Microwave-Assisted Synthesis, NMR, and Cyclic Voltammetric Study of Some Novel 3,5-Disubstituted 1H-1,2,4-Triazoles Containing Hetaryl Fragments

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Authors’ contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

The synthesis of the title compounds 5a-c has been accomplished by a Suzuki cross coupling reaction between arylbromide 3 and 5-Indole boronic acid to furnished precursor 4, which was used as a key intermediate for the synthesis of the preceding targets. Thus, treatment of 4 with variously-substituted arylsulfonyl chlorides, the sulfonate derivatives 5a-c were obtained in good yields and high purity. The structures of 5a-c were characterized by 1H, 13C NMR, and liquid chromatography-mass spectroscopy techniques. Further, the electrochemical behavior of compound 5c has been investigated.

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by cyclic voltammetry using Britton-Robinson (B-R) buffer at pH 3, pH 7 and pH 9, acetate buffer pH 3, and Phosphate buffer pH 3. A broad anodic cyclic voltammetric wave at Eap= 640 mV was observed.

Keywords: Synthesis; suzuki cross coupling; 1, 2, 4-triazoles; cyclic voltammetry.

1. INTRODUCTION

A large number of heterocyclic compounds containing the 1,2,4-triazole ring exhibit anticonvulsant, antifungal, antimicrobial, antihypertensive, analgesic, antiviral, anti-inflammatory, and antioxidant activity [1-15]. Some compounds containing the 1,2,4-triazole ring are well known drugs which include Ribavirin (antiviral) [16], Rizatriptan (antimigraine) [17], Alprazolam (anxiolytic) [18], Vorozole, Letrozole, and Anastrozole (antitumoral) [19] (Scheme 1).

Over the past ten years, we have prepared many compounds containing the 1,2,4-triazole skeleton and screened them for antitumor and anti-HIV activities [20-26]. Additionally, we have synthesized a series of bis(hydroxyphenyl)-1-methyl-1H-1,2,4-triazoles as nonsteroidal inhibitors of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) [27,28].

In the present investigation, three new 1H-1,2,4-triazole derivatives 5a-c were prepared by short and simple reaction sequences according to the synthetic protocols described in the Experimental Section.

2. EXPERIMENTAL SECTION

2.1 Chemical and Analytical Methods

Chemical names follow IUPAC nomenclature. Starting materials were purchased from Aldrich, Acros, Lancaster, Merck, or Fluka, and were used without further purification.
Preparative thin layer chromatography (TLC) on 1 mm SIL G-100 UV254 glass plates (Macherey-Nagel) was prepared. Reaction progress was monitored by TLC on Alugram SIL G UV254 (Macherey-Nagel). Melting points were measured on a Mettler FP1 melting point apparatus and are uncorrected. All new compounds were analyzed for C, H, and N, and the observed results agreed with the calculated percentages to within ±0.4%. 1H and 13C-NMR spectra were recorded on a Bruker DRX-500 instrument unless otherwise noted. Chemical shifts are given in parts per million (ppm), and tetramethylsilane (TMS) was used as an internal standard. All coupling constants (J) are given in Hertz. The 1D and 2D NMR spectra shown in Fig. 1 for 5b were recorded on Avance II Bruker FT-NMR spectrometer 400 (400 MHz) using THF-D8 as a solvent and TMS as an internal standard. Mass spectra (ESI) were measured on a TSQ Quantum (Thermo Electron Corporation) instrument with a RP18 100-3 column (Macherey Nagel) with water/acetonitrile mixtures as eluents. All microwave irradiation experiments were carried out in a CEM-Discover monomode microwave apparatus.

