A simple, convenient, and one pot synthetic route for the preparation of 1,3,5-thiadiazines-2-thione heterocyclic compounds and their antifungal activity

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A simple, convenient, and one pot synthetic route for the preparation of 1,3,5-thiadiazines-2-thione heterocyclic compounds and their antifungal activity

Sohail Saeed¹*

Abstract: A series of new heterocyclic 1,3,5-thiadiazines-2-thione with aryl/aryl substituents (3a-c) were synthesized by reacting isothiocyanates with N- (propan-2-yl) propan-2- amine in the presence of tetrabutylammonium bromide as phase transfer catalyst. The structures of these novel compounds were characterized by IR, mass spectrometry, and elemental analysis. The crystal structures were determined from single-crystal X-ray diffraction data. The synthesized compounds were tested in vitro against Fusarium solani, A. fumigatus, and Aspergillus flavus using standard drugs.

Subjects: Chemical Spectroscopy; Crystallography; Organic Chemistry

Keywords: thiadiazines; heterocyclic compounds; single-crystal X-ray diffraction; phase transfer catalyst (PTC); antimicrobial activity

1. Introduction
Heterocyclic compounds are attractive to medicinal chemists because of their unique chemical properties and wide-ranging biological activities. Despite significant research progress on heterocyclic ring systems, efforts are ongoing to identify novel heterocyclic compounds with potent bioactivities.

ABOUT THE AUTHOR
Sohail Saeed has completed his MSc in Organic Chemistry from the University of the Punjab, Lahore, and PhD in Organic Chemistry in 2013 under the supervision of Naghmana Rashid from the Allama Iqbal Open University, Islamabad, Pakistan. He has commissioned a state-of-the-art “Phenolic and Epoxy based Prepregging Laboratory” in the Centers of Excellence in Science and Applied Technologies, Islamabad. He has 15 years’ experience in the field of prepreg development, high-pressure curing, bagging techniques for autoclave curing, and various other processes for the production of hi-tech composite structures. His current research interest focuses on hi-tech composite materials, CVD, semiconducting thin films from single-source precursors, medicinal chemistry, and heterocyclic chemistry. He has published more than 60 research papers in well-reputed international journals. He has won three consecutive Research Productivity Awards (2010–2012) from the Ministry of Science and Technology, Pakistan. He is presently working as a deputy project director in CESAT, Islamabad, Pakistan.

PUBLIC INTEREST STATEMENT
Compounds derived from thiadiazines-2-thione have received particular attention due to their pharmacological properties. Numerous studies have been published on the antiparasitic properties of these derivatives. These compounds also present antibacterial, antifungal, antiviral, and anticancer activity. In addition, the high lipid solubility and ease of enzymatic hydrolysis generally associated with this heterocycle have promoted its use as a biolabile prodrug in the design of drug delivery systems. Generally, lipophilic groups at both the N-3 and N-5 positions lead to compounds with high antimicrobial activity, but also high toxicity. The presence of a hydrophobic group at N-5 favored the antimicrobial activity of the thiadiazine derivatives. The aforementioned properties and the possibility to attach several structurally distinct substituents to the heterocycle ring to modify either the biological or physicochemical properties of these compounds prompted to use this heterocycle as a template in many research programs aimed at the development of new bioactive compounds.
Five-membered heterocycles, such as thiazine, imidazole, oxazole, thiazole, oxadiazole, and thiadiazole, are common and typically possess biological activities. In recent decades, research has indicated that the thiazine ring is an important framework with broad-spectrum biological activity. 1,3,5-Thiadiazines are useful as herbicides (Rodríguez, Suárez, & Albericio, 2012), antimicrobial drugs (El-Shorbagi, 2000), insecticides (Coro, Piñeiro, Monzote, Rodríguez, & Suárez, 2011), and miticides (Aboul-Fadl, Hussein, El-Shorbagi, & Khalili, 2002). Most reported 3,4-dihydro-2H-1,3,5-thiadiazines contain ring carbonyl or thiocarbonyl groups: such compounds were previously synthesized (Scheme 1) by (i) treatment of heterocyclic primary thioamides with phenoxycarbonyl isocyanate (Coburn, Ho, & Bronstein, 1982; (ii) cyclization of perchloroethyl isocyanate with thioamides (Eltsov et al., 2008); (iii) reaction of...
thiobenzoyl isocyanates with C=N bonds in arylhydrazones, benzaldazines (Tsuge & Kanemasa, 1972), carbodimides, or anilis (Tsuge & Sakai, 1972); (iv) [4 + 2] cycloaddition of 1-thia-3-azadienes with electron-deficient nitriles; (v) dimerization of thiocarbamoylisothiocyanates; or (vi) dimerization of carbamoyl isothiocyanates (Goerdeler & Lüdke, 1968). Previously reported compounds of type 5 were made by thermolysis of 4-substituted and 2,4-disubstituted 6H-1,3,5-oxathiazines followed by dimerization (Giordano, Belli, & Abis, 1979) (Scheme 1), (vii). In view of the utility of these compounds in various fields and as a part of the wider program to provide alternative routes for the synthesis of various five and six-membered organic heterocyclic compounds, now the method for the synthesis 1,3,5-thithiazines-2-thione heterocyclic is reported.

