

Waste to wealth: Agro-waste catalyzed green method synthesis of 5-aryl-1,2,4-triazolidine-3-thiones and 1,2,4-triazospiro-3-thiones

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Abstract: This paper describes novel agro-waste derived Water Extract of Orange Fruit Shell Ash (WEOFSA) catalyzed synthesis of 5-aryl-1,2,4-triazolidine-3-thiones and 1,2,4-triazospiro-3-thiones under microwave irradiation. Herein, we have developed inexpensive, facile and green method synthesis of cyclic thiones by the reaction of aromatic aldehyde and cyclic ketone, with thiosemicarbazide in presence of agro-waste derived catalyst. The obtained product is chromatographically pure after recrystallization from ethanol, and final product is characterized by various spectroscopic techniques FT-IR, ¹H-, ¹³C-NMR and HR-MS.

Keywords: Agro-waste; green method; cyclic ketone; semicarbazide; microwave. © 2021 ACG Publications. All rights reserved.

1. Introduction

The chemistry of heterocyclic is a promising area of research in the organic chemistry¹, due to the vast number of molecules emerged blockbuster lifesaving drug candidates²⁻³. The triazole heterocycle chemistry occupied an important place, due to their wide range of biological applications exhibited⁴⁻⁵. Further, the chemistry of 1,2,4-triazoles and their fused heterocycle has received considerable attention owing to their simple synthetic and effective biological importance⁶. Triazole is a five-membered heterocycle having three nitrogen, two carbon atoms and two double bonds having general formula C₂H₃N₃⁷, and exhibited two isomeric forms 1,2,3-triazole and 1,2,4-triazole (Figure 1)⁸, but later one isomeric form has



Figure 1. Two isomeric structure of triazoles

found diverse synthetic and biological applications⁷. A large number of 1,2,4-triazole containing ring system have been reported their wide range of pharmacological applications including CNS stimulants⁹, sedatives¹⁰, anti-inflammatory¹¹, anti-microbial agents¹², anti-anxiety and anti-mycotic activity such as Intraconazole¹³, Fluconazole and Voriconazole¹⁴⁻¹⁵. In addition, some of the recent using drugs containing 1,2,4-triazole group are; Triazolam¹⁶, Alprazolam¹⁷, Etizolam and Furacylin¹⁸⁻¹⁹ (Figure 2).

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The sulphur containing heterocycle represented important practical applications in mycobacterial and hypoglycemic treatment²⁰⁻²². Among these heterocycle of mercapto and thione-substituted 1,2,4-triazole ring systems showed variety of pharmacological applications have been reported²³, anti-cancer²⁴ and anti-HIV. Addition to these important bioactive applications, mercapto-1,2,4-triazoles are also greater utility in the preparative organic chemistry²⁵, for example in the preparation of thiazolotriazoles²⁶, triazolothiadiazoles²⁷, triazolothiazines²⁸, triazolothiazepines and triazolothiadiazines²⁹.

