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MICROWAVE ASSISTED SOLVENT FREE SYNTHESIS OF SCHIFF BASE OF FUNCTIONALIZED1,3,4-THIADIAZOLE IN IONIC LIQUID

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Abstract

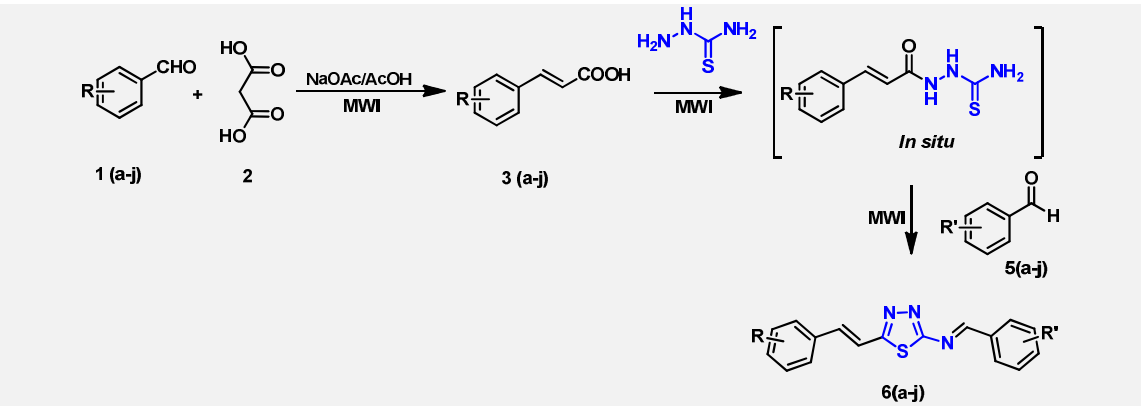
A facile an eco-friendly microwave assisted synthesis of Schiff base of functionalized 1, 3, 4-thiadiazole starting from easily available reactant molecule under solvent free condition. We synthesized substituted unsaturated aromatic carboxylic acid **3** from aldehyde with malonic acid catalyzed by sodium acetate, further multicomponent cyclization followed by Schiff base formation **6a-j**using thiosemicarbazide and aldehydes, solvent free catalyzed by ionic liquid [Et_3N H_2SO_4] under microwave irradiation method.

Keywords: Ionic Liquid, Solvent free, Acid, Thiosemicarbazide, 1, 3, 4-thiadiazol, Microwave assisted reaction

Introduction

Nitrogen and Sulfur containing heterocyclic compound particular 1,3,4-thiadiazole and its derivatives bear a great interest of researchers owing to their great pharmaceutical and industrial fields. Thiadiazole scaffold and derivatives possessed a wide range of therapeutic activities such as anti-microbial[iii], anti-fungal[iv], anti-leshmanial[v], anti-mycobacterial[vi], analgesic, anti-inflammatory[viii] anti-depressant[viii], anti-psychotic[ix] and anti-convulsant [ix,x]. 1,3,4 - thiadiazole derivatives exhibited interesting in *vitro*[xi-xiii] and in *vivo*[xiv-xvii]anti-tumor activities. Inhibition of DNA and RNA syntheses specifically without appreciably affecting protein synthesis[xviii], inhibition of carbonic anhydrase[xix], phosphodiesterase-7 [xx] histone deacetylase [xxi] or as adenosine A3 receptor antagonists[xxii]. Analgesic, Anti-inflammatory and anti-bacterial activity of Schiff Bases of 2-amino-5-aryl-1,3,4-thiadiazoles[xxiii].In past, some 1,3,4-thiadiazole and its derivatives has been studied and investigated[xxiv-xxx].

The remarkable properties of Ionic Liquids Room-temperature ILs, organic salts that are liquid below 100˚C, have received considerable attention as substitutes for volatile organic solvents,nonflammable, non-volatile and recyclable, solvating potential[xxxi]thermal stability[xxxii] and their tunable properties by suitable choices of cations and anions[xxxiii]ILs as they simultaneously possess the proton acidity and the characteristic properties of an ionic liquid[xxxiv, xxxv].



