Iranian Journal of Organic Chemistry Vol. 6, No. 2 (2014) 1281-1285

Synthesis of iminosaccharides of 2-aminobenzothiazole: A comparative study of conventional and green chemical routes

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Received: April 2014; Revised: April 2014; Accepted: April 2014

Abstract: In this study, iminosaccharides of 2-aminobenzothiazole were synthesized using three different methods *i.e.* conventional synthesis, microwave assisted synthesis using ethanol as a solvent and microwave assisted solvent free synthesis using HY Zeolite as a solid support. Comparison of all mentioned methods has been presented, which clearly indicates that solvent free synthesis of iminosaccharides of 2-aminobenzothiazole in microwave afforded better yield in short time via eco friendly route as compared to other two methods. Iminosaccharides of 2-aminobenzothiazole was synthesized by the reaction of 2-aminobenzothiazole (**1**) with various hexoses (**2 a-e**). Structures of all the synthesized products have been elucidated on the basis of their elemental and spectral analysis.

Keywords: Iminosaccharides, 2-Aminobenzothiazole, Microwave irradiation, HY zeolite, Green synthesis.

Introduction

"Better things for better living through chemistry" has always been the motto of chemists to improve the general quality of life but there are some adverse outcomes due to all these endeavors undertaken by the scientists all over the world. That is why there is an increasing local and global concern for environmental pollution. This offers incentive to explore new greener route for chemical synthesis. Hence, efforts to minimize the major disadvantages of conventional synthesis, i.e. pollution, led to the advent of green chemistry. Microwave assisted organic synthesis (MAOS) is an important part of green chemistry. In the recent year MAOS has emerged as a new tool in organic synthesis [1-4]. The salient features of these high yield protocols are the enhanced reaction rates, greater selectivity and the experimental ease of manipulation.

Solvent creates environmental pollution in traditional methods and microwave-assisted synthesis also. But, if the reaction is carried out in a solvent-free condition by using clays, silica, zeolite or any other solid support, then it will be a green chemical method. Such reactions, not only take care of the environment but these are having easier work up and time saving also [5-8]. Therefore, a microwave-assisted synthesis on solid support avoids the use of solvent and it provides a clean and efficient technology giving higher yields in relatively in short time period and it is economically viable also.

Iminosaccharide are five or six member ring sugar analogues where a nitrogen atom has replaced the oxygen atom in ring of the structure. In other words,

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iminosaccharide are small organic molecules, which mimic monosaccharides but contain a nitrogen atom in place of the endocyclic oxygen. Iminosaccharide are important class of biologically compounds and play a vital role in medicinal chemistry. Iminosaccharide derivatives exert antiviral effects against several human viral pathogens including HIV, HBV, Dengue and Japanese Encephalitis viruses [9]. Iminosaccharides show anti-diabetic and anti-cancer activities with glycosidase and β-glycosidase inhibitory properties and work as therapeutic agents [10-16].

In view of the role of iminosaccharides in medicinal chemistry and urgent need of its green synthesis, it was planned to synthesis iminosaccharides of 2-aminobenzothiazole using three different methods including conventional and green synthesis and represents a comparative study for all these methods.

Results and discussion

The structures of the final products were established on the basis of their analytical and spectral data. Disappearance of two bands at 3400 and 3260 cm^{-1} due to -NH_2 stretching (symmetric and asymmetric) and appearance of bands in the region of 3300-3450 cm^{-1} for OH stretching and 1620-1640 cm^{-1} corresponding to C=N stretching confirms the assigned structure of iminosaccharides. In ^{1}H NMR spectrum the absence of signals at δ 5.81-5.88 due to proton of NH_2 and presence of a doublet for imino protons (CH=N-) at δ 8.50 and a singlet for OH proton at δ 5.01 favors the formation of final product **(3 a-e)**. The signals of proton of sugar chain were congregated with the solvent absorption in a broad signal at δ 4.49-3.60. Further, mass spectrum also supported the structure of iminosaccharides.