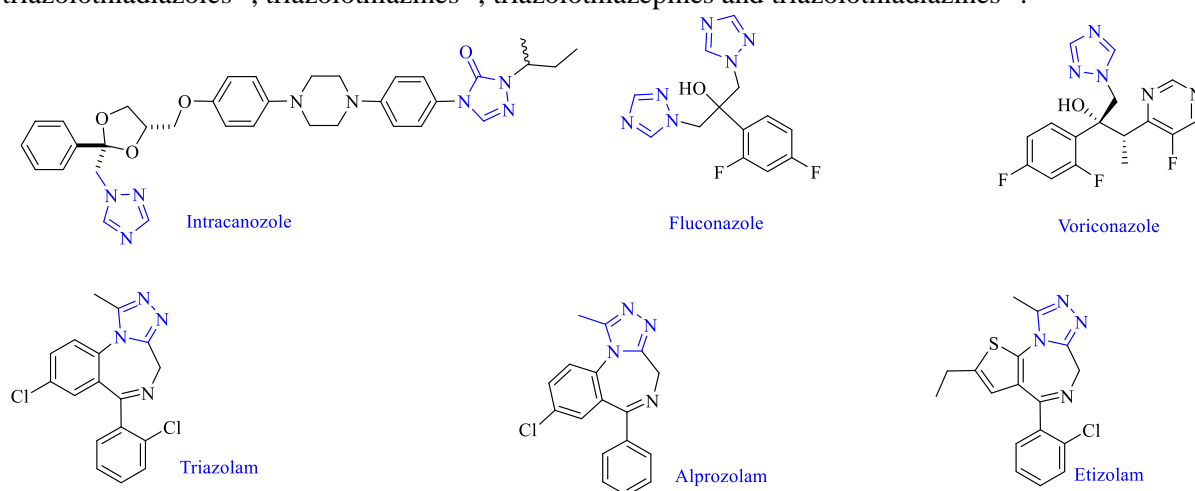


Figure 2. Some drug molecules containing triazole moieties

Nowadays chemist are exploring alternative synthetic route to conventional or existing, to overcome hazardous and harmful use of organic solvent or catalyst³⁰. The synthetic route is environmentally benign for the privileged ‘drug-like’ heterocycle synthesis from readily available precursors with green catalyst is substantial utility in academia as well as in the industrial research³¹. In recent years, chemist have on track to replace hazardous and volatile organic solvent used in reaction media to develop sustainable alternative greener solvent such as PEG³², water³³, ionic liquids³⁴, agro-waste extract³⁵ and solvent-free condition³⁶. In addition, a catalyst-free synthetic route is one of the remarkable tool in scientific society, because they are associated with minimization of pollution, cost and impurity³⁷.

In recent year’s chemist are demonstrated alternative catalytic media derived from agro-waste extraction and employed preparation of valuable organic transformations³⁸. The advantage of using alternative these agro-waste based media showed its non-toxicity, bio-compatibility and solubility of reactants. Some of the agro-waste based media have been employed in organic transformation includes oxidation and reduction reactions³⁹, Heck reaction⁴⁰, substitution reactions, Suzuki cross-coupling reaction, Henry reactions, Sonogashira reaction, and Hiyama cross-coupling.

The hetero-cyclization of readily existing linear compounds is one of the most common and admired line of synthesizing valuable heterocycles⁴¹. Several synthetic and natural heterocyclic bioactive molecules have been demonstrated as a potential drug material^{42,43}. One of its kind heterocycle 1,2,4-triazoles synthesis has attracted wide spread attention, due to their additional agrochemical properties such as insecticidal⁴⁴, fungicidal⁴⁵, herbicidal⁴⁶ bactericidal⁴⁷ and industrial dyes⁴⁸, lubricants⁴⁹ and analytical reagents⁵⁰. Researcher demonstrated these derivatives can be easily transformed to 1,2,4-triazoles, which are more potent. To the best of our knowledge, a very few synthetic methods are available in the literature for the synthesis of 1,2,4-triazoles. Due to pharmacological significance and agrochemical application of the 5-aryl-1,2,4-triazolidine-3-thiones and 1,2,4-triazospiro-3-thiones. Various research groups are striving to make the synthetic method more easy, eco-friendly and greener method. There are some literature reports are available employing sulphamic acid, 4-dimethylaminopyridine (DMAP)⁵¹, presence of ionic liquid [C₁₆MPy]AlCl₃, 25% ethanol @80 °C, 80% Acetic acid and CoFe₂O₄@SiO₂ under room temperature stirring condition, ionic liquids [(Py)₂SO][HSO₄] in ethanol, and PEG-400 under room temperature stirring condition. In this paper, we wish to account agro-waste extract of WEOFSA as a potential greener catalytic solvent media for the

synthesis of a diverse 1,2,4-triazolidine-3-thione and 1,2,4-triazospiro-3-thione derivatives from substituted aromatic aldehyde and thiosemicarbazide under microwave irradiation condition.

2. Experimental

2.1. Materials and Methods

All the reagents are used in the synthesis are purchased from Sd-fine chemicals and were used without further purification. Custom made microwave oven having facility to fit reflux condenser and magnetically stirrer is used for the irradiation reaction at power of 450 W. The melting points were determined by the open capillary method and are uncorrected. The WEOFSA solution is subjected to elemental analysis by the ESICO Microprocessor Flame Photometry model 1382. The ash powder subjected to EDX and SEM and obtained by CARL ZEISS OXFORD instrument, Japan. FT-IR spectra were measured with Thermo Fischer scientific using KBr pellet method, ¹H-, ¹³C-NMR spectra were collected in DMSO-*d*₆ on Agilent spectrometer at 400 MHz. The chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard. The molecular weight is analyzed by HR-MS(ESI)

2.2. Preparation of Water Extract of Orange Fruit Shell Ash (WEOFSA)

It is prepared by orange fruit peel (*Citrus sinensis*), it is collected from local area, and the peel is cleaned with distilled water, dried in sunlight and burnt them to ash on Bunsen burner, 10 gm of the ash is soaked in 100 mL of double distilled water for about 2-3 h and filtered, the filtrate is termed as WEOFSA. The pH of the solution found to be 10.12⁴⁵.

2.3. General Procedure for Synthesis of Compounds (3a-r, 5a-e)

In a round bottomed flask, aldehyde (**1**)/cyclic ketone (**4**) (1 mmol), thiosemicarbazide (**2**) (1 mmol) and WEOFSA (3.5 mL) is added. The reaction mixture is subjected to the microwave irradiation in a custom made microwave oven. After the reaction completion, diluted with distilled water (10 mL), filtered crude product and recrystallized with ethanol. The recrystallized product is characterized by UV-visible, FT-IR, ¹H-NMR, ¹³C-NMR and HR-MS(ESI).

