Research Article

ZINC ACETATE AS AN EFFICIENT CATALYST FOR THE SYNTHESIS OF SUBSTITUTED QUINAZOLINONES

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Abstract
We successfully developed an effective and sustainable synthesis of a number of substituted quinazolinone derivatives using a one-pot multi-component Biginelli type condensation reaction of aromatic aldehydes, urea, and dimedone in the presence of $Zn(OAc)_2•2H_2O$ as a Lewis acidic catalyst in toluene under reflux conditions. This low-cost, environmentally friendly methodology has several advantages, including high catalytic activity, great yields, convenience of use, a wide range of functional group tolerance, and a column-free approach.

Keywords:
Aldehydes; dimedone, urea;$Zn(OAc)_2•2H_2O$;Biginelli-type; quinazolinones; Lewis acid; multi-component reactions

Introduction

Nearly one-third of recent papers in organic chemistry are in the important field of heterocyclic chemistry.[1-3] Heterocyclic compounds are vital to our biological system. They are vital parts of many natural products, pharmacologically active substances, and nucleic acids.[4–7] Because of their diverse biological activity and pharmacological characteristics, substances containing nitrogen in particular are of interest.[8–11]

A unique class of useful synthetic organic reactions known as multicomponent reactions (MCRs) produces a final product by reacting one or more different starting materials in a single pot.[12] High yields, atom-/step economy, quicker reaction times, and environmental friendliness are only a few benefits of the MCR process. This method is highly helpful for creating a library of new chemical entities (NCEs) in the process of creating novel medications.[13–19] The Biginelli reaction has garnered significant interest as a simple and effective technique for the synthesis of nitrogen-containing heterocyclic frameworks among the several MCR-based transformations.[20]]Condensation of an active methylene molecule, urea (or thiourea), with an aldehyde offers quick access to structurally varied heterocycles with important biological and therapeutic applications.[21] As a result, a lot of work has gone into creating effective and safe catalytic systems for Biginelli-type reactions.

One such Biginelli-type reaction is synthesis of substituted quinazolinone derivatives, which have garnered interest recently due to their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, anti-cancer properties, and calcium antagonist properties.[22–25]

Variants of the traditional one-pot multi-component Biginelli reaction, including dimedone, aromatic aldehydes, and urea, are used to synthesize them. There aren't many publications on the synthesis of octahydroquinazolinone derivatives employing catalysts in the Biginelli reaction extension. These catalysts include nano-Bi_2O_3, trimethylsilyl chloride, concentrated sulfuric acid, Nafion-H, NH_4VO_3, and other Lewis and Brønsted acids.[26–32] However, many of these processes are costly, hazardous, and challenging to manage, particularly on a big scale. They also necessitate longer reaction times, involve extremely acidic conditions, produce inadequate yields, and result in the creation of side products.

After carefully reviewing the literature, we discovered that $Zn(OAc)_2$•$2H_2O$ (ZA) has not been utilized for the target reaction. One of the several easily accessible zinc complexes that is stable in air and moisture under ambient circumstances is zinc acetate ($Zn(OAc)_2$).[33] After reading multiple studies proving ZA's catalytic effectiveness, we implemented the processes to create functionalized quinazolinones.[34–40]

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 toUV light. Organic solutions were concentrated by rotary evaporation on a BUCHI-SwitzerlandR-120 rotary evaporator and vacuumpump V-710. Column chromatography was performed on Merck silica gel, 230- 400 mesh size. ^1H and ^{13}C NMR spectra were recorded with Bruker 400 MHz NMR instruments. Mass spectra were recorded with an Agilent LC-MS instrument. FTIR spectra were recorded from KBr disks on the FT-IR Bruker Tensor 27 spectrometer.

General procedure for one-pot synthesis of functionalized quinazolinones (4a-k): A mixture of urea **2** (1 mmol) and dimedone **3** (1 mmol) in toluene (2 mL) was stirred in the presence of 20 mol% ZA at reflux conditions. Then, the appropriate aldehyde **1** (1 mmol) was added and the reaction mixture was heated for the appropriate time as mentioned in **Table 2**.

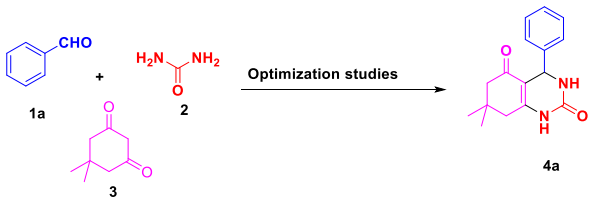
The reaction progress was monitored by thin-layer chromatography (TLC) using ethyl acetate: hexane (7:3) as the solvent system. After completion of the reaction, the reaction mixture was quenched with crushed ice, and the solid was isolated by simple filtration and washed with water. The crude product was crystallized from a mixture of ethanol and chloroform (1:1) to afford pure product (**4**).

