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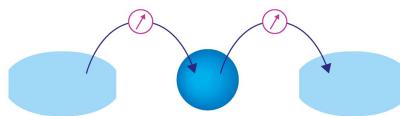
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Synthesis of a New Class of Pyrazolyl-1,2,4-Triazole Amine Derivatives

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Abstract. The olefin moiety presents in styrylsulfonylmethyl-1,2,4-triazolylamine (**1**) was exploited to build up five-member heterocycle-pyrazoles. The series of novel pyrazolyl-1,2,4-triazole amine derivatives (**2-3**) have been synthesized. All the entities compounds were characterized by ¹H and ¹³C NMR spectra.

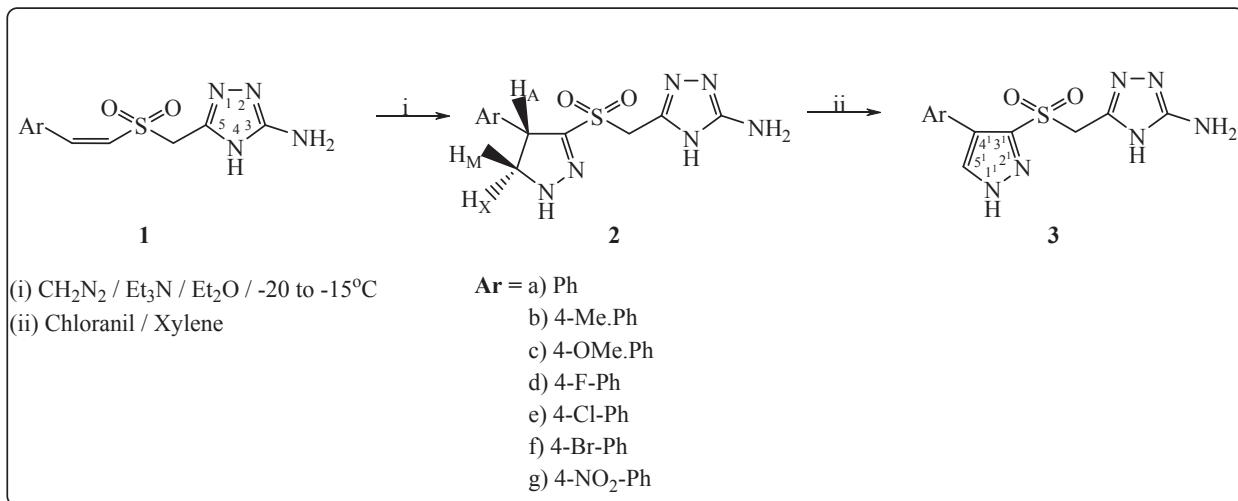
INTRODUCTION

Nitrogen containing heteroarenes have great utility in synthetic medicinal and material chemistry. One such class of compounds are triazoles and pyrazoles. 1,2,3-Triazole derivatives possess significant biological and pharmacological properties, inclusive of antimalarial¹, antitubercular,² antiviral,³ and antibacterial activity.⁴ Therefore, 1,2,3-Triazole derivatives are privileged scaffolds for the development of novel drugs.⁵ Pyrazole and its derivatives represent one of the most active classes of compounds, which exhibit broad spectrum of pharmacological activities like antimicrobial,⁶ anticonvulsant,⁷ anticancer,⁸ analgesic,⁹ anti-inflammatory,¹⁰ cardiovascular¹¹ etc. Pyrazole moiety makes the core structure of various drugs such as Difenamizole, Celecoxib, Tepoxalin¹² etc. In continuation of our studies to synthesis of sulfonyl methyl linked bis-heterocycles having different heterocyclic moieties has been taken up.

RESULTS AND DISCUSSION

The olefin moiety present in styrylsulfonylmethyl-1,2,4-triazolylamine (**1**) was exploited to build up five-member heterocycle-pyrazoles. 5-(4-Aryl-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (**3**) was prepared by the 1,3-dipolar cycloaddition of ethereal diazomethane to compound **1** in the presence of Et₃N in ether at -20 to -15°C gave 5-(4,5-dihydro-4-aryl-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (**2**). In the ¹H NMR spectrum of **2a** an AMX splitting pattern was observed due to pyrazoline ring protons. Thus, three double doublets present at δ 3.53, 4.19, 4.55 in **2a** was assigned to H_X, H_M and H_A, respectively. The coupling constant values $J_{AM} \approx 12.4$, $J_{MX} \approx 10.3$ and $J_{AX} \approx 6.4$ Hz indicated that H_A, H_M are *cis*, H_A, H_X are *trans* while H_M, H_X are *geminal*. Further **2a** showed signals at δ 4.47 (CH₂), 5.51, 5.41 (NH₂) and 12.71 ppm (NH) respectively. The signals due to NH₂ and NH disappeared on deuteration. Aromatization of the compound **2** with chloranil in xylene afforded 5-(4-phenyl-1*H*-

pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (**3**). The absence of AMX splitting pattern due to pyrazoline ring protons in **3** designated that aromatization took place. The structures of all the compounds were further confirmed by ¹³C NMR, mass spectra and elemental analyses.



SCHEME 1. Synthesis of pyrazolyl-sulfonylmethyl-1,2,4,-triazolylamines

EXPERIMENTAL

The ¹H NMR spectra were recorded in $\text{CDCl}_3/\text{DMSO}-d_6$ on a Jeol JNM λ -400 MHz spectrometer. The ¹³C NMR spectra were recorded in $\text{CDCl}_3/\text{DMSO}-d_6$ on a Jeol JNM spectrometer operating at λ -100 MHz. All chemical shifts were reported in δ (ppm) using TMS as an internal standard. The elemental analyses were determined on a PerkinElmer 240C elemental analyzer. The temperature was measured by flexible probe throughout the reaction.

CHEMISTRY

General method for the preparation of 5-(4,5-dihydro-4-aryl-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (**2a-g**)

An ice-cold ethereal solution of diazomethane (40 mL, 4 mmol) and triethylamine (2 mL) were added to a well cooled solution of **1a-c** (1 mmol) in dichloromethane (20 mL). The reaction mixture was kept at -20°C to -15°C for 44-49 h. The solvent was removed under *vacuum* and the resultant solid was purified by passing through a column of silica gel using hexane-ethyl acetate (2:1) as an eluent.

General method for the preparation of 5-(4-aryl-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (**3a-g**)

A mixture of compound **2** (1 mmol) and chloranil (1.4 mmol) in xylene (10 mL) was refluxed for 15-17 h. Then the reaction mixture was treated with 5% NaOH solution. The organic layer was separated and repeatedly washed with water. It was dried over anhydrous Na_2SO_4 and the solvent was removed on a rotary evaporator. The resultant solid was recrystallized from 2-propanol.

5-(4,5-Dihydro-4-phenyl-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (2a**).** Yield 79%, mp 129-131°C. ¹H-NMR ($\text{CDCl}_3/\text{DMSO}-d_6$, 400 MHz): δ = 3.53 (dd, 1H, H_X , $J_{AX} = 6.4$ Hz, $J_{MX} = 10.3$ Hz), 4.19 (dd, 1H, H_M , $J_{AM} = 12.4$ Hz), 4.47 (s, 2H, CH_2), 4.55 (dd, 1H, H_A), 5.41 (br. s, 2H, NH_2), 7.14-7.63 (m, 5H, Ar-H), 10.06 (br. s, 1H, NH), 12.71 (br. s, 1H, CH_2NH). ¹³C-NMR ($\text{CDCl}_3/\text{DMSO}-d_6$, 100 MHz) δ = 38.2 (C-4'), 54.2 (CH_2), 59.1 (C-5'), 157.8 (C-3), 161.3 (C-5), 127.4, 129.2, 130.3, 142.7, 157.1 (aromatic carbons). Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_6\text{O}_2\text{S}$: C, 47.05; H, 4.61; N, 27.43; Found: C, 47.18; H, 4.64; N, 27.66

5-(4-(4-Methylphenyl)-4,5-dihydro-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (2b**).** Yield 84%, mp 132-134°C. ¹H-NMR ($\text{CDCl}_3/\text{DMSO}-d_6$, 400 MHz): δ = 2.26 (s, 3H, Ar-CH₃), 3.55 (dd, 1H, H_X , $J_{AX} = 6.6$ Hz, $J_{MX} = 10.5$ Hz), 4.21 (dd, 1H, H_M , $J_{AM} = 12.6$ Hz), 4.49 (s, 2H, CH_2), 4.57 (dd, 1H, H_A), 5.43 (br. s, 2H, NH_2), 7.16-7.65 (m, 4H, Ar-H), 10.08 (br. s, 1H, NH), 12.73 (br. s, 1H, CH_2NH). ¹³C-NMR ($\text{CDCl}_3/\text{DMSO}-d_6$, 100 MHz)