5-(4-Chlorophenyl)-1,2,4-triazolidine-3-thione (3b): Product white crystalline, FT-IR: ν 3438 (NH stretching), 3298 (NH stretching), 3155 (C=H stretching), 1588, 1542, 1456, 1361, 1281 (C=S stretching), 1225, 1165, 1076, 1011, 935, 863, 687, 510 cm⁻¹; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.32 (d, 2H, ArH, *J* = 8.4 Hz), 7.73 (d, 2H, ArH, *J* = 8.4 Hz), 8.07 (s, 1H, CH), 8.18 (s, 1H, NH), 8.41 (s, 1H, NH), 11.12 (s, 1H, NH). ¹³C-NMR (DMSO-*d*₆): 129.1, 129.3, 133.6, 134.6, 141.4, 178.6 ppm; HR-MS (ESI): (C₈H₈ClN₃S) *m/z* (Calcd.) = 213.6900 Da; *m/z* (Obs.) = 213.6101 Da.

5-(4-Bromophenyl)-1,2,4-triazolidine-3-thione (3d): Product white crystalline, FT-IR: ν 3467 (NH stretching), 3284 (NH stretching), 3168 (CH stretching), 1659 (C=C), 1521, 1284, 1394, 1264 (C=S stretching), 1148, 1080, 1062, 1016, 924, 694, 610 cm⁻¹; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.56-7.58 (d, 2H, ArH, *J* = 8.4 Hz), 7.74-7.76 (d, 2H, ArH, *J* = 8.4 Hz), 7.99 (s, 1H, CH), 8.05 (s, 1H, NH), 8.21 (s, 1H, NH), 11.46 (s, 1H, NH); ¹³C-NMR (DMSO-*d*₆): 128.0, 134.3, 136.7, 138.6, 146.0 and 183.2 ppm; HR-MS (ESI): (C₈H₈BrN₃S) *m/z* (Calcd.) = 256.9602 Da; *m/z* (Obs.) = 257.9139 [M+H]⁺Da.

5-(4-(Trifluoromethyl) phenyl)-1,2,4-triazolidine-3-thione (3e): Product white crystalline, FT-IR: ν 3433 (NH stretching), 3247 (NH stretching), 3145 (CH stretching), 1657 (C=C stretching), 1528, 1459, 1358, 1326, 1250 (C=S stretching), 1162, 1064, 1012, 929, 843, 567, 523 cm⁻¹; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.76 (d, 2H, ArH, *J* = 8.12 Hz), 8.11 (d, 2H, ArH, *J* = 8.7 Hz), 8.16 (s, 1H, CH), 8.19 (s, 1H, NH), 8.30 (s, 1H, NH), 11.61 (s, 1H, NH); ¹³C-NMR (DMSO-*d*₆): 114.2, 124.6, 126.2, 129.2, 143.5, 164.4 and 179.2 ppm; HR-MS (ESI): (C₉H₈F₃N₃S) *m/z* (Calcd.) = 247.2406 Da; *m/z* (Obs.) = 247.4716 Da.

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5-(4-Methoxyphenyl)-1,2,4-triazolidine-3-thione (3f): Product White solis, FT-IR: ν 3423 (NH stretching), 3267 (NH stretching), 3152 (CH stretching), 1620, 1521, 1356, 1223, 1176, 1070, 1010, 962, 831, 602, 521 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 3.54 (s, 3H, OCH₃), 6.86 (d, 2H, ArH, $J = 8.7$ Hz), 7.56 (d, 2H, ArH, $J = 8.7$ Hz), 7.81 (s, 1H, CH), 7.96 (s, 1H, NH), 8.21 (s, 1H, NH), 11.45 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): 55.7, 114.2, 127.2, 129.4, 142.5, 161.6, 177.9 ppm; HR-MS (ESI): (C₉H₁₁N₃OS) m/z (Calcd.) = 209.2700 Da; m/z (Obs.) = 209.2602 Da.

5-(p-Tolyl)-1,2,4-triazolidine-3-thione (3h): Product white crystalline, FT-IR: ν 3421 (NH stretching), 3251 (NH stretching), 3141 (CH stretching), 1589 (C=C stretching), 1547, 1458, 1359, 1301, 1248 (C=S stretching), 1089, 957, 816, 624, 511 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 2.23 (s, 3H, CH₃), 7.31 (d, 2H, ArH, $J = 8.7$ Hz), 7.70 (d, 2H, ArH, $J = 8.4$ Hz), 7.94 (s, 1H, CH), 8.02 (s, 1H, NH), 8.16 (s, 1H, NH), 11.37 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): 23.6, 126.7, 125.6, 129.4, 139.5, 146.5 and 176.2 ppm; HR-MS(ESI): (C₉H₁₁N₃S) m/z (Calcd.) = 193.2756 Da; m/z (Obs.) = 193.5152 Da.

