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Research Article

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Microwave Assisted Anhydride Catalyzed by Synthesis of 2-Amino-5-Aryl-1,3,4-Thiadiazoles

Jadhav SA, Dengle ST, Vaidya SR, Nagre HB

Department of Chemistry Vivekanand Arts Sardar Dalipsingh Commerce and Science College, Aurangabad, India

Abstract Cyclization of Thiosemicarbazide with substituted aromatic aldehyde over the hazardous reagent and catalyst for the synthesis of 2-amino, 5-aryl-1,3,4-thiadiazoles under microwave irradiation conditions. Screened a sample of a molecule under the conventional and microwave method. The expeditious reaction with good to excellent yield was obtained under the Microwave irradiation method. The synthesized compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR analysis.

Keywords Acetic anhydride, 2-amino-5-aryl-1,3,4-thiadiazoles, MWI technique.

Introduction

Five member heterocyclic compound containing Sulfur and Nitrogen hetero atoms such as azoles, thiazole, diazole in particular that 2-amino-1,3,4-thiadiazoles are well well-known biologically active compounds. Sulfur atom of the Thiadiazole imparts improved liposolubility and mesoionic nature (figure 1) reported as anti-parasitic, anti-convulsan and anti-coagulant [1], anti-microbial [2], anti-cancer [3], anti-inflammatory [4-5], anti-tubercular [6],anti-fungal [7], diuretic [8], anthelmintic activity [9], anti-tumor [10], anti-diabetic [11], anti-platelet [12].

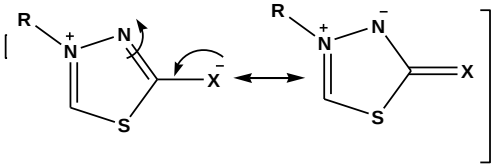
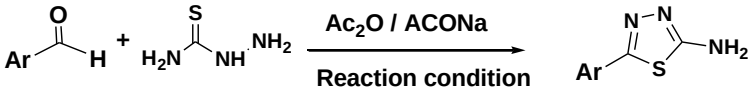


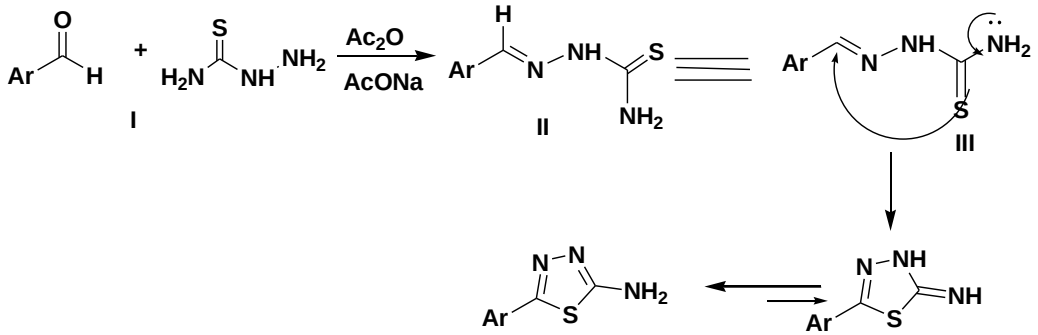
Figure 1: Mesoionic structure 1,3,4-thiadiazole



1 **2** **3**

Scheme 1 *Synthesis of 2-amino 1,3,4 Thiadiazole derivatives*

The use of microwave energy is one of the eco-friendly methods to accelerate the organic reactions which may attract many researchers and have a number of advantages such as short reaction time, easy work-up procedure, no side product and high yield. Hence, the use of microwave reaction for the synthesis of organic molecules is considered as part of green chemistry [13-14]. Previously various research has been studied for the synthesis of 1,3,4-thiadiazole investigated [15-23]. Earlier our research work to develop research methodology for the synthesis of 2-amino-5-aryl-1,3,4-Thiadiazoles [24]. In continuation of our green approach research work [25], herein we report synthesis of 2-amino-5-aryl-1,3,4-Thiadiazoles using acetic anhydride and sodium acetate catalyst and solvent over those hazardous acid catalyst such as $POCl_3$, $SOCl_2$, Conc.H_2SO_4, acid-anhydride etc.



