RASĀYAN *J. Chem.*
Vol. 17 | No. 2 |451-455| April - June | 2024
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

ONE-POT SYNTHESIS OF 5-(ARYL)-1,3,4-THIADIAZOLE-2-AMINES IN PEG-400

Kshitija Tambe, Devendra Wagare, and Sangita pawar
Department of Chemistry, Vivekanand Arts, Sardar Dalipsingh Commerce & Science College, Aurangabad, Maharashtra, India
✉Corresponding Author: sangitapawarvca@gmail.com

ABSTRACT

A relatively green one-pot environmentally benign protocol has been developed for the smooth access of 5-(Substituted-phenyl)-[1,3,4]thiadiazole-2-amine derivatives. Present research involved the cyclo-condensation response of substituted fragrant carboxylic acid and thiosemicarbazide under microwave irradiation with the usage of PEG-400 as a green catalyst. The protocol was found to be an easy, cheaper, and metallic-free green medium. The remarkable features of the present investigation are safe and environmentally benign, inexpensive, and use of nontoxic and non-volatile PEG-400 as a medium. The present study involved direct condensation of aromatic carboxylic acid with thiosemicarbazide in a minimum reaction time to obtain an excellent yield of thiadiazol-2-amines.

Keywords: Aromatic Acids, Thiadiazole, Thiosemicarbazide, PEG-400, Pharmacological Activity, Green Catalyst, Synthesis.

RASĀYAN *J. Chem.*, Vol. 17, No. 2, 2024

INTRODUCTION

In search of the azole family, the synthesis of thiadiazole has been the focus of interest in recent years. This could be probably due to the many pharmacological activities associated with its certain novel derivatives, like antibacterial,[1] antimicrobial[2], antidepressant[3], antituberculosis[4], anti-inflammatory[5], anticonvulsant[6], antihypertensive[7], local anesthetic, antifungal[8], antidiabetic[9], and anticancer.[10] Thiadiazole-containing medications, such as diuretics in clinics, acetazolamide, and methazolamide, as well as the medicines cefazedone and cefazoline sodium, are already in use. A growing body of evidence has also shown a slew of thiadiazole derivatives with various activities in a variety of in vitro and in vivo scenarios. In recent years, heterocyclic compounds have been used not only for the development of heterocyclic derivatives but also for the justification of applications in the medicinal and chemical fields.[11] Current epilepsy medications, which include phenytoin, carbamazepine, and lamotrigine, are associated with considerable adverse effects and have limited use. Anti-epileptic drug development has been one of the most important research topics in recent years, with a thorough grasp of the biology of epilepsy. Thiadiazole is a flexible moiety with a diverse set of biological functions, containing both a “hydrogen binding domain” and a "two-electron donor system”. It also functions as a restricted pharmacophore. There are numerous medications on the market that contain the thiadiazole nucleus, including acetazolamide, methazolamide, sulfamethazine, and others.[12] Due to its high therapeutic potential for diseases of the central nervous system (CNS), thiadiazole has generated a lot of interest as a preferred scaffold. The pharmacological effects of thiadiazole derivatives have been found to include analgesic, depressive, anxiolytic, and anticonvulsant properties. The thiadiazole-ring sulfur atom confers increased lip solubility, which is crucial one for medicines with CNS activity. Thiadiazoles are messianic substances that can traverse cellular membranes and interact with biological targets with different affinities.[13] Microwave irradiation has arisen in recent years as a potent and well-controlled heating source for different chemical reactions because it decreases reaction times and boosts product yields. Aqueous phase one-pot multicomponent reactions have emerged as a valuable tool in organic synthesis, particularly in green chemistry.

In a few reported literatures on the synthesis of thiadiazoles, H_2SO_4 has been used, which is not a green solvent; the yield is low, and the reaction is time-consuming. The use of ionic liquid in such synthesis has several disadvantages, such as toxicity because of its possible release into the soil or watercourses. Ionic

http://doi.org/10.31788/RJC.2024.1728791

liquids could become persistent pollutants, pose environmental risks, and also be costly, making them somewhat impractical for larger industrial applications such as metal electro-deposition and biocatalysts.[14] $POCl_3$ is a hazardous and non-green reagent.[15] PEG-400 (Polyethylene glycol 400) is water–soluble, hygroscopic polymer with a molecular weight of 400 Da. It exists as a colorless viscous liquid at ambient temperature. PEG-400-promoted reactions have generated interest due to their ease of preparation, low cost, and environmentally beneficial nature. It can also serve as a catalyst for phase transitions.[16] The current study reported the synthesis of substituted thiadiazole in a one-step reaction using PEG-400 under solvent-free and simple conditions, with good purity and yield.

