Ammonium Metavanadate(H_4NO_3V): An Efficient Catalyst in the Synthesis of 3,4-Dihydro-3-substituted-*2H*-naphtho[2,1-e][1,3]oxazine Derivatives.

A PG Dissertation Report of a Project Carried out as a Part of Curriculum for the Degree of Master of Science in Organic Chemistry

SUBJECT CODE: 33424C
[CBOP-5 CHO-453 C]

Submitted by
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Under the Guidance of
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Submitted to

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Affiliated to

SAVITRIBAI PHULE PUNE UNIVERSITY, PUNE

(2020-2021)

DECLARATION BY THE STUDENT

I declare that the dissertation entitled **"Ammonium Metavanadate(H_4NO_3V): An Efficient Catalyst in the Synthesis of 3,4-Dihydro-3-substituted-2*H*-naphtho[2,1-e][1,3]oxazine Derivatives."** submitted by me for the degree of Master of Science in Organic Chemistry **SUBJECT CODE: 33424C [CBOP-5 CHO-453 C]** is the record of work carried out by me under the guidance of **DR. AMOL H. KATEGAONKAR** and has not formed the basis for the award of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning. I further declare that the material obtained from other sources has been duly acknowledged in the dissertation

Date-

Place- Nashik

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STUDENT

CERTIFICATE OF RESEARCH SUPERVISOR (GUIDE)

Certificate of the Guide CERTIFIED that the work incorporated in the PG dissertation entitled **"Ammonium Metavanadate(H_4NO_3V): An Efficient Catalyst in the Synthesis of 3,4-Dihydro-3-substituted-2*H*-naphtho[2,1-e][1,3]oxazine Derivatives."** submitted by **MR. ABHISHEK PRAMOD JOSHI** was carried out by the candidate under my supervision/guidance. Such material has been obtained from other sources has been duly acknowledged in the dissertation.

Date: -

Place: - Nashik

DR. AMOL H. KATEGAONKAR
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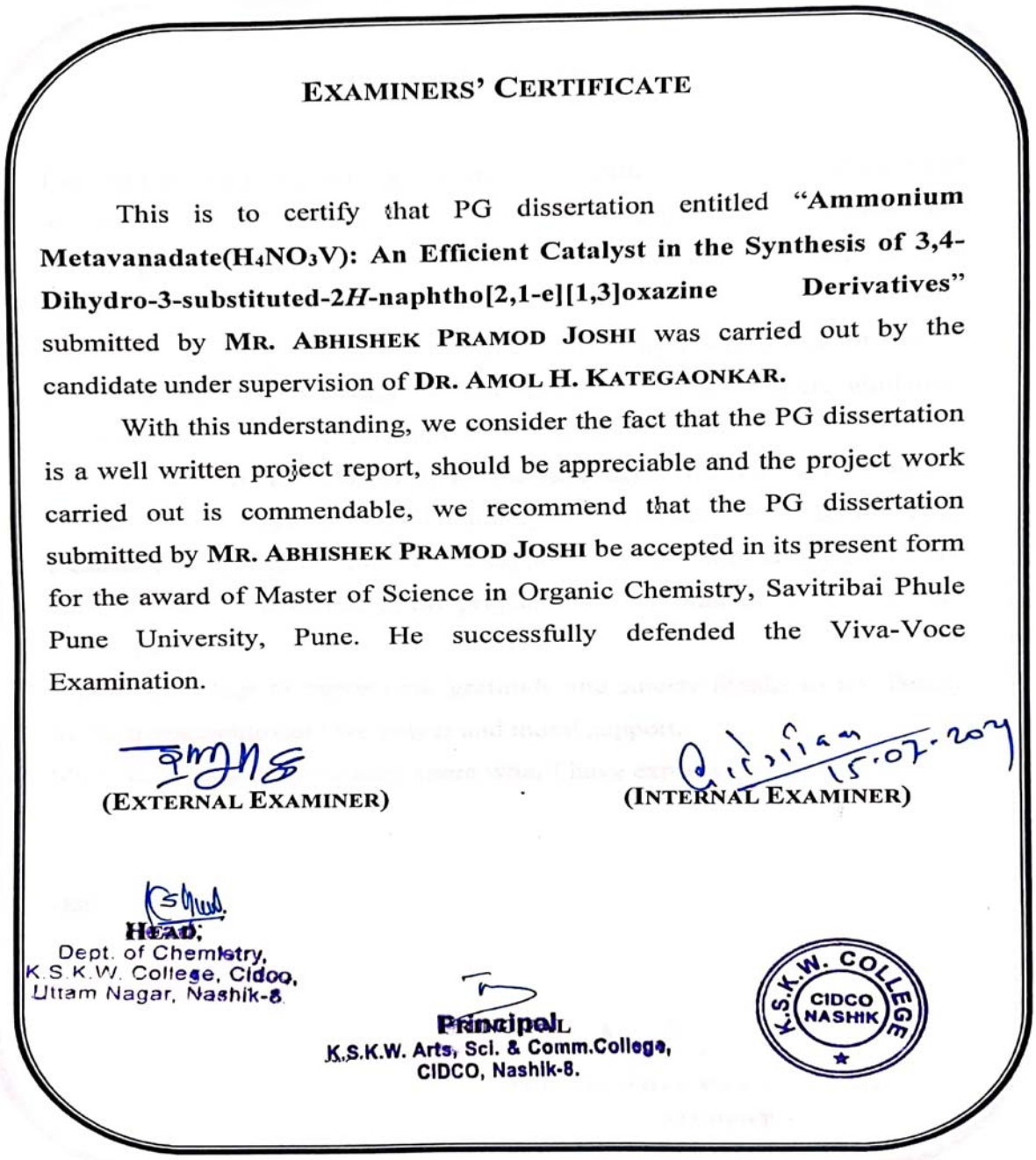

