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ORIGINAL ARTICLE

2nd Heterocyclic Update

An efficient synthesis of styryl 1,3,4-thiadiazoles using Lawesson's reagent and Propylphosphonic anhydride-precursors for bis heterocycles

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Abstract The compounds styryl 1,3,4-thiadiazoles were prepared adopting one and two step methodologies to optimize the yield of the products. The two-step methodology *via* benzohydrazide followed by treatment with Lawesson's reagent in the presence of Propylphosphonic anhydride and triethylamine produced styryl 1,3,4-thiadiazoles in excellent yields. The olefin moiety in these compounds is utilized to develop pyrazole and isoxazole rings by 1,3-dipolar cycloaddition methodology followed by oxidation.

1. Introduction

The five membered heterocycles, particularly pyrazoles, isoxazoles and 1,3,4-thiadiazoles are the primary skeletons of a large number of compounds produced by nature and play a vital role in pharmacological chemistry (Bhat et al., 2011; Kritsanida et al., 2002). Pyrazole framework plays an essential role in biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemists (Foks et al., 2005; Gilbert et al., 2006; Liu et al., 2008; Shamroukh et al., 2007). One of the most important methods used for the synthesis of pyrazole derivatives is 1,3-dipolar cycloaddition utilizing diazomethane, nitrile imine to activated olefins or [2 + 3] cyclocondensation of α,β-unsaturated ketones with hydrazine hydrate (Wen et al., 2011). Using the dipolar cycloadditions for the synthesis of heterocycles the regiochemistry can be also controlled (Bonini et al., 2009; Chandanshive et al., 2010). The pyrazoles are also reported by the nucleophilic attack of hydrazines to chromones, flavones or isoxazoles (Levai et al., 2006; Sviridov et al., 2007). The isoxazoles besides being potential pharmaceutical agents are also precursors to useful intermediates such as γ-amino alcohols

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and β-hydroxy ketones (Kozikowski, 1984). The 1,3-dipolar cycloaddition of nitrile oxides to alkynes is the most direct and frequently used approach for the synthesis of isoxazoles (Dadiboyena et al., 2007; Jawalekar et al., 2011; Sanders et al., 2011). Apart from these, 1,3,4-thiadiazole constitutes the active part of several biologically active compounds including antibacterial (Foroumadi et al., 2003; Karaku and Rollas, 2002; Thomasco et al., 2003), antimycotic (Dogan et al., 2002; Mamolo et al., 1996) and anti-inflammatory activities (Palaska et al., 2002; Santagati et al., 1994; Schenone et al., 2006). The common method for the preparation of 1,3,4-thiadiazoles involves the reaction of aldehydes, hydrazine hydrate and elemental sulfur under conventional and microwave conditions (Mazzone et al., 1983; Mounim et al., 2005). Thionation of dibenzoylhydrazines using Lawesson's reagent or Phosphorus pentasulfide followed by cyclization and dehydrosulfurization is also one of the methods to produce 1,3,4-thiadiazoles (Gierczyk and Zalas, 2005; Kiryanov et al., 2001). In addition, the cyclization of 1,2-diacylhydrazine or its thia analogs in the presence of a coupling agent such as $SOCl_2$ or $POCl_3$ and a strong mineral acid also resulted in 1,3,4-thiadiazoles (Borg et al., 1995; Mavrova et al., 2009; Sun et al., 2001; Xu et al., 1998). The other important route is *via* exchange of oxygen atom in 1,3,4-oxadiazole to sulfur using thiourea and tetraphosphorus decasulfide (Padmaja et al., 2012; Linganna and Rai, 1998). In fact, we have been continuously focusing on the synthesis of a variety of bis heterocycles held by different pharmacophoric units (Padmaja et al., 2011a,b; Padmavathi et al., 2008, 2009, 2011; Reddy et al., 2013). Our successful efforts in this direction made us to design molecules having pyrazole and isoxazole moieties in combination with 1,3,4-thiadaizoles.

2. Experimental

2.1. Chemistry

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, EtOAc/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers are given in cm^{-1}. The ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker-400 spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Jeol JMS-D 300 and Finnigan Mat 1210 B at 70 eV with an emission current of 100 μA. The microanalyses were performed on a Perkin–Elmer 240C elemental analyzer. The 2-((arylsulfonyl)aminosulfonyl)acetohydrazide (**1**) and *Z*-styrylsulfonylacetic acid (**2**) were prepared by the literature procedure (Reddy et al., 2013).

2.2. Typical one-pot procedure for the synthesis of 2-(((arylsulfonyl)amino-sulfonyl)methyl)-5-[Z-(styrylsulfonyl)methyl]-1,3,4-thiadiazole 3a–c

To a mixture of 2-((arylsulfonyl)aminosulfonyl)acetohydrazide (**1**) (1.0 mmol), *Z*-styrylsulfonylacetic acid (**2**) (1.0 mmol) and Phosphorus pentasulfide (P_2S_5) (0.66 g, 1.5 mmol) in ethyl acetate (EtOAc) (5 mL), triethylamine (TEA) (0.34 mL, 2.5 mmol) followed by Propylphosphonic anhydride (T3P) (0.36 mL, 1.2 mmol) in EtOAc (3 mL) was added dropwise under nitrogen atmosphere and heated to 60 °C for 5–7 h. Then, the reaction mixture was cooled, poured into ice-water and extracted with EtOAc. The combined organic phase was washed successively with saturated sodium hydrogen carbonate solution and brine. The organic phase was dried (an. $MgSO_4$) and the solvent was removed under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 60–120 mesh) using hexane/EtOAc (6:1) as eluent.

