An Efficient Synthesis of Thiazolo and Thiadiazolo Quinoxaline Derivatives in Ionic Liquid

B. PRASANNA*, B. SRINIVAS, Y. JAGANNADHAM and SUMANGALA RAO

Research Centre, Department of Chemistry
Chaitanya PG College, Warangal-506 001, India
prasschem@gmail.com

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Abstract: A series of 3-substitutedphenyl-1-thia-tetrazopentaleno[1,2-b]naphthalene 4(a-d) and 2-substitutedphenyl-1-thia-pentazopentaleno[1,2-b]naphthalene 5(a-d) were synthesized via., the reaction of 2-aminothiazoles 2(a-d) and 2-aminothiadiazoles 3(a-d) with 2,3-dichloro quinoxaline 1 in ionic liquid without using any catalyst. This protocol has the advantages of easier workup, milder reaction conditions, high yields, and environmentally benign procedure over traditional methods. The synthesized compounds 4(a-d) and 5(a-d) tested for their anti-fungal activity and these compounds were characterized by IR, NMR and Mass spectral analysis.

Keywords: Aminothiazoles, Aminothiadiazoles, Dichloroquinoxaline.

Introduction

Compounds containing the quinoxaline nucleus exhibit a broad spectrum of biological activity such as, anti-viral1, antiinflammatory, antiprotazoal2, antihelmintthic3, anticancer4, antimalarial5, and antidepressant activities6. Some of the antibiotics such as levomycin, actinoleutin, and echinomycin also contain a quinoxaline scaffold and these are known to inhibit the growth of gram positive bacteria7 and are active against various transplantable tumours8. Besides the biological activities, quinoxalines are also used in the synthesis of organic semiconductors, dyes9, and electroluminescent materials10. Some of quinoxalines exhibit potent central nervous system (CNS) activities such as analgesic and anti-inflammatory activities11. Few of azolopyrimidoquinaxalines, pyrimidoquinazolines exhibited good antioxidants, anti-inflammatory, and analgesic activities12-15. Furthermore, organic compounds bearing thiazolopyrimidines and pyrithiazoled quinoxaline nuclei were found to possess potent anticancer activities16. These biological applications and development of new route to heterocyclic systems in ionic liquid prompted us to synthesize some new heterocyclic derivatives having phenylthiazoles, thiadiazoles, and quinoxaline moieties starting from 2, 3-dichloro quinoxaline in ionic liquid without using any catalyst and search of better anti-fungal activity. (Schemes 1 & 2).
Experimental
Melting points were measured in open capillary on Buchi melting point B-540 apparatus and were uncorrected. IR spectra were recorded on Simadzu FTIR-8400 spectrometer using KBr pellets. $^1$H NMR (300 MHz) spectra recorded in DMSO-$d_6$ on a Bruker AVANCE 300 instrument with the TMS as an internal standard. All the chemical shifts values were recorded as $\delta$ ppm. Mass spectra (EI-MS) were taken on Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV. CHNS analysis was carried out on Carlo Erba E A 1108 automatic analyzer. The progress of each reaction was monitored and purity of the compounds was checked by thin layer chromatography.

