International Journal of Chemical Studies

P-ISSN: 2349–8528
E-ISSN: 2321–4902
www.chemijournal.com
IJCS 2021; 9(4): 408-412

Received: 06-06-2021
Accepted: 11-07-2021

**Mallinath Langade**
Department of Chemistry, Jawahar Art Science and Commerce College, Andur, Osmanabad, Maharashtra, India

**Corresponding Author:**
**Mallinath Langade**
Department of Chemistry, Jawahar Art Science and Commerce College, Andur, Osmanabad, Maharashtra, India

# Ultrasound assisted one pot method for the synthesis of substituted 4, 5-dihydropyridazin-3(2*H*)-ones

## Mallinath Langade

**Abstract**
A simple, convenient and ultrasound assisted method for one-pot synthesis of substituted 4, 5-dihydropyridazin-3(2*H*)-ones via three-component reaction of aromatic arenes, succinic anhydride and substituted phenyl hydrazine have been reported using oxalic acid as a catalyst for first time. Some of the derivatives are reported for first time. The key features of this method are excellent yields and shorter reaction times.

**Keywords:** Substituted 4, 5-dihydropyridazin-3(2*H*)-one, Aromatic arenes, Succinic anhydride, Substituted phenyl hydrazine, Oxalic acid catalyst

## 1. Introduction
Ultrasonic-assisted synthetic approach is a powerful technique that is being used in synthetic organic chemistry as a green chemistry approach to accelerate the organic reactions. Ultrasound irradiation in past decade, have been widely developed as the unconventional source of energy, accelerating several synthetic reactions and has great impact on the approach of chemist exploring the alternative path for classical organic synthesis. Ultrasound irradiations provide an convenient practical eco-friendly protocol, reduces the time by accelerating the reaction and improves the yield of product [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]. 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 [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 synthesis of pyridazin-3(2*H*)-ones can be accomplished in several ways, like by the use of condensation of 4-oxoalkanoic acid with hydrazine,[15]the reaction of α-diketones with hydrazine derivatives in the presence of an ester containing active methylene protons [15]. Condensation of phenylhydrazine with *γ*-keto acids in toluene at reflux temperature [15], condensation of phenylhydrazine with 2-diethoxyphosphoryl-4-oxoalkanoates [15], condensation of hydrazine with *γ*-keto acids followed by *N*-alkylation [16], condensation of a variety of α -keto-esters with commercially available hydrazinocarbonyl-acetic acid ethyl ester [16], and the condensation of phenylhydrazine with arene and anhydrides [17]. The major drawback, of these methods are the requirement of expensive catalyst, longer reaction time,

requirement of additional step for *N*- Alkylation, scarcity of the appropriately substituted substrates like γ-keto acids and α –diketones.

Considering these limitation and in continuation of our research on development of new methodologies for synthesis of biologically important heterocycles [18], 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 oxalic acid as a catalyst by both ultrasound assisted and by conventional method. The key features of this methodology are excellent yields with milder conditions, short reaction times compared with the reported methods.

## 2. Results and Discussion

Our continued interests for the development of efficient and environmentally friendly procedures for the synthesis of heterocyclic compounds [18] and the catalytic activity of oxalic acid with its cheap cost, easy availability and operational simplicity propelled us to explore the synthesis of substituted 4, 5-dihydropyridazin-3(2*H*)-ones in a one-pot reaction in the presence of oxalic acid.

To develop the optimum reaction conditions initially, we investigated the catalytic efficiency of oxalic acid for the synthesis of 2, 6- diphenyl-4, 5-dihydropyridazin-3(2*H*)-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 oxalic acid was found to be best suited for the completion of the reaction and higher concentration of oxalic acid did not lead to substantial change in the yields of the reaction. The Table 1 also indicates that the catalyst is required for the progress of the reaction and oxalic 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(2*H*)-one 4a was carried out using different solvents as mentioned in Table 2 by both ultrasound assisted and 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.

To study the effect of temperature on the reaction the synthesis of 2, 6- diphenyl-4, 5- dihydropyridazin-3(2*H*)-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. 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 robustness of this method was evaluated for both methods by using substituted aromatic arenes and substituted phenyl hydrazine to give the corresponding products in good yields as mentioned in Table 4. It was observed that the introduction of electron withdrawing group on phenyl hydrazine decreases the yield and increases the time required for completion of the reaction compared to that of electron donating group, and simple phenyl hydrazine respectively.

