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Research Article

Zinc Acetate as an Efficient Catalyst for the Synthesis of Multi substituted Piperidines

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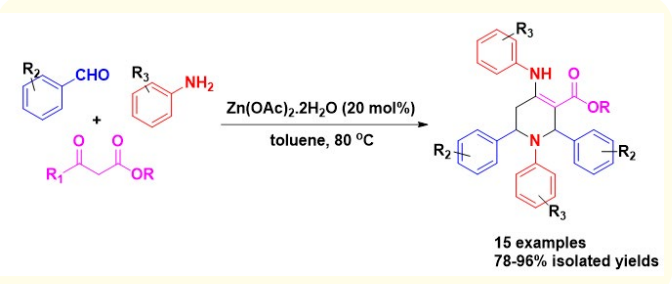
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Abstract

Through a one-pot multi-component condensation reaction of aromatic aldehydes, anilines, and β-ketoester in the presence of $Zn(OAc)_2 \bullet 2H_2O$ as a Lewis acidic catalyst in toluene at 80 oC, we have successfully developed an efficient and environmentally friendly synthesis of a series of 1,2,5,6-tetrahydropyridine-3-carboxylate derivatives. High catalytic activity, decent yields, ease of use, a broad range of functional group tolerance, and column-free approach are some of the benefits of this low-cost, ecologically friendly protocol.

Keywords: Aldehydes; Anilines; β-keto Esters; $Zn(OAc)_2 \bullet 2H_2O$; Tetrahydropyridines; Lewis Acid; Multi-Component Reactions

Graphical Abstract



Introduction

A significant area of organic chemistry, heterocyclic chemistry makes for almost one-third of current publications [1-3]. In our biological system, heterocyclic molecules are essential. They are essential components of numerous natural products, nucleic acids, and pharmacologically active compounds [4-7]. Nitrogen-containing compounds in particular are of interest due to their varied biological activity and pharmacological properties [8-11].

Because of their numerous biological actions, functionalized piperidines and their derivatives constitute a significant family of nitrogeneous heterocyclic compounds (Figure 1) [12-15]. Numerous substances containing this heterocyclic unit have demonstrated a variety of intriguing biological effects, including anti-inflammatory, antibacterial, antimalarial, anticonvulsant, and anti-hypertensive qualities [16-19]. Additionally, several of them that involve the MAO-based process have been reported to be

helpful in Parkinson's disease. Bismuth nitrate, molecular iodine, bromodimethylsulfonium bromide (BDMS), tetrabutylammonium tribromide (TBATB), $InCl_3$, CAN, $ZrOCl_2.8H_2O$, picric acid, VCl_3, *p*TSA, $Bi(NO_3)_3$, cerium(IV) triflate, acetic acid, nano-sphere silica sulfuric acid, camphoresulfonic acid, nano-$TiCl_4/SiO_2$, citric acid, calix[n]arenes, α-Fe_2O_3 immobilized benzimidazolium tribromide, cyanuric chloride, alum, and grapheme oxide have all been reported as catalytic systems [20-58]. The utilization of costly and excessive volumes of catalysts, high temperatures, lengthy reaction times, dangerous organic solvents, reagents, and low yields are only a few of the numerous drawbacks, despite the several methods that have been documented. Because of their potential biological and pharmacological actions, it is crucial to develop new techniques for the synthesis of functionalized piperidines.

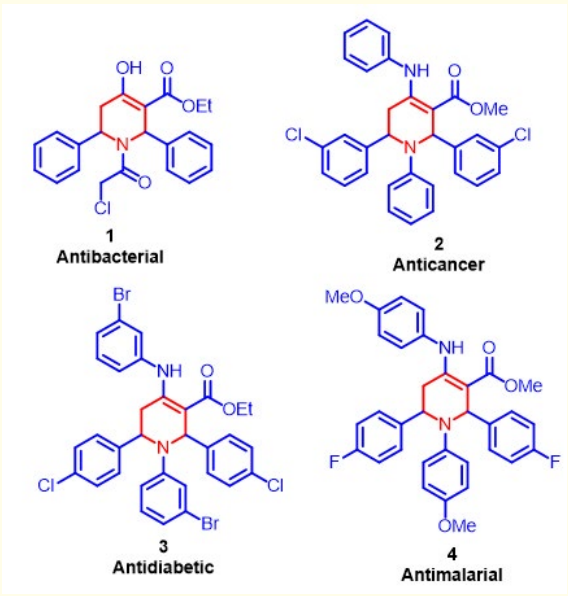


Figure 1: Biologically relevant piperidine derivatives.

