A PROJECT REPORT ENTITLED

"NINPS-THIAMINE HYDROCHLORIDE (VB_1) IN WATER: A PRIVILEGED SYNTHETIC ROUTE FOR BENZIMIDAZOLE DERIVATIVES"

SUBMITTED TO

UNIVERSITY GRANTS COMMISSION

SUBMITTED BY,

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TULJARAM CHATURCHAND COLLEGE, BARAMATI

DIST: PUNE, MAHARASHTRA, INDIA

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My special thanks to the Hon'ble chairman and Hon'ble secretary, Anekant Education society Baramati, for granting permission for laboratory work

I am very much thank full to *Dr.C.V.Murumkar* (Principal, Tuljaram Chaturchand College, Baramati), who has inspired and helped me towards successful completion of this project work.

I take this opportunity to express deep sense of gratitude and sincere thanks to all faculty members librarian, laborotary and office staff and students , my friends and well-wishers for their support shown during preparation of this project.

Date: 21/05/15

Place: Baramati

Mr.Havappa Mallikarjun Wadde

Principal Investigator

DECLERATION

I hereby declare that research project entitled, ***"NiNPs-Thiamine hydrochloride (VB_1) in water: A Privileged Synthetic Route For Benzimidazole Derivatives"*** is completed and written by me sanctioned under the financial support by UGC, New Delhi at Tuljaram Chaturchand College, Baramati is the original work not been previously published or form of the any degree, diploma, research projector any similar title.

Date: 21/05/15

Place: Baramati

Mr. H.M. Wadde

Principal Investigator

CERTIFICATE

This is to certify that research project entitled, ***"NiNPs-Thiamine hydrochloride (VB_1) in water: A Privileged Synthetic Route For Benzimidazole Derivatives"*** is being submitted for the research project sanctioned under the financial support by UGC, New Delhi is the original work completed by Mr. H.M. Wadde and not the part of any earlier summation of any degree, diploma, research projector any similar title.

Date: 21/05/15

Place: Baramati

Tuljaram Chaturchand College Baramati 413102 Pune

Dr.C.V.Murumkar

Principal,

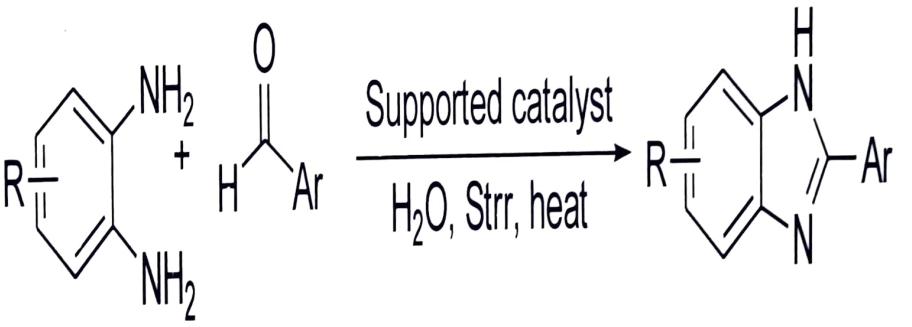
Tuljaram Chaturchand College,

Baramati

Abstract

NiNPS-Thiamine Hydrochloride (VB_1) in Water: A Privileged Synthetic Route for Benzimidazole Derivatives

NiNPS supported Thiamine hydrochloride (VB_1) is found to be an inexpensive, efficient, non-toxic and mild catalyst for the cyclocondensation of *o*-phenylinediamine and aromatic/heteroaromatic/aliphatic aldehydes in water at moderate temperature. The present work contributes a greener approach for the synthesis of benzimidazole derivatives under gracious (water) reaction medium which resulted into facile, sustainable and high yielding methodology.



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INTRODUCTION

In a sustainable civilization manufacturing processes are either designed so as not to produce waste products or it should be recycled/ biodegradable. Green chemistry has produced itself the landlord of organic chemistry, since its fundamental scientific methodologies can protect human health and the environment in an economically beneficial manner.

Therefore, there has been great expedition towards the improvement of greener chemical processes. The present research involves the use of natural solvent i.e. "Water" that can be surrogates for organic solvents. Water could be dedicated solvent under reflux temperature of reaction condition for organic transformations, because it is readily available, highly polar, nonflammable, nontoxic, cheap, and could offer the easy separation of reagents or catalysts from many organic products. Several organic transformations has been performed by using water as a solvent. Considering the above worthwhile advantages of water as competent reactions medium herein, attempt has been made to perform the cyclocondensation of *o*-phenylinediamine and aromatic/heteroaromatic/aliphatic aldehydes catalyzed by NiNPs-VB_1 in water for obtaining the desired benzimidazoles.