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With this understanding, we consider the fact that the PG dissertation is a well written project report, should be appreciable and the project work carried out is commendable, we recommend that the PG dissertation submitted by **MR. ABHISHEK PRAMOD JOSHI** be accepted in its present form for the award of Master of Science in Organic Chemistry, Savitribai Phule Pune University, Pune. He successfully defended the Viva-Voce Examination.

15.07.2024

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HEAD

PRINCIPAL

ACKNOWLEDGEMENT

I would like to take the privilege to thank the selfless people from the core of me heart who with their constant support, affection, inspiration and encouragement made us feel comfortable to successfully complete this venture.

My deep sense of gratitude and harmful thank to my PG Dissertation Project Guide/Supervisor **Dr. Amol H**. **Kategaonkar** for his expert guidance, constant encouragement, stimulating discussion.

I am thankful **to Dr. (Mrs.) J. D. Sonkhaskar** Principal, MVP Samaj's KSKW ASC College, CIDCO, Uttamnagar, Nashik and **Dr. S. K. Kushare** Head Department of Chemistry, for support and providing all the necessary facilities during the course of my project work and guided me in light path of the life.

It is my privilege to express our gratitude and sincere thanks to my family for their unconditional love prayer and moral support.

My acknowledgement is many more what I have expressed here.

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Place: - Nashik

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INDEX

1. INDRODUCTION

There were various researches has been carried out for the synthesis of 1,3-oxazine compounds some of them were condensation of 3-amino propanol with carboxylic acid derivatives using solvent-free conditions[1]. From methyl aminosalicylatereaction with amino acids. from phenol, aniline, and formaldehyde. From Antharanilic acid or its derivatives as precursor[2].Over the past decade, this condensation reactions has been investigated in the presence of the various catalyst, such as cerium ammonium nitrate, ionic liquids, tin tetrachloride, silica perchloric acid and P_2O_5 supported on SiO_2[3,4]. It is Multicomponent reactions (MCRs), in which three or more different reactants react to give a product in a one-pot procedure, which has been used as a powerful tool to achieve this goal[5]. Multicomponent is one of the most suitable methods for synthetic efficiency and reaction design[6].

These methodologies allow molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation. Because MCRs combine two major principles of organic synthesis, convergence, and atom economy, this class of reactions is well-known applications in organic and medicinal chemistry[5]. Multicomponent reactions play a significant role in organic synthesis, medicinal chemistry, and material science[7].

The development of the environmentally benign and cost-efficient synthetic procedure has been demanded from the viewpoints of green sustainable chemistry[8].

