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Synthesis and characterization of benzoylated sulfamoyl carboxylic acids

Abstract

The systematic synthesis of new benzoylated sulfamoyl carboxylic acids derivatives is reported. The process involved the mild reaction of benzoyl chloride with sulfamoyl carboxylic acids in the presence of sodium hydroxide via benzoylation reaction mechanism. The characterization of the compounds was done using FTIR,[1]H-NMR, [13]C-NMR and elemental analysis.The synthesized compounds were found to agree perfectly with the spectra data confirming the successful synthesis of benzoylated sulfamoyl carboxylic acids. The yields of the compounds were between 60% and 99% while their melting points were in the range 105°C to 113°C. Compounds 2b (3.04g, 98.7%) and 2g (3.04g, 98.5%) gave the highest yields while compound 1a (1.50g, 62.5%) gave the smallest yield. The reaction methodology was found to be efficient thereby resulting to excellent yields of benzoylated sulfamoyl carboxylic acids.

Keywords: benzoylation, sulphamoyl carboxylic acids, benzyl chloride, synthesis

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Introduction

Benzoylation is a reaction process that incorporates a benzoyl group (C_6H_5CO-) into a compound.[1,2] this reaction method is carried out *via* a facile and efficient methodology, wherein the benzoylating agent provides the needed benzoyl group. benzoyl chloride and Lewis acids are generally employed as benzoylating agents.[3] Benzoylation process enables the prevention of unwanted side reactions and ensures regioselectivity which could not be achieved with alkylation.[4,5] Being essential in organic synthesis, benzoylation can be used in the identification and characterization of amines[4] including the protection of amino functional groups of sulfonamides during aminolysis and amonnolysis.[6,7] Sulfonamides being the amides of euphonic acids are pharmacologically active agents[8] with significant antimicrobial,[9] ant malarial, anticancer, antithyroid,[10] antioxidant activities,[11] and they are usually a first line drug of choice in the treatment and management of acute systematic or local infections. Several disease conditions such as coccidiosis, metritis and respiratory infections can also be treated with sulfonamide drugs.[12,13] In spite of the versatility of benzoylated sulphonamides in pharmacy and chemical industries, there is just a few report on synthesis of these important pharmaceutical compounds and their derivatives. Considering the usefulness of benzyl and sulfonamide functionalities, we found it necessary to synthesize and characterize certain benzoylated sulfamoyl carboxylic acids.

Materials and methods

Chemistry

Reagents were sourced from Sigma Aldrich. Melting points of the synthesized compounds were determined using electrothermal melting point apparatus and were uncorrected. Infrared spectra data were recorded on 8400s Fourier Transform Infrared (FTIR) (ABU, Zaria, and Kaduna State, Nigeria). Nuclear Magnetic Resonance (1H-NMR and [13]C-NMR) were run on 400MHz using NMR spectrophotometer at SandeepVermaLaboratory, Department of Chemistry, Indian Institute of Technology, and Kanpur. Chemical shifts were reported in δ scale (neat) using Tetramethyl silage as a standard. The elemental analysis was carried out with elemental analyzer (Exeter Analytical Inc. model:CE440). Precipitation of the tittle compounds was in analytical grade and the reactions were monitored using TLC.

Synthesis of alkanoylated 4-methylphenyl sulphonamides

Using a 100ml beaker, 2grams of the various sulfamoyl carboxylic acids was dissolved in 5ml of 1molar sodium hydroxide 1.5mmol of benzoyl chloride was added in three portions over a period of one hour and stirred for 2 hours to ensure complete dissolution of the solutes. The solution was cooled to 0°C after stirring and acidified to pH of 2 using Hydrochloric acid (2M) to enable crystallization. It was filtered by suction and recrystallized with Carbon tetrachloride (5ml) to obtain benzoylated sulfamoyl carboxylic acids in good to excellent yields.

