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Synthesis, characterisation of some derivatives of 3-[(4-chlorophenyl) sulfonyl] propane hydrazide

L. Vinay Kumar, P. Jagan Naik, T. Chandrasekhar, A. Babul Reddy, M. Karuna sree N. Penchalaiah and G. Narayana Swamy*

Department of Chemistry, Sri Krishnadevaraya University, Anantapur, India

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ABSTRACT

*Reaction of methyl acrylate with 4-chlorobenzenethiol gave methyl 3-[(4-chlorophenyl)thio]propanoate **1**. The latter on oxidation with hydrogen peroxide gave methyl-3-[(4-chlorophenyl)sulfonyl]propanoate **2**. 3-[(4-chlorophenyl)sulfonyl] propane hydrazide **3** was prepared from methyl-3-[(4-chlorophenyl)sulfonyl] propanoate **2** by reaction with hydrazine hydrate. A new series of derivatives were synthesised from 3-[(4-chlorophenyl)sulfonyl] propane hydrazide **3**. The structural elucidation of these compounds was based on their IR, ^{1}H NMR and Mass spectral data.*

Key words: 3-[(4-chlorophenyl)sulfonyl]propanehydrazide, diacyl hydrazine, pyrrole, pyrazole, oxadiazole.

INTRODUCTION

The biological studies on sulfones revealed that they can be used in chemotherapy, agriculture, dyes, and detergents[1]. Vinyl sulfones have been known for their synthetic utility in organic chemistry, easily participating in 1,4-addition reactions. This functional group has also recently been shown to potently inhibit a variety of enzymatic processes, providing unique properties for drug design and medicinal chemistry[2]. Divinyl sulfones and hydroxydiethyl sulfones are used to give crease-resistant finishes, while other sulfones are used as fuel additives, plasticizers, and anti-icing additives[3]. On the other hand, Pyrrole is one of the most important heterocyclic compounds, having become increasingly important in medicinal chemistry and organic synthesis. This heterocycle is an important structural attribute in many bioactive natural products[4], therapeutic compounds[5], new organic materials[6] and in biological processes[7]. Pyrazole and its derivatives, a class of well known nitrogen containing heterocyclic compounds, occupy an important position in medicinal and pesticide chemistry with having a wide range of bioactivities such as anticancer8, anti-inflammatory[9], antidepressant[10], anticonvulsant[11], antibacterial[12] and antifungal activities[13]. *N,N*1-diacylhydrazines are important intermediates for the synthesis of several heterocycles such as, 1,3,4-oxadiazoles[14] and 1,3,4-thiadiazoles[15]. Fascinated by the varied biological activity of sulfone derivatives and that of various derivatives of hydrazide, it was contemplated to synthesize a new series of derivatives of 3-[(4-chlorophenyl)sulfonyl]propane hydrazide.

MATERIALS AND METHODS

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by thin-layer chromatography (TLC; silica gel, chloroform: methanol, 19:1). The infrared

(IR) spectra were recorded on a Spectrum 100 Fourier transform (FT)–IR spectrometer as KBr pellets, and the wave numbers were given in centimeters. The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker-400 spectrometer (400 MHz). All chemical shifts are reported in δ (ppm) using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on shimadzu LC mass spectrometer. The starting compound 3-[(4-chlorophenyl)sulfonyl] propanehydrazide (1) was prepared by the literature procedure.[16]

Synthesis of *N*'-benzoyl-3-[(4-chlorophenyl)sulfonyl]propanehydrazide (4)
A mixture of 3-[(4-chlorophenyl)sulfonyl]propanehydrazide (**3**) (1.0 g, 0.0038 mol) and the benzoyl chloride (0.44 ml, 0.038 mol), in dry pyridine (10 ml), was heated under reflux for 30 min. On cooling, the mixture was poured onto cold water (50 ml) and stirred for 10 min. The separated solid was filtered, washed thoroughly with cold water, dried and recrystallised from aqueous ethanol to yield *N*'-benzoyl-3-[(4-chlorophenyl)sulfonyl]propanehydrazide (**11**).

Yield 1.26 g (90%); m.p.190-193^o C; ^{1}H NMR (DMSO-d_6 δ (ppm): 2.53-2.57 (t, 2H, CH_2), 3.56-3.60 (t, 2H, SO_2-CH_2), 7.45-7.96 (m, 9H, Ar-H), 10.07 (CH_2CONH, 1H), 10.38 (PhCONH); IR (KBr, cm^{-1}): 3245 (N-H), 3074 (Ar-H), 2944 (Aliphatic C-H), 1677 (C=O), 1610 (PhC=O), 1088 (S-Ar), 1305, 1149 (SO_2); ESI Mass: 389 (M+Na).