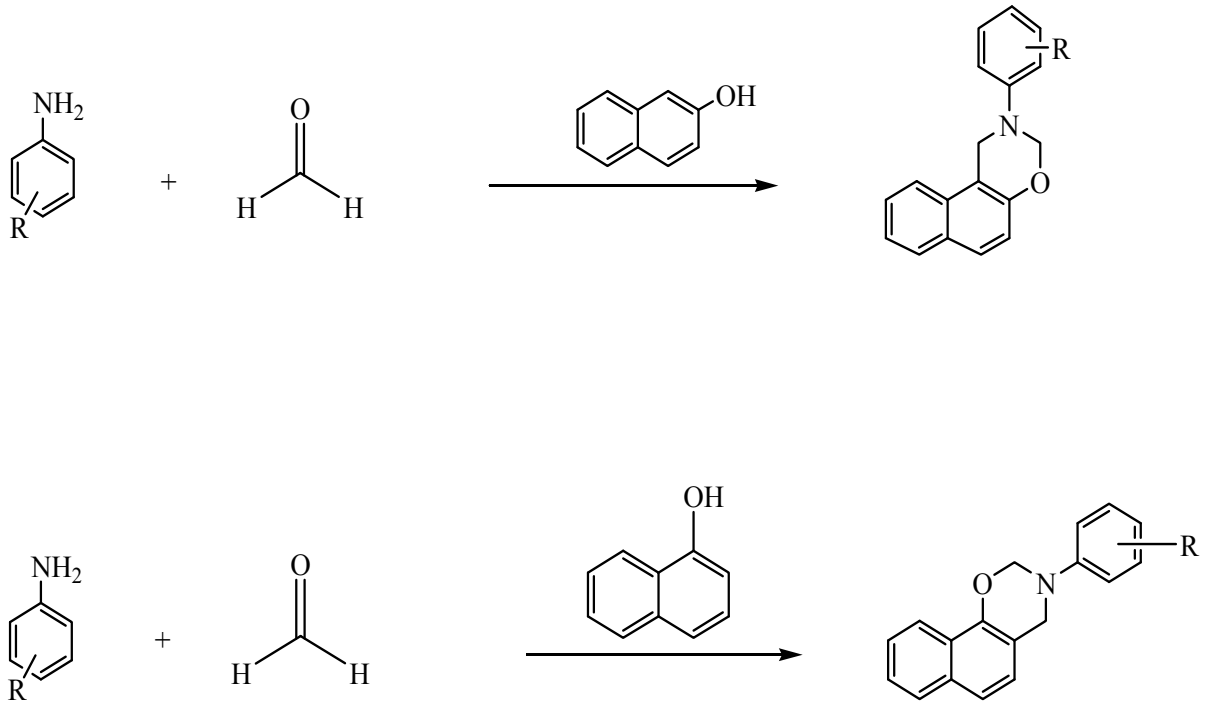
Oxazines are a very important class of heterocyclic compounds, they are classified into three isomeric forms like 1,2oxazine, 1,3 oxazines, and 1,4 oxazines[9]. They are an important class of heterocycles, which has attracted much synthetic interest due to their

wide range of biological activities[10].1,3oxazine is a six-membered heterocyclic ring it is the prominent nucleus of the number of biodynamic natural and synthetic molecules[11]. It has been reported to exhibit a wide array of biological and pharmacological activities[12]. Several methods have been reported for the synthesis of 1,3-oxazines owing to their biological importance[13,14]. The *in-vitro* anti-inflammatory and anti-oxidant activities reported in some of the researches. Isomeric oxazine derivatives synthesized from chalcone are known to possess various activities, like anti-hyperglycemic, antiulcer, anti-inflammatory[15], anti-microbial, anti-viral[16], antimalarial, analgesic, anti-cancer, anti-tubercular[17], anti-oxidant, and anti-leishmanial[18], anti-coagulant activities[19].

Oxazine derivatives have played a very important role in the improvement of heterocyclic chemistry and are ordinarily used in organic synthesis[20]. Oxazine derivatives have been reported to possess anti-fungal, antibacterial activities[21]. Amino acids have a unique bifunctional, structure that serves to conveniently from peptides, peptidomimetics, and proteins. Due to its numerousbiological activities reported[22].