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\begin{align*}
\text{Scheme 1} \quad & \quad \begin{array}{c}
\text{R= H, Cl, Br, CH}_3
\end{array} \\
& \quad \begin{array}{c}
\text{R= H, Cl, Br, CH}_3
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\text{R= H, Cl, Br, CH}_3
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\text{R= H, Cl, Br, CH}_3
\end{array} \\
& \quad \begin{array}{c}
\text{R= H, Cl, Br, CH}_3
\end{array}
\end{align*}
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\begin{align*}
\text{Scheme 2} \quad & \quad \begin{array}{c}
\text{R= H, Cl, Br, CH}_3
\end{array} \\
& \quad \begin{array}{c}
\text{R= H, Cl, Br, CH}_3
\end{array} \\
& \quad \begin{array}{c}
\text{R= H, Cl, Br, CH}_3
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\text{R= H, Cl, Br, CH}_3
\end{array} \\
& \quad \begin{array}{c}
\text{R= H, Cl, Br, CH}_3
\end{array}
\end{align*}
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General Procedure for the Synthesis of 3-Substitutedphenyl-1-thiatetrazopentaleno-[1,2-b]naphthalene 4(a-d) and 2-substituted phenyl-1-thiatetrazopentaleno[1,2-b] naphthalene 5(a-d)
A dry 50 mL flask was charged with 2, 3-dichloroquinoxaline$^{17-18}$ 1 (1 mmol) and substituted 2-aminothiazoles 2(a-d) (1 mmol)/2-aminothiadiazoles 3(a-d) (1 mmol) and ionic liquid [bmm] BF$_4$ (2 mL). Then the reaction mixture was stirred for 1.5 h to 2.5 h to complete the reaction (monitored by TLC) at 80°C. The reaction mixture was cooled to room temperature and poured into 10 mL of water. The solid product collected by filtration and re-crystallized from methanol to give pure compounds 4(a-d) and 5(a-d). The filtration was washed with acetic ester for several times concentrated under reduced pressure at 100°C for several hours to give reusable solvent. A similar procedure was used in preparing all the compounds.

Spectral Data of the Synthesized Compounds 4(a-d) and 5(a-d)

3-Phenyl -1-thia-3a,4,9,10-tetrazopentaleno[1,2-b]naphthalene (4a)
Mp: 240-242°C; IR (KBr): $\nu$ (cm$^{-1}$) 1612 (C=N); $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.12 (s, 1H, CH), 7.22-7.40 (m, 5H, Ar-H), 7.48-7.52 (dd, 1H, quin-H), 7.80 (dd, 1H, quin-H), 8.12 (dd, 2H, quin-H). EI-MS: 303 [M$^+$]$^+$. Anal.Caled for C$_{17}$H$_{10}$N$_4$S: C, 67.53; H, 3.33; N, 18.53%. Found: C, 67.56; H, 3.31; N, 18.51%. 
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3-(4-Chlorophenyl)-1-thia-3a,4,9,10-tetrazopentaleno[1,2-b]naphthalene (4b)
Mp: 232-233°C; IR (KBr): ν (cm⁻¹) 1618 (C=N); ¹H NMR (300 MHz; DMSO-d₆): δ 7.02-7.18 (m, 4H, Ar-H), 7.20 (s, 1H, CH₂), 7.42 (dd, 1H, quin-H), 7.80 (dd, 1H, quin-H), 8.12-8.14 (dd, 2H, quin-H). EI-MS: 338 [M+1]+. Anal. Caled for C₁₇H₂ClNS: C, 60.62; H, 2.69; N, 16.64%. Found: C, 60.64, H, 2.67, N, 16.62%.

3-(4-Bromophenyl)-1-thia-3a,4,9,10-tetrazopentaleno[1,2-b]naphthalene (4c)
Mp: 238-240°C; IR(KBr): ν (cm⁻¹) 1610 (C=N); ¹H NMR (300 MHz, DMSO-d₆): δ 7.16-7.34 (m, 4H, Ar-H), 7.20 (s, 1H, CH₂), 7.54 (dd, 1H, quin-H), 7.86 (dd, 1H, quin-H), 8.14-8.18 (dd, 2H, quin-H). EI-MS: 382 [M+1]+. Anal. Caled for C₁₇H₂BrNS: C, 53.56; H, 2.38; N, 14.70%. Found: C, 53.54; H, 2.40; N, 14.72%.

