Current Chemistry Letters 13 (2024) 677–682

Contents lists available at GrowingScience

Current Chemistry Letters

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$Zn(OAc)_2•2H_2O$- Catalyzed Synthesis of Chromeno[2,3-*d*] Pyrimidinones under Solvent-free Conditions

P. Rama Krishna Veni[a*], Ch. Vijaya Saradhi[b] and G. Usha Rani[c]

[a]*Department of Applied Sciences & Humanities, Sasi Institute of Technology & Engineering, Tadepalligudem, West Godavari-534101, Andhra Pradesh, India*
[b]*Department of Science and Humanities, Guntur Engineering College, Yanamadala, Prathipadu (M), Guntur-522019, Andhra Pradesh, India*
[c]*Department of Basic Sciences and Humanities, Kallam Haranadhareddy Institute of Technology, Guntur-522019, Andhra Pradesh, India*

C H R O N I C L E

Article history:
Received January 20, 2024
Received in revised form
March 21, 2024
Accepted May 14, 2024
Available online
May 14, 2024

Keywords:
Aldehydes
Barbituric acid
Chromeno[2,3-d]pyrimidinones
Cyclohexane-1,3-diones
Solvent-free condition and zinc acetate

A B S T R A C T

Due to their high synthetic efficiency, multi-component reactions (MCRs) have shown to be extraordinarily effective at producing compounds in a single synthetic operation. The chromeno[2,3-*d*] pyrimidine moieties represent important building blocks in synthetic bioactive compounds. The reaction of barbituric acid, aldehydes, and cyclohexane-1,3-diones in the presence of zinc acetate (5 mol%) under neat conditions at 70 ^{0}C, yielded a facile and one-pot synthesis of corresponding chromeno[2,3-*d*]pyrimidineones. Thirteen compounds containing neutral, withdrawing and electron donating groups (H, NO_2, -CN, -Cl; -OH, $-CH_3$ and $-OCH_3$) were synthesized in good, isolated yields ranging from 78-91%. The successful involvement of *o*-, *m*-, and *p*- substituted nitro benzaldehydes suggested that steric hindrance had no effect. All of the synthesized compounds are well-known, and this process is unique in that it makes use of zinc acetate, an accessible, low-cost Lewis acid catalyst.

1. Introduction

Heterocyclic compounds are a distinct class of organic chemicals with a wide range of synthetic and medicinal applications.[1] Pyrimidine and its analogues play an important role in medicinal chemistry due to their vast spectrum of pharmacological actions.[2] Pyrimidines are the building blocks of several natural substances such as vitamins, liposaccharides, and antibiotics.[3] Pyrimidinones and their fused analogues, such as chromenopyrimidinones, pyridopyrimidinones, pyranopyrimidinones, thienopyrimidinones, furopyrimidinones, and quinazolinones, have received particular attention in this regard, partly due to their nucleobase mimicry, which forges their intriguing medicinal properties.[4-6] The medicinal chemistry research community has seen an increase in the number of articles documenting the study of these scaffolds to generate effective therapeutic medicines throughout the years. Several biological actions, including antibacterial, antiviral, anticancer, antidiabetic, anti-inflammatory, anticonvulsive, and antihistaminic, have been thoroughly reported.[7-9] Chromene is a necessary medicinal moiety that emerges as a fundamental structural component in natural compounds and has piqued the curiosity of researchers because of its fascinating biological activity.[10-12] Chromene is a necessary component of several types of polyphenols. It can be found in alkaloids, tocopherols, flavonoids, and anthocyanins in nature. Chromene has an important core structure and exhibits a variety of pharmacological and biological activities such as antiviral, anticancer, anti-inflammatory, antitumor, antimicrobial, antiproliferative, anticholinesterase, antivascular, TNF- (Tumour Necrosis Factor-) inhibitor, antifungal, estrogenic, herbicidal, analgesic and anticonvulsant, antituberculosis, antidiabetic.[13-14] The chromene (benzopyran) derivatives easily pass the cell membrane due to their lipophilic character. Chromene derivatives are also utilized in the production of highly efficient fluorescent dyes for synthetic fibres, daylight fluorescent pigments, and electrophotographic and electroluminescent devices.

