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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

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Andur Tal. Tuljapur Dist, Osmanabad

03

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

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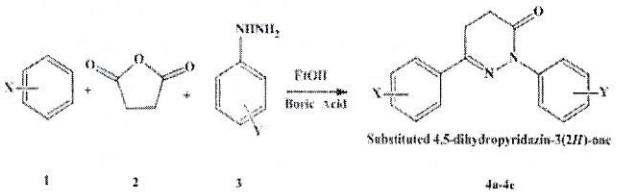
Abstract:

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] antituberculosis, [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 ã-keto acids and á □ &□p□5□□iketones.

Considering these limitation and erein 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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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;

^{1}H NMR ($CDCl_3$, 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_2SO_4	50	Ethanol	5	60	240	65
4	$NaHSO_3$	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

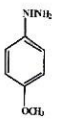
Sr. No.	Temperature	Time (min)	Yield %
1	Room Temperature	720	0
2	50	540	55
3	60	360	65
4	Reflux	150	92

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

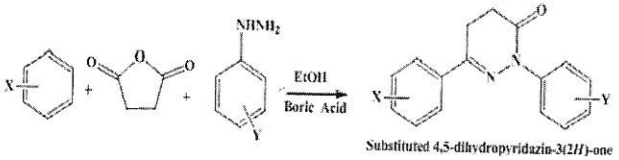
Sr. no.	Substituted Arene	N-Phenyl Hydrazine	With US[a] Time	With US[a] Yield (min) %	Without US[a] Time (min)	Without US[a] Yield %	Melting point/Boiling Point °c
4a			2	97	150	92	92-94 (92-94)[15]
4b			2	95	150	88	Oil (Oil)[15]
4c			3	97	180	90	Oil (Oil)[15]
4d			3	96	180	91	Oil (Oil)[15]
4e			3	97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



1 2 3 4a-4e

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