Method A: The compound **5** (1.0 mmol), Lawesson's reagent (LR) (0.60 g, 1.5 mmol) and EtOAc (5 mL) were refluxed for 8–12 h at 65 °C. After completion of the reaction, the solvent was evaporated under vacuum and the resultant semi-solid was chromatographed on silica gel (60–120 mesh) using EtOAc/hexane (7:3) as eluent to afford pure product.

Method B: To a solution of compound **5** (1.0 mmol) in EtOAc (10 mL), LR (0.60 g, 1.5 mmol), TEA (0.34 mL, 2.5 mmol), T3P (0.36 mL, 1.2 mmol) in EtOAc (7 mL) was added dropwise. The reaction mixture was heated to 55 °C for 4–6 h, cooled and poured into ice-water. The separated solid was extracted with dichloromethane. The solvent was removed *in vacuo*. The resultant residue was purified by column chromatography (silica gel, 60–120 mesh) using hexane/EtOAc (4:1) as eluent.

2.2.1. 2-(((Phenylsulfonyl)aminosulfonyl)methyl)-5-[Z-(styrylsulfonyl)methyl]-1,3,4-thiadiazole (3a)

Yield 39% (0.19 g, One-step method), 55% (0.26 g, Method A), 85% (0.41 g, Method B) as a white solid. M.p. 157–159 °C. IR (KBr): ν = 3225 (NH), 1632 (C=C), 1570 (C=N), 1319, 1151 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 4.74 (s, 2H, CH_2-(C-5)), 5.02 (s, 2H, CH_2-(C-2)), 6.56 (d, 1H, H_B, J = 9.4 Hz), 7.14–7.72 (m, 11H, H_A, ArH), 10.26 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 43.2 (CH_2-(C-5)), 48.2 (CH_2-(C-2)), 121.2 (C-H_B), 123.1, 123.7, 124.2, 125.6, 127.8, 128.4, 129.2, 130.4 (ArC), 140.1 (C-H_A), 155.3 (C-5), 157.4 (C-2) ppm. MS (*m*/*z*): 499.61 ($M^{+\cdot}$). Anal. Calcd. for $C_{18}H_{17}N_3O_6S_4$: C 43.27, H 3.43, N 8.41; found C 43.51, H 3.58, N 8.76.

2.2.2. 2-(((4-Methylphenylsulfonyl)aminosulfonyl)methyl)-5-[Z-(4-methylstyryl-sulfonyl)methyl]-1,3,4-thiadiazole, (3b)

Yield 36% (0.18 g, One-step method), 52% (0.27 g, Method A), 90% (0.46 g, Method B) as a white solid. M.p. 135–137 °C. IR (KBr): ν = 3220 (NH), 1627 (C=C), 1562 (C=N), 1305, 1145 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.16 and 2.24 (s, 6 H, Ar–CH_3), 4.62 (s, 2H, CH_2-(C-5)), 4.94 (s, 2H, CH_2-(C-2)), 6.52 (d, 1H, H_B, J = 9.2 Hz), 7.10–7.56 (m, 9 H, H_A, ArH), 10.14 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 21.5 and 21.7 (Ar–CH_3), 42.4 (CH_2-(C-5)), 47.3 (CH_2-(C-2)), 120.2 (C-H_B), 122.1, 123.4, 124.2, 124.9, 125.5, 126.9, 127.5, 128.6 (ArC), 136.4 (C-H_A), 152.2 (C-5), 154.6 (C-2) ppm. MS (*m*/*z*): 527.67 ($M^{+\cdot}$). Anal. Calcd. for $C_{20}H_{21}N_3O_6S_4$: C 45.52, H 4.01, N 7.96; found C 45.67, H 4.29, N 7.91.

2.2.3. 2-(((4-Chlorophenylsulfonyl)aminosulfonyl)methyl)-5-[Z-(4-chlorostyryl-sulfonyl)methyl]-1,3,4-thiadiazole, (3c)

Yield 38% (0.21 g, One-step method), 49% (0.27 g, Method A), 88% (0.49 g, Method B) as a white solid. M.p. 171–

173 °C. IR (KBr): ν = 3228 (NH), 1638 (C═C), 1575 (C═N), 1324, 1158 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 4.90 (s, 2H, CH_2-(C-5)), 5.12 (s, 2H, CH_2-(C-2)), 6.61 (d, 1H, H_B, J = 9.6 Hz), 7.19–7.84 (m, 9 H, H_A, ArH), 10.35 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 46.6 (CH_2-(C-5)), 49.8 (CH_2-(C-2)), 122.4 (C-H_B), 126.2, 127.6, 128.4, 129.7, 130.2, 132.6, 133.8, 135.4 (ArC), 143.6 (C-H_A), 157.4 (C-5), 159.2 (C-2) ppm. MS (m/z): 568.51 ($M^{+\cdot}$). Anal. Calcd. for $C_{18}H_{15}Cl_2N_3O_6S_4$: C 38.02, H 2.65, N 7.39; found C 38.41, H 2.84, N 7.70.

2.3. Typical procedure for the synthesis of N′-(2-((arylsulfonyl) aminosulfonyl)acetyl)-2-(styrylsulfonyl)acetohydrazide ***5a–c***

The *Z*-styrylsulfonylacetic acid (**2**) (1.0 mmol) was dissolved in dry *N*,*N*-Dimethylformamide (DMF) (10 mL). To this, O-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumhexafluorophosphate (HATU), (0.38 g, 1.0 mmol) was added at room temperature and stirred for 10 min. Then 2-((arylsulfonyl)aminosulfonyl)acetohydrazide (**1**) (2.0 mmol) was added and stirred for 20 min followed by *N*,*N*-Diisopropylethylamine (DIPEA) (0.52 mL, 3.0 mmol) *via* syringe. The reaction mixture was further stirred for 22–25 h and then saturated solution of sodium chloride was added. The mixture was cooled to 4 °C and the separated precipitate was isolated by vacuum filtration over sintered glass, washed with deionized water and recrystallized from 2-propanol.