2. Experimental protocols

2.1. Materials and physical measurements
Analytical grade 3,5-dinitrobenzoyl chloride (≥98.0%), 4-bromobenzoyl chloride (99%), 4-nitrobenzoyl chloride (99%), sodium thiocyanate (99%), tetrabutylammonium bromide (TBAB) (≥98%), and N-(propan-2-yl) propan-2-amine were purchased from Sigma-Aldrich. Analytical grade solvents, such as tetrahydrofuran, acetonitrile, dichloromethane, ethanol, and others, were purchased from Riedel-de Haén (Germany). The ethanol and acetone were dried using standard procedures (Perrin, Armarego, & Perrin, 1988). Infrared spectra were recorded on a Specac single reflectance Attenuated Total Reflectance instrument (4,000–400 cm⁻¹, resolution 4 cm⁻¹). Melting point was recorded on Electrothermal IA9000 series digital melting point apparatus. Elemental analysis was carried out using Perkin Elmer CHNS/O 2400. Obtained results were within 0.4% of the theoretical values. The mass spectrum was run on a Finnigan TSQ-70 spectrometer (Finnigan, USA) at 70 eV. Thin layer chromatography analysis were carried out on 5 × 20 cm plate coated with silica gel GF₂₅₄ type 60 (25–250 mesh) using an ethyl acetate–petroleum ether mixture (1:2) as solvent.

2.2. X-ray structure determination
A red-orange plate 0.42 × 0.18 × 0.06 mm³ was mounted on a glass fiber in inert oil. Measurements were performed at 123 K on an Oxford Diffraction Xcalibur Ruby Gemini diffractometer with mirror-focused Cu-Kα radiation to 2θ max 67.50° (99.1% complete to 67.50°). The data were corrected for absorption using the multi-scan method. The structure was solved by direct methods and refined by full-matrix least-squares techniques on F² using the program SHELXL-97 (Sheldrick, 2008). The non-hydrogen atoms were refined anisotropically. NH hydrogens were refined freely, other H atoms using a riding model.

2.3. Synthesis

2.3.1. Synthesis of 6-(dipropan-2-ylamino)-4-(4-nitrophenyl)-2H-1,3,5-thiadiazine-2-thione (3a)
A solution of 4-nitrobenzoyl chloride (0.01 mol) in anhydrous acetone (80 mL) and 0.3 mol % TBAB in acetone was added dropwise to a suspension of ammonium thiocyanate (0.01 mol) in acetone (50 mL) and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a solution of the corresponding N-(propan-2-yl) propan-2-amine (0.01 mol) in acetone (25 mL) was added and the resulting mixture refluxed for 1.5 h. The reaction mixture was poured into five times its volume of cold water, whereupon the red-orange target compound precipitated. The solid product was washed with water and purified by recrystallization from an ethanol–dichloromethane mixture (1:2). M.p.: 127–128°C. Yield: 3.5 g (89%). IR (νmax/cm⁻¹): 2,932, 2,839 (C–H), 1,584 (C=N), 1,280 (C–N), 1,258 (C=S). Elemental analysis for C₁₅H₁₈N₄O₂S₂ (MW = 350.45) in wt % calc. C = 51.41, H = 5.18, N = 15.99, S = 18.30 and found to be C = 51.37, H = 5.21, N = 16.10, S = 18.28. EI MS, m/z (%): 350.42.

2.3.2. Synthesis of 4-(3,5-dinitrophenyl)-6-(dipropan-2-ylamino)-2H-1,3,5-thiadiazine-2-thione (3b)
A solution of 3,5-dinitrobenzoyl chloride (0.01 mol) in anhydrous acetone (80 mL) and 0.3 mol % TBAB in acetone was added dropwise to a suspension of ammonium thiocyanate (0.01 mol) in acetone (50 mL) and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a
solution of the corresponding N-(propan-2-yl)propan-2-amine (0.01 mol) in acetone (25 mL) was
added and the resulting mixture refluxed for 1.5 h. The reaction mixture was poured into five times its
volume of cold water, whereupon the target compound precipitated. The solid product was washed
with water and purified by recrystallization from ethanol. M.p.: 155–156°C. Yield: 3.4 g (86%). IR (ν max/cm): 2,931, 2,840 (C–H), 1,586 (C=N), 1,282 (C–N), 1,259 (C=S). Elemental analysis for C_{15}H_{17}N_{5}O_{4}S_{2}
(MW = 395.45) in wt % calc. C = 45.56, H = 4.33, N = 17.71, S = 16.22 and found to be C = 45.59,
H = 4.31, N = 17.68, S = 16.25. EI MS, m/z (%): 395.44.