3-p-Tolyl-1-thia-3a,4,9,10-tetrazopentaleno[1,2-b]naphthalene (4d)
Mp: 245-247°C; IR (KBr): ν (cm⁻¹) 1610 (C=N); ¹H NMR (300 MHz, DMSO-d₆): δ 2.32 (s, 3H,CH₃), 7.04-7.18 (dd, 2H, Ar-H), 7.24-7.26 (dd, 2H, Ar-H), 7.14 (s, 1H, CH₂), 7.60-7.64 (dd, 2H, quin-H), 8.17-8.19 (dd, 2H, quin-H). EI-MS: 317 [M+1]+. Anal. Caled for C₁₅H₁₂N₄S: C, 68.33; H, 3.82; N, 17.71%. Found: C, 68.31; H, 3.80; N, 17.69%.

2-Phenyl-1-thia-3a,4,9,10-pentazopentaleno[1,2-b]naphthalene (5a)
Mp: 246-248°C; IR (KBr): ν (cm⁻¹) 1612 (C=N); ¹H NMR (300 MHz, DMSO-d₆): δ 7.34-7.64 (m, 5H, Ar-H), 7.72-7.74 (dd, 2H, quin-H), 8.14-8.16 (dd, 2H, quin-H). EI-MS: 304 [M+1]+. Anal. Caled for C₁₆H₁₃N₅S: C, 63.32; H, 2.99; N, 23.09%. Found: C, 63.32; H, 2.97; N, 23.11%.

2-(4-Chlorophenyl)-1-thia-3a,4,9,10-pentazopentaleno[1,2-b]naphthalene (5b)

2-(4-Bromophenyl)-1-thia-3a,4,9,10-pentazopentaleno[1,2-b]naphthalene (5c)

2-(p-Tolyl)-1-thia-3a,4,9,10-pentazo pentaleno[1,2-b]naphthalene (5d)
Mp: 242-244°C; IR (KBr): ν (cm⁻¹) 1610 (C=N); ¹H NMR (300 MHz; DMSO-d₆): δ 2.34 (s, 3H, CH₃), 7.12-7.16 (dd, 2H, Ar-H), 7.54-7.60 (dd, 2H, Ar-H), 7.72-7.78(dd, 2H, quin-H), 8.12-8.16 (dd, 2H, quin-H). EI-MS: 318 [M+1]+. Anal. Caled for C₁₇H₁₁N₅S: C, 64.34; H, 3.49; N, 22.07%. Found: C, 64.32; H, 3.51; N, 22.06%.

Antifungal Activity
The antifungal activity was assayed by sabouraud dextrose agar media plate disc diffusion method at the concentration of 50 μg per disk. All the synthesized compounds were tested in vitro for their antifungal activity against microorganisms such as Candida albicans, Microsporum gypsum and microsporum canis. Each test compound was dissolved in dimethylsulphoxide (DMSO) to get a concentration of 10 mg/mL. The disc (6 mm in diameter was impregnated with 5 μL of each test solution to get 50 μg/mL; air dried and placed on the sabouraud dextrose agar media, previously seeded with 0.2 mL of broth culture of each organism for 18 h. The plates were incubated at 22°C for 48 h and the inhibition zones were
measured in mm. Discs impregnated with DMSO were used as a control and flucanazole disc as antifungal reference standard.

**Results and Discussion**

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. Room temperature ionic liquids, especially those based on 1-alkyl-3-methylimidazoliums have shown great promise as an attractive alternative to conventional organic solvents and more attention has been currently focused on organic reactions prompted by ionic liquids. They are nonvolatile, recyclable, non explosive, easily operable, and thermally robust. To search for the optimal reaction solvent, the reaction of 2,3-dichloroquinoxaline 1 with substituted 2-aminothiazoles 2(a-d) and substituted 2-aminothiadiazoles 3(a-d) were examined using ionic liquid such as [bmim]BF₄ and conventional reaction solvent such as acetic acid at different reaction temperatures. The results are summarized Table 1. It can be seen from Table 1 that the best result was obtained when the reaction was carried out in [bmim]BF₄ at 80°C. It was chosen as solvent for the reactions as it is environmentally friendly and the toxic organic reagents can be avoided. Under these optimized reaction conditions a series of 3-substituted phenyl-1-thiatetrazopentaleno-[1,2-b]-naphthalene 4(a-d) and 2-substituted phenyl-1-thiapentazopentaleno-[1,2-b]-naphthalene 5 (a-d) were synthesized.