5-(4-Nitrophenyl)-1,2,4-triazolidine-3-thione (3j): Product yellow solid, FT-IR: ν 3341 (NH stretching), 3145 (NH stretching), 2983 (CH stretching), 1589 (C=C stretching), 1539, 1441, 1391, 1271 (C=S stretching), 1194, 1071, 1002, 923, 855, 692, 508 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 7.53 (d, 2H, ArH, $J = 6.9$ Hz), 7.76 (d, 2H, ArH, $J = 6.9$ Hz), 8.02 (s, 1H, CH), 8.07 (s, 1H, NH), 8.32 (s, 1H, NH), 11.48 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): 127.7, 128.5, 132.8, 134.2, 142.8 and 179.7 ppm; ESI-MS:(C₈H₈N₄O₂S) m/z (Calcd.) = 224.2442 Da; m/z (Obs.) = 225.8140 Da.

5-(2-Hydroxyphenyl)-1,2,4-triazolidine-3-thione (3n): Product white crystalline, FT-IR: ν 3444 (NH stretching), 3334 (NH stretching), 3165 (CH stretching), 2987, 1646 (C=C stretching), 1535, 1472, 1361, 1282 (C=S stretching), 1202, 1119, 1045, 945, 826, 758, 621, 521 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 6.79 (t, 2H, ArH, $J = 9$ Hz), 7.24 (s, 1H, CH), 7.88 (m, 2H, CH), 8.21 (s, 1H, NH), 8.29 (s, 1H, NH), 9.94 (s, 1H, OH), 11.46 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): 115.2, 118.5, 121.3, 125.5, 132.3, 140.0, 154.4 and 176.0 ppm; HR-MS (ESI): (C₈H₉N₃OS) m/z (Calcd.) = 195.2451 Da; m/z (Obs.) = 195.1021 Da.

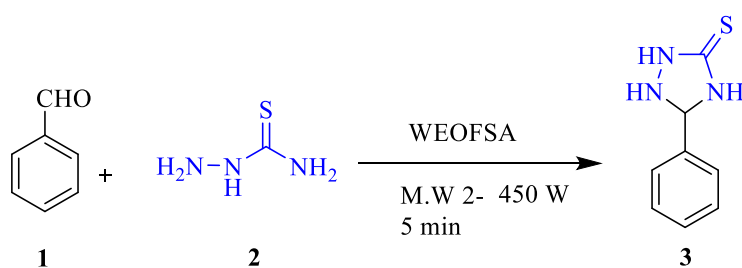
1,2,4-Triazospiroheptane-3-thione (5b): Product white crystalline, FT-IR: ν 3381 (NH stretching), 3217 (NH stretching), 2946 (NH stretching), 1589 (C=C stretching), 1254 (C=S stretching), 1074, 856, 832 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 1.49-1.52 (m, 4H, CH₂), 1.61 (d, 2H, $J = 6$ Hz), 2.37-2.43 (m, 2H), 2.45-2.48 (s, 2H, CH₂), 7.58 (s, 1H, NH), 8.03 (s, 1H, NH), 9.68 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): 29.0, 32.2, 34.8, 35.4, 41.4, 44.0, 44.2, 44.4, 44.6, 44.8, 45.0, 45.2, 164.4, 183.6 ppm; HR-MS (ESI):(C₈H₁₅N₃S) m/z (Calcd.) = 185.2901 Da; m/z (Obs.) = 186.0830 Da.

5'-Thioxospiro[indoline-3,3'-[1,2,4]-triazolidin]-2-one (5c): Product Yellow solid, FT-IR: ν 3389 (NH stretching), 3274 (NH stretching), 3169, 1592, 1514, 1452, 1368, 1322, 1249 (C=S stretching), 1049, 895, 739, 584 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 6.83 (d, 1H, ArH, $J = 7.8$ Hz), 7.21 (t, 1H, ArH, $J = 7.5$ Hz), 7.42 (t, 1H, ArH, $J = 6.9$ Hz), 7.72 (d, 1H, ArH, $J = 7.5$ Hz), 8.29 (s, 1H, NH), 9.32 (s, 1H, NH), 11.81 (s, 1H, NH), 12.63 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): 111.5, 120.5, 121.4, 122.9, 131.7, 132.5, 142.8, 163.1, 179.2 ppm; HR-MS(ESI): (C₉H₈N₄OS) m/z (Calcd.) = 220.0401 Da; m/z (Obs.) = 220.0131 Da.

