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A Green Approach for the Synthesis of Pyridine Linked Bis-(Oxadiazoles) / (Thiadiazoles) / (Triazoles) and Evaluation as Antioxidants

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Abstract. The sulfone moiety is an important core unit in organic synthesis and medicinal chemistry. Amongst different heteroaromatic compounds oxadiazoles, thiadiazoles and triazoles form the basis of many pharmaceuticals and agrochemicals. In fact, pyridine exhibits diversified biological activities. The presence of different pharmacophores in the same unit is an attracting approach to develop new drugs due to synergetic effect. Besides, application of green chemistry concepts is an important goal to prepare biologically active compounds. In view of the above, the present study deals with the synthesis of pyridine linked bis(arylsulfonylmethyl) azoles.

INTRODUCTION

1,3,4-Oxadiazoles, 1,3,4-thiadiazole and 1,2,4-triazoles are important structural units in medicinal chemistry due to their wide spectrum of biological activities such as antioxidant, antibacterial, anti-inflammatory and antifungal, antimicrobial and anticancer activities [1-4]. The familiar drugs viz., raltegravir, zibotentan, megazol, cefazedone, anastrozole and letrozole contain oxadiazole, thiadiazole and triazole moieties [5-7]. In addition, pyridine is useful as building block in the synthesis of natural products as well as biologically active compounds [8]. The sulfone is an important functional group found in a wide variety of natural products, drugs and materials [9]. The combination of different pharmacophores in one molecular frame would lead to the formation of potential therapeutics. Thus, the development of simple and more efficient green methods for the synthesis of azoles remains a goal for synthetic chemists. Ultrasound has increasingly been used in recent years, since it offers in higher yield, shorter reaction time and milder reaction conditions under ultrasonic irradiation [10] comparison to the traditional method [11]. As part of an ongoing multifaceted program aimed towards development of bioactive heterocycles [12, 13], herein we report the synthesis and antioxidant activity of pyridine linked bis(arylsulfonylmethyl) azoles.
RESULTS AND DISCUSSION

The synthetic intermediates methyl arylsulfonylacetic acid hydrazide (1) and pyridine-2,6-dicarboxylic acid (2) were utilized to synthesize some bis(aryl sulfonfyl)methylazo]yl)pyridines. The reaction of 2 moles of compound 1 with 1 mole of compound 2 in the presence of POCl₃ under ultrasonication produced 2,6-bis(2-arylsulfonylmethyl-1,3,4-oxadiazol-5-yl)pyridine (3). The compound 3 was interconverted to thiadiazole and triazole by reaction with appropriate nucleophiles. Adopting similar methodology, the reaction of 3 with thiourea in tetrahydrofuran yielded 2,6-bis(2-arylsulfonylmethyl-1,3,4-thiadiazol-5-yl)pyridine (4). Besides, 2,6-bis(3-arylsulfonylmethyl-4-amino-1,2,4-triazol-5-yl)pyridine (5) was obtained by the treatment of 3 with hydrazine hydrate in n-butanol (Scheme 1).

The ¹H NMR spectra of 3a, 4a and 5a displayed a singlet at δ 4.52, 4.50 and 4.54 due to methylene protons attached to C-2 / C-3 respectively. Apart from these, a broad singlet observed at δ 5.62 ppm in compound 5a was assigned to NH₂. The structures of all the synthesized compounds were further confirmed by IR, ¹³C NMR, mass spectra and microanalyses.

SCHEME 1. Synthesis of Pyridine Linked Bis-(Oxadiazoles)/(Thiadiazoles)/(Triazoles) 4, 5

Antioxidant Activity

The compounds 3-5 were tested for antioxidant activity by DPPH, NO, and H₂O₂ methods at 100 μM concentration (Table 1). The results revealed that the compounds having oxadiazole moieties showed higher radical scavenging activity when compared with those having thiadiazole and triazole units in all the three methods. It was also observed that compounds having triazole showed slightly higher activity than with thiadiazole. Further, it was noticed that methoxy substituted compounds displayed higher antioxidant activity than the corresponding bromo and nitro substituted compounds. In fact, compound 3a exhibited excellent antioxidant activity than the standard Ascorbic acid.