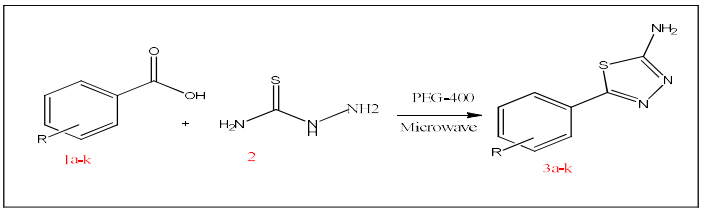
EXPERIMENTAL

Material and Methods

All the chemicals and solvents used were of AR grade and were utilized without additional purification. Melting points were determined in open capillary tubes and were uncorrected. ^{1}H NMR measurements were taken on a Bruker AC–400F, 400 MHz spectrometer for solutions in deuterochloroform ($CDCl_3$) and deuterated dimethyl sulfoxide (DMSO-d6) and are presented in parts per million (PPM) downfield from (Me_4Si) as an internal reference standard.

General Procedure

Substituted benzoic acid (1mmol) and thiosemicarbazide (1mmol) were added to Polyethylene glycol 400 (PEG-400). The reaction mixture was heated at 120°C for 2 h. The progress of the reaction was monitored by TLC (n-Hexane: ethyl acetate). The reaction was quenched by the addition of crushed ice and the solid separated was filtered, basic solution. The crude thiadiazole was purified by recrystallization in ethanol to afford a 90% yield.



Scheme-1: One-Pot Synthesis Of 5-(Aryl)-1,3,4-Thiadiazole-2-Amines In Peg-400

Characterization of Compound 3a-K

5-(4-Fluoro-phenyl)-[1,3,4]thiadiazole-2-amine (3a)

IR (, cm–1): 3361 (N-H stretching), 1635 (C= N stretch), 857 (C-S-C str, thiadiazole); ^{1}H NMR (DMSO-d6, d, ppm); 7.3–7.9 (m, 4H), 5.2 (s, 2H); 13C NMR 400MHz, (DMSO-d6, d, ppm): 175.3, 169.2, 152.3, 135.9, 125.6, 120.2; LCMS (m/z): 194 (M+), 196 (M+1); Elemental Analysis (C8H6FN3S), Found % (Calculated %): C, 48.042 (48.27); H, 3.058 (3.10); N, 22.45 (21.53); S, 17.38 (15.47).
All the characterization data is in agreement with the literature data.[10]

5-(4-Chloro-phenyl)-[1,3,4]thiadiazole-2-amine (3b)

IR (, cm–1): 3357 (N-H stretching), 1638 (C= N str,), 883 (C-S-C str, thiadiazole; 1 H NMR (DMSO-d6, d, ppm); 7.2–7.5 (m, 4H), 5.4 (s, 2H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 174.4, 161.9, 137.9, 135.1, 129.2, 127.9; LCMS (m/z): 215(M+), 221 (M+1); Elemental Analysis (C8H6ClN3S), Found % (Calculated %): C, 44.24 (44.40); H, 2.82 (2.85); N, 20.79 (20.85); S, 15.22 (15.26).
All the characterization data is in agreement with the literature data.[10]

5-(4-Bromo-phenyl)-[1,3,4]thiadiazole-2-amine (3c)

IR (cm–1): 3378 (N-H stretching), 1652 (C= N stretching), 889 (C-S-C str, thiadiazole); 1 H NMR (DMSO-d6, d, ppm); 7.4–7.12 (m, 4H), 5.6 (s, 2H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 175.6, 168.2, 132.9, 133.1, 130.2, 119.9; LCMS (m/z): 254 (M+), 260 (M+1); Elemental Analysis (C8H6BrN3S), Found % (Calculated %): C, 38.35 (38.52); H, 2.46 (2.46); N, 16.44 (16.51); S, 12.49 (12.56). All the characterization data is in agreement with the literature data.[10]