Multicomponent reactions (MCRs) are a special class of practical synthetic organic reactions that react one or more distinct starting materials in a single pot to produce a final product [59]. The MCR process has several advantages, including high yields, atom-/step economy, faster reaction times, and environmental friendliness. In the process of developing novel drugs, this approach is very beneficial for building a library of new chemical entities (NCEs) [60-66].

We discovered that $Zn(OAc)_2•2H_2O$ (ZA) has not been used for the target reaction after a thorough study of the literature. Zinc acetate ($Zn(OAc)_2$) is one of the several readily available zinc complexes that is stable in air and moisture under ambient conditions [67]. We carried out the procedures to synthesize functionalized piperidines after reading several articles demonstrating ZA's catalytic efficacy [68-74].

Results and Discussion

Screening of catalyst

In order to maximize the optimal reaction parameter and efficiency of ZA as a catalyst for the synthesis of representative compound (4a), we first conducted a one-pot, multi-component cyclocondensation reaction of benzaldehyde (1a), aniline (2a), and ethyl acetoacetate (3a) as a model reaction (Scheme 1). The model reaction was carried out under a variety of optimization settings, such as screening several zinc salts as a catalyst (Table 1), the impact of solvent (Table 2), the impact of catalyst loading (Table 3), and the impact of temperature (Table 4). ZA was determined to be the most effective zinc catalyst among those examined, both in terms of yield and reaction time (entry 6, Table 1). Although $ZnCl_2$ also appeared to be superior, ZA was selected due to its affordability and accessibility.

Entry	Catalyst	Time (min/h)	Yield (%)[b]
1	-	48 h	-
2	$ZnCl_2$	4 h	83
3	$ZnBr_2$	5.5 h	62
4	Zn dust	24 h	48
5	Zinc montmorillonite	48 h	32
6	$Zn(OAc)_2•2H_2O$	30 min	95
7	Zinc-Hydroxyapatite	24 h	<5%
8	$Zn_3(PO_4)_2$	48 h	trace

Table 1: Screening of catalyst for the synthesis of 4a[a].

[a]Reaction conditions: 1a (2 mmol), 2a (2 mmol), 3a (1 mmol), 20 mol% ZA, toluene at 80 °C. [b]Isolated yields.

Effect of solvent

Following the catalyst's successful screening, we are motivated to conduct additional optimization research. Additionally, employing 20 mol% of ZA as a catalyst at 80 °C, the model reaction has been examined for the effects of several solvents, including chloroform, DCM, ethanol, DMF, DMSO, toluene, and CH_3CN, as well as solvent-free conditions (Table 2, entries 1-8). Among the conditions evaluated, toluene proved to be the most effective (entry 6, Table 2).

Entry	Solvents	Time (min/h)	Yield (%)[b]
1	$CHCl_3$	2 h	12
2	CH_2Cl_2	3 h	7
3	EtOH	2 h	45
4	DMF	2 h	23
5	DMSO	3 h	trace
6	Toluene	30 min	95
7	CH_3CN	4 h	17
8	Solvent-free	12 h	-

Table 2: Effect of solvent on the synthesis of 4a[a].

[a]Reaction conditions: 1a (2 mmol), 2a (2 mmol), 3a (1 mmol), 20 mol% ZA. [b]Isolated yields.

Optimization of the catalyst

In the subsequent effort, we screened the impact of catalyst loading on the model reaction and found that the reaction mixture was not transformed into the target product in the absence of catalyst (Table 3, entry 1). Table 3 shows that 20 mol% ZA was sufficient to fully convert the raw ingredients into the intended product 4a.

Effect of temperature

Additionally, the effect of temperature on the model reaction has been optimized (entries 1-6, Table 4). It has been observed that temperature significantly influences the formation of the desired product 4a. As can be seen from the results of Table 4, 80 °C was found to be optimal (entry 6, Table 4).

Entry	Catalyst (mol%)	Yield (%)[b]
1	-	-
2	5	28
3	10	55
4	15	76
5	20	95

Table 3: Effect of catalyst loading for synthesis of 4a[a].

[a]Reaction conditions: 1a (2 mmol), 2a (2 mmol), 3a (1mmol). [b]Isolated yields.

Entry	Temp. (°C)	Time (min/h)	Yield (%)
1	RT	48 h	-
2	27	24 h	trace
3	50	12 h	11
4	60	12 h	17
5	70	8 h	53
6	80	30 min	95
7	90	45 min	90
8	100	45 min	89
9	110	45 min	89
10	120	45 min	78

Table 4: Effect of temperature on the synthesis of 4a[a].

