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Synthesis and Characterization of 2,5-Disubstituted-1,3,4-oxadiazole Derivatives with Thioether Groups

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New 2,5-disubstituted-1,3,4-oxadiazole derivatives were synthesized by the reaction of 2-(ethylsulfanyl)benzohydrazide with CS_2 in KOH to afford 5-[2-(ethylsulfanyl)phenyl]-1,3,4-oxadiazole-2(3*H*)-thione. On alkylation with benzylic halides in the presence of anhydrous potassium carbonate as a base and dry acetone as a solvent gave the new 1,3,4-oxadiazole derivatives. An attempt to design a series of new derivatives derived from thiosalicylic acid by coupling 1,3,4-oxadiazole with benzimidazole moiety and another 1,3,4-oxadiazole ring has been put forward for the first time. The structure of the compounds was confirmed by IR, ^{1}H NMR,^{13}C NMR and mass spectra.

Keywords: 2-(Ethylsulfanyl)benzohydrazide, 1,3,4-Oxadiazole derivatives, Alkylation, Benzimidazole.

INTRODUCTION

Organic sulphur compounds exhibited a significant role in industry[1], medicine[2] and organic synthesis[3]. Ring-linked sulfur compounds of the C-S-H type such as thiosalicylic acid and its derivatives posses a wide range of applications as photo-initiators for free radical polymerization[4] and in medicine as tumor growth ras-inhibitors[5]. Thiosalicylic acid has been used in the synthesis of 1,3,4-oxadiazole derivatives[6] but corresponding S-ethyl derivatives have not used thiosalicylic acid. The introduction of aromatic or hetero aromatic thioether group into the molecule could exert a huge influence on antibacterial activity and pharmacokinetics[7] and also they serve as secondary antioxidants[8]. On the other hand 1,3,4-oxadiazole is an important class of heterocyclic compounds with a wide range of biological activities such as antifungal activity[9] and as potent anticancer agents[10]. Here in we report the synthesis of 5-[2-(ethylsulfanyl)-phenyl]-1,3,4-oxadiazole-2(3*H*)-thione followed by alkylation in order to synthesize new 2,5-disubstituted-1,3,4-oxadiazole derivatives.

EXPERIMENTAL

Organic solvents were distilled prior to use. Melting points were determined and uncorrected using MEL-TEMP II apparatus. IR spectra were recorded using PerkinElmer400 fourier transforms infrared (FTIR) Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER-AVN using DMSO-d_6 and $CDCl_3$ as solvents and TMS as an internal standard. The massspectra were recorded on Agilent 5975 for EI/MS and Finnegan TSQ7000 for HREI/MS.

5-[2-(Ethylsulfanyl)phenyl]-1,3,4-oxadiazole-2(3*H*)-thione (1): Potassium hydroxide (0.21 g, 3.75 mmol) was added to the solution of 2-(ethylsulfanyl)benzohydrazide (1 g, 3.75 mmol) and excess of carbon disulfide (0.8 g, 0.6 mL) in absolute ethanol. The mixture was stirred under reflux for 18 h and the solvent was evaporated. Distilled water (25 mL) was added to the residue, filtrated and acidified with 5 % hydrochloric acid. The white precipitate was filtrated, washed with water and recrystallized from ethanol. 0.91 g, 84 % finny powder m.p. 178-180 °C. IR (KBr, ν_{max}, cm^{-1}): 3314 (br, NH), 3059 (C-H aromatic), 2959 (C-H aliphatic), 1602 (C=N), 1558 (C=C), 1337 (C=S). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.28 (t, 3H, CH_3), 3.06 (q, 2H, CH_2), 7.35 (ddd, 1H, Ar-H), 7.57 (m, 2H, Ar-H), 7.81 (dd, 1H, Ar-H), 14.83 (br. s., 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 13.27, 25.67, 119.93, 124.87, 126.70, 129.51, 132.06, 138.18, 159.46, 176.99. HREIMS (ESI): m/z = 237.0155 $[M-H]^-$ (calc. for $C_{10}H_9N_2OS_2$ 237.0162).

General procedure for alkylation of 5-[2-(ethylsulfanyl)phenyl]-1,3,4-oxadiazole-2(3*H*)-thione (1): Substituted benzyl halide was added in small portion to a stirred suspension of 1,3,4-oxadiazole (**1**) in dry acetone and anhydrous potassium carbonate. The mixture was stirred over night at ambient temperature. The solvent was evaporated and the residue was extracted with ethyl acetate (25 mL), dried under

anhydrous magnesium sulfate. The mixture was then left to crystallized.

