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विद्येविना मति गेली, मतीविना नीति गेली
नीतिविना गति गेली, गतिविना वित्त गेले
वित्तविना शूद्र खचले, इतके अनर्थ एका अविद्येने केले

-महात्मा ज्योतीराव फुले

❖ विद्यावार्ता या आंतरविद्याशाखीय बहुभाषिक त्रैमासिकात व्यक्त झालेल्या मतांशी मालक, प्रकाशक, मुद्रक, संपादक सहमत असतीलच असे नाही. न्यायक्षेत्र:बीड



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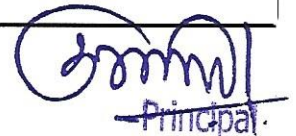
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|| Index ||

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- | | |
|--|----|
| 01) STUDIES ON ZOOPLANKTON DIVERSITY FROM GHOLSGAON TANK, DIST. SOLAPUR, ...
S. A. Shaikh, A. D. Babare, M.G. Babare, Osmanabad. | 10 |
| 02) The Inheritance of Loss: A Saga of Lost Dream
Dr. Uddhav Jane, Wasim | 11 |
| 03) One pot method for the synthesis of substituted 4, 5-dihydropyridazin...
A.M.Pachpinde, M.M.Langade, Osmanabad | 16 |
| 04) Edmodo, Concept Attainment and Mathematics: Structuring a Research
Vinod Kumar Kanvaria, Pooja Gupta, Delhi | 20 |
| 05) DOES FINANCIAL PERFORMANCE HAVE ANY IMPACT ON LEVERAGE ? A STUDY ON ...
Hasan Rana, Dr. Sandip K Bhatt, Gujarat | 27 |
| 06) Demographic study of landhaura constituency in case of voting behavior
Dr. Sonia w/o Sanjay kaushik, uttrakhand | 29 |
| 07) Europe and America on ISIS Target: An Analysis
Dr.Shailendra Deolankar, Amravati | 33 |
| 08) Quest for World Peace and Solutions on Terrorism : A study of Mahesh Dattani's Final ...
Prof. Sidhartha B. Sawant, Maharashtra. | 37 |
| 09) Socio-Economic Voting Behavior in Landhora Constituency
Dr. Sonia Sanjay kaushik, Haridwar | 41 |
| 10) THE CHALLENGES OF TEACHING ENGLISH LISTENING SKILLS
Dr. G. Sujatha, Machilipatnam | 44 |
| 11) माध्यमिक शाळांतील विद्यार्थ्यांच्या जीवनकौशल्ये विकासावरील सहकार्यात्मक अभ्ययन
श्री. परेश फर्डे, डॉ. जाधव के. आर, मुंबई विद्यापीठ | 55 |
| 12) वर्तमान आणि मराठी नाटक
प्रा.डॉ.विवेक कमलाकर खरे, नाशिक. | 58 |
| 13) कृतिसंशोधन
प्रा. डॉ. वाय. एच. सधनेर, धुळे | 61 |

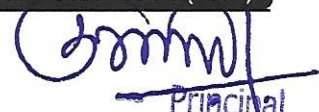

Principal

14) नागपूर शहरातील १९४२ चा स्वातंत्र्यलढा —एक चिकित्सक अध्ययन प्रा. डॉ. राजु भा. खरडे, जि.नागपूर ४	63
15) लोकसाहित्य आणि समाज जीवन श्री. अनिल हनमनलु मुनगेलवार, जि.नांदेड	70
16) पंचायतराज आणि ग्रामीण विकास प्रा.डॉ. अशोक सालोटकर, नागभीड.	73
17) ताण / तणावाचे व्यवस्थापन प्रा. डॉ. एम बी. राठोड, जि. यवतमाळ	75
18) भारतीय स्वतंत्रता आंदोलनात विदर्भातील स्त्रियांचे योगदान प्रा. डॉ. विष्णू रायभान पडवाल, जि. बुलडाणा	78
19) दुर्गों का सुरक्षात्मक योगदान उत्तराखण्ड के परिप्रेक्ष्य में। डॉ. राजा हृदयेश अण्डोला, अल्मोड़ा	81
— 20) महाकवि कालिदास की रचनाओं में प्रकृति चित्रण बिन्दूदेवी, डॉ. रामप्रकाश शर्मा, राजस्थान	82
21) भारतीय समाज के परिप्रेक्ष्य में पंचायत राज व्यवस्था में महिलाओं की भूमिका डॉ. भावना डोभाल	84
22) इक्कीसवीं शताब्दी के प्रथम दशक की दलित कविता डॉ. संजय गडपायले, परभणी	87
23) उच्च शिक्षा के कौशल विकास शिक्षा अन्तर्गत निर्धारित हिंदी भाषा कौशल विकास पाठ्यक्रम प्रा.डॉ.संजय जाधव, परभणी	91
24) कत्यूरी ताम्रपत्रों का विश्लेषण डॉ. मदन मोहन जोशी, हल्द्वानी	97
25) महाश्वेता देवी का उपन्यास 'दुष्कर' और समाज काना राम मीना, नई दिल्ली	101
26) गरीबी और श्रम पलायन श्रीमती स्नेहलता खलखो, सरगुजा	105