2-{benzoyl [(4-methylphenyl) sulfonyl] amino} propanoic acid (2a)

A white solid, yield 1.50g(62.5%), mp103-104°C, IR (KBr) cm-[1]:3311 (O-H); 2981(C-Aliphatic) 1982(C-H aromatic); 1792, 1681(C=O); 1641, 1602 (C=C); 1323, 1289 (2S=O);1177 (SO_2-N); 1123, 1119 (C-N); 741 (Ar-H).[1]H-NMR ($DMSOd_6$, 400 MHz)δ: 8.967-8.948 (d, J=7.8.Hz, 2H, ArH), 7.525-7.506 (d, J=8.4 Hz, 2H, ArH), 7.654-7.635(m, 2H, ArH) 7.194-7.175(m, 3H, ArH), 5.735 (s-br, 1H, OH), 2.499 (s,3H, CH3-Ar), 2.185-2.168(t, J= 7.4 Hz, IH, CH-

CH_3), 1.231-1.123(m, 3H, CH_3-CH). ^{13}C-NMR ($DMSOd_6$, 400MHz) δ: 172.252, 169.249 (C=O); 149.939, 144.134, 138.615, 128.477, 125.355, 123.353, 121.122, 120.543 (aromatic carbons); 38.143, 21.349, 19.553 (aliphatic carbons). Anal.calcd (%) for $C_{17}H_{17}NO_5S$ (347.08): C, 58.78; H, 4.90; N, 4.03; S, 9.21. Found: C, 58.81; H, 4.88; N, 4.05; S, 9.19.

2-[benzoyl (phenylsulfony) amino] propanoic acid (2b)

A white solid, yield 3.04g (98.7%), mp.101-102°C, IR (KBr) cm-^{1}: 3335 (O-H); 2981 (C-H aliphatic) 1988 (C-H aromatic); 1793, 1677(C=O); 1651, 1613 (C=C); 1324, 1285 (2S=O);1179(SO_2-N); 1113, 1025(C-N); 704(Ar-H). ^{1}H-NMR ($DMSOd_6$, 400 MHz)δ: 8.478-8.459 (m,2H, ArH),7.336-7.317 (d, J=8.2 Hz, 2H, ArH),7.211-7.172(m, 2H, ArH) 7.168-7.101 (m, 3H, ArH), 5.037 (s-br, 1H, OH), 2.954-2.926(t, J = 7.7 Hz, IH, CH-CH_3), 1.531-1.283(m, 3H, CH_3-CH).^{13}C-NMR($DMSOd_6$,400MHz):173.358,168.248(C=O);146.938,143.139,136.610,127.479,5.356,122.358,120.127,118.545(aromaticcarbons);37.143,18.554(aliphaticcarbons).Anal.calcd(%)for $C_{17}H_{17}NO_5S$(332.08): C, 58.82; H,4.22; N, 4.22; S, 9.64. Found: C, 58.84; H, 4.19; N, 4.23; S, 9.61.

2-{benzoyl [(4-methylphenyl) sulfonyl] amino}-3-sulfanylpropanoicacid (2c)

Dark tan solids, yield 1.95g (79.8%), mp 110 -111°C, IR (KBr) cm-^{1} : 3389 (O-H), 2821(C-H aliphatic); 2560 (S-H); 1994 (C-H aromatic); 1712, 1684 (C=O); 1623, 1612 (C=C); 1222, 1271 (S=O); 1121 (SO_2NH); 1131, 1127 (C-N); 704 (Ar-H). ^{1}H-NMR ($DMSOd_6$, 400 MHz) δ: 8.457-8.439 (d, J=7.9.Hz, 2H, ArH), 8.321-8.303 (d, J=8.2 Hz, 2H, ArH), 7.551 -7.452(m,2H, ArH) 7.025-7.016(m, 3H, ArH), 5.442 (s-br, 1H, OH), 4.724(s, IH, SH), 2.521 (s,3H, CH3-Ar), 2.229-2.206(t, J=7.1 Hz, IH, CH-CH_3), 1.457-1.321(m, 3H, CH_2-SH). ^{13}C-NMR ($DMSOd_6$, 400 MHz)δ: 173.412,170.233 (C=O);147.123, 146.239,137.616,126.479,125.981,122.146, 120.258, 120.141 (aromatic carbons); 40.142, 28.345, 17.558 (aliphatic carbons). Anal. calcd (%) for $C_{17}H_{17}NO_5S_2$ (379.14): C, 53.81; H, 4.52; N, 4.03; S, 16.88. Found: C, 53.78; H, 4.49; N, 4.05; S, 16.91.

