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**Research Article**

# A CONVENIENT SYNTHESIS AND SPECTRAL STUDIES OF N, N-BIS ((2-CHLOROTHIAZOLE-5-YL) METHYL)-6-METHYLBENZO (D)THIAZOL-2-AMINE

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**A B S T R A C T**

4-methylaniline in chlorobenzene reacted with sulphuric acid, sodium thiocyanate and sulfuryl chloride to give 2-amino-6-methyl benzothiazole. This 2-amino-6-methyl benzothiazole was later further reacted with 2-chloro-5-chloromethylthiazole in the presence of N, N'-dimethyl formamide (DMF) and anhydrous potassium carbonate ($K_2CO_3$) to afford N,N-bis((2-chlorothiazole-5-yl)methyl)-6-methylbenzo(d)thiazol-2-amine.



## INTRODUCTION

Benzothiazoles are bicyclic ring systems with a thiazole ring fused with benzene. The substituted derivative of 2-amino-6-methyl benzotiazole comprises the broad spectrum for a number of biologically active compounds. In recent years, substituted benzothiazole are the most extensively investigated class of compounds, which exhibit various biological activities, such as antimicrobial, anti-inflammatory, anti-HIV and analgesic [9-12]. Further, there are few references available on the synthesis of heterocycles fused with an substituted methyl benzothiazole ring [1]. Very recently in 2016, Jaikhan, Pattaporn *et al* [14] reported the synthesis of N-((2-chlorothiazole-5-yl) methyl)-6-methylbenzo [d] thiazole-2-amine. Reaction scheme is given below-

***Reagents and conditions***

R: Triethylamine, S: Acetonitrile, 72 h, reflux

A large number of drugs and biologically relevant molecules contain heterocyclic systems. Often the presence of hetero atoms or groupings imparts preferential specificities in their biological responses. The chemistry and biological study of heterocyclic compounds has been interesting field for a long time due to medicinal and agricultural reasons. The number of heterocyclic derivatives containing nitrogen and sulfur atom possess broad spectrum of biological activities. One of the most important heterocycle in medicinal chemistry is substituted benzothiazole with wide application of Nicotinic Acetylcholine Receptor Antagonists [1]. And the other most important heterocycle in medicinal chemistry is pyridine with wide application including antimicrobial, anti-inflammatory, anti-HIV, antiplasmodial, anti-tubercular, antibacterial and anticonvulsant [2-8] activities (scheme-2), and has much other important biological significance.

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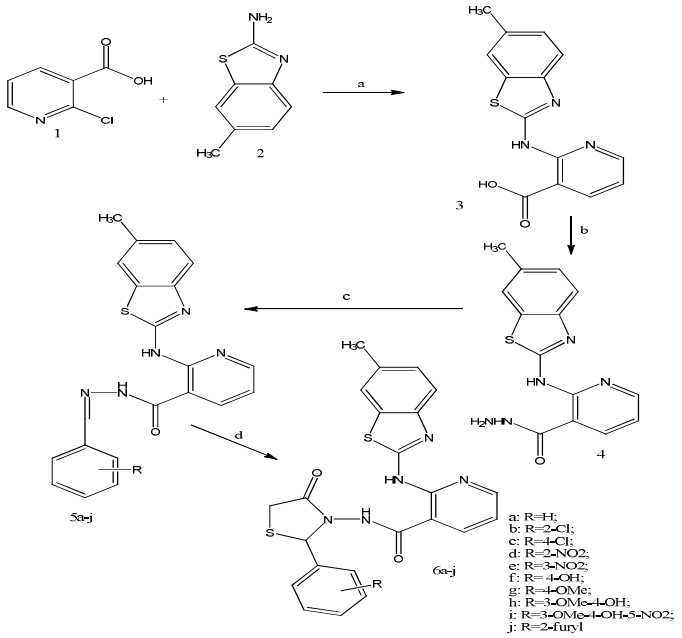



**Scheme 2**

Reagents and conditions: (a) Ullmann condensation, Cu-Bronze, anhydrous
$K_2CO_3$, DMF, reflux 5 h; (b) (i) $SOCl_2$ and (ii) $NH_2NH_2H_2O$ in $CHCl_3$; (c) substituted aromatic aldehydes, DMF, reflux 5-6 h; (d) $HSCH_2COOH$, anhydrous $ZnCl_2$, 1,4-dioxane 12-14 h

## MATERIALS AND METHODS

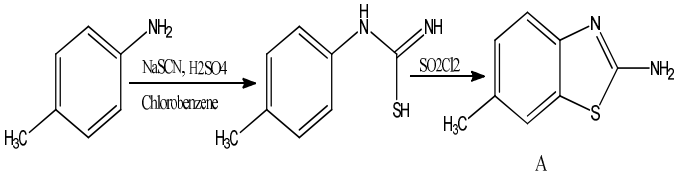
Melting points were recorded by open capillary method and are uncorrected. Infrared spectra were recorded on Agilent FT-IR (Diffuse reflectance attachment) using KBr. Spectra were calibrated against the polystyrene absorption at 1610 $cm^1$. 1H spectra were recorded on Bruker Avance II 400 spectrometer. Making a solution of samples in DMSO d6 solvents using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned, and are given in the δ scale. The standard abbreviations s, d, t, q, m, dd, dt, br s refer to singlet, doublet, triplet, quartet, multiplet, doublet of a doublet, doublet of a triplet, AB quartet and broad singlet respectively. Mass spectra were recorded on Waters LC - MS spectrometer using direct injection probe technique equipped with a standard electron spray-ionization (ESI) interface. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel-G $F_{254}$ aluminium plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light. The chemicals used for the synthesis of intermediates and end products were purchased from Spectrochem, Sisco Research Laboratories (SRL), Thomas Baker, Sd fine chemicals, Loba chemie and SU-Lab. All the reactions were carried out in Labguard fume hood which was locally modified for carrying out chemical reactions. All evaporation of solvents was carried out under reduced pressure on Buchi Rotaevaporator-100. % Yield reported are isolated yields of material judged homogeneous by TLC and after crystallization. Column chromatography was performed on silica gel 100-200 mesh. The structures and names of all compounds given in the experimental section and in physical data table were generated using Chem Draw Ultra 12.0. For all reactions, analytical grade solvents were used. All moisture-sensitive reactions were carried out in oven-dried glass-ware (135 °C). All HPLC analysis were performed on Shimadzu-UPLC 2010 using UV detector on C-18 reverse phase column and Acetonitrile - Water as mobile phase and diluents.

