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AMMONIUM MOLYBDATE PROMOTED EFFICIENT AND FACILE SYNTHESIS OF 3,4 DIHYDROPYRIMIDONE/THIONE DERIVATIVES

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ABSTRACT
A straightforward and efficient synthesis of dihydropyrimidinones (DHPMs) has been developed through the Biginelli reaction by employing ammonium molybdate as a catalyst. This approach involves one-pot condensation of substituted benzaldehydes, urea/thiourea, with ethyl acetoacetate, resulting in the corresponding DHPMs in high yields. The experimental procedure is environmentally benign, safe, and advantageous due to its simplicity, catalyst reusability, and the use of ethanol as a green solvent. This method offers high product yields (75-90%) and reduced reaction times. The utility of this approach was successfully applied for the synthesis of anticancer agent monastrol, which has well-established anticancer activity.
Keywords: Biginelli Reaction, Multi-component Reaction, Ammonium Molybdate, Monastrol, Anticancer Agent.
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INTRODUCTION

Multi-component reactions (MCRs) are those reaction in which three or more reactants reacts in one pot and form a product which contain that contains the characteristics of all starting materials.[1] These transformations, often referred to as cascade, domino, tandem, or one-pot processes, have captivated chemists for over a century due to their versatility in constructing complex heterocycles. In 1850, Strecker had reported the first MCR, which was followed by the development of several reactions, such as Hantzsch, Passerini, and Ugi reactions. The first Biginelli reaction was reported by Pietro Biginelli in 1893. In recent years, the Biginelli reaction has gained enormous recognition due to various applications of DHPMs.[3] Now recognized as the classical Biginelli reaction; this transformation has garnered significant attention due to the diverse applications of DHPMs. Although relatively unexplored until the 1980s, the reaction has since become a cornerstone in heterocyclic synthesis, inspiring numerous reviews and book chapters and mechanistic investigations.[4-5] The Biginelli reaction is found to be very important due to the presence of DHPMs as structural motifs in marine alkaloids.[6] The DPHMs are exhibiting anti-inflammatory, anti-malarial, antiviral, antitumor, anti-tubercular, anti-leishmanial, antibacterial, anti-proliferative and anti-diabetic (Fig.-1).[7] In recent years, it has been found that DHPMs are emerging as calcium channel blockers, antihypertensive agents,[8] α1a-adrenergic antagonists,[9] mPGES-1 inhibitors,[10] and antagonists etc.[11] Beyond medicinal chemistry, the Biginelli reaction play an important role in asymmetric synthesis, solid-phase synthesis, green chemistry applications (using microwave irradiation, ionic liquids, and solvent-free conditions), and chemical biology.[12] In materials science, the DHPM scaffold has been employed to design heterocycles with novel optical properties, as well as functional materials such as polymers, adhesives, nanomaterials, and fluorescent probes.[13]

In recent years, dihydropyrimidinones (DHPMs) was developed by several novel methodologies. Notable catalysts and reaction conditions that have been reported include Ionic Liquids,[14] $Yb(OTf)_3$,[15] Indium(III) Chloride,[16] Trifluoroacetic acid (TFA),[17] Chlorotrimethylsilane,[18] Ferric Chloride/Tetraethyl Orthosilicate,[19] Ruthenium(III) Chloride,[20] N-Bromosuccinimide,[21] Ferric or Nickel Chloride Hexahydrates,[22] a variety of fruit juices as catalysts,[23] Microwave-assisted reactions,[24] Triethylammonium

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acetate ionic liquid,[25] Fe_3O_4 nanoparticles,[26] Bismuth triflate,[27] organocatalysts,[28] (L)-prolinamide-containing imidazolium ionic liquids,[29] spinol-phosphoric acids,[30] 4-hydroxyproline-containing podands,[31] methanopyrrolines/thiourea-based dual organocatalysts,[32] nanosized metal oxides,[33] nanosized TiO_2-SiO_2 composites,[34] silicon, titanium and aluminum oxides,[35] mixed oxides of silicon, titanium, and zirconium modified with carboxylic acids,[36] 1-glycyl-3-methyl imidazolium chloride-copper (II) complexes,[37] eutectic salts,[38] and bio-waste-derived sustainable heterogeneous catalysts.[39-44]