δ = 22.1 (Ar-CH₃), 38.4 (C-4'), 54.4 (CH₂), 59.3 (C-5'), 158.0 (C-3), 161.5 (C-5), 129.1, 130.2, 137.6, 139.4, 157.3 (aromatic carbons). Anal. Calcd. for C₁₃H₁₆N₆O₂S: C, 48.74; H, 5.03; N, 26.23; Found: C, 48.62; H, 5.06; N, 26.47

5-(4-(4-Methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (2c). Yield 90%, mp 138-140°C. ¹H-NMR (CDCl₃ / DMSO-*d*₆, 400 MHz): δ = 3.57 (dd, 1H, H_X, J_{AX} = 6.8 Hz, J_{MX} = 10.7 Hz), 3.91 (s, 3H Ar-OCH₃), 4.23 (dd, 1H, H_M, J_{AM} = 12.8 Hz), 4.51 (dd, 1H, H_A), 4.93 (s, 2H, CH₂), 5.45 (br. s, 2H, NH₂), 7.18-7.68 (m, 4H Ar-H), 11.00 (br. s, 1H NH), 12.75 (br. s, 1H, CH₂NH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ = 57.4 (Ar-OCH₃), 38.6 (C-4'), 54.6 (CH₂), 59.5 (C-5'), 158.2 (C-3), 161.7 (C-5), 116.8, 130.1, 135.2, 157.5, 159.3 (aromatic carbons). Anal. Calcd. for C₁₃H₁₆N₆O₂S: C, 46.42; H, 4.79; N, 24.98; Found: C, 46.54; H, 4.82; N, 25.21.

5-(4-(4-Fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (2d). Yield 92%, mp 137-139°C. ¹H-NMR (CDCl₃ / DMSO-*d*₆, 400 MHz): δ = 3.58 (dd, 1H, H_X, J_{AX} = 6.9 Hz, J_{MX} = 10.8 Hz), 4.24 (dd, 1H, H_M, J_{AM} = 12.9 Hz), 4.52 (s, 2H, CH₂), 4.60 (dd, 1H, H_A), 5.46 (br. s, 2H, NH₂), 7.20-7.69 (m, 4H, Ar-H), 11.01 (br. s, 1H, NH), 12.76 (br. s, 1H, CH₂NH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ = 38.7 (C-4'), 54.7 (CH₂), 59.6 (C-5'), 158.3 (C-3), 161.8 (C-5), 117.2, 132.1, 138.3, 157.6, 162.7 (aromatic carbons). Anal. Calcd. for C₁₂H₁₃FN₆O₂S: C, 44.44; H, 4.04; N, 25.91; Found: C, 44.57; H, 4.06; N, 26.13.

5-(4-(4-Chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (2e). Yield 81%, mp 147-149°C. ¹H-NMR (CDCl₃ / DMSO-*d*₆, 400 MHz): δ 3.54 (dd, 1H, H_X, J_{AX} = 6.5 Hz, J_{MX} = 10.4 Hz), 4.20 (dd, 1H, H_M, J_{AM} = 12.5 Hz), 4.48 (s, 2H, CH₂), 4.56 (dd, 1H, H_A), 5.42 (br. s, 2H, NH₂), 7.15-7.64 (m, 4H, Ar-H), 10.07 (br. s, 1H, NH), 12.72 (br. s, 1H, CH₂NH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ = 38.3 (C-4'), 54.3 (CH₂), 59.2 (C-5'), 157.9 (C-3), 161.4 (C-5), 130.6, 131.4, 133.8, 140.2, 157.2 (aromatic carbons). Anal. Calcd. for C₁₂H₁₃ClN₆O₂S: C, 42.29; H, 3.84; N, 24.66; Found: C, 42.40; H, 3.85; N, 24.90.