Representative example: 4-Phenyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (**4a**): IR (KBr, cm-1): 3262, 2960, 1702, 1660, 1455, 1376.^1H NMR (DMSO-*d6*, δ, ppm): 0.89 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.00-2.44 (m, 4H, CH_2-8, CH_2-6), 5.14 (d, *J*=2.74 Hz, 1H, H-4), 7.19-7.33 (m, 5H, Ar-H), 7.78 (s, 1H, N3-H), 9.48 (s, 1H, N1-H). Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36%. Found: C, 71.14; H, 6.62; N 10.24%.

Results & Discussion

We first carried out a one-pot, multi-component cyclocondensation reaction of benzaldehyde (**1a**), urea (**2**), and dimedone (**3**) as a model reaction in order to optimize the ideal reaction parameter and efficiency of ZA as a catalyst for the synthesis of representative chemical (**4a**) (**Table 1**). In terms of time, yield, economic viability, readily available, catalyst loading, and reaction time, ZA was shown to be the most efficient zinc catalyst among those studied (entry 14, **Table 1**).

Table 1. Optimization studies for the synthesis of substituted quinazolinones



Entry	Catalyst	Reaction conditions	Yield (%)[a]
1[b]	ZnO NPs	EtOH, reflux, 10 min	95
2[b]	$ZnCl_2$	EtOH, reflux, 30 min	89
3[b]	$Zn_3(PO_4)_2$	EtOH, reflux, 24 h	trace
4[b]	$Zn(OAc)_2•2H_2O$	EtOH, reflux, 15 min	95
5[b]	ZnB_2	EtOH, reflux, 60 min	57
6[b]	Zinc dust	EtOH, reflux, 48 h	NR[c]
7[b]	$Zn(OAc)_2•2H_2O$	CH_3CN, reflux, 1 h	87
8[b]	$Zn(OAc)_2•2H_2O$	toluene, reflux, 30 min	95
9[b]	$Zn(OAc)_2•2H_2O$	$CHCl_3$, reflux, 1 h	68
10[b]	$Zn(OAc)_2•2H_2O$	Neat, reflux, 4 h	38
11	$Zn(OAc)_2•2H_2O$ (5 mol%)	toluene, reflux, 1 h	57
12	$Zn(OAc)_2•2H_2O$ (10 mol%)	toluene, reflux, 1 h	78
13	$Zn(OAc)_2•2H_2O$ (15 mol%)	toluene, reflux, 30 min	95
14	**$Zn(OAc)_2•2H_2O$ (20 mol%)**	**toluene, reflux, 15 min**	**98**
15	$Zn(OAc)_2•2H_2O$ (20 mol%)	toluene, RT, 48 h	NR[c]
16	$Zn(OAc)_2•2H_2O$ (20 mol%)	toluene, 50, 48 h	Trace
17	$Zn(OAc)_2•2H_2O$ (20 mol%)	toluene, 80 °C, 48 h	13
18	$Zn(OAc)_2•2H_2O$ (20 mol%)	toluene, 100 °C, 48 h	48

[a]Isolated yields; [b]catalyst loading (10 mol%); NR: [c]No reaction

We attempted to assess the viability of structurally and electrically divergent aldehydes using the optimal conditions, and **Table 2**summarises the findings. The target heterocyclic compounds were produced in outstanding isolated yields (67–98%) within extremely compressed reaction timeframes (15–60 min) without the creation of any observable side products or complex mixtures thanks to the smooth and effective multi-component condensations.

This green synthesis protocol's strong efficiency and excellent selectivity are highlighted by its exceptional operational simplicity and lack of competing side reactions.

Table 2. Synthesis of functionalized quinazolinone derivatives

Entry	Aldehyde	Product	Isolated yield (%) / Time (min)
1	PhCHO	**4a**	98/15
2	4-CH_3PhCHO	**4b**	92/45
3	2-CH_3PhCHO	**4c**	91/45
4	4-OMe PhCHO	**4d**	90/45
5	4-Cl PhCHO	**4e**	96/30
6	4-NO_2PhCHO	**4f**	97/30
7	3-OH PhCHO	**4g**	89/45
8	Cinnamaldehyde	**4h**	67/60
9	Furfural	**4i**	85/45
10	2-Pyridine	**4j**	81/45

	carboxaldehyde		
11	1-naphthaldehyde	**4k**	92/30

Aromatic aldehydes that were substituted with either electron-donating or electron-withdrawing groups consistently underwent a smooth reaction and produced products in excellent yields (entries 1-7, **Table 2**). It was also discovered that heteroaromatic aldehydes were vulnerable to this reaction (entry 9–10, **Table 2**). The IR, ^{1}H, ^{13}CNMR, and mass spectra of compounds **4a–k** were analyzed and compared to data from previous studies[26,30].

Conclusions

In conclusion, we successfully developed a green and efficient protocol for the synthesis of functionalized quinazolinones through a Biginelli-type reaction using a one-pot multi-component condensation reaction involving aromatic aldehydes, urea, and dimedone in the presence of ZA as a Lewis acid catalyst under ideal conditions. Among the obvious benefits of the current approach are high catalytic activity with short reaction times, consistently good to exceptional yields, operational simplicity and ease of work-up, and broad functional group tolerance that enables the synthesis of a variety of derivatives.

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Conflict of interests

The authors claim that there is no conflict of interest.

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