Scheme 2: *Plausible mechanism of 2-amino-1,3,4-Thiadiazole derivatives*

Results and Discussion

Initially, weoptimized various catalystat different temperature (60-120 °C) for the synthesis of 2-amino-thiadiazole starting from aromatic aldehyde with thiosemicarbazide selected as acid anhydride as cyclisation as well as dehydrated agent over the various acid such as $POCl_3$, $SOCl_2$,Conc.H_2SO_4 etc. for a model reactions of Benzaldehyde (0.05mol), thiosemicarbazide (0.05 mol), acetic anhydride (0.062 mol), base catalyst (0.12 mol) (Table 1). Without catalyst reaction did not detected even after 100 °C (Table 1, entry 1). Better yield was obtained in sodium acetate at three hour, if we increase the time of reaction more than three hour there is no significant effect was observed on the yield of product (Table 1, entry 5). The same reaction was carried out under the microwave irradiation method (Table 2). Excellent yield was obtained again the same catalyst (Table 2, entry 5). There is no more significant effect was observed on the yield of product if increase the time of reaction as well as temperature of reaction. Thus we decided that the reaction carried out insodium acetate and acetic anhydride, all example were tested reasonably good to excellent yields could be achieved in less time 3 min by using microwave irradiation (Table 3).

An electronic effect was observed, electron withdrawing groups (-NO_2) gave better yield than un-substituted and electron donating groups to aromatic acid (Table **3**). Finally, the structure of compounds were substantiated by IR and ^{1}H NMR and ^{13}CNMR spectra and compared with their reported methods [15-24].

Table 1: Screening of solvents with temperature for 2-amino-5-aryl-1, 3, 4-thiadiazoles by conventional method

Entry	Base	Temperature (°C)				Yield[a] (%)/ Time (h)			
		a	b	C	d	a	b	c	d
1	Without	70	85	95	110	00/2	00/3	00/5	00/6
2	Diethyl amine	70	85	95	100	10/2	20/2	30/3	30/4
3	Triethyl amine	70	85	95	100	15/2	38/2	42/3	42/4
4	Sodium chloride	70	85	95	100	10/2	20/2	38/3	38/4
5	**Sodium acetate**	70	85	95	100	12/2	82/2	**90/3**	**90/4**
6	Sodium carbonate	70	85	95	100	15/2	60/2	68/3	68/4
7	Potassium carbonate	70	85	95	100	10/2	62/2	68/3	68/4
8	Potassium hydroxide	70	85	95	100	00/2	00/2	30/3	45/5

[a]***Reaction Condition [Conventional method]:*** Benzaldehyde (0.05mol), thiosemicarbazide (0.05 mol), acetic anhydride (0.062 mol), catalyst (0.12 mol). [a] Isolated yield.

Table 2: Screening of solvents with temperature for 2-amino-5-aryl-1,3,4-thiadiazoles by Microwave method

Entry	Base	Temperature (°C)				Yield[a] (%)/ Time(min)			
		a	b	C	d	a	b	c	d
1	Without	40	80	90	120	00/2	00/3	00/5	00/6
2	Diethyl amine	40	80	90	100	10/2	20/2	40/3	40/4
3	Triethyl amine	40	80	90	100	15/2	48/2	52/3	52/4
4	Sodium chloride	40	80	90	100	10/2	30/2	48/3	48/4
5	**Sodium acetate**	40	80	90	100	12/2	82/2	**98/3**	**98/4**
6	Sodium carbonate	40	80	90	100	15/2	63/2	78/3	78/4
7	Potassium carbonate	40	80	90	100	10/2	66/2	74/3	74/4
8	Potassium hydroxide	40	80	90	100	15/2	30/2	50/3	55/5

[a]***Reaction Condition: [Microwave irradiation method]:*** Benzaldehyde (0.05mol), thiosemicarbazide (0.05 mol), acetic anhydride (0.062 mol), catalyst (0.12 mol). [a] Isolated yield.

Experimental Section

Thiosemicarbazide and substituted aromatic aldehyde were commercially available and anhydride was prepared fromacid halide and sodium acetate. The major chemicals were purchased from Sigma Aldrich the progressed reaction monitored by TLC on silica gel precoated F254 Merc plates, the developed plates were examined with ultraviolet lamps (254 nm) IR spectra were recorded on a FT-IR (Bruker). Melting points were recorded on open head capillary tube was uncorrected. ^{1}H NMR and ^{13}CNMR spectra were recorded on a 400 MHz on a DRX-300 Bruker FT-NMR spectrophotometer. The microwave reactions were performed in "Catalyst synthesizer" The values of chemical shift are expressed in δ ppm as a unit.

