9. Microwave Assisted Synthesis, Characterization and Biological Activities of Some Newly Synthesized 3-Aryl-Substituted Benzothiazolyl Thiocarbamide

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Abstract

Heating reactions with traditional equipment, such as oil baths, sand baths and heating mantles, is not only slow but it creates a hot surface on the reaction vessel where products, substrates and reagents often decompose over time. A benzene solution of phenyl isothiocynate (1) (0.1 M, 1.35 g in 5 ml) was mixed with suspension of 2-amino benzothiazole (2a) (0.1 M, 1.50g in 5 ml) the vial was placed in microwave synthesis reactor with the conditions; Temp. 100°C and time 1–5 min. monitoring of reaction was carried out by TLC in ethyl acetate: hexane (1:4 solvent systems).and the time required for completion of reaction in microwave is varied from 1 to 3 minutes. The reactions were monitored with TLC intermittently for microwave assisted synthesis. After the completion of reaction benzene was distilled off and the sticky mass obtained as residue was triturated several times with petroleum ether (60-80^{o}C). Finally it was treated with ethanol then a white solid (1.5 g) was obtained. It was crystallized from aqueous ethanol, m.p. 151^{o}C. The newly synthesized compounds have been characterized by analytical and IR, ^{1}HNMR and Mass spectral studies. These compounds showed appreciable activity towards used strains of bacteria and fungi.

Keywords - phenyl isothiocynate, 2-amino benzothiazole, 3-substituted benzothiazolyl thiocarbamide.

Introduction

Microwave energy, in contrast, is introduced into the chemical reactor remotely and passes through the walls of the reaction vessel, heating the reactants and solvents directly. Microwave dielectric heating drives chemical reactions by taking advantage of the ability of some liquids and solids to transform electromagnetic radiation into heat wherein chemical reactions are accelerated because of selective absorption of microwave energy by the polar molecules[1] . A properly designed vessel allows the temperature increase to be uniform throughout the sample, leading to fewer by-

products and/or product decomposition. The use of microwave energy instead of conventional heating often results in good yields in a short time as compared with reaction by classical synthetic methods[2-4]. Benzothiazole is a heterocyclic compound weak base, having varied biological properties and still of great scientific interest now a day. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. They have also found application in industry as an antioxidant, vulcanization accelerators various benzothiazole such as 2-aryl benzothiazole received much attention due to unique structure and its uses as radioactive amyloidal imagining agent[5] and anticancer agent[6]. Benzothiazole are bicyclic ring system with multiple applications. A number of 2-aminobenzothiazole were intensively studied in medicinal chemistry[7-8] and reported cytotoxic on cancer cells[9]. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imagining agents[10], and anticancer agents[11]. Benzothiazoles are bicyclic ring system with multiple applications. A number of 2-aminobenzothiazoles were intensively studied, as in medicinal chemistry[12], and reported cytotoxic on cancer cells[12].

Materials and Methods

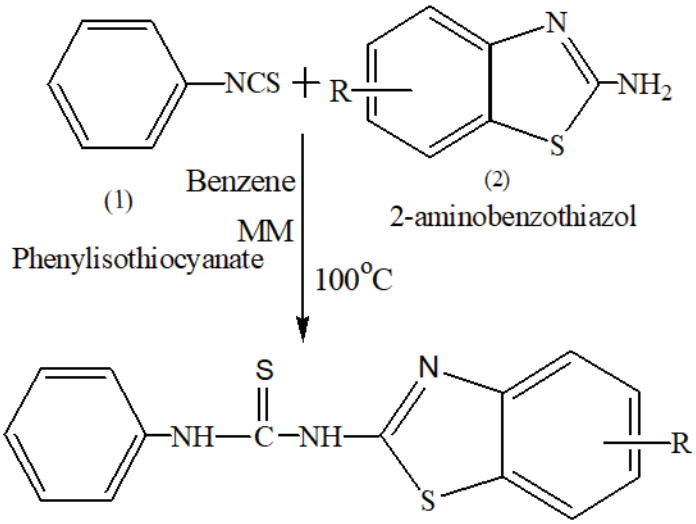
All chemicals were research grade. Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI (4000-450cm-1) spectrophotometer. 1H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in CDCl3 solution with TMS as internal reference. The Mass spectra were recorded on a WATERS, Q-TOF MICROMASS (LC-MS) Mass spectrometer. Optical rotation [α]D31 measured on a Equip-Tronics Digital Polarimeter EQ-800 at 310C in CHCl3. Thin layer chromatography (TLC) was performed on silica Gel G and spots were visualized by iodine vapour. The compounds describe in this paper were first time synthesized by the multistep reaction protocol.