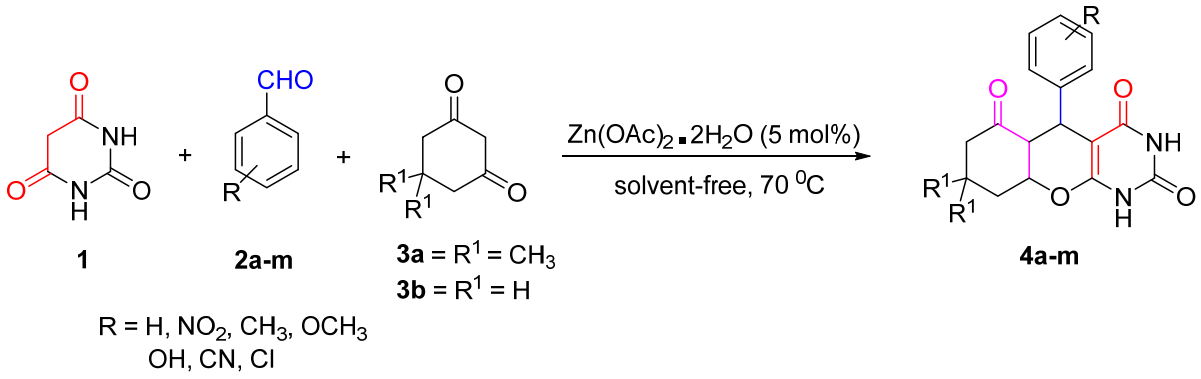
Given the two significant heterocyclic pharmacophores discussed above, the desire to synthesize chromeno[2,3-*d*]pyrimidinones (hybrid compounds) has grown among synthetic and medicinal chemists. However, there are very few reports in the literature pertaining to the synthesis of the title compounds using *p*-toluenesulfonic acid under reflux condition, $InCl_3$ or P_2O_5 under near conditions at 100 ^{0}C, L-proline in H_2O at RT, $Sc(OTf)_3$ under near conditions at 100 ^{0}C, glycerol-proline combination at 75 ^{0}C, etc.[15-20]

* Corresponding author
E-mail address pramakv2023@gmail.com (P. R. K. Veni)

doi: 10.5267/j.ccl.2024.5.003

As a result, we set out to create a novel and feasible method for synthesizing pyrimidinone derivatives. Among the various zinc salts accessible, zinc acetate is one of the inexpensive, readily available, low-hazardous Lewis acids. The solid, colourless hydrate and anhydrous forms are both utilized as dietary supplements. According to the E650 code, it is a food preservative. Some drugs contain zinc acetate, most notably lozenges used to treat common colds. As a daily oral supplement, it works by preventing the body from absorbing copper, which is how Wilson's illness is treated. As an astringent for the topical treatment of acne, zinc acetate is also sold as an ointment, topical lotion, or in conjunction with an antibiotic like erythromycin. Being a cofactor for about 3000 human proteins, such as hormones, enzymes, and nuclear factors, it is associated with multiple cellular processes. Zinc is essential for healthy taste and smell, as well as for regular growth and development during infancy, childhood, and puberty. It is said to have antioxidant properties that could speed up the healing process after an injury and help prevent premature ageing. In adults, zinc ions can produce symptoms such delayed sexual development, growth retardation, increased susceptibility to infections, and diarrhoea in children, even in small amounts. It is typically offered for sale as a lotion to relieve itchy skin.[21]

It is known as a multifunctional catalyst because of its unusual physical and chemical properties, which demonstrate that it is useful in permitting a wide range of synthetic transformations in both organic synthesis and catalysis.[22-27]After doing a thorough review of all relevant published information, we concluded that the relevant reaction did not involve $Zn(OAc)_2$•$2H_2O$. Under laboratory settings, zinc acetate is not only inexpensive, but also simple to obtain and resistant to change in the presence of moisture and air.



Scheme 1. $Zn(OAc)_2$•$2H_2O$-catalyzed synthesis of chromeno[2,3-*d*]pyrimidinones

The purpose of green chemistry is to provide a method to reduce or eliminate the use of such hazardous, poisonous solvents. Nontoxic chemicals, renewable resources, and solvent-free reaction conditions are thus critical components of the green synthetic approach.[28-31] We provide a solvent-free $Zn(OAc)_2$•$2H_2O$ (5 mol%) catalyzed synthesis of chromeno[2,3-*d*]pyrimidinones (4a-m) from the reaction of barbituric acid (1), aldehydes (2a-m), and cyclohexane-1,3-diones (3a-b) (Scheme 1).