2.2 Procedure for the Preparation of 5-{3-[5-(methoxyphenyl)-2-methyl-2H-1, 2, 4-triazol-3-yl]-phenyl]-1H-indole (4).

Indole-5-boronic acid (121 mg, 0.75 mmol), 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1H-1,2,4-triazole (3) (257 mg, 0.75 mmol), and tetrakis(triphenyl-phosphine)palladium(0) (43 mg, 0.0375 mmol, 5 mol %) were suspended in 1.5 mL DMF in a 10 mL septum-capped microwave vessel containing a stirring magnetic bar. To this was added a solution of NaHCO3 (189 mg, 2.25 mmol) in 1.5 mL of water and the vial was sealed with a teflon cap. The mixture was irradiated with microwaves for 15 min at a temperature of 150°C with an initial irradiation power of 100 W and with 15 bar pressure [27]. The vial was cooled to 40°C and the crude mixture was partitioned between ethyl acetate and water and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over MgSO4, filtered, and evaporated to dryness. The combined organic layers were dried over MgSO4, filtered, and concentrated to dryness. The cross coupling products were purified by preparative TLC (CH2Cl2/MeOH, 10: 0.25). yield: 0.222 g (78%), m.p. 188-190°C (dec), white powder; 1H NMR (DMSO-d6, 500 MHz): δ 11.18 (bs, NH), 8.08 (t, J = 1.6 Hz, 1H), 7.93 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.67-7.58 (m, 3H), 7.53-7.49 (m, 2H), 7.42-7.39 (m, 2H), 7.00 (dd, J = 3.8, 5.0 Hz, 1H), 6.52 (t, J = 3.8 Hz, 1H), 4.01 (s, 3H, NCH3), 3.83 (s, 4H, OCH2). 13C NMR (DMSO-d6, 125 MHz): δ 159.5, 155.1, 142.5, 135.71, 132.3, 130.4, 129.9, 129.3, 128.3, 128.3, 128.7, 126.8, 126.4, 126.2, 120.4, 118.5, 118.1, 115.0, 111.9, 110.7, 101.6, 55.1 (OCH3), 37.2 (NCH3); MS (ESI): m/z = 381 [M+H]+. Anal. calc.d for C24H20N4O: C, 75.77; H, 5.30; N, 14.73. Found: C, 75.53; H, 5.44; N, 14.91.

2.3 General Procedure for the Preparation of 1-Arylsulfonyl-5-{3-[5-(methoxyphenyl)-2-methyl-2H-1, 2, 4-triazol-3-yl]-phenyl]-1H-indole (5a-c)

The Arylsulfonyl chloride (1.0 mmol) was added to a solution of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1H-1,2,4-triazole (3) [29] (0.380 g, 1.0 mmol) in CH2Cl2 (20 mL) containing Et3N (0.10 g, 1.0 mmol) and stirred at 23°C for 4 h. Few drops of water were added, the solution was stirred for 1 h, and then partitioned between CHCl3 (3×20 mL) and water (20 mL). The combined organic layers were dried (Na2SO4), filtered, and evaporated to dryness. The residue was co-evaporated with EtOH (3×20 mL) and then recrystallized from EtOH to give the desired sulfonate derivatives.
2.3.1 1-Benzzenesulfonyl-5-[3-[5-(3-methoxyphenyl)-2-methyl-2H-1,2,4-triazol-3-yl]-phenyl]-1H-indole (5a)

From benzenesulfonyl chloride (0.176 g, 1.0 mmol). White powder. Yield: 0.380 g (73%). m.p. 135-137°C (dec). 1H NMR (DMSO-d6, 500 MHz): 7.96-7.85 (m, 8H), 7.81-7.78 (m, 1H); 7.75 (dd, J = 1.8, 8.7 Hz, 1H), 7.68-7.63 (m, 3H), 7.60-7.56 (m, 2H), 7.40 (t, J = 7.7 Hz, 1H), 7.00-6.98 (m, 1H), 6.94 (d, J = 3.6 Hz, 1H). 13C NMR (DMSO-d6, 125 MHz): δ 159.4, 154.8, 140.7, 138.8, 135.3, 133.7, 132.4, 132.2, 131.3, 129.9, 129.6, 128.6, 128.3, 127.8, 127.5, 127.1, 124.2, 123.1, 122.1, 122.0, 120.2, 118.1, 115.0, 114.1, 113.9, 113.6, 110.7, 110.3, 55.1 (OCH3), 37.2 (NCH3); MS (ESI): m/z = 521 [M+H]+. Anal. Calcd for C30H22N2O3S: C, 69.41; H, 4.56; N, 10.76. Found: C, 69.44; H, 4.85; N, 10.91.

