyclable catalysts, using a non-environmental-friendly organic solvent, difficult separation of the products and longer reaction times. Furthermore, some of the catalysts are corrosive and volatile, and often cause environmental hazards. It is thus evident that there remains a wide scope for the development of clean and efficient methodologies for the preparation of β -amino carbonyl compounds through a convenient and environmentally friendly method.

In this account we describe a mild, convenient, and simple procedure for efficient one-pot, three-component reaction of an aldehyde, an amine, and a ketone in the preparation of β -amino carbonyl compounds under solvent-free conditions using silzic as a reusable and efficient solid catalyst (Scheme 1).

2. Results and Discussion

In order to delineate the standard operating conditions, the reaction between benzaldehyde, aniline and cyclohexanone in the presence of supported (silzic) and unsupported ZnCl_2 in various solvents including CH_3CN , CHCl_3 , EtOH and solvent-free conditions was chosen as a model. The results, summarized in Table 1, showed that 2.5 mol % of ZnCl_2 efficiently catalyze the one-pot three-

Table 1: Mannich reactions of benzaldehyde, aniline, and cyclohexanone at room temperature.^a



| Entry | Catalyst (Mol %) | Solvent | Time (min) | Yield (%) |
|-------------------------|-----------------------|------------------------|------------|-----------|
| 1 | ZnCl_2 (2.5) | CH_3CN | 180 | 80 |
| 2 | ZnCl_2 (2.5) | CHCl_3 | 180 | 57 |
| 3 | ZnCl_2 (2.5) | EtOH | 180 | 95 |
| 4 | ZnCl_2 (2.5) | – | 20 | 92 |
| 5 | ZnCl_2 (1) | – | 180 | 65 |
| 6 | Silzic 10% (1) | – | 15 | 97 |
| 7 (1 th run) | Silzic 10% (1) | – | 20 | 92 |
| 8 (2 nd run) | Silzic 10% (1) | – | 20 | 90 |
| 9 (3 rd run) | Silzic 10% (1) | – | 20 | 90 |

^a The ratio of benzaldehyde : aniline : cyclohexanone is 2:2:3.

component Mannich reaction in ethanol or under solvent-free conditions (entries 1–5). However, the recovery of ZnCl_2 is not possible. To overcome this shortcoming, a recoverable heterogeneous zinc(II) catalyst (silzic)⁹ was prepared and used for the model reaction under solvent-free conditions. It was found that in the presence of lower amount of the supported catalyst the reaction was comple-

ted in a shorter time (Table 1, entry 6). Furthermore, the catalyst can be easily separated from the reaction mixture by a simple filtration after addition of hot ethanol to the reaction mixture. The catalyst can be reactivated (80 °C, vacuum) and reused for at less three runs without obvious loss of its activity (Table 1, entries 6–9). Reaction products were crystallized upon concentration and cooling of the filtrated solution in excellent yields.

In order to study the generality of the protocol, several examples were considered and are presented in Table 2. The reaction of substrates with electron-donating and weak electron-withdrawing substituents on benzaldehyde ring were completed in short reaction times (Table 2, entries 1–3, 5). The presence of a strong electron-withdrawing nitro group in 4-nitrobenzaldehyde molecule decreased both the rate and the yield of the reaction (Table 2, entry 4). The procedure worked well with a variety of structurally and electronically diverse aldehydes, and with no side products. The use of 1 mol % of silzic was sufficient to catalyze the reaction. Results of using silzic (1 mol %) was also compared with the similar reactions using homogeneous ZnCl_2 (2.5 mol %) as the catalyst (Table 2).

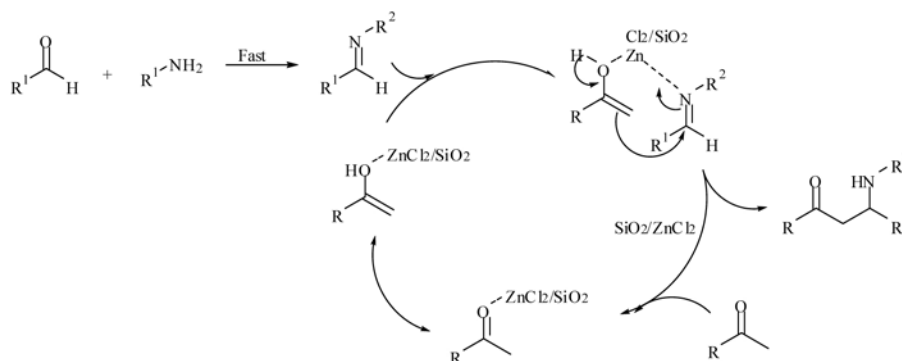
In addition the one-pot three-component Mannich reactions of different anilines with acetophenone were studied (Table 2, entry 10–15). It was found that the corresponding β -amino carbonyl compounds were formed in moderate to good yields. However, acetophenone was less reactive than cyclohexanone and require a greater quantity of catalyst (10 mol %) and longer reaction times. It is notable that a control reaction with the same amount of unsupported catalyst had no significant yield of product (Table 2, entry 10).

