Heterocyclic Letters
Vol. 6| No.1|75-82| Nov-Jan| 2016
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

CYANURIC CHLORIDE CATALYZED SYNTHESIS OF 2-AMINO, 5-SUBSTITUTED (ARYL/HETEROCYCLIC) 1, 3, 4-THIADIAZOLE

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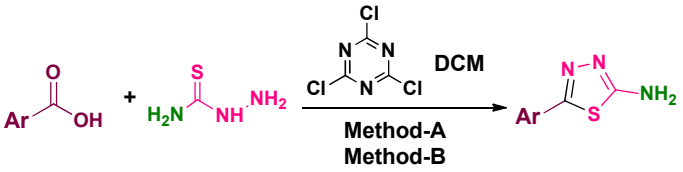
Abstract: 2,4,6-trichloro-1,3,5-triazine (TCTA) has been used for cyclization of Thiosemicarbazide with substituted aromatic acid / heterocyclic acid over the hazardous reagent and catalyst for the synthesis of 2-amino, 5-aryl, 1, 3, 4-thiadiazoles under conventional and microwave irradiation conditions. The reaction time is very short and good to excellent yield was obtained by MWI technique over the conventional method. The compounds are characterizes by IR, NMR, ^{13}CNMR analysis.

Keywords: 2,4,6-trichloro-1,3,5-triazine (TCTA), 2-amino,5-aryl,1,3,4-thiadiazoles, Conventional and MWI technique.

Introduction

Heterocyclic compounds occur widely in nature and are essential to life. Sulfur and Nitrogen containing hetero atoms, five-membered heterocyclic azoles, thiazole, diazole in particular that 2-amino 1,3,4-thiadiazole are well established biologically active compounds. Sulfur atom of the thiadiazole imparts improved liposolubility and mesoionic nature reported as anti-parasitic, anti-convulsant and anti-coagulant[i], anti-microbial[ii], anti-cancer[iii], anti-inflammatory[iv-v], anti-tubercular,[vi] anti-fungal[vii], diuretic[viii] , anthelmintic activity[ix], anti-tumor[x], anti-diabetic[xi], anti-platelet[xii].



Ar = Ph, 4-CH_3Ph, 4-OHPh, 4-OMePh, 4-ClPh, 4-BrPh, 4-NO_2Ph, 3-pyridyl, 2-thiophenyl, 2-furyl.

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 transformation is considered as part of green chemistry[xiii-xiv]. In past, various research has been studied for the synthesis of 1,3,4-thiadiazole investigated[xv-xxiv]. However the suffer

from disadvantages like hazardous reagent, catalyst and solvent. Present research work is synthesis of amino, aryl thiadiazole by using green catalyst as symmetrical 1,3,5-triazine (cyanuric chloride) in various aromatic and heterocyclic acids with thiosemicarbazides and compared these by conventional and microwave irradiation methods with respect to time and yield. In continuation of our earlier research work[xxv], herein we first time report synthesis of 2-amino, 5-aryl 1,3,4-Thiadiazoles using Cyanuric chloride as environmentally benign catalyst over those hazardous acid catalyst such as $POCl_3$, PCl_5, $SOCl_2$, Conc.H_2SO_4, acid-anhydride etc.

Experimental Section

Thiosemicarbazides and substituted aromatic acid, 2,4,6-trichloro-1,3,5-triazine (TCTA) were commercially available. The major chemicals were purchased from Sigma Aldrich the progressed reaction monitored by TLC on silica gel precoated F254 Merc plates, microwave reaction were carried out by microwave synthesizer (Micro SYNTH) the developed plates were examined with ultraviolet lamps (254nm) 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 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 acid (0.05mol), thiosemicarbazides (0.05 mol), 2,4,6-trichloro-1,3,5-triazine (TCTA) (0.05 mol) were added in 0.13 mol of DCM was stirred under reflux condition for 3h. Progress the reaction was monitored by TLC, after completion of reaction water was added to the reaction mixture and stirred further few minute, crude product was obtained, filtered and recrystalized from ethanol, yield 62-89%

Microwave irradiation method:

Mixture of substituted acid (0.05mol), thiosemicarbazides (0.05 mol), 2,4,6-trichloro-1,3,5-triazine TCTA (0.05 mol) were added in 0.13 mol of DCM was subjected to microwave irradiation at 300 w. for 4-5 min. Progress the reaction was monitored by TLC, after completion of reaction water was added to the reaction mixture and stirred further few minute, crude product was obtained, filtered and recrystalized from ethanol, yield 70-93%