2.3.2 1-(3-Fluorobenzenesulfonyl)-5-[3-[5-(3-methoxyphenyl)-2-methyl-2H-1,2,4-triazol-3-yl]-phenyl]-1H-indole (5b)

From 3-fluorobenzenesulfonyl chloride (0.194 g, 1.0 mmol). Yield: 0.440 g (82 %), m.p. 148-150°C (dec), white powder; 1H NMR (1,4-dioxane-d6, 500 MHz): 8.12 (s, 1H), 8.13 (d, J = 8.5 Hz, 2H), 7.82-7.77 (overlapping multiplets, 5H), 7.78-7.72 (m, 2H), 7.69 (dd, J = 1.8, 8.7 Hz, 1H), 7.66 (d, J = 3.6 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.29 (t, J = 8.3 Hz, 1H), 7.05 (dd, J = 3.8, 5.0 Hz, 1H), 6.90 (ddd, J = 0.9, 2.6, 8.2 Hz, 1H), 6.80 (t, J = 3.6 Hz, 1H), 4.07 (s, 3H, NCH3), 3.82 (s, 3H, OCH3). 13C NMR (1,4-dioxane-d6, 125 MHz): δ 161.4, 161.3, 156.1, 143.1, 139.1, 137.3, 135.7, 135.2, 134.9, 133.9, 133.0, 132.7, 130.4, 130.3, 130.1, 129.8, 128.8, 128.4, 125.2, 121.2, 119.6, 116.0, 115.1, 112.3, 111.0, 55.7 (OCH3), 37.9 (NCH3); MS (ESI): m/z = 539 [M+H]+. Anal. calcd for C30H22FN4O3S: C, 66.90; H, 4.30; N, 10.40. Found: C, 67.04; H, 4.25; N, 10.63.

2.3.3 5-[3-[5-(3-Methoxyphenyl)-2-methyl-2H-1,2,4-triazol-3-yl]-phenyl]-1-(thiophene-2-sulfonyl)-1H-indole (5c)

From thiophene-2-sulfonyl chloride (0.182 g, 1.0 mmol). Yield: 0.350 g (67 %), m.p. 104-107°C (dec), white powder; 1H NMR (CD3COCD3, 500 MHz): 8.19 (t, J = 1.6 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 1.4 Hz, 1H), 7.95 (dd, J = 1.3, 5.0 Hz, 1H), 7.93-7.90 (m, 2H), 7.89-7.87 (m, 1H), 7.80 (dd, J = 1.8, 8.7 Hz, 1H), 7.76-7.71 (m, 4H), 7.41 (t, J = 7.7 Hz, 1H), 7.17 (dd, J = 3.8, 5.0 Hz, 1H), 7.05 (m, 1H), 6.92 (ddd, J = 0.9, 2.6, 8.2 Hz, 1H), 4.18 (s, 3H, NCH3), 3.87 (s, 3H, OCH3). 13C NMR (CD3COCD3, 125 MHz): δ 161.1, 159.5, 155.3, 142.7, 138.6, 136.8, 136.0, 135.4, 134.9, 132.7, 132.0, 130.8, 130.4, 130.3, 129.0, 128.7, 128.5, 128.2, 128.1, 125.1, 121.2, 119.5, 116.6, 114.9, 112.2, 111.2, 55.7 (OCH3), 38.1 (NCH3); MS (ESI): m/z = 527 [M+H]+. Anal. calcd for C29H22N2O3S: C, 63.86; H, 4.21; N, 10.64. Found: C, 63.64; H, 4.33; N, 10.49.

