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ORIGINAL PAPER

An efficient synthesis of *β*-aminoketone compounds through three-component Mannich reaction catalyzed by calcium chloride

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Abstract Various *β*-aminoketones were synthesized in a three-component reaction of ketones, aldehydes, and amines in the presence of calcium chloride as catalyst in ethanol in high yields as compared to other synthetic methods. The advantages of this new method are a short reaction time (2 h), high yields, easy workup, convenience, low cost, and eco-friendly protocol.

Keywords *β*-aminoketone · Calcium chloride · Mannich reaction · Three-component reaction

Introduction

Mannich-type reactions are a class of very important carbon–carbon bond-forming reactions in organic synthesis and represent some of the most widely utilized chemical transformations for the construction of nitrogenous molecules [1–3]. In Mannich transformations, three-components, a ketone, an aldehyde, and an amine, react to form *β*-aminoketones, which in turn are important synthetic intermediates for various pharmaceutical and natural products [4–9]. The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen in drugs and natural products as well as by the potential of this three-component reaction to generate diversity. Both direct variants with unmodified ketone donors and indirect variants utilizing preformed enolate equivalents have been described [1–3]. In addition, the imine intermediate may be preformed, or its amine and aldehyde precursors may be used directly (Scheme 1).

Direct Mannich reactions of aldehydes, ketones, and aryl amines have recently been realized via organic and mineral acids, such as proline [10–12], acetic acid [13], *p*-dodecylbenzenesulfonic acid [14], and some Lewis acids [15, 16]. However, these methods often suffer from the drawbacks of long reaction times and harsh reaction conditions, toxicity, and difficulty in product separation, which limit their use in the synthesis of complex molecules. This has led organic chemists to focus on developing more convenient methods for the synthesis of *β*-aminoketones. Recent achievements in the efficient construction of these molecules include the development of various catalysts, such as Lewis acid catalysts [17], Bronsted acid catalysts [18, 19], and Lewis base catalysts [20], to facilitate Mannich reactions. For example, scandium triflate, copper triflate, scandium tris(dodecyl sulfate), and scandium tris(dodecanesulfonate) [21]. Cl_3 [22], HBF_4 [23], zirconium catalyst [24], ionic liquid [25], and $NbCl_5$ [26] have also been used to catalyze these reactions and good yields were obtained, but these catalysts are associated with long reaction times, and sterically hindered *β*-aminoketones could not be obtained. Lanthanide triflate in certain solvents, such as dichloromethane and acetonitrile, have also been known to catalyze the Mannnich reaction [27, 28].

Results and discussion

Calcium chloride is inexpensive, non-toxic to the environment, and easily available. This salt has been used as an efficient Lewis base in an aldol reaction of dimethylsilyl enolates in aqueous *N*,*N*-dimethylformamide [29], the Biginelli reaction [30], and in the formation of

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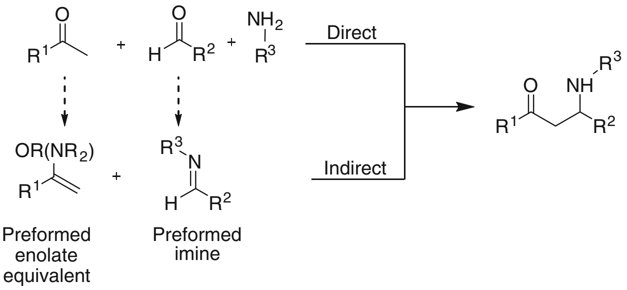
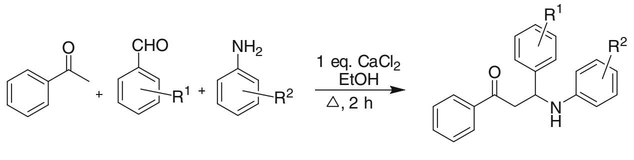