Result and Discussion

From our literature survey, we choose cyanuric chloride as environmentally benign instead of various hazardous acid such as $POCl_3$, PCl_5, $SOCl_2$,Conc.H_2SO_4 etc, for a model reactions of substituted acid (0.05mol), thiosemicarbazides (0.05 mol), 2,4,6-trichloro-1,3,5-triazine (TCTA) (0.05 mol). To optimized reaction condition in variable solvent in different a temperature 60-120^{0}C (Table **1**). At low temperature of reaction, yield of product was fall down, if we increased the temperature more than 100°C the yield of product was reduced (Table **1**). Herein we observed that an excellent yield was obtained at 90-100°C in DCM (Table**1**, entry **5**) this is due to TCTA-DCM is good paired emerged as catalyst and solvent. Thus we decided reaction carried out in DCM as solvent with cyanuric chloride as easily available environmentally benign reagent for the screened temperature 90-100°C, all example were tested reasonably good to excellent yields could be achieved in less time 4-5 min by microwave irradiation and 3-4 h by conventional method, better yield was obtained under the microwave irradiation method (Table **2**). An electronic effect was observed, electron withdrawing groups (-NO_2) gave better yield than unsubstituted and electron donating groups to aromatic acid (Table **2**, entry **3g**), five and six member heterocyclic acid gave corresponding good yield (Table **2**, entry **3h, 3i,3j**).

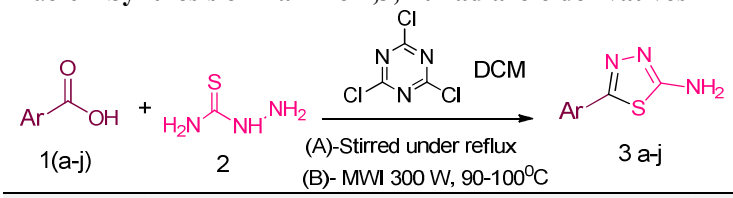
Finally, the structure of compounds were substantiated by IR and ^{1}H NMR and ^{13}CNMR spectra and compared with their reported methods[xv-xxiv].

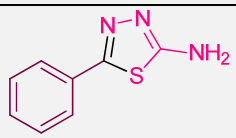
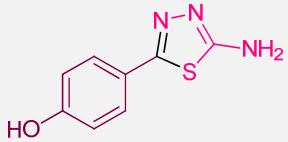
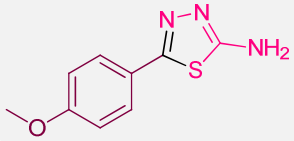
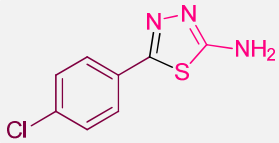
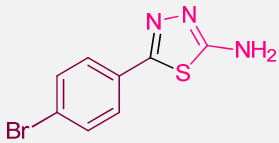
Table **1 Optimization of solvent with different temperature:**

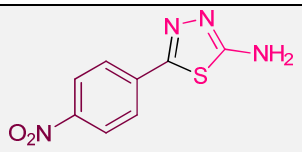
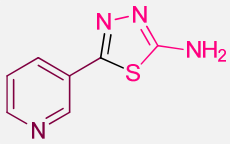
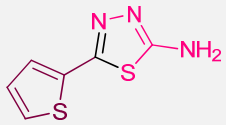
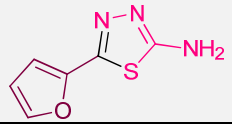
Entry	**Solvent**	**Temperature (^{0}C)**				**Yield[a] (%)**			
		a	b	c	d	a	b	**c**	d
1	H_2O	60-80	80-90	90-100	110-120	-	-	-	-
2	CH_3CN	60-80	80-90	90-100	110-120	-	30	40	15
3	EtOH	60-80	80-90	90-100	110-120	-	60	72	62
4	MeOH	60-80	80-90	90-100	110-120	-	56	62	50
5	DCM	60-80	80-90	**90-100**	110-120	-	82	**93**	**80**
6	$CHCl_3$	60-80	80-90	90-100	110-120	-	53	63	50
7	DMF	60-80	80-90	90-100	110-120	-	45	53	50
8	Toluene	60-80	80-90	90-100	110-120	-	48	56	43
9	Xylene	60-80	80-90	90-100	110-120	-	43	52	38

[a]Isolated yield, method (B): 300 watt, 90-100°C for 4-5 min.