Scheme 1. Synthesis of carboxylic acid and substituted 1,3,4-thiadiazol-2-schiff base analogues

The use of microwave energy is one of the eco-friendly methods to accelerate the organic reactions and having a number of advantages such as short reaction time, cleaner reaction profile, no side product and high yield[xxxvi] few earlier our research work[xxxvii-xl] Here, we wish to mention to synthesis of novel 4-((E)-2-(5-((E)-benzylideneamino)-1,3,4-thiadiazol-2-yl)vinyl)-2-methoxyphenol **6a-j** (**Table**4), (Scheme1) in good yieldsand in continuation of our earlier research work[xli,xlii] to exploring this research as green approach for the synthesis of Schiff base of 2-amino 1,3,4-thiadiazole containing Cinnamic and Ferulic acid solvent free condition, under microwave irradiation method (Figure **2**).

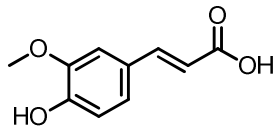
Materials and Method

The chemicals with high purity, high purity were purchased from Alfa Aesar, playing important role in the present synthesis of functionalized 1,3,4 -thiadiazole starting from easily available Cinnamic acid, aromatic acid, malonic acid and various aromatic aldehyde, amine in presence of ionic liquid. Melting points of synthesized products were recorded on OptiMELT digital melting point apparatus and were uncorrected. The microwave reactions were carried out in MicroSYNTH Lab station of Ethusi Milestone. The Ionic Liquid [Et_3N H_2SO_4] is prepared using reported method [xliii]. An appropriate molar proportion of starting materials was taken and the protocols of standard techniques were followed for the in *situ*multi-component synthesis of acid containing Schiff base of 2- amino 1,3,4-thiadiazole (Figure **2**). Melting points of synthesized product were recorded with the help of capillary tube and thermometer apparatus and were uncorrected. The IR spectra were recorded on a FT-IR (Bruker). ^{1}H NMR spectra were recorded on a 400 MHz Bruker spectrometer in solvent DMSO-d_6 and $CDCl_3$ as part per million (ppm) downfield from a tetra methyl silane (TMS) internal standard.

General Procedure for the synthesis of Compounds 3(a-j)

In a small round bottom flask take Malonic acid(0.073 mol), sodium acetate and acetic acid (0.073 mol) (1:1) were mechanically stirredto homogeneous mixing (sticky solid). To this solution substituted aromatic aldehyde (0.073 mol) was added and solution mixture were irradiated with microwave synthesizer at power 600watt at 40°C for appropriate time (TLC check) as shown in**Table**2. At this stage reaction mixture changes to pale yellow coloured viscous liquid. Obtained viscous liquid quickly solidified at room temperature to offer solid. The products were purfied by recrystalisation with hot ethanol and little acetic acid mixture,yield: (90-96%)

3-(3-Hydroxy-4-methoxy-phenyl)-acrylic acid / Ferulic acid (3):

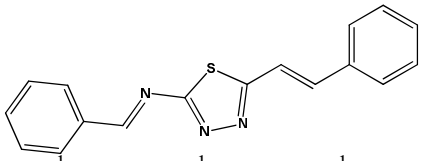


Yield: 96%; Melting point:170–172 °C; IR (FTIR): 1062 cm^{-1}, 1492 cm^{-1}, 1628 cm^{-1}, 2802 cm^{-1}, 2836 cm^{-1}, 2846 cm^{-1}, 2916 cm^{-1}, 2932 cm^{-1}, 2971 cm^{-1}, 3027 cm^{-1}, 3262 cm^{-1} ;^{1}H NMR (200 MHz, DMSO-d6) δ 12.16 (brs, 1H), 9.14 (brs, 1H), 7.41 (dd, J = 15.6, 6.6 Hz, 1H), 6.97 (m, 3H), 6.21 (dd, J = 15.7, 6.7 Hz, 1H), 3.78 ppm (s, 3H); ^{13}C NMR (75MHz, DMSO-d_6) 168.27, 150.24, 147.08, 144.66, 127.52, 121.45, 116.69, 114.54, 112.34, 55.97.; Formula: $C_{10}H_{10}O_4$; MS (ESI):*m/z*(%) 195.06 (M+H).; HRMS-EI: found: 194.0500., calculated: 194.0570.