2.3.3. Synthesis of 6-(dipropan-2-ylamino)-4-(4-bromophenyl)-2H-1,3,5-thiadiazine-2-thione (3c)
A solution of 4-bromobenzoyl chloride (0.01 mol) in anhydrous acetone (80 mL) and 0.3 mol % TBAB
in acetone was added dropwise to a suspension of ammonium thiocyanate (0.01 mol) in acetone
(50 mL) and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a solu-
tion of the corresponding N-(propan-2-yl)propan-2-amine (0.01 mol) in acetone (25 mL) was added
and the resulting mixture refluxed for 1.5 h. The reaction mixture was poured into five times its vol-
ume of cold water, whereupon the target compound precipitated. The solid product was washed
with water and purified by re-crystallization from ethanol. M.p.: 129–130°C. Yield: 3.3 g (91%). IR (ν max/cm): 2,933, 2,838 (C–H), 1,587 (C=N), 1,281 (C–N), 1,255 (C=S). Elemental analysis for C_{15}H_{18}BrN_{3}S_{2}
(MW = 384.35) in wt % calc. C = 46.87, H = 4.72, N = 10.93, S = 16.68 and found to be C = 46.85,
H = 4.73, N = 10.91, S = 16.67. EI MS, m/z (%): 384.33.

3. Antifungal screening
The antifungal activity was carried out in DMSO using the agar tube dilution method. Sabouraud dext-
rose agar (Merck) was prepared by dissolving 6.5 g/mL in distilled water and the pH was adjusted to
5.6. The contents were dissolved and dispensed in 4 mL aliquots into screw-capped tubes and were
autoclaved at 121°C for 21 min. The tubes were allowed to cool to 50°C and non-solidified SDA was
loaded with 66.6 μL of compound by pipette from stock solution, giving a final concentration of 200 μg/
ML. The tubes were then allowed to solidify in a leaning position at room temperature. Tubes were
prepared in triplicate for each fungus species. The tubes containing solidified media and test compound
were inoculated with 4 mm diameter pieces of inocula, taken from a 7-day-old culture of fungus. Other
media supplemented with DMSO and nystatin were used as negative and positive control, respectively.
The tubes were incubated at 27°C for 7 days. Cultures were examined twice weekly during the incuba-
tion. Growth in media was determined by measuring linear growth (mm) and growth inhibition was
calculated with reference to the negative control (Saeed, Rashid, Jones, Hussain, & Bhatti, 2010).

4. Results and discussion

4.1. Synthesis and characterization
A series of new heterocyclic 1,3,5-thiadiazines 3a-c with aryl substituents (Scheme 2) were prepared
by slight modification of published procedures (Saeed, Rashid, Hussain, Jasinski et al., 2013; Saeed,
Rashid, Hussain, & Jones, 2009; Saeed, Rashid, Hussain, Malik, & O’Brien, 2013; Saeed, Rashid, Jones, & Tahir, 2011). The use of phase transfer catalysts (PTCs) as a method of promoting a heterogeneous reaction system is gaining recognition (Saeed, Rashid, Jones, Ali, & Hussain, 2010; Saeed & Wong, 2012). In search of improved methods to prepare the target heterocyclic 1,3,5-thiadiazines-2-thione by reacting isothiocyanates with nucleophiles, we have found the use of TBAB as PTC can afford substituted aroyl isothiocyanates in good yield, as reported here. All the structures of newly synthesized compounds were assigned on the basis of their IR, elemental analysis, and mass spectrometric data. All the synthesized heterocyclic compounds were soluble in DMF, DMSO, ethanol, and ethyl acetate.

4.2. Single-crystal X-ray crystallography

Single crystals of 3a suitable for X-ray diffraction studies were obtained by evaporation from dichloromethane: ethanol mixture (2:1). The bond lengths and angles are similar to those in structurally related compounds (Bélai, Sohár, Maekawa, Párkányi, & Matolcsy, 1981). The thia diazine ring exists in a half-chair conformation with S1A, C8A, C9A, N2A, and N3A all coplanar. The phenyl ring is slightly inclined to the above plane. There are no unusually short intermolecular interactions. The structures of the other compounds were assigned by analogy and by spectral comparison. Figure 1 shows a perspective view of the molecular structure and Figure 2 represents the packing diagram. The crystal data and structure refinement and selected bond lengths and angles are listed in Tables 1 and 2, respectively. Table 3 illustrates the data of hydrogen bonding.

