Journal of Science and Technology
ISSN: 2456-5660 Volume 9, Issue 4 (April -2024)
www.jst.org.in *DOI:https://doi.org/10.46243/jst.2024.v9.i4.pp1-7*

Three-Component $Zn(OAc)_2$-Catalyzed one pot synthesis of mono and disubstituted Pyrimidine Derivatives.

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To Cite this Article

Dr. Swanand Shrinivasrao Mukhedkar, Dr.Balaji Digambar Kokane, Jitendra Hanmantrao Deshmukh, Shivraj Shankarrao Anjanikar." Three-Component $Zn(OAc)_2$-Catalyzed one pot synthesis of mono and disubstituted Pyrimidine Derivatives." *Journal of Science and Technology, Vol. 09, Issue 04 - April 2024, pp1-7*

Article Info

Received: 28-02-2023 Revised: 05 -03-2024 Accepted: 23-03-2024 Published: 8-04-2024

ABSTRACT

The $Zn(OAc)_2$-catalyzed three-component coupling reaction using triethyl orthoformate (3 eq.), and ammonium acetate (2 eq.), to synthesis mono & disubstituted pyrimidine derivatives in single step. This method is successfully applied to the efficient synthesis of mono- and disubstituted pyrimidine derivatives, using methyl ketone derivatives by using biodegradable,ecofriendly polychem@36 as solvent in ultrasound condition at 80^0C giving good yield upto 80-90% .The reaction is completed in short period of time i.e. 1-3 hrs as compared to other reaction.

Introduction

The pyrimidines possess wide spectrum of biological activities like significant in vitro activity against unrelated DNA and RNA, viruses including polioherpes viruses, diuretic, antitumour, anti-HIV, activity. The disubstituted pyrimidine nucleus is found in biologically active and naturally occurring compounds[1] such as voriconazole[2] and avitriptan[3] and has been utilized as a central and precious intermediate for clinical drug discovery.[4] Although a number of approaches to the preparation of the pyrimidine derivatives have been developed by a number of organic/pharmaceutical chemists,[5,6.]

Nomenclature is included if necessary
A radius of
B position of
C further nomenclature continues down the page inside the text box

Review of Literature:

The Bredereck-type synthesis,[7] of pyrimidine derivatives, is one notable exception. This procedure requires temperature of more than 160°C, which results decrease in the product yield. Pinner-type synthesis[8] of polysubstituted pyrimidines and s-triazine.[9,10] These procedures requires strong bases and acids, relatively inaccessible reagents, multiplestep syntheses, and harsh reaction conditions. Thus novel synthetic process for the highly efficient preparation of 4,5-disubstituted pyrimidines by single-step method. During our current studies we have used zinc diacetate synthesis of nitrogen-containing heterocycles in a single step. by the use of methyl ketone derivatives, instead of enamines, for the production of monosubstituted pyrimidine derivatives in good yield.

Experimental

In $CDCl_3$ at 300 MHz, the ^1H NMR spectra were captured using TMS as the internal standard. For solid materials, KBr pellets were used to record IR spectra, and neat was used for liquid samples. Using silica gel, column chromatography was carried out (100-200 mesh). In relation to internal TMS, chemical changes are expressed in ppm, while J values are reported in Hz.

General procedure:

On the basis of above studies, the three-component coupling reaction procedure, we applied the $Zn(OAc)_2$-catalyzed multicomponent coupling reaction for the synthesis of a simple and less substituted pyrimidine derivative using ketone 1 instead of enamine (Table 2).by using ammonium acetate as nitrogen source and zinc acetate as catalyst and Polychem@36 provides a low viscocity, bio-degradable, and recyclable, Environmentally friendly solvent in ultrasound method. Under low pressure, the organic layer was dried (with Na_2SO_4) and concentrated. By using column chromatography (silica gel 100-120 mesh, petroleum ether: ethyl acetate = 4:1), the crude product was refined to afford the corresponding β-enaminoester All the compound synthesized are known and compared with the known literature data.