Recently, it has been proved that Ni nanoparticles as catalysts offer great opportunities for a wide range of applications in organic synthesis and chemical manufacturing processes including the chemo selective oxidative coupling of thiols, reduction of aldehydes and ketones, hydrogenation of olefins and supports for hydrogen adsorption. The metal nanoparticles are generally unstable, and the exploration of appropriate support for stabilizing catalytic nanoparticles is a key factor in their

successful and wide applications in heterogeneous catalysis. Thus the remarkable catalytic activity and easy synthesis, operational simplicity, ecofriendliness and recoverability of the Ni nanoparticle encouraged us to utilize this as a catalyst for the synthesis of desired benzimidazole moiety.

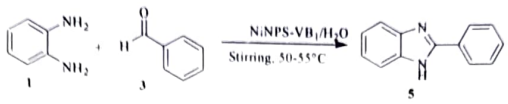
In the last few decades benzimidazoles have been much utilized for the synthesis of diverse highly functionalized molecules because of their broad spectrum of biological/pharmacological activities. It has been observed that numerous benzimidazole derivatives are successfully commercialized as potent Active Pharmaceutical Ingredients (APIs). Several benzimidazole derivatives find application as promising drugs in different therapeutic categories as potential anticancer agent, antitubercular, antifungal, antiprotozoal and antibacterial, anthelmintic agent, antiviral and antitumor, antiinflammatory and analgesic, lipase inhibition and antioxidant, aurora A/B kinase inhibitor, and antidiabetic activity.

Realizing the importance of benzimidazole derivatives in the synthesis of various drug sources, numerous routs have been reported. The other methods involve the use of catalysts like $ZnCl_2$-SiO_2 under microwave irradiation, CAN in PEG-400, boron sulfonic acid, $NaHSO_4$ in DMF at 80°C, $NaHSO_4$-SiO_2 under solvent free condition at 100°C, HCL/H_2O in ethanol under reflux condition, $CdCl_2$ in acetonitrile at 80-85°C, SDS micelles, mono and bifunctionalized Pd-MgO, and aluminosilicate (AlKIT-5) in acetonitrile under reflux condition.

Undesirably, these methodologies have been declined few aspect of sustainability for further improvement. Herein, to overcome

theseaspects more emphasis is laid on greener features by using NiNPs-VB_1 in water at mild temperature for the synthesis of benzimidazoles (**Scheme 1**). It has been recognized that VB_1 is an organo catalyst that surrogates inorganic reagents, it is water soluble and provides near neutral reaction medium, it is reusable, inexpensive, user/eco-friendly and compatible reagent for organic transformations.

CHEMISTRY



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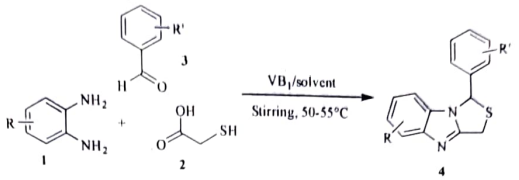
Scheme 1: General reaction for benzimidazole synthesis.

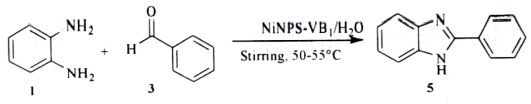
In continuation of author's interest to develop greener research methodologies for the synthesis of various heterocyclic compounds herein, initial investigation was focused on the synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole derivatives **4** from *o*-phenylinediamine **1**, thioglycolic acid **2** and benzaldehyde **3** using NiNPs-VB_1 as a catalyst (**Scheme 2**). Because the targeted products having promising biological activities *viz* HIV-1 RT inhibitors, antitrichinellosis, antidepressants and antiprotozoal.

Initially equimolar quantity of *o*-phenylinediamine, thioglycolic acid and vanillin were stirred in the presence of NiNPs-VB_1 in aqueous ethanol at room temperature to afford thiazolo-benzimidazole derivatives. Even after couple of hours the reaction was not completed. The same substrates were reacted in aqueous ethanol at 50-55°C little conversion is observed on TLC. Then a question was arrived in mind, why not to perform this reaction in water? Likewise the reaction is performed in water where no complete transformation is observed. Nevertheless, during the same reaction course in water at moderate temperature 50-55°C providentially remarkable product formation is observed. Therefore interest is more focused on development of new protocol by using NiNPs-VB_1 in water medium.



