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Comparative study of one pot synthetic methods of 2-amino-1,3,4-thiadiazole

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ABSTRACT

Substituted Carboxylic acid condensed with Thiosemicarbazide to form 2-amino-5-substituted 1,3,4-Thiodiazole in various reaction conditions. Present work is comparative study of synthesis of 2-amino- 1, 3, 4-Thiodiazole with respect to yield, reaction time and reaction conditions. All products are characterized by spectral data and elemental analysis.

Keywords: Thiodiazole, Cyclisation, Comparative study.

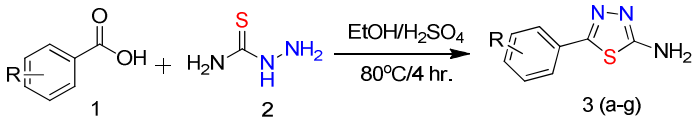
INTRODUCTION

Five membered heterocycles are well known for their biological properties. 1,3,4-Thiadiazole is well estabilished biologically active five membered heterocyclic compounds. Thiadiazole is a biologically identical to that of pyrimidine and oxadiazole and given the prevalence of pyrimidine in nature, it is not surprising that thiadiazole shown significant therapeutic potential properties, the sulfur atom of the thiadiazole imparts improved liposolubility and mesoionic nature reported as anti-parasitic, anti-convulsan and anti-coagulant[1], anti-microbial[2], anti-cancer[3], anti-inflammatory[4,5], anti-tubercular [6]. Various research study reports 1, 3, 4-Thiadiazole pharmacologically active as anti-fungal[7], diuretic[8] , anthelmintic activity[9], anti-tumor[10], anti-diabetic[11], anti-platelet [12], Several substituted thiadiazole being reported for their biological activity and due to its outstanding pharmacological importance several methods of synthesis of 1,3,4-thiadiazole investigated. Present study is comparison between various synthetic methods like from aromatic carboxylic acid with thiosemicarbazide to obtained thiadiazole and another well established method is synthesis of thiadiazole from aromatic/ aliphatic aldehydes and thiosemicarbazide. Present work is focused on aromatic carboxylic acids with thiosemicarbazides.

MATERIALS AND METHODS

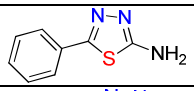
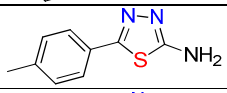
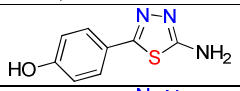
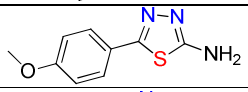
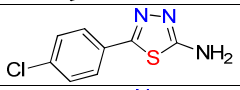
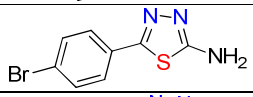
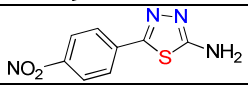
The melting points of all the compounds were determined in open head capillary and are uncorrected. The IR spectra of the compounds were recorded in the region of 4000-400 cm^{-1} by using KBr pallet on FT-IR Perkin spectrophotometer. H^1 NMR spectra were recorded on Bruker FT-NMR spectrophotometer with TMS as internal standard. The values of chemical shift are expressed in δ ppm as a unit. All the compounds were checked for purity by thin layer chromatography (TLC).

Reaction Scheme: 1.



Reaction Scheme 1. Selection of appropriate substituted aromatic carboxylic acid for the comparative study of synthesis of 2-amino-1, 3, 4-thiadiazole by conventional method using ethanol and catalytic conc. Sulfuric acid.

Table 1.