General Procedure for the synthesis of Compounds 6(a-j)

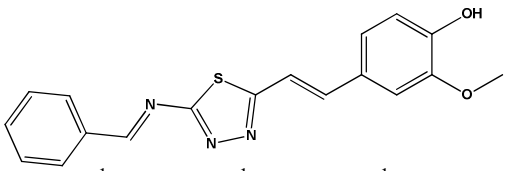
A mixture of substituted aromatic carboxylic acid (0.1mole), Thiosemicarbazide (0.1mole)were transfer to [Et_3N H_2SO_4]ILs (20 mole %) and catalytic amount of acetic anhydride and finally irradiated under microwave synthesizer at power 600 watt and 70°C (TLC) for appropriate time (**Table 4**).To this hot reaction mixture Aromatic aldehyde (0.1 mole) was added and reaction mixture exposed to irradiation for the appropriate time (**Table4**). Progress of the reaction was monitored by thin layer chromatography (TLC).On completion of reaction was extracted with ethyl acetate / Et_2O, the etheral layer was concentrated by rotary evaporator and the crude productswere purified by the column chromatography on silica gel (60×120 mesh) using a mixture of petroleum ether and ethyl acetate as eluent to offered pure products **6**(89-96%):

(E)-N-benzylidene-5-((E)-styryl)-1,3,4-thiadiazol-2-amine (6a):



Yield: 96%; IR (FTIR): 1042 cm^{-1}, 1471 cm^{-1}, 1543 cm^{-1}, 1562 cm^{-1}, 1627 cm^{-1}, 2803 cm^{-1}, 2830 cm^{-1}, 2842 cm^{-1}, 2926 cm^{-1}, 2930 cm^{-1}, 2971 cm^{-1}, 3024 cm^{-1}, 3077 cm^{-1}, 3262 cm^{-1} ;^{1}H NMR (200 MHz, DMSO-d6) δ 6.96 (2H, *dd*), 8.35 (1H, s), 7.61(2H, *d*), 7.31-7.43 (3H, m), 7.53-7.82(5H, m); ^{13}C NMR (75MHz, DMSO-d_6) 6.94, 6.98, 7.32, 7.41,7.41,7.61,7.61, 7.53, 7.53, 7.53, 7.84, 7.84, 8.36.; Formula: $C_{17}H_{13}N_3S$; MS (ESI):*m/z*(%) 292.08 (M+H).; HRMS-EI: found: 291.0780, calculated: 291.0830.

4-((E)-2-(5-((E)-benzylideneamino)-1,3,4-thiadiazol-2-yl)vinyl)-2-methoxyphenol (6j):



Yield: 96%; IR (FTIR): 1042 cm^{-1}, 1471 cm^{-1}, 1546 cm^{-1}, 1562 cm^{-1}, 1629 cm^{-1}, 2802 cm^{-1}, 2832 cm^{-1}, 2843 cm^{-1}, 2928 cm^{-1}, 2933 cm^{-1}, 2972 cm^{-1}, 3026 cm^{-1}, 3079 cm^{-1}, 3261 cm^{-1};

^{1}H NMR (200 MHz, DMSO-d6) δ 6.97 (2H, *dd*), 8.35 (1H, s), 7.16 (1H, s), 7.12 (1H, *d*), 6.98 (1H, *d*), 5.35 (1H, s), 3.82 (3H, s), 7.51-7.85(5H, m);^{13}C NMR (75MHz, DMSO-d_6) 3.84, 5.36, 6.96, 6.98, 6.99, 7.13, 7.16, 7.52,7.52, 7.52, 7.83, 7.84, 8.37.; Formula: $C_{18}H_{15}N_3O_2S$; MS (ESI):*m/z*(%) 338.08 (M+H).; HRMS-EI: found: 337.0794, calculated: 337.0854

Results and Discussion

Reaction condition optimizations were done by using model reaction of Malonic acid (0.073 mol) and benzaldehyde (0.073 mol) were taken in small RBFwith different catalyst such as Et_3N, Pyridine, Piperidine, NaOAc, $NaHCO_3$ and mixture of NaOAc:AcOH(1:1)buffer solution under microwave irradiation power at 600 watt and 40°C (microwave synthesizer)**Table1**. Herein we observed that in sodium acetate gave better yield at 18 min (**Table1**. entry 5).If weused sodium acetate-acetic acid (1:1), the yield of product elevated to 96% in less time of reaction (**Table**1; Entry 6). For further reaction of synthesis of derivatisation of unsaturated aromatic carboxylic acid sodium acetate-acetic acid (1:1) were used as standard reaction condition.