5-(4-(4-Bromophenyl)-4,5-dihydro-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (2f). Yield 76%, mp 154-156°C. ¹H-NMR (CDCl₃ / DMSO-*d*₆, 400 MHz): δ 3.52 (dd, 1H, H_X, J_{AX} = 6.3 Hz, J_{MX} = 10.2 Hz), 4.18 (dd, 1H, H_M, J_{AM} = 12.3 Hz), 4.46 (s, 2H, CH₂), 4.54 (dd, 1H, H_A), 5.40 (br. s, 2H, NH₂), 7.13-7.62 (m, 4H, Ar-H), 10.05 (br. s, 1H, NH), 12.70 (br. s, 1H, CH₂NH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ = 38.1 (C-4'), 54.1 (CH₂), 59.0 (C-5'), 157.7 (C-3), 161.2 (C-5), 122.9, 133.4, 134.6, 141.2, 157.0 (aromatic carbons). Anal. Calcd. for C₁₂H₁₃BrN₆O₂S: C, 37.41; H, 3.40; N, 21.82; Found: C, 37.53; H, 3.42; N, 22.03.

5-(4-(4-Nitrophenyl)-4,5-dihydro-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (2g). Yield 88%, mp 152-154°C. ¹H-NMR (CDCl₃/DMSO-*d*₆, 400 MHz): δ = 3.56 (dd, 1H, H_X, J_{AX} = 6.7 Hz, J_{MX} = 10.6 Hz), 4.22 (dd, 1H, H_M, J_{AM} = 12.7 Hz), 4.50 (s, 2H, CH₂), 4.58 (dd, 1H, H_A), 5.44 (br. s, 2H NH₂), 7.17-7.66 (m, 4H, Ar-H), 10.09 (br. s, 1H, NH), 12.74 (br. s, 1H, CH₂NH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ = 38.5 (C-4'), 54.5 (CH₂), 59.4 (C-5'), 158.1 (C-3), 161.6 (C-5), 125.6, 130.4, 147.2, 149.3, 157.4 (aromatic carbons). Anal. Calcd. for C₁₂H₁₃N₇O₄S: C, 41.02; H, 3.73; N, 27.91; Found: C, 41.15; H, 3.75; N, 28.15.

5-(4-Phenyl-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (3a). Yield 77%, mp 142-144°C. ¹H-NMR (CDCl₃/DMSO-*d*₆, 400 MHz): δ = 4.89 (s, 2H, CH₂), 5.49 (br. s, 2H NH₂), 7.51-7.64 (m, 5H, Ar-H), 8.87 (s, 1H, C_{5'}-H), 11.64 (br. s, 1H, NH), 12.84 (br. s, 1H, CHNH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ = 62.1 (CH₂), 157.3 (C-3), 159.8 (C-5), 126.4, 129.3, 130.1, 131.3, 132.7, 134.3, 137.2 (aromatic carbons). Anal. Calcd. for C₁₂H₁₂N₆O₂S: C, 47.36; H, 3.97; N, 27.62; Found: C, 47.48; H, 3.98; N, 27.84.

5-(4-(4-Methylphenyl)-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (3b). Yield 81%, mp 143-145°C. ¹H-NMR (CDCl₃/DMSO-*d*₆, 400 MHz): δ = 2.30 (s, 3H Ar-CH₃), 4.91 (s, 2H, CH₂), 5.51 (br. s, 2H, NH₂), 7.53-7.66 (m, 4H, Ar-H), 8.86 (s, 1H, C_{5'}-H), 11.66 (br. s, 1H, NH), 12.67 (br. s, 1H, CHNH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ = 22.6 (Ar-CH₃), 62.3 (CH₂), 157.5 (C-3), 160.0 (C-5), 126.7, 129.2, 131.8, 132.8, 133.4, 134.9, 135.6 (aromatic carbons). Anal. Calcd. for C₁₃H₁₄N₆O₂S: C, 49.05; H, 4.43; N, 26.40; Found: C, 49.18; H, 4.46; N, 26.64.

5-(4-(4-Methoxyphenyl)-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (3c). Yield 87%, mp 152-154°C. ¹H-NMR (CDCl₃/DMSO-*d*₆, 400 MHz): δ 3.94 (s, 3H Ar-OCH₃), 4.93 (s, 2H, CH₂), 5.53 (br. s, 2H, NH₂), 7.55-7.68 (m, 4H, Ar-H), 8.91 (s, 1H, C_{5'}-H), 11.68 (br. s, 1H, NH), 12.88 (br. s, 1H, CHNH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ = 57.8 (Ar-OCH₃), 62.5 (CH₂), 157.7 (C-3), 160.2 (C-5), 116.3, 127.2, 129.6, 130.4, 132.5, 134.7, 164.0 (aromatic carbons). Anal. Calcd. for C₁₃H₁₄N₆O₃S: C, 46.70; H, 4.22; N, 25.14; Found: C, 46.82; H, 4.24; N, 25.35.