2.4 Voltammetric Measurements

The cyclic voltammetric measurements were carried out with 797 VA computrace (Metrohm, Switzerland) in connection with Dell computer and controlled by VA computrace 2.0 control software. A conventional three electrode system was used in the voltammetric mode; Graphite working electrode vs. Ag/AgCl reference electrode and platinum auxiliary electrode. pH values were measured with Hanna instruments pH 211 (Romania made) pH meter. The general procedure adopted for obtaining cyclic voltammograms was as follows: A 10 mL aliquot of supporting buffer (unless otherwise stated) at the desired pH was pipetted in a clean and dry voltammetric cell and the required standard solutions of compound 5b were added. The test solutions were purged with nitrogen for 100 sec. initially, while the solution
was stirred. The accumulation potential of 0.0 V was applied to a UT (Ultra Trace graphite) electrode while the solution was stirring for 30 seconds. Following the preconcentration period, the analysis was stopped and after 10 seconds had elapsed, anodic scans were carried out over the range 0.0 to 1.2 V. All cyclic voltammetric measurements were made at room temperature.

3. RESULTS AND DISCUSSION

3.1 Synthesis

The triazole derivatives 5a-c were synthesized according to the route described in Scheme 2. The 1H-1,2,4-triazole moiety was prepared in a two-step reaction: first, a nucleophilic addition-elimination reaction of the ethyl imino ester to the acyl chloride afforded the N-acyliminoesters intermediate X which was not isolated. This was followed by nucleophilic addition of methylhydrazine and a subsequent cyclization to produce the brominated 1H-1,2,4-triazole 3. Suzuki cross coupling reaction between the arylbromide derivative 3 and indole-5-boronic acid under standard conditions [27] afforded the cross coupled product 4 in 78% yield. Treatment of the latter precursor with variously-substituted arylsulfonyl chlorides in the presence of Et$_3$N afforded the sulfonate derivatives 5a-c in 73, 82, and 67 % yields, respectively.

Scheme 2. Reagents and conditions: (a) CH$_2$Cl$_2$, Et$_3$N, 30-40 °C, 6 h; (b) CH$_3$NHNH$_2$, CH$_2$Cl$_2$, 30-40 °C, 4 h; (c) NaHCO$_3$, Pd(Ph$_3$)$_4$, DMF, MWI, 15 min.; (d) ArSO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, 23 °C, 4 h

3.2 Structure Elucidation by Elemental Analysis, Mass Spectral Measurement, and by $^1$H, $^{13}$C, DEPT 135, and 2-D Correlation NMR Spectrometry

Proof of structure of the novel compounds was secured via spectroscopic and microanalytical methods. Thus, the microanalyses were in satisfactory agreement with the calculated values (C, H, N values were within±0.4%), and the mass spectra produced the
correct molecular ion peaks with the appropriate isotopic distributions where applicable. Structures of the prepared compounds were further elucidated by the use of 1D/2D $^1$H NMR, and $^{13}$C NMR techniques. Oddly, it is noted that the $^{19}$F-$^{13}$C coupling is absent in the $^{13}$C NMR spectrum of 5b given that the spectrum was not decoupled. Thus, we were further interested in performing a more elaborate structural analysis study of 5b.

