International Journal of Research Studies on Environment, Earth, and Allied Sciences (IJRSEAS)
| Volume-2 Issue--5 |October-2025 | ISSN: 3066-0637 | Website: https://eesrd.us

Manuscript ID:
IJRSEAS-2025-020502

OPEN ACCESS

Quick Response Code:

Website: https://eesrd.us

DOI:10.5281/zenodo.17375248
DOI Link:
https://doi.org/10.5281/zenodo.17375248

Volume: 2

Issue: 5

Pp. 10-13

Month: October

Year: 2025

E-ISSN: 3066-0637

Submitted: 05 Sept. 2025

Revised: 10 Sept. 2025

Accepted: 05 Oct. 2025

Published: 31 Oct. 2025

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How to cite this article:
Parveen, A. (2025). Molecular Iodine Assisted Green Synthesis of Pyrazolo[3,4-d]-pyrimidine Thiones. International Journal of Research Studies on Environment, Earth, and Allied Sciences, 2(5), 10–13.
https://doi.org/10.5281/zenodo.17375248

Molecular Iodine Assisted Green Synthesis of Pyrazolo[3,4-d]-pyrimidine Thiones

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Abstract

An efficient and green method for the preparation of 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine Thiones derivatives in minutes of time with high yields is accomplished by the mixture of ethyl acetoacetate, hydrazine hydrate, thiourea, and different benzaldehydes. The reaction is accomplished in the presence of molecular iodine in an excellent yield.

A green and efficient method for synthesizing 3-phenyl-1H-pyrazolo[3,4-d]pyrimidine thiones is presented. The reaction employs ethyl acetoacetate, hydrazine hydrate, thiourea, and substituted benzaldehydes in the presence of molecular iodine. The process is solvent-free, rapid, and produces high yields under mild conditions. This approach avoids toxic catalysts and long reaction times, offering an eco-friendly and scalable alternative for heterocyclic compound synthesis.

Keywords: *Benzaldehyde, ethyl acetoacetate, thiourea, ionic liquid, hydrazine hydrate*

Introduction

Pyrazolo pyrimidine found to be most potent molecule in pharmaceutical chemistry. Due to N-Containing ring which is analogue with purines it has various applications [1] like [2] antitumor antimicrobial [3] neuroleptic [4], anti-metabolites in purine biochemical reactions [5] tuberculostatic [6]. They show wide pharmacological activities like antihypertensive [2] and antileishmanial activities [8]. The great biological activity of pyrazolo pyrimidine derivatives attracted many researchers. The 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine Thiones derivatives **(3a-r)** represent important building blocks in both natural and synthetic bioactive compounds [9].They show anxiolytic activity along with xanthine oxidase inhibitors, cholesterol formation inhibitor, and anti-Alzheimer [10].Hence, different methods have been reported for pyrimidine derivatives [11-16] However; some of these methods still suffer from certain demerits, such as recycle of catalyst, long reaction times, low yields, air sensitive catalysts, multistep and low selectivity's. Thus, the development of simple and environmentally protocol is still in demand.

Material and Method:

A number of synthetic methods for the preparation of 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine Thiones **5(a-e)** have been reported in the literature [17-20] due to its broad-spectrum biological activities and its skeleton. In this section we have reviewed some of the important synthetic methods for the preparation. The reported methods suffer from one or two drawbacks like prolong reaction time, poor yield and use of expensive catalysts. We have reported simple and a green method for the preparation of 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine Thiones derivatives 5(a-e) in minutes of time with high yields is accomplished by the mixture of different benzaldehydes**1**, ethyl acetoacetate **2**, hydrazine hydrate **3**, thiourea **4**. The reaction is accomplished in the presence of molecular iodine in an excellent yield.