Comp.	Structure of Product	Molecular Formula	Molecular Weight	Melting point (°C)	Yield of product	IR (KBr) cm^{-1}	Elemental Analysis Found %
3a		$C_8H_7N_3S$	177	226-231°C	77%	3403,1514, 1057,680	C= 53.22;H=2.99 ,N=22.90 S=18.01
3b		$C_9H_9N_3S$	191	218-222°C	81%	3214,1500, 1180 1054, 693,	C=56.51;H=4.75; N=21.98;S=16.71
3c		$C_8H_7N_3OS$	193	138-142°C	74%	3394,3140,1480 1449,1051,704.	C=49.71;H3.63; N=21.74; O=8.214 S=16.58
3d		$C_9H_9N_3OS$	207	192-195°C	94%	3406,1525,1402, 1053.	C=52.14;H=4.29 N=20.26;O=7.73 S=15.45
3e		$C_8H_6ClN_3S$	211	229-232°C	79%	3340,1520,1050, 678	C=45.40;H=2.84;N=19.83 S=15.14; Cl=16.74
3f		$C_8H_6BrN_3S$	256	228-231°C	90%	3350,1531,1052, 688	C=37.52;H=2.37;N=16.41 S=12.51; Br=31.19
3g		$C_8H_6N_4O_2S$	222	258-261°C	74%	3410,1512, 1022,621	C=43.23;H=2.71;N=25.19 O=14.42;S=14.43

1. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Conventional method using Conc. Sulphuric acid [13]

An ethanolic solution of aromatic carboxylic acid (0.05mol) was added to aqueous solution of Thiosemicarbazide (0.05mole) with constant starring, few drop of conc. Sulphuric acid was added and heated for 4 hours at 80-90^{0}C, after completion of reaction (TLC), cool and poured to ice-cold water, basify with 10% Na_2CO_3 solution, filter, dried and recrystalised from suitable solvent.

NMR (δ ppm) (DMSO-D6): 7.11 (2H, s), 3.96 (3H, s), 6.87-6.92 (4H, m).
IR (KBr, cm-1): 3406 (NH stretching), 1525 (C-N stretch), 1053 (C-O stretch).
MS: (m/z): 209, 208, 207(bp).

2. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Conventional Method by using $POCl_3$. [14]

An equimolar amount of mixture of aromatic carboxylic acid (0.1mole) and thiosemicarbazide (0.1mole), in $POCl_3$ (excess), was heated for half an hour, water (90ml) was added and reaction mixture was reflux for another 3 hour, on completion of reaction (TLC), cool to room temperature and poured in ice-cold water, neutralized by saturated KOH solution, filter, dried and recrystalised from suitable solvent.

3. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Conventional method using $SOCl_2$[15]

Aromatic carboxylic acid (0.01mole) and thionyl chloride (0.012) was heated for 1 hour at 70^{0}C with calcium chloride guard tube. Thiosemicarbazide (0.012mole) was added to this hot reaction mixture and heated for another 4

hours at same temperature. On completion of reaction (TLC), basify with aqueous $NaHCO_3$, filter, dried and recrystalised from suitable solvent.

4. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Microwave method using Conc. Sulfuric acid [16]

A mixture of aromatic carboxylic acid (0.05 mole) and thiosemicarbazide (0.05mole) was dissolved in DMF (10ml) to this added conc. sulfuric acid (10 drop) and irradiated in microwave oven (480 watt) for 5 minutes. On completion of reaction (TLC) pour to ice cold water, filter, dried and recrystalised from suitable solvent.

5. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Microwave Method using $POCl_3$ [17]

A aromatic carboxylic acid (0.01mole), thiosemicarbazide(0.012mole) and catalytic amount of $POCl_3$ were mixed thoroughly and irradiated in microwave oven (600 Watt) for 5 minute on completion of reaction (TLC) pour to crushed ice and pH was adjust to alkaline, filter, dried and recrystalised from suitable solvent.

6. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by microwave method using $SOCl_2$ [18]

A mixture of aromatic carboxylic acid (0.01mole) and thionyl chloride (0.012mole) was irradiated at 300 watt for 1 minutes, upon cooling thiosemicarbazide (0.012 mole) was added and irradiated (480 watt) for 3 minute, on completion of reaction (TLC) poured to ice cold water, filter, dried and recrystalised from suitable solvent.

7. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by Microwave method using $MgSO_4$ as a catalyst [19]

A mixture of aromatic carboxylic acid (0.01mole) and thiosemicarbazide (0.01mole) was irradiated in presences of magnesium sulphate (2 gm) for 5 minutes (250 watt) (TLC), poured to ice cold water neutralized by sodium carbonate solution. Obtained solid was filter, dried and recrystalised from suitable solvent.

8. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine Neat reaction condition [20]

A mixture of aromatic carboxylic acid (0.1mole) and Thiosemicarbazide (0.1mole) was heated under solvent free condition for 3 hours then reaction mixture was cooled at room temperature. Water was added, filters, dried and recrystalised from suitable solvent.

9. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by ultrasonic irradiation[21]

The equimolar quantity of aromatic carboxylic acid (0.1 mol), thiosemicarbazide (0.1 mol) in 15ml of ethanol was added conc. Sulphuric acid (10 drops) and the reaction mixture was subjected to Ultrasonic irradiation for 30 minute at 80^0C, on completion of reaction (TLC) solid obtained was poured to ice cold water, filter, dried and recrystalised from suitable solvent.

10. Synthesis of 5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-amine by simple grinding method.

Aromatic carboxylic acid (0.01mole), Thiosemicarbazide (0.01 mole) and catalytic amount of H_2SO_4, grind in mortar and pestle for one and half hour, then stand at room temperature for another 4 hours with occasional grinding. On completion of reaction (TLC) cold water was added, basified with sodium hydroxide (10%), obtained solid was filtered, dried and recrystalised from suitable solvent.

RESULTS AND DISCUSSION

For comparative study of various synthetic methods of 2-amino-1, 3, 4-thiadiazole, series of reactions (Scheme 1; Table 1; Entry 3a-3g) were performed and *p*-Anisic acid (Table 1; Entry 4) were taken as a standard aromatic acid. Among various methods ten methods were taken which are very common. Our study underline the importance of sulfuric acid (Table 2; Entry 1) catalyzed conventional reaction is most efficient product obtaining method. Conversion of acid to acid chloride is key step when chlorinating reagents used. Unlike sulfuric acid, phosphorus oxychloride (Table 2; Entry 5) improve yield of reaction when used in microwave irradiation. Ultrasonic method and grinding methods (Table 2; Entry 9 and 10) gives 2-amino thiadiazole with comparative fewer yields.

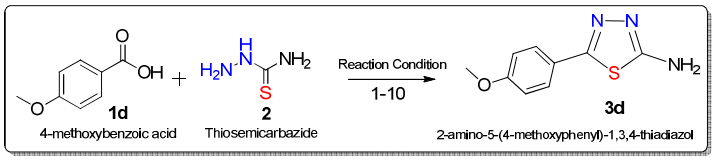
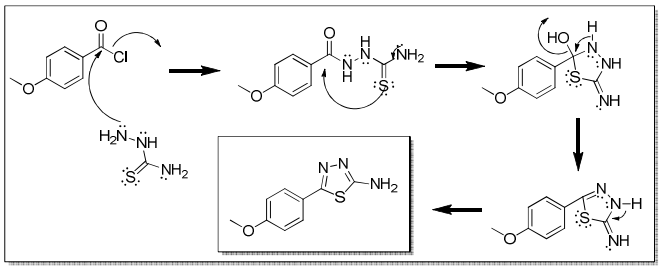


Table No. 2. Table of Reaction condition, Time, Temperature and Yield of Compounds

1	**3d**	4 Hrs./80° C	Ethanol as solvent and catalytic Conc. Sulfuric acid.	94%
2	**3d**	3-4 Hrs./ 90° C	$POCl_3$ heat, then reflux with water	86%
3	**3d**	4 Hrs./ 80° C	$SOCl_2$ heat, then reflux with water	70%
4	**3d**	5 Min./480 W	Conc. Sulfuric acid as catalyst./ MWI	78%
5	**3d**	5 Min./600 W	$POCl_3$ as catalyst./ MWI	90%
6	**3d**	3 Min./480 W	$SOCl_2$ as catalyst./ MWI	80%
7	**3d**	5 Min./250 W	$MgSO_4$ catalyst./ MWI	88%
8	**3d**	3 Hrs./Heat	Neat, No catalyst.	66%
9	**3d**	30 min./ 80° C	Ultrasound irradiation	61%
10	**3d**	1Hrs./ RT	Catalytic Conc. Sulfuric acid, Grinding technique	77%

Probable Mechanism of Reaction:



CONCLUSION

In conclusion, synthesis of 2-amino-1,3,4-thiadiazole by sulfuric acid conventional method is one of the efficient and simple way to obtained desire product, particularly in term of yield. Unlike any other general synthetic method, this study reports that Sulfuric acid catalyzed conventional way of synthesis of 2-amino-1, 3, 4-thiadiazole is more productive over sulfuric acid MWI method.

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