Scheme 1



Scheme 2

phosphonates [31]. To the best of our knowledge, direct Mannich-type reactions catalyzed by calcium chloride have not been reported. Here, we report a calcium chloride-catalyzed three-component Mannich-type reaction of ketones, substituted aromatic aldehydes, and substituted aromatic amines that leads to the efficient synthesis of β-aminoketones under mild conditions. Our experiments demonstrated that stirring acetophenone, benzaldehyde, aniline, and 1 equivalent of calcium chloride in ethanol for 8 h led to the formation of the corresponding Mannich product (Scheme 2). We observed that the same reaction catalyzed with calcium chloride, in the presence of one drop HCl in ethanol, reduced the reaction time to 2 h and achieved a higher yield of pure product. The scope of the reaction was then studied by substituting various amines and aldehydes. The results are summarized in Table 1. In general, high yields of β-aminoketones were obtained in 2 h using $CaCl_2$ in ethanol. Substrates bearing various functional groups such as CH_3, OCH_3, Cl, NO_2, and OH all reacted to produce the corresponding β-aminoketones; *m*- and *p*-substituted aromatic amines gave good results, while *o*-substituted amines and aldehydes gave a low yield due to steric hindrance. Aromatic aldehydes gave good yields, but an electron-withdrawing substituent on aldehydes resulted in low yields of product. Finally, the scope of the reaction was studied using cyclohexanone, benzaldehyde, and substituted amines (Scheme 3). Cyclohexanone was observed to be more reactive than acetophenone and did not require the addition of HCl to increase the catalytic activity of $CaCl_2$. In general, high yields of β-aminoketones were obtained in 2 h using $CaCl_2$ in ethanol. The results are summarized in Table 2.

In conclusion, the method described here is a convenient way to produce β-aminoketones under mild conditions and may find widespread usage in organic synthesis.

Experimental

All purchased chemicals were of analytical grade and used without further purification. Melting points were determined by the open capillary method. IR spectra were recorded on a FT-IR 3.1 Win-BOMEM apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer using deuterated chloroform ($CDCl_3$) as the solvent and tetramethylsilane (TMS) as the internal standard.

Table 1 Three-component calcium chloride-catalyzed Mannich-type reactions with substituted amines and substituted aldehydes

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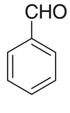
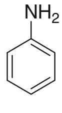
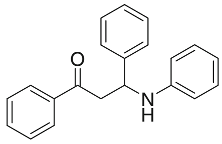
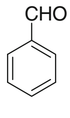
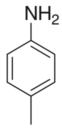
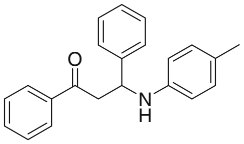
			2	86	169–170 [26]
			2	82	170–171 [34]

Table 1 continued

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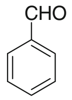
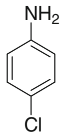
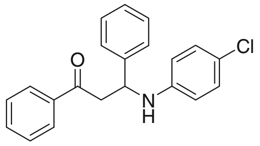
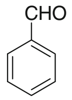
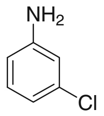
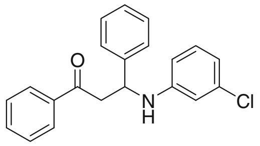
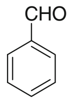
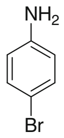
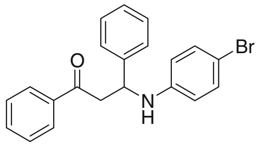
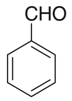
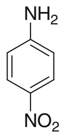
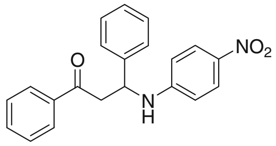
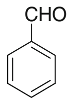
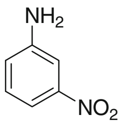
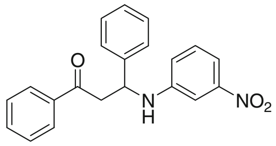
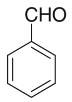
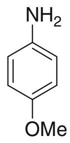
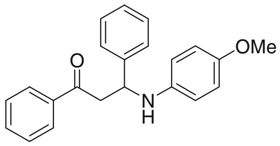
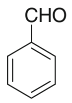
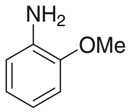
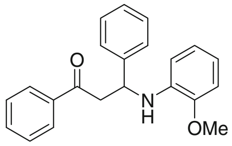
			2	90	172–173 [34]
			2	84	131–132 [26]
			2	91	130–131 [33]
			2	84	185–186 [34]
			2	84	139–140 [35]
			2	91	163–164 [34]
			2	40	107–108 [32]