Synthesis of *N*'-acetyl-3-[(4-chlorophenyl)sulfonyl]propanehydrazide (5)
3-[(4-chlorophenyl)sulfonyl]propanehydrazide (**3**) (1.0 g, 0.003 mol) was warmed with acetic anhydride (5 ml) for 1 hour and then the mixture was allowed to attain room temperature. The deposited pale yellow solid was filtered, washed and recrystallised from ethanol to *N*'-acetyl-3-[(4-chlorophenyl)sulfonyl]propane hydrazide (**12**) as pale yellow crystals.

Yield 0.88 g (76%); m.p. 158-161^o C; ^{1}H NMR (DMSO-d_6 δ (ppm): 1.81 ($COCH_3$), 3.12-3.16 (t, 2H, CH_2), 3.51-3.55 (t, 2H, SO_2-CH_2), 7.71-7.92 (m, 4H, Ar-H), 9.80 (CH_2CONH), 9.89 (CH_3CONH); IR (KBr, cm^{-1}): 3229 (N-H), 3068 (Ar-H), 1697 (CH_3C=O), 1651 (C=O), 1087 (S-Ar), 1312, 1142 (SO_2); ESI Mass: 305 (M+1).

Synthesis of 5-[2-{(4-chlorophenyl)sulfonyl}ethyl]-1,3,4-oxadiazole-2-thiol (6)
3-[(4-chlorophenyl)sulfonyl]propanehydrazide (**3**) (1.0 g, 0.0038 mol) was dissolved in a solution of potassium hydroxide (0.336 g, 0.006 mol) in water (2 ml) and ethanol (20 ml). Carbon disulfide (2 ml) was then added while stirring and the reaction mixture was heated under reflux for 8 hours. The solvents were removed under reduced pressure, the residue was treated with water and then filtered. The filtrate was cooled, neutralized to pH 6 using dilute hydrochloric acid and the separated product was filtered, washed with water, dried and recrystallised from benzene as yellow crystals.

Yield 0.82 g (71%); m.p. 204-206^o C; ^{1}H NMR ($CDCl_3$ δ (ppm): 3.14-3.18 (t, 2H, CH_2), 3.48-3.51 (t, 2H, SO_2-CH_2), 7.57-7.60 (d, 2H, Ar-H), 7.85-7.87 (d, 2H, Ar-H); IR (KBr, cm^{-1}): 3051 (Ar-H), 2931 (Aliphatic C-H), 2762 (S-H), 1626 (C=N), 1092 (S-Ar), 1315, 1137 (SO_2); LC Mass: 305 (M+1).

Synthesis of 3-[(4-chlorophenyl)sulfonyl]-N-(2,5-dimethyl-1*H*-pyrrol-1-yl) propanamide (7)
To a solution of 3-[(4-chlorophenyl)sulfonyl]propanehydrazide (**3**) (1.0 g, 0.0038 mol) in ethanol (10 ml) were added acetonyl acetone (0.684 g, 0.006 mol) and glacial acetic acid (1 ml), and the reaction mixture was heated on a boiling water bath for 4 hours. The reaction mixture was concentrated to half of original volume and poured into crushed ice (50 g). The separated solid was filtered, washed with water, dried and recrystallised from ethanol as brown crystals.

Yield 0.82 g (63%); m.p. 134-137^o C; ^{1}H NMR ($CDCl_3$ δ (ppm): 2.05 (s, 6H, $2CH_3$), 2.86-2.89 (t, 2H, CH_2), 3.39-3.42 (t, 2H, SO_2-CH_2), 5.75 (s, 2H,Pyrrole CH), 7.51-7.87 (m, 4H, Ar-H), 8.29 (NH); IR (KBr, cm^{-1}): 3299 (N-H), 3093 (Ar-H), 2925 (Aliphatic C-H), 1679 (Amide C=O), 1084 (S-Ar), 1311, 1154 (SO_2); LC Mass: 341 (M+1).

Synthesis of 3-[(4-chlorophenyl)sulfonyl]-N-(1H-pyrrol-1-yl)propanamide (8)
2,5-dimethoxy tetrahydrofuran (0.39 ml, 0.0038 mol) was added to a solution of 1.0 g (0.0038 mol) of 3-[(4-chlorophenyl) sulfonyl]propanehydrazide (**3**) in glacial acetic acid and the reaction mixture was refluxed for 1 hour. The reaction mixture was concentrated to half of its original volume and poured on crushed ice. The separated solid was filtered, washed with water, dried and recrystallised from ethanol.

