Heterocyclic Letters
Vol. 5 | No.3 |375-382 | May-July| 2015
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

AN ALUM CATALYZED SOLVENT FREE ONE POT MULTICOMPONENT SYNTHESIS OF 4-THIAZOLIDINONE DERIVATIVES

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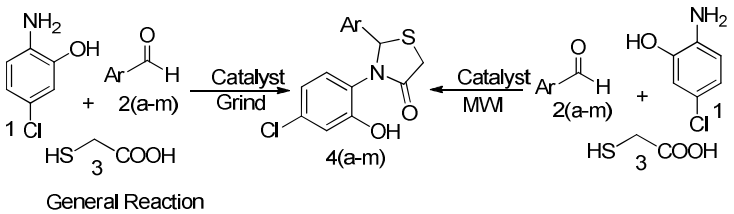
Abstract: 2-amino-5-chlorophenol (**1)** condensed with aromatic, heterocyclic-aldehydes (**2**a-m) and 2-mercaptoacetic acid (**3**) in presence of alum catalyst, solvent free condition using grinding , microwave irradiation techniquie, synthesis of series of thiazolidinone derivatives (**4**a-m) expeditious in enviro-ecofriendly condition, with an excellent yield. The compounds are characterizes by IR, NMR, CHN analysis.

Keywords: Thiazolidin-4-one, green approach, solvent free condition, alum catalyst.

Introduction

Heterocyclic compounds occur widely in nature and are essential to life. In particular five-membered heterocyclic molecules Sulfur and Nitrogen containing hetero atom having thiazole nucleus with carbonyl group on fourth carbon such as Thiazolidinone-4-one exhibit a variety of biological activities like anti-bacterial[i], anti-inflammatory[ii,iii], anticancer[iv-vii], anti-tuberculosis[viii], anticonvulsant[ix] and analgesic[x], Previously studies on the pharmacological activities of thiazolidin 4-ones showed wide spectrums ofantimicrobial activities[xi-xiii]

Alum [$KAl(SO_4)_2.12H_2O$] has been found to be effective in the synthesis of cis-isoquinolicacids[xiv], mono and disubstituted 2,3-dihydroquinazolin-4(1H)-ones[xv], dihydropyrimidines via Biginelli reaction[xvi], coumarins[xvii], 1,3,4-oxadiazoles[xviii], dibenzoxanthenes[xix], 1, 5 benzodiazepines[xx], and a different number of synthetic methods for 2-amino thiadiazole.[xxi]



General Reaction

Many research study reported for green grinding method with formation of carbon carbon or carbon hetero atom single as well as double bond, some of name reactions example is Grignard[xxii], Reformatsky[xxiii], Dieckmann[xxiv], Aldolreaction[xxv] and various other coupling type of reactions[xxvi-xxviii] , an environmentally benign process are requested for crucial perventation of pollution, enviro-economic factors, low cost and simplicity in processing these factors are beneficial to industries as well as environment[xxix].

Microwave assisted reactions have become an established tool forthe rapid synthesis of novel chemical entities.[xxx] The application of microwaveirradiation is the use of catalysts or mineral supported reagents, under solvent-free conditions in organic reactions to occur expeditiously at ambient pressure, thus providing exclusive chemical processes with special attributes such as enhanced reaction rates and higher yields[xxxi-xxxii] and a functionalized thiadiazole

Experimental Section

2-amino-5-chlorophenol, substitute aldehydes, 2-mercaptoacetic acid (Thioglycolic acid) were commercially available. 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 (254nm) IR spectra were recorded on a FT-IR (Bruker). Melting points were recorded on open head capillary tube are uncorrected.^{1}H NMR spectra were recorded on a 400 MHz H^{1} NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer The values of chemical shift are expressed in δ ppm as a unit.

Result and Discussion

Keeping focus on green protocol, we select alum as an efficient catalyst for the condensation of multicomponent in one pot synthesis. We used microwave irradiation and novel green approach techniques grinding. We herein report synthesis of a various thiazolidinone derivatives by novel, unique, expeditious method.