The IR spectra of compounds 4(a-d) and 5(a-d), show absorption bands within the ν 1620-1604 cm⁻¹ region. They are due to symmetric vibration of C=N group. The absence of the absorption band corresponding to amino stretching frequency of the compound substituted 2-aminothiazoles 2(a-d) and 2-aminothiadiazoles 3(a-d) clearly confirm the formation of compound 4(a-d) and 5(a-d).

**Antifungal Activity**

The antifungal activity was determined by the disc diffusion method at the concentration of 50 per disk. All the synthesized compounds were tested in vitro for their antifungal activity against microorganisms such as *Candida albicans*, *Microsporum gypseum*, and *Microsporum canis*, using flucanazole as standard antifungal. The compounds 4b and 5b were highly active. Compounds 4a and 5a were inactive, while rest of the compounds showed moderate activity.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Zone of Inhibition</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>C.albicans</td>
</tr>
<tr>
<td>4a</td>
<td>-</td>
</tr>
<tr>
<td>4b</td>
<td>+++</td>
</tr>
<tr>
<td>4c</td>
<td>++</td>
</tr>
<tr>
<td>4d</td>
<td>++</td>
</tr>
<tr>
<td>5a</td>
<td>-</td>
</tr>
<tr>
<td>5b</td>
<td>+++</td>
</tr>
<tr>
<td>5c</td>
<td>++</td>
</tr>
<tr>
<td>5d</td>
<td>++</td>
</tr>
<tr>
<td>Flucanazole</td>
<td>+++</td>
</tr>
</tbody>
</table>

Inactive (inhibition zone < 6 mm); slightly active= ‘+’ (inhibition zone 7-9 mm); moderately active = ‘++’ (inhibition zone 10-13 mm ); highly active = ‘+++’ (inhibition zone > 14 mm).
Table 1. Solvent and temperature optimization for the synthesis of 4(a-d) and 5(a-d).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield, %/Time, h</th>
<th>1^[bmim]VBF_4</th>
<th>2^[AcOH]</th>
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<tbody>
<tr>
<td>4a</td>
<td>H</td>
<td>92/1.8</td>
<td>62/16</td>
<td></td>
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<tr>
<td>4b</td>
<td>Cl</td>
<td>93/1.5</td>
<td>65/14</td>
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<tr>
<td>4c</td>
<td>Br</td>
<td>95/1.5</td>
<td>67/14</td>
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<td>5a</td>
<td>H</td>
<td>91/2.1</td>
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<tr>
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<td>Cl</td>
<td>93/2</td>
<td>62/14</td>
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</tr>
<tr>
<td>5c</td>
<td>Br</td>
<td>94/2</td>
<td>64/15</td>
<td></td>
</tr>
<tr>
<td>5d</td>
<td>Me</td>
<td>90/2.5</td>
<td>57/16</td>
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</tbody>
</table>

^1 reaction temperature at 80°C, *2 reaction temperature at reflux.

Conclusion

We developed an efficient and economical safe and environmentally benign procedure for synthesis of 3-substituted phenyl-1-thia-tetrazopentaleno-[1,2-b]-naphthalene 4(a-d) and 2-substituted phenyl-1-thia-pentazopentaleno-[1,2-b]-naphthalene 5(a-d) through the reaction of 2-aminothiazoles 2(a-d) and 2-aminothiadiazoles 3(a-d) with 2,3-dichloro quinoxaline 1 in ionic liquid [bmim][BF_4] without using any catalyst. A series of the synthesized compounds 4(a-d) and 5(a-d) were tested for antifungal activity, the compounds 4b and 5b were found highly active against Candida albicans, microsporium gypsum and microsporium canis when compared to Fluconazole as standard antifungal agent.

References


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