Yield 0.78 g (66%); m.p. 128-131^{o} C; ^{1}H NMR ($CDCl_3$ δ (ppm): 2.78-2.81 (t, 2H, CH_2), 3.38-3.42 (t, 2H, SO_2-CH_2), 6.14-6.20 (d, 2H,Pyrrole CH), 6.59-6.66 (d, 2H,Pyrrole CH), 7.23-7.88 (m, 4H, Ar-H), 8.67 (NH); IR (KBr, cm^{-1}): 3247 (N-H), 3033 (Ar-H), 2925 (Aliphatic C-H), 1667 (Amide C=O), 1088 (S-Ar), 1317, 1153 (SO_2); LC Mass: 313 (M+1).

Synthesis of 3-[4-(chlorophenyl)sulfonyl]-1-(3,5-dimethyl-1*H*-pyrazol-1-yl) propan-1-one (9)
A mixture of 1.0 g of 3-[(4-chlorophenyl)sulfonyl]propanehydrazide (**3**) (0.0038 mol) and 0.38 ml acetyl acetone was refluxed for 4 hours. To this mixture acetic acid was added and refluxed for 1 hour. The excess of the solvent was distilled off and the residue was poured into ice water. The separated solid was filtered, washed with water and recrystallised from aqueous alcohol.

Yield 0.69 g (56%); m.p. 60-63^{o} C; ^{1}H NMR ($CDCl_3$ δ (ppm): 2.17 (s, 6H, $2CH_3$), 2.81-2.83 (t, 2H, CH_2), 3.40-3.44 (t, 2H, SO_2-CH_2), 7.26 (s, 1H, Pyrazole CH), 7.55-7.87 (m, 4H, Ar-H); IR (KBr, cm^{-1}): 3088 (Ar-H), 2977 (Aliphatic C-H), 1732 (Amide C=O), 1583 (C=N), 1087 (S-Ar), 1307, 1152 (SO_2); LC Mass: 327 (M+1).

Synthesis of 1-[3-{4-(chlorophenyl)sulfonyl}propanoyl]-3-methyl-1H-pyrazol-5(4*H*)-one (10)
A mixture of 3-[(4-chlorophenyl)sulfonyl]propanehydrazide (**3**) (1,0g 0.0038 mol) and 15 ml of ethylacetoacetate was heated on water bath for two hours with stirring on a magnetic stirrer. The resultant solution was allowed to cool to room temperature. It was washed thoroughly with ether to remove coloured impurities. The solid thus separated out was filtered, dried and purified by recrystallisation from ethanol.