Reaction of 2-aminobenzothiazole (**1**) with various hexoses (**2 a-e**) in ethanol using acetic acid as a catalyst afforded iminosaccharides (Schiff bases) with azomethine linkage **(3 a-e)**. In this conventional method, 10-15 hours of refluxing is required. When the same reactions were carried out in microwave, the reaction time was reduced from hours to minutes and the yield of products was also increased. But in these processes ethanol and acetic acid is still to be used, which is not eco-friendly. Therefore, iminosugars were synthesized using zeolite as a solid support under microwave irradiation *i.e.* under solvent free conditions. As a result, solvent was eliminated from the synthesis and reaction time was also found to be reduced and the yield of product was also increased. A comparison of time required for synthesis of product and yield of products in conventional method and microwave methods (with and without using NaY zeolite) has been reported in Table **1**.

Table 1: Physical data of synthesized compounds.

Compounds	R	Mol. Formula	Mol. Weight	M.P. (°C)	Yield[a] (%) [Time] (hr.)	Yield[b] (%) [Time] (min.)	Yield[c] (%) [Time] (min.)
3a	D-Glucose	$C_{13}H_{16}N_2O_5S$	312	255-258	87 [12-14]	88 [17]	93 [14]
3b	D - Galactose	$C_{13}H_{16}N_2O_5S$	312	270-274	72 [12-13]	75 [16]	92 [10]
3c	D- Allose	$C_{13}H_{16}N_2O_5S$	312	292-296	68 [12-14]	75 [17]	92 [15]
3d	D-mannose	$C_{13}H_{16}N_2O_5S$	312	267-271	83 [13-15]	88 [18]	95 [12]
3e	D-Altrose	$C_{13}H_{16}N_2O_5S$	312	249-252	84 [13-16]	90 [20]	97 [15]

a = Conventional synthesis, b = Microwave assisted synthesis using solvent, c = microwave assisted solvent free synthesis using zeolite as a solid support

Antimicrobial Activity:

Five synthesized compounds (**3a-e)** were *in vitro* screened for their antibacterial and antifungal activity using 100 ppm concentration in DMF by cup and well method [17]. The micro-organisms used as antibacterial are *Escherichia coli, Bacillus subtilis,*

Proteus mirabilis, *Pseudomonas aeruginosa* and the fungal strains *Candida albicans* and *Aspergillus fumigatus* were used. The activity is presented as zone of inhibition in mm and compared with activity of controls C_1 (for antibacterial activity C_1= Ciprofloxacin and for antifungal activity C_1= Amphotericin B) giving activity index value (Table **2**).

Table 2: Antimicrobial activity of the synthesized compounds on 100 ppm (3a-e).
Zone of Growth Inhibition (mm) (activity index).

Compd. No.	Antibacterial Activity				Antifungal Activity	
	E. coli	*B. subtilis*	*P. mirabilis*	*P. aeruginosa*	*C. albicans*	*A. fumigatus*
3a	23 (1.43)	20 (1.17)	18 (1.12)	19 (1.05)	26 (1.52)	27 (2.70)
3b	24 (1.50)	22 (1.29)	17 (1.06)	18 (1.00)	27 (1.58)	28 (2.80)
3c	25 (1.56)	23 (1.35)	19 (1.18)	20 (1.11)	29 (1.70)	29 (2.90)
3d	21 (1.31)	21 (1.23)	17 (1.06)	17 (0.94)	28 (1.64)	26 (2.60)
3e	21 (1.31)	18 (1.05)	19 (1.18)	17 (0.94)	26 (1.52)	27 (2.70)
C_1	16	17	16	18	17	10

(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug.For antibacterial activity: C_1 = Ciprofloxacin
For antifungal activity: C_1 = Amphotericin B.

All the compounds have shown moderate activity against *P. aeruginosa* where as strong activity against *B. subtilis, P. mirabilis* and *E. coli*. Activity index value against *B. subtilis, P.mirabilis* and *E. coli* was more than one for all the synthesized compounds. It was observed that all the compounds show stronger activity then the standard used against fungal strain *Candida albicans* and *Aspergillus fumigatus.*

It may be concluded from the activity study that compounds **3c** and **3d** were found to be the strongest amongst all synthesized compounds. Compounds have more comprehensive fungus-inhibiting properties than that of the bacteria. Even two folds antifungal activity was observed than standards.

Conclusion

It is clear from Table **1** that yield of final products is highest for microwave assisted synthesis using zeolite and lowest for conventional synthesis. Moreover, time required for synthesis is lowest for solvent free conditions in microwave. Thus, synthesis of reported product in microwave using zeolite as a solid support and catalyst is an efficient and environmental benign route.