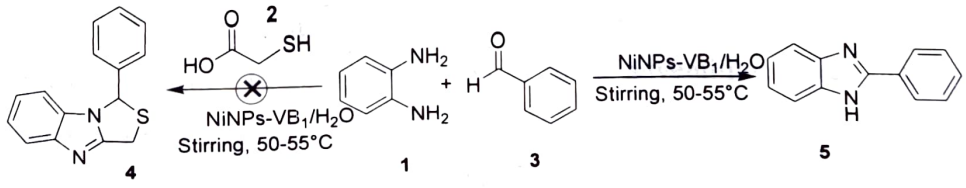
Scheme 2: General reaction for thiazolo-benzimidazole synthesis.

To confirm the formation of product **4** of this three component reaction (**Scheme 2**), parallel two component reaction has been carried out by same protocol (**Scheme 3**). The observation on TLC plate in iodine chamber revealed that RF value of thioglycolic acid was found equal with the RF value of one of the spot of reaction mixture.



Scheme 3: Standard model reaction

Also it is observed that RF values of compound **4** and **5** as well as their physical constants after isolation of the products are same. Hence, three components reaction is failed to afford thiazolo-benzimidazoles **4** whereas two component reactions are successful to achieve simple benzimidazole **5** (**Scheme 4**).



Scheme 4 A plausible product formation catalyzed by NiNPs-VB_1 in water.

Result and Discussion

After clarifying this trouble regarding formation of product further attempts were made to optimize the reaction condition for the synthesis of benzimidazoles. In search of the best experimental reaction conditions for the preparation of benzimidazole, reaction of *o*-phenylinediamine and benzaldehyde was selected as a model reaction (Scheme 3). To evaluate the effect of solvent, model reaction was performed using VB_1 in aqueous ethanol and water as solvent because, previously different protic as well as aprotic solvents has been utilized for benzimidazole syntheses. Worthwhile evaluation of present work *i.e.* synthesis of benzimidazoles catalyzed by NiNPs-VB_1 in water at 55°C is comparatively summarized with literature reports in table 1. Aqueous ethanol medium did not bring the reaction up to completion even after 8 hours although; it gives 65% yield of the product at moderate temperature 50-55°C (Table 1, entry 16). Promisingly, on the other hand water found to furnish the product in a good to excellent yield (96%) after 3.5 hours (Table 1, entry 15), but water at room temperature gives only 60% yield and requires prolonged reaction time 24 hours (Table 1, entry 14). To examine the catalytic efficiency of NiNPs-VB_1 the model reaction was run in the absence of NiNPs-VB_1 in water but there was little conversion even after 24 hours.

The conclusion drawn from the table 1 revealed that the present protocol (Table 1, entry 15) is more adventitious over other literature reports (Table 1, entries 1-13). Therefore NiNPsVB_1 is efficient catalyst for the synthesis of benzimidazole derivatives.

The plausible step-up interaction with NiNPs-VB_1 in water medium is shown in figure 1 in which aldehyde oxygen is co-ordinated with thiamine cation that increases electron deficiency on carbonyl carbon. The deficient aldehyde is then ready to form imines as an intermediate which on cyclocondensation followed by air oxidation resulted into desired benzimidazoles.

Thus, to determine the proper concentration of the NiNPs-VB_1 as a catalyst, model reaction was investigated at different concentrations such as 2, 4, 6, 8, and 10 mol %. It was found that the products obtained is 30%, 45%, 70%, 95%, and 96% yields, respectively. This indicates that 8 mol % of NiNPs-VB_1 is enough to carry out the reaction efficiently (Figure 2).

Table 1 Comparison of effect of solvent for benzimidazole synthesis with literature reports.

Entry	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield[a] (%)
1	Toluene	I_2	65	6	90
2	Toluene	$FeCl_3$	110	24	85
3	THF	$MgSO_4$/Ti $(Bu)_4$	RT	24	71
4	Acetonitrile	$Al_2O_3.SiO_3$	Reflux	4	95
5	DMF	$Na_2S_2O_3$	90	12	82
6	DMF	VB_1	RT	1.5	93
7	DCM	$SOCl_2.SiO_2$	RT	5	98
8	Methanol	$PdCl_2$	RT	4	78
9	Ethanol	H_2NSO_3H	85	3	72
10	Ethanol	NaY (zeolite)	RT	48	71
11	Ethanol	-	Reflux	14	65
12	Water	Laccase	RT	18	90
13	Water	H_2O_2/CAN	50	1.5	93
14	Water	NiNPs-VB_1	RT	24	60[P]
15	Water	NiNPs-VB_1	55	3.5	96[P]
16	Aq.Ethanol	NiNPs-VB_1	55	8	65[P]

[a]Isolated Yield, RT = Room temperature, CAN = Cerium ammonium nitrate, P = Presewnt work, Aq. = Aqueous.