Spectroscopic data of compounds:

2,5-dimethyl-4-oxopyrimidine-6-carboxylic acid (3) as colorless plak. yield 7.10 g (65%); mp 259-261 "C; A- (C&H 50H, 224 (6300); A- (CzHSOH, pH 10) 273 (5400), 232 (9100); IR (KBr) 3112,3072,2922,2605,1930,1695,1597,1455,1373,1295,1145 cm-'; NMR (MezSO-ds, DzO, (CH_3),Si) 6 2.0 (8, 3 H), 2.15 (8, 3 H); mass spectrum, mle 168 (M'), 150, 124,94,55,44, 42.

Materials and nethods: We synthesized mono & disubstituted pyrimidines as shown in Scheme 1 & 2. Starting from methyl ketones, and alcohols and cyclic amines, several kinds of substituted pyrimidine in the presence of zinc acetate as catalyst and polychem@36 as solvent to afford mono & disubstituted pyrimidines. It is noted that the use of **polychem@36 and ultrasound** in this transformation led to formation of the desired products in higher yields within short time.

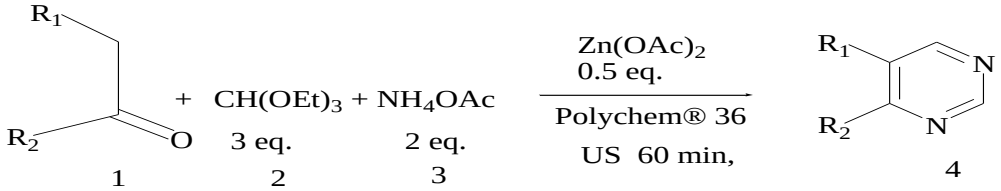
Thus, we found that heating with polychem.@36 as solvent at 80 °C in the presence of 0.1 equiv of $Zn(OAc)_2$ were the model conditions for pyrimidine synthesis shown in table 1.

Table 1: Effect of Lewis acid catalyst and change of solvent on yield and reaction time.

Sr	Catalyst	Solvent	Time (h)	Yield%
1	$InCl_3$	Toluene	25	65
2	$Cu(OTf)_2$	Toluene	23	61
3	$Yb(OTf)_3$	Toluene	19	66
4	$ZnCl_2$	Acetonitrile	24	79
5	$ZnBr_2$	Acetonitrile	22	59
6	$Zn(OTf)_2$	Acetonitrile	20	60
7	**$Zn(OAc)_2$**	**PolyChem@36**	**2**	**85**

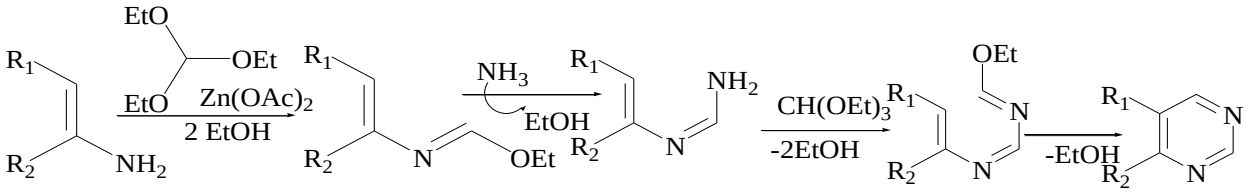
Mono- and disubstituted pyrimidine derivatives 4a-n in moderate to good yields (1-7).

Ketone derivative 1a effectively gave bicyclic pyrimidine derivative 4a in good yield (1). When acetophenone (1c) was utilized as the reaction substrate, monosubstituted 6-phenylpyrimidine (4c) was obtained in 80-90% yield (3). This method successfully accommodated other acetophenone derivatives with an electron-donating group and an electron-withdrawing group (4 and 5). A plausible mechanism for the coupling reaction is shown in Scheme 1. ketone, with an orthoester and ammonium acetate. This has proven to be a facile and practical method for the preparation of a pyrimidine skeleton.