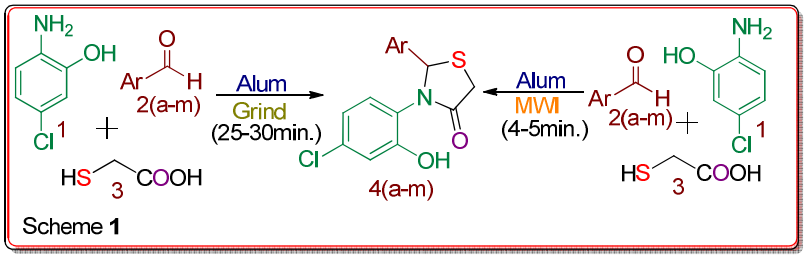
Initially, we optimized a different types of acid-catalyst (10 mol%) in appropriate time (Table **1**.) among these alum is a very good catalyst for the increase the rate of reaction as well as yield of product. If we decrease amount of catalyst less than 10 mol % yield of product was fall down while increase amount of catalyst there is no significant effect (Table **1**, entry no.**7**). Thus we choose 10 mol% alum for the synthesis of 4-thiazolidinones, all example were tested reasonably good to excellent yield (Table **2**) could be achived in short reaction time. An electronic effect was observed, electron with drawing and unsubstituted group gave better yield than electron donating substituent to the aromatic aldehydes (Table **2**, entry no. 1,2,5), hetero-aryl aldehydes gave moderate yield (Table **2**. entry no.**12, 13**). Finally, we observed an excellent yield, in short reaction time by MWI than grinding technique, first one is energy consume process while second one is totally green approach process, and structure of compound were substantiated by FTIR, ^{1}HNMR and CHN-analysis.

Table 1. Optimization of catalyst:

Sr. no.	Catalyst	Mole(%)	Isolated yield [b] (%)	
			Grind/Time(min.)	MWI/Time(min.)
1.	Mon.K-10	10	62/25	60/4
2.	PMA-SiO_2	10	60/25	58/4
3.	AcOH	10	65/25	60/4
4.	Boric Acid	10	60/25	58/4
5.	Oxalic Acid	10	20/25	15/4
6.	Alum	**10**	**93/25**	**98/4**
7.	Alum	15	93/25	98/4

[b] Isolated yield
PMA= Phosphomolybdic acid supported on silica

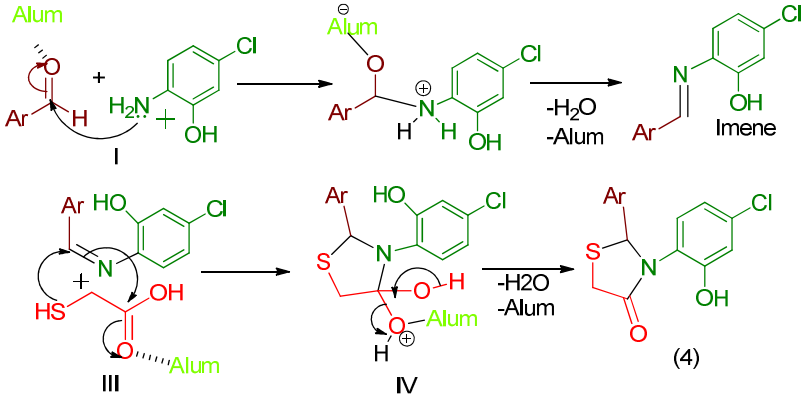
Table 2. Synthesis of 4-thiazolidinones **4**