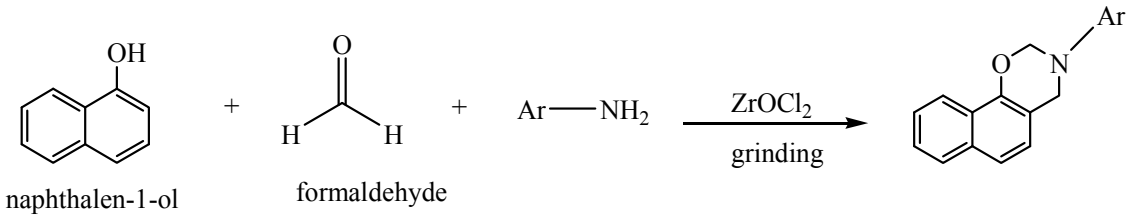
2. LITERATURE REVIEW

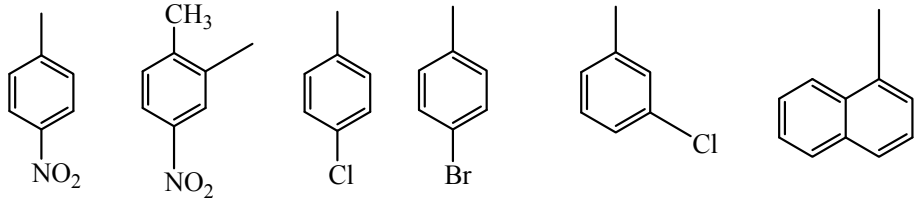
An efficient and convenient synthesis of 1,3-oxazine derivatives has been achieved by the one-pot procedure, multicomponent condensation of α/β-naphthol, and aniline and formaldehyde using thiamine hydrochloride (Scheme-1) as a versatile biodegradable and reusable catalyst in water as a universal solvent[5].



(Scheme 1)

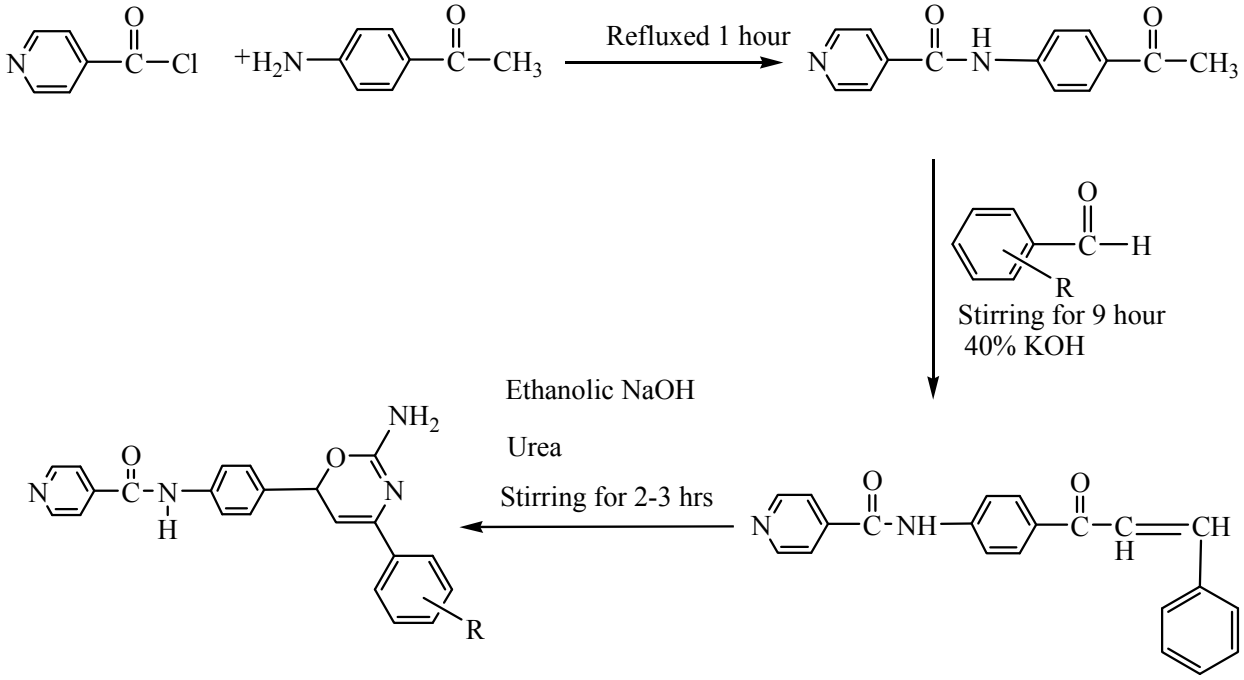
Oxazine compounds were found to have versatile applications in pharmacology and medicine nowadays. Their values and application as drug and co-drug have drawn the attention of chemists to find different ways for the synthesis of this important type of heterocyclic compounds. They are not only important as pharmaceutical chemical compounds but also as synthetic intermediates for other chemical and medicinal compounds. Accordingly, we tried to find a green and friendly procedure for the synthesis of new oxazine compounds (Scheme 2) using the grinding technique. The synthesized compounds were studied by spectral methods and are discussed[1].