Results and Discussion

Several 1-phenyl, 3-substituted aryl benzothiazolyl thiocarbamides (3a-d) have been synthesized by the interaction of various substituted benzothiazoles (2a-d) with phenyl isothiocyanate (1). A benzene solution of phenyl isothiocynate (1) (0.1 M, 1.35 g in 5 ml) was mixed with suspension of 2-amino benzothiazole (2a) (0.1 M, 1.50g in 5 ml) the vial was placed in microwave synthesis reactor with the conditions; Temp. 100°C, rpm-600, and time 1–5 min. monitoring of reaction was carried out by TLC in ethyl acetate: hexane (1:4 solvent systems).and the time required for completion of reaction in microwave is varied from 1 to 3 minutes. The

reactions were monitored with TLC intermittently for microwave assisted synthesis. After the completion of reaction benzene was distilled off and the sticky mass obtained as residue was triturated several times with petroleum ether (60-80oC). Finally it was treated with ethanol then a white solid (1.5 g) was obtained. It was crystallized from aqueous ethanol, m.p. 151°C. The IR spectra of products shows bands due to Ar-H, N-H, C=S, C=N, C-N, C-S stretching and 1HNMR spectra of products distinctly displayed signals due to aromatic protons and N-H Protons. The Mass spectrum of product was also observed. The identities of these new N-lactosides have been established on the basis of usual chemical transformations and also IR, 1H NMR and Mass spectral studies[13-15].

3a:- Synthesis of 1-phenyl, 3-phenyl benzothiazolyl thiocarbamide



R= (a) Phenyl, (b) o-Cl-phenyl, (c) m-Cl-phenyl, (d) p-Cl-phenyl,

3a: IR (KBr): υ 3363 (N-H), 3030 (Ar-H), 1629 (C=N), 1438 (C-C), 1309 (C-N), 1159 (C=S), 750 (C-S). H NMR (δ in ppm, CDCl3): δ7.156-7.321 (9H, S) δ7.508-7.438 (2H, S) Mass (m/z): 285 (M+), 225, 151; Anal. Calcd for $C_{14}H_{11}N_3S_2$: C, 65.26; H, 3.85; N, 14.75; S, 22.45; Found: C, 65.20; H, 3.81; N, 14.71; S, 22.42.

On the basis of all above facts the product with m. p. 151°C. Was assigned the structure 1-phenyl, 3-phenyl benzothiazolyl thiocarbamide (3a)

When the reaction of phenyl isothiocynate was extended to several other 2-amino benzothiazole corresponding 1-Phenyl-3-Substituted Aryl Benzothiazolyl thiocarbamide were prepared.

3c: IR (KBr): υ 3363 (N-H), 3030 (Ar-H), 1629 (C=N), 1438 (C-C), 1309 (C-N), 1159 (C=S), 750 (C-S). H NMR (δ in ppm, CDCl3): δ7.156-7.321 (9H, S) δ7.508-7.438 (2H, S) Mass (m/z): 319 (M+), 320, 280, 246; Anal. Calcd for C14H10N3S2Cl: C, 52.66; H, 3.13; N, 13.16; S, 20.06; Found: C, 52.70; H, 3.15; N, 13.20; S, 20.10.