2. Results and Discussion

To begin, the catalytic performance of $Zn(OAc)_2$•$2H_2O$ and the effect of media on the reaction were evaluated using a model reaction comprising barbituric acid (1), benzaldehyde (2a), and dimedone (3a). The effect of solvents and reaction temperature on yield was first investigated (**Table 1**). Using EtOH and MeOH as solvents in the presence of $Zn(OAc)_2$•$2H_2O$ under reflux conditions resulted in 100% conversion of the starting material after 8 hours (**Table 1**, entries 1 and 2). The method was unaffected by other organic solvents (Table 1, entries 3, 4, 5, and 6). We also tried the reaction in solvent-free conditions, and data analysis revealed that the reaction performed significantly better in solvent-free conditions (**Table 1**, entry 11), with a greater yield and a shorter reaction time.

Table 1. Optimization studies

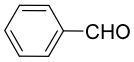
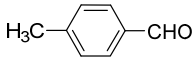
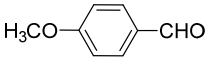
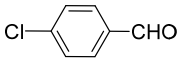
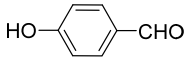
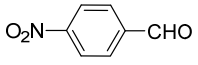
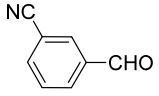
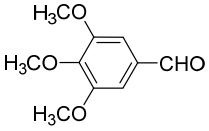
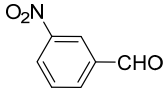
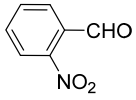
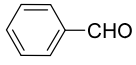
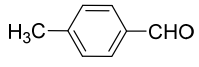
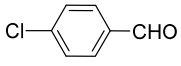
Entry	Solvent	$Zn(OAc)_2$•$2H_2O$	T (^{0}C)	Time (h)	Yield (%)[a,b]
1	EtOH	5	reflux	8	80 (100)
2	MeOH	5	reflux	8	79 (100)
3	toluene	5	reflux	12	20 (30)
4	THF	5	reflux	10	15 (24)
5	$CHCl_3$	5	reflux	10	25 (43)
6	CH_2Cl_2	5	reflux	10	25 (32)
7	none	5	RT	12	30 (38)
8	none	5	40	9	40 (47)
9	none	5	50	7	60 (68)
10	none	5	60	6	75 (89)
11	**none**	**5**	**70**	**4**	**85 (100)**
12	none	5	80	4	83 (100)
13	none	2	70	6	70 (90)
14	none	3	70	6	75 (95)
15	none	7	70	4	83(100)

[a]Isolated yields; [b]The data presented in parenthesis refer to the conversion of benzaldehyde

The reaction was further studied at various temperatures and under solvent-free conditions. The findings revealed that temperature has a significant impact on the reaction rate. The activity of the catalyst increased with increasing temperature (**Table 1**, entries 7-12),

with the activity maximum at 70 ºC (**Table 1**, entry 11). During our optimization studies, we adjusted the molar concentration of $Zn(OAc)_2•2H_2O$ under solvent-free conditions at 70 ºC. When 5 mol% of catalyst was employed, a good yield of product 4a was obtained; however, a poor yield was obtained when 2-3 mol% of catalyst was utilized (**Table 1**, entries 13 and 14). Increases in catalyst mol% had no effect on the outcome (**Table 1**, entry 15). To test the method's universality and applicability, a variety of substituted aromatic aldehydes and cyclic-1,3-diketones were reacted with barbituric acid under identical experimental conditions to give the relevant chromeno[2,3-*d*]pyrimidinones (**Table 2**).

Table 2: $Zn(OAc)_2•2H_2O$-Catalyzed cyclocondensation of barbituric acid, aldehyde and cyclohexane-1,3-diones