*2.3.1. N′-(2-((Phenylsulfonyl)aminosulfonyl)acetyl)-2-(styrylsulfonyl)acetohydrazi-de (**5a**)*

Yield 94% as a white solid (0.47 g). M.p. 149–151 °C. IR (KBr): ν = 3264 (NH), 1682 (C═O), 1618 (C═C), 1316, 1154 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.30 (s, 2H, CH_2–CONH), 5.46 (s, 2H, CH_2–SO_2NH), 6.84 (d, 1H, H_B, J = 9.7 Hz), 7.41–7.94 (m, 11H, H_A, ArH), 8.24 (bs, 1H, CH_2 CO–NH), 8.82 (bs, 1H, NH–$COCH_2$), 10.44 (bs, 1H, NH–SO_2Ar) ppm. ^{13}C NMR (DMSO-d_6): δ = 51.8 (CH_2–SO_2NH), 53.4 (CH_2–CONH), 125.2 (C-H_B), 125.7, 126.6, 127.4, 128.8, 130.2, 131.5, 132.7, 133.8 (ArC), 137.2 (C-H_A), 168.4 (NH–CO), 170.2 (CO–NH) ppm. MS (m/z): 501.56 ($M^{+\cdot}$). Anal. Calcd. for $C_{18}H_{19}N_3O_8S_3$: C 43.11, H 3.82, N 8.38; found C 43.59, H 3.99, N 8.64.

*2.3.2. N′-(2-((4-Methylphenylphenylsulfonyl)aminosulfonyl) acetyl)-2-(4-methyl-styrylsulfonyl)acetohydrazide (**5b**)*

Yield 90% as a white solid (0.46 g). M.p. 121–123 °C. IR (KBr): ν = 3256 (NH), 1676 (C═O), 1610 (C═C), 1312, 1148 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.41 and 2.54 (s, 6 H, Ar–CH_3), 5.27 (s, 2H, CH_2–CONH), 5.40 (s, 2H, CH_2–SO_2NH), 6.79 (d, 1H, H_B, J = 9.6 Hz), 7.32–7.92 (m, 9 H, H_A, ArH), 7.98 (bs, 1H, CH_2CO–NH), 8.75 (bs, 1H, NH–$COCH_2$), 10.46 (bs, 1H, NH–SO_2Ar) ppm. ^{13}C NMR (DMSO-d_6): δ = 22.6 and 23.8 (Ar–CH_3), 50.2 (CH_2–SO_2NH), 52.6 (CH_2–CONH), 124.3 (C-H_B), 124.6, 125.5, 126.2, 127.5, 128.4, 130.1, 131.3, 132.6 (ArC), 136.8 (C-H_A), 165.9 (NH–CO), 169.4 (CO–NH) ppm. MS (m/z): 529.61 ($M^{+\cdot}$). Anal. Calcd. for $C_{20}H_{23}N_3O_8S_3$: C 45.36, H 4.38, N 7.93; found C 45.41, H 4.49, N 7.98.

*2.3.3. N′-(2-((4-Chlorophenylphenylsulfonyl)aminosulfonyl) acetyl)-2-(4-chloro-styrylsulfonyl)acetohydrazide (**5c**)*

Yield 92% as a white solid (0.52 g). M.p. 162–164 °C. IR (KBr): ν = 3276 (NH), 1694 (C═O), 1621 (C═C), 1321, 1159 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.34 (s, 2H, CH_2–CONH), 5.52 (s, 2H, CH_2–SO_2NH), 6.92 (d, 1H, H_B, J = 9.7 Hz), 7.46–7.98 (m, 9 H, H_A, ArH), 8.38 (bs, 1H, CH_2CO–NH), 8.85 (bs, 1H, NH–$COCH_2$), 10.49 (bs, 1H, NH–SO_2Ar) ppm. ^{13}C NMR (DMSO-d_6): δ = 52.4 (CH_2–SO_2NH), 54.8 (CH_2–CONH), 125.8 (C-H_B), 126.4, 127.2, 128.7, 129.6, 130.4, 131.2, 133.4, 134.1 (ArC), 138.1 (C-H_A), 168.9 (NH–CO), 170.8 (CO–NH) ppm. MS (m/z): 570.45 ($M^{+\cdot}$). Anal. Calcd. for $C_{18}H_{17}Cl_2N_3O_8S_3$: C 37.90, H 3.00, N 7.37; found C 38.21, H 3.51, N 7.78.

2.4. Typical procedure for the synthesis 2-(((arylsulfonyl) aminosulfonyl)methyl)-5-((4′,5′-dihydro-1′,3′-diphenyl-5′-aryl-1′H-pyrazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole ***6a–c***

The compound **3** (1.0 mmol), benzaldehyde phenylhydrazone (1.2 mmol), chloramine-T (0.33 g, 1.2 mmol) and methanol (20 mL) were refluxed for 23–25 h. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with dichloromethane. The organic layer was washed with water, brine and dried (an. Na_2SO_4). Evaporation of the solvent under reduced pressure yielded a solid which was purified by column chromatography (silica gel, 60–120 mesh) using hexane/EtOAc (4:1) as eluent.