2-(Benzylsulfanyl)-5-[2-(ethylsulfanyl)phenyl]-1,3,4-oxadiazole (2): White crystals; yield: 85 %. m.p.79 °C. IR (KBr, ν_{max}, cm^{-1}): 2996 (C-H aromatic), 2973 (C-H aliphatic), 1593 (C=N), 1570 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.26 (t, *J* = 7.3, 3H, CH_3), 3.03 (q, 2H, S-CH_2), 4.59 (s, S-$\underline{CH_2}$-ph, 2H), 7.32 (m, 4H, Ar-H), 7.53 (m, 4H, Ar-H), 7.81 (dd, *J* = 7.8, Ar-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 13.33, 25.77, 35.89, 120.93, 124.86, 126.83, 127.75, 128.55, 129.01, 129.77, 131.81, 136.49, 138.22, 163.16 and 164.25. HREIMS *m/z* 328.0701 [M^+] (calcd. for $C_{17}H_{16}N_2O_1S_2$ 328.0704).

2-[({5-[2-(Ethylsulfanyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfanyl)methyl]-1*H*-benzimidazole (3): Yellow crystals ; yield: 86 %. m.p. 154 °C. IR (KBr, ν_{max}, cm^{-1}): 3203 (br. NH), 2971 (C-H aliphatic) 1621 (C=N), 1590, 1567 (C=C), 1093 (C-O-C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.43 (t, *J* = 7.4, 3H, CH_3), 3.07 (q, *J* = 7.4, 2H, CH_2), 4.72 (s, 2H, S-CH_2-imidazole), 7.26 (m, 3H), 7.46 (m, 4H), 7.86 (dd, *J* = 7.9, 1H), 11.07 (br.s, 1H, N-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 8.16, 21.51, 24.58, 115.37, 117.76, 119.40, 121.22, 124.49, 126.45, 134.12, 144.51 and 160.25. HREIMS *m/z* 368.0755 [M^+] (calcd. for $C_{18}H_{16}N_4O_1S_2$ 368.0766).

2-[2-(Ethylsulfanyl)phenyl]-5-({[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}sulfanyl)-1,3,4-oxadiazole (4): White precipitate; yield: 80 %. m.p. 106-108 °C. IR (KBr, ν_{max}, cm^{-1}): 2930, 2845 (C-H aliphatic), 1610 (C=N), 1905,1787 (C=C), 1252 (C-O), 1087 (C-O-C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.23 (t, *J* = 7.3, 3H, CH_3), 3.01 (q, 2H, CH_2), 3.85 (s, 3H, O$\underline{CH_3}$), 4.49 (s, 2H, S-CH_2-oxadiazole), 7.12 (m, 2H, Ar-H), 7.33 (m, 1H, Ar-H), 7.57 (m, 2H, Ar-H), 7.87 (m, 3H, Ar-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 13.29, 25.70, 30.64, 55.51, 114.89, 115.33, 120.72, 124.84, 126.83, 128.31, 129.88, 131.99, 138.37, 161.78, 162.13, 162.54, 164.47 and 164.72. HREIMS (ESI) *m/z* 427.0879 [M + H]$^+$ (calcd. for $C_{20}H_{19}N_4O_3S_2$ 427.0899).

2-[2-(Ethylsulfanyl)phenyl]-5-({[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]methyl}sulfanyl)-1,3,4-oxadiazole (5): Orange crystals: yield: 78 %. m.p. 96-98 °C. IR (KBr, ν_{max}, cm^{-1}): 2927 (C-H aliphatic), 1613 (C=N), 1787 (C=C), 1247 (C-O), 1079 (C-O-C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.23 (t, *J* = 7.3, 3H, CH_3), 2.39 (s, 3H, $\underline{CH_3}$), 3.0 (q, 2H, CH_2), 4.95 (s, 2H, S-CH_2-oxadiazole), 7.32 (t, *J* = 7.5, 1H, Ar-H), 7.38 (d, *J* = 8.1, 2H, Ar-H), 7.56 (m, 2H, Ar-H), 7.84 (m, 3H, Ar-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 13.25, 21.07, 25.69, 25.84, 120.22, 120.25, 120.66, 124.81, 126.39, 126.78, 129.85, 129.95, 131.96, 138.36, 142.36, 142.38, 161.75, 162.85, 164.62 and 164.70. HREIMS (ESI) *m/z* 411.0950 [M + H]$^+$ (calcd. for $C_{20}H_{19}N_4O_2S_2$ 411.0944).