(Scheme 2)

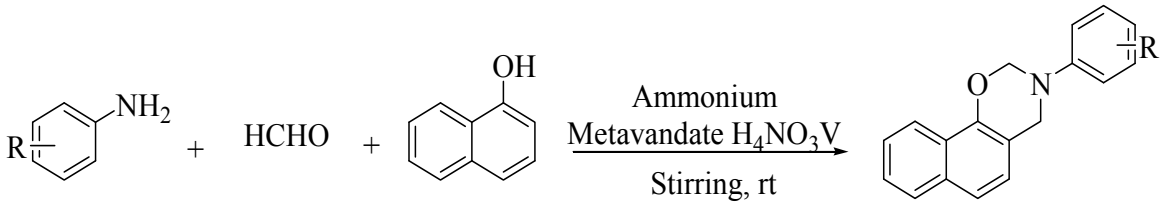
Oxazineheterocycleshave special interest due to their important class of natural and non-natural products and show high biological activities in pharmaceutical and biological fields. Research work was planned to synthesize 1,3-oxazine derivatives from chalcone and screened for their anti-inflammatory and anti-oxidant activity. The structure of synthesized compounds (Scheme 3) was established from UV, IR, ^{1}H NMR, ^{13}C NMR, and Mass spectral data. All the synthesized compounds were screened for *in-vitro* anti-inflammatory by bovine serum albumin and protease method and *in-vitro* anti-oxidant by diphenylpicrylhydrazide and nitric oxide method. Among synthesized derivatives, the screening results revealed and to be significant ata concentration of 10 µg /ml[15].



(Scheme 3)

3. PRESENT WORK

We have demonstrated the Synthesis of 3,4-dihydro-3-Substituted-2*H*-naphtho[2,1-e][1,3]oxazine derivative in the acidic medium of substituent α-naphthol, Ar–amine, and formaldehyde in the presence of ammonium metavanadate.



1(a-i) **2** **3** **4(a-i)**

(Scheme-4)

4. RESULTS AND DISCUSSION

We had performed the Multicomponent reaction of α-naphthol, formaldehyde and Ar-amine, (1:2:1) in the presence of (10 mol%) various acid catalysts to synthesize 1,3 oxazine derivative at room temperature.

Ammonium metavanadate is a catalyst that we used to synthesis 1,3 oxazine derivative through which we obtained the maximum quantitative yield for the Synthesis of 3,4-dihydro-3-Substituted-2*H*-naphtho[2,1-e][1,3]oxazine derivative.i,e 85 to 96% and in minimum time i,e 30 to 45 min.

We have synthesis the model reaction with the Aniline by using various acid catalysts through which we obtained the best results with H_4NO_3V. Further we have obtimisedthe reaction by using different-different model reactions (Table 1) in presence of H_4NO_3V as a catalyst (Table 2).

The Synthesis is performed by using acetic acid and oxalic acid through which we obtained about 70 to 80% yield and in 60 to 90 min for obtaining the desired product.

By using boric acid and citric acid as a catalyst and we found that the product obtained is having a yield of about 58 to 65% and the time required for the reaction is about 90 to 120 min to obtain the product. H_4NO_3V is used as an oxidizing agent for the condensation of 1,3oxazine derivative which is one of the most suitable and efficient acid catalysts for obtaining a maximum yield of a product in a minimum time.