Considering the well established applications of ultrasound to promote variety of chemical reactions, the model reaction carried out using optimized reaction conditions under ultrasound irradiation to investigate whether, (i) the reaction rate could be accelerated and, (ii) the product yield could be enhanced. The use of ultrasound irradiation significantly improved the yield of product to 97% from conventional method (92%). It is worth noting here, that the reaction time also reduced significantly (2 min) as compared to conventional method (150 min).

The difference in the reaction times may be due to the specific effects of ultrasound due to the phenomenon of acoustic cavitation [1-2]. The collapse of cavitation bubbles result in the formation of extremely reactive chemical species having short lifetime which facilitates the rapid synthesis of a-functionalized 4, 5-dihydropyridazin-3(2*H*)-one derivatives. The advantage of this method over the reported method [17] is, use of easily available and cheap catalyst, operational simplicity, the time required for the completion of reaction is less by both ultrasound assisted (2-3 min) and by conventional method (2.5-3 hrs) as compared to that of the literature method [17] which requires more than (8 hrs) for its completion.

## 3. Conclusion

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(2*H*)-one catalyzed by oxalic 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(2*H*)-one catalyzed by oxalic acid and offers several advantages over the conventional and literature method,[17] with considerable improvement in the reaction time to give high yields in eco-friendly manner making the protocol economically attractive for industrial application.

## 4. Experimental

### 4.1. General Chemical Procedures

Aromatic arenes, Succinic anhydride, Substituted phenyl hydrazine were commercially available. Melting points were recorded on SRS Optimelt melting point apparatus and are uncorrected. Ultrasonication was performed in an Ultrasonic Bath Sonicator of PCI Analytics,® having ultrasound cleaner with a frequency of 35 kHz and an nominal power of 200 W. The reaction flask was located in close proximity of the maximum energy area in the cleaner such that the reaction vessel was slightly lower than the water level and the temperature of the water bath was controlled at 40 °C. The reaction temperature was controlled by addition or removal of water from ultrasonic bath. $^1$H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplate (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

### 4.2. General Procedure for the synthesis of Substituted 4, 5-dihydropyridazin-3(2H)-one

#### 4.2.1. Conventional Method (Method A)

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), oxalic 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.

**4.2.2. Ultrasound Assisted Method (Method B)**

A 100 mL flask was charged with substituted arenes 1 (10 mmol), succinic anhydride 2 (10 mmol), oxalic acid (0.1 mmol) and substituted phenyl hydrazine 3 (10 mmol) in ethanol (10 mL). The mixture was sonicated in the water bath of an ultrasonic cleaner at 30 °C 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 95–97% yields.

**4.2.3 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)

**6-(4-chlorophenyl)-2-(4-nitrophenyl)-4,5-dihydropyridazin-3(2*H*)-one (4d)**

Yellow Solid;

$^1$H NMR ($CDCl_3$, 400 MHz):2.72 (t, 2H), 3.30 (t, 2H), 7.40 (m, 4H), 7.88 (m, 5H);

ES-MS m/z (%): 331 (M+H)

**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 Yield[b] (min)% | | Time Yield[b] (min)% | |
| 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 |
| 5 | Oxalic Acid | 50 | Ethanol | 2 | 97 | 150 | 92 |
| 6 | Oxalic Acid | 40 | Ethanol | 2 | 97 | 150 | 92 |
| 7 | Oxalic Acid | 30 | Ethanol | 2 | 97 | 150 | 92 |
| 8 | Oxalic Acid | 20 | Ethanol | 2 | 97 | 150 | 92 |
| 9 | Oxalic Acid | 10 | Ethanol | 2 | 97 | 150 | 92 |
| 10 | Oxalic Acid | 5 | Ethanol | 5 | 85 | 150 | 82 |

[a] Reaction of benzene(10 mmol) with phenylhydrazine (10 mmol) and succinic anhydride (10 mmol) in presence of catalysts with ultrasonic waves(US) at 40 °C and without ultrasonic waves at reflux temperature.

[b] Isolated yield.

**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 Yield[b] (min)% | | Time Yield[b] (min)% | |
| 1 | Water | 15 | 90 | 720 | 52 |
| 2 | Acetonitrile | 25 | 80 | 60 | 65 |
| 3 | Ethanol-Water (1:1) | 5 | 90 | 540 | 70 |
| 4 | Ethanol | 2 | 97 | 150 | 92 |

[a] Reaction of benzene(10 mmol) with phenylhydrazine (10 mmol) and succinic anhydride (10 mmol) in presence of oxalic acid(1 mmol) under with ultrasonic waves(US) at 40 °C and without ultrasonic waves at reflux temperature.