Principal

http://www.vidyawarta.blogspot.com
http://www.vidyawartajournal
https://sites.google.com/site/vidyawartajournal

27) इन्टरनेट से बदलता हिन्दी का विज्ञापन युग डॉ. शिवानंद एच कोली, गुलबर्गा	110
28) स्थानीय स्वशासन में महिला प्रतिनिधियों की भूमिका एन्सी कुजूर,, जबलपुर	114
29) मनरेगा योजना महात्मा गांधी राष्ट्रीय ग्रामीण रोजगार गारंटी अधिनियम (एक संक्षिप्त परिचय) डॉ. लक्ष्मी	118
30) स्वाध्याय : वेदों का अध्ययन मीनाक्षी, हरियाणा	120
31) जनजातीय महिला विकास एवं संवैधानिक प्रावधान पल्लवी नंदी, जबलपुर	122
32) कुबेरनाथ राय के ललित निबन्धों का तात्विक विवेचन डॉ. रमेश चन्द्र सत्यवली, नैनीताल	126
— 33) उच्च शिक्षा के समस्याओं के समाधान में राष्ट्रीय ज्ञान आयोग का योगदान संजय कुमार पाण्डेय, वाराणसी	129
34) डॉ. लक्ष्मी नारायण लाल का कथा-साहित्य : एक दृष्टि डॉ. राजेश कुमार सिंह, लखनऊ	131
35) भारत की आंतरिक सुरक्षा और साइबर क्राइम सुनील कुमार, रोहतक	136
36) भारतीय संस्कृति की आदर्श यशोधरा शालिनी वर्मा, कौशाम्बी	141
37) सर्वशिक्षा अभियान के अन्तर्गत आवासीय ब्रिज कोर्स कार्यक्रम के प्रति विद्यार्थियों की प्रतिक्रिया का निलेश वास्केल, डॉ. महेन्द्र तिवारी, जिला. खरगोन	144
38) सहकारिता आंदोलन विकास एवं उपलब्धियाँ डॉ. प्रीतम सिंह ठाकुर, छिंदवाड़ा मध्यप्रदेश	147
39) उच्चतर माध्यमिक स्तर के विभिन्न विद्यालयों के विद्यार्थियों की समायोजन क्षमता का ... डॉ. श्रीमती स्मिता भवालकर, उज्जैन म.प्र.	152



- 40) ग्रामीण सामाजिक विकास में नवा अंजोर परियोजना की भूमिका का अध्ययन
डॉ. महेन्द्र शर्मा, दुर्ग || 156
- 41) गीतांजलि श्री के कहानियों में व्यक्त सामाजिकता
डॉ. रेखा गाजरे, तायडे राजाराम बाबुराव, महाराष्ट्र || 162
- 42) समावेशी शिक्षा के अन्तर्गत विशेष आवश्यकता वाले बालक— बालिकाओं का सामान्य ...
डॉ. अर्चना अग्रवाल, रायसेन || 165
- 43) शैक्षिक विकास में निरक्षरता उन्मूलन कार्यक्रमों का योगदान
डॉ. अनीता जायसवाल, बरेली || 170
- 44) उच्च माध्यमिक स्तर के विद्यार्थियों के आकांक्षा स्तर का उनके लिंग एवं क्षेत्र के आधार पर ...
सुधीर कुमार, डॉ. अरुण कुमार, उ.प्र. || 173
- 45) शास्त्रों का महत्त्व एवं उनकी मूल्यपरकता
डॉ. रामप्रकाश शर्मा, श्रीगंगानगर || 179
- 46) भारतीय लोकसंगीत में डोगरी लोक संगीत
डॉ. कुणाल इंगले || 184
- 47) संगच्छ्वं संवदध्वं सं वो मनासि जानताम्
डॉ. कृष्णमोहनपाण्डेय, हि.प्र. || 188


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One pot method for the synthesis of substituted 4, 5-dihydropyridazin-3(2H)-ones