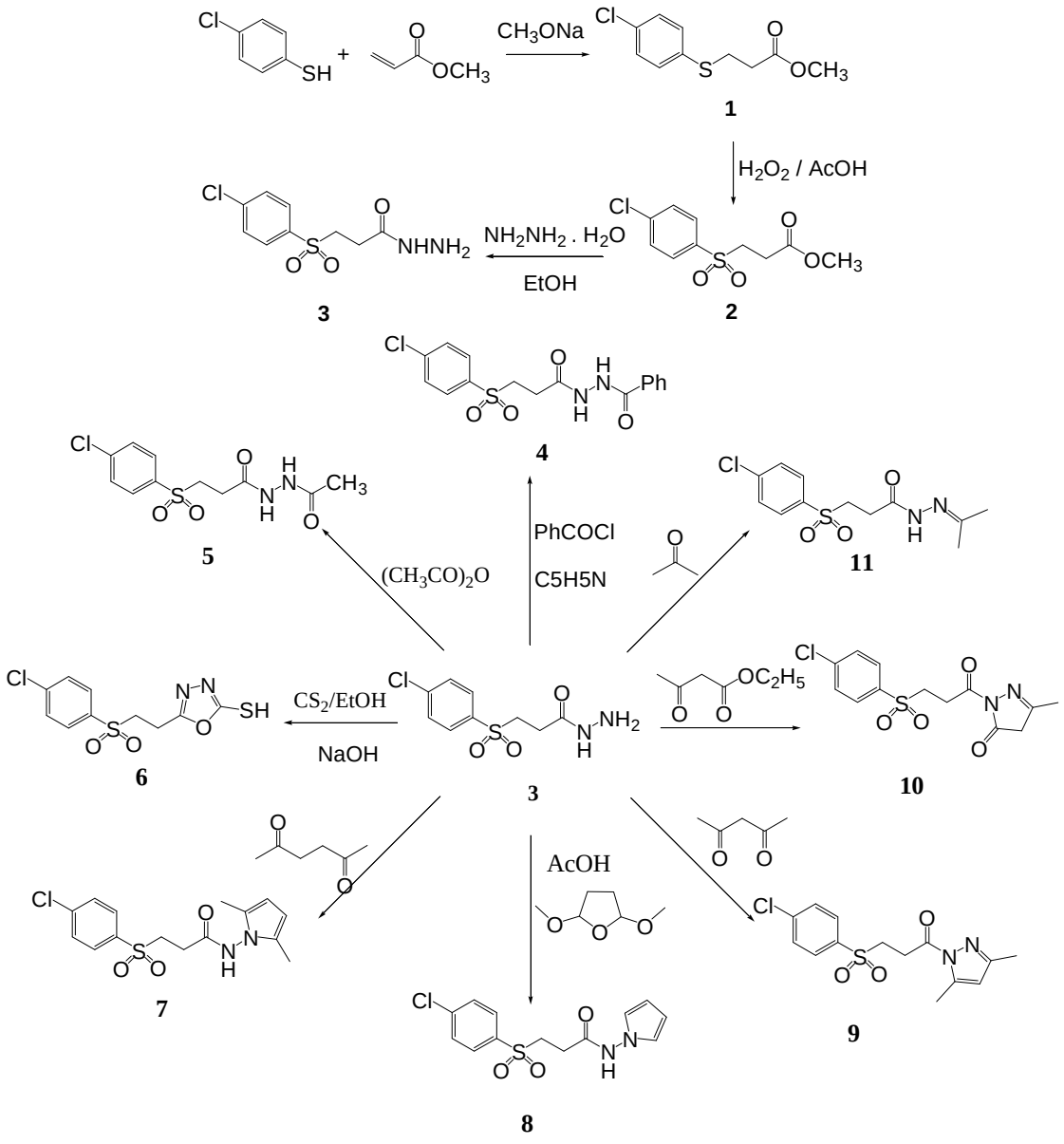
Yield 0.91 g (73%); m.p. 218-220^{o} C; ^{1}H NMR (DMSO-d_6 δ (ppm): 2.16 (s, 3H, CH_3), 3.09-3.13 (t, 2H, CH_2), 3.47-3.51 (t, 2H, SO_2-CH_2), 4.21 (m, 2H, Pyrazoline CH_2), 7.54-7.88 (m, 4H, Ar-H); IR (KBr, cm^{-1}): 3073 (Ar-H), 2986, 2933 (Aliphatic C-H), 1737 (Amide C=O), 1664 (Ring C=O), 1583 (C=N), 1090 (S-Ar), 1310, 1137 (SO_2); LC Mass: 329 (M+1).

Synthesis of 3-[(4-chlorophenyl)sulfonyl]-*N*'-(propan-2-ylidene)propane hydrazide (11)
A solution of 3-[(4-chlorophenyl)sulfonyl]propanehydrazide (**3**) (1.0 g, 0.0038 mol) in 15 ml of acetone was refluxed for 1 hour. Evaporation of solvent furnished a solid. It was recrystallised from ethanol to get 3-[(4-chlorophenyl)sulfonyl]-*N*'-(propan-2-ylidene)propane hydrazide (**11**).

Yield 0.86 g (75%); m.p. 178-180^{o} C; ^{1}H NMR (DMSO-d_6 δ (ppm): 1.80 (s,3H, CH_3), 1.99 (s,3H, CH_3), 3.08-3.12 (t, 2H, CH_2), 3.48-3.51 (t, 2H, SO_2-CH_2), 7.53-7.56 (m, 2H, Ar-H), 7.86-7.89 (m, 2H, Ar-H), 8.29 (NH); IR (KBr, cm^{-1}): 3214 (N-H), 3091 (Ar-H), 2985, 2932 (Aliphatic C-H), 1682 (Amide C=O), 1557 (C=N), 1091 (S-Ar), 1315, 1158 (SO_2); LC Mass: 303 (M+1).