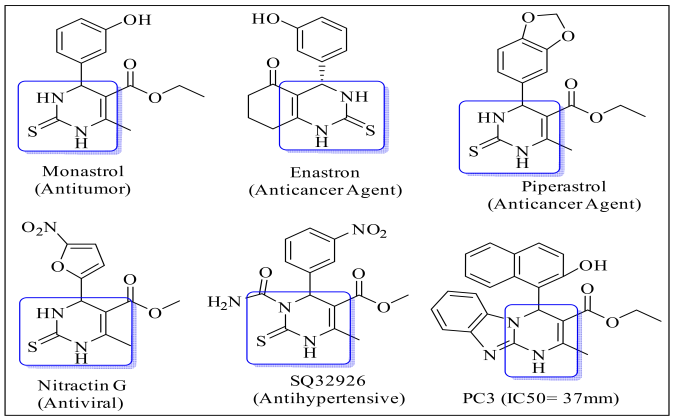
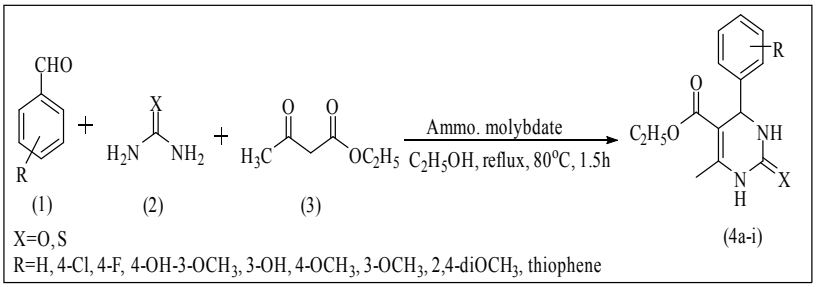


Fig.-1: Biologically Active DHPM Molecules

Despite the wide range of catalysts and conditions employed, these methods often present limitations such as complex work-up procedures, sensitivity to moisture, the use of toxic or volatile solvents, expensive and non-recyclable catalysts, high operating temperatures, and prolonged reaction times. Given these challenges, there is a pressing need for the development of new reaction conditions for the Biginelli reaction that operate under mild and environmentally friendly conditions. Monastrol is a potent inhibitor of the mitotic kinesin Eg5. Inhibition of Eg5 leads to cell cycle arrest during mitosis. Importantly, Monstrol was the first small molecule identified through phenotypic screening that directly targets Eg5, highlighting the biological and therapeutic significance of DHPM derivatives [45-46] While several metal catalysts have been explored for the Biginelli reaction, to our knowledge, ammonium molybdate $[(NH_4)_6Mo_7O_{24}.4H_2O]$ has not been utilized for this transformation. Therefore, in continuation of our ongoing work and recognizing the unique biological properties of DHPMs, we herein report an efficient and straightforward Biginelli reaction mediated by ammonium molybdate. This approach offers a new pathway for the synthesis of DHPMs under mild, green and cost-effective conditions (Scheme-1).



Scheme-1: Ammonium Molybdate-Mediated Synthesis of DHMP (4a-i)

EXPERIMENTAL

Material and Methods

All the chemicals were commercial vendors and used without further purification. The TLC was performed on silica gel 60 F_{254} plates (Merck), using a typical mobile phase of petroleum ether: ethyl acetate (8: 2). Melting points were measured using a hot-plate microscope apparatus and are presented without any correction. The ^{1}H-NMR spectra were obtained using a Bruker Avance III 500 MHz spectrometer and $CDCl_3$ were used as the solvent, TMS serving as the internal standard. Mass spectra

were acquired using an Agilent G6160A Infinity Lab LC/MSD/IQ mass spectrometer in electrospray ionisation (ESI) mode.