*2.4.1. 2-(((Phenylsulfonyl)aminosulfonyl)methyl)-5-((4′,5′-dihydro-1′,3′-diphenyl-5′-phenyl-1′H-pyrazol-4′-ylsulfonyl) methyl)-1,3,4-thiadiazole (**6a**)*

Yield 73% as a pale yellow solid (0.50 g). M.p. 189–191 °C. IR (KBr): ν = 3230 (NH), 1563 (C═N), 1318, 1147 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 4.68 (s, 2H, CH_2-(C-5)), 5.08 (s, 2H, CH_2-(C-2)), 5.15 (d, 1H, $C_{4'}$-H, J = 7.1 Hz), 5.30 (d, 1H, $C_{5'}$-H, J = 7.2 Hz), 7.20–7.72 (m, 20 H, ArH), 10.42 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 46.2 (CH_2-(C-5)), 51.1 (CH_2-(C-2)), 64.1 (C-4′), 82.5 (C-5′), 123.6, 124.3, 125.5, 126.1, 127.3, 128.2, 130.1, 131.3, 132.4, 132.8, 133.2, 133.9, 134.2, 134.8, 136.4, 138.2 (ArC), 153.4 (C-3′), 155.8 (C-5), 156.8 (C-2) ppm. MS (m/z): 693.84 ($M^{+\cdot}$). Anal. Calcd. for $C_{31}H_{27}N_5O_6S_4$: C 53.66, H 3.92, N 10.09; found C 53.82, H 4.21, N 10.20.

*2.4.2. 2-(((4-Methylphenylsulfonyl)aminosulfonyl)methyl)-5-((4′,5′-dihydro-1′,3′-diphenyl-5′-(4-methylphenyl)-1′H-pyrazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**6b**)*

Yield 67% as a pale yellow solid (0.48 g). M.p. 204–206 °C. IR (KBr): ν = 3226 (NH), 1555 (C═N), 1311, 1135 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.19 & 2.36 (s, 6 H, Ar–CH_3), 4.62 (s, 2H, CH_2-(C-5)), 4.98 (s, 2H, CH_2-(C-2)), 5.09 (d, 1H, $C_{4'}$-H, J = 6.8 Hz), 5.24 (d, 1H, $C_{5'}$-H, J = 6.8 Hz), 7.12–7.58 (m, 18 H, ArH), 10.38 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 21.9 & 22.3 (Ar–CH_3), 45.6 (CH_2-(C-5)), 51.8 (CH_2-(C-2)), 62.8 (C-4′), 81.1 (C-5′), 122.3, 123.2, 124.5, 125.5, 126.1, 126.6, 127.5, 128.4, 130.2, 131.6, 132.9, 133.2, 133.8, 134.6, 135.3, 137.4 (ArC), 151.8 (C-3′), 154.1 (C-5), 155.6 (C-2) ppm. MS (m/z): 721.89 ($M^{+\cdot}$). Anal.

Calcd. for $C_{33}H_{31}N_5O_6S_4$: C 54.90, H 4.32, N 9.70; found C 55.24, H 4.69, N 9.91.

*2.4.3. 2-(((4-Chlorophenylsulfonyl)aminosulfonyl)methyl)-5-((4′,5′-dihydro-1′,3′-diphenyl-5′-(4-chlorophenyl)-1′H-pyrazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**6c**)*

Yield 79% as a pale yellow solid (0.60 g). M.p. 218–220 °C. IR (KBr): ν = 3235 (NH), 1567 (C═N), 1327, 1151 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 4.79 (s, 2H, CH_2-(C-5)), 5.13 (s, 2H, CH_2-(C-2)), 5.22 (d, 1H, $C_{4'}$-H, J = 7.4 Hz), 5.33 (d, 1H, $C_{5'}$-H, J = 7.3 Hz), 7.25–7.72 (m, 18 H, ArH), 10.45 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 47.8 (CH_2-(C-5)), 52.2 (CH_2-(C-2)), 66.6 (C-4′), 84.2 (C-5′), 124.4, 125.6, 126.1, 127.2, 128.8, 130.2, 131.7, 132.3, 132.9, 134.2, 135.1, 136.5, 137.2, 138.6, 139.2, 139.9 (ArC), 154.6 (C-3′), 156.3 (C-5), 158.2 (C-2) ppm. MS (m/z): 762.74 (M^+). Anal. Calcd. for $C_{31}H_{25}Cl_2N_5O_6S_4$: C 48.81, H 3.30, N 9.18; found C 49.01, H 3.54, N 9.26.

*2.5. Typical procedure for the synthesis of 2-(((arylsulfonyl)aminosulfonyl)methyl)-5-((4′,5′-dihydro-3′-phenyl-5′-arylisoxazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole **7a–c***

A mixture of compound **3** (1.0 mmol), benzaldehyde oxime (1.2 mmol), chloramine-T (0.33 g, 1.2 mmol) and methanol (20 mL) was refluxed for 17–20 h. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with dichloromethane. The organic layer was washed with water, brine and dried (an. Na_2SO_4). The solvent was removed under vacuum. The resultant residue was purified by column chromatography (silica gel, 60–120 mesh) using hexane/EtOAc (4:1) as eluent.