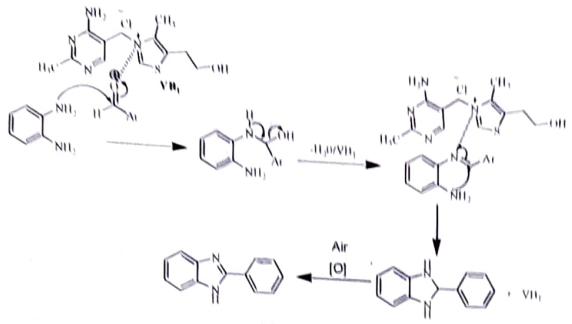


Figure 1: Mechanistic role of NiNPs supported VB1for benzimidazole synthesis.

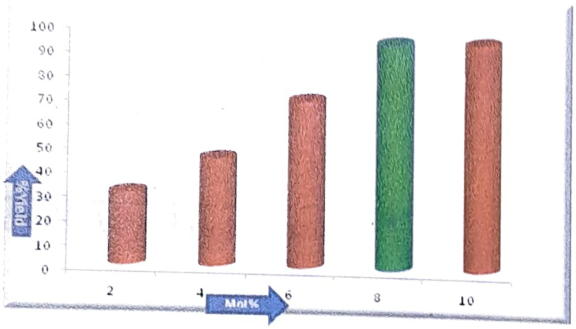


Figure 2 Screening of catalyst concentration for model reaction.

Table 2 NiNPs-VB_1 catalyzed synthesis of benzimidazoles in water.

Entry	Ar	R	Time (hr)	Yield[a] (%)
1	C_6H_5	H	4.5	96
2	2Cl- C_6H_4	H	6	84
3	4 Cl- C_6H_4	H	5	89
4	4 OMe- C_6H_4	H	5	87
5	3 OMe- C_6H_4	H	6	81
6	3 OMe, 4 OH- C_6H_3	H	5.5	90
7	4 $N(Me)_2$ C_6H_4	H	5	92
8	Furfural	H	4.5	91
9	C_6H_5	Me	7	80
10	C_3H_7	H	10	78
11	C_6H_5	EDA	15	75

[a] Isolated yields, EDA = ethylene diamine.

To establish the scope and generality of the optimized reaction conditions, various aldehydes such as aromatic, heteroaromatic, and aliphatic aldehydes with electron withdrawing as well as electron donating substituents and diamines were allowed to undergo this cyclocondensation reaction (Table 2). Almost all the aromatic aldehydes proved to be amenable to these reaction conditions to afford good to excellent yield of the products. Moreover, no significant substituent effect was found on the yield of the products and reaction also proceeds smoothly. On the other hand, aliphatic aldehydes and ethylene diamine

gives comparatively less yields and takes more time for completion of reaction (Table 2, entry 10 & 11).

SUMMARY

The synthetic utility of the methodologies demonstrated in this work, contributed some part of green and clean chemistry to sustain the environment unaffected. Hence the proposed objectives are achieved at all.

The remarkable advantages offered by these methods are helpful in research and development sector as well as in academic laboratories. On this research methodology one research article is presented in the national seminar which was held at IICT Hyderabad entitled "NiNPS-Thiamine Hydrochloride (VB_1) in Water: A Privileged Synthetic Route for Benzimidazoles Derivatives"

NiNPS supported Thiamine hydrochloride (VB_1) is found to be an inexpensive, efficient, non-toxic and mild catalyst for the cyclocondensation of o-phenylinediamine and aromatic/heteroaromatic/aliphatic aldehydes in water at moderate temperature. Herein, it is established that water can be used as reaction media for NiNPs-VB1 catalyzed reactions, especially for reactions proceeding through imine intermediates followed by induced hydrophobic aggregation of substrates.

This protocol is user-friendly and could be an attractive tool for the synthesis of highly functionalized bioactive benzimidazoles with several faithful advantages such as facile, sustainable and high yielding

procedure at moderate temperature. And therefore reactions mediated by water should constitute the ideal concepts of green chemistry.

The present work contributes a greener approach for the synthesis of benzimidazole derivatives under gracious (water) reaction medium which resulted into facile, sustainable and high yielding methodology.