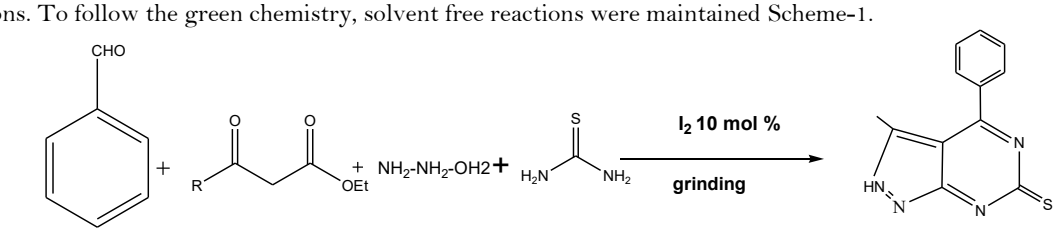
Table 1. Catalytic study of Molecular Iodine for the synthesis of 5a

Entry	I_2 (mol %)	Time (min.)	Yield [a] (%)
1	No I_2	90	00
2	1	68	traces
3	5	63	75
4	8	52	80
5	10	14	94
6	15	26	93
7	20	12	89

After that we performed the same reaction again to optimize the reaction condition and time for complete conversion.

We found that starting material completely disappeared after 10 min. No reaction was observed when Reaction carried out in absence of molecular iodine for 90min (Table 1, entry 1), thus highlighting the role of the molecular iodine I_2 as a promoter. It was also ascertained that a minimum of an equimolar proportion of the I_2 with respect to the product is needed to achieve optimum conversion. Any excess of molecular iodine I_2 beyond this proportion did not show any further increase in conversion and yield (Table 1, Entry 5). It is found that 10 mol% amount of I_2 is sufficient to give maximum yield in short reaction time. It is observed that if we increase the mol% of ionic liquid it again short the reaction time but yield is not significant.

Molecular iodine found to be better catalysts for organic synthesis. Bronsted acidic molecular iodine catalysed the reactions with excellent yield in short reaction time. Experimental data revealed that RT method is a more superior method than conventional. Reaction times and yield of the products were studied in (Table 1). All synthesized molecules are confirmed by FT-IR, 3300–3400 cm−1 (NH group of pyrazole) and 1630–1660 cm−1 (C=S), 1 HNMR by 6.7 ppm–8.5 ppm confirms aromatic hydrogen, and 8.5–10.1 indicated the presence of -NH protons. To follow the green chemistry, solvent free reactions were maintained Scheme-1.



1 **2** **3** **4** **5(a-e)**

Scheme1:- Synthesis of 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine Thiones5(a-e)

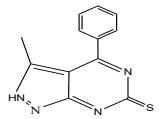
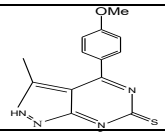
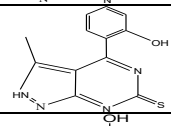
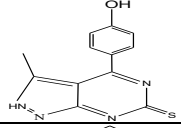
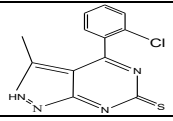
Result and Discussion:

We are increasingly aware of the environmental impact of human activity, and consequently of the need to develop cleaner and more energy-efficient technologies. It has long been recognized that the large-scale use of volatile organic solvents has important implications for environmental contamination. [21] Approaches to the problems presented by organic solvents include the use of more benign solvents (especially water and supercritical CO2), or solvents with negligible vapor pressures (ionic liquids). It has also been said that 'the best solvent is no solvent [22], Despite the power of this statement, our use and understanding of solvent-free synthesis, especially where solid starting materials are concerned, has remained undeveloped in comparison to solvent-based methods. use of grinding to promote reactions between solid reactants is known as mechanochemistry and while its useful appearance has been recognized for a long time it has become neglected in comparison to solvent-based methods.

Molecular iodine is possible green catalyst acts as alternatives for several catalytic reactions. I_2 attracted attention of researchers due to their mild reaction conditions, short reaction times and better yield, solvating ability [23]. Various reactions have been reported recently using I_2 as a catalyst, reaction media and as rate enhancers [24].

From the observations of the literature, it is noted that the yield is low to moderate in the conventional methods some time due to catalyst or due to solvent therefore we choose a novel methodology in which we used IL as catalyst as well as solvent so it will become green synthesis (Scheme-1) we used I_2.