5-(4-(4-Fluorophenyl)-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (3d). Yield 89%, mp 148-150°C. ¹H-NMR (CDCl₃/DMSO-*d*₆, 400 MHz): δ = 4.94 (s, 2H, CH₂), 5.54 (br. s, 2H NH₂), 7.56-7.69 (m, 4H, Ar-H), 8.92 (1H, s, C_{5'}-H), 11.69 (br. s, 1H, NH), 12.89 (br. s, 1H, CHNH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ

= 62.6 (CH₂), 157.8 (C-3), 160.3 (C-5), 120.2, 127.4, 132.6, 133.3, 134.9, 135.2, 164.2 (aromatic carbons). Anal. Calcd. for C₁₂H₁₁FN₆O₂S: C, 44.72; H, 3.44; N, 26.07; Found: C, 44.85; H, 3.45; N, 26.29.

5-(4-(4-Chlorophenyl)-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (3e). Yield 78%, mp 157–159°C. ¹H-NMR (CDCl₃/DMSO-*d*₆, 400 MHz): δ = 4.90 (s, 2H, CH₂), 5.50 (br. s, 2H, NH₂), 7.52–7.65 (m, 4H, Ar-H), 8.88 (s, 1H, C_{5'}-H), 11.65 (br. s, 1H, NH), 12.85 (br. s, 1H, CHNH). ¹³C-NMR (CDCl₃/DMSO-*d*₆, 100 MHz) δ = 62.2 (CH₂), 157.4 (C-3), 159.9 (C-5), 126.5, 130.4, 131.2, 132.5, 134.2, 136.2, 136.7 (aromatic carbons). Anal. Calcd. for C₁₂H₁₁CIN₆O₂S: C, 42.54; H, 3.27; N, 24.81; Found: C, 42.64; H, 3.29; N, 25.03.

5-(4-(4-Bromophenyl)-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (3f). Yield 73%, mp 167–169°C. ¹H-NMR (CDCl₃/DMSO-*d*₆, 400 MHz): δ = 4.8 (s, 2H, CH₂), 5.48 (br. s, 2H, NH₂), 7.50–7.63 (m, 4H, Ar-H), 8.86 (s, 1H, C_{5'}-H), 11.63 (br. s, 1H, NH), 12.83 (br. s, 1H, CHNH). ¹³C-NMR (CDCl₃/ DMSO-*d*₆, 100 MHz) δ = 62.0 (CH₂), 157.2 (C-3), 159.7 (C-5), 126.3, 124.3, 124.6, 130.2, 132.2, 133.1, 137.6 (aromatic carbons). Anal. Calcd. for C₁₂H₁₁BrN₆O₂S: C, 37.61; H, 2.89; N, 21.93; Found: C, 37.73; H, 2.90; N, 22.14.

5-(4-(4-Nitrophenyl)-1*H*-pyrazol-3-sulfonylmethyl)-4*H*-1,2,4-triazol-3-amine (3g). Yield 85%, mp 163–165°C. ¹H-NMR (CDCl₃/DMSO-*d*₆, 400 MHz): δ 4.92 (s, 2H, CH₂), 5.52 (bs, 2H NH₂), 7.54–7.67 (m, 4H, Ar-H), 8.90 (s, 1H, C_{5'}-H), 11.67 (br. s, 1H, NH), 12.87 (br. s, 1H, CHNH). ¹³C-NMR (CDCl₃ / DMSO-*d*₆, 100 MHz) δ = 62.4 (CH₂), 157.6 (C-3), 160.1 (C-5), 126.9, 126.2, 129.4, 134.5, 144.3, 149.6 (aromatic carbons). Anal. Calcd. for C₁₂H₁₁N₇O₄S: C, 41.26; H, 3.17; N, 28.07; Found: C, 41.37; H, 3.19; N, 28.29.

CONCLUSION

The olefin moiety presents in styrylsulfonylmethyl-1,2,4-triazolylamine (**1**) was exploited to build up five-member heterocycle- pyrazoles. The series of novel pyrazolyl-1,2,4-triazole amine derivatives (**2-3**) have been synthesized. All the entities compounds were characterized by ¹H and ¹³C NMR spectra.

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