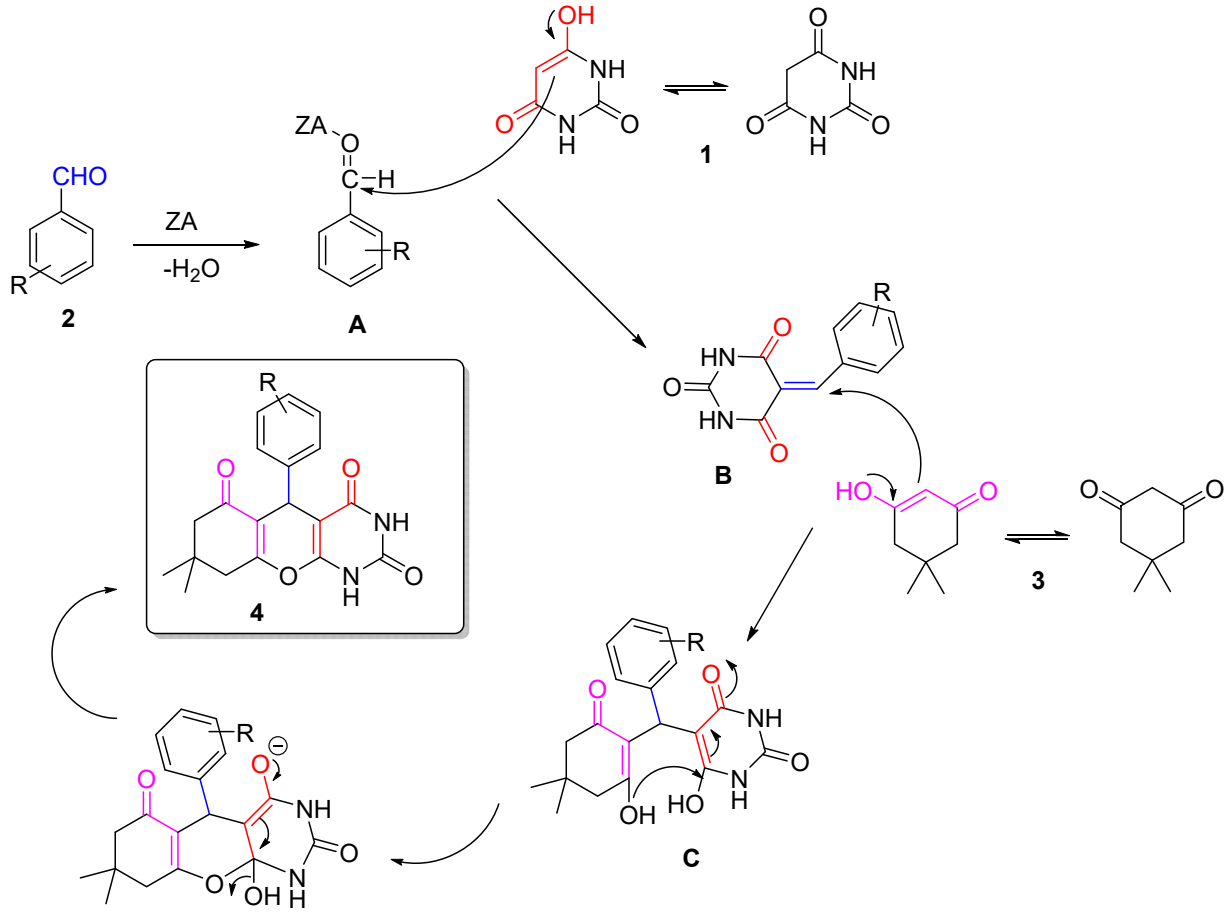
Entry	Aldehyde (**2**)	1,3-diketone (**3a/3b**)	Product (**4**)	Time/h	Yield (%)[a, ref]
1		**3a**	**4a**	4.00	85[17,18,19]
2		**3a**	**4b**	2.50	88[17,18,19]
3		**3a**	**4c**	3.50	82[17,19]
4		**3a**	**4d**	2.00	87[17,18,19]
5		**3a**	**4e**	3.50	83[16]
6		**3a**	**4f**	3.50	80[17,18,19]
7		**3a**	**4g**	4.00	78[16]
8		**3a**	**4h**	3.00	89[16]
9		**3a**	**4i**	4.00	82[17,18,19]
10		**3a**	**4j**	1.00	86[16]
11		**3b**	**4k**	1.50	91[17,18,19]
12		**3b**	**4l**	1.30	90[17,19]
13		**3b**	**4m**	3.50	82[17,18,19]

[a]Isolated yields after column chromatography

$Zn(OAc)_2•2H_2O$ was shown to be compatible with a wide range of substituents (both electron withdrawing and donating substituents), including ''OMe'', ''OH'', ''NO_2'', ''Cl'', ''CN'', and ''Me'', with good results (**Table 2**, entries 1-13). The reaction between barbituric acid, aliphatic aldehydes (propionaldehyde, cyclohexanecarboxaldehyde, and isobutyraldehyde), and dimedone was studied to broaden the scope and utility of this protocol under the optimized reaction parameters but went in vain producing a mixture of compounds and the desired products in negligible yields.

A plausible mechanism was proposed, as shown in **Scheme 2**. The reaction proceeds with the formation of an intermediate (A) from aldehyde (2) and $Zn(OAc)_2•2H_2O$. The greater reactivity of the iminium ion in comparison to the carbonyl moiety may speed up

Knoevenagel condensation between barbituric acid (1) and aldehyde after the removal of $Zn(OAc)_2•2H_2O$. Then, (B) is attacked *via* Michael addition of 1,3-diketone (3) to give the intermediate (C), followed by intramolecular dehydration to give the desired product (4).