Experimental

All compounds and reagents were commercially available and were used without further purification. All the commercial reagents and compounds were purchased from Sigma Aldrich, Spectrochem, Himedia and Merck. All reactions were carried out in a domestic microwave oven (Videocon, Model No.–VH19SWWM-MM2). Melting points were determined in open capillaries and are uncorrected. All the reactions were monitored by thin layer chromatography (TLC) using TLC plate purchased from Merck, using ethyl acetate: n-hexane (2:8) as eluent and visualization was accomplished by iodine vapors. The IR spectra of compounds were recorded using KBr discs on FTIR RX1 Perkin Elmer Spectrophotometer. The Nuclear Magnetic Resonance spectra (NMR) were recorded on Bruker Advance II 400 spectrometer with DMSO–d_6 as a solvent using TMS as an internal standard. The FAB mass spectra were recorded on JEOL SX-102/DA-6000 mass spectrometer. Elemental analysis was conducted using a Perkin Elmer CHN analyzer.

Conventional synthesis of iminosaccharides of 2-aminobenzothiazole (3 a-e):

2-aminobenzothiazole (**1** 0.01 mol) and various hexoses (**2 a-e** 0.02 mol) were dissolved in ethanol and a few drops of acetic acid were added to it. Then the reaction mixture was refluxed for 15-25 hours. After cooling, the product separated was washed with H_2O and extracted with ethyl acetate. The combined organic layers were dried under anhydrous Na_2SO_4. The solvent was evaporated by vacuum distillation and the crude product was dried and purified by recrystallization from ethanol.

Microwave assisted synthesis of iminosaccharides of 2-aminobenzothiazole (3 a-e):

2-aminobenzothiazole (**1**, 0.01 mol) and various hexoses (**2 a-e**, 0.02 mol) were dissolved in ethanol and a few drops of acetic acid were added to it. The reaction mixture was transferred in an Erlenmeyer flask and irradiated under microwave irradiation for 10 min with a time interval of 30 seconds. After cooling, the product separated was washed with H_2O and extracted with ethyl acetate. The combined organic layers were dried under anhydrous Na_2SO_4. The solvent was evaporated by vacuum distillation and the crude product was dried and purified by recrystallization from ethanol.

Microwave assisted solvent free synthesis of iminosaccharides of 2-aminobenzothiazole using HY Zeolite as a solid support and catalyst (3a-e):

2-aminobenzothiazole (**1**, 0.01 mol), various hexoses (**2**, a-e 0.02 mol) and HY zeolite (4.0 g) were mixed in pestle and mortar and irradiated under microwave irradiation for 10-15 min. The product was separated from zeolite by stirring it with ethanol for 15-20 min two to three times and evaporating the solvent by vacuum distillation. Product was purified by recrystallization from ethanol. Zeolite was reused after washing with ethanol and drying in air overnight.

Compound **3a:** IR (KBr): 3430, 3329 (OH str.), 3085 (CH str., Ar-H), 2940, 2880 (CH str.), 1590 (cyclic C=N str.), 1638 (open C=N str.), 1530, 1460, and 1423 (C=C str.) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.50 (d, 1H, CH=N), 7.76 – 7.10 (m, 9H, Ar-H), 5.01 (s, 1H, OH), 4.49–3.60 (sugar proton); ^{13}CNMR: 68.34, 70.12, 72.32, 73.21, 74.21, 117.54, 118.43, 121.11, 122.78, 135.92, 156.11, 168.54, 170.05; Mass (m/z): 312 $[M]^{+\cdot}$, 178 [M-C_7H_4NS], 161 [M-$C_5H_{11}O_5$], 164 [M-$C_9H_6N_2S$], 151 [M-$C_8H_5N_2S$], 148 [M-$C_6H_{12}O_5$], 134 [M-$C_6H_{12}O_5N$], 66 [M-$C_7H_{12}NO_5S$]; Analytical data calculated / Found: C - 49.99 / 49.95, H - 5.16 / 5.18, N - 8.97 / 8.99