5-(4-Iodo-phenyl)-[1,3,4]thiadiazole-2-amine (3d)

^{1}H NMR (DMSO-d6, d, ppm); 7.5–7.6 (m, 4H), 5.4 (s, 2H); ^{13}C NMR 400 MHz, (DMSO-d6, d, ppm): 178.2, 164.5, 137.9, 129.1, 127.8, 97.2; LCMS (m/z): 307 (M+), 306 (M+1); Elemental Analysis

(C8H6IN3S), Found % (Calculated %): C, 30.88 (31.01); H, 1.90 (2.12); N, 12.89 (12.86); S, 10.67 (10.68). All the characterization data is in agreement with the literature data.[10]

5-(4-Methyl-phenyl)-[1,3,4]thiadiazole-2-amine (3e)
IR (, cm–1): 3391 (N-H stretching), 1645 (C ¼ N str, ring), 1377 (C-H bend, aliphatic), 894 (CS-C str, thiadiazole); 1 H NMR (DMSO-d6, d, ppm); 7.5–7.8 (m, 4H), 5.4 (s, 2H); 1.8 (s, 3H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 169.7, 162.6, 134.8, 131.7, 128.2, 126.1, 20.9; LCMS (m/z): 194 (M+), 196 (M+1); Elemental Analysis (C9H9N3S), Found % (Calculated %): C, 58.45 (58.54); H, 4.85 (4.84); N, 22.00 (22.19); S, 16.87 (16.87). All the characterization data is in agreement with the literature data.[10]

5-(4-Hydroxy-phenyl)-[1,3,4]thiadiazole-2-amine (3f)
IR (, cm–1): 3458 (O-H, stretching), 3345 (N-H str),1634 (C ¼ N str, ring), 889 (C-S-C str, thiadiazole);1 H NMR (DMSO-d6, d, ppm); 7.3–7.7 (m, 4H), 5.4 (s, 2H), 2.7 (s, 1H); 13C NMR 400 MHz,(DMSO-d6, d, ppm): 172.9, 162.5, 157.3, 124.5, 126.8, 118.2; LCMS (m/z): 195 (M+), 196 (M+1); Elemental Analysis (C8H7N3OS), Found % (Calculated %): C, 49.62 (49.63); H, 3.44 (3.45); N, 22.67 (22.75); S, 16.57 (16.61). All the characterization data is in agreement with the literature data.[10]

5-(4-Methoxy-phenyl)-[1,3,4]thiadiazole-2-amine (3g)
1 H NMR (DMSO-d6, d, ppm); 7.2–7.4 (m, 4H), 5.3 (s, 2H); 3.7 (s, 3H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 171.9, 160.8, 159.4, 128.1, 126.0, 113.5, 55.9; LCMS (m/z): 206 (M+), 207 (M+1); Elemental Analysis (C9H9N3OS), Found % (Calculated %): C, 51.28 (51.17); H, 2.51 (4.33); N, 20.71 (20.65); S, 15.40 (15.52). All the characterization data is in agreement with the literature data.[10]

5-(4-Ethoxy-phenyl)-[1,3,4]thiadiazole-2-amine (3h)
1 H NMR (DMSO-d6, d, ppm); 7.2–7.5 (m, 4H), 5.2 (s, 2H); 3.5 (q, 2H), 1.5 (t, 3H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 174.0, 161.8, 159.1, 128.9, 125.7, 114.2, 63.8, 13.7; LCMS (m/ z):222 (M+), 223 (M+1); Elemental Analysis (C10H11N3OS), Found % (Calculated %): C, 55.22 (55.28); H, 6.00 (6.01); N, 18.95 (19.00); S, 14.56 (14.59). All the characterization data is in agreement with the literature data.[10]

5-(2-Hydroxy-phenyl)- [1,3,4]thiadiazole-2-amine (3i)
IR (, cm–1): 3458 (O-H, stretching), 3362 (N-H str),1643 (C ¼ N str, ring), 892 (C-S-C str, thiadiazole); 1 H NMR (DMSO-d6, d, ppm); 7.2–7.6 (dm, 2H), 6.6 - 6.8 (dd, 2H) 5.2 (s, 2H), 2.6 (s, 1H); 13C NMR 400 MHz,(DMSO-d6, d, ppm): 172.2, 149.2, 154.1, 128.3, 125.7, 135.8; LCMS (m/z): 193 (M+), 194 (M+1); Elemental Analysis (C8H7N3OS), Found % (Calculated %): C, 48.72 (48.74); H, 3.74 (3.75); N, 21.77 (21.85); S, 16.68 (16.70).

