Synthesis and characterization of n-(4 sulfamoylphenyl) benzamide derivatives

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ABSTRACT

A series of molecules containing sulfonyl and amide coupling structure were developed, synthesized and characterized. Sulfonamides are a very important class of compounds in the pharmaceutical industry. In this work, a new class of sulfonamide derivatives is being synthesized from 4-aminobenzene-1-sulfonamide with benzoic acid and its derivatives (1a-ah) using peptide coupling reagent EDCI and HOBt with different melting point. The progress of reaction was monitored by the use of thin layer chromatography and the structures of the synthesized compounds were elucidated and confirmed by FT-IR, $^1$H NMR and $^{13}$C -NMR spectroscopic analysis.

Keywords: Benzamide, Benzoic acid, FTIR, H NMR, Sulfonamides

INTRODUCTION

Sulfonamides are a very important class of compounds in the pharmaceutical industry, being widely used as anticancer, anti-inflammatory, antiviral agents (Hansch et al., 1990) and well known for their antibacterial and enzyme inhibitor properties (Pandya et al., 2003). Sulfonamide derivatives have continuously absorbed attention of the medicinal chemists in view of their intense range of biological activities (Rostom et al., 2006; Rami et al., 2011; Moeker et al., 2012). Sulfonamides comprise a significant class of drugs with diverse biological properties such as antimicrobial (Genç et al., 2008; Ozbek et al., 2007), anticancer (Mun et al., 2012; El Sayed et al., 2011), anti-inflammatory (Borne et al., 1974), and antiviral activities as well as HIV protease inhibitors (De Clercq et al., 2001). Benzamide is a carboxylic acid amide of benzoic acid. Amide is a group of organic chemicals with the general formula RCO-NH$_2$ in which a carbon atom is attached to oxygen in double bond and also attached to an hydroxyl group, where ‘R’ groups range from hydrogen to various linear and ring structures or a compound with a metal replacing hydrogen in ammonia such as sodium amide, NaNH$_2$. Amides are divided into subclasses according to the number of substituents on nitrogen. The primary amide is formed by replacement of the carboxylic hydroxyl group by the NH$_2$ amino group. An example is acetamide (acetic acid+amide). The secondary and tertiary amides are the compounds in which one or both hydrogens in primary amides are replaced by other groups. The names of secondary and tertiary amides are denoted by the replaced groups with the prefix capital N (meaning nitrogen) prior to the names of parent amides. Low molecular weight amides are soluble in water due to the formation of hydrogen bonds. Primary amides have higher melting and boiling points than secondary and tertiary amides (Asif., 2016). In this paper, we described synthesis and characterization studies of N-(4-sulfamoylphenyl) benzamide derivatives.

MATERIALS AND METHODS

Chemicals and all solvents (analytical grade) were purchased from the commercial firms, Sigma Aldrich, Rankem and Hi-Media. All the reactions requiring anhydrous conditions were conducted in flame dried
apparatus. The synthesis was carried out in 0°C to room Temperature. Melting points were determined in open capillaries on a Perfit India digital melting point apparatus and are uncorrected. Thin layer chromatography (TLC) were performed to monitor the reaction and to determine the purity of the products using TLC plates pre-coated with silica gel GF\textsubscript{254} aluminium sheets, Merck (Germany), employing CHCl\textsubscript{3}:MeOH (9:1, chloroform:methanol) as eluent and spots were visualized under iodine vapors and Ultraviolet (UV) irradiation. IR spectra (4000-400 cm\textsuperscript{-1}) were recorded on a Perkin Elmer IR spectrophotometer using KBr Pellets. \textsuperscript{1}H-NMR spectra were recorded in DMSO-d\textsubscript{6} as solvent on Bruker Avance 500 MHz model spectrophotometer and tetramethysilane (TMS) as an internal standard with \textsuperscript{1}H resonant frequency of 500 MHz and chemical shifts are expressed as δ (ppm). The IR and \textsuperscript{1}H-NMR spectral analysis were performed in SASTRA University, Tanjaore, India.