Scheme 2. Plausible mechanism for the synthesis of chromeno [2,3-*d*]pyrimidines catalyzed by $Zn(OAc)_2•2H_2O$

Table 3 compares zinc acetate findings to recently published approaches and demonstrates that the current methodology performs better in terms of catalyst loading (5 mol%), easily accessible, and cost effectiveness.

Table 3. Comparison study of various catalysts for the synthesis of chromeno [2,3-*d*]pyrimidine **4a**

Catalyst	Solvent	Temperature	Time (h)	Isolated yield (%)[Ref]
p-TSA (0.3 mmol)	ethanol	reflux	4 h	84%[19]
$Sc(OTf)_3$ (5 mol%)	solvent-free	100 ^{0}C	2 h	98%[17]
L-Proline (15 mol%)	millipore water	RT	4 h	85%[16]
$Zn(OAc)_2•2H_2O$ (5 mol%)	**solvent-free**	**70 ^{0}C**	**4 h**	**85% [present method]**
Proline (10 mol%)	glycerol	75 ^{0}C	3.15 h	88%[18]

3. Conclusions

In summary, we have disclosed a practical and efficient approach for the synthesis of chromeno[2,3-*d*]pyrimidinones from aldehydes, 1,3-diketones and barbituric acid in the presence of a catalytic amount of $Zn(OAc)_2•2H_2O$ under solvent-free conditions at 70 ºC. Ten substituted aldehydes, one barbituric acid, and two cyclohexane-1,3-diones were selected for the library validation. Many researchers are drawn to investigate the catalytic properties of this easily available and affordable $Zn(OAc)_2•2H_2O$ catalyst (1.5-2 USD for 1 kg, >99% purity). In good isolated yields ranging from 78-91%, thirteen compounds (NO_2, -CN, -Cl, -OH, $-CH_3$, and $-OCH_3$) containing neutral, withdrawing and electron donating groups were synthesized. The absence of steric hindrance was suggested by the effective involvement of *o*-, *m*-, and *p*-substituted nitro benzaldehydes. The synthesized compounds are all well known. The simple procedure combined with the use of a novel catalyst at low temperature, short reaction times, solvent-free conditions, and high product yields make this method economical, safe and user-friendly for the synthesis of chromeno[2,3-*d*]pyrimidinones of biological and medicinal importance. The present approach is a simple and intriguing alternative for many of the reported methods that involve the use of toxic and expensive chemicals as well as hazardous solvents.

4. Typical experimental procedure

A combination of barbituric acid (1 mmol), bezaldehyde (1 mmol), dimedone (1 mmol), and 5 mol% $Zn(OAc)_2•2H_2O$ was agitated at 70 °C for the duration given in Table 2. TLC was used to monitor the reaction's progress. After the reaction was completed, the reaction mixture was cooled to room temperature and 15 mL of water was added. The precipitate that formed was extracted with ethyl acetate (3x20 mL). The mixed organic extract was washed with water, then brine, before being dried on anhydrous $MgSO_4$. The product was purified by column chromatography over silica gel with petroleum ether-ethyl acetate (2:1) as the eluent after the solvent was evaporated under reduced pressure.

8,8-Dimethyl-5-phenyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione (Table 2, entry 1): White powder; 85% yield; mp: 162-164°C; UV-Vis: λ_{max} 254 nm; IR ν_{max} (KBr): 3201, 2938, 1722, 1685,1247, 789 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 10.01 (1H, s, NH); 9.55 (1H, s, NH), 6.96-7.17 (m, 5H, Ar-H), 5.98 (s, 1H, 4*H*), 2.02-2.33 (m, 2H, CH_2), 1.85-1.98 (m, 2H, CH_2), 1.02 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 195.8, 166.7, 161.5, 155.2, 150.7, 141.6, 128.5, 127.8, 127.3, 127.2, 124.8, 114.4, 90.7, 46.7, 38.7, 31.2, 30.6, 28.2, 27.8.

*** Supporting Information is available for the characterization of title compounds.**

This work confirms that heterocyclic compounds are very important in different fields due to the high variety of their applications.[32-37]

ORCID

P. Rama Krishna Veni: 0000-0002-6924-1254

Ch. Vijaya Saradhi: 0009-0000-2137-6910

G. Usha Rani: 0000-0001-5312-2704

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