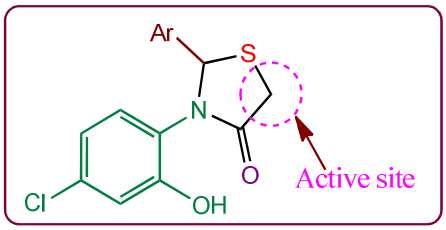
Scheme **1**

Sr.no.	Compoud	Ar	Yield 4[a] (%) / Time (min.)		Melting Point (^{0}C) (Lit.)[32(b)]	Color
			Grinding	MWI		
1	**4a**	H	**93/25**	**98/4**	89-91(88-90)	Yellow solid
2	**4b**	4-$O_2NC_6H_4$	**93/30**	**98/4**	191-193(190-192)	Yellow solid
3	**4c**	2-ClC_6H_4	91/30	96/5	128-130(127-129)	Yellow solid
4	**4d**	4-ClC_6H_4	89/30	96/5	120(118-120)	Lightyellowsolid
5	**4e**	2,4-$Cl_2C_6H_3$	**93/25**	**98/4**	130-132(131-133)	Lightyellow solid
6	**4f**	4-FC_6H_4	88/30	92/5	129(126-128)	Yellow solid
7	**4g**	3-FC_6H_4	86/30	90/5	135-140(138-140)	Yellow solid
8	**4h**	4-$H_3COC_6H_4$	89/30	92/5	51-53(48-50)	Yellow solid
9	**4i**	2,4$(OCH_3)2C_6H_3$	88/30	93/5	45-50(46-48)	Yellow solid
10	**4j**	4-HOC_6H_4	85/30	86/5	45(42-44)	Yellow solid
11	**4k**	4-benzonitrile	89/30	92/5	140-142(142-143)	Yellow solid
12	**4l**	4-thiazoyl	85/30	86/5	88-9290	Pale yellow solid
13	**4m**	2-Pyridyl	88/30	90/5	105-107(106-108)	Yellow solid

[a] Isolated yield



Plausible mechanism:



Active Handle of Compound

General procedure For the synthesis of 4-thiazolidinone derivatives (4a-m):

Microwave irradiation method:

An equimolar amount of 2-amino-5-chlorophenol (1mmol) **1**, substitute aldehydes (1mmol) **2**, 2-mercaptoacetic acid (Thioglycolic acid) (1mmol) **3** and Alum (10 mol%) were added in small RBF subjected to MW irradiation (800 watt.) at 100^0C for 4-5 min. completion of reaction progress was monitored by TLC (Ethyl acetate :n-Hexane), the product obtained was poured in crushed ice, filtered and extracted with ethyl acetate and petroleum ether (8:2), compound were recrystallized from ethyl alcohol to obtained pure product (4a-m)

Grinding method:

An equimolar amount of 2-amino-5-chlorophenol (1mmol) **1**, substitute aldehydes (1mmol) **2**, 2-mercaptoacetic acid (Thioglycolic acid) (1mmol) **3** and Alum (10 mol%) were taken in Mortar vigorous grind for 25-30 min. by Pestle at room temperature completion of reaction progress was monitored by TLC (Ethyl acetate :n-Hexane), Starting was disappear and the product obtained was poured in crushed ice, filtered and extracted with ethyl acetate and petroleum ether (8:2), compound were recrystallized from ethyl alcohol to obtained pure product,(4a-m), IR, NMR, CHN-Analysis of 3-(4-chloro-2-hydroxyphenyl) 2-phenylthiazolidin-4-one (**4a**):

IR (cm^{-1}):3390, 3050, 2930, 1683

^{1}H NMR: δppm = 4.41–4.57 (d, 1H, CH_2), 4.60–4.69 (d, 1H, CH_2), 5.72 (s, 1H, OH), 6.23 (s, 1H, S–CH–N), 7.04–7.23 (m, 3H Ar-H), 7.21–7.27 (m, 5H, Ar-H)

^{13}NMR: δppm = 33.2, 73.2, 116.8, 121.7, 124.2, 125.3, 126.2, 128.5, 129.1, 133.8, 139.4, 151.2, 171.9.; Anal. Calcd for $C_{15}H_{12}ClNO_2S$ (305.03): C, 58.92; H, 3.96; Cl, 11.51; N, 4.58; S, 10.47, Found: C, 58.93; H, 3.93; Cl,11.55; N, 4.55; S,10.45.

Spectral data:

*3-(4-chloro-2-hydroxyphenyl) 2-phenylthiazolidin-4-one (**4a**)*:
IR (cm^{-1}):3390, 3050, 2930, 1683
^{1}H NMR: δppm = 4.41–4.57 (d, 1H, CH_2), 4.60–4.69 (d, 1H, CH_2), 5.72 (s, 1H, OH), 6.23 (s, 1H, S–CH–N), 7.04–7.23 (m, 3H Ar-H), 7.21–7.27 (m, 5H, Ar-H)
^{13}NMR: δppm = 33.2, 73.2, 116.8, 121.7, 124.2, 125.3, 126.2, 128.5, 129.1, 133.8, 139.4, 151.2, 171.9.; Anal. Calcd for $C_{15}H_{12}ClNO_2S$ (305.03): C, 58.92; H, 3.96; Cl, 11.51; N, 4.58; S, 10.47, Found: C, 58.93; H, 3.93; Cl,11.55; N, 4.55; S,10.45.