CONCLUSION

Herein, it is established that water can be used as reaction media for NiNPs-VB_1 catalyzed reactions, especially for reactions proceeding through imine intermediates followed by induced hydrophobic aggregation of substrates.

This protocol is user-friendly and could be an attractive tool for the synthesis of highly functionalized bioactive benzimidazoles with several faithful advantages such as facile, sustainable and high yielding procedure at moderate temperature. And therefore reactions mediated by water should constitute the ideal concepts of green chemistry.

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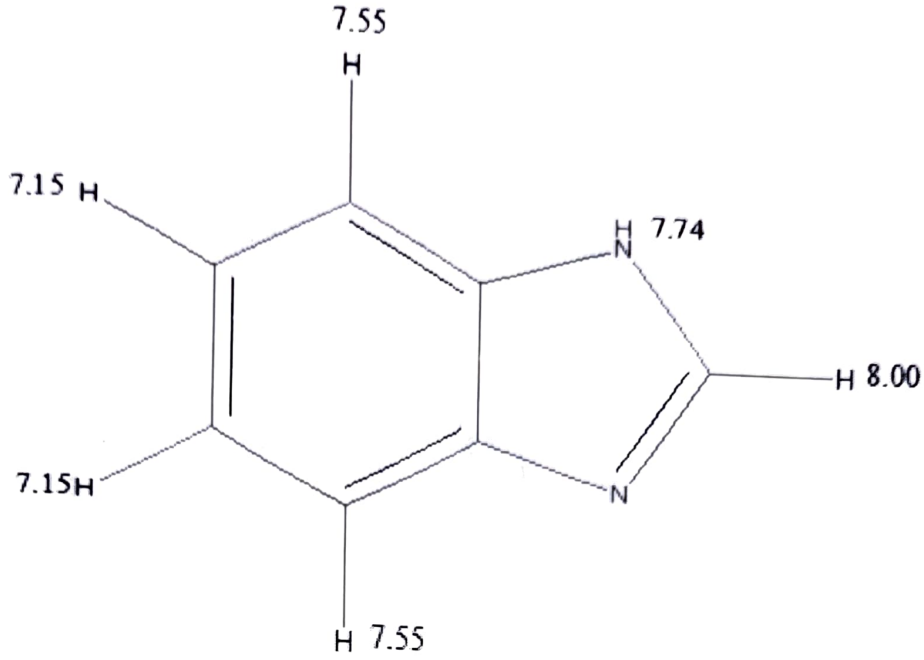
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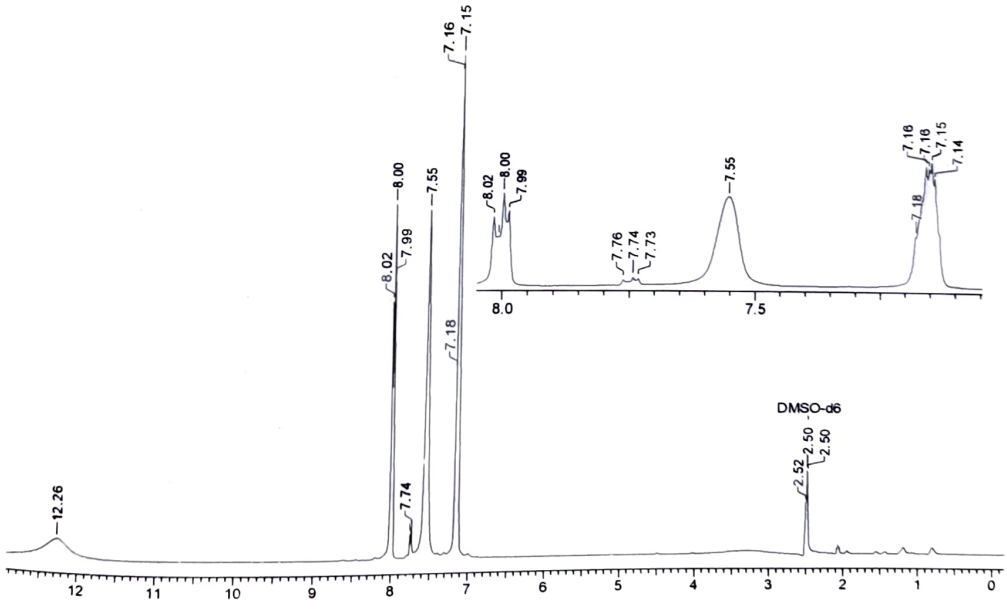
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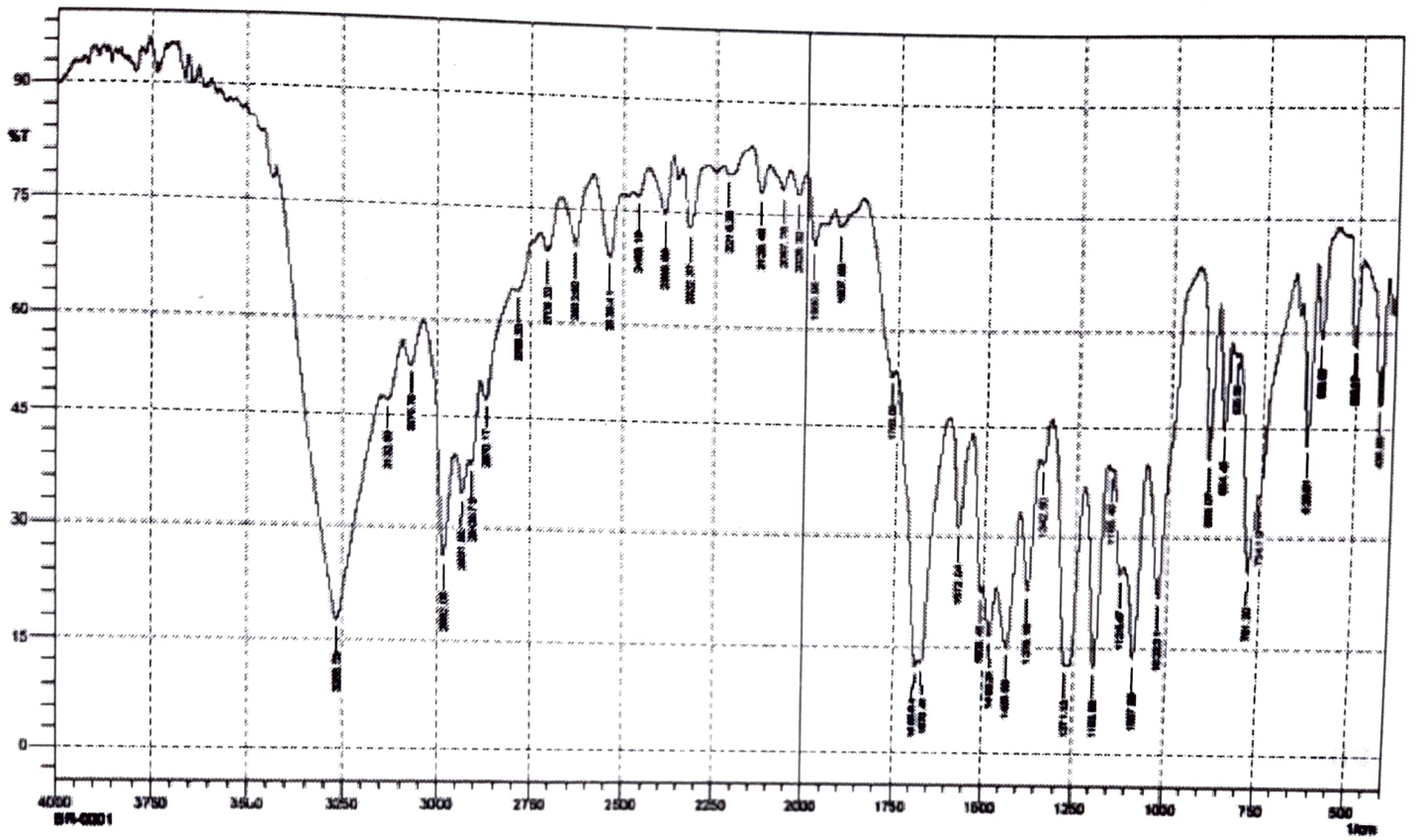