Table 2:- Synthesis of 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine Thiones5(a-e)

Entry	Product	Time(min)	Yield[a,b] (%)
5a		12	94
5b		14	93
5c		11	94
5d		14	91
5e		17	85

[a,b] **isolated yield separated by column chromatography**

From **Table 1**, we found that ***5a*** and ***5c*** molecules completed the reaction at shortest time and yielded the highest quantity (%). Due to electron releasing group present at the 2-position of phenyl substituent, both ***5a,5c*** are found to be stable molecules. Hence, these molecules yield excellent. Similarly, ***5e*** molecules possess electron-withdrawing group at phenyl substituent and, therefore, yield lower than the molecules possessing electron releasing group. Under the convention method, ***5a*** and ***5c*** compounds ended the reactions at shortest time. ***5e*** molecules yield lower than the remaining molecules due to the presence of electron-withdrawing group at phenyl substituent.

Experimental:

All chemicals were purchased by LOBA CHEMIE Company. Reactions were managed by magnetic stirrer (ChemiTech). Melting point was determined by open capillary tubes in Buchi B-540 melting point apparatus. The reaction was monitored by thin-layer chromatography (TLC) using silica gel in iodine chamber and purified by using Colum Chromatography. FT-IR (Vertex version from Bruker), 1 HNMR (Bruker, 400 MHz), 13C-NMR, and elemental analyser were used.

General procedure for the synthesis of pyrazolo [3, 4-d]- pyrimidine-thiones:-

To a solution of ethyl acetoacetate (10 mmol), add hydrazine hydrate (10 mmol), thiourea (10 mmol), and different benzaldehydes (10 mmol) in a round bottom flask. The reaction mixture along with I_2 was grind at room temperature to proceed and monitored by TLC. The solid precipitate out in the solution and filtered off. After completion on the reaction, the mixture was extracted 5 X 20 ml. of ethyl acetate: petroleum ether (50%+50%). Compound comes in organic layer, was again treated with water, brine & dried over MgSO4. Organic solvent is evaporated to afford pure product. The crude solid was recrystallized by hot water, ethanol, and finally dried. The obtained products were identified by comparison with authentic samples 1H NMR and their melting points.

3-methyl-4-phenyl-1, 3a-dihydro-6H-pyrazolo[3, 4-d]pyrimidine-6- thione: (5a):

Yellow crystals, m.p. 218–220°C, yield (81.00%). IR (KBr) νmax/ cm−1 3343 (NH), 1652 (C=S). 1 H-NMR (CDCl3 , 400 MHz, δppm): 3.80 (s, 3H, OCH3), 6.82 (d, 2H, J=9.0Hz, ArH), 7.00 (d, 1H, J=4.8Hz, pyrimidine), 7.12 (t, 1H, ArH), 7.33–7.46 (m, 5H, ArH), 7.62 (d, 2H, J=9.0 Hz, ArH), 7.54 (d, 2H, J=8.4 Hz, ArH), 8.11 (d, 2H, J=8.3 Hz, ArH), 8.48 (d, 1H, J=4.8 Hz, pyrimidine), 9.39 (s, 1H, NH), 10.05 (s, 1H). 13C-NMR (CDCl3 , 100 MHz, δppm):55.5 (C,OCH3), 87.6 (C,C3 –Pyrazolopyrimidine), 106.0 (C,C6 –Pyrazolopyrimidine), 114.7, 118.2, 120.8, 123.7, 126.7, 129.6, 129.8, 129.9(14C,Ar), 134.8 (C,C3a–pyrazolopyrimidine), 137.8, 142.8, 145.7 (3C,Ar), 147.7 (C,C7 –pyrazolopyrimidine), 163.2 (C=S). Anal. calculated (%) for C12H10N4 S (242.00): C, 59.78; H, 4.26; N, 23.28, S, 12.68. Found: C, 59.69; H, 4.11; N, 23.00, S, 13.2%