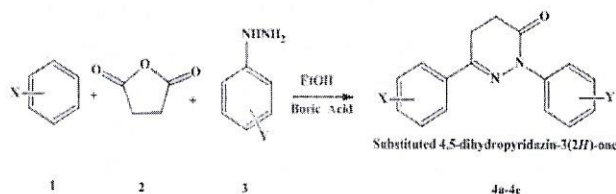
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Department of Chemistry,
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Osmanabad

Abstract:

A simple, convenient method for one-pot synthesis of substituted 4, 5-dihydropyridazin-3(2H)-ones via three-component reaction of aromatic arenes, succinic anhydride and substituted phenyl hydrazine have been reported using boric acid as a catalyst has been reported. The main features of this method are good yields and shorter reaction times.



1. INTRODUCTION

The multi component reactions are gaining importance and have advantage over the multi-step reaction due to its operational simplicity, giving higher yields in a single step saving the time and energy thus becoming economically attractive and environment friendly.¹

The synthesis of biodiverse heterocycles by employing the multicomponent reaction in ultrasonicator is the emerging trend amongst the chemist to develop a green chemistry protocol for the reaction.² Pyridazine is an important class of heteroaromatic organic compound.

Pyridazine and its derivatives are being explored in past few decades for their physiological and biological importance. The synthesis of Pyridazine derivatives, especially the pyridazinones, is gaining importance as the molecule is found to be used in herbicides such as credazine, pyridafol and pyridate.³ It is also an important pharmacophore of pharmaceutical drugs such as, Azelastine (antiasthmatic, antiallergic, antihistaminic), Amezinium metalilsulfate (selective noradrenergic antihypertensive), Emorfazone (anti-inflammatory), Cadralazine (antihypertensive), Hydralazine (antihypertensive), Minaprine (antidepressant), and Sulfamethoxypyridazine (antibacterial).⁴ Besides in addition to the above activities Pyridazine molecule and its derivatives are also known to possess a wide range of biological activities, such as anticancer,⁵ antiviral,⁶ anti-tuberculosis,⁷ antiulcer,⁸ antipsychotic,⁹ antidepressant,⁹ anticonvulsant,¹⁰ analgesic,¹¹ antibacterial,¹² antifungal,¹³ and in platelet aggregation.¹⁴ The major drawback, of the reported methods are the requirement of expensive catalyst, longer reaction time, requirement of additional step for N- Alkylation, scarcity of the appropriately substituted substrates like α -keto acids and α & β diketones.

Considering these limitation and herein we wish to report the synthesis of pyridazine, by the simple and convenient one-pot three-component reaction of substituted aromatic arenes, succinic anhydride and substituted phenyl hydrazine using boric acid as a catalyst by conventional method.

2. EXPERIMENTAL

2.1. General Chemical Procedures

Aromatic arenes, Succinic anhydride, Substituted phenyl hydrazine were commercially available. Melting points were recorded are uncorrected. **4.2. General Procedure for the synthesis of Substituted 4, 5-dihydropyridazin-3(2H)-one**

2.2 Procedure

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Principal

To a gently heated stirring reaction mixture in a 100 mL flask was charged with substituted arenes **1** (10 mmol), succinic anhydride **2** (10 mmol), boric acid (0.1 mmol) and substituted phenyl hydrazine **3** (10 mmol) in ethanol (10 mL). The mixture was refluxed for 2.5-3 hrs and the progress of the reaction was monitored till completion on TLC (Ethyl acetate: n hexane 1:4). Subsequently, the solvent was removed by concentrating on rotary evaporator to get the residue. The solid residue was washed with ethanol to afford the pure product as solid in 85–92 % yields.

2.3 Representative Spectral Data

2, 6-diphenyl-4, 5-dihydropyridazin-3(2H)-one (4a)

Off white solid;

¹H NMR (CDCl₃, 400 MHz): 2.81 (t, 2H), 3.15 (t, 2H), 7.35 (m, 1H), 7.49 (m, 5H), 7.68 (d, 2H), 7.90 (m, 2H);

ES-MS m/z (%): 251 (M+H)

3. RESULTS AND DISCUSSION

To develop the optimum reaction conditions initially, we investigated the catalytic efficiency of boric acid for the synthesis of 2, 6-diphenyl-4, 5-dihydropyridazin-3(2H)-one **4a**. To optimize the catalyst loading, different sets of reactions were performed. The results of which are summarized in Table 1 by both ultrasound assisted and by conventional method. The 10 mol% of boric acid was found to be best suited for the completion of the reaction and higher concentration of boric acid did not lead to substantial change in the yields of the reaction.

