Synthesis and Characterization of Some New Sulfadiazine derivatives

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Abstract
A series of three and four member rings has been synthesized by N-substituted for 4- (1,3dioxoisooindolin-2-yl)-N-(pyrimidin-2-yl) benzenesulfonamide (sulfadiazine). The nitrogen atoms have been alkylated first to form N-carboxymethyl followed by cyclization reactions to form heterocyclic/substituted aryl group (diaziridine, diazirine and diazetidin derivatives). All the synthesized compounds have been identified using FT-IR, 1H NMR, C13-NMR.

Keywords: 4- (1,3dioxoisooindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide, 1,2-Diazetidine, 1,2-diaziridine, 1,2-diazine.

INTRODUCTION:
The molecular structures of sulfa drugs that containing the 4-aminobenzenesulfonamide moiety play important roles as a chemotherapeutic agent (1). The biological activity of these drugs is thought to come from the structural similarity between sulfanilamide group and p-amino benzoic acid where the sulphur drug simulators this metabolite and blocks folic acid synthesis in bacteria, thereby causing cell death(2). The SO2NH moiety as a drug simulators this metabolite and blocks folic acid synthesis in is thought to come from the structural similarity between chemotherapeutic agent (1). The biological activity of these drugs anminobenzenesulfonamide moiety play important roles as a

Compounds (N) 4-amino-N-(pyridin-2-yl) benzenesulfonamide (N1)

Synthesis of: 4-(1,3dioxoisooindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (N1)

Compound (N) 4-amino-N-(pyridin-2-yl) benzenesulfonamide (0.01mol, 2.5gm) Phthalic anhydride (0.01mol, 1.48gm) were heated under reflux in glacial acetic acid (20ml) for 3 h (bath temperature at 118 C),this reaction monitored by TLC. The acetic acid was evaporated under vacuum. Water (14ml) was added to the residue and the mixture were refluxed for 1 hour. The reaction monitored by TLC. After cooling, the reaction mixture was extracted with ether:water (1:4). Then it was filtered and dried under vacuum to give white crystal. The precipitate was recrystallized from ethanol.

Color: Crystalline white; Yield: 86%; m.p. 318-320 °C ; IR (v, cm-1): 3116 cm-1(N-H_arom), 3078 cm-1(CH_arom),1242-1338 cm-1(CN), 1655 cm-1(C=O_amid),2870-2939(CH_aliph),1720 cm-1(C=O_amid), H1-NMR (300 MHz, DMSO-d6) δ (ppm): 3.43 (S , 1H, NH), 7.08 (d, 1H, =CHpyrimiden), 8.55 (d, 2H, =CHpyrimiden), 7.56-8.01 cm-1(d, 10H, CH_arom),. TLC Rf = 0.8 (DCM: n-hexane).

Synthesis of:2-(4-(1,3dioxoisooindolin-2-yl)-N-(pyrimidin-2-yl) benzenesulfonamide acet acid (N2)

Chloroacetic acid (0.05mol, 4.72gm) was dissolved in (20 ml) of dry chloroform and (4ml) pyridine. To which an equimolar amount of (1,3dioxoisooindolin-2-yl)-N-(pyrimidin-2-yl) benzenesulfonamide was added and reaction mixture was refluxed for 4h. The reaction monitored by TLC. After cooling the residue obtained was washed with DCM/aceton and. The precipitate was recrystallized from ethanol.

Color: Crystalline plat brown; Yield: 86%; m.p. 295-298 °C ; IR (v, cm-1): 2493-3419 cm-1(=O_arom), 1724 cm-1(C=O_amid),1597(C=O_arom),1242-1338cm-1(C-N), 3047 cm-1(CH_arom), 1159(CN); H1-NMR (300 MHz, DMSO-d6) δ (ppm): 4.44 (S , 2H, -NCH2), 7.08 (d, 1H, =CHpyrimiden), 8.54 (d, 2H, =CHpyrimiden), 7.56-7.99 (d, 10H, CH_arom),. TLC Rf = 0.62 (DCM: n-hexane).