5-(2-Methyl-phenyl)-[1,3,4]thiadiazole-2-amine (3j)
IR (, cm–1): 3377 (N-H stretching), 1643 (C ¼ N str, ring), 1377 (C-H bend, aliphatic), 886 (CS-C str, thiadiazole); 1 H NMR (DMSO-d6, d, ppm); 7.3–7.5 (dm, 2H),); 6.5–6.7 (dd, 2H), 5.6 (s, 2H); 2.2 (s, 3H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 179.7, 169.6, 142.6, 141.2, 136.6, 129.9, 27.9; LCMS (m/z): 195 (M+), 196 (M+1); Elemental Analysis (C9H9N3S), Found % (Calculated %): C, 56.54 (56.62); H, 4.15 (4.24); N, 21.18 (21.27); S, 11.77 (11.77).

5-phenyl-[1,3,4]thiadiazole-2-amine (3k)
1 H NMR (DMSO-d6, d, ppm); 7.3–7.4 (m, 2H), 6.3–6.6 (dd, 2H), 4.2 (s, 2H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 171.1, 151.4, 131.3, 131.8, 119.7, 92.6; LCMS (m/z): 301 (M+), 302 (M+1); Elemental Analysis (C8H6IN3S), Found % (Calculated %): C, 31.56 (31.60); H, 1.98 (2.00); N, 13.99 (13.96); S, 12.57 (12.58).

RESULTS AND DISCUSSION

Most of the reported reaction for the synthesis of thiadiazoles involves aldehyde and thiosemicarbazide as reactants that lead to different thiadiazoles. We have reported the synthesis of thiadiazoles carboxylic acid and thiosemicarbazide in PEG-400 as green solvents. To investigate the efficiency of various catalysts for the present chemical conversion catalyst mentioned in Table-1 have been studied experimentally and found PEG-400 as the most efficient catalyst and reaction medium. Reaction completed in 30 min. To

generalize the scope of the method a variety of aromatic acids have been treated with thiosemicarbazide in the presence of PEG-400 to obtain thiadiazoles. It is observed that, in the microwave, the yield of products significantly increases with high yield and purity. It has been also observed that electron electron-withdrawing ring increases the rate of reaction. All the synthesized derivatives were characterized by IR, NMR, and Mass spectral analysis.

Table-1: Selection of the Catalyst

S. No.	Catalyst	Reaction time(h/min)	Yield (%)
1	Net reaction	24 h	Trace
2	Cyclodextrin	8 h	52
3	Glycine	5 h	56
4	SiO_2Cl	4 h	63
5	PEG-300	2 h	82
6	PEG-400	30 min	90

Table-2: Optimization of Techniques and PEG-400 Catalyzed Synthesis of Thiadiazole

3a-k	3 (R)	% Yield		
		Reflux (t, hr)	Ultrasonic (t, hr)	Microwave (t,min)
3a	4-F	70(4:00)	85(2:00)	92(30min)
3b	4-Cl	69(4:05)	80(2:05)	90(31min)
3c	4-Br	65(3:50)	82(2:10)	91(29min)
3d	4-I	72(4:00)	87(1:50)	91(30min)
3e	4-CH_3	75(3:45)	82(2:00)	93(30min)
3f	4-OH	71(3:20)	83(2:02)	90(31min)
3g	4-OCH_3	77(3:56)	85(2:08)	89(29min)
3h	4-OCH_2CH_3	68(4:00)	81(2:00)	92(31min)
3i	2-OCH_3	73(3:30)	80(1:55)	90(30min)
3j	2-CH3	76(3:42)	82(2:05)	93(30min)
3k	-	80(4:05)	85(2:00)	90(31min)

CONCLUSION

A multicomponent, environmentally benign strategy for the synthesis of substituted thiadiazole from the direct coupling of differently substituted aromatic carboxylic acids and thiosemicarbazide in the presence of PEG-400 as a green catalyst has been developed. The use of a green, affordable, the absence of metal, and the purity of the products (90% -93%) are key advantages of the current approach.