1,2,4-Triazospirooctane-3-thione (5d): Product white crystalline, FT-IR: ν 3434 (NH stretching), 2945 (NH stretching), 2856 (NH stretching), 1587 (C=C stretching), 1273 (C=S stretching), 1010 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 1.45-1.47 (t, 2H, $J = 6$ Hz), 1.58-1.59 (m, 4H), 1.72-1.82 (m, 4H), 2.33-2.45 (m, 4H), 6.50 (s, 1H, NH), 7.32 (s, 1H, NH), 8.57 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): 17.5, 27.4, 38.8, 72.8 and 184.2 ppm; HR-MS(ESI): (C₉H₁₇N₃S) m/z (Calcd.) = 199.3684 Da; m/z (Obs.) = 199.4061 Da.

3. Results and Discussions

Researchers from other laboratories and our own group described various novel agro-waste based solvent media for alternative greener and facile synthesis of various important organic transformations. In continuation of our effort to develop greener catalytic media, herein we have developed straightforward efficient, greener, inexpensive and high yielding protocol for the one-pot synthesis of 5-aryl-1,2,4-triazolidine-3-thione catalyzed by novel agro-waste WEOFSA is reported. Firstly, water extract of orange fruit shell ash is prepared by agro-waste of orange shells collected from the local; the shell is washed with distilled water, dried, and followed direct burning to ash using Bunsen flame. The burnt ash is soaked in double distilled water about 2 h and filtered, the resulted light brown colored water extract termed as a WEOFSA. The pH of the extract solution found to be 10.12. To explore the extracted WEOFSA as a catalytic solvent media for the synthesis of thiones is attempted. Initially started with 1 mmol scale reaction of benzaldehyde with thiosemicarbazide as a model reaction in presence of WEOFSA under stirring at room temperature afford target product with 80% yield in 180 min (Scheme 1).



Scheme 1. Synthesis of 5-aryl-1,2,4-triazolidine-3-thiones

This preliminary model reaction indicated the reaction between aryl aldehyde with thiosemicarbazide proceed smoothly in the absence of organic solvent and catalyst. Further to examine the role of the agro-waste extract media and minimal volume required for the reaction, a series of reactions set-up (Table 1) and carried out in a model reaction in the absence of catalyst, and surprisingly no product separation observed even after 10 min of irradiation (S. No 1, Table1). Hence, it is confirmed that, the reaction required catalyst for the condensation followed by cyclization to form a desired product. For the minimum dose of solvent media required for the reaction, a model reaction chosen under optimized microwave irradiation power (450 W) with varied volume of WEOFSA by 0.5 mL interval from 1 mL to 4 mL in a separate reaction under microwave irradiation of 6 min. The percentage product isolation with respect to change in agro-waste solvent media volume in mL is tabulated in Table 1. The optimized volume from experiment data reveled that, for 1 mmol reaction required 3.5 mL of WEOFSA, the below volumes (3.0, 2.5, 2.0...1 mL) gave lesser product yield, optimized volume 3.5 mL gave highest product isolation, and next volume higher (4.0 mL) ended with no change in product yield isolation.

Table 1. Optimization of WEOFSA in a model reaction

S. No	WEOFSA (mL)	Time (min)	Yield (%)
1	-	6-30	ND
2	1.0	6	30
3	1.5	6	32
4	2.0	6	44
5	2.5	6	59
6	3.0	6	61
7	3.5	6	93
8	4.0	6	93

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To study the effect of temperature on the rate of the reaction as well as yield of the product, we carried out model reaction in a ultrasound and microwave irradiation using WEOFSA. It is observed, the reaction under microwave and ultrasound assisted proceeds reaction very smoothly with increased yield isolation in shorter reaction time compared to the conventional method (Table 2). The optimized reaction method revealed that, microwave accelerated reaction go product formation very faster as compared to other two methods (S. No. 1 and 2, Table 2). To check the required optimum microwave power for the reaction, we have carried

Table 2. Optimization of different reaction methods

S. No	Methods	Time (min)	Yield (%)
1	Stirring@ RT	60-180	75-80
2	Ultra-sonication	30-40	79-81
3	Microwave irradiation	2-6	90-93

out reaction in a model reaction with optimized agro-waste media (3.5 mL) by varying microwave power available in a custom-made microwave oven with a measure of temperature after each power irradiation (Table 3). The optimized microwave power at 450W with exposure time of 6 min gave highest product isolation compared to low power of 100, 180 and 300 W. Further increased power 600 W showed no change in the product yield isolation or reaction time. Hence, the optimized microwave power for the 5-aryl-1,2,4-triazolidine-3-thiones synthesis used in the present method is 450 W with exposure time of 6 min.