<table>
<thead>
<tr>
<th>Compound</th>
<th>DPPH</th>
<th>NO</th>
<th>H₂O₂</th>
</tr>
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<tr>
<td>3a</td>
<td>82.27</td>
<td>80.54</td>
<td>81.47</td>
</tr>
<tr>
<td>3b</td>
<td>50.81</td>
<td>41.23</td>
<td>47.51</td>
</tr>
<tr>
<td>3c</td>
<td>45.29</td>
<td>39.30</td>
<td>43.15</td>
</tr>
</tbody>
</table>

TABLE 1. The in vitro antioxidant activity of 3a-c / 4a-c / 5a-c by DPPH, NO and H₂O₂ methods

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EXPERIMENTAL SECTION

Apparatus and Analysis

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The homogeneity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm⁻¹. The ¹H NMR and ¹³C NMR spectra were run in DMSO-d₆ on a Jeol JNM spectrometer operating at 400 MHz and 100 MHz. High-resolution mass spectra were recorded on Micromass Q-TOF micromass spectrometer using electrospray ionization. All chemical shifts were reported in δ (ppm) using TMS as an internal standard. The elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. Ultrasound irradiation was carried out in a Bandelin Sonorex RK 102H ultrasonic bath operating at frequency of 35 KHz. The methyl arylsulfonylacteic acid hydrazide was prepared as per the literature procedure [14].

General procedure for the synthesis of 2,6-bis(2-arylsulfonylmethyl-1,3,4-oxadiazol-5-yl)pyridines (3).

A mixture of compound 1 (2 mmol), 2 (1 mmol) and phosphorus oxychloride (5 mL) was subjected to ultrasound irradiation at a frequency of 35 KHz for 30-42 min at room temperature. The progress of the reaction was checked by TLC. The excess phosphorus oxychloride was removed under vacuum. The residue was poured onto crushed ice and the separated solid was filtered on a Buchner funnel. It was washed with brine followed by water, dried and recrystallized from 2-propanol.

2,6-Bis(2-(4-methoxyphenylsulfonylmethyl)-1,3,4-oxadiazol-5-yl)pyridine (3a). Yield 90%; white solid, mp 180-184 °C; IR (KBr cm⁻¹): 1578 (C=N), 1316 & 1162 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 3.80 (s, 6H, Ar-OCH₃), 4.52 (s, 4H, CH₂), 7.08-8.10 (m, 11H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): 55.2 (Ar-OCH₃), 56.5 (CH₂), 164.3 (C-5), 163.0 (C-2), 115.0, 121.5, 129.3, 132.6, 142.4, 157.9, 165.2 ppm (aromatic carbons); HRMS (m/z): 606.5791 [M+Na]⁺. Anal. Calcd. for C₂₅H₂₁N₅O₈S₂: C 51.45, H 3.63, N 12.00; Found: C 51.55, H 3.61, N 12.22%.

2,6-Bis(2-(4-bromophenylsulfonylmethyl)-1,3,4-oxadiazol-5-yl)pyridine (3b). Yield 87%; white solid, mp 196-198 °C; IR (KBr cm⁻¹): 1582 (C=N), 1313 & 1154 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 4.56 (s, 4H, CH₂), 7.89-8.14 (m, 11H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): 57.2 (CH₂), 163.4 (C-5), 162.7 (C-2), 121.4, 128.6, 129.5, 132.0, 136.2, 142.3, 157.1 ppm (aromatic carbons); HRMS (m/z): 704.3187 [M+Na]⁺. Anal. Calcd. for C₂₃H₁₅Br₂N₅O₆S₂: C 40.55, H 2.22, N 10.28; Found: C 40.67, H 2.25, N 10.55%.