*2.5.1. 2-(((Phenylsulfonyl)aminosulfonyl)methyl)-5-((4′,5′-dihydro-3′-phenyl-5′-phenylisoxazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**7a**)*

Yield 74% as a white solid (0.45 g). M.p. 174–176 °C. IR (KBr): ν = 3240 (NH), 1565 (C═N), 1326, 1132 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 4.88 (s, 2H, CH_2-(C-5)), 5.08 (d, 1H, $C_{4'}$-H, J = 7.5 Hz), 5.14 (s, 2H, CH_2-(C-2)), 5.41 (d, 1H, $C_{5'}$-H, J = 7.5 Hz), 7.21–7.80 (m, 15 H, ArH), 10.50 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 47.4 (CH_2-(C-5)), 52.8 (CH_2-(C-2)), 63.4 (C-4′), 84.4 (C-5′), 125.6, 126.4, 127.3, 128.6, 129.2, 130.4, 131.1, 132.1, 132.8, 133.6, 134.3, 136.2 (ArC), 154.2 (C-3′), 156.2 (C-5), 157.4 (C-2) ppm. MS (m/z): 618.73 (M^+). Anal. Calcd. for $C_{25}H_{22}N_4O_7S_4$: C 48.53, H 3.58, N 9.05; found C 48.61, H 3.72, N 9.09.

*2.5.2. 2-(((4-Methylphenylsulfonyl)aminosulfonyl)methyl)-5-((4′,5′-dihydro-3′-phenyl-5′-(4-methylphenyl)isoxazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**7b**)*

Yield 68% as a white solid (0.43 g). M.p. 196–198 °C. IR (KBr): ν = 3236 (NH), 1560 (C═N), 1321, 1124 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.26 & 2.38 (s, 6 H, Ar–CH_3), 4.80 (s, 2H, CH_2-(C-5)), 5.01 (d, 1H, $C_{4'}$-H, J = 7.1 Hz), 5.06 (s, 2H, CH_2-(C-2)), 5.36 (d, 1H, $C_{5'}$-H, J = 7.1 Hz), 7.18–7.73 (m, 13 H, ArH), 10.47 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 22.4 & 23.9 (Ar–CH_3), 46.2 (CH_2-(C-5)), 51.4 (CH_2-(C-2)), 61.8 (C-4′), 83.6 (C-5′), 123.8, 124.2, 126.4, 127.2, 128.5, 129.3, 130.5, 131.1, 132.4, 133.6, 134.2, 135.4 (ArC), 152.2 (C-3′), 155.6 (C-5), 156.3 (C-2) ppm. MS (m/z): 646.79 (M^+). Anal. Calcd. for $C_{27}H_{26}N_4O_7S_4$: C 50.14, H 4.05, N 8.66; found C 50.08, H 3.95, N 8.62.

*2.5.3. 2-(((4-Chlorophenylsulfonyl)aminosulfonyl)methyl)-5-((4′,5′-dihydro-3′-phenyl-5′-(4-chlorophenyl)isoxazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**7c**)*

Yield 78% as a white solid (0.53 g). M.p. 210–212 °C. IR (KBr): ν = 3250 (NH), 1573 (C═N), 1332, 1139 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 4.92 (s, 2H, CH_2-(C-5)), 5.14 (d, 1H, $C_{4'}$-H, J = 7.7 Hz), 5.18 (s, 2H, CH_2-(C-2)), 5.48 (d, 1H, $C_{5'}$-H, J = 7.6 Hz), 7.26–7.89 (m, 13 H, ArH), 10.52 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 48.2 (CH_2-(C-5)), 53.6 (CH_2-(C-2)), 64.5 (C-4′), 84.7 (C-5′), 125.9, 126.4, 127.6, 128.5, 129.8, 130.4, 131.8, 133.6, 134.2, 135.3, 136.6, 137.4 (ArC), 154.9 (C-3′), 157.9 (C-5), 158.8 (C-2) ppm. MS (m/z): 687.62 (M^+). Anal. Calcd. for $C_{25}H_{20}Cl_2N_4O_7S_4$: C 43.67, H 2.93, N 8.14; found C 44.01, H 3.41, N 8.37.

*2.6. Typical procedure for the synthesis of 2-(((arylsulfonyl)aminosulfonyl)methyl)-5-((1′,3′-diphenyl-5′-aryl-1′H-pyrazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole **8a–c**/2-(((arylsulfonyl)aminosulfonyl)methyl)-5-((3′-phenyl-5′-arylisoxazol-4′-ylsulfonyl)-methyl)-1,3,4-thiadiazole **9a–c***

To a solution of compound **6**/**7** (1.3 mmol) in benzene (50 mL), Manganese dioxide (MnO_2) (0.43 g, 5.0 mmol) was added and stirred for 6–8 h at room temperature. After completion of the reaction, the reaction mixture was filtered. Removal of the solvent under reduced pressure resulted in a residue which was purified by column chromatography (chloroform/EtOAc, 2:1).

*2.6.1. 2-(((Phenylsulfonyl)aminosulfonyl)methyl)-5-((1′,3′-diphenyl-5′-phenyl-1′H-pyrazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**8a**)*

Yield 86% as a white solid (0.59 g). M.p. 180–182 °C. IR (KBr): ν = 3246 (NH), 1622 (C═C), 1584 (C═N), 1330, 1145 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.05 (s, 2H, CH_2-(C-5)), 5.28 (s, 2H, CH_2-(C-2)), 7.12–7.76 (m, 20 H, ArH), 10.58 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 45.4 (CH_2-(C-5)), 48.9 (CH_2-(C-2)), 122.7, 123.8, 124.2, 125.9, 126.4, 127.3, 128.6, 129.2, 130.4, 131.7, 132.4, 133.5, 134.1, 135.8, 136.4, 137.2 (ArC), 137.8 (C-4′), 144.2 (C-3′), 147.2 (C-5′), 153.1 (C-5), 154.6 (C-2) ppm. MS (m/z): 691.83 (M^+). Anal. Calcd. for $C_{31}H_{25}N_5O_6S_4$: C 53.81, H 3.64, N 10.12; found C 53.86, H 3.71, N 10.47.

