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SYNTHESIS AND CHARACTERIZATION OF 6-CHLORO-*N*-(SUBSTITUTED BENZYLIDENE)BENZOTHIAZOL-2-AMINE BY MICROWAVE IRRADIATION

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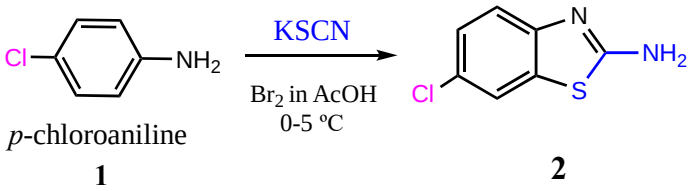
Abstract – A series of 6-chloro-*N*-(substituted benzylidene)benzothiazol-2-amine (**3 a-e**) have been synthesized under microwave irradiation and conventional heating for comparison. 2-Amino-6-chlorobenzothiazol (**2**) was condensed with substituted aromatic aldehyde in ethanol/DMF in the presence of glacial acetic acid as a catalyst under conventional heating and microwave irradiation to yield the Schiff base respectively (**3 a-e**). 2-Amino-6-chlorobenzothiazole (**2**) was synthesized by the reaction of *p*-chloroaniline (**1**) and KSCN in glacial acetic acid in presence of Br_2 as a catalyst. Further, these Schiff bases were purified by column chromatography over silica gel using hexane: ethyl acetate (7:3) as an eluent. The structures of synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and Mass Spectral data.

Microwave irradiation of organic reactions has gained popularity as it accelerates the reaction towards a variety of synthetic transformations, solvent-free procedures, decreased in reaction time, higher yields and easier work up as compared to conventional methods. Chemical transformations that took hours or even days to complete can now be accomplished in minutes.[1] Also the use of microwave for the synthesis of organic compounds has proved to be efficient, safe and environmentally benign techniques with shorter reaction time.[2] Benzothiazoles are bicyclic ring system, consist of a 5-membered 1,3-thiazole ring fused with a benzene ring. Benzothiazole derivatives have been studied and found to have various chemical reactivity and pharmacological activities such as antibacterial,[3] antimicrobial,[4] antidiabetic,[5] antitumor,[6] anti-inflammatory,[7] anthelmintic[8] activities and many more. The presence of hydrophobic moieties in benzothiazole derivative shows cytotoxic activity against cell lines. The -NH_2, -OH, -Cl group containing benzothiazole shows better anticancer activity.[9]

Azomethine groups (–C=N–) typically known as Schiff bases have been synthesized by the condensation

of primary amines with active carbonyl group. Both benzothiazole and Schiff base compounds are important structures in the medicinal and pharmaceutical fields,[10] and it has been suggested that the azomethine linkage might be responsible for the biological activities. Due to the great flexibility and diverse structural aspects of Schiff bases, a wide range of these compounds have been synthesized and studied for their complexation behavior.[11,12] Benzothiazole-Schiff base scaffold plays an important role in medicinal chemistry and the related research has been being remarkably active subjects. A pleasant, comprehensive and systematic review was reported on biological activities of Schiff bases incorporating benzothiazole moiety, which explains the current developments of benzothiazole-based molecules in medicinal chemistry.[13] The benzothiazole conjoined Schiff bases were reported to produce new biologically active molecular hybrids dotted with significant chemotherapeutic properties.[14]

We have suggested that 2-amino-6-chlorobenzothiazole was used to produce the azomethine compounds while taking into account the literature that has been read. The goal of this study was to investigate the percentage yield and time required for the completion of reaction for Schiff bases by microwave and conventional conditions. All synthesized compounds were characterized by IR spectroscopy, mass spectroscopy, ^{1}H NMR and ^{13}C NMR spectroscopy.