[b] Isolated yield.

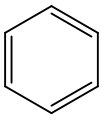
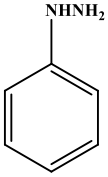
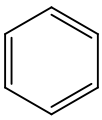
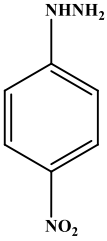
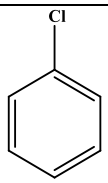
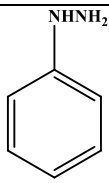
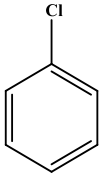
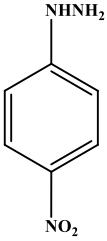
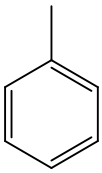
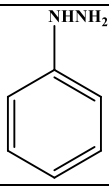
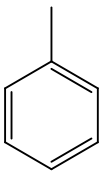
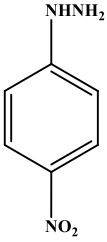
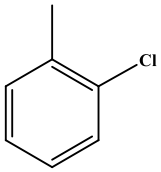
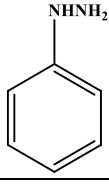
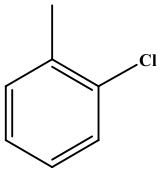
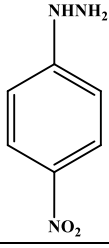
**Table 3:** Synthesis of 2, 6-diphenyl-4, 5-dihydropyridazin-3(*2H*)-one (4a)[a] using different temperatures

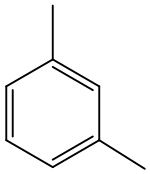
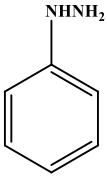
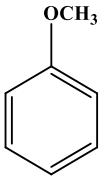
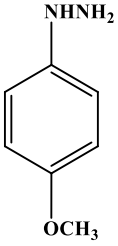
| Sr. No. | Temperature | Time (min) | Yield% |
|---|---|---|---|
| 1 | Room Temperature | 720 | 0 |
| 2 | 50 | 540 | 55 |
| 3 | 60 | 360 | 65 |
| 4 | Reflux | 150 | 92 |

[a] Reaction of benzene(10 mmol) with phenylhydrazine (10 mmol) and succinic anhydride (10 mmol) in presence of oxalic acid (1 mmol) by conventional method at reflux temperature.

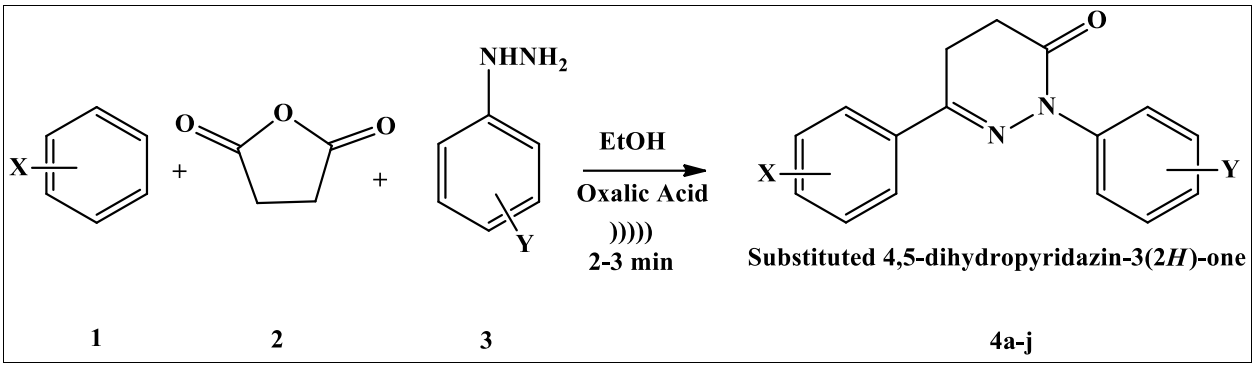
[b] Isolated yield.