4.3. Pharmacological evaluation

Primary bioassay screening provides the first indication of bioactivities and helps in the selection of lead compounds for secondary screening for detailed pharmacological evaluation. The synthesized heterocyclic 1,3,5-thiadiazines 3a-c were checked for their antifungal activity against three fungal strains: Fusarium solani, A. fumigatus, and Aspergillus flavus. The antifungal activity was carried out in DMSO using the agar tube dilution method (Reiner, 1980). Growth in the media was determined by measuring linear growth (mm) and growth inhibition was calculated with reference to the negative control. No significant activity against yeast was detected. All the compounds in the series showed weak antimicrobial activity against F. solani, A. fumigatus and A. flavus with 25–30% inhibition, which shows low activity.

Figure 1. Perspective view of the X-ray structure of 3a.
**Figure 2. Unit cell diagram of 3a.**

![Unit cell diagram of 3a.](image)

**Table 1. Crystal data and structure refinement for 3a**

| Property                             | Value                                           |
|--------------------------------------|-------------------------------------------------|
| Empirical formula                    | C_{15}H_{18}N_{4}O_{2}S_{2}                     |
| Formula weight                       | 350.45                                          |
| Temperature                          | 123(2) K                                        |
| Wavelength                           | 1.54184 Å                                       |
| Crystal system                       | Triclinic                                       |
| Space group                          | P −1                                            |
| Unit cell dimensions                 | a = 7.5609(4) Å  
|                                      | b = 15.0360(8) Å  
|                                      | c = 15.4171(8) Å  |
|                                      | α = 81.481(4)°  
|                                      | β = 84.569(4)°  
|                                      | γ = 75.774(5)°  |
| Volume                               | 1,677.12(16) Å³                                 |
| Z                                    | 4                                               |
| Density (calculated)                 | 1.388 Mg/m³                                     |
| Absorption coefficient               | 3.005 mm⁻¹                                      |
| F(000)                               | 736                                             |
| Crystal size                         | 0.42 × 0.18 × 0.06 mm³                          |
| Theta range for data collection      | 2.90–78.53°                                     |
| Index ranges                         | −9 ≤ h ≤ 9, −18 ≤ k ≤ 17, −19 ≤ l ≤ 13         |
| Reflections collected                | 11,213                                          |
| Independent reflections              | 6,648 (R(int) = 0.0558)                         |
| Completeness to θ = 67.50°           | 99.1%                                           |
| Absorption correction                | Semi-empirical from equivalents                 |
| Maximum and minimum transmission     | 1.00000 and 0.55357                             |
| Refinement method                    | Full-matrix least-squares on F²                 |
| Data/restraints/parameters           | 6,648/0/423                                     |
| Goodness of fit on F²                | 1.182                                           |
| Final R indices (I>2sigma(I))        | Rw1 = 0.0628, wR2 = 0.2002                      |
| R indices (all data)                 | R1 = 0.0835, wR2 = 0.2661                       |
| Largest diff. peak and hole          | 0.945 and −0.736 e.Å⁻³                         |
5. Conclusion
In this work, a series of 1,3,5-thiadiazines-2-thione with aryl/aryl substituents (3a-c) were synthesized and tested for antimicrobial activity. In spite of the variations of the antimicrobial activity with the three different nitro and bromophenyl groups, all the three compounds exhibited a weak antimicrobial
activity and can be considered for further studies to improve the biological activities by substitution with other functional groups. Preparation of other derivatives with various types of side chain and testing of their antimicrobial activity and structure–activity relationship will be carried out in future.

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Supplementary material
Crystallographic data for the structure reported in this article have been deposited with Cambridge Crystallographic Data Centre, CCDC 849486 (3a). Copies of this information may be obtained free of charge from the Director, CCDC 12 Union Road, Cambridge, CBZ 1EZ, UK. Faccsimile (+44) 01223 336 033, E-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/deposit.

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Table 3. Hydrogen bonds (Å and °) for 3a

| D–H…A                  | d(D–H) | d(H…A) | d(D…A) | <(DHA) |
|------------------------|--------|--------|--------|--------|
| C(14B)–H(14E)…O(1A)   | 0.98   | 2.47   | 3.28(5) | 140.3  |
| C(3B)–H(3BA)…O(2A)    | 0.95   | 2.60   | 3.257(5) | 126.3  |

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