3-methyl-4-(2-methoxy-phenyl)-1,3a-dihydro-6H-pyrazolo[3,4-d] pyrimidine-6-thione: (5b) :Yellow crystals, m.p. 206–208°C, yield(76.00%). IR (KBr) νmax/ cm−1 3340 (NH), 1646 (C=O). 1 H-NMR (CDCl3 , 400 MHz, δ ppm): 3.80 (s, 3H, OCH3), 3.91 (s, 3H, OCH3), 6.87 (d, 2H, J=8.9 Hz, ArH), 6.89 (d, 1H, J=4.8 Hz), 7.05 (d, 2H, J=8.8 Hz, ArH), 7.11 (t, 1H, ArH), 7.37 (t, 2H, ArH), 7.60 (d, 2H, J=8.9 Hz, ArH), 7.72 (d, 2H, J=7.6 Hz, ArH), 8.18 (d, 2H, J=8.8 Hz, ArH), 8.40 (d, 1H, J=4.8 Hz), 9.36 (s, 1H, NH), 10.02 (s, 1H, NH). 13C-NMR (CDCl3 , 100 MHz, δ ppm): 55.5 (C,OCH3), 55.6 (C,OCH3), 87.4 (C,C3 –pyrazolopyrimidine), 106.4 (C,C6 –pyrazolopyrimidine), 113.9, 114.2, 119.0, 120.0, 122.4, 123.5, 128.9, 131.3 (14C,Ar), 134.0 (C,C3a– pyrazolopyrimidine), 162.2 (C,Ar), 163.2 (C=O). Anal. calculated (%) for C13H12N4 OS (272.00): C, 57.35; H, 4.41; N, 20.58; O, 5.88; S, 11.76. Found: C, 57.41; H, 4.45; N, 20.54; O, 5.79; S. 11.97%.

4-(2-chlorophenyl)-3-methyl-1,3a-dihydro-6H-Pyrazolo[3,4-d] pyrimidine-6-thione: (5e):-

Yellow crystals, m.p. 219–221°C, yield(74.00%). IR (KBr) νmax/ cm−1 3334 (NH), 1648 (C=S). 1H-NMR (CDCl3, 400 MHz, δppm): 2.45 (s, 3H, CH3), 3.6 (s, 3H, OCH3), 6.77 (d, 2H, J=8.9 Hz, ArH), 6.66 (d, 1H, J=4.7 Hz), 7.06 (t, 1H, ArH), 7.26 (d, 2H, J=8.3 Hz, ArH), 7.28 (t, 2H, ArH), 7.56 (d, 2H, J=8.9 Hz, ArH), 7.72 (d, 2H, J=7.6 Hz, ArH), 8.10 (d, 2H, J=8.1 Hz, ArH), 8.33 (d, 1H, J=4.7Hz), 9.33 (s, 1H, NH), 10.01 (s, 1H, NH). 13C-NMR (CDCl3, 100 MHz, δ ppm): 21.5 (C,CH3), 55.6 (C,OCH3), 86.9 (C,C3–pyrazolopyrimidine), 107.1 (C,C6–pyrazolopyrimidine), 113.9, 119.1, 120.1, 123.5, 127.5, 129.0, 129.4, 129.6 (14C,Ar), 133.8 (C,C3a–pyrazolopyrimidine), 138.8, 142.2, 146.4 (3C, Ar), 163.1 (C=S). Anal. calculated (%) for C13H8 N4 OSCl (303.00): C, 51.48; H, 2.64; N, 18.48; O, 5.28; S, 10.56; Cl, 11.55. Found: C, 51.45H, 2.56; N, 18.56; O, 5.27; S, 10.55; Cl, 11.60%.

Conclusion:

In conclusion, we have developed a mild, simple, straight far ward, convenient and green protocol for the synthesis of a library of Synthesis of 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine Thiones 5 (a-e) with shorter reaction time. The method is clean and simple, which can be used as an alternative to the existing methods. The excellent isolated yield, high reaction rate. Absence of organic solvent and any acid or base catalyst makes this an environment friendly methodology amenable for scale up.

Acknowledgment

Author wants to thanks Dept. of Chemistry and Principal B.Raghunath College Parbhani.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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