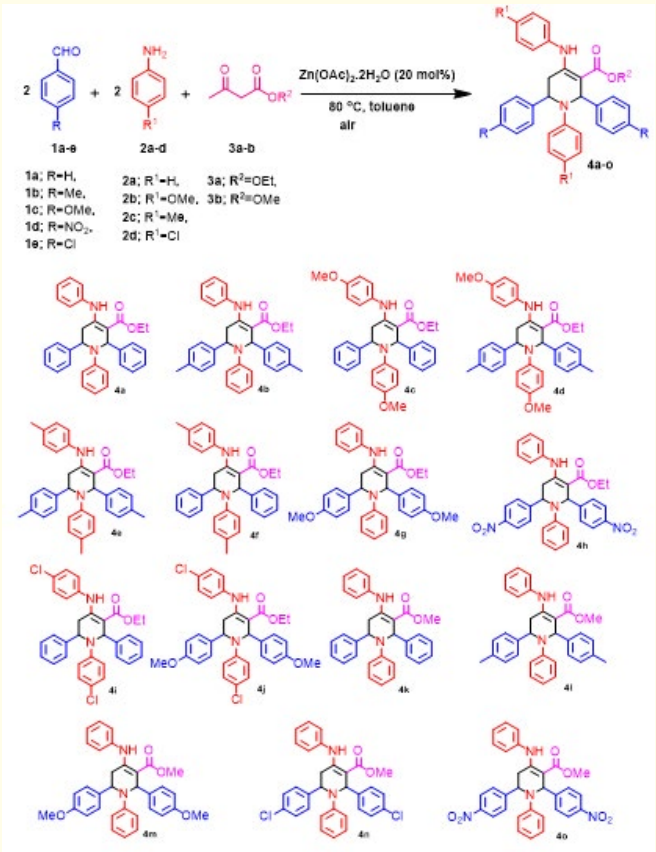
[a]Reaction conditions: 1a (2 mmol), 2a (2 mmol), 3a (1mmol), 20 mol% ZA (20 mol%); [b]Isolated yields.

These results led to a one-pot pseudo five-component cyclo-condensation procedure that produced a high yield of 4a (95%) by using 20 mol% of ZA as a catalyst in toluene at 80 °C. Testing the compatibility of different aromatic aldehydes and anilines with both electron-donating and electron-withdrawing substituents highlights the synthetic flexibility of the current methodology after examining the various reaction parameters (Scheme 1). The findings

demonstrate that the reaction produces good to exceptional yields for the relevant products while operating smoothly and tolerating a wide range of functional groups, including methyl-, methoxy-, nitro-, and chloro-.

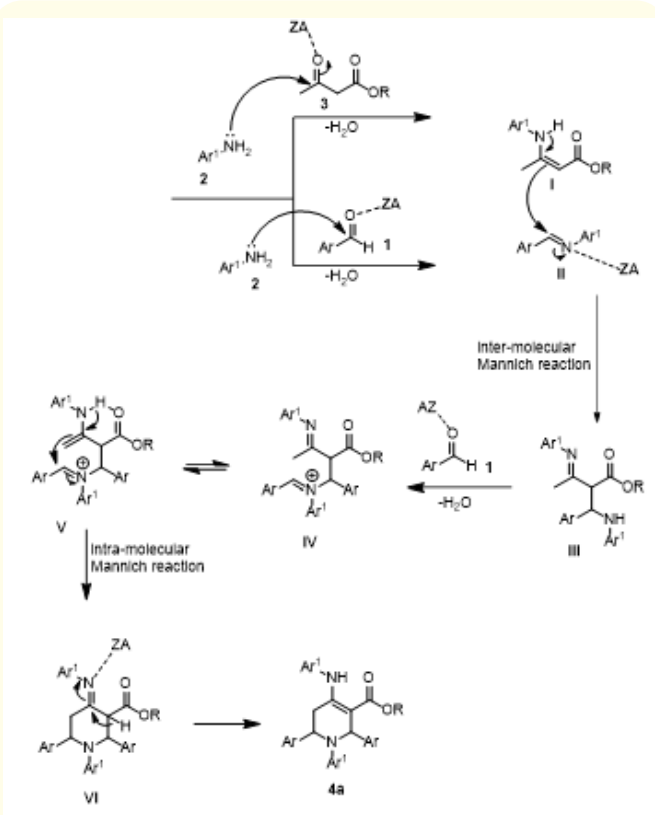
In every instance, the reactions proceeded effectively under ideal circumstances using 20 mol% of ZA as a Lewis catalyst. To avoid laborious work-up, the pure products were produced by recrystallizing the crude products in an ethanol-chloroform (1:1) mixture. Because of this, the current approach is generally applicable and can accommodate a wide range of replacement patterns. Spectral data of representative compounds and the melting points of the produced [58].