The electrospray ionization (ESI) spectrum in positive ionization mode for 5b showed a quasi-molecular ion peak at $m/z$ 539 [M+H]+, suggesting a nominal atomic mass of 538 u. The molecular formula C$_{30}$H$_{23}$FN$_4$O$_3$S was deduced from the elemental composition, C-67.04%, H-4.25%, and N-10.63% and ESI mass spectral data. Such inference at this point is still pending further characterization data (vide infra). In order to fully establish the structure and position of heteroatoms, extensive $^1$H, $^{13}$C, DEPT-135, and correlation NMR spectrometry experiments were conducted in tetrahydrofuran-d$_8$ and are shown in Fig. 1 and summarized in Table 1. The $^{13}$C NMR DEPT-90/135 revealed the presence of 15 signals in the aromatic region representing 17 CH's (δ 135.7 (2xCH), 134.8, 130.4, 130.3, 129.8, 128.8, 128.7, 128.3 (2xCH), 125.2, 121.2, 119.6, 116.0, 115.2, 112.3, 111.0 ppm), and two methyl groups in the aliphatic region (δ 55.8, 37.9 ppm). Inverse gated decoupling experiments allowed reliable quantitative intensity information in regards to which overlapped signals represent more than one absorption. Accordingly, the CH signals at δ 135.7 and 128.3 ppm represented four CH's. The $^{13}$C NMR indicated the presence of 9 quaternary signals representing 11 carbon atoms (δ 161.5, 161.3, 156.2, 143.1, 139.4, 137.3, 133.9, 133.0, 130.1 ppm) in addition to the remaining signals observed in the $^{13}$C NMR DEPT-135 spectrum. Integration values and multiplicities in the $^1$H NMR spectra were in agreement with the assigned structure. There were several useful absorptions that provided a point of entry into the correlation spectra. The distinctive indole methine protons (a & b) were correlated to each other by a cross peak in the COSY spectrum and were traced to carbon signals with chemical shifts at δ 128.3 and 111.0 ppm, respectively, in the HSQC spectrum. Further, the same protons in the HMBC spectrum showed long range correlation to carbon signals with chemical shifts at δ 133.0, 121.2, and 128.7 ppm (h, d, and g carbons). The aromatic methine protons f, g, and d showed strong cross peaks in the COSY, where the latter also showed strong long range correlation with carbons b and f in the indole system. The methoxyphenyl protons and carbons were assigned based on using the methine proton w as a point of entry due to its characteristic upfield absorption ($^1$H/$^{13}$C: δ 6.9/116 ppm) and ddd multiplicity. In addition, proton x provided a useful point as well due to its well resolved triplet appearance. Thus, intense cross peaks were observed between proton x and the two flanking protons, y and w. In addition, proton x assisted in assigning the quaternary carbons as it showed long range coupling with carbons v and z, whereas the methoxy substituent displayed clear long range coupling with carbon v (δ 161.3 ppm). It is noted that the signal at δ 161.3 ppm comprises two absorptions as determined by inverse gated decoupling experiments and has also been assigned to the quaternary carbon z'. The 3-fluorobenzenesulfonyl $^1$H chemical shifts were assigned using proton k which showed correlations with protons l, j, and n in the COSY spectrum and were traced to their respective carbon signals in the HSQC spectrum. More informative were the long range couplings of proton k with carbons j, n, and the quaternary carbon l. The N-Me group of the triazine ring showed a useful long range coupling with a signal at δ 156.2, thus establishing the shift as stemming from carbon q'. Finally, the central phenyl group was assigned based on proton s which appears as a triplet and shows very strong COSY off diagonal peaks with the two flanking protons r and t. Further, the p proton is a singlet as anticipated, although overlapping with another absorption and is correlated via long range coupling with proton d on the indole ring. Interestingly, protons r, s, and t all displayed long range coupling with the triazine quaternary carbon q'.
As can be seen from Fig. 13−has an irreversible character.

A proposed mechanism for the electrochemical oxidation of this electroactive process generates a radical cation which can further undergo 1e− oxidation to yield intermediates susceptible to nucleophilic attack or dimerization by radical−radical or radical−substrate coupling [30,31]. Detailed mechanistic studies are beyond the scope of this work and will be the subject of a future investigation.