Table 3. Optimization of microwave power

S. No.	Microwave Power (W)	Temperature generated (°C)	Time (min)	Yield (%)
1	100	78	6	20
2	180	96	6	32
3	300	104	6	85
4	450	130	6	93
5	600	142	6	93

To evaluate the present method substrate scope, a variety of substituted aromatic aldehydes are reacted with thiosemicarbazide under optimized reaction condition to afford corresponding 5-aryl-1,2,4-triazolidine-3-thiones in good to excellent yield Table 4. Aromatic aldehyde bearing electron donating **3h** and **3o**, and withdrawing groups **3b**, **3c** and **3d** were converted into their corresponding triazolidine-3-thiones with excellent yields of 87-93%. From the experimental results we conclude that, there is no measurable EDG (electron donating) and EWG (electron withdrawing) substituent role on the rate of reaction and isolation of yield, and most of the reaction completed in a shorter reaction time with negligible difference in their product yield. It is worth to share our experience to this reaction that, the reaction work-up found easier and it involves simple filtration gave pure targeted product are listed in Table 4.

Table 4. Synthesis of 5-aryl-1,2,4-triazolidine-3-thiones and physical data

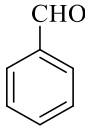
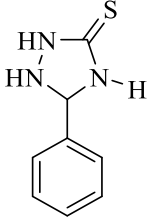
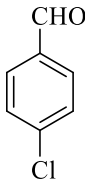
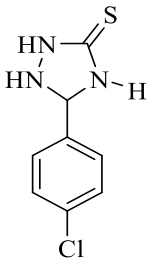
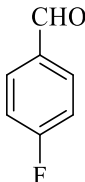
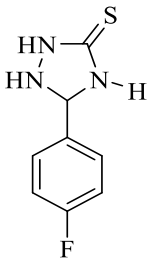
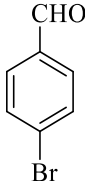
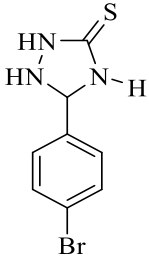
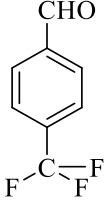
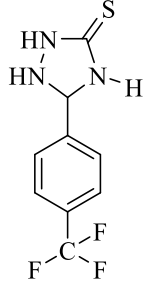
Entry	Aldehyde	Product	Time (min)	Yield (%)	m.p (°C)	Colour
1	 1	 3a	4	93	184-186	White solid
2	 	 3b	3	89	206-208	White solid
3	 	 3c	6	90	172-174	White solid
4	 	 3d	4	88	202-204	White solid
5	 	 3e	5	82	162-164	White solid

Table 4. continued..

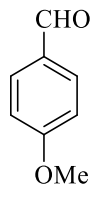
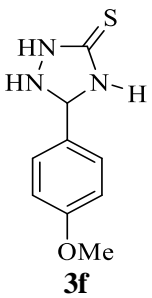
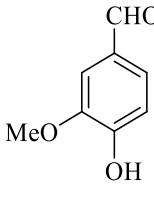
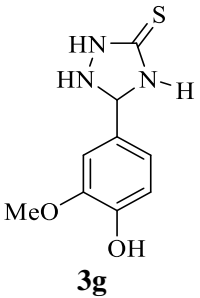
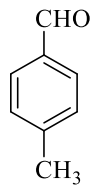
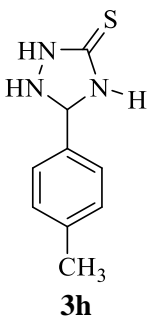
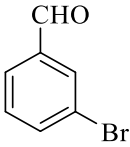
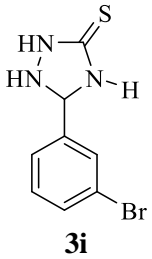
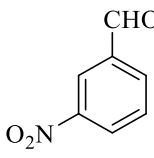
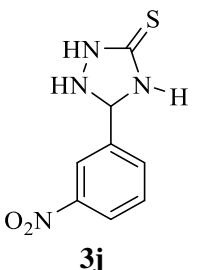
Entry	Aldehyde	Product	Time (min)	Yield (%)	m.p (°C)	Colour
6		 3f	4	79	154-156	White solid
7		 3g	4	83	196-198	White solid
8		 3h	4	88	174-176	White solid
9		 3i	3	88	172-174	White solid
10		 3j	2	90	202-204	Pale yellow solid

Table 4. continued..