General Procedure

General Procedure for the Biginelli reaction (**4a-i**)

Aromatic aldehyde (10 mmol), ethyl acetoacetate (10 mmol), and urea or thiourea (20 mmol) were taken in 25ml of ethanol, then the catalyst, ammonium molybdate 5mmol was added. The reaction mixture was magnetically stirred and heated under reflux for 1.5 hours, as monitored by TLC. The initially syrupy reaction mixture solidified within 25-30 minutes. After completion, the solid mass was poured onto crushed ice and filtered. The obtained solids were recrystallized by using ethyl acetate to afford Biginelli products (**4a-i**) in good to excellent yields. All compounds were characterized by their melting points, ^{1}H-NMR (500 MHz, $CDCl_3$) and mass spectral data. The corresponding mass and ^{1}H-NMR spectra are provided in the supplementary materials as supporting information.

Spectral Data for Representative Compounds (4a-i)

Compound-4a: δ 8.01 (s, 1H), 7.32 (s, 2H), 7.31 (d, *J* = 1.5 Hz, 2H), 7.28 (d, *J* = 2.2 Hz, 1H), 5.80 (s, 1H), 5.40 (s, 1H), 4.07 (s, 2H), 2.35 (s, 3H), 1.16 (s, 3H). HRMS Mass: Chemical Formula: $C_{14}H_{16}N_2O_3$. Calculated mass: 260.12, Obtained mass: 261.12.

Compound-4b: δ 7.68 (s, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.9 Hz, 2H), 5.64 (s, 1H), 5.31 (d, *J* = 2.4 Hz, 1H), 4.02 (s, 2H), 2.28 (s, 3H), 1.11 (s, 3H). HRMS Mass: Chemical Formula: $C_{14}H_{15}ClN_2O_3$, Calculated mass: 294.08; Obtained: 295.08.

Compound-4c: δ 8.16 (s, 1H), 7.21 (dd, *J* = 8.0, 2.7 Hz, 2H), 6.92 (t, *J* = 8.6 Hz, 2H), 5.83 (s, 1H), 5.32 (s, 1H), 3.98 (s, 2H), 2.10 (s, 3H), 1.08 (s, 3H). HRMS Mass: Chemical Formula: $C_{14}H_{15}FN_2O_3$.Calculated mass: 278.11, Obtained mass: 279.11.

Compound-4d: δ 6.77 (dd, *J* = 5.9, 8.0 Hz, 2H), 6.54 (s, 1H), 5.74 (s, 1H), 5.26 (d, *J* = 8.0 Hz, 1H), 4.89 (dd, *J* = 5.9, 3.2 Hz, 2H), 4.03 (s, 2H), 3.80 (s, 3H), 2.28 (s, 3H), 2.01 – 1.93 (m, 3H). HRMS Mass: Chemical Formula: $C_{15}H_{18}N_2O_5$. Calculated mass: 306.12; Obtained mass: 306.10.

Compound-4e: δ 8.16 (s, 1H), 7.23 – 7.19 (m, 2H), 6.92 (t, *J* = 8.6 Hz, 2H), 5.83 (s, 1H), 5.31 (d, *J* = 2.4 Hz, 1H), 4.11 – 3.91 (m, 2H), 2.27 (s, 3H), 1.62 (s, 1H), 1.09 (t, *J* = 7.1 Hz, 3H). HRMS Mass: Chemical Formula: $C_{14}H_{16}N_2O_3S$. Calculated mass: 292.09; Obtained mass: 321.14 (M^{-1}+30 i.e., M^{-1}+MeOH adduct)

Compound-4f: ^{1}H NMR (500 MHz, DMSO) δ 8.46 (s, 1H), 7.05 (s, 1H), 6.50 (d, *J* = 4.9 Hz, 1H), 6.15 – 6.07 (m, 1H), 6.03 (d, *J* = 3.3 Hz, 1H), 4.56 (d, *J* = 3.5 Hz, 1H), 3.21 (q, *J* = 7.1 Hz, 2H), 1.36 (s, 3H), 0.34 – 0.29 (m, 3H). HRMS Mass: Chemical Formula: $C_{12}H_{14}N_2O_2S_2$. Calculated mass: 282.05; Obtained mass: 312.09 (M^{-1}+30 i.e., M^{-1}+MeOH adduct)