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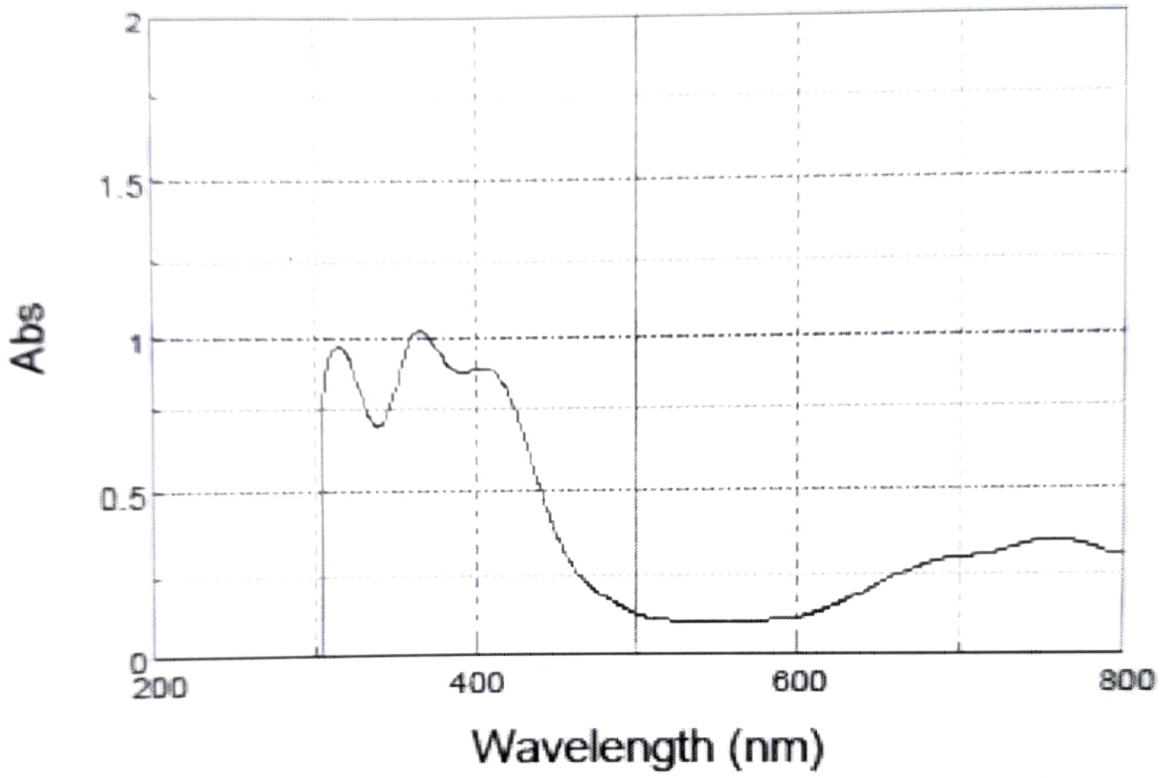