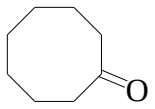
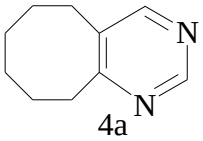
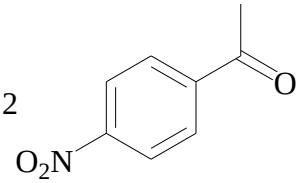
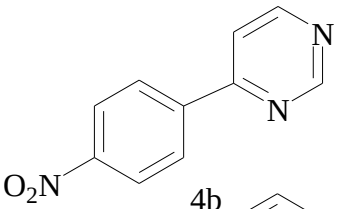
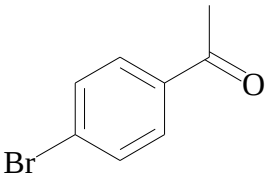
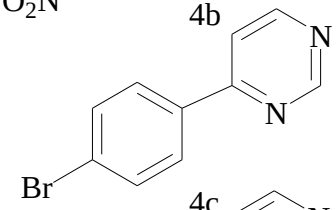
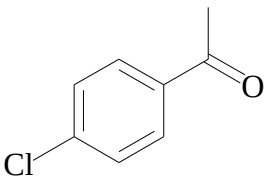
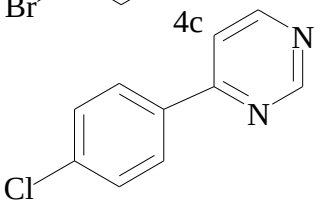
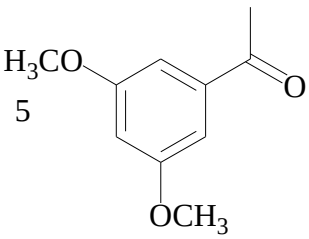
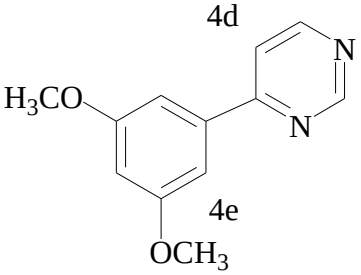
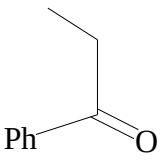
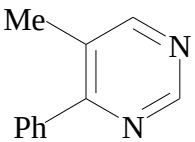
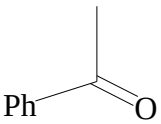
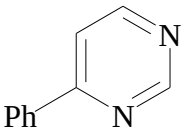
Scheme 1:Synthesis of substituted pyrimidines.

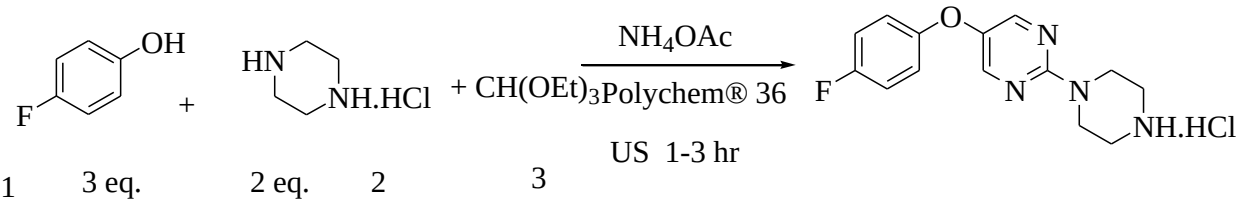
Reaction mechanism:



Scheme:2 plausible mechanism for pyrimidine synthesis

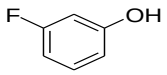
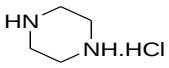
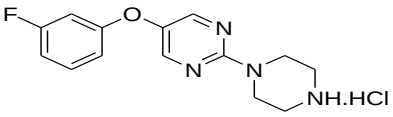
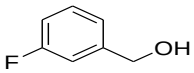
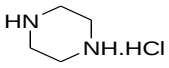
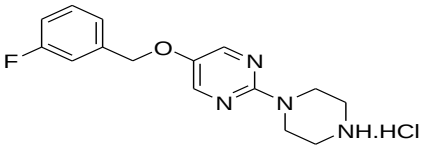
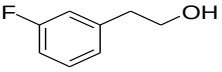
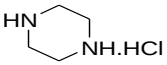
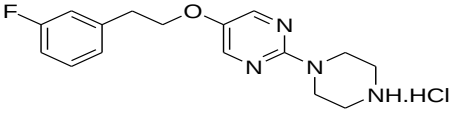
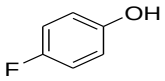
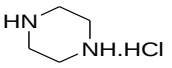
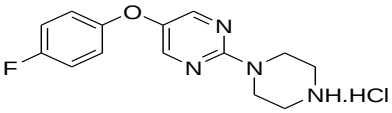
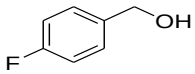
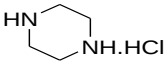
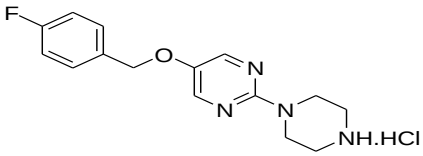
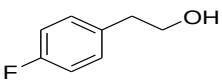
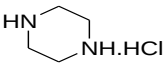
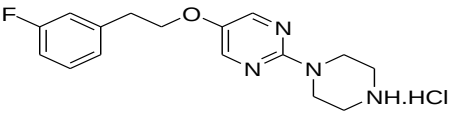
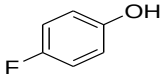
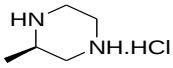
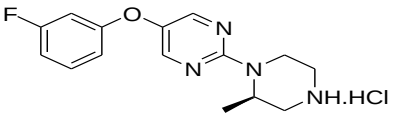
Table 2. One-Pot Synthesis of Substituted Pyrimidines

Sr	1 a-g	4 a-g	time (h)	Yield %
1		 4a	1	90
2		 4b		82
3		 4c	1	86
4		 4d	1	85
5		 4e	1	75
6		 4f	1	80
7		 4g	1	79



1 3 eq. 2 eq. 2 3

Scheme 2: Synthesis of disubstituted pyrimidine.

Sr	1 h-n	amines	Product 4 h-n	time(h)	Yield(%)
8				2	75
9				3	73
10				3	77
11				1.5	80
12				1.5	80
13				2	75
14				1	70

Conclusion:

Thus, we synthesized two series of mono & disubstituted pyrimidine derivatives as a series of pyrimidines, possessing different cyclic amines, with good yield by using biodegradable, ecofriendly, recyclable solvent polychem@36 with improved yield. Pyrimidine-condensed derivatives as the pharmacophore exhibit broad spectrum of biological activities possessing antibacterial, antifungal, anti viral, antimalarial, anti cancer, anti –HIV activity.

Acknowledgment.

We thank Dr. S.G.Patil and Dr.Ravi sir for discussing some of his experimental results prior to publication. We thank for assistance in optimization of certain synthetic transformations. This investigation was not supported by any funding agency.

Conflict of Interest:

Authors declare that there is no conflict of interests regarding the publication of the paper.

Author Contribution:

The authors confirm contribution to the paper as follows: ***study conception and design:*** Swanand Shrinivasrao Mukhedkar, ***data collection:*** Shivraj. S. Anjanika*;* ***analysis and interpretation of results:*** Kokane Balaji Digambar,*;* ***draft manuscript preparation:*** Jitendra Hanmantrao Deshmukh *All authors reviewed the results and approved the final version of the manuscript*.

Appendix A:

Supporting information is available.

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Journal

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