2-[benzoyl (phenylsulfonyl) amino]-3-sulfanylpropanoic acid (2d)

Dark tan solids, yield 2.50g (92.8%), mp 113 -114°C, IR (KBr) cm-^{1} :3388 (O-H), 2825(C-H aliphatic); 2569 (S-H); 1999 (C-H aromatic); 1736, 1677 (C=O); 1631,1617 (C=C); 1289, 1279(S=O);1121 (SO_2NH);1127,1025(C-N); 709 (Ar-H).^{1}H-NMR($DMSOd_6$,400 MHz)δ: 8.726-8.701 (d, J=8.1.Hz, 2H,ArH), 8.459-8.403 (m, 3H, ArH), 7.941-7.832(m,2H, ArH), 7.021-7.014(m, 3H, Ar H), 5.112 (s-br, 1H, OH), 4.891(s, IH, SH), 2.429-2.406(t, J=7.2 Hz, IH, CH-CH_3),1.432-1.321(m,3H,CH_2-SH).^{13}C-NMR($DMSOd_6$,400MHz) δ:174.419,169.238(C=O);149.126,148.238, 139.619,125.474,124.984,123.149,121.259,120.168 (aromaticcarbons);31.145,9.347,15.552 (aliphaticcarbons). Anal.calcd (%) for $C_{16}H_{14}NO_5S_2$ (364.1)4: C, 52.73; H, 3.88; N, 3.84; S, 17.58. Found: C, 52.70; H, 3.91; N, 3.83; S, 17.61.

2-{benzoyl [(4-methylphenyl) sulfonyl] amino}-3-hydrroxypropanoic acid (2e)

Light yellow solids, yield 2.976g(89.8%), mp105-106°C, IR (KBr) cm-^{1}:3630, 3311(O-H), 2993(C-H aliphatic); 1923(C-H aromatic); 1729, 1684 (C=O); 1644, 1620 (C=C); 1319, 1226(S=O); 1159 (SO_2NH); 1130, 1121 (C-N); 682 (Ar-H). ^{1}H-NMR ($DMSOd_6$, 400 MHz)δ: 8.882-8.863 (d, J=7.7.Hz, 2H, ArH), 8.424-8.403(d, J=7.9 Hz, 2H, ArH), 7.786-7.652(m, 2H, ArH) 7.123-7.104(m, 3H, ArH), 5.042 (s-br, 1H, OH), 4.424(s, IH, SH), 2.341 (s, 3H, CH3-Ar), 3.113-3.096(t, J=7.6 Hz, IH, CH-CH_3), 1.862-1.632(m, 3H, CH_2-OH). ^{13}C-NMR ($DMSOd_6$, 400 MHz)δ: 174.412, 168.236 (C=O);140.125, 139.239, 136.619, 128.475, 127.982, 120.143, 119.251, 116.142(aromatic carbons); 32.149, 23.348, 15.551 (aliphatic carbons). Anal.calcd(%) for $C_{17}H_{17}NO_6S$ (363.136): C, 56.18; H, 4.72; N, 3.86; S, 8.81. Found: C, 56.21; H, 4.70; N, 3.86; S, 8.81.

2-[benzoyl (phenylsulfonyl) amino]-3-sulfanylpropanoic acid (2f)

Light yellow solids, yield 2.04g(89.8%), mp 107-108°C IR (KBr) cm-^{1}:3421, 3207(O-H), 2885(C-H aliphatic); 1929 (C-H aromatic); 1712, 1659 (C=O); 1633, 1611 (C=C);1317, 1220(S=O); 1128 (SO_2NH); 1123, 1118 (C-N); 691 (Ar-H).^{1}H-NMR ($DMSOd_6$, 400 MHz)δ: 8.781-8.764 (m, 3H, ArH), 8.554-8.533 (d, J=7.5 Hz, 2H, ArH), 7.642 -7.612(m,2H, ArH), 7.223-7.104(m, 3H, ArH), 5.119 (s-br, 1H, OH), 3.124-3.105(t, J =7.9 Hz, IH, CH-CH_3), 1.753-1.699(m,3H,CH_2-OH).^{13}C-NMR($DMSOd_6$,400MHz) δ:173.411,169.231(C=O);140.124,133.236,132.619, 129.478,125.989,122.149,112.256,116.147 (aromatic carbons); 35.144, 20.348 (aliphatic carbons). Anal.calcd (%) for $C_{14}H_{14}NO_6S$ (324.136): C, 51.83; H, 4.35; N, 4.32; S, 9.87. Found: C, 51.80; H, 4.35; N, 4.34; S, 9.90.