4.1.MECHANISM: *Synthesis of 1,3-Oxazine derivatives catalyzed in H_4NO_3V*

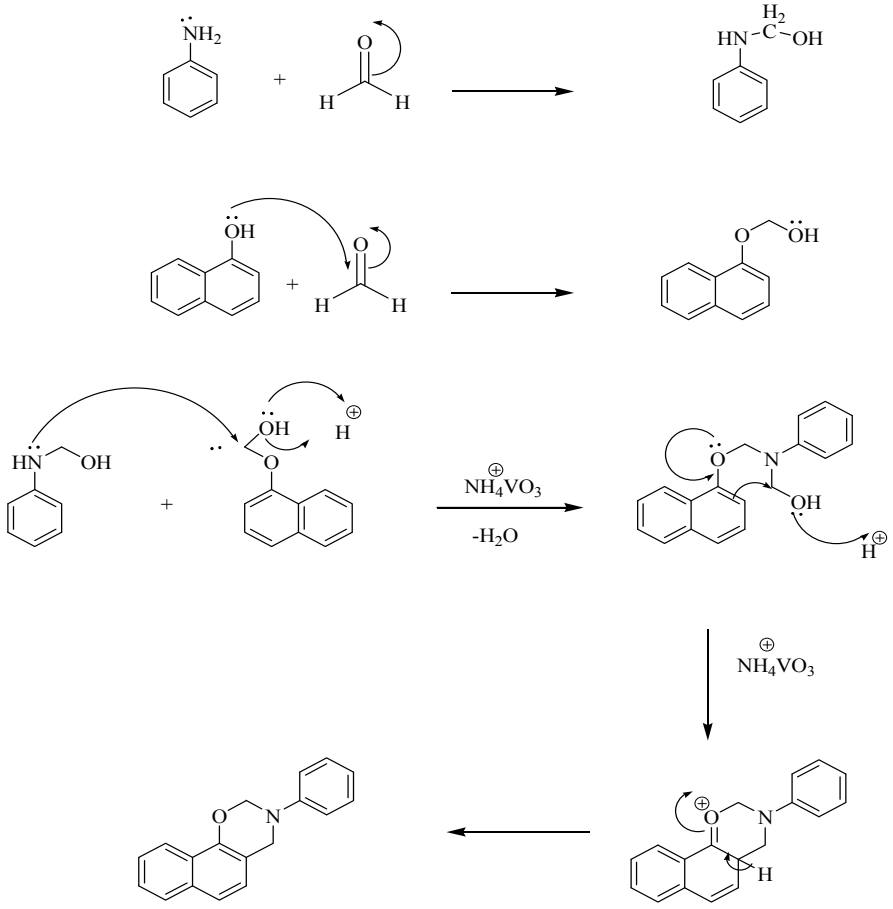


Table 1. Effect of catalyst loading on model reaction on Aniline (1a).

Entry	Catalyst	Time (min)	Yield(%)
1a	H_4NO_3V	42	91
1a	CH_3COOH	78	80
1a	Oxalic Acid	76	76
1a	Citric Acid	112	58
1a	Boric Acid	98	65

Table 2. Synthesis of 1,3-Oxazine derivatives catalyzed in H_4NO_3V

Compound	R	Time (min)	Yield (%)[a]	M. P. (°C)
4a	H	42	91	60-62
4b	4-OMe	48	85	280 (d)
4c	4-OEt	50	87	78-80
4d	2,4,6-Tri Br	60	78	70-72
4e	4-Me	45	83	194-196
4f	2-OEt	44	90	188(d)
4g	4-F	50	96	120-122
4h	3-OMe	52	85	290(d)
4i	2-Me	54	88	88-90

5. CONCLUSION

We have developed a solvent-free, environmentally protocol for the Synthesisof3,4-dihydro-3-Substituted-2*H*-naphtho[2,1-e][1,3]oxazine derivative in an acidic medium by using H_4NO_3V as a catalyst. this method is of green solvent and benign catalyst, at room temperature reaction, and with simple workup, and high yields of product.