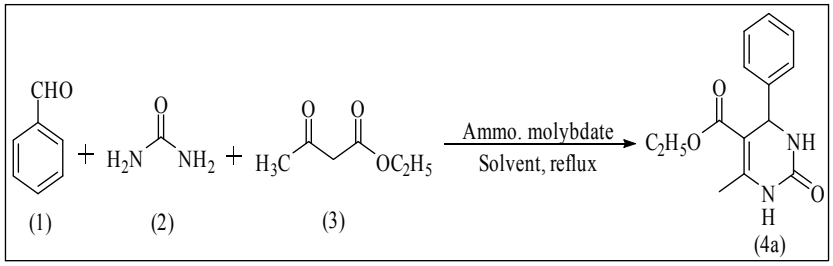
Compound-4g: δ 7.94 (s, 1H), 7.20 – 7.15 (m, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 5.66 (s, 1H), 5.28 (s, 1H), 3.99 (s, 2H), 3.71 (s, 3H), 2.27 (s, 3H), 1.09 (s, 3H). HRMS Mass: Chemical Formula: $C_{15}H_{18}N_2O_4$. Calculated mass: 290.13; Obtained mass: 312.09 (M^{-1}+23 i.e., M^{-1}+Na salt)

Compound-4h: δ 7.26 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.91 – 6.87 (m, 1H), 6.84 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.57 (s, 1H), 5.41 (s, 1H), 5.30 (s, 1H), 4.12 (dd, *J* = 7.1, 1.5 Hz, 2H), 3.82 (s, 3H), 2.38 (s, 3H), 1.25 – 1.16 (m, 3H). HRMS Mass: Chemical Formula: $C_{15}H_{18}N_2O_4$. Calculated mass: 290.13; Obtained mass: 312.09 (M^{-1}+23 i.e., M^{-1}+Na salt)

Compound-4i: ^{1}H NMR: The compound is hygroscopic- NMR is not obtained: HRMS Mass: Chemical Formula: $C_{16}H_{20}N_2O_5$. Calculated mass: 320.14; Obtained mass: 321.14.

RESULTS AND DISCUSSION

To optimize the reaction conditions for the synthesis of the Biginelli product (4a), the condensation of benzaldehyde (1), urea (2), and ethyl acetoacetate (3) was first attempted under solvent-free conditions using ammonium molybdate as the catalyst. However, no product formation was observed (Entry-1, Table-1). Subsequently, the effects of different solvents and the stoichiometry of ammonium molybdate were investigated. When the reaction was performed in aprotic solvents like toluene, dichloromethane, acetonitrile and THF at RT for 24 h, no reaction was observed (Entries 2-8, Table-1). Similarly, when these solvents were refluxed for 4 h, no product was obtained (Entries 2-8, Table-1). In contrast, protic solvents such as ethanol and methanol afforded the desired product under specific conditions. At room temperature, only a low yield (5%) of 4a was obtained after 24 h (Entries 9 & 11, Table-1). However, refluxing ethanol or methanol with ammonium molybdate for 1.5 h led to a significant improvement, affording the product in 80% yield (Entries 10 & 12, Table-1). A control reaction confirmed the essential catalytic role of ammonium molybdate: in its absence, no product formation was observed (Entries 13 & 14, Table-1). Between ethanol and methanol, both produced similar yields; however, ethanol was chosen as the solvent of choice due to its greener and safer nature (Table-1, Scheme-2).