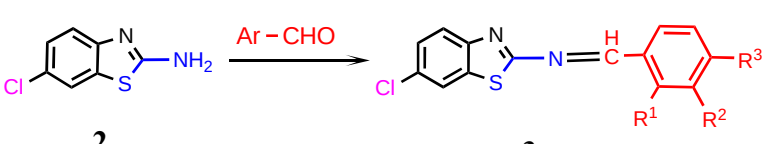


p-chloroaniline

1 **2**

Scheme 1

Scheme 1 represents, 2-amino-6-chlorobenzothiazole (**2**) was synthesized by the reaction of *p*-chloroaniline (**1**) and KSCN in glacial acetic acid in presence of Br_2 as a catalyst. Synthesis of Schiff bases by both the methods i.e. microwave and conventional heating (refluxed), which gives good yield, stable at room temperature and are non-hygroscopic are shown in **Scheme 2**. It is observed that the Schiff bases should be a facile reaction due to the good electrophilic and nucleophilic characteristic properties of the carbonyl and amino groups respectively. 2-Amino-6-chlorobenzothiazole (**2**) on reaction with different substituted aromatic aldehyde (a-e) gives 6-chloro-*N*-(substituted benzylidene)benzothiazol-2-amine (**3**).



2 **3 a-e**

3a= R^1-OH, R^2-H, R^3-H
3b= R^1-H, R^2-H, R^3-OMe
3c= R^1-OH, R^2-OMe, R^3-H
3d= R^1-H, R^2-H, R^3-NMe_2

3e= 

Scheme 2

All microwave-irradiated reactions were completed in 5-10 min with above 90% yield, whereas comparable conventional heating (refluxed) procedures yielded unsatisfactory yields with considerably lengthy reaction time periods of 1-2 h. For the production of compound **3a-e**, the effects of microwave irradiation and conventional heating have been examined. Additionally, the study of the reaction's time and yield percentage was conducted, with the findings compiled in Table 1.

The structures of the target compounds were well characterized by GCMS, IR, ^{1}H and ^{13}C NMR spectra. All the structures of the above compounds were in good agreement with spectral data. The Schiff bases were identified by IR spectra in the range 4000–400 cm^{-1}. IR spectrum shows (C=N) stretching at 1615 cm^{-1}, besides that it shows the disappearance of a doublet of -NH_2 group of 2-amino-6-chlorobenzothiazole and disappearance of the stretching frequency that belongs to -C=O group i.e. 1740 cm^{-1}. The absorption bands at 3300-3390 cm^{-1} is due to *ortho*-OH group, 1514–1600 cm^{-1} corresponding to (C=C) of benzene ring. The characteristic sharp bands at 820-800 cm^{-1} due to C-Cl stretching respectively. The molecular ion peaks are in agreement with the molecular weights of the synthesized compounds. ^{1}H NMR spectra of compounds were studied in DMSO-d_6 showed characteristics signals in different region. The compounds exhibit a singlet at 9.44-8.77 δ for -HC=N, another singlet at 8.90-7.92 δ for -CCl=CH-C, and singlet at upfield region i.e. 3.05 δ for Me_2 and 3.86 δ for OMe. In order to get further information the ^{13}C NMR spectra were investigated. The ^{13}C NMR spectrum of the exhibited signals found at δ 153-155 corresponding to the –CH=N group. The signals observed at δ 156-156 ppm are assigned to group –N=C-S. The signals observed at δ 129 ppm for C-Cl group. Details of the experimental protocols used are shown in the experimental section.

Table 1. Comparison of conventional heating and microwave heating for the synthesis of Schiff bases

	Conventional heating		**Microwave heating**		
Compd No	Reaction Time (min)	Yield (%)	Reaction Time (min)	Yield (%)	M.P. (ºC)
3a	60-70	64	5-10	95	144
3b	50-60	62	5-10	90	110
3c	60-70	68	5-10	92	224
3d	60-70	68	5-10	95	203
3e	60	71	5-10	90	180

We have presented the synthesis and characterization of a new set of Schiff base derivatives, using conventional heating method as well as microwave irradiation by coupling of benzothiazole pharmacophore and suitably substituted aromatic. The simple microwave technique affords various Schiff base with short reaction times, excellent yields and without formation of adverse by-products. This work will therefore be highly helpful for further research into the easy and practical manufacture of biologically active benzothiazole Schiff base compounds, which may be beneficial in the synthesis of other analogues.

EXPERIMENTAL

Materials:

All reagents were commercially available and used without further purification. The melting points were taken with the help of an open capillary tube and were uncorrected. The purity of the synthesized compounds were checked by TLC on pre-coated silica gel aluminium plates (E-Merck) using EtOAc: n-hexane (3:7) and visualized in a UV chamber. The IR spectra of the compounds were recorded on Perkin Elmer FTIR Spectrum 2 with UATR accessory. ^{1}H and ^{13}C NMR spectra was recorded in DMSO-d_6 with tetramethylsilane (TMS) as the internal standard at 400 MHz on a Bruker spectrophotometer. The chemical shifts are reported as parts per million (ppm). Mass spectroscopy was recorded on Shimadzu GCMS QP 5000. All microwave reactions were carried out on Anton Paar Microwave Synthesis Reactor (400 W) in a closed glass vessel system. The physical properties are given in the Table.