Table 1 continued

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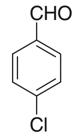
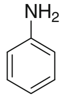
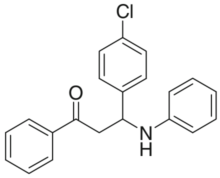
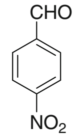
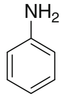
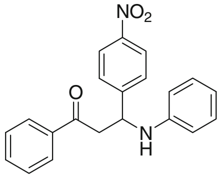
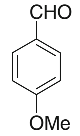
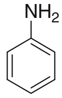
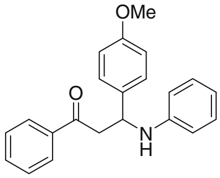
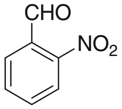
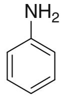
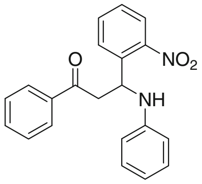
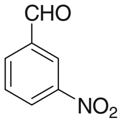
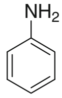
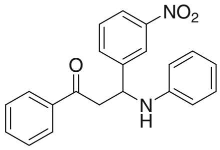
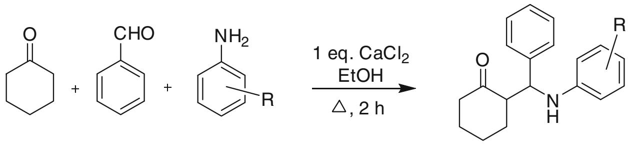
			2	72	117–118 [34]
			2	64	105–106 [26]
			2	61	149–151 [34]
			2	57	158–162 [36]
			2	79	131–132 [35]

Reaction conditions 1 mmol aromatic aldehyde, 1 mmol acetophenone, 1 mmol aromatic amine, 1 equiv $CaCl_2$, EtOH, heat for 2 h

[a] Isolated yield—structures of products were confirmed by ^1H NMR

General procedure for synthesis of β-aminoketones

One equivalent of $CaCl_2$ was added to a mixture of acetophenone or cyclohexanone (5 mmol), benzaldehyde (5 mmol) and aniline (5 mmol) in 5 cm^3 ethanol. One drop of HCl was added when acetophenone was the starting material. The resulting mixture was stirred at 60–80°C for 2 h. Workup with 5% $NaHCO_3$ resulted in the precipitation of the product as a solid, which was filtered, washed with water, and recrystallized from EtOH.



Scheme 3

All of the products are known, and physical data were found to be identical with those reported in the literature (Tables 1, 2).

Table 2 Three-component calcium chloride-catalyzed Mannich-type reactions with cyclohaxanone, benzaldehyde, and various amines

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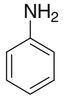
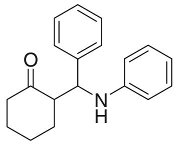
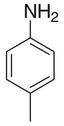
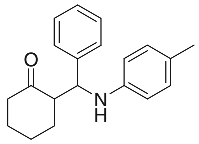
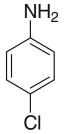
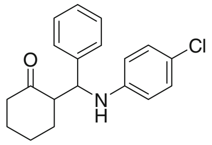
		2	84	139–140 [34]
		2	82	118–119 [34]
		2	77	137–138 [34]

Reaction conditions 1 mmol aromatic aldehyde, 1 mmol cyclohexanone, 1 mmol aromatic amine, 1 equiv $CaCl_2$, EtOH, heated for 2 h

[a] Isolated yield—structures of products were confirmed by ^1H NMR

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