Scheme-2: Optimization of Ammonium Molybdate Mediated Synthesis of DHMP (4a)

Table-1: Optimization of the Biginelli Reaction

Entry	Solvent	Reaction Condition	Product 4a (Yield %)
1	C_6H_5CHO(1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	No solvent/Ammonium Molybdate/RT, 24h	No reaction
2	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	Toluene/Ammonium Molybdate/RT, 24h	No reaction
3	C_6H_5CHO (1a) / NH_2CONH_2 (2) $C_2H_5OCOCH_2COCH_3$(3)	THF/Ammonium Molybdate/Reflux, 4h	No reaction
4	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	THF/Ammonium Molybdate/RT, 24h	No reaction
5	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	Acetonitrile/Ammonium Molybdate/RT, 24h	No reaction
6	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	Acetonitrile/Ammonium Molybdate/Reflux, 4h	No reaction
7	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	DCM/Ammonium Molybdate/RT, 24h	No reaction
8	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	DCM/Ammonium Molybdate/Reflux, 4h	No reaction
9	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	Ethanol/ Ammonium Molybdate, RT, 24h	5%
10	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	Ethanol/Ammonium Molybdate/Reflux, 80^0C, 1.5h	80
11	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	Methanol/Ammonium Molybdate/RT, 24h	5%
12	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	Methanol/Ammonium Molybdate/Reflux, 1.5h	40
13	C_6H_5CHO (1a) / NH_2CONH_2 (2) /	Ethanol/Without Ammonium	No reaction

	$C_2H_5OCOCH_2COCH_3$ (3)	Molybdate/Reflux, 1.5h	
14	C_6H_5CHO (1a) / NH_2CONH_2 (2) / $C_2H_5OCOCH_2COCH_3$ (3)	Ethanol/Without Ammonium Molybdate/Reflux, 1.5h	No reaction

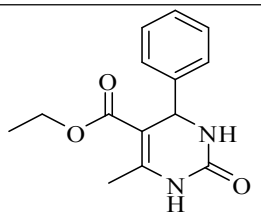
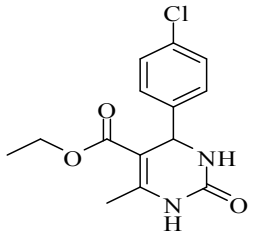
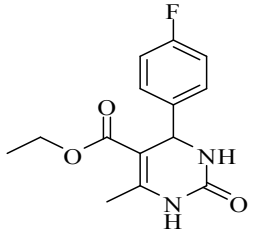
After solvent optimization, the effect of catalyst loading was studied (Table-2). The reaction failed in the absence of ammonium molybdate (Entry 1, Table-2). Varying the catalyst equivalents revealed that 1 equivalent was optimal, providing the best yield of 4a (Entries 2-6, Table-2). These results clearly indicate that ammonium molybdate is indispensable for efficiently promoting the transformation.

Table-2: Ammonium Molybdate (AM) Effect on the Biginelli Reaction of Benzaldehyde (4a)

Entry	AM (in equiv.)	Conversion (%)
1	In the absence of AM	Reaction did not proceed
2	0.10	20
3	0.25	30
4	0.50	40
5	0.75	60
6	1	90

The general applicability of the method was then evaluated by extending it to various substituted benzaldehydes (1a-i). The reactions proceeded smoothly, affording the corresponding dihydropyrimidinones in good yields (Table-3). The recyclability of ammonium molybdate was also examined. The ammonium molybdate can be effortlessly recovered via a filtration process and reused after being washed and dried. The results of the recycling process show that the activity of ammonium molybdate is retained up to three consecutive runs, affording good yields of 4a (Table-4). The structures of all synthesized products are provided in Table-5.

Table-3: Amonium Molybdate Promoted the Synthesis of DHMP (4a-i)

S. No.	Compound	%Yield	Time (in hr)	M.P Reported (Obtained)
1	 4a	80	1.5	195-196 (198-200)
2	 4b	90	1.5	206-208 (207-210)
3	 4c	90	1.5	188-189 (189-191)