6. EXPERIMENTAL WORK

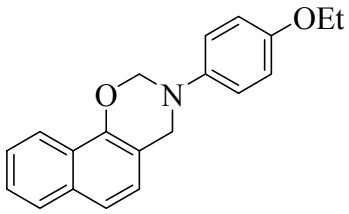
All the melting points were determined by using a paraffin oil bath in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Mercury Plus Varian in DMSO-*d6* at 400 MHz using TMS as an internal standard. Mass spectra were recorded on MicromassQuattro II using the electrospray ionization technique. The progress of the reactions was monitored by TLC.

6.1.GENERAL PROCEDURE

Take (5 mmol) Ar-NH_2 in 50ml beaker to it add (10 mmol) of formaldehyde and (5 mmol) α-naphtholin it. Now stir the mixture for 5 to 10 min at room temperature. Now, to a stirred mixture of α-naphthol, Formaldehyde and Ar-NH_2, Like **1(a-i)** add acid catalyst i,e. H_4NO_3V to a mixture. then again stir the mixture for around 42–54 min at room temperature. A thick paste product is obtained. The reaction is monitored by TLC. After completion of reaction, reaction mixture was extracted with methylene dichloride (3×50 mL), washed with water (2×10 mL) and brine (2×20 mL). Thus separated organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The

obtained crude product was purified by column chromatography on silica gel by hexane: ethyl acetate as an eluent.

6.2. SPECTRAL ANALYSIS

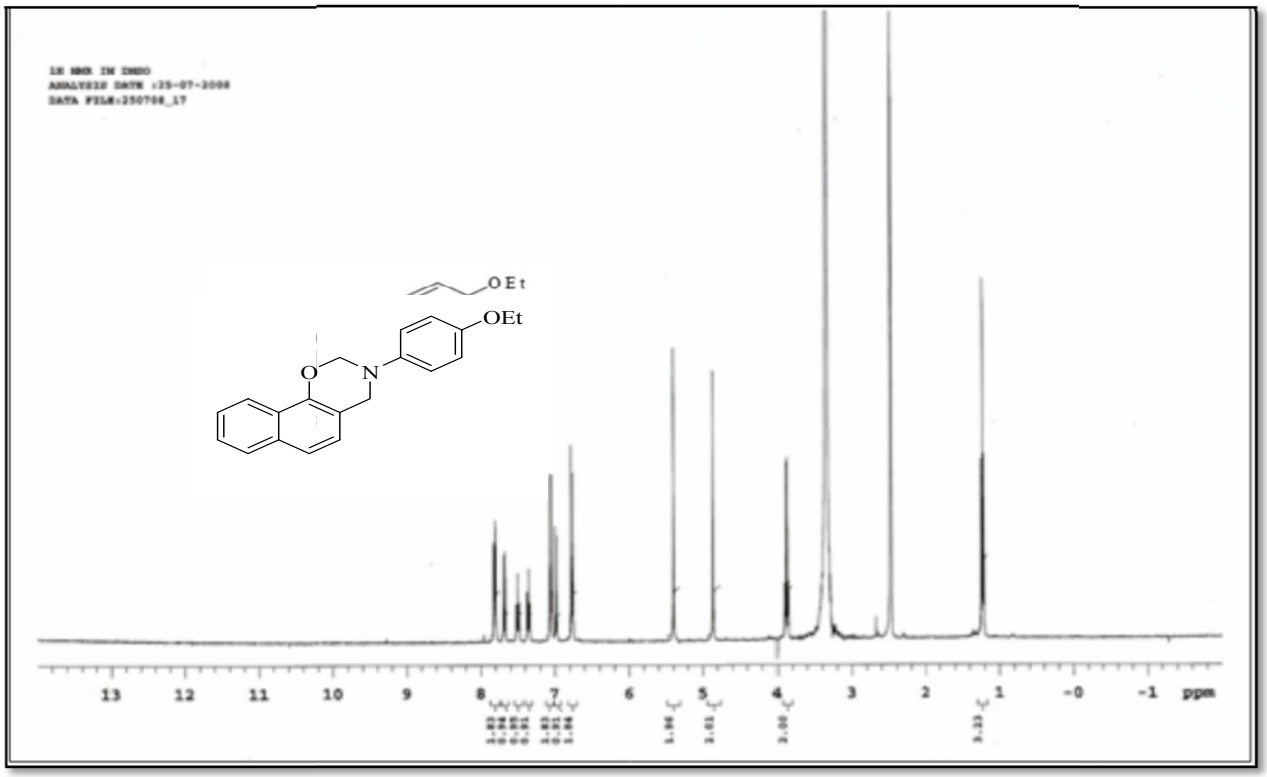


4-(ethoxy)-3,4-dihydro-3-Substituted-2H-naphtho[2,1-e] [1,3] oxazine (4c)

IR (KBr, ν_{max}/cm^{-1}): 1028 (sym.C-O-C), 1224 (asym. C-O-C).