Synthesis of: N-(1H-diazirin-3-yl)-4-(1,3dioxoisooindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (N3)

In a round bottom flask containing (0.01mol, 4.38 gm) of compound (N2), a mixture of hydrazine (0.01 mol, 0.32gm), (20ml) concentrated HCl (4N) have been added. The mixture has been refluxed with stirring for 5- 6 hrs. The reaction monitored by TLC. The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol.

Color: Crystalline brown; Yield: 86%; m.p. 307-309 °C ; IR (v, cm-1): 1714 (C=O_arom), 1597(C=O_amid), H1-NMR (300 MHz, DMSO-d6) δ (ppm): 7.10 (S , 1H, NH), 7.30 (d, 1H, CHpyrimiden), 3.52(S, 2H , -NCH2), 7.87-8.10 (d, 10H, CH_arom),. TLC Rf = 0.7 (DCM: n-hexane).

Synthesis of: 4-(1,3dioxoisooindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (N4)

In around bottom flask containing (0.01mol, 4.38 gm) of compound (N2), a mixture of hydrazine (0.01mol, 0.32 gm) and
ethanol (20 ml) and two drop of glacial acetic acid have been added. The mixture refluxed for 8 hrs. The reaction monitored by TLC. The precipitate was filtered of and dried. The precipitate was recrystallized from absolute ethanol. Color: Crystalline plate brown; Yield: 78%; m.p. 293-295 °C; IR (v, cm⁻¹): 1720 (C=O amide), 3282 (NH), 2934-3421 (NH2), 1680-2935 (C=O amid). 3076 (C-Har); ¹HNMR (300 MHz, DMSO-d6) (δ ppm): 4.37 (S, 2H, -NH2), 7.02 (d, 2H, -CH2), 2.00 (S, 1H, -NH2), 7.56-8.57 (d, 10H, CHar). ¹C-NMR: 53(CH₂-diaazirine), 157 (CH=O), 167 (C=O), 116 (CH₃pyrimidine), 168 (N=O) ppm. 119, 123, 125, 129 ppm (1H, CHar) TLC Rf = 0.62 (DCM: n-hexane).

Synthesis of: 4-amino-N-(2-hydrazinyl-2-oxoethyl)-N-(pyrimidin-2-yl)benzenesulfonamide (N5)

Compound (N4) (0.001mol, 0.5gm) dissolved in hexane (15 ml) and aqueous hydrazine (0.044ml, 1.28gm) was added slowly. The mixture was stirred for 4h at room temperature. The reaction monitored by TLC. The solvent was evaporated and water was added. The aqueous phase was extracted three times with chloroform and the combined organic layer was dried with magnesium sulfate. Further evaporation under reduced pressure. The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol. Color: Crystalline plate oily; Yield: 66%; IR (v, cm⁻¹): 1633 (C=O amide), 3155 (NH), 3327-3427 (NH2) cm⁻¹. ¹HNMR (300 MHz, DMSO-d6) (δ ppm): 4.73 (S, 2H, -CH₂-C=O), 2.03 (S, 2H, NH₂), 6.26 (S, 2H, NH₂), 8.06 (S, 1H, NH), 7.03 (d, 1H, CH₃pyrimidine), 7.09-8.19 (d, 6H, CHar) TLC Rf = 0.62 (DCM: n-hexane).

Synthesis of: N-(2-(3,4-dioxo-1,2-diazetidin-1-yl)-2-oxoethyl)-4-(1,3-dioxoisooindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (N6)

In around bottom flask containing (0.01mol, 4.52 gm) of compound (N4), a mixture of oxalic acid (0.015 mol, 1.35gm) and ethanol (20 ml) have been added. The mixture refluxed for 5-6 hrs. The reaction monitored by TLC. The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol. Color: Crystalline brown; Yield: 75%; m.p. 321-322 °C; IR (v, cm⁻¹): 1718 (C=O amide), 3282 (NH diazetidin), 2868-2935 (C-H aliph), 3076 (C-Har); ¹HNMR (300 MHz, DMSO-d6) (δ ppm): 4.07 (S, 2H, -CH₂-C=O), 2.03 (S, 1H, -NH2), 7.06-8.57 (d, 10H, Char). ¹C-NMR: 53 (CH₂-diaazirine), 157 (CH=O), 167 (C=O), 116 (CH₃pyrimidine), 168 (N=O) ppm. 119, 123, 125, 129 ppm (1H, CHar) TLC Rf = 0.62 (DCM: n-hexane).