Table 1. 1H and 13C NMR data of 5b

| 1H-NMR | Hydrogen | 5b Protons | Annotated Structure |
|--------|----------|------------|---------------------|
| p      | 8.13 (IH, s) |            |                     |
| g      | 8.12 (IH, d, J = 8.5 Hz) |            |                     |
| d      | 7.90 (IH, d, J = 1.6 Hz) |            |                     |
| u, n, j, t | 7.82-7.77 (5H, overlapping multiplets) |            |                     |
| l      | 7.78-7.75 (IH, m) |            |                     |
| y      | 7.73-7.72 (IH, m) |            |                     |
| f      | 7.69 (IH, dd, J = 8.7, 1.8 Hz) |            |                     |
| a      | 7.65 (IH, d, J = 3.6 Hz) |            |                     |
| s      | 7.59 (IH, t, J = 7.7 Hz) |            |                     |
| x      | 7.29 (IH, t, J = 8.3 Hz) |            |                     |
| k      | 7.05 (IH, dd, J = 5.0, 3.8 Hz) |            |                     |
| w      | 6.90 (IH, ddd, J = 8.2, 2.6, 0.9 Hz) |            |                     |
| b      | 6.80 (IH, d, J = 3.6 Hz) |            |                     |
| p'     | 4.07 (3H, s) |            |                     |
| v'     | 3.82 (3H, s) |            |                     |

| 13C-NMR | Carbon | 5b Carbons |
|---------|--------|------------|
| p, g, d, u, n, t | 115.2, 128.7, 121.2, 129.8, 135.7 (2xCH), 134.8 |
| l, y, f, a/r, s, x, k, w | 119.6, 112.3, 125.2, 128.3 (2xCH), 130.3, 130.4, 128.8, 116.0 |
| b, p', v, m, v/z', q, c | 111.0, 37.9, 55.8, 161.5, 161.3 (2xC), 156.2, 143.1 |
| i, c, z/q, h, c | 139.4, 137.3, 133.9, 133.0, 130.1 |

3.3 Cyclic Voltammetric Behaviour of 1-(3-fluorobenzenesulfonyl)-5-{3-[5-(3-Methoxyphenyl)-2-methyl-2H-[1, 2, 4] Triazol-3-yl]-phenyl}-1H-indole (5b)

The electrochemical behaviour of compound 5b (1x10^{-5} mol.L^{-1}) was studied using cyclic voltammetry method in phosphate buffer at pH3, resulting an anodic cyclic voltammetric wave at E_{pa} = 640 mV under the following optimum conditions: 50 mV/s scan rate, 30 s accumulation time, 0.0 V accumulation potential, 0.45 mm² working electrode area and 2000 rpm convection rate. As can be seen from Fig. 2, voltammetric peak was observed on the measured cyclic voltammogram, indicating the irreversibility nature of the anodic oxidation process. In the cyclic voltammetric experiments over all pH values, no peaks were observed in the reverse scans. This suggests that the oxidation of 5b has an irreversible character. The observed voltammetric wave is probably due to the electrochemical oxidation of the indole moiety. A proposed mechanism for the electrochemical oxidation of this electroactive group is given in Scheme 3. It is assumed that initial oxidation occurs on the nitrogen atom of the indole ring, which is electroactive in both acidic and basic media. The one-electron process generates a radical cation which can further undergo 1e− oxidation to yield intermediates susceptible to nucleophilic attack or dimerization by radical−radical or radical−substrate coupling [30,31]. Detailed mechanistic studies are beyond the scope of this work and will be the subject of a future investigation.
Fig. 1. (a) 1H NMR spectrum of 5b (C4D8O, 400 MHz); (b) DEPT-90 spectrum (C4D8O, 100 MHz), CH's (positive phase); (c) DEPT-135 spectrum (C4D8O, 100 MHz), CH's and CH3's (positive phase), CH2's (negative phase); (d) 13C NMR spectrum (C4D8O, 100 MHz); (e) MQFCOSY NMR spectrum; (f) HSQC NMR spectrum; (g) HMBC NMR spectrum
4. CONCLUSION

We have successfully synthesized novel derivatives of 3,5-disubstituted 1H-1,2,4-triazoles containing hetaryl fragments, in good yields. The structures of all the compounds were confirmed by their spectral data. It is suggested that 3,5-disubstituted 1H-1,2,4-triazoles derivatives are worthy for investigations as potential antitumor, anti-HIV and nonsteroidal inhibitors of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) activities.
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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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