2,6-Bis(2-(4-nitrophenylsulfonylmethyl)-1,3,4-oxadiazol-5-yl)pyridine (3c). Yield 89%; white solid, mp 190-192 °C; IR (KBr cm⁻¹): 1589 (C=N), 1312 & 1154 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 4.65 (s, 4H, CH₂), 8.04-8.50 (m, 11H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 58.7 (CH₂), 164.8 (CH₃), 163.4 (C-2), 120.8, 124.6, 129.4, 142.6, 143.4, 152.3, 157.2 ppm (aromatic carbons); HRMS (m/z): 636.5210 [M+Na]⁺. Anal. Calcd. for C₂₃H₁₅N₇O₁₀S₂: C 45.03, H 2.46, N 15.98; Found: C 45.12, H 2.45, N 16.23%.

General procedure for the synthesis of 2,6-bis(2-arylsulfonflylacetamic acid hydrizide as prepared per the literature procedure [14].

The compound 3 (0.5 mmol), thiourea (2 mmol) and tetrahydrofuran (6 mL) were taken in a sealed tube and heated at reflux conditions under ultrasonication for 72-85 min. After completion of the reaction (monitored by TLC), the contents of the flask were extracted with dichloromethane. The organic layer was washed with water followed by brine. It was dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure and the resultant residue was purified by column chromatography (silica gel, 60-120 mesh) using ethyl acetate-hexane (1:3) as eluent.
2,6-Bis[2-(4-methoxyphenylsulfonylmethyl)-1,3,4-thiadiazol-5-yl]pyridine (4a) Yield 84%; white solid, mp 173-175 °C; IR (KBr cm⁻¹): 1592 (C=N), 1330, 1130 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 3.78 (s, 6H, Ar-OCH₃), 4.50 (s, 4H, CH₂), 7.09-8.13 (m, 11H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 54.8 (Ar-OCH₃), 55.8 (CH₂), 173.8 (C-5), 167.7 (C-2), 129.7, 132.2, 142.3, 157.2, 165.1 ppm (aromatic carbons); HRMS (m/z): 638.7026 [M+Na]+. Anal. Calcd. for C₂₅H₂₁N₅O₆S₄: C 48.77, H 3.44, N 11.37; Found: C 48.88, H 3.45, N 11.60%.

2,6-Bis[2-(4-bromophenylsulfonylmethyl)-1,3,4-thiadiazol-5-yl]pyridine (4b). Yield 86%; white solid, mp 179-181 °C; IR (KBr cm⁻¹): 1579 (C=N), 1320, 1126 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 4.62 (s, 4H, CH₂), 7.84-8.10 (m, 11H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 56.2 (CH₂), 174.3 (C-5), 167.7 (C-2), 120.9, 128.3, 127.7, 124.6, 129.5, 142.5, 157.1 ppm (aromatic carbons); HRMS (m/z): 736.4406 [M+Na]+. Anal. Calcd. for C₂₃H₁₅Br₂N₅O₄S₄: C 38.72, H 2.12, N 9.82; Found: C 38.85, H 2.16, N 10.11%.

2,6-Bis[2-(4-nitrophenylsulfonylmethyl)-1,3,4-thiadiazol-5-yl]pyridine (4c). Yield 88%; white solid, mp 177-179 °C; IR (KBr cm⁻¹): 1594 (C=N), 1334, 1137 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 4.64 (s, 4H, CH₂), 8.07-8.49 (m, 11H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 58.4 (CH₂), 173.9 (C-5), 167.8 (C-2), 121.3, 124.6, 129.5, 142.3, 143.2, 152.1, 157.4 ppm (aromatic carbons); HRMS (m/z): 668.6447 [M+Na]+. Anal. Calcd. for C₂₃H₁₅N₇O₈S₄: C 42.79, H 2.34, N 15.19; Found: C 42.91, H 2.32, N 15.46%.

General procedure for the synthesis of 2,6-(bis(3-arylsulfonylmethyl-4-amino-1,2,4-triazol-5-yl)pyridines (5). A solution of 3 (1 mmol), hydrazine hydrate (4 mmol) and n-butanol (5 mL) were subjected to ultrasound irradiation for 50-60 min. To this, potassium hydroxide (2 mmol) was added and the precipitate formed was separated by filtration. The solid obtained was acidified with conc. HCl to pH 3. It was washed with water and dried. The solid was purified by column chromatography (silica gel, 160-120 mesh) using ethyl acetate-hexane (1:3) as eluent.