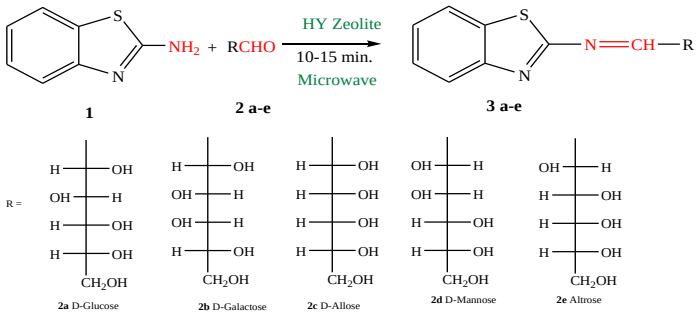
3b: IR (KBr): 3428, 3320 (OH str.), 3088 (CH str., Ar-H),2942, 2882 (CH str.),1596 (cyclic C=N str.), 1636 (open C=N str.), 1533, 1464,1428 (C=C str.); ^{1}HNMR (400 MHz, DMSO-d_6)**:** 8.59 (d, 1H, CH=N),7.78 – 6.97 (m, 9H, Ar-H),5.11 (s, 1H, OH),4.56 – 3.39 (sugar proton): ^{13}CNMR:67.12, 70.12, 71.65,72.34,73.89, 118.23, 119.02, 121.11, 123.55, 136.23, 158.10, 169.62, 171.90: Analytical data calculated / Found: C- 49.99 / 49.94, H- 5.16 / 5.21, N- 8.97 / 8.99

3c: 3424 (OH str.), 3078, 3310 (CH str., Ar-H),2944, 2889 (CH str.), 1594 (cyclic C=N str.), 1630 (open C=N str.), 1540, 1462, 1412 (C=C str.); ^{1}HNMR (400 MHz, DMSO-d_6)**:**8.59 (d, 1H, CH=N), 7.78 – 6.97 (m, 9H, Ar-H), 5.11 (s, 1H, OH),4.56 – 3.39 (sugar proton): ^{13}CNMR:68.2 72.11, 74.25, 74.81, 75.21, 120.12, 120.56, 121.56,122.90, 139.11, 160.16, 170.78, 174.67. Analytical data calculated / Found: C- 49.99 / 49.98, H- 5.16 / 5.19, N-8.97 / 9.00

3d: 3426, 3312 (OH str.), 3087 (CH str., Ar-H),2945, 2886 (CH str.), 1593 (cyclic C=N str.), 1633 (open C=N str.), 1533, 1455, 1418 (C=C str.),^{1}HNMR (400 MHz, DMSO-d_6)**;** 8.54 (d, 1H, CH=N), 7.75 – 7.16 (m, 9H, Ar-H), 5.09 (s, 1H, OH), 4.53 – 3.62 (sugar proton) ^{13}CNMR: 69.11, 73.34, 73.88, 74.12, 75.21, 120.11, 121.56, 121.89,122.03, 138.22, 158.21, 168.34, 172.69. Analytical data calculated / Found: C- 49.99 / 49.96, H-5.16 / 5.20, N-8.97 / 9.01

3e: 3428, 3334 (OH str.), 3082 (CH str., Ar-H), 2943, 2877 (CH str.), 1600 (cyclic C=N str.), 1636 (open C=N str.),1528, 1461, 1424 (C=C str.), ^{1}HNMR (400 MHz, DMSO-d_6); 8.60 (d, 1H, CH=N), 7.70 – 7.21 (m, 9H, Ar-H),5.12 (s, 1H, OH), 4.44–3.63 (sugarproton),^{13}CNMR:69.21,70.29.70.91,71.45,71.78, 119.01,120.56,120.94,121.11,139.62,159.56, 169.23,172.34. Analytical data calculated /Found: C- 49.99 / 50.01, H-5.16 / 5.21, N-8.97 / 8.92.

The syntheses of compounds (**3a-e**) are shown in Scheme **1** given below:



Scheme 1: Synthesis of iminosaccharides of 2-aminobenzothiazole

Acknowledgements

The authors would like to thanks **University Grant Commission** (UGC) for the financial support through UGC minor research project. The authors are also thankful to Dr. T. P. Sharma, Director, V.B.R.I. Udaipur for providing laboratory facilities and to the Director, SAIF (Sophisticated Analytical Instrument Facility) Punjab University, Chandigarh, for spectral and analytical studies.

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