A reasonable pathway for the reaction of an aldehyde with an amine and an enolizable ketone conducted in the presence of silzic ($\text{ZnCl}_2/\text{SiO}_2$) is presented in Scheme 2. The reaction proceeds *via* formation of imine which undergoes addition with the enolate moiety to afford Mannich products. Silzic activates the in situ generated imine and also shift the keto-enole equilibrium towards enole formation which subsequently reacts with the imine moiety to give Mannich product.

3. Experimental

3.1. General

Chemicals were purchased from Merck and Fluka Chemical Companies. All products are known compounds and were characterized by comparison of their physical data with those reported in the literature. IR spectra were performed on a Shimadzu 8300 FT-IR spectrophotometer, and NMR spectra were recorded on a Bruker Avance DPX-250 spectrometer. Purity of the products and the progress of the reactions were monitored by TLC on silica-gel polygram SILG/UV₂₅₄ plates.



Scheme 2: Proposed reaction mechanism for Mannich reactions catalyzed by silicic ($\text{ZnCl}_2/\text{SiO}_2$).

3. 2. Preparation of Silzic ($\text{ZnCl}_2/\text{SiO}_2$)

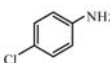


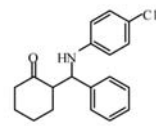
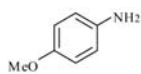
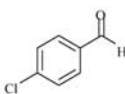

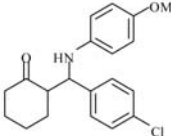
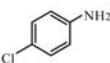
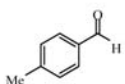

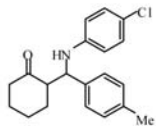



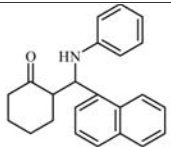



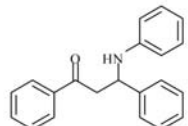
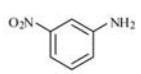


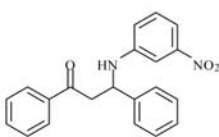


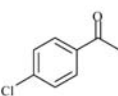
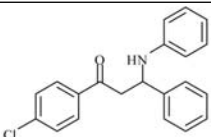
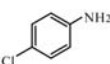


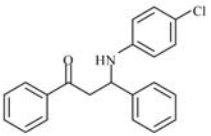


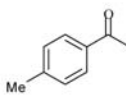
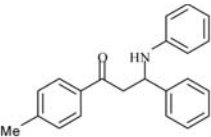

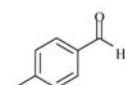

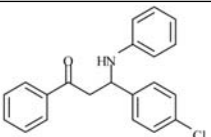
Silzic is easily prepared according to the literature method:⁹ 10% (w/w) ZnCl_2 /silica gel (silzic 10%) was prepared by co-grinding anhydrous zinc chloride (1 g) with dry silica gel (9 g) in an agate mortar. Thorough mixing is required to attain uniform dispersion of ZnCl_2 over silica surface. This was attained by co-grinding the mixture at room temperature for 20–25 min. This results in formation of homogenized, white free flowing powder. This sample was further activated in vacuum at 80 C for 2 hours. Despite of ZnCl_2 , silzic is highly water tolerant, non-corrosive and stable solid catalyst with high Lewis acid activity.