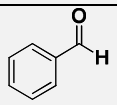
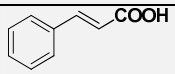
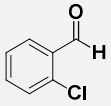
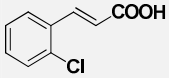
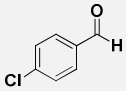
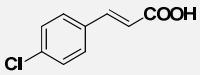
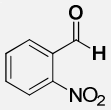
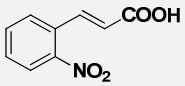
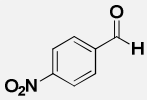
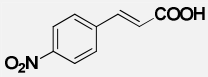
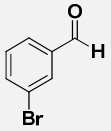
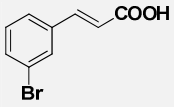
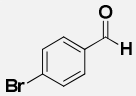
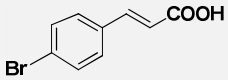
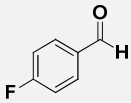
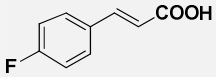
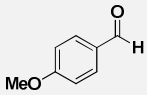
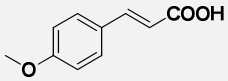
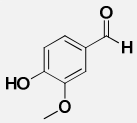
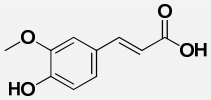
Secondly, we synthesizedthiadiazoles using MWI techniques. The various series of reactions were performed to obtained optimized reaction condition with respect to solvent and ionic liquid catalyst. We screened various solvent such as MeOH, EtOH, Tert-BuOH, Iso-pr.alcohol, H_2O,THF, Toluene, CH_3CN and also solvent free condition**Table3** for the model multicomponent reaction of Cinnamic acid or Ferulic acid (0.1mole), Thiosemicarbazide (0.1mole), Aromatic aldehyde (0.1 mole) in [Et_3N H_2SO_4] ILs (20 mole %) and catalytic amount of acetic anhydride were heatedunder microwave irradiation power at450 watt and70-80°Cfor the appropriate time (**Table3**). Herein, we observed that at solvent free condition gave good to excellent yield with increasing temperature at 60 to 90° C(**Table3** entry 9-12). Thus, all the derivatives of Ferulic and Cinnamic acids were synthesized using solvent free condition under microwave irradiation power at 450 watt and 80 °C in [Et_3N H_2SO_4] ILs (20 mole %) at 6-7 min (**Table4**). Progress of the reaction was monitored on thin layer chromatography (TLC). After completion of reaction the reaction mixture was extracted with ethyl acetate / Et_2O, the etheral layer was concentrated by rotary evaporator and the crude product was purified by the preparative thin-layer chromatography on silica gel using a mixture of petroleum ether and ethyl acetate as eluent to provide the corresponding pure products **6** (89-96%)Table**4**.

Table 1. Optimization of catalyst for the synthesis of compound **3a**

Entry	Catalyst	MWI Time (min)			Yield[a] (%)		
		I	II	III	I	II	III
1	Without	10	12	25	00	00	00
2	Et_3N	10	12	22	00	40	40
3	Pyridine	10	12	20	00	48	50
4	Piperidine	10	12	20	00	35	40
5	NaOAc	10	12	18	00	52	68
6	NaOAc :AcOH (1:1)	10	12	14	00	79	96
7	$NaHCO_3$	10	12	15	00	39	46

[a]*Reaction Condition:*Malonic acid (0.073 mol), sodium acetate and acetic acid (0.073 mol) (1:1), substituted aromatic aldehyde (0.073 mol) microwave synthesizer power at 600 watt and 40 ° C (TLC).

Table 2. Microwave assisted synthesis of compound **3(a-j):**

Sr.	Aldehyde	Reactant	Product	Time (min)	Yield[a] (%)
1		Malonic acid		14	96
2		Malonic acid		14	93
3		Malonic acid		14	93
4		Malonic acid		14	90
5		Malonic acid		14	96
6		Malonic acid		15	92
7		Malonic acid		15	93
8		Malonic acid		14	92
9		Malonic acid		14	94
10		Malonic acid		14	96