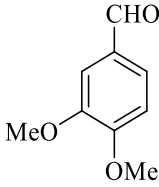
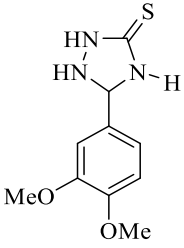
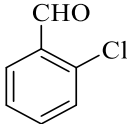
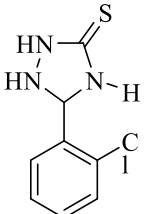
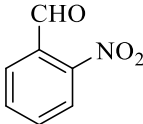
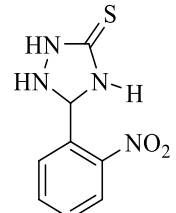
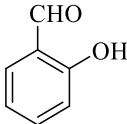
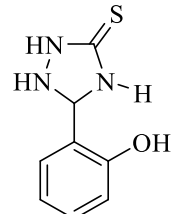
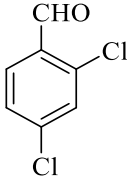
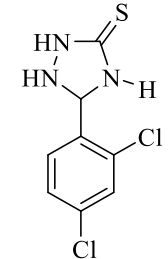
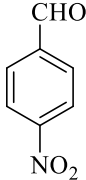
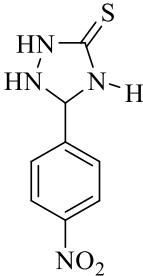
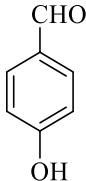
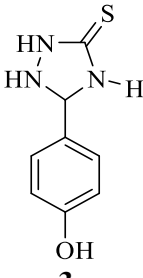
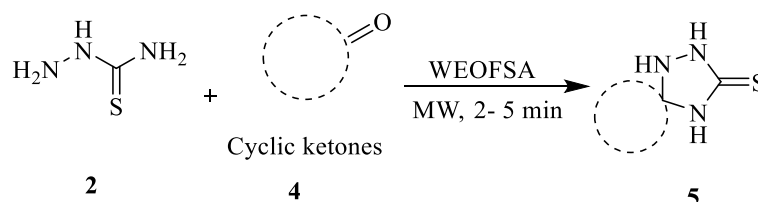
Entry	Aldehyde	Product	Time (min)	Yield (%)	m.p (°C)	Colour
11		 3k	3	91	226-228	White solid
12		 3l	4	81	196-198	White solid
13		 3m	3	76	198-200	Pale yellow solid
14		 3n	5	84	218-220	White solid
15		 3o	5	81	232-234	White solid

Table 4. continued..

Entry	Aldehyde	Product	Time (min)	Yield (%)	m.p (°C)	Colour
16		 3p	4	86	224-226	Yellow solid
17		 3q	5	82	220-222	White solid

Excited by the present method, we further extended to substrate cyclic ketone in place of aromatic aldehyde in a model reaction with all optimized above reaction condition followed (Scheme 2). Notably, the reaction proceeded very smoothly with product isolated in excellent yield (Table 5). It is worth to



Scheme 2. Synthesis of 1,2,4-triazospiro-3-thiones

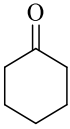
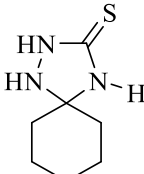
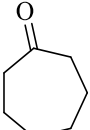
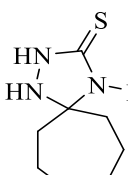
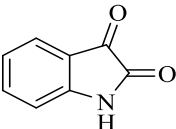
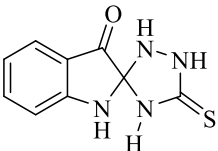
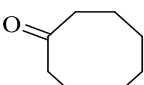
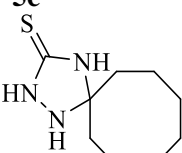
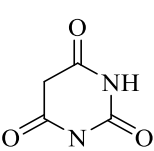
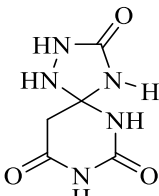
state that, the substituted derivatives captivated spirocentre *via* simple green protocol transformation gave to access bicyclic units in a highly efficient manner. The experimental observation of the above studies clearly indicated that, the present agro-waste catalyzed reaction can be applied to build library of 1,2,4-triazolidine-3-thiones and 1,2,4-triazaspiro[5.4]-hexanone-3-thione scaffolds.

The molecular structure and purity of the synthesized compounds are established by using various spectroscopic techniques. To analyze compound 5-aryl-1,2,4-triazolidine-3-thiones **3c** (Table 4) taken for complete spectral analysis. The FT-IR spectrum of **3c** showed prominent stretching bands at 3286 and 3185 cm^{-1} are due to the NH stretching, band at 1686 cm^{-1} due to C=C and band at 1227 cm^{-1} is due to C=S (Figure S1); $^1\text{H-NMR}$ (δ) in $\text{DMSO-}d_6$ showed different peaks at 7.19-7.23 doublet due to 2H of ArH, multiplet at 7.83-7.86 is due to 2H of ArH, singlet at 8.00 due to 1H of CH, singlets at 8.00, 8.17 and 11.40 due to NH protons (Figure S2); $^{13}\text{C-NMR}$: 116.0, 116.2, 129.9, 130.0, 131.3, 141.8, 162.2, 164.7 and 178.5 ppm (Figure S3) and mass spectrometry confirm the molecular weight m/z (Calcd.) = 197.0943 Da; m/z (Obs.) = 196.0371 Da (Figure S4).