2-Amino-6-chlorobenzothiazole (2)

p-Chloroaniline **1** (0.045 mol) and KSCN (0.077 mol) were dissolved in sufficient amount of glacial acetic acid. The mixture was kept for mixing in a beaker, fitted with a mechanical Teflon stirrer (below 10 °C). A solution of bromine in acetic acid (7.5 mL in 30 mL), 4-5 mL was added gradually with continuous stirring for 45 min. After bromine addition, stirring was continued for the next 2 h (below 15 °C). Filter the solution, collect the filtrate, neutralized the solution to form a yellow precipitate, as a crude product. Get rid of impurities from the crude product by treating with water, to get off-white product, dry and weight the compound; Molecular formula: $C_7H_5ClN_2S$; Molecular Weight: 184.65 g/mol; Off-white powder; Yield: 30%; Mp: 198 °C; IR(cm^{-1}): 3455 (N-H), 1633 (C=N), 1275 (C-N), 810 (C-Cl), 563 (C-S); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 7.50 (s, 1H), 7.38 (1H, d, J = 8.0), 7.22 (1H, d, J = 8.0), 5.30 (s, 2H); EI-MS (*m/z*, %): 184.70 (100), 185.80 (18), 186.70 (51).

6-Chloro-*N*-(substituted benzylidene)benzo[*d*]thiazol-2-amine (3 a-e)

Conventional Method

In a clean 50 mL round bottom flask, dissolved 5 mmol of substituted aromatic aldehyde in EtOH, add catalytic amount of glacial acetic acid and stir well. Dissolved 5 mmol of 2-amino-6-chlorobenzothiazole **2** in EtOH and transfer it into the above solution, stir well at room temperature for 1 min. The reaction mixture was then refluxed. The progress of reaction was monitored by TLC. The mixture was allowed to stand at room temperature for overnight and then concentrated. The product was filtered off, washed with water, dried, and purified by using EtOH/EtOAc/DCM to furnish the colored solid.

Microwave Method

Placed an equimolar mixture of 2-amino-6-chlorobenzothiazole **2** (5 mmol), substituted aldehyde (5 mmol) and catalytic amount of glacial acetic acid in microwave tube. Add 3 to 4 mL of DMF to dissolve the contents. The contents were subjected to microwave irradiation at 400 W for about 5-10 min. Progress of the reaction was monitored by TLC. After completion of the reaction, pour the reaction mixture into ice cold water to obtain the crude product. The product was filtered off, washed with water, dried, and purified by using EtOH/EtOAc/DCM to furnish the colored solid.

2-(((6-Chlorobenzo[*d*]thiazol-2-yl)imino)methyl)phenol (3a):

Molecular formula: $C_{14}H_9ClN_2OS$, Molecular Weight: 288.75 g/mol, Color: yellow, IR(cm^{-1}): 3366 (Ar-OH), 3080 (Ar-H), 2965 (aliphatic CH), 1615 (C=N), 1553 (Ar-C=C), 810 (C-Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 9.44 (1 H, s), 8.90 (1 H, s), 8.26 (1 H, d, *J* 2.2), 7.95 (1 H, dd, *J* 7.2, 2.9), 7.81 (1 H, dd, *J* 8.5, 3.1), 7.60 – 7.52 (2 H, m), 7.36 – 7.29 (2 H, m), 7.22 (1 H, dd, *J* 5.9, 2.0), 7.07 – 7.00 (1 H, m); ^{13}C NMR (100 MHz, DMSO-d_6, δ in ppm): 118.0, 119.4, 120.5, 120.9, 121.3, 125.3, 129.3(Cl-C-), 130.6, 134.3, 134.6, 153.3, 154.3 (-N=C-), 156.1 (-N=C-S), 162.1 (OH-C-); EI-MS (*m/z*): 289 (M^{+1})

6-Chloro-*N*-(4-methoxybenzylidene)benzo[*d*]thiazol-2-amine (3b):