3. 3. General Procedure for the Synthesis of β -aminocarbonyl Compounds

A mixture of aldehyde derivatives (2.0 mmol), aniline derivatives (2.0 mmol), cyclohexanone (3 mmol) and silzic 10% (0.03 g, 1 mol % of zinc) was stirred under solvent-free conditions at room temperature for appropriate time indicated in Table 2 until the reaction was completed as monitored by TLC (*n*-hexane/ EtOAc = 80/ 20). After completion of the reaction, hot ethanol was added to reaction mixture to dissolve the product and catalyst was recovered by filtration. The sole product of Mannich reaction was crystallized after reducing the vo-

Table 2: ZnCl_2 and silica-supported ZnCl_2 (silzic) catalyzed Mannich reactions at room temperature under solvent free conditions.

| Entry | Amine | Aldehyde | Ketone | Product ^a (Syn/Anti) ^b | Time (min) / Yield (%) ZnCl_2 / Silzic | Ref. |
|-------|-------|----------|--------|--|--|------|
| 1 | | | | (15/85) | 20/92 / 15/97 | 7c,8 |
| 2 | | | | (30/70) | 65/90 / 30/94 | 7c |
| 3 | | | | (27/73) | 45/90 / 40/92 | 6b |
| 4 | | | | (44/56) | 180/85 / 150/84 | 7c |
| 5 | | | | (20/80) | 50/85 / 55/94 | 5d |

| Entry | Amine | Aldehyde | Ketone | Product ^a (Syn/Anti) ^b | Time (min) / Yield (%) ZnCl ₂ / Silzic | Ref. |
|-------|---|---|---|--|--|-------|
| 6 |  |  |  |  (23/76) | 25/89 / 10/91 | 7c, 8 |
| 7 |  |  |  |  (12/88) | 150/81 / 60/90 | 6a |
| 8 |  |  |  |  (17/83) | 60/90 / 55/89 | 7c |
| 9 |  |  |  |  (10/90) | 35/78 / 30/91 | 5d |
| 10 |  |  |  |  | 24h/00 / 20/95 | 8 |
| 11 |  |  |  |  | 24h/00 / 24h/90 | 6a |
| 12 |  |  |  |  | – / 15h/89 | 6a |
| 13 |  |  |  |  | – / 16h/93 | 8 |
| 14 |  |  |  |  | – / 22h/92 | 7b |
| 15 |  |  |  |  | – / 24h/91 | 8 |

^a Products were identified by IR and NMR spectroscopic methods. ^b Ratios were determined by ¹H NMR spectroscopy.

lume of ethanol and cooling. The reaction procedure for acetophenone is similar to the above protocol with the ratio of aldehyde (2.0 mmol) : amine (2.0 mmol) : acetop-

henone (2.5 mmol) : silzic 30% (0.09 g, 10 mol % of zinc) and the appropriate reaction times as indicated in Table 2.

The selected spectroscopic data for 3-phenyl-3-(phenylamino)-1-p-tolylpropan-1-one: (Table 2 Entry 14): ^1H NMR (250 MHz, CDCl_3), δ 2.36 (s, 3H), 3.35 (dd, $J_1 = 16.0$, $J_2 = 7.6$, 1H), 3.47 (dd, $J_1 = 16.0$, $J_2 = 5.2$, 1H), 4.55 (b, NH, 1H), 4.98 (dd, $J_1 = 7.6$, $J_2 = 5.2$, 1H), 6.54 (d, $J = 7.6$, 2H), 6.64 (t, $J = 7.8$, 1H), 7.04–7.07 (m, 2H), 7.20–7.31 (m, 5H), 7.41–7.45 (m, 2H), 7.80 (d, $J = 8.2$, 2H) ppm; ^{13}C NMR (62.9 MHz, CDCl_3) δ , 21.6, 46.2, 54.9, 113.8, 117.7, 126.3, 127.3, 128.3, 128.9, 129.1, 129.4, 134.2, 143.1, 144.3, 147.0, 197.9 ppm; IR (KBr) ν , 3384, 1664 cm^{-1} .

3. Conclusions

It was demonstrated that silzic is highly effective heterogeneous zinc(II) catalyst for one-pot three-component Mannich reaction of ketone, aldehyde and amine. This novel catalyst provides a clean and convenient alternative for the Mannich reaction. The reaction proceeded smoothly and selectively in the presence of moisture under solvent-free conditions and produced Mannich base in high yields at room temperature. Silzic is stable, reusable and an environmental friendly catalyst that offers easy handling and simple work-up.

4. Acknowledgements

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Povzetek

V prispevku je predstavljena uporaba $\text{ZnCl}_2/\text{SiO}_2$ (silzic) kot učinkovitega in obnovljivega katalizatorja za neposredno trokomponentno reakcijo med aldehidi, amini in ketoni. Pri reakciji nastanejo ustrezne β -aminokarbonilne spojine z visokimi izkoristki in brez uporabe topila. Prednosti predstavljenega protokola so visoki izkoristki, mili reakcijski pogoji, enostavna izolacija produkta in manjše onesnaževanje okolja. Katalizator pripravimo na enostaven način in je bolj učinkovit kot sam ZnCl_2 .