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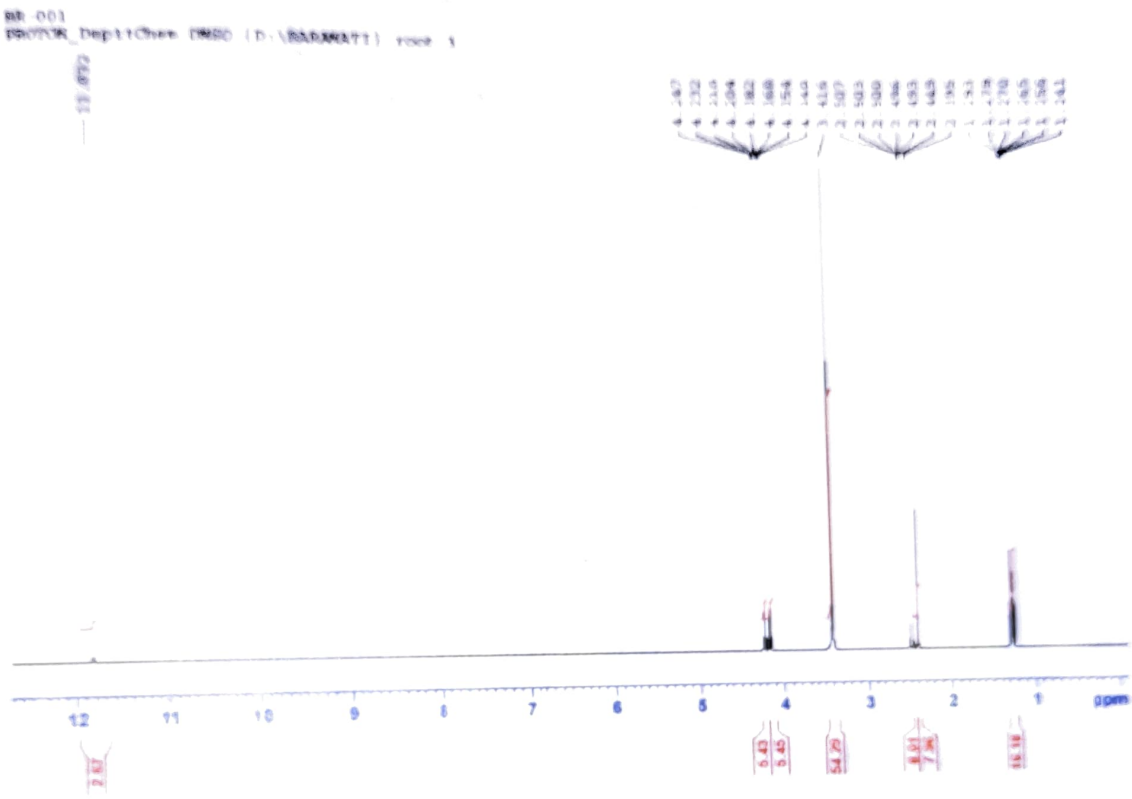
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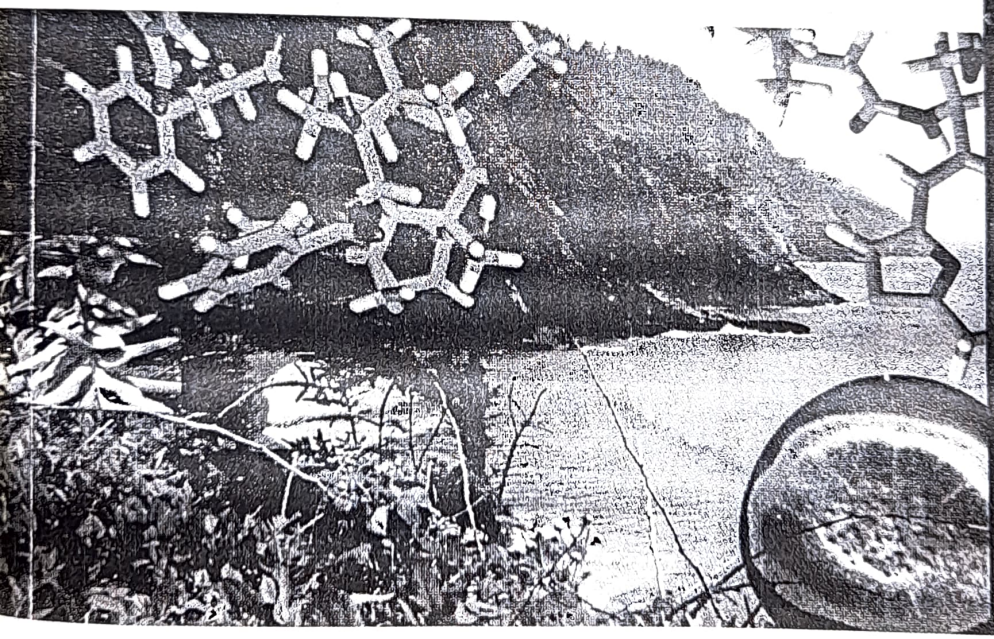