2-{benzoyl [(4-methylphenyl) sulfonyl] amino}-4-methylpentanoic acid (2g)

A white solid, yield 3.04g (98.5%), mp.118-119°C, IR (KBr) cm-^{1}: 3246 (O-H); 2988(C-H aliphatic), 1989 (C-H aromatic); 1701, 1671(C=O); 1623, 1601 (C=C); 1223, 1219 (2S=O); 1178 (SO2-N); 1113, 1021 (C-N); 745 (Ar-H). ^{1}H-NMR ($DMSOd_6$, 400 MHz) δ: 8.777-8.758 (d, J=8.1.Hz, 2H, ArH), 7.925-7.906 (d, J=8.9 Hz, 2H, ArH), 7.892-7.655(m, 2H, ArH) 7.294-7.189(m, 3H, ArH), 5.772 (s-br, 1H, H), 2.864 (s,3H, CH_3-Ar), 2.228-2.209(t, J= 7.2 Hz, 2H, CH), 2.051-2.032(d, J=7.0 Hz, 2H, CH_2-CH), 1.031-0.923(m, 6H, CH_3). ^{13}C-NMR ($DMSOd_6$,400 MHz)δ: 175.255, 169.029 (C=O); 147.937, 146.135, 137.613, 128.479,124.357,122.357,120.121,120.544 (aromatic carbons); 42.141, 40.344, 32.559, 26.321, 22.786, 18.621, (aliphatic carbons). Anal.calcd (%) for $C_{20}H_{23}NO_5S$ (389.18): C, 61.67; H, 5.96; N, 3.60; S, 8.22. Found: C, 61.70; H, 5.96; N, 3.60; S, 8.22.

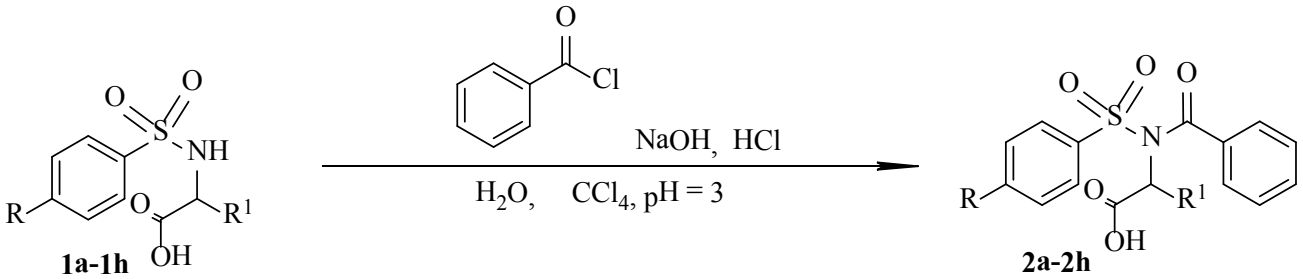
2-[benzoyl (phenylsulfonyl) amino]-4-methylpentanoic acid (2h)

A white solid, yield 2.65g (82.7%), mp.110-112°C, IR (KBr) cm-^{1}:3533 (O-H); 2978(C-H aliphatic), 1988 (C-H aromatic);1789,1677 (C=O);1620, 1611 (C=C); 1323,1285 (2S=O);1174 (SO2-N);1116, 1029 (C-N); 704 (Ar-H). ^{1}H-NMR ($DMSOd_6$, 400 MHz)δ:8.321-8.211(m, 2H, ArH), 7.888-7.866 (d, J=8.1 Hz, 2H, ArH), 7.552-7.355(m, 2H, ArH) 7.299-7.162(m, 3H, ArH), 4.923 (s-br, 1H, OH), 2.333-2.314(t, J=7.3 Hz, 2H, CH), 2.278-2.252(d, J = 7.1 Hz, 2H, CH_2-CH), 1.131-0.993(m,6H,CH_3).^{13}C-NMR ($DMSOd_6$, 400 MHz) δ: 174.254, 169.902 (C=O); 149.936, 147.137, 139.615, 129.478, 121.358, 123.359,121.122, 121.546 (aromatic carbons); 41.143, 39.346, 31.557, 25.324, 21.789, 17.624, (aliphatic carbons). Anal. calcd (%) for $C_{19}H_{20}NO_5S$ (374.16): C, 60.94; H, 5.39; N, 3.74; S, 8.55. Found: C, 61.92; H, 5.36; N, 3.71; S, 8.52.