*2.6.2. 2-(((4-Methylphenylsulfonyl)aminosulfonyl)methyl)-5-((1′,3′-diphenyl-5′-(4-methylphenyl)-1′H-pyrazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**8b**)*

Yield 83% as a white solid (0.58 g). M.p. 193–195 °C. IR (KBr): ν = 3238 (NH), 1615 (C═C), 1572 (C═N), 1324, 1138 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.20 & 2.34 (s, 6 H, Ar–CH_3), 5.01 (s, 2H, CH_2-(C-5)), 5.20 (s, 2H, CH_2-(C-2)), 7.06–7.54 (m, 18 H, ArH), 10.54 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 21.4 & 22.6 (Ar–CH_3), 44.8 (CH_2-(C-5)), 49.6 (CH_2-(C-2)), 122.1, 122.9, 123.4, 124.3, 125.5, 125.9, 126.4, 127.2, 128.6, 129.3, 130.6, 132.7, 133.2, 134.6, 135.4, 136.2 (ArC), 136.4 (C-4′), 142.6 (C-3′), 145.4 (C-5′), 152.8 (C-5), 155.2 (C-2) ppm. MS (m/z): 719.88 (M^+). Anal. Calcd. for $C_{33}H_{29}N_5O_6S_4$: C 55.05, H 4.06, N 9.72; found C 55.34, H 4.09, N 10.01.

*2.6.3. 2-(((4-Chlorophenylsulfonyl)aminosulfonyl)methyl)-5-((1′,3′-diphenyl-5′-(4-chlorophenyl)-1′H-pyrazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**8c**)*

Yield 88% as a white solid (0.66 g). M.p. 225–227 °C. IR (KBr): ν = 3254 (NH), 1626 (C=C), 1590 (C=N), 1335, 1149 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.11 (s, 2H, CH_2-(C-5)), 5.32 (s, 2H, CH_2-(C-2)), 7.22–7.94 (m, 18 H, ArH), 10.60 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 46.2 (CH_2-(C-5)), 50.4 (CH_2-(C-2)), 124.3, 124.6, 125.9, 126.3 127.6 128.5, 129.8, 130.5, 131.6 132.3, 133.6, 134.2, 135.4, 136.6, 137.2, 138.1 (ArC), 138.6 (C-4′), 146.3 (C-3′), 149.6 (C-5′), 153.8 (C-5), 157.8 (C-2) ppm. MS (*m*/*z*): 760.72 (M^+). Anal. Calcd. for $C_{31}H_{23}Cl_2N_5O_6S_4$: C 48.94, H 3.04, N 9.21; found C 49.15, H 3.37, N 9.08.

*2.6.4. 2-(((Phenylsulfonyl)aminosulfonyl)methyl)-5-((3′-phenyl-5′-phenylisoxazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**9a**)*

Yield 85% as a white solid (0.52 g). M.p. 186–188 °C. IR (KBr): ν = 3256 (NH), 1642 (C=C), 1580 (C=N), 1342, 1160 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.28 (s, 2H, CH_2-(C-5)), 5.39 (s, 2H, CH_2-(C-2)), 7.30–7.82 (m, 15 H, ArH), 10.62 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 46.8 (CH_2-(C-5)), 50.6 (CH_2-(C-2)), 125.7, 126.2, 127.4, 128.8, 129.2, 131.4, 132.8, 133.5, 134.2, 135.6, 136.1, 136.8 (ArC), 138.2 (C-4′), 145.6 (C-3′), 150.2 (C-5′), 155.2 (C-5), 156.1 (C-2) ppm. MS (*m*/*z*): 616.72 (M^+). Anal. Calcd. for $C_{25}H_{20}N_4O_7S_4$: C 48.68, H 3.26, N 9.08; found C 48.83, H 3.84, N 9.22.

*2.6.5. 2-(((4-Methylphenylsulfonyl)aminosulfonyl)methyl)-5-((3′-phenyl-5′-(4-methylphenyl)isoxazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**9b**)*

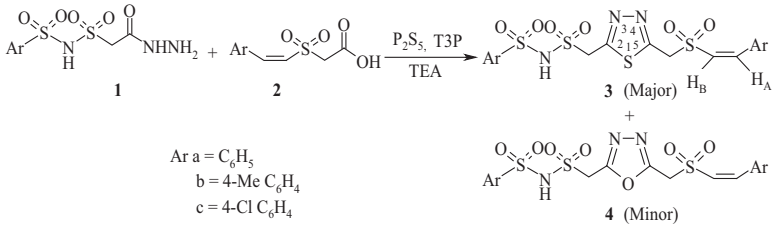
Yield 82% as a white solid (0.52 g). M.p. 197–199 °C. IR (KBr): ν = 3252 (NH), 1638 (C=C), 1582 (C=N), 1335, 1152 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 2.24 & 2.41 (s, 6 H, Ar–CH_3), 5.16 (s, 2H, CH_2-(C-5)), 5.35 (s, 2H, CH_2-(C-2)), 7.22–7.71 (m, 13 H, ArH), 10.55 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 22.1 & 23.4 (Ar–CH_3), 44.6 (CH_2-(C-5)), 50.2 (CH_2-(C-2)), 124.5, 125.2, 126.4, 127.8, 128.7, 129.4, 130.6, 132.9, 133.4, 134.2, 135.6, 136.2 (ArC), 137.6 (C-4′), 143.5 (C-3′), 149.4 (C-5′), 154.4 (C-5), 155.8 (C-2) ppm. MS (*m*/*z*): 644.77 (M^+). Anal. Calcd. for $C_{27}H_{24}N_4O_7S_4$: C 50.29, H 3.75, N 8.68; found C 50.38, H 3.61, N 8.74.