**General procedure for synthesis of N-(4-sulfamoylphenyl)benzamide derivatives**

![Scheme](image)

A 100 ml round bottom flask fitted with magnetic stirrer was charged with 4-aminobenzene-1-sulfonamide (A, 0.7g, 0.004M), benzoic acid (B, 0.56 g, 0.004M), EDCI (0.76 g, 0.0042mol), HOBt (0.52 g, 0.0042M) in 15 ml THF. To the resulting solution was added with TEA (2.7 ml, 0.020M) at 0°C. The reaction mixture was allowed to RT and stirred for few hours. After addition of water (100 ml), the solution was extracted with ethyl acetate. The organic layer was extracted with 2N HCl, 10% NaHCO\textsubscript{3} and brine solution. The combined organic layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure to afford final products 1a-1h (Table.1).

**Table 1. Physicochemical parameters used in the synthesis of N-(4-sulfamoylphenyl)benzamide derivatives**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Functional Group (R)</th>
<th>Temperature (°C)</th>
<th>Time (Hrs)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>H</td>
<td>RT</td>
<td>6</td>
<td>1a</td>
<td>2</td>
</tr>
<tr>
<td>2.</td>
<td>CH\textsubscript{3}</td>
<td>35</td>
<td>7</td>
<td>1b</td>
<td>76</td>
</tr>
<tr>
<td>3.</td>
<td>OC\textsubscript{2}H\textsubscript{5}</td>
<td>RT</td>
<td>7</td>
<td>1c</td>
<td>71</td>
</tr>
<tr>
<td>4.</td>
<td>C\textsubscript{2}H\textsubscript{5}</td>
<td>40</td>
<td>7.5</td>
<td>1d</td>
<td>69</td>
</tr>
<tr>
<td>5.</td>
<td>C\textsubscript{2}H\textsubscript{5}</td>
<td>RT</td>
<td>7</td>
<td>1e</td>
<td>76</td>
</tr>
<tr>
<td>6.</td>
<td>OH</td>
<td>RT</td>
<td>7</td>
<td>1f</td>
<td>77</td>
</tr>
<tr>
<td>7.</td>
<td>Cl</td>
<td>RT</td>
<td>6</td>
<td>1g</td>
<td>75</td>
</tr>
<tr>
<td>8.</td>
<td>NH\textsubscript{2}</td>
<td>RT</td>
<td>7</td>
<td>1h</td>
<td>71</td>
</tr>
</tbody>
</table>

**RESULTS AND DISCUSSION**

**Analytical data for N-(4-sulfamoylphenyl) benzamide derivatives**

N-(4-sulfamoylphenyl) benzamide (1a)
Yield- 72%, mp 171°C. \textsuperscript{1}H NMR (500 MHz, DMSO-d\textsubscript{6}), δ ppm: 7.31 (s,2H), 7.42 (s,1H), 7.38 (d,2H, J=9.1Hz), 7.84 (d,2H,J=8.7Hz), 7.91 (d,2H, J=9.1Hz), 7.96 (d,2H, J=8.7 Hz), 9.20 (s,1H). \textsuperscript{13}C –NMR (151 MHz, DMSO-

Yield - 71%, mp 169°C 1H NMR (500 MHz, DMSO-d6), δ ppm: 7.17 (s,2H), 6.90 (d,2H, J=9.1Hz), 7.92 (d,2H, J=9.0 Hz), 9.35 (s, 1H). 13C –NMR (151 MHz, DMSO-d6) δ ppm: 126.8(C1), 129.1 (C2,C6), 115.4(C3,C5), 148.7 (C4), 15.5 (CH3), 29.2 (CH2) 165.7(C=O), 142.1(C1’), 119.0 (C2’, C6’), 130.4(C3’,C5’), 137.5(C4’). IR 1648 cm⁻¹ (CO), 3441 cm⁻¹(NH), 1127 cm⁻¹ (SO2v=1), 1464 cm⁻¹ (SO2v=2), m/e =304(M⁺).