*3-(4-chloro-2-hydroxyphenyl) -2-(4-nitrophenyl)thiazolidin-4-one (**4b**):*
IR (cm^{-1}): 3380 (OH), 3055 (Ar-H stretch.), 2935 (aliphatic CH stretch.), 1685 (C=O);
^{1}HNMR(∂ppm): 4.44.55 (d, 1H, CH_2), 4.57–4.65 (d, 1H, CH_2)5.33 (s, 1H, OH), 6.60 (s, 1H, S–CH– N), 7.03–7.21 (m, 3H, Ar-H), 8.11–8.25(d,2H, Ar-H)

*3-(4-chloro-2-hydroxyphenyl) -2-(2-chlorophenyl)thiazolidin-4-one (**4c**)*
IR (cm^{-1}): 3390 (OH), 3061 (Ar-H stretch.), 2945 (aliphatic CH stretch.), 1690 (C=O); H NMR: δppm = 3.99–4.09 (d, 1H, CH_2), 4.13–4.23 (d, 1H, CH_2) 5.20 (s, 1H, OH), 6.45 (s, 1H, S–CH– N), 7.02–7.23 (m, 3H, Ar-H), 7.24–7.37 (m, 4H, Ar-H).

*3-(4-chloro-2-hydroxyphenyl) 2-(4-chlorophenyl)thiazolidin-4-one (**4d**):*
IR (cm^{-1}): 3387 (OH), 3045 (Ar-H stretch.), 2935 (aliphatic CH stretch.), 1689 (C=O); 1H NMR: δppm = 4.0 –4.15 (d, 1H, CH_2), 4.18–4.28 (d, 1H, CH_2), 5.31 (s, 1H, OH), 6.45 (s, 1H, S–CH– N), 7.05–7.27 (m, 3H,Ar-H), 7.27–7.37 (d, 2H, Ar H), 7.38–7.48 (d, 2H, Ar-H)

*3-(4-chloro-2-hydroxyphenyl) 3-(4-chloro-2-hydroxyphenyl) (**4e**)*
IR (cm^{-1}): 3393 (OH), 3051 (Ar-H stretch.), 2931 (aliphatic CH stretch.), 1685 (C=O); 1H NMR: δppm = 4.46–4.56 (d, 1H, CH_2), 4.57–4.68 (d, 1H, CH 5.32 (s, 1H, OH), 6.41 (s, 1H, S–CH– N), 7.04–7.24 (m, 3H, Ar-H), 7.27–7.35(d, 2H,Ar-H)

*3-(4-chloro-2-hydroxyphenyl)-2-(4-fluorophenyl)thiazolidin-4-one (**4f**):*
IR (cm^{-1}): 3375 (OH), 3044 (Ar-H stretch.), 2934 (aliphatic CH stretch.), 1693 (C=O); 1H NMR: δppm = 3.5–4.05 (d, 1H, CH_2), 4.08–4.18 (d, 1H, CH_2) 5.37 (s, 1H, OH), 6.47 (s, 1H, S–CH– N), 7.07–7.21 (m, 3H, Ar-H), 7.22–7.32 (d, 2H, Ar-H), 7.25–7.43 (d, 2H, Ar-H) Ar-H), 7.27–7.35 (d, 2H, ArH), 7.65 (s, 1H, Ar-H).

*3-(4-chloro-2-hydroxyphenyl) -2-(3-fluorophenyl)thiazolidin-4-one (**4g**):*
IR (cm^{-1}): 3388 (OH), 3039 (Ar-H stretch.), 2934 (aliphatic CH stretch.), 1687 (C=O); ^{1}H NMR: δppm = 3.97-4.03(d1H, CH_2), 4.10–4.18 (d, 1H, CH_2) 5.30 (s, 1H, OH), 6.42 (s, 1H, S–CH–N), 6.77 (s, 1H, Ar-H), 7.06–7.21 (m, 3H, Ar-H), 7.22 –7.33 (m, 3H, Ar-H)

*3-(4-chloro-2-hydroxyphenyl) -2-(4-methoxyphenyl)thiazolidin-4-one (**4h**):*
IR (cm^{-1}): 3393 (OH), 3054(Ar-H stretch.), 2949 (aliphatic CH stretch.), 1686 (C=O);
^{1}H NMR: (δppm) 3.76 (s, 3H, CH_3), 3.90–3.98 (d, 1H, CH_2), 4.01– 4.12 (d, 1H, CH_2), 5.29 (s, 1H, OH), 6.44 (s, 1H (s, 1H, S–CH –N), 6.81–6.98 (d, 2H, Ar-H), 7.12–7.24 (m, 3H, Ar-H), 7.87–7.93 (d, 2H, Ar-H)

