

Glycerol-Water Act As A Green Media For The One-Pot Synthesis Of 4-Aryl-2-Aminothiazoles Under Microwave Irradiation

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ABSTRACT: Thiazole ring system found to be important in pharmaceutical and medicinal chemistry, therefore there is urgent need to synthesize by environmentally benign method. So, Various 4-aryl-2-aminothiazoles derivatives has been prepared via one-pot microwave assisted reaction of N-bromosuccinimide and aromatic ketones followed by addition of thiourea in glycerol-water as an environmentally green and recyclable media with excellent yield (91-98%) with minimum reaction time.

Graphical abstract

Scheme

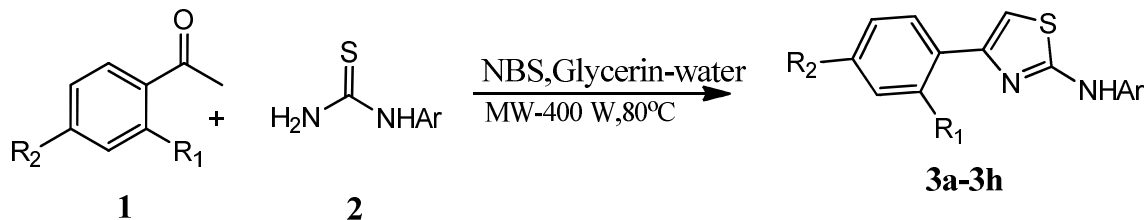


Fig.1 One-pot synthesis of 4-aryl-2-aminothiazole 8 example

KEYWORDS: 4-aryl-2-aminothiazoles, Glycerol-water, green method, N-bromosuccinimides

INTRODUCTION: Recently one-pot synthesis emerged as an important tools in organic synthesis especially for heterocyclic compounds, because of atom economy, simple and convenient and easy work-up procedures. Aminothiazoles is an important heterocyclic ring present in various bioactive molecules (Lewis J R 1999) and found to be best precursor of the preparation of various drugs like, antibacterial, (Tsuji, K. and Ishikawa, H.1944) antiinflammation, (Clemence, F et al.1988) anti allergies, (Hargrave, K. D et. al.1983) antihelminthic, antibiotic, and it also used on the treatment of schizophrenia. (Jaen, J. C et al. 1990) It also possesses inhibitors activity against enzyme cycloindependent kinase. (K. S. Kim et. al 2002).

Various methods have been employed for the synthesis of 4-phenyl-2-aminothiazoles ammonium-12-molybdophosphate in methanol, (Das, B et al.2006) β -cyclodextrin in water, (Narender, M et al.2005) iodine, (Siddiqui, H.L et al.2006) silica chloride, (Karade, H et

al.2007) microwave energy,(Devendra S. Wagare et.al. 2016,) PEG-400-water,(Devendra S. Wagare et.al.2017) but, most of them suffering from various problems like, tedious work-up, used of hazardous precursors like alpha-halo ketones, iodines, bromines and poisonous catalyst as well as solvents and time consuming procedures. It prompted our interest to designed new rapid methods for the one-pot synthesis of 2-aminothiazoles in an environmentally friendly condition.

We synthesized 8 derivatives of 4-aryl-2-aminothiazoles [3a-3h] using glycerol-water as a greener reaction medium under microwave irradiation to obtained excellent yield.(**scheme1**)

Scheme

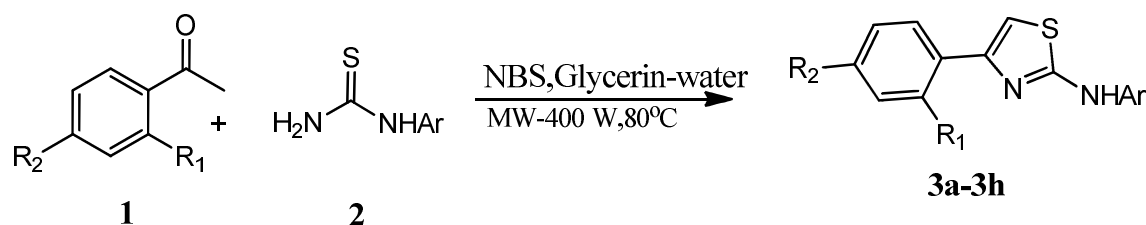


Fig.1 One-pot synthesis of 4-aryl-2-aminothiazole 8 example

EXPERIMENTAL SECTION

Material & Methods

The melting points of synthesized compounds were determined in open capillaries with the help of thermonic melting point apparatus and are uncorrected. The completion of reaction was monitored by thin layer chromatography (TLC) on silica gel G plates. The microwave synthesizer model (MAS-II) used for irradiation. The IR spectra were recorded on a Beckman Acualab-10. Spectrometer (ν max in cm^{-1}) and the ^1H NMR spectra were recorded by Brucker DPX-400MHz using TMS as a references and CDCl_3 as solvent.