4-methoxy-N-(4-sulfamoylphenyl)benzamide (1e) Yield - 76%, mp 186°C 1H NMR (500 MHz, DMSO-d6), δ ppm: 7.85 (s,2H), 3.83 (s,3H), 7.17 (d,2H,J=9.1Hz), 7.84 (d,2H,J=8.7Hz), 7.92 (d,2H, J=9.0 Hz), 9.35 (s, 1H). 13C –NMR (151 MHz, DMSO-d6) δ ppm: 127.5 (C1), 129.5 (C2,C6), 115.4(C3,C5), 165.0 (C=O), 142.1(C1’), 119.0 (C2’, C6’), 130.4(C3’,C5’), 137.5(C4’). IR 1636 cm⁻¹ (CO), 3416 cm⁻¹(NH), 1108 cm⁻¹ (SO2v=1), 1421 cm⁻¹ (SO2v=2), m/e =306(M⁺).

4-hydroxy-N-(4-sulfamoylphenyl)benzamide (1f) Yield - 75%, mp 156°C 1H NMR (500 MHz, DMSO-d6), δ ppm: 7.45 (s, 2H), 7.67 (d, 2H, J=9.1Hz), 7.84 (d, 2H, J=8.7Hz), 7.96 (d, 2H, J=9.1 Hz), 9.73 (s, 1H). 13C –NMR (151 MHz, DMSO-d6) δ ppm: 133.1(C1), 131.1 (C2,C6), 129.9 (C3,C5), 138.5 (C4), 165.7(C=O), 142.1(C1’), 119.6 (C2’, C6’), 130.1(C3’,C5’), 137.8 (C4’). IR 1647 cm⁻¹ (CO), 3395 cm⁻¹(NH2), 1147 cm⁻¹ (SO2v=1), 1429 cm⁻¹ (SO2v=2), m/e =311(M⁺).

The target compounds have been synthesized by the method outlined in Scheme-1. The preparation of N-(4-sulfamoylphenyl) benzamide derivatives were achieved by reacting 4-aminobenzen-1-sulfonamide (A) with benzoic acid (B) in the presence of coupling reagents. Progress of reaction was monitored on the TLC plate. The IR and 1H-NMR spectrum of synthesized compounds (1a-1h) exhibited four sets of doublet appearing in the

region δ 7.29-8.03 for eight protons revealed the presence of two aromatic rings in resulting synthesized compounds. The signals appeared near δ 9.3 ppm is due to new amide NH protons. The peaks of aromatic protons were observed at δ 7.96 ppm and were found to be in accordance with substitution pattern on phenyl ring. Similarly Mahdavi (2014) and coworkers synthesized, docked 3-aryloyl-1-(4-sulfamoylphenyl)thiourea derivatives and carried out biological evaluations. Saleem et al., (2018) have reported the design, synthesis and characterization studies on three different sulphonamide derivatives.

The IR spectra of 1a-h show three bands at 3034-3089 cm⁻¹, 1340 cm⁻¹ and 1160 cm⁻¹ indicative of NH and SO₂ groups. Mass spectrum showed the expected molecular ion peak and fragmentation pattern is according with the proposed structure were shown in Fig 1. Many researchers, Behmadi et al., (2009) have used the same characterization techniques to evaluate the nature of synthesized compounds (disulfonamides), Savant et al., (2017) demonstrated the process of sulfonamide group bearing pyrazolopyridones with high yields, Pawar et al., (2017) have designed and synthesized a series of molecules containing sulfonamide coupling and amide coupling structures.

Fig.1. FTIR Spectra

CONCLUSION

In conclusion, we have synthesized new sulfonamides 1a-h containing benzamide using EDCI and HOBt coupling agents. The reaction was carried out under easy conditions and is high yielding and product isolation is very forthright. A number of derivatives of the title compounds with different substituents were synthesized to show the diversity of the method.

REFERENCES