Table **2 Synthesis of 2-amino 1,3,4-thiadiazole derivatives**



Compound	Structure of product	Molecular formula	Yield (%)/Time Conventional(h)	Microwave (min)	Melting Point(°C)
3a		$C_8H_7N_3S$	86/3	90/4	224-226
3b		$C_9H_9N_3S$	82/3	86/4	219-221
3c		$C_8H_7N_3OS$	68/4	72/5	138-140
3d		$C_9H_9N_3OS$	76/4	80/5	192-194
3e		$C_8H_6ClN_3S$	80/3	87/4	229-231
3f		$C_8H_6BrN_3S$	78/3	82/4	228-231

3g		$C_8H_6N_4O_2S$	**89/3**	**93/4**	258-260
3h		$C_7H_6N_4S$	72/3	76/4	240-243
3i		$C_6H_5N_3O_2$	72/4	64/5	256-260
3j		$C_6H_5N_3OS$	70/4	62/5	248-250

Reaction condition: substituted acid (0.05mol), thiosemicarbazides (0.05 mol) TCTA (0.05 mol), DMF (0.13 mol).
mehod (A): stirred under reflux condition for 3-4h.
method (B): 300 watt, 90-100°C for 4-5 min.

Spectral dataof synthesized products:

5-phenyl-1,3,4-thiadiazol-2-amine (3a):
IR (cm^{-1}): 3400, 3150, 1050, 680.
^{1}HNMR:δppm = 6.98 (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}): 3215, 3152, 1505, 1180, 1050, 690.
^{1}H NMR: δ ppm =6.98 (s, 2H, -NH_2), 2.35 (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}): 3390, 3150, 3140, 1480, 1450, 1050,705.
^{1}H NMR : δ ppm =6.98 (s, 2H, -NH_2), 5.35 (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}): 3405, 3150, 1530, 1402, 1050.
^{1}H NMR: δ ppm =6.98 (s, 2H, -NH_2), 3.85 (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}): 3340, 3153, 1520, 1050, 670.
^{1}H NMR: δ ppm =6.98 (s, 2H, -NH_2), 7.50 (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}): 3350, 3150, 1531, 1052, 680.
^{1}H NMR: δ ppm =6.98 (s, 2H, -NH_2), 7.80 (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}): 3410, 3150, 1512, 1022, 621.
^{1}H NMR: δ ppm =6.98 (s, 2H,-NH_2), 8.65 (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

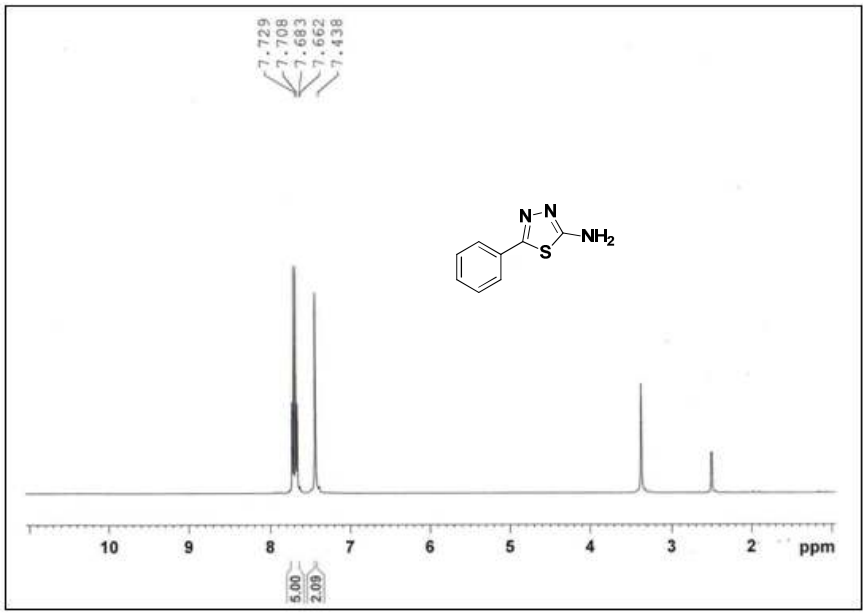
5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine (3h):
IR (cm^{-1}): 3452, 3405, 3150, 1515,1060, 675.
^{1}H NMR: δ ppm =6.98 (s, 2H, -NH_2), 9.24 (s, 1H, Ar-H), 8.40 (d, 1H, Ar-H), 8.70 (d, 1H, Ar-H), 7.53 (t, 1H, Ar-H).
^{13}C NMR: δ ppm= 174.3, 161, 148.1, 147, 134, 133.2, 124.2

5-(thiophen-2-yl)-1,3,4-thiadiazol-2-amine (3i):c
IR (cm^{-1}): 3405, 3150, 1516, 1345, 1060, 675.
^{1}H NMR: δ ppm =6.98 (s, 2H, -NH_2), 7.70 (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