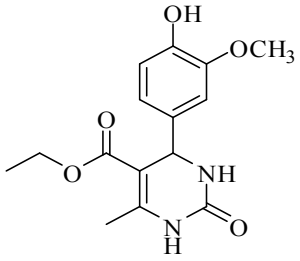
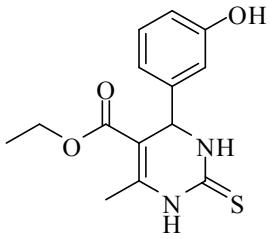
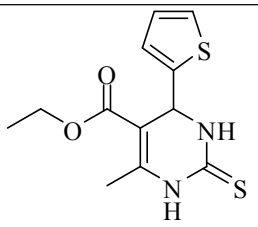
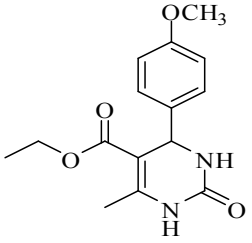
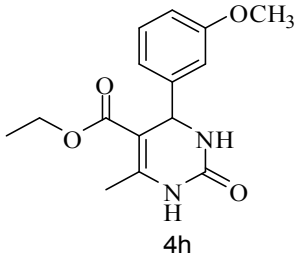
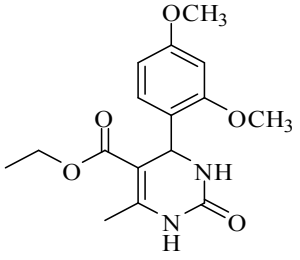
4	 4d	90	1.5	214-216 (215-218)
5	 4e	90	1.5	184-185 (184-186)
6	 4f	80	1.5	219-220 (220-221)
7	 4g	88	1.5	199-200 (200-202)
8	 4h	85	1.5	203-205 (204-206)
9	 4i	75	1.5	60-65 (67-69) (Hygroscopic)

Table-4: Recyclability of the Ammonium Molybdate on the Biginelli Reaction of Benzaldehyde (4a)

Entry	Ammonium molybdate (Runs)	Product 4a Yield (%)		Recovery of Catalyst (%)
1	1	80	10	90
2	2	85	15	90
3	3	80	20	80

To validate the efficiency of ammonium molybdate, its performance was compared with other reported catalysts (Table-5).[46-63] Catalysts such as sulfonated biochar (98% yield in 30 min, cheapest),[63] Fe_3O_4 nanoparticles (90% yield in 16 min, cheap), and zirconia sulfuric acid (81-98% yield, 30-70 min) showed faster reaction times and higher yields. More advanced systems, including Mo_{132} and Fe_3O_4@C@OSO_3H, afforded excellent yields in shorter durations but are prohibitively expensive and less practical for scale-up. In contrast, ammonium molybdate is very cheap, environmentally benign, recyclable, and easy to handle. Although its reaction time (1.5 h) and yield (75-90%) are moderate compared to nanocatalysts, it offers a unique balance of cost-effectiveness, simplicity, and sustainability, making it an attractive choice for green and scalable synthesis.

Table-5 Comparison with other Reported Catalysts

S. No.	Catalyst	Amount	Conditions	Yield (%)	Time	Cost-effectiveness	Ref.
	Phthalimide-*N*-sulfonic acid (PISA)	10 mol %	SF / 120^{0}C	94	120 min	Cheap	[37]
	Er(III) chloride hexahydrate	5.0 mol %	MW/SF	-	90 min	Expensive	[46]
	p-Toluenesulfonic acid	6 mmol	Reflux/Ethanol	-	6-8 h	Very cheap	[47]
	$[Al(H_2O)_6](BF_4)_3$	10 mol %	Acetonitrile, reflux	80-95	20 h	Moderate	[48]
	Mg-Al-CO_3 /Ca-Al-CO_3 hydrotalcites	0.02g	MW/SF	-	2-8 min	Low cost	[49]
	$SnCl_2{\cdot}2H_2O$	0.02 mmol	SF / 80^{0}C	-	80-90 min	Cheap	[50]
	(BNPs@$SiO_2(CH_2)_3NHSO_3H$)	0.05g	80°C, SF	90-97	30-60 min	Cost effective	[51]
	Zirconia sulfuric acid	0.05g	SF / 90^{0}C	81-98	30-70 min	Moderate	[52]
	Fe_3O_4@C@OSO_3H	8.1 mol %	SF / 80^{0}C	93	20 min	Expensive	[53]
	Mo_{132}	0.10 g	SF / 110^{0}C	93	15-20 min	Extremely expensive	[54]
	Fe_3O_4 nanoparticles	0.046 g	SF / 80^{0}C	90	16 min	Cheap	[55]
	Imidazol@Fe_3O_4 Nps	0.15 g	SF / 80^{0}C	91	30 min	Expensive	[56]
	γ-Fe_2O_3-SO_3H	0.1 g	SF / 60^{0}C	95	180 min	Expensive	[57]
	Fe_3O_4@SiO_2-imid-$H_3PMo_{12}O_{40}$	–	SF / 80^{0}C	92	30 min	Moderate	[58]
	$H_4[PVW_{11}O_{40}].32H_2O$, (HPV) supported on activated natural clay (HPVAC)	0.05 g	SF / 120^{0}C	91	1.5 h	Expensive	[59]
	Cocn. HCl	2-3 drops	Ethanol/reflux	-	12 h	Cheap	[60]
	praseodymium (III) nitrate ($Pr(NO_3)_3{\cdot}6H_2O$)	10 mol %	SF / 80^{0}C	85-98	15-25 min	Moderate	[61]
	Sulfonated biochar derived from eucalyptus bark	0.5 g	80^{0}C	98	30 min	Cheapest	[62]
	Ammonium molybdate	1 eq.	Reflux, ethanol / 80^{0}C	75-90	1.5 h	Very cheap	Our work