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Poster Abstract - 175

NiNPS-Thiamine hydrochloride (vb_1) in water: a privileged synthetic route for benzimidazole derivatives

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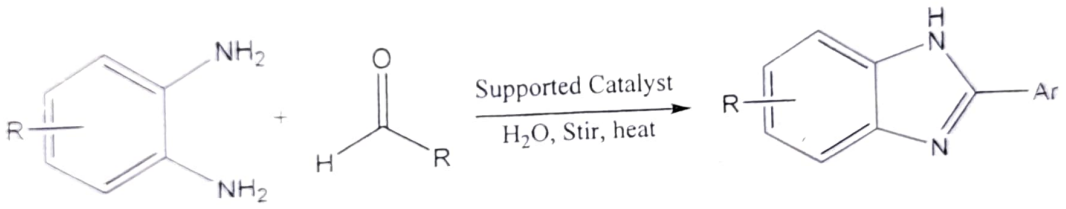
Pune, MAH-413102

NiNPS supported Thiamine hydrochloride (VB_1) is found to be an inexpensive, efficient, non-toxic and mild catalyst for the cyclocondensation of *o*-phenylinediamine and aromatic/heteroaromatic/aliphatic aldehydes in water at moderate temperature. The present work contributes a greener approach for the synthesis of benzimidazole derivatives under gracious (water) reaction medium which resulted into facile, sustainable and high yielding methodology.



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From T. C. College, Baramati has participated/presented a paper (Oral or Poster) in the NIICT-2014 held at the CSIR-Indian Institute of Chemical Technology, Hyderabad, India.

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