1. General Procedure for Preparation of Substituted 4-aryl-2-aminothiazoles (3b)

The mitxure of acetophenones (0.01mmol) and NBS (0.01 mmol) in glycerol and water (6 ml) irradiated for 1 minute and formation of α -bromoacetophenone monitored by thin layer chromatography. To this reaction mixture 2-chloro-phenylthiourea (0.01mmol) was added and irradiated for 1 min. reaction mixture poured on crushed ice and basified with ammonium hydroxide, residue obtained was filtered. The separated solid was recrystallised from aqueous ethanol.

Characterization data of some compounds

4-Phenylthiazol-2-amine (3a). Mp.148-151 $^{\circ}\text{C}$ (Lit.Ref.13 150-151 0C).

^1H NMR(CDCl_3): d 4.94 (brs, 2H), 6.71 (s, 1H), 7.22-7.37 (m, 3H), 7.71-7.77 (m, 2H).; EIMS m/z (%): 177 (m+1100), spectral data consistent with Literature.[18,19]

2-(2-Chlorophenyl)amino-4-phenylthiazole 3b: 76-78 $^{\circ}\text{C}$, lit.75-77 $^{\circ}\text{C}$; $^1\text{HNMR}$ (400 MHz, CDCl_3): δ 6.87 (1H, s, NH D_2O exchangeable); 7.31-8.31 (10H, m, Ar-H and thiazole proton). Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{S}$: C, 62.82; H, 3.87; N, 9.77; found C, 62.79; H, 3.84; N, 9.79,spectral data consistent with Literature.[18,19]

4-(4-chlorophenyl)-N-phenylthiazol-2-amine 3c 151-153 $^{\circ}\text{C}$, lit.152-153 $^{\circ}\text{C}$;

6.78 (br s, 1 H, NH, exchangeable with D₂O), 6.80 (s, 1H, thiazole H), 7.37 (d, 2H, J = 8.6 Hz, ArH), 7.40–7.52 (m, 5H, ArH) and 7.76 (d, 2H, J = 8.6 Hz, ArH). spectral data consistent with Literature.[18,19]

2-(4-Chlorophenyl)amino-4-(4-chlorophenyl)thiazole 3d: 233-235⁰C, lit.231-233 ⁰C
¹HNMR (400 MHz, CDCl₃): δ 6.81(1H, s, NH D₂O exchangeable); 7.10-8.01(9H, m, C-H). Anal. Calcd. For C₁₅H₁₀Cl₂N₂S: C, 56.09; H, 3.14; N, 8.72; found C, 56.07; H, 3.11; N, 8.74; spectra data was consistent with previous literature report.Lit. [18,19]

2-(4-Fluorophenyl)amino-4-(4-chlorophenyl)thiazole 3e:169-172 ⁰C lit.169-170 ⁰C;
¹HNMR (400 MHz, CDCl₃): δ 6.73(1H, s, NH D₂O exchangeable); 7.11-8.01 (9H, m, Ar-H and thiazole proton at 5).. Anal. Calcd. for C₁₅H₁₀ClFN₂S: C, 56.11; H, 3.31; N, 9.19; found C, 56.09; H, 3.29; N, 9.16 spectra data was consistent with previous literature report. Lit.[18,19]

4-(4-Bromophenyl)-Thiazol-2-amine 3f . Mp.164-166 0C (Lit.Ref.6 176-177 0C).

¹H NMR (CDCl₃): d 4.97 (brs, 2H, NH₂), 6.73 (s, 1H), 7.50 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.0 Hz).:EIMS *m/z* (%): 257 (m+2 100), 255 (m+ 90), 149 (10).