RESULTS AND DISCUSSION

The synthetic pathway followed for the synthesis of hydrazones is presented in the **Scheme-1**. Reaction of methyl acrylate with 4-chlorobenzenethiol afforded methyl 3-[(4-chlorophenyl)thio]propanoate (**1**). The sulfide **1** on reaction with hydrogen peroxide in acetic acid gave corresponding sulfone i.e. 3-[(4-chlorophenyl)sulfonyl]propanoate (**2**). This on treatment with hydrazine hydrate in ethanol under reflux condition resulted in the formation of 3-[(4-chlorophenyl)sulfonyl]propane hydrazide (**3**). The hydrazide **3** was heated with benzoyl chloride in pyridine to give *N*'-benzoyl-3-[(4-chlorophenyl)sulfonyl]propanehydrazide (**4**). While *N*'-acetyl-3-[(4-chlorophenyl)sulfonyl]propane hydrazide (**5**) was prepared by the reaction with acetic anhydride. The hydrazide **3** was cyclised with carbondisulphide and potassium hydroxide followed by acidification to get 5-[2-{(4-chlorophenyl)sulfonyl}ethyl]-1,3,4-oxadiazole-2-thiol (**6**). Reaction of hydrazide **3** with acetonyl acetone afforded 3-[(4-chlorophenyl)sulfonyl]-N-(2,5-dimethyl-1*H*-pyrrol-1-yl) propanamide (**7**). In another reaction hydrazide **3** on treatment with 2,5-dimethoxy tetrahydrofuran in acetic acid gave 3-[(4-chlorophenyl)sulfonyl]-N-(1H-pyrrol-1-yl)propanamide (**8**). Reaction of hydrazide **3** with acetyl acetone gave 3-(4-chlorophenylsulfonyl)-1-(3,5-dimethyl-1*H*-pyrazol-1-yl) propan-1-one (**9**). 1-[3-(4-chlorophenylsulfonyl)propanoyl]-3-methyl-1H-pyrazol-5(4H)-one (**10**) was prepared by the reaction of hydrazide **3** with ethyl acetoacetate. Hydrazide **3** on reaction with acetone in presence of catalytic amount of acetic acid provided 3-[(4-chlorophenyl)sulfonyl]-*N*'-(propan-2-ylidene)propane hydrazide (**11**).



Scheme-I

IR Spetra of compounds **4**, **5** and **7-11** showed strong absorption bands in the range of 1651-1734 cm^{-1} and are accounted for the presence of C=O group. Compounds 6, 9, 10 and 11 showed peaks in the range of 1557-1626 cm^{-1} and are assigned to C=N bond stretching. All the compounds showed two strong stretching bands in the regions, 1137- 1158 cm^{-1} and 1305-1317 cm^{-1} due to symmetric and asymmetric stretching of SO_2 group. The band observed at about 1085 cm^{-1} is assigned to S-Ar bond stretching. Compounds **4**, **5**, **7**, **8**, **10** and **11** showed absorption bands in the range of 3183-3299 cm^{-1}, these are attributed to N-H bond stretching. Compound **6** exhibited a band at 2762 cm^{-1}, is assigned to S-H bond stretching. A triplet observed in ^1H NMR spectra of compounds **4-11** in the range of 2.46-3.18 ppm is assigned to Ar-CH_2 group attached to another CH_2 group. Another triplet appeared in the region, 3.38-3.60 cm^{-1} is accounted for the CH_2 group attached to SO_2 group. Protons attached to aromatic nucleus are appeared in the region 7.23-7.96 ppm. Compounds **4**, **5**, **7**, **8** and **11** exhibited singlet in the range, 8.29-11.76 ppm is assigned to protons attached to nitrogen atom (NH). Singlet observed in the ^1H NMR spectrum of compound **7** at 2.05 ppm is assigned to protons of methyl groups attached to C-2 and C-5 of 2,5-dimethyl pyrrole ring. Another

singlet at 5.75 ppm is assigned to protons attached to C-3 and C-4 of 2,5-dimethyl pyrrole ring. Doublets observed in ^{1}H NMR spectrum of compound **7** in the ranges 6.14-6.20 ppm and 6.59-6.66 ppm are assigned to protons attached to C-2, C-5 and C-3, C-4 of 2,5-dimethyl pyrrole ring respectively. Compound **9** showed a singlet at 2.17 ppm and is assigned to protons of methyl groups attached to pyrazole ring. Another singlet appeared at 7.26 ppm is assigned to proton attached to pyrazole ring. Compound **10** showed a singlet at 2.16 ppm and is assigned to protons of methyl group attached to pyrazolone ring. Another singlet appeared at 4.21 ppm is assigned to proton attached to pyrazolone ring. Compound **11** showed two singlets at 1.80 ppm and 1.99 ppm are assigned to protons of isopropylidene group. Compounds **4**-**11** showed corresponding M+1 peaks in their mass spectra.

CONCLUSION

A new series of derivatives of 3-[(4-chlorophenyl)sulfonyl]propane hydrazide, The structure of these compounds was confirmed by their IR, ^{1}H NMR, and MS spectral data.

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