Table -1: Physical data for Characterization of Compounds (3a-d)

Sr. No	Compd	Yield %	M.P. ^{0}C	R_f (pet ether: EtOAC) (1:1)	Analysis (%): Found (calcd)	
					N	S
1	Phenyl(3a)	80.00	151	0.65	14.71 (14.75)	22.44(22.45)
2	o-Chloro(3b)	79.00	121	0.58	13.12(13.16)	20.08(20.06)
3	m-Chloro(3c)	82.00	110	0.73	13.20(13.16)	20.10 (20.06)
4	p-Chloro(3d)	81.00	132	0.48	13.18(13.16)	20.02(20.06)

C and H analysis was found satisfactory in all cases.

Antimicrobial Activity

All the compounds were also screened for their antimicrobial activities by using disc diffusion assay[16]. The compounds were taken at a concentration or 1mg/ml using dimethyl sulphoxide as a solvent.

Antibacterial Activity

Inhibition zones read after incubation at 37^{0}C for 24 h. for bacterial strains. Amikacin (100 ug/ml) was used as standard for antibacterial. The compounds were screened for antibacterial activity against Escherichia coli, Staphylococcus aureus, in nutrient agar medium. It has been observed that all the compounds showed nearly same activity against bacteria. Compounds 3b, 3c exhibites most significant activity against Escherichia coli All other compounds exhibited low to moderate activity.

Applications

The synthesized benzothiazolyl thiocarbamides lead for the development of new drugs due to presence of sulphur and nitrogen in it. The applicability of synthesized compounds is also supported by the various references quoted in the script.

Conclusion

In this research work, the characterizations of newly synthesized products were established on the basis of UV, IR, 1H NMR, & Mass spectral studies. Various 1-phenyl, 3-substituted aryl benzothiazolyl thiocarbamide were synthesized and yield of product ranged from 75-85%.

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References

1. Varma RS. Solvent-free accelerated organic syntheses using microwaves. *Pure Appl Chem*;73:193–8, (2001)
2. Mavandadi F, Pilotti A. The impact of microwave-assisted organic synthesis in drug discovery. *Drug Discov Today*; 11:165–74, (2006).
3. Vasudevan A. Microwave-assisted organic synthesis an enabling technology with disruptive potential. *Drug Discov World*: 83–90. Fall, (2008).
4. Kidwai M. Dry media reactions. *Pure Appl Chem*; 73:147–51, (2001).
5. P. Reddy, Y. Lin and H. Chang, *Arkivoc; XVI*, 113-122, (2007).
6. Y. Heo, Y. Song, B. Kim, J. Heo., *Tetrahedral*, *Letter ,* 47, 3091-3094, (2006).

A. Rauf, S.Gangal and Sharma, *Indian J. Chem.,* **47B***,* 601-605, (2005).

7. F. Piscitelli, C. Ballastore, A. Smith, B*ioorg. Med, Chem ,* 20,644-648, (2010).
8. H. Suter and H. Zutter., *Helv. Chem. Acta.*, 50**,** 1048, (1976).
9. P. Reddy, Y. Lin and H. Chang, Arkivoc., xvi., 113-122 (2007).
10. Y. Heo, Y. Song, B. Kim and J. Heo , Tetrahedr. Letters. 47, 3091-3094 (2006)
11. F. Piscitelli, C. Ballatore and A. Smith, Bioorg. Med. Chem. Lett., 20, 644-648 (2010).
12. R. M. Silverstein and F. X. Webster, "Spectrometric Identification of Organic Compounds", 6th ed., John Wiley and Sons, Inc, New York; (2011).
13. D. H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", 5th ed., Tata McGraw-Hill; (2004).
14. J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", PHI Learning Private Limited, New Delhi; (2010).
15. J. G. Collee and W. Marr Laboratory control of anti-microbial therapy. In: college JG, Duguid JP, Fraser AG, Marmion BP (eds) Mackie and Mc Cartney *Practical Medical Microbiology*. 14th edition. Edinburgh Churchill Livingeston., pp. 114-115, (1996).