Results and discussion

Chemistry

Various sulphamoyl carboxylic acids were subjected to benzoylation reaction using benzoyl chloride and sodium hydroxide. This reaction process was carried out based on Schotten-Baumann mechanism which is normally employed in the benzoylation of active hydrogen-containing compounds using benzoyl chloride.[14,15] The presence of the diagnostic peaks at 3311-3630cm^{-1} due to (OH of COOH), 1792, 1681(C=O);1641,1602 (C=C); 1323, 1289 (2S=O);1177 (SO_2-N);1123,1119 (C-N);741 (Ar-H) in the FTIR spectra confirmed successful benzoylation of sulfamoyl carboxylic acids and the peculiar peaks of 1.531-1.283(m,3H,CH_3-CH) in the ^{1}H-NMR spectra confirmed the synthesis of compounds 2a-2bwhichwere derivatives of aniline.The diagnostic peaks at 2560-2569cm^{-1} due to (S-H) frequencies in FTIR spectra and the peculiar peaks of4.724(s, IH, SH) in the H-NMR spectra confirm the synthesis of compounds 2c-dwhich were derivatives ofthreonine.The presence of the diagnostic double peaks at 3421, 3207(O-H) in the FTIR spectra and double 5.119 (s-br, 1H, OH) in the FTIR ^{1}H-NMR spectra indicated the synthesis of compound 2e-fwhich were derivatives of serine. The presence of the diagnostic peaks at1.031-0.923 and1.131-0.993 due to (m, 6H, CH_3-CH_3) in H-NMR spectra indicated the synthesis of compounds 2g and 2h respectively which were derivatives of leucine as shown in (Figures 1&3).



R = H, CH_3

R^1 = CH_3 in **2a-2b**, CH_2-SH in **2c-2d,** CH_2-OH in **2e-2f**, CH_2-CH-CH_3 in **2g-2h**

Figure 1 synthesis of benzoylated sulfamoyl carboxylic acids.

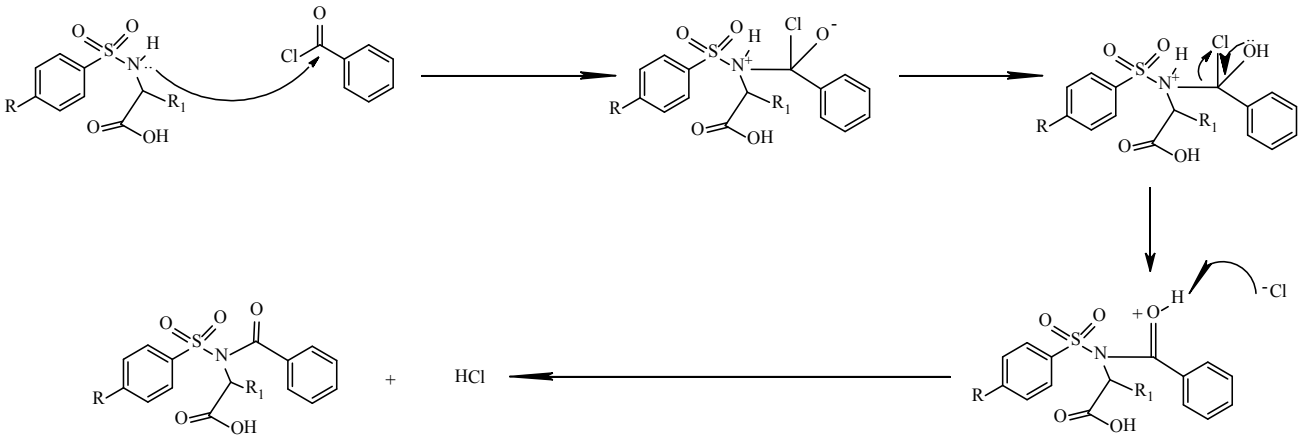


Figure 2 reaction mechanism for the synthesis of benzoylated sulfamoyl carboxylic acids.