Molecular formula: $C_{15}H_{11}ClN_2OS$, Molecular Weight: 302.78 g/mol, Color: Lemon Yellow, IR(cm^{-1}): 3088 (Ar-H), 2977 (aliphatic CH), 1612 (C=N), 1540 (Ar-C=C), 815 (C-Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 8.20 (1 H, d, *J* 4.4), 8.06 (1 H, d, *J* 8.8), 7.75 (2 H, d, *J* 5.6), 7.58 (1 H, s), 7.29 (2 H, d, *J* 8.4), 7.20 (1 H, dd, *J* 8.9, 3.2), 3.86 (3 H, s); ^{13}C NMR (100 MHz, DMSO-d_6, δ in ppm): 56.0 (-CH_3), 114.5, 114.5, 119.4, 120.9, 125.3, 128.3 (-C-C), 129.3 (Cl-C-), 132.3, 132.3, 134.6, 153.3, 153.6 (-N=C-), 156.1 (-N=C-S-), 164.1 (-O-C-); EI-MS (*m/z*): 303 (M^{+1})

2-(((6-Chlorobenzo[*d*]thiazol-2-yl)imino)methyl)-6-methoxyphenol (3c):

Molecular formula: $C_{15}H_{11}ClN_2O_2S$, Molecular Weight: 318.78 g/mol, Color: Yellow, IR (cm^{-1}): 3370 (Ar-OH), 3440 (O-H), 1620 (C=N), 1247 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 9.43 (1 H, s),

8.25 (1 H, s), 7.95 (1 H, d, *J* 8.7), 7.77 (1 H, s), 7.54 (1 H, dd, *J* 17.7, 9.1), 7.30 – 7.20 (2 H, m), 6.96 (1 H, t, *J* 4.9), 3.86 (3 H, s); ^{13}C NMR (100MHz, DMSO-d_6, δ in ppm): 56.8 (-CH_3), 118.9, 119.4, 120.9, 122.4 (-C-Ar), 125.0, 125.3, 129.3 (C-Cl), 134.6, 149.6 (-O-CH_3), 151.1 (OH-C-), 153.3, 155.4 (-N=C-), 156.1 (-N=C-S-); EI-MS (*m/z*): 319 (M^{+1}).

6-Chloro-*N*-(4-(dimethylamino)benzylidene)benzo[*d*]thiazol-2-amine (3d):

Molecular formula: $C_{16}H_{14}ClN_3S$, Molecular Weight: 315.82 g/mol, Color: Orange, IR(cm^{-1}): ; 3000 (Ar-CH), 1611 (C=C), 1610 (C=N), 1179 (C-N); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 8.77 (1 H, s), 7.92 (1 H, s), 7.80 (1 H, d, *J* 10.5), 7.62 (1 H, dd, *J* 9.3, 2.6), 7.09 (2 H, d, *J* 4.6), 6.68 (2 H, dd, *J* 8.9, 2.3), 3.09 – 3.01 (6 H, m); ^{13}C NMR (100MHz, DMSO-d_6, δ in ppm): 41.9 (-*N*-CH_3), 41.9 (-*N*-CH_3), 111.6, 111.6, 119.4, 120.9, 122.9, 125.3, 129.3(Cl-C-), 131.2, 131.2, 134.6, 153.3, 153.6 (-N=C-), 154.6 (-C-N(CH_3)$_2$, 156.1 (-N=C-S-); EI-MS (*m/z*): 316.1 (M^{+1}).

6-Chloro-*N*-(furan-2-ylmethylene)benzo[*d*]thiazol-2-amine (3e):

Molecular formula: $C_{12}H_7ClN_2OS$, Molecular Weight: 262.71 g/mol, Color: Brown, IR: 3012 (Ar-CH), 1603 (C=C), 1590 (C=N), 2000–700, 1225 and 1020; ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 8.78 (1 H, s), 7.92 (1 H, d, *J* 2.8), 7.81 (1 H, d, *J* 10.4), 7.62 (1 H, d, *J* 7.4), 7.22 (1 H, dd, *J*, 9.8, 3.1), 7.09 (1 H, d, *J* 10.4), 6.69 (1 H, t, *J* 5.0); ^{13}C NMR (100MHz, DMSO-d_6, δ in ppm): 112.8, 115.3, 119.4, 120.9, 125.3, 129.3(Cl-C-), 134.6, 145.0 (-O-C-), 145.9 (-C-O-), 153.3, 157.8 (-N=C-S-), 167.8 (-N=C-); EI-MS (*m/z*): 263 (M^{+1}).

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