Table 1

Comparison of effect of catalysts and optimization of catalyst loading for the synthesis of 2, 6-diphenyl-4, 5-dihydropyridazin-3(2H)-one (4a)^a

Sr. No.	Catalyst	Mol % of Catalyst	Solvent	With US ^a		Without US ^a	
				Time (min)	Yield ^b %	Time (min)	Yield ^b %
1	No Catalyst	0	Ethanol	60	10	720	0
2	HCl	50	Ethanol	10	55	360	55
3	H ₂ SO ₄	50	Ethanol	5	60	240	65
4	NaHSO ₄	50	Ethanol	60	80	360	75
7	boric Acid	30	Ethanol	2	97	150	92
8	boric Acid	20	Ethanol	2	97	150	92
9	boric Acid	10	Ethanol	2	97	150	92

The Table 1 also indicates that the catalyst is required for the progress of the reaction and boric acid was better catalyst compared to sodium bisulphite in terms of reaction time and yield of the reaction.

To explore the optimal solvent for this reaction, the synthesis of 2, 6-diphenyl-4, 5-dihydropyridazin-3(2H)-one **4a** was carried out using different solvents as mentioned in Table 2 by conventional method and it was observed that ethanol was most suitable for the reaction in terms of the yield and reaction time compared with the other solvents.

Table 2

Synthesis of 2, 6-diphenyl-4, 5-dihydropyridazin-3(2H)-one (4a)^a using different solvents.

Sr. no.	Solvent	With US ^a		Without US ^a	
		Time (min)	Yield ^b %	Time (min)	Yield ^b %
1	Acetonitrile	25	80	60	65
2	Ethanol-Water (1:1)	5	90	540	70
3	Ethanol	2	97	150	92

To study the effect of temperature on the reaction the synthesis of 2, 6-diphenyl-4, 5-dihydropyridazin-3(2H)-one **4a** was carried out using different sets of temperature as mentioned in Table 3 by conventional method and it was observed that refluxing temperature is required for completion of reaction in a shorter time.

Table 3

Synthesis of 2, 6-diphenyl-4, 5-dihydropyridazin-3(2H)-one (4a)^a using different temperatures

Sr. No.	Temperature	Time (min)	Yield %
1	Room Temperature	720	0
2	50	540	55
3	60	360	65
4	Reflux	150	92

There is decrease in the rate of reaction with the gradual decrease in the temperature. It was also observed that higher temperature is required for the reaction to go to completion and the reaction was not initiated at the room temperature.

The corresponding products in good yields as mentioned in Table 4.

Table 4
Synthesis of Substituted 4, 5-dihydropyridazin-3(2H)-one derivatives using boric acid catalyst using various substituted arenes, succinic anhydride and substituted phenyl hydrazine

Sr. no.	Substituted Arene	N-Phenyl Hydrazine	With US ^a		Without US ^a		Melting point/Boiling Point °c
			Time	Yield (min) %	Time (min)	Yield %	
4a			2	97	150	92	92-94 (92-94) ¹⁵
4b			2	95	150	88	Oil (Oil) ¹⁵
4c			3	97	180	90	Oil (Oil) ¹⁵
4d			3	96	180	91	Oil (Oil) ¹⁵
4e			3	97	180	91	Oil (Oil) ¹⁵

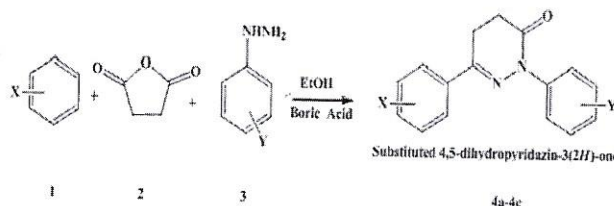
3. CONCLUSIONS

In conclusion, in our present study we have developed a highly efficient, time saving, convenient eco-friendly, one-pot method for the synthesis of substituted 4, 5-dihydropyridazin-3(2H)-one catalyzed by boric acid. The developed method is applicable for both ultrasound assisted and conventional method and is convenient and practical procedure requiring usual reagents and proceeds without any special handling technique. Thus, in summary present work is the first report on ultrasound assisted one-pot reaction of substituted 4, 5-dihydropyridazin-

3(2H)-one catalyzed by boric acid and offers several advantages over the conventional and literature method, with considerable improvement in the reaction time to give high yields in eco-friendly manner making the protocol economically attractive for industrial application.

Scheme 1

Ultrasound assisted synthesis of substituted 4, 5-dihydropyridazin-3(2H)-one derivatives.



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