2,6-Bis[3-(p-methoxyphenylsulfonylmethyl)-4-amino-1,2,4-triazol-5-yl]pyridine (5a). Yield 91%; white solid, mp 191-193 °C; IR (KBr cm⁻¹): 3438, 3331 (NH₂), 1587 (C=N), 1328, 1129 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 3.77 (s, 6H, Ar-OCH₃), 4.54 (s, 4H, CH₂), 5.60 (br. s, 4H, NH₂), 7.04-8.12 (m, 11H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 56.4 (Ar-OCH₃), 57.6 (CH₂), 151.2 (C-3), 144.9 (C-5), 115.0, 120.6, 129.3, 131.4, 141.2, 154.7, 165.1 ppm (aromatic carbons); HRMS (m/z): 634.6409 [M+Na]+. Anal. Calcd. for C₂₅H₂₅N₉O₆S₂: C 49.09, H 4.12, N 20.61; Found: C 49.16, H 4.16, N 20.84%.

2,6-Bis[3-(p-bromophenylsulfonylmethyl)-4-amino-1,2,4-triazol-5-yl]pyridine (5b). Yield 85%; white solid, mp 203-205 °C; IR (KBr cm⁻¹): 3429, 3325 (NH₂), 1600 (C=N), 1328, 1124 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 4.62 (s, 4H, CH₂), 5.63 (br. s, 4H, NH₂), 7.46-8.04 (m, 11H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 58.4 (CH₂), 151.2 (C-3), 144.9 (C-5), 120.4, 127.6, 128.0, 131.9, 135.6, 141.4, 154.7 ppm (aromatic carbons); HRMS (m/z): 732.3812 [M+Na]+. Anal. Calcd. for C₂₃H₁₉Br₂N₉O₄S₂: C 38.94, H 2.70, N 17.77; Found: C 39.05, H 2.72, N 17.95%.

2,6-Bis[3-(p-nitrophenylsulfonylmethyl)-4-amino-1,2,4-triazol-5-yl]pyridine (5c). Yield 92%; white solid, mp 196-198 °C; IR (KBr cm⁻¹): 3448, 3344 (NH₂), 1578 (C=N), 1326, 1131 (SO₂); ¹H NMR (400 MHz, DMSO-d₆): δ 4.64 (s, 4H, CH₂), 5.62 (br. s, 4H, NH₂), 8.02-8.36 (m, 11H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 59.4 (CH₂), 151.3 (C-3), 144.7 (C-5), 120.8, 124.0, 128.7, 141.6, 143.1, 152.6, 154.5 ppm (aromatic carbons); HRMS (m/z): 664.5830 [M+Na]+. Anal. Calcd. for C₂₃H₁₉N₁₁O₈S₂: C 43.06, H 2.99, N 24.01; Found: C 43.19, H 2.98, N 24.23%.

Antioxidant Assays

The compounds 3-5 were tested for antioxidant property by 2,2-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide (NO) and hydrogen peroxide (H₂O₂) methods at 100 μg/mL concentration [15].

CONCLUSION

In conclusion, some new bis(arylsulfonylmethylxadiazolyl)pyridines, bis(arylsulfonylmethylthiadiazolyl)pyridines and bis(arylsulfonylmethyltriazolyl)pyridines were synthesized from pyridine-2,6-dicarboxylic acid and methyl arylsulfonylacetic acid hydrazides adopting a green approach - ultrasonication. All the synthesized compounds were obtained with high yield and in shorter reaction time. The structures of all the synthesized compounds were characterized by spectral parameters and elemental analyses. All the target compounds were...
evaluated for antioxidant activity. Methoxy substituted bis(arylsulfonylmethyloxadiazolyl)pyridine was emerged as potential antioxidant agent among the screened samples.

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