ACKNOWLEDGEMENTS

The authors are grateful to the Principal, Vivekanand Arts, Sardar Dalipsingh Commerce, and Science College, Aurangabad, for supporting our study endeavor by making available a central research facility.

DISCLOSURE STATEMENT

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

Kshitija Tammbe https://orcid.org/0009-0001-9779-282X
Devendra Wagare https://orcid.org/0000-0002-7138-5425
Sangita Pawar https://orcid.org/0009-0008-1104-6932

REFERENCES

1. M. Szeliga, *Pharmacological Reports*, **72**, 1079(2020), https://doi.org/org/10.1007/s43440-020-00154-7
2. E. E. Oruç, S. Rollas, F Kandemirli, N. Shvets, A. S. Dimoglo, *Journal of Medicinal Chemistry*, **47 (27)**, 6760(2004), https://doi.org/org/10.1021/jm0495632
3. A. Ç. Karaburun, U. Acar Çevik, D. Osmaniye, B. N. Sağlık, B. Kaya Çavuşoğlu, S. Levent, Y. Özkay, A. S. Koparal, M. Behçet, Z. A. Kaplancıklı, *Molecules*, **23(12)**, 3129(2018), https://doi.org/org/10.3390/molecules23123129
4. P. A. Datar, T. A. Deokule, *Medicinal Chemistry*, **4(4)**, 390(2014), https://doi.org/org/10.2174/1573399815666190618093315
5. M. D. Altıntop, Ö. D. Can, Ü. Demir Özkay, Z. A. Kaplancıklı, *Molecules*, **21(8)**, 1004(2016), https://doi.org/org/10.3390/molecules21081004
6. N. Ö. Can, Ö. D. Can, D. Osmaniye, Ü. Demir Özkay, *Molecules*, **23(4)**, 716(2018), https://doi.org/org/10.3390/molecules23040716
7. S. Khan, S. Verma, *Bulletin of the Korean Chemical Society*, **32(3)**, 1011(2011), https://doi.org/org/10.5012/bkcs.2011.32.7.2489
8. V. Raj, A. Rai, M. Singh, A. Kumar, V. Kumar, S. K. Sharma, *EC Pharmaceutical Science*, **2(1)**, 202(2015), https://doi.org/org/10.3389/fchem.2021.671212
9. H. Bhuva, D. Sahu, B. N. Shah, D. C. Modi, M. B. Patel, *Pharmacologyonline*, **1**, 528(2011), https://doi.org/org/10.1257/aer.99.1.528
10. N. Pahade, D. Wagare, D. Shinde, D. Lingampalle, *Polycyclic Aromatic Compounds,* 43(10), 8593(2023), https://doi.org/10.1080/10406638.2022.2150239
11. U. P. Singh, *Synlett*, **23(18)**, 2721(2012), https://doi.org/org/10.1055/s-0032-1317353
12. D. Wagare, A. Sonone, M. Farooqui, A. Durrani, *Polycyclic Aromatic Compounds*, **41(8)**, 1749(2021), https://doi.org/org/10.1080/10406638.2019.1695637
13. C. T. Keerthi Kumar, J. Keshavayya, T. N. Rajesh, S. K. Peethambar, A. R. Shoukat Ali, *Organic Chemistry International,* **2013**, Article ID 370626(2013), https://doi.org/org/10.1155/2013/370626
14. K. S. Bhat, B. Poojary, D. J. Prasad, P. Naik, B. S. Holla, *European Journal of Medicinal Chemistry,* **44 (12)**, 5066(2009), https://doi.org/org/10.1016/j.ejmech.2009.09.010
15. G. B. Bagihalli, P. G. Avaji, S. A. Patil, P. S. Badami, *European Journal of Medicinal Chemistry,* **43,(12)**, 2639(2008), https://doi.org/org/10.1016/j.ejmech.2008.02.013
16. Z. H. Chohan, S. H. Sumrra, M. H. Youssoufi, T. B. Hadda, *European Journal of Medicinal Chemistry,* **45(7)**, 2739(2010), https://doi.org/org/10.1016/j.ejmech.2010.02.053

[RJC- 8791/2024]