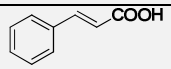
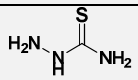
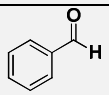
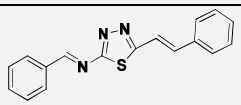
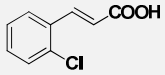
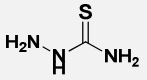
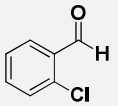
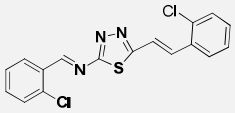
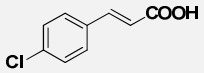
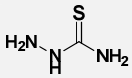
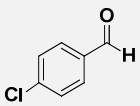
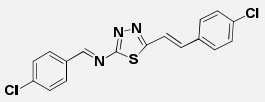
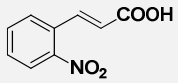
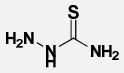
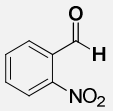
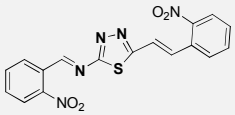
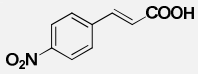
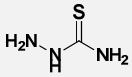
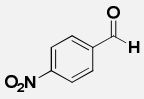
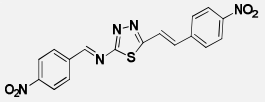
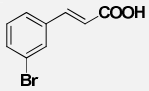
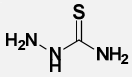
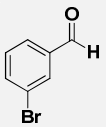
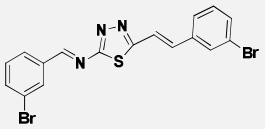
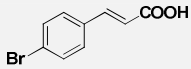
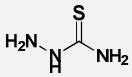
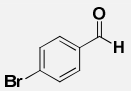
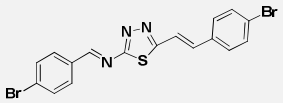
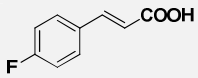
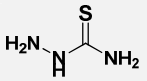
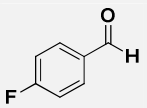
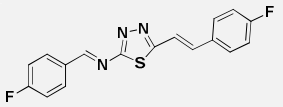
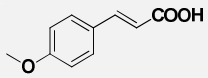
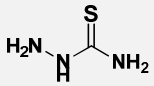
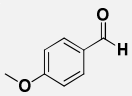
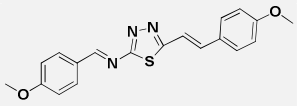
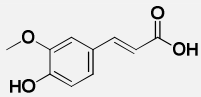
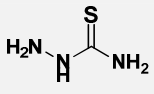
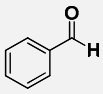
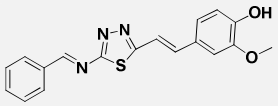
[a]***Reaction Condition:*** Malonic acid (0.073 mol), sodium acetate and acetic acid (0.073 mol) (1:1), substituted aromatic aldehyde (0.073 mol), microwave synthesizer power at 600 watt and 40°C (TLC); Yield : 90-96%

Table 3. Optimization of Solvent for the synthesis of compound **6**

Sr. no.	Solvent	Temperature (°C)	Yield[b] (%)
1.	MeOH	80	45
2.	EtOH	80	48
3.	*t*-BuOH	80	53
4.	*i*-Propyl alcohol	80	50
5.	H_2O	80	30
6.	THF	80	38
7.	Toluene	80	53
8.	CH_3CN	80	49
9.	Solvent free	40	50
10.	Solvent free	60	68
11.	Solvent free	70	82
12.	Solvent free	80	96

[b]*Reaction condition*: Cinnamic acid or Ferulic acid (0.1mole), Thiosemicarbazide (0.1mole) in [Et_3N H_2SO_4] ILs (20 mole %), Aromatic aldehyde (0.1 mole) and catalytic amount of acetic anhydride were irradiated under microwave synthesizer power at 450 watt and 80°C (TLC).

Table 4. Microwave assisted synthesis of compound **6** (a-j)**:**

Sr.	Reactant	Reactant	Reactant t	Product	Time (min)	Yield[b] (%)
1				 **(6a)**	6	96
2				 **(6b)**	6	90
3				 **(6c)**	6	89
4				 **(6d)**	6	96
5				 **(6e)**	6	96
6				 **(6f)**	7	90
7				 **(6g)**	7	89
8				 **(6h)**	6	89
9				 **(6i)**	6	96
10				 **(6j)**	6	96

[b]*Reaction condition*: Cinnamic acid or Ferulic acid (0.1mole), Thiosemicarbazide (0.1mole) in [Et_3N H_2SO_4] ILs (20 mole %), Aromatic aldehyde (0.1 mole) and catalytic amount of acetic anhydride were irradiated under microwave synthesizer power at 450 watt and 80°C (TLC).

Conclusion

We have successfully developed facile an eco-friendly synthesis of α,β-unsaturated aromatic carboxylic acid and 2-amino-1,3,4-thiadiazole schiffs base under the solvent free condition in Ionic Liquid (ILs) by microwaveirradiation technique. The shorter reaction time with good to excellent yield of the products increases significant importance of this method. Another considerable advantage is easily availablestaring chemicalswith cost effective. Further research is ongoing in our laboratory for thefacile and green synthesis of bioactive 'Nitrogen' and 'Sulfur' containing medicinally important heterocyclic compound and its derivative by environmentally benign protocols.

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