*2.6.6. 2-(((4-Chlorophenylsulfonyl)aminosulfonyl)methyl)-5-((3′-phenyl-5′-(4-chlorophenyl)isoxazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**9c**)*

Yield 90% as a white solid (0.61 g). M.p. 206–208 °C. IR (KBr): ν = 3260 (NH), 1651 (C=C), 1585 (C=N), 1350, 1165 (SO_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.37 (s, 2H, CH_2-(C-5)), 5.45 (s, 2H, CH_2-(C-2)), 7.28–7.89 (m, 13 H, ArH), 10.64 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ = 47.2 (CH_2-(C-5)), 51.6 (CH_2-(C-2)), 126.7, 127.4, 128.2, 129.6, 130.3, 131.9, 133.2, 134.8, 135.4, 136.2, 137.6, 138.1 (ArC), 138.8 (C-4′), 147.2 (C-3′), 152.6 (C-5′), 155.9 (C-5), 156.8 (C-2) ppm. MS (*m*/*z*): 685.61 (M^+). Anal. Calcd. for $C_{25}H_{18}Cl_2N_4O_7S_4$: C 43.80, H 2.64, N 8.17; found C 44.31, H 2.92, N 8.39.

3. Results and discussion

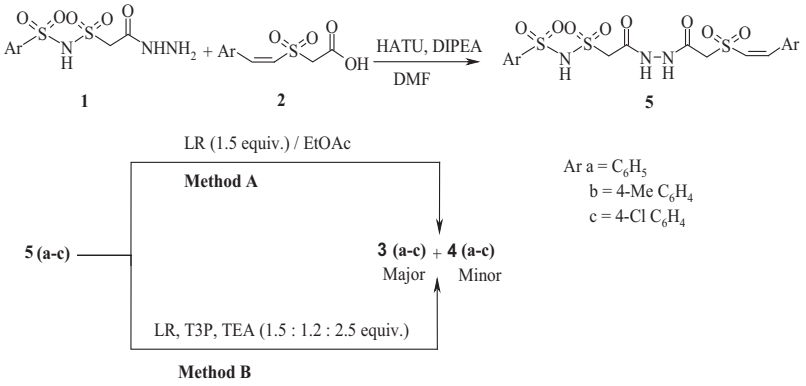
The bis heterocycles, pyrazolyl and isoxazolyl 1,3,4-thiadiazoles were synthesized from the synthetic intermediate 2-(((arylsulfonyl)aminosulfonyl)methyl)-5-[*Z*-(styrylsulfonyl)methyl]-1,3,4-thiadiazole (**3**). The compound **3** was prepared in different routes in order to optimize the yield. Earlier 1,3,4-thiadiazole moiety was built by the exchange of oxygen atom in oxadiazole with sulfur (Padmaja et al., 2012). However this transformation failed when 2-(((arylsulfonyl)aminosulfonyl)methyl)-5-((styrylsulfonyl)methyl)-1,3,4-oxadiazole was treated with thiourea. In order to prepare compound **3**, initially one-pot reaction of 2-((phenylsulfonyl)aminosulfonyl)acetohydrazide (**1a**) and *Z*-styrylsulfonylacetic acid (**2a**) with P_2S_5 in the presence of T3P and TEA in equimolar ratio was carried out (Scheme 1). After heating for 5 h, the product 2-(((phenylsulfonyl)aminosulfonyl)methyl)-5-[*Z*-(styrylsulfonyl)methyl]-1,3,4-thiadiazole (**3a**) was isolated in 35% yield along with the by product 2-(((phenylsulfonyl)aminosulfonyl)methyl)-5-[*Z*-(styrylsulfonyl)methyl]-1,3,4-oxadiazole (**4a**) in 20% yield. In the literature, it was reported that the reaction of 1 equivalent of 4-toluic acid and 3-fluorophenylhydrazide with 1.5 equivalents of P_2S_5 in the presence of 1.2 equivalents of T3P and 2.5 equivalents of TEA gave the desired 1,3,4-thiadiazole in 92% yield (Augustine et al., 2009). Employing similar reaction conditions, we repeated the reaction of **1a** and **2a** with 1.5 equivalents of P_2S_5, 1.2 equivalents of T3P and 2.5 equivalents of TEA but there was no appreciable increase in the yield of compound **3** (Table 1). Later a two-step route *via* benzohydrazide followed by cyclization was adopted. The hydrazide, *N*′-(2-((arylsulfonyl)aminosulfonyl)acetyl)-2-(styrylsulfonyl)acetohydrazide (**5**) was prepared by the reaction of **1** with **2** in the presence of HATU and DIPEA in DMF. The compound **5** was obtained in almost quantitative yields. The compound **5a** was heated with 1.5 equivalents of LR in EtOAc for 8 h. The product **3a** was formed in 55% along with 1,3,4-oxadiazole (**4a**) in 19% yield (Method A). However, when the same reaction was performed with 1.5 equivalents of LR, 1.2 equivalents of T3P and 2.5 equivalents of TEA compound **3a** was obtained in 85% yield along with a minor amount of **4a** in 2% yield



Scheme 1 Single-step synthesis of 1,3,4-thiadiazoles.

Table 1 Comparison of yields in different equivalents of reagents.