2-(4-Chlorophenyl)amino-4-(4-bromophenyl)thiazole 3g: 141-142 ⁰C lit.142⁰C;
¹HNMR (400 MHz, CDCl₃): δ 6.62 (1H, s, NH D₂O exchangeable); 7.21-7.74 (9H, m, Ar-H and thiazole proton). Anal. Calcd. for C₁₅H₁₀BrClN₂S: C, 49.27; H, 2.76; Br, 21.85; N, 7.66; found C, 49.23; H, 2.48; N, 7.54; *m/z* 366 (M+). spectra data was consistent with previous literature report.Lit. [18]

2-(4-Fluorophenyl)amino-4-(4-methylphenyl)thiazole 3h:105-107⁰C lit.103⁰C [18] ;
¹HNMR (400 MHz, CDCl₃): δ 2.32 (3H, d, CH₃); 6.67(1H, s, NH); 7.12 - 8.11 (8H, m, Ar-H); 8.01 (1H, s, thiazole H). Anal. Calcd. for C₁₆H₁₃FN₂S: C, 67.58; H, 4.61; N, 9.85; found C, 67.54; H, 4.58; N, 9.84; spectra data was consistent with previous literature report.Lit. [18]

RESULT AND DISSCUSSION: On the onset of study, initially, we have tried reaction of acetophenones with NBS in glycerol under microwave irradiation and it was surprised that formation of phenacyl bromide in good yield. Synthesis of 2-aminothiazoles in glycerol already reported. So we approached towards one-pot synthesis of 4-aryl-2-aminothiazoles in glycerol. Again we tried same reaction in glycerol and water, yield of product increases with minimum reaction time. Glycerol is thermally stable solvent, keeping this in view, we tried this reaction under microwave and optimized reaction condition under different solvent ,it was observed that glycerol and water in 5:1 proportion best choice of solvent for this reaction. Entry 4.To generalised the scope of this protocol we synthesized 8 derivatives of 4-aryl-2-aminothiazoles using glycerol and water as greener solvent and result are shown in **table 2**. The yield was obtained in this method quite higher and reduced the time of reaction using microwave irradiation due to the good paired emerged of glycerol-water.

The IR spectra of (**3a-h**) showed absorption bands of the N-H in the range 3300-3580 cm⁻¹ , there was a lack of strong stretching band at around 1680 cm⁻¹of C=O of carbonyl of

acetophenones. The $^1\text{H-NMR}$ spectra showed *singlets* at 7.68-7.78 ppm due to proton of the thiazole rings. these evidences confirmed that the thiazole ring had clearly been formed.

CONCLUSION: We have developed facile, expeditious, environmental friendly, microwave assisted, one pot method for the synthesis of 4-aryl-2-aminothiazole from easily available aromatic ketones and in-situ generated α -bromoacetophenone in glycerol and water (5:1) as a recyclable medium. Here we avoided unstable and hazardous α -chloro and α -bromocarbonyl compounds and organic, expensive catalyst and poisonous solvents.

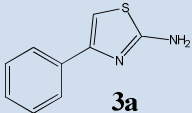
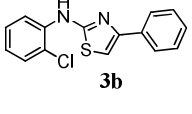
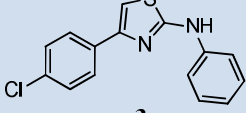
Acknowledgement: Authors are thankful to the Principal, Dr. Rafiq Zakaria College for women, Aurangabad for providing the necessary equipment and infrastructure facilities.

Table1. Optimization of solvent for the synthesis of 4-aryl-2-aminothiazole

Entry	Solvent	Reaction time	Microwave power	Yield ^a %
1	Solvent free	28 MIN.	400	00
2	Methanol	20 min.	400	60
3	Ethanol	25 MIN.	400	45
4	Glycerol	10 MIN.	400	84-89
6	Glycerol-water(1:1)	8 MIN.	400	81-87
7	Glycerol-water(3:1)	5 MIN.	400	85-90
8	Glycerol-water(5:1)	2-3 MIN.	400	91-98

^aisolated yield

Table 2. Synthesis of 4-aryl-2-aminothiazole in glycerol-water

Entry	products	Mw. power	Time (sec.)	Yield ^a %
1	 3a	400 watt	125	5
2	 3b	400 watt	110	97
3	 3c	400 watt	114	95

4	 3d	400 watt	115	97
5	 3e	400 watt	115	98
6	 3f	400 watt	120	97
7	 3g	400 watt	126	91
8	 3h	400 watt	128	93

Reaction conditions: acetophenones (0.01 mmol), N-bromosuccinimide (0.01mmol) and thiourea (0.01mmol) in glycerol-Water (5:1) and microwave power at 400 watt at 80°C;

^aIsolated yield

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