General procedure for the synthesis of 4-thiazolidinone derivatives (3a-l):

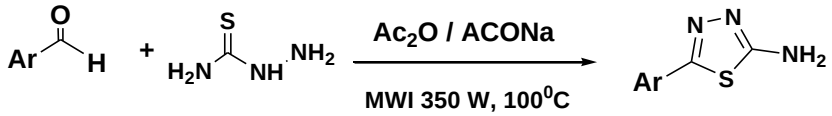
Conventional Method

In a small round bottom flask substituted aromatic aldehyde (0.05mol), thiosemicarbazide (0.05 mol), acetic anhydride (0.062 mol) and were added in cold condition of sodium acetate (0.12 mol) stirred to reflux condition for three to three-four hour. Progress the reaction was monitored by TLC, after completion of reaction cold water was added to the reaction mixture and stirred further few minute, crude product was obtained, filtered and recrystallized from ethanol, yield 90%

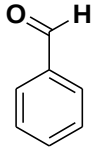
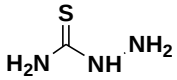
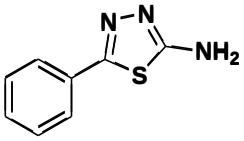
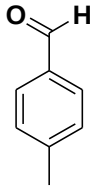
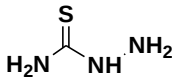
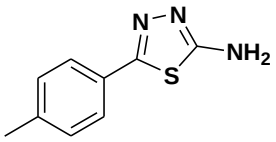
Microwave Irradiation Method

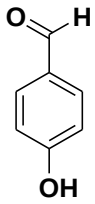
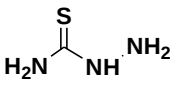
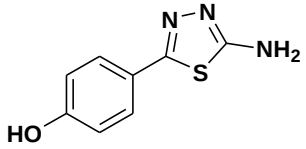
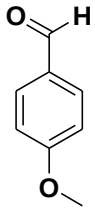
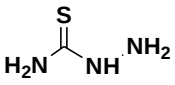
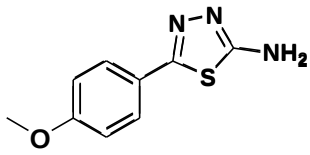
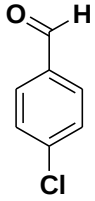
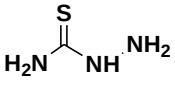
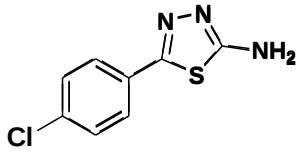
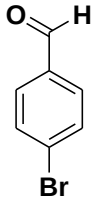
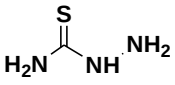
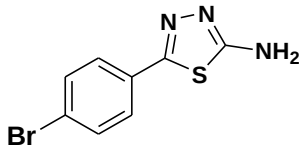
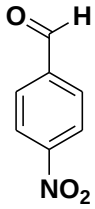
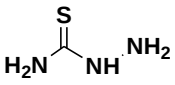
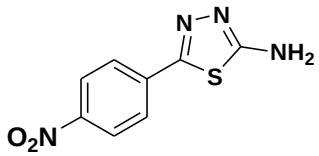
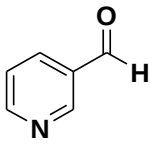
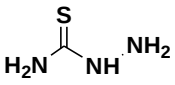
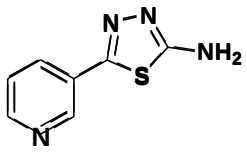
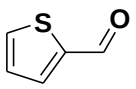
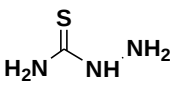
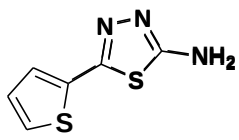
An mixture of substituted aromatic aldehyde (0.05mol), thiosemicarbazide (0.05 mol), acetic anhydride (0.062 mol) and were added were added in cold condition of sodium acetate (0.12 mol) becomes to homogeneous solution and were subjected to microwave irradiation at 350 w. for 3 min. Progress the reaction was monitored by TLC, after completion of reaction cold water was added to the reaction mixture, crude product was obtained, filtered and recrystallized from ethanol, yield 90-98%

Table 3: Synthesis of 2-amino-5-Aryl-1,3,4-thiadiazole derivatives under microwave irradiation method



1(a-j) **2** **3(a-j)**

Entry	Structure of reactant (Ar-Substituted)	Structure of reactant	Structure of product	Yield (%)/Time (min)	Melting Point(°C)
1			 3a	96/3	224-225
2			 3b	92/3	219-220

3			 3c	90/3	138-139
4			 3d	93/3	192-193
5			 3e	95/3	229-230
6			 3f	92/3	228-230
7			 3g	98/3	258-259
8			 3h	96/3	240-241
9				90/3	256-257

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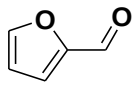
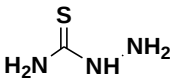
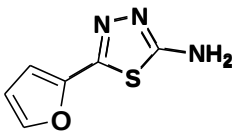
10				90/3	248-250
			3j		

[a]***Reaction Condition:*** Benzaldehyde (0.05mol), thiosemicarbazide (0.05 mol), acetic anhydride (0.062 mol), sodium acetate (0.12 mol). [a] Isolated yield.; 350 watt, 100^0C for 3 min.