Compounds were used to validate their structures [58].



Scheme 1: ZA-Catalyzed synthesis of the piperidine derivatives.

The feasible mechanism for the synthesis of tetrahydropyridine 4 has been proposed by us (Scheme 2). The non-covalent interaction with Lewis acid zinc acetate upon reacting with aniline (2) may enhance the electrophilic character of the carbonyl oxygen of the aldehyde (1) and β-ketoester (3). This reaction results in the formation of intermediate enamine I and imine II, which subsequently undergo an intermolecular Mannich type reaction to yield intermediate III. Intermediate IV is the result of a subsequent reaction between intermediate III and the second aldehyde molecule (1). IV tautomerizes to produce V, which is then further cyclized via an intermolecular Mannich type reaction to produce product 4 *via* intermediate VI.



Scheme 2: ZA-Catalyzed synthesis of functionalized pyridines.

Experimental

Materials and Methods

$Zn(OAc)_2 \cdot 2H_2O$ was purchased from BLD Pharma. Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F254MERCK (20x20 cm). Visualization was achieved by exposure to UV light. Organic solutions were concentrated by rotary evaporation on BUCHI-Switzerland; R-120 rotary evaporator and vacuum pump V-710. Column chromatography was performed on Merck silica gel 230-400 mesh size. 1H and 13C NMR spectra were recorded with Bruker 400 MHz NMR instruments. Mass spectra were recorded with Agilent LC-MS instrument. FTIR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27 spectrometer.

General procedure for one-pot synthesis of functionalized tetrahydropyridines (4a-o)

A mixture of appropriate aniline 2 (2 mmol) and β-ketoester 3 (1 mmol) was sonicate for 10 min in the presence of 20 mol% ZA at 80 °C. Then, the appropriate benzalaldehyde 1 (2 mmol) was added and the reaction mixture was heated for the appropriate time. The progress of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate: hexane (7:3) as a solvent system. After completion of the reaction, the reaction mixture was quenched with crushed ice and the solid was isolated by simple filtration and washed with water. The obtained crude product was crystallized in mixture of ethanol and chloroform (1:1) to afford pure products (4).

Representative example:

Ethyl-1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4a): White solid; mp: 174-176 ^oC; FT-IR ν_{max} cm^{-1}: 3229, 2991, 1644, 1595, 1230; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 1.46 (t, 3H, J = 7.01 Hz), 2.78 (dd, 1H, J = 15.1, 2.31 Hz),2.87 (dd, 1H, J = 15.1, 5.81 Hz), 4.33 (dd, 1H, J = 10.81, 7.10 Hz), 4.46 (dd, 1H, J = 10.81, 7.10 Hz), 5.15 (d, 1H, J = 4.01 Hz), 6.29-6.31 (m, 2H), 6.48 (s, 1H), 6.54 (d, 2H, J = 8.0 Hz), 6.60 (t, 1H, J = 8.01 Hz), 7.07-7.12 (m, 5H), 7.16-7.19 (m, 2H), 7.21 (d, 1H, J = 8.0 Hz), 7.28-7.31 (m, 5H), 7.33 (d, 2H, J = 8.01 Hz) and 10.30 (s, 1H); ^{13}CNMR (125 MHz, $CDCl_3$, δ ppm): 14.81 (Methyl Carbon), 33.60 (CH_2 in ring), 55.12 (Methine carbon adjacent to N & CH_2), 58.21 (Methine carbon adjacent to N & double bond), 59.74 (O-CH_2), 98.21, 113.01, 116.12, 125.71, 126.34, 126.61, 127.12, 128.21, 128.60, 128.91, 137.91, 144.02, 147.01 and 168.31 (C=O).

Conclusion

In conclusion, using a one-pot multi-component condensation reaction involving aromatic aldehydes, anilines, and β-ketoesters in the presence of ZA as a Lewis acid catalyst under ideal conditions, we have successfully developed a green and effective protocol for the synthesis of a series of 1,2,5,6-tetrahydropyridine-3-carboxylate derivatives. High catalytic activity with short reaction times, consistently good to excellent yields, operational simplicity and ease of work-up, and broad functional group tolerance that permits the synthesis of a variety of derivatives are just a few of the clear advantages of the current method. The method's economy, sustainability, and efficiency point to its potential use in both academic and industrial settings for the synthesis of heterocyclic scaffolds with synthetic and pharmacological applications.

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