SF*= Solvent-free

The ammonium molybdate catalyzed Biginelli reaction, the possible mechanism is shown in Fig.-2. In the first step, Mo activates ethyl acetoacetate to form an enolate intermediate. Simultaneously, benzaldehyde condenses with urea to form an imine (Schiff base). These intermediates undergo nucleophilic addition, followed by intramolecular cyclisation and dehydration to afford the final dihydropyrimidinone (**4a**).

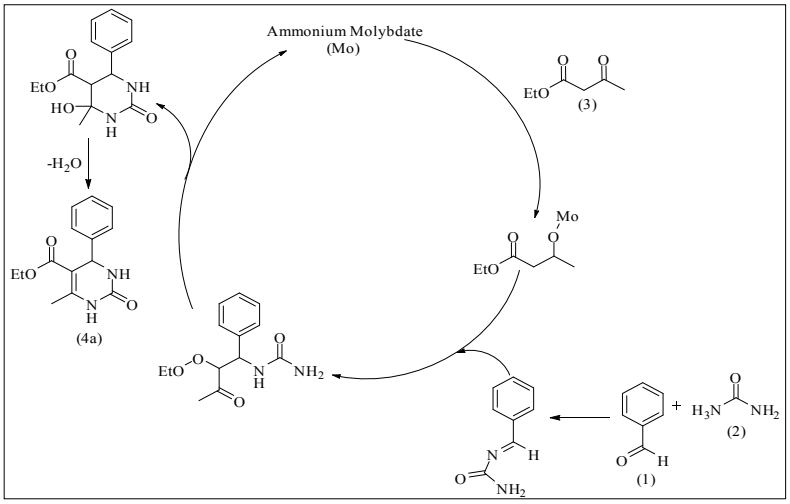


Fig.-2: Proposed Mechanism for Ammonium Molybdate-Mediated Biginelli Reaction

CONCLUSION

In conclusion, it can be said that we successfully demonstrated that ammonium molybdate acts as an efficient, inexpensive and recyclable catalyst for the Biginelli reaction, affording up to 75-90% yield of dihydropyrimidinones. Optimization studies confirmed that 1 equivalent of the catalyst and ethanol as a green solvent is essential for good yields. The ammonium molybdate can be recycled 3 times without losing much activity. Compared with reported catalysts, ammonium molybdate shows moderate activity but offers distinct advantages of very low cost, operational simplicity, and sustainability. While nanocatalysts and heteropolyacid systems often provide higher yields in shorter times, their expense and limited scalability make ammonium molybdate a more practical and eco-friendly alternative for large-scale applications.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-9: Industry, Innovation and Infrastructure*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID IDs, given below:

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