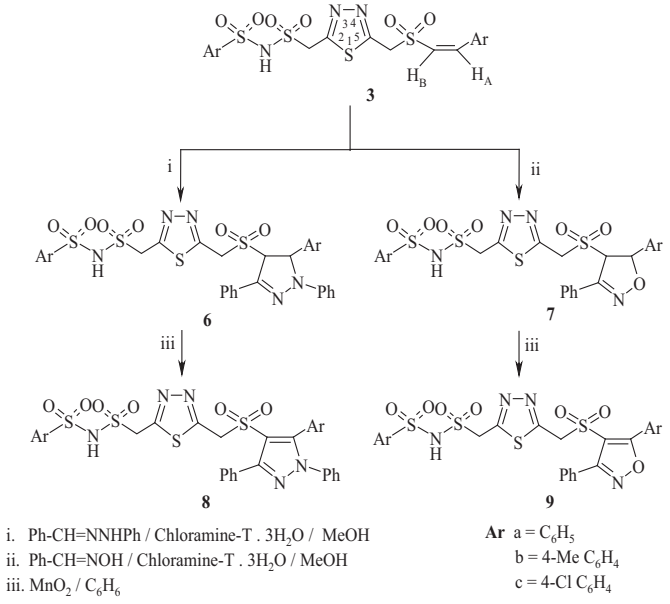
Entry	Reagent (equivalents)	Ar	Product **3**		Product **4**	
	P_2S_5:T3P:TEA		Yield (%)	mp (°C)	Yield (%)	mp (°C)
1	1:1:1	C_6H_5	35	157–159	20	128–130
2	1.5:1.2:2.5	C_6H_5	39	157–159	18	128–130
3	1.5:1.2:2.5	4-Me C_6H_4	36	135–137	23	115–117
4	1.5:1.2:2.5	4-Cl C_6H_4	38	171–173	21	139–141



Scheme 2 Two-step synthesis of 1,3,4-thiadiazoles.

Table 2 Comparison of yields in Method A and Method B.

Entry	Ar	Method A, Yield (%)		Method B, Yield (%)	
		Product **3**	Product **4**	Product **3**	Product **4**
1	C_6H_5	55	19	85	2
2	4-Me C_6H_4	52	14	90	2
3	4-Cl C_6H_4	49	16	88	3



Scheme 3 Synthesis of bis heterocycles.

Table 3 Yields of compounds **6–9**.

Entry	Compound	Yield	Entry	Compound	Yield
1	**6a**	73	7	**8a**	86
2	**6b**	67	8	**8b**	83
3	**6c**	79	9	**8c**	88
4	**7a**	74	10	**9a**	85
5	**7b**	68	11	**9b**	82
6	**7c**	78	12	**9c**	90

(Method B). Adopting similar methodology, the compounds **3b** and **3c** were prepared (Scheme 2 and Table 2).

The (3 + 2) π 1,3-dipolar cycloaddition reaction of dipolar reagents to Michael acceptors is a simple and a facile technique to prepare five-membered heterocycles. The olefin moiety present in compound **3** was exploited to synthesize pyrazoles and isoxazoles by cycloaddition of dipolar reagents—nitrile imines and nitrile oxides. Thus, 2-(((arylsulfonyl)amino-sulfonyl)methyl)-5-((4′,5′-dihydro-1′,3′-diphenyl-5′-aryl-1′*H*-pyrazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**6**) and 2-(((arylsulfonyl)amino-sulfonyl)methyl)-5-((4′,5′-dihydro-3′-phenyl-5′-aryl-isoxazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**7**) were prepared by cycloaddition of nitrile imine and nitrile oxide generated from benzaldehyde phenylhydrazone and benzaldoxime in the presence of chloramine-T to **3** (Scheme 3). In 1,2-disubstituted ethylenes bearing two vicinal electron withdrawing substituents a regioisomeric mixture of cycloadducts is expected. However, the reaction of 1-aryl-2-aroylethylenes with diazomethane and its derivatives produced exclusively 3-aroyl-4-aryl-2-pyrazolines (Bhaskar Reddy et al., 1986). Similarly, the cycloaddition of nitrile imines and nitrile oxides to 1,4-bis-((*E*)-2(aroylsulfonyl)vinyl)benzene gave pyrazolines and isoxazolines. In the present study, the addition of nitrile imines and nitrile oxides to **3** resulted in only one pure regioisomer 6 and **7** respectively. A small amount of the other isomer if any, formed could not be isolated by this process. There are several methods for oxidation of pyrazolines and isoxazolines to the corresponding aromatized products (Padmaja et al., 2011a,b; Srivastava et al., 2003). We focused our attention toward the transformation of pyrazolines and isoxazolines to pyrazoles and isoxazoles adopting the oxidation protocol using activated MnO_2 to achieve better yields. In fact, the oxidation of compounds **6** and **7** with MnO_2 in benzene led to the formation of 2-(((arylsulfonyl)aminosulfonyl)methyl)-5-((1′,3′-diphenyl-5′-aryl-1′*H*-pyrazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**8**)/2-(((arylsulfonyl)aminosulfonyl)meth-yl)-5-((3′-phenyl-5′-arylisoxazol-4′-ylsulfonyl)methyl)-1,3,4-thiadiazole (**9**) in 80–90% yield (Table 3). All the new compounds (**3**, **5**, **6–9**) were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analyses.

4. Conclusion

The compounds styryl 1,3,4-thiadiazoles were prepared from different routes to optimize the yield of the products. The two-step methodology *via* benzohydrazide followed by treatment with Lawesson's reagent in the presence of Propylphosphonic anhydride and triethylamine produced styryl 1,3,4-thiadiazoles in excellent yields. The olefin moiety in these compounds is utilized to develop pyrazole and isoxazole rings by 1,3-dipolar cycloaddition methodology followed by oxidation.

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