The formation of a novel 1,2,4-triazaspiro[5.4]hexanone-3-thione **5a** (Table 5) was confirmed by various spectral techniques. FT-IR shows prominent bands at 3380, 3216 and 3145 cm^{-1} are due to the NH stretching, band at 2940 cm^{-1} CH stretching, band at 1245 cm^{-1} is due to C=S (Figure S9); $^1\text{H-}$

NMR (δ) in DMSO- d_6 shows different peaks at δ 1.52-1.58 multiplet due to 6H, 2.17-2.20 multiplet due to 2H, $-\text{CH}_2$, peak at 2.37-2.48 doublet due to 2H, $-\text{CH}_2$, peaks at 7.49, 7.94 and at 10.13 singlet due to NH protons (Figure S10); ^{13}C -NMR shows prominent peaks in DMSO- d_6 solvent are 25.5, 26.2, 27.4, 27.6, 35.4, 39.4, 39.6, 39.8, 40.0, 40.2, 40.4, 40.6, 157.4 and 179.0 ppm (Figure S11); HR-MS(ESI): m/z (Calcd.) = 171.2601 Da; m/z (Obs.) = 172.0887 $[\text{M}+\text{H}]^+$ Da (Figure S12).

Table 5. Synthesis of 5-aryl-1,2,4-triazospiro-3-thiones and its physical constants

Entry	Cyclic ketones	Product	Time (min)	Yield (%)	m.p ($^{\circ}\text{C}$)	Colour
1	 4a	 5a	5	86	156-158	White solid
2	 4b	 5b	6	79	145-147	White solid
3	 4c	 5c	6	88	250-252	Yellow solid
4	 4d	 5d	6	78	-	White solid
5	 4e	 5e	8	84	243-245	Pale yellow solid

Further, we compared present agro-waste catalytic solvent media demonstrated with various literature reported methods for the 5-aryl-1,2,4-triazolidine-3-thiones and 5-aryl-1,2,4-triazospiro-3-thiones synthesis. Namely, expensive magnetically separable heterogeneous catalyst $\text{CoFe}_2\text{O}_4@\text{SiO}_2$ employed in the synthesis and reaction completed in faster manner gave 98% yield (entry 1, Table 6)⁵³. Reaction carried out in a 25% ethanol under room temperature stirring condition and completed in 15 min afford 95% yield (entry 2, Table 6)⁵⁴. Reaction in the presence of ionic liquid $[(\text{Py})_2\text{SO}][\text{HSO}_4]$

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was carried out and taken longer reaction time of about 60 min with 75% yield (entry 3, Table 6)⁵⁵. Another research group reported PEG-400 accelerated synthesis required elevated temperature for about 12 min to complete the reaction (entry 4, Table 6)^{42,43}. Synthesis catalyzed in 80% of CH₃COOH required 30 min for the conversion of all reactants into product with 90% yield (entry 5, Table 6)⁵⁶. The multicomponent reaction in one-pot in the presence of ionic liquid (glycine nitrate) required 4 h for the completion of the reaction and the method took long reaction time compared above discussed methods with 88% yield (entry 6, Table 6)⁵⁷. The sulfamic acid catalyzed reaction afford product after the reflux temperature of reactants for about 30 min (entry 7, Table 6)⁵⁸. So, it is revealed that, there are number of reported protocols suffering from various limitations, to overcome some of these, we have demonstrated a simple, inexpensive and greener protocol for the synthesis of valuable 1,2,4-triazolidine-3-thiones derivatives (entry 8, Table 6).

Table 6. Comparison of reported with present method

Entry	Catalyst	Time (min)	Yield (%)
1	CoFe ₂ O ₄ @SiO ₂ @ r.t	10	98
2	25% Ethanol@ r.t	15	95
3	[(Py) ₂ SO][HSO ₄]	60	75
4	PEG-400@80 °C	12	97
5	80% CH ₃ COOH	30	90
6	Glycinenitrate@80 °C	240	88
7	Sulfamic acid, Ethanol, Reflux	30	92
8	WEOFSA, MW 450 W (Present method)	2-5	93

4. Conclusion

The present method is successfully demonstrated the synthesis of 5-aryl-1,2,4-triazolidine-3-thiones and 5-aryl-1,2,4-triazospiro-3-thiones in the presence of agro-waste derived WEOFSA as greener catalytic media. The developed method is added advantages like not required external base, inexpensive, environment friendly, moderate to excellent yield isolation in a simple method. The isolated product is found chromatographically pure and are analyzed by using various spectroscopic techniques FT-IR, ¹H-, ¹³C-NMR and HR-MS.

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Supporting information

Supporting information accompanies this paper on <http://www.acgpubs.org/journal/organic-communications>

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