3-(4-chloro-2-hydroxyphenyl) 2-(2,4-dimethoxyphenyl)thiazolidin-4-one ***(4i):***
IR (cm^{-1}): 3380 (OH), 3049 (Ar-H stretch.), 2939 (aliphatic CH stretch.), 1691 (C=O);^{1}H NMR: δppm = 3.80 (s, 6H, CH_3), 3.89–4.08 (d, 1H, CH_2), 4.10– 4.29 (d, 1H, CH_2), 5.32 (s, 1H, OH), 6.47 (s, 1H, S–CH–N), 6.57 (s, 1H, Ar-H), 7.02–7.34 (m, 3H, Ar-H), 7.24–7.33 (d, 2H, Ar-H)

3-(4-chloro-2-hydroxyphenyl) -2-(4-hydroxyphenyl)thiazolidin-4-one ***(4j)****:*
IR (cm^{-1}): 3390 (OH), 3062 (Ar-H stretch.), 2933 (aliphatic CH stretch.), 1683 (C=O);
^{1}H NMR: δppm 3.97–4.01 (d, 1H,CH_2), 4.31–4.31 (d, 1H, CH_2), 5.55 (s, 2H, OH), 6.70 (s, 1H, S–CH–N), 6.73–6.68 (d, 2H, Ar-H), 7.02–7.21 (m, 3H, Ar-H), 7.757.01–7.20 (m, 3H, Ar-H), 7.73–7.88 (d, 2H, Ar-H).

4-(3-(4-chloro-2-hydroxyphenyl)-4-oxothiazolidin-2-yl)benzonitrile ***(4k)****:*
IR (cm^{-1}): 3345 (OH),3060 (Ar-H stretch.), 2931 (aliphatic CH stretch.),2223 (CN), 1692 (C=O);
^{1}H NMR: δppm3.70–3.81 (d, 1H, CH_2), 4.10–4.21 (d, 1H, CH_2), 5.36 (s, 1H, OH), 6.43 (s, 1H, S–CH–N), 7.31–7.30 (m, 3H, Ar-H), 7.40–7.45 (d, 2H,Ar-H), 7.51–7.67 (m, 2H, Ar-H).

3-(4-chloro-2-hydroxyphenyl)-2-(4-methylthiazol-5-yl)thiazolidin-4-one ***(4l):***
IR (cm^{-1}): 3383 (OH), 3061(Ar-H stretch.), 2935 (aliphatic CH stretch.), 1689 (C=O);
^{1}H NMR: δppm = 2.41 (s, 3H, CH_3) 3.81–3.93 (d, 1H, CH_2), 4.01–4.21 (d, 1H, CH2), 5.33 (s, 1H, OH), 5.81 (s, 1H, S–CH–N), 7.06,7.21 (m, 3H, Ar-H), 8.67 (s, 1H,Ar-H)

3-(4-chloro-2-hydroxyphenyl)2-(pyridin-2-yl)thiazolidin-4-one ***(4m)****:*
IR (cm^{-1}): 3391 (OH), 3069(Ar-H stretch.), 2931 (aliphatic CH stretch.), 1685 (C=O);1H NMR: δppm = 91–3.91 (d, 1H,CH_2), 4.10–4.18 (d, 1H, CH_2), 5.38 (s, 1H, OH), 6.11 (s, 1H, S–CH–N), 7.01-7.20(m,3H,Ar-H), 7.32-7.43(m, 4H,Ar-H)

Conclusion

In conclusion we report the synthesis of 4-thiazolidinone derivatives in alum (10 mol%) catalyzed under solvent free condition using grinding and microwave assisted techniques, concluded that comparing MWI and Grinding techniques, expeditious with excellent yield was obtained by microwave irradiation method. Developed novel green grinding method as non requirement of heat and electrical energy.

Acknowledgement

Authors are thankful to the Principal, Sant Ramdas college, Ghansawangi, Jalna. for constant encouragement and providing necessary facilities and also thankful to Head, Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004(MS), India.

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Received on April 16, 2015.