Spectral Characterization data:

5-phenyl-1,3,4-thiadiazol-2-amine (3a): IR (cm^{-1}): 3405, 3150, 1050, 685. ^{1}H NMR: δppm = 6.96 (s, 2H, -NH_2), 7.40-8.05 (m, 5H, Ar-H). ^{13}C NMR: δ ppm=174.3, 161.2, 133.1, 130.4, 130, 129.7, 129, 128.1.

5-(p-tolyl)-1,3,4-thiadiazol-2-amine (3b): IR (cm^{-1}): 3210, 3152, 1505, 1180, 1050, 695. ^{1}H NMR: δ ppm =6.96 (s, 2H, -NH_2), 2.32 (s, 3H, -CH_3), 7.28 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H). ^{13}C NMR: δ ppm=174.3, 162.2, 131.2, 130.4, 130, 129.7, 128, 127.7, 127, 21.3.

4-(5-amino-1,3,4-thiadiazol-2-yl)phenol (3c):IR (cm^{-1}): 3392, 3150, 3140, 1480, 1450, 1050,710. ^{1}H NMR : δ ppm =6.96 (s, 2H, -NH_2), 5.30 (s, 1H, -OH), 6.82 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H). ^{13}C NMR: δ ppm= 174.3, 161.6, 158.3, 129.7, 128, 126.7, 116, 115.8.

5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-amine (3d): IR (cm^{-1}):3410, 3150, 1530, 1402, 1055. ^{1}H NMR: δ ppm =6.96 (s, 2H, -NH_2), 3.82 (s, 3H), 7.01 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H). ^{13}C NMR: δ ppm=174.3, 161.6, 160.3, 128.7, 125.2, 114.7, 114.9, 113.8, 55.8.

5-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine (3e):

IR (cm^{-1}):3345, 3153, 1520, 1050, 672.

^{1}H NMR: δ ppm =6.96 (s, 2H, -NH_2), 7.52 (d, 2H, Ar-H), 8.01 (d, 2H, Ar-H).

^{13}C NMR: δ ppm= 174.3, 161, 134.3, 131.7, 129.2, 128.7, 128, 127

5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine(3f): IR (cm^{-1}):3352, 3150, 1531, 1052, 682. ^{1}H NMR: δ ppm =6.96 (s, 2H, -NH_2), 7.82 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H). ^{13}C NMR: δ ppm= 174.3, 161, 133.3, 132.7, 131.3, 129.2, 128.7, 128.

5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine(3g): IR (cm^{-1}):3415, 3150, 1512, 1022, 625. ^{1}H NMR: δ ppm =6.96 (s, 2H,-NH_2), 8.68 (d, 2H, Ar-H), 8.29 (d, 2H, Ar-H). ^{13}C NMR: δ ppm= 174.3, 161, 147.3, 139.2, 128.1, 124.2, 123

5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine (3h): IR (cm^{-1}):3450, 3405, 3150, 1515,1060, 670. ^{1}H NMR: δ ppm =6.96 (s, 2H, -NH_2), 9.20 (s, 1H, Ar-H), 8.40 (d, 1H, Ar-H), 8.70 (d, 1H, Ar-H), 7.53 (t, 1H, Ar-H). ^{13}C NMR: δ ppm= 174.3, 161, 148.1, 147, 134, 133.2, 124.2

5-(thiophen-2-yl)-1,3,4-thiadiazol-2-amine (3i): IR (cm^{-1}): 3410, 3150, 1516, 1345, 1060, 670. ^{1}H NMR: δ ppm =6.96 (s, 2H, -NH_2), 7.82 (d, 1H, Ar-H), 7.68 (d, 1H, Ar-H), 7.15 (t, 1H, Ar-H). ^{13}C NMR: δ ppm= 174.3, 161, 128.1, 127.8, 127

5-(furan-2-yl)-1,3,4-thiadiazol-2-amine (3j): IR (cm^{-1}):3405, 3160, 1520, 1065, 685. ^{1}H NMR: δ ppm =6.96 (s, 2H, -NH_2), 7.82 (d, 1H, Ar-H, 7.06 (d, 1H, Ar-H), 6.65 (t, 1H, Ar-H). ^{13}C NMR: δ ppm= 174.3, 161, 146.1, 112.3, 111.7

Conclusion

In conclusion, we have successfully developed a new synthetic strategy for the synthesis of 2-amino-5-aryl-1,3,4-thiadiazole derivatives under the microwave irradiation method by using acetic anhydride/ sodium acetate as catalyst solvent to avoiding hazardous acid catalysts or reagents such as $POCl_3$, $SOCl_2$,Conc.H_2SO_4 etc. here in concluded that good to excellent yield was obtained. The reaction was carried out in a very short time with excellent yield (90-98%).

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