RESULTS AND DISCUSSION

The designated compounds were synthesized according to the Scheme in Figure 1. The reaction of 4-amino-N-(pyrimidin-2-yl) benzenesulfonamid (N) and phthalic anhydride gave 4-(1,3-dioxoisooindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (N1) compound. The IR spectrum of the product was indicated by the disappearance of band (3500-3400) cm⁻¹ due to primary amine group. The ¹H-NMR spectrum of compound N1, shows the proton signals at 3.43 ppm due(S,1H,NH) group, 7.08(d,1H,CHpyrimidine),8.55(d,2H,CHpyrimidine),7.56-8.01(d,8H,CH ar) ppm. The IR spectrum of compound (N2) has shown the appearance of broad absorption band due to carboxyl group but appearance of absorption band at (1597) cm⁻¹ due to the primary amine and absorption band at (1720) cm⁻¹ due to amide group. Also the appearance of NH absorption bands at (3282) cm⁻¹. The ¹H-NMR spectra of compound N4 has shown singlet peak resonated at 1.82 ppm due to NH group and peak singlet resonate at 8.93 ppm due to NH group. Compound (N5) have been identified by IR spectrum through the appearance of absorption band at (3433-3421) cm⁻¹ due to primary amine and absorption band at (1720) cm⁻¹ due to amide group. Also the appearance of NH absorption bands at (3282) cm⁻¹. The ¹H-NMR spectra of compound N4 has shown singlet peak resonated at 1.82 ppm due to NH group and peak singlet resonate at 8.93 ppm due to NH group. Compound (N5) have been identified by IR spectrum through the appearance of absorption band at (3354-3421) cm⁻¹ due to primary amine and absorption band at (1720) cm⁻¹ due to amide group. Also the appearance of NH absorption bands at (3282) cm⁻¹. The ¹H-NMR spectra of compound N4 has shown singlet peak resonated at 1.82 ppm due to NH group and peak singlet resonate at 8.93 ppm due to NH group. Compound (N5) have been identified by IR spectrum through the appearance of absorption band at (3354-3421) cm⁻¹ due to primary amine and absorption band at (1720) cm⁻¹ due to amide group. Also the appearance of NH absorption bands at (3282) cm⁻¹.
The $^1$H-NMR spectra of compound N6 have shown the disappearance of the singlet peak resonated at (1.82 ppm) due to NH$_2$ group and remaining the single peak resonates at (8.00 ppm) due to NH group and appearance of the singlet peak resonated at (4.38 ppm) due to (N-CH$_2$-C=O) group was a good indication for the formation of compound N6. Compound N7 have been identified by IR spectrum through the appearance of absorption band at (1720 cm$^{-1}$) due to the amide carbonyl group. Beside the appearance of NH absorption bands at (3290 cm$^{-1}$) was a good indication for the formation of compound N7. The $^1$H-NMR spectra of compound N7 has shown the disappearance of the singlet peak resonated at (1.82 ppm) due to NH$_2$ group and remaining the single peak resonates at (2.05 ppm) due to NH group and appearance of the singlet peak resonated at (3.44 ppm) due to (CH$_2$-CH$_2$) group was a good indication for the formation of compound N7. The $^{13}$C-NMR spectra of compound N7 has shown the appearance of the number peaks due to the groups, 43 ppm (CH$_2$-CH$_2$), 53 ppm (CH$_2$-C=O), 167 ppm (C=O). Compound N8 have been identified by IR spectrum through the appearance of absorption band at (1714 cm$^{-1}$) due to the amide carbonyl group. Beside the appearance of NH absorption bands at (3286 cm$^{-1}$) was a good indication for the formation of compound N8. The $^1$H-NMR spectra of compound N8 has shown the disappearance of the singlet peak resonated at 1.82 ppm due to NH$_2$ group and remaining the single peak resonates at 2.00 ppm due to NH group. The $^{13}$C-NMR spectra of compound N8 has shown the appearance of the number peaks due to the groups, 53 ppm (CH$_2$-azidine), 55 ppm (CH$_2$-C=O), 167 ppm (C=O), 168 ppm (==O).
REFERENCES