^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 1.20 (t, 3H, J = 8 Hz, O-CH_2-$\underline{CH_3}$), 3.90 (q, 2H, J = 8 Hz ,O-$\underline{CH_2}$-CH_3), 4.90 (s, 2H, -Ar-CH_2-N-), 5.40 (s, 2H, -O-CH_2-N-), 6.80-7.80 (m, 10H, Ar-H).

ES MS: m/z 306.2 (m+1).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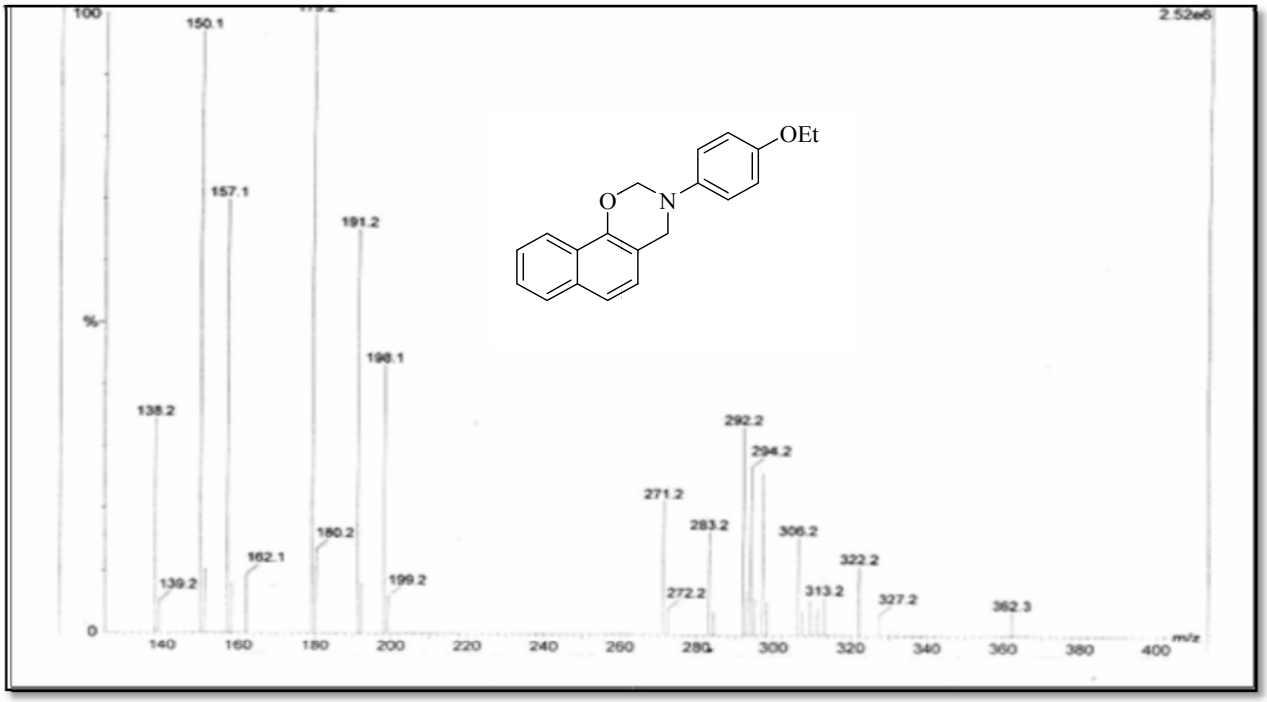
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283.2
306.2
322.2
313.2
272.2
327.2
362.3
2.52e6
OEt
O
N
140
160
180
200
220
240
260
280
300
320
340
360
380
400
m/z

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