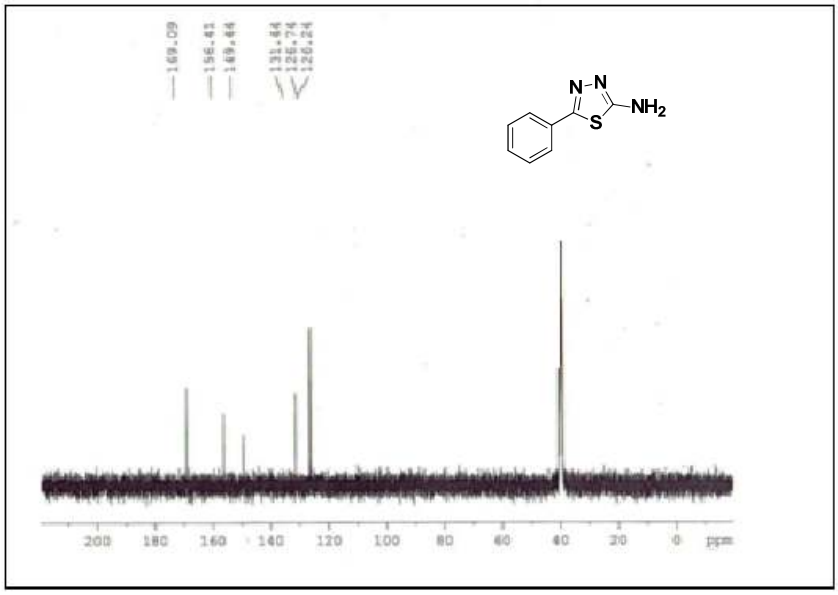
5-(furan-2-yl)-1,3,4-thiadiazol-2-amine (3j):
IR (cm^{-1}): 3402, 3160, 1520, 1065, 680.
^{1}H NMR: δ ppm =6.98 (s, 2H, -NH_2), 7.80 (d, 1H, Ar-H, 7.06 (d, 1H, Ar-H), 6.65 (t, 1H, Ar-H).
^{13}C NMR: δ ppm= 174.3, 161, 146.1, 112.3, 111.7

♦ NMR Spectra Copy of some selected compounds:

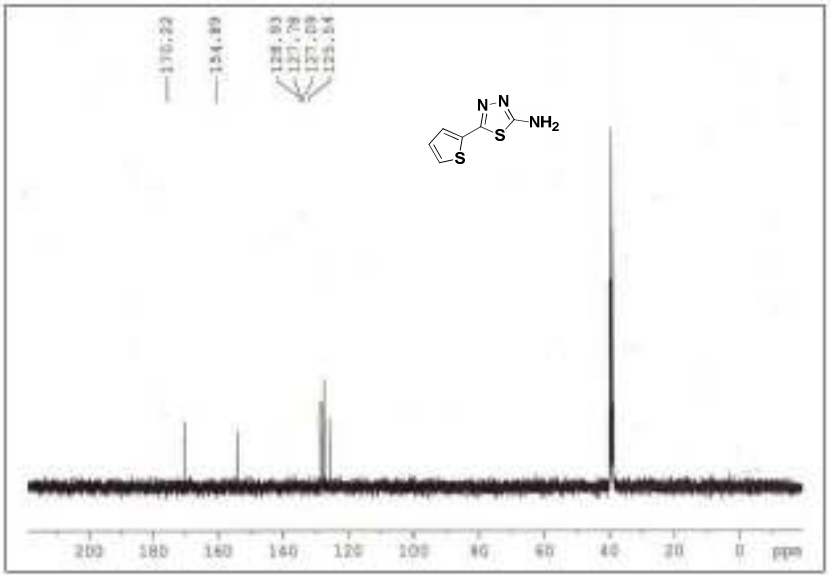
^{1}HNMR spectra of 5-phenyl-1,3,4-thiadiazol-2-amine (3a):



^{13}CNMR spectra of 5-phenyl-1,3,4-thiadiazol-2-amine (3a):



^{13}CNMR of 5-(thiophen-2-yl)-1,3,4-thiadiazol-2-amine (3i):



Conclusions

We, first time used cyanuric chloride (TCTA) as environmentally benign catalyst over hazardous acid catalyst such as $POCl_3$, PCl_5, $SOCl_2$,Conc.H_2SO_4 etc. for the synthesis of 2-amino 1,3,4-thiadiazoles under conventional and microwave irradiation technique, here in concluded that comparing both techniques, an excellent yield was obtained by microwave irradiation method in a very less time of reaction. Here we developed a new green approach methodology for the synthesis of 2-amino 1,3,4-thiadiazoles.

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Received on November 2, 2015.