**Table 4:** Synthesis of Substituted 4, 5-dihydropyridazin-3(*2H*)-one derivatives using oxalic 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 Yield (min)% | | |
| 4a |  |  | 2 | 97 | 150 | 92 | 92-94 (92-94)[15] |
| 4b |  |  | 3 | 95 | 180 | 86 | Oil |
| 4c |  |  | 2 | 95 | 150 | 88 | Oil (Oil)[15] |
| 4d |  |  | 3 | 96 | 180 | 87 | 228-230 |
| 4e |  |  | 3 | 97 | 180 | 90 | Oil (Oil)[15] |
| 4f |  |  | 3 | 95 | 180 | 85 | 265-267 |
| 4g |  |  | 2 | 95 | 150 | 88 | 216-218 |
| 4h |  |  | 3 | 96 | 180 | 85 | 199-201 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 4i |  |  | 3 | 96 | 180 | 91 | Oil (Oil)[15] |
| 4j |  |  | 3 | 97 | 180 | 91 | Oil (Oil)[15] |

[a] Reaction of benzene(10 mmol) with phenylhydrazine (10 mmol) and succinic anhydride (10 mmol) in presence of oxalic acid(1 mmol) under with ultrasonic waves(US) at 40 °C and without ultrasonic waves at reflux temperature.
[b] Isolated yield.




**Scheme 1:** Ultrasound assisted synthesis of substituted 4, 5-dihydropyridazin-3(*2H*)-one derivatives

## 5. References


1. Mason T. Chem Soc Rev. 1997;26:443.
2. Ganem B. Acc Chem Res. 2009;42:463. Sunderhaus JD, Martin SF. Chem Eur J. 2009;15:1300.
3. Dayan FE, Duke SO. Encyclopedia of Agrochemicals. New Jersey: Wiley-Interscience; 2003. p. 744.
4. Li JJ, Gordon WG. Tetrahedron Organic Chemistry Series. 2007;26:541.
5. Wiesaw M, Redzicka A, Lozach O. Il Farmaco. 2004;59:457.
   Won Y, Park M. Arch Pharm Res. 2010;33:189.
6. Rashad AE, Shamroukh AH, Ali MA, Abdel-Motti FM. Het Chem. 2007;18:274. Shamroukh AH, Ali MA. Arch Pharm. 2008;341:223.
7. Mantu D, Luca MC, Moldoveanu C, Zbancioc G, Mangalagiu II. Eur J Med Chem. 2010;45:5164.
8. Yamada T, Nobuhara Y, Shimamura H, Yoshihara K, Yamaguchi A, Ohki M. Chem Pharm Bull. 1981;29:3433.
9. Castro ME, Rosa E, A-Osuna J, Garcia-Ferreiro T, Loza M, Cadavid MI, *et al*. Eur J Med Chem. 1994;29:831.
10. Moreau S, Coudert P, Rubat C, Gardette D, Vallee-Goyet D, Couquelet J, *et al*. J Med Chem. 1994;14:2153.
11. Abdel-Hafez SH. Eur J Med Chem. 2008;43:1971.
12. Nagawade R, Khanna VV, Bhagwat SS, Shinde DB. Eur J Med Chem. 2005;40:1325. Akbas E, Berber I. Eur J Med Chem. 2005;40:401.
13. Jian W, Baoan S, Hongjun C, Bhadury P, Hu D. Molecules. 2009;9:3676.
14. Coelho A, Sotelo E, Fraiz N, Yanez M, Laguna R, Canoand E, *et al*. Eur J Med Chem. 2004;14:321. Crespo A, Meyers C, Coelho A, Yanez M, Fraiz N, Sotelo E, *et al*. Bioorg Med Chem. 2006;16:1080.
15. Van der Mey M, Hatzelmann A, Van der Laan IJ, Sterk GJ, Thibaut U, Timmerman H. J Med Chem. 2001;44:2511. Albrecht A, Koszuk J, Kobucinski M, Janecki T. Org Biomol Chem. 2008;6:1197.
16. Mantu D, Moldoveanu C, Nicolescu A, Deleanu C, Mangalagiu II. Ultrason Sonochem. 2009;16:452. Murphy DE, Dragovich PS, Ayida BK, Bertolini TM, Li L, Ruebsam F, *et al*. Tetrahedron Lett. 2008;49:811.
17. Zare L, Mahmoodi N, Yahyazadeh A, Mamaghani M, Tabatabaeian K. J Het Chem. 2011;4:8864.
18. Pachpinde AM, Kalam Khan FA, Lohar KS, Langade MM. J Chem Pharm Res. 2011;3:950-956.