Reaction mechanism

This reaction is a base-catalyzed reaction in which sodium hydroxide being the base is required to enhance equilibrium shift to favor the product yield and neutralize the hydrochloric acid formed in the reaction, thereby preventing further protonation.[14, 15] the reaction between benzoyl chloride and the amino group of the sulfamoyl carboxylic acid led to the formation of a protonated compound. The nitrogen of the amino group provided a lone pair of electrons towards a carbon-nitrogen bond formation and the opposite charges on nitrogen and oxygen atoms are neutralized by a proton exchange between them.Sodium hydroxide being the catalyst absorbed the acidic proton formed by the attempt of oxygen to reform a double bond with the carbonyl carbon. Finally the benzoylated sulfamoyl carboxylic acid product is formed together with HCl which is neutralized by the base catalyst as well.[14,15]

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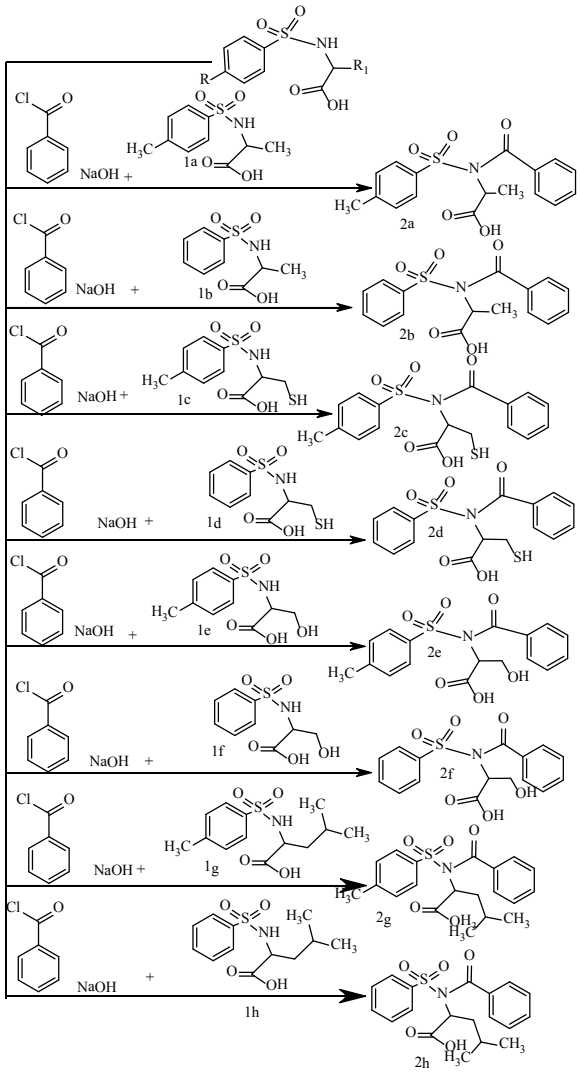

Figure 3 Benzoylated sulfamoyl carboxylic acid derivatives.

Conclusion

In conclusion, a facile and efficient synthesis of benzyolated sulfamoyl carboxylic acids (2a-2h) using benzoyl chloride and sodium chloride was successful. The benzoylation reaction methodology which utilized benzoyl chloride was found to be appropriate for the synthesis of the target compounds. The assigned structures were in agreement with the FTIR, ^{1}H-NMR, ^{13}C-NMR and elemental spectral data. Compounds 2b (3.04g, 98.7%) and 2g(3.04g,98.5%) gave the highest yields while compound 1a(1.50g,62.5%) gave the smallest yield. It is expected that carrying out antimicrobial, antioxidant and in silico studies on the the synthesized compounds will unveil the biological and pharmacological activities of the compounds.

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Conflicts of interest

There is no conflict of interest.

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