## RESULTS

***Synthesis of 2-amino-6-methyl benzothiazole (13)***

A solution of 5 g. (0.0466 mole) of 4-methylaniline in 30 ml. of chlorobenzene is prepared in a three-necked, round-bottom flask fitted with a stirrer, reflux condenser, thermometer, and dropping funnel. Over a period of 5 minutes, 2.5 g. (0.0225 mole) of concentrated sulfuric acid is added dropwise. To the finely divided suspension of p-toluidine sulfate is added 4.2 g. (0.0518 moles) of sodium thiocyanate, and the mixture is heated for 3 hours at 100° (inside temperature) in an oil bath. The solution, which now contains the thiourea, is cooled to 30°, and 8.45 g. (0.0626 moles) of sulfuryl chloride is added over a period of 15 minutes, with care that the temperature does not exceed 50°. The mixture is kept at 50° for 2 hours (no further evolution of hydrogen chloride), after which the chlorobenzene is removed by filtration.

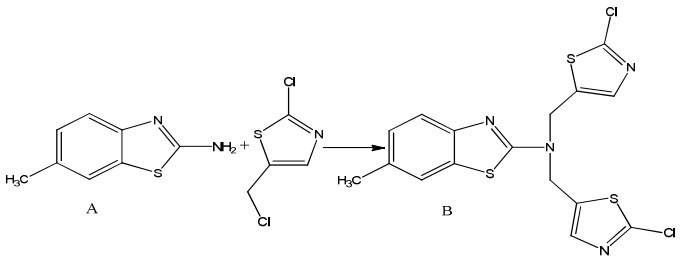
The solid residue is then dissolved in 100 mL. of hot water, alkaline the solution with concentrated ammonium hydroxide, The precipitated, 2-amino-6-methyl benzothiazole is filtered and washed with water. Solid product was washed with water, The crude product was isolated and crystallized from absolute ethanol. After drying to constant weight, the product weight 110 g. yield 67%, Melting point 135-136°C. 1H NMR (500 MHz, DMSO-d6) δ 7.43(s, 1H), 7.38 (s, 2H), 7.23-7.21 (d, 1H), 7.02-7.00(d,1H), 2.33-2.30(s,3H). LC-MS (AP+): m/z=164.23, calcd. for C8H8N2S (M+H+): 165.2.




A

***Synthesis of N,N-bis((2-chlorothiazole-5-yl)methyl)-6-methylbenzo(d)thiazol-2-amine***

A solution of 2-Chloro-5-chloromethyl thiazole (2.15g, 12.8mmole) in DMF (4mL) was added slowly to a stirred solution of 2-Amino-6-methylbenzothiazole (Cas no. 2536-91-6) (1g, 6.1mmol) and potassium carbonate (1.76g, 12.75mmol) in DMF (5mL) at 100 °C. The reaction mixture was stirred at 100 °C temperature for overnight. TLC (ethyl acetate: Hexane - 20:80), shows the reaction completion. Excess 2-Chloro-5-chloromethyl thiazole was quenched by the addition of an aqueous sodium hydroxide solution (50 mL). The reaction mixture was diluted with H2O (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried with Na2SO4, filtered, and concentrated in vacuo to give a off-white solid. This solid was further crystallized with methanol (100%) dried product at 50°C to give (1.24g, 48%). A sample was again crystallised from MeOH for melting point analysis. Mp 239°C (MeOH); 1H NMR (500 MHz, SMSO- d6) δ 7.736 (s, 2H), 7.641 (s ,1H), 7.445-7.479 (d, 1H); 4.947 (s,4H), 2.361 (s,3H), IR (KBr / cm-1) 2956, 2922, 2853, 2116, 1736, 1568, 1542, 1520, 1411, 1117, 1045, 812, LC-MS (ES+): m/z=427, calculated for C16H12N4S3 (M-H+): 427.



## CONCLUSION

All the reactions were performed in oven-dried glasswares and under nitrogen atmosphere. Column chromatography was performed using silica gel (60-120 mesh). All melting points are uncorrected and were recorded on open tube capillary method. 1H spectra were recorded at NMR Brucker 500 MHz. IR spectra were recorded on a Agilent technology FTIR spectrophotometer, using potassium bromide pellets; the frequencies are expressed in cm-1. Thin-layer chromatography was performed using commercially prepared 60 F254 silica gel plates and visualization was effected with short wavelength UV light (254 nm) and staining over an Iodine chamber. Liquid chromatography mass spectra were recorded on Waters Acquity UPLC system.

As a result, N, N-bis ((2-chlorothiazole-5-yl) methyl)-6-methylbenzo (d)thiazol-2-amine (B) is formed smoothly with the reaction of 2-amino-6-methyl benzothiazole (A), and 2-chloro-5 chloromethylthiazole. Reaction completed is in the presence of N,N-dimethylformamide and Potassium carbonate. Reactions proceeded in acceptable yields. These derivatives present a class of compounds that can be used as procedures for the synthesis of new derivatives with useful biological activities.

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