RESULTS AND DISCUSSION

5-[2-(Ethylsulfanyl)phenyl]-1,3,4-oxadiazole-2(3*H*)-thione (**1**) was obtained by the reaction of 2-(ethylsulfanyl) benzohydrazide with CS_2 in KOH, followed by its cyclization in acidic medium (Fig. 1). Alkylation of **1** in the presence of anhydrous potassium carbonate as a base and dry acetone as a solvent gave the new 2,5-disubstituted-1,3,4-oxadiazole derivatives, **2-5**. The structures of compounds **2-5** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

The IR spectrum of the compound **1** showed a broad absorption peak at 3314 cm^{-1}, which was due N-H stretching and an absorption peak at 1602 cm^{-1} was due to C=N stretching respectively. The ^{1}H NMR spectrum of **1** showed the signals of the ethyl group as triplet at 1.28 ppm and quartet at 3.06 ppm, a broad singlet at 14.83 ppm due to NH group.

Infrared spectra of compounds **2-5** show the absence of NH peak, indicating the aromatization of heterocyclic ring occurred. The appearance of a singlet peak in the ^{1}H NMR spectrum of these compounds at 4.49-4.95 ppm, which was assigned to S-CH_2 group confirms the formation of the new 2,5-disubstituted-1,3,4-oxadiazole derivatives. In addition ^{1}H NMR spectrum of compound **2** showed an absorption band due to aromatic protons in the region of 7.32-7.81 ppm. The ^{13}C NMR spectrum of compound **2** showed peaks at 163.16 ppm and 164.25 which were assigned to Ar-C=N and S-C=N of oxadiazole ring, respectively.

^{1}H NMR spectrum of compound **3** recorded the presence of a singlet at about 11.07, which was due to the NH proton of

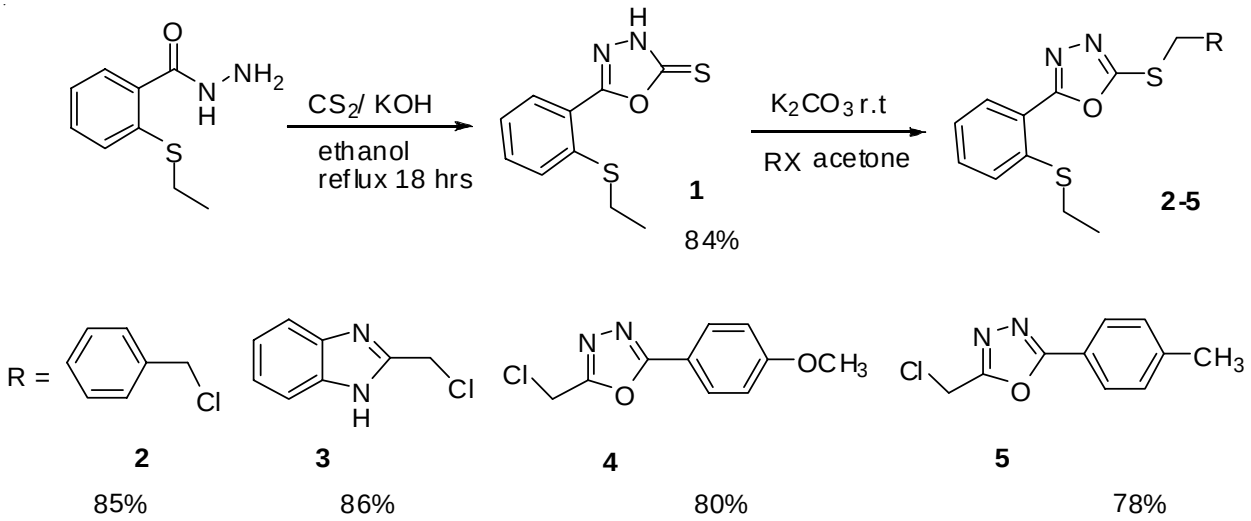

Fig. 1. Synthesis of new 1,3,4-oxadiazole derivatives

the imidazole. The ^{13}C NMR spectrum of **3** showed a great difference compared to compound **2**, due to the presence of imidazole instead of benzyl and this new environment lowered the chemical shift of S-CH_2 to 24.58 ppm.

The appearence of a singlet at 3.85 ppm in the ^{1}H NMR spectrum of compound **4** revealed the presence of protons of OCH_3 group attached to the aromatic ring. ^{13}C NMR showed new absorptions which were due to the new oxadiazole ring at 164.47 ppm for the CH_2-C=N oxadiazole and at 162.54 ppm due to the C=N-OCH_3 while C-OCH_3 appears at 161.78 ppm.

The difference in the attachment group in compound **5** showed a singlet peak at about 2.39 ppm for the methyl group in the ^{1}H NMR spectrum and for the ^{13}C NMR recorded C-CH_3 at about 131.96 ppm. Mass spectral data were in agreement with the structures of the newly synthesised compounds as recorded in the experimental section.

Conclusion

All 5-disubstituted-1,3,4-oxadiazole derivatives (**2-5**) were successfully prepared and the structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR and HREIMS methods. The biological activities of these newly synthesized compounds are now under investigation.

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