

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

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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.

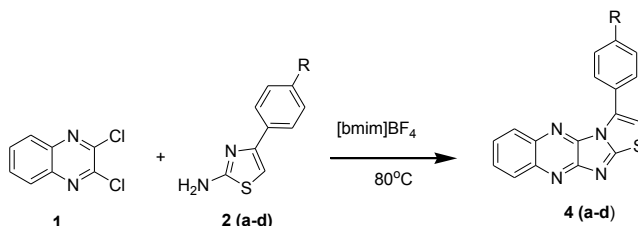
Keywords: Aminothiazoles, Aminothiadiazoles, Dichloroquinoxaline.

Introduction

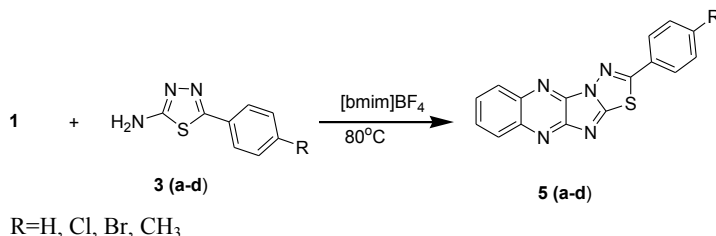
Compounds containing the quinoxaline nucleus exhibit abroad spectrum of biological activity such as, anti-viral¹, antiinflammatory, antiprotozoal², antihelminthic³, anticancer⁴, antimalarial⁵, and antidepressant activities⁶. Some of the antibiotics such as levomycin, actinoleutin, and echinomycin also 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 azolopyrimidoquinoxalines, pyrimidoquinazolines exhibited good antioxidants, anti-inflammatory, and analgesic activities¹²⁻¹⁵. Furthermore, organic compounds bearing thiazolopyrimidines and pyridothiazolo 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. ^1H 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 δ 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.



Scheme 1



Scheme 2

General Procedure for the Synthesis of 3-Substitutedphenyl-1-thia-tetrazopentaleno-[1,2-b]naphthalene 4(a-d) and 2-substituted phenyl-1-thia-pentazopentaleno[1,2-b] naphthalene 5(a-d)

A dry 50 mL flask was charged with 2, 3-dichloroquinoxaline¹⁷⁻¹⁸ **1** (1 mmol) and substituted 2-aminothiazoles **2(a-d)** (1mmol)/2-aminothiadiazoles **3(a-d)** (1 mmol) and ionic liquid [bmim] BF₄ (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): ν (cm⁻¹) 1612 (C=N); ^1H NMR (300 MHz, DMSO- d_6): δ 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+1]⁺. Anal.Cald for C₁₇H₁₀N₄S: C, 67.53; H, 3.33; N, 18.53%. Found: C, 67.56; H, 3.31; N, 18.51%.

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

Mp: 232-233⁰C; IR (KBr): ν (cm⁻¹) 1618 (C=N); ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.02-7.18 (m, 4H, Ar-H), 7.20 (s, 1H, CH), 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. Calcd for C₁₇H₉ClN₄S: 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: 238-240⁰C; IR(KBr): ν (cm⁻¹) 1610 (C=N); ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.16-7.34 (m, 4H, Ar-H), 7.20 (s, 1H, CH), 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. Calcd for C₁₇H₉BrN₄S: 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: 245-247⁰C; IR (KBr): ν (cm⁻¹) 1610 (C=N); ¹H NMR (300 MHz, DMSO-*d*₆): 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, CH), 7.60-7.64 (dd, 2H, quin-H), 8.17-8.19 (dd, 2H, quin-H). EI-MS: 317 [M+1]⁺. Anal. Calcd for C₁₈H₁₂N₄S: C, 68.33; H, 3.82; N, 17.71%. Found: C, 68.31; H, 3.80; N, 17.69%.

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

Mp: 246-248⁰C; IR (KBr): ν (cm⁻¹) 1612 (C=N); ¹H NMR (300 MHz, DMSO-*d*₆): 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. Calcd for C₁₆H₉N₅S: C, 63.32; H, 2.99; N, 23.09%. Found: C, 63.32; H, 2.97; N, 23.11%.

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

Mp: 250-251⁰C; IR (KBr): ν (cm⁻¹) 1618 (C=N); ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.38-7.42 (dd, 2H, Ar-H), 7.74-7.76 (dd, 2H, Ar-H), 7.82 (dd, 2H, quin-H), 8.20-8.22 (dd, 2H, quin-H). EI-MS: 339 [M+1]⁺. Anal. Calcd for C₁₆H₈ClN₅S: C, 56.89; H, 2.39; N, 20.73%. Found: C, 56.87, H, 2.41, N, 20.71%.

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

Mp: 258-260⁰C; IR (KBr): ν (cm⁻¹) 1620 (C=N); ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.32-7.36 (dd, 2H, Ar-H), 7.70-7.72 (dd, 2H, Ar-H), 7.84-7.86 (dd, 2H, quin-H), 8.18-8.20 (dd, 2H, quin-H). EI-MS: 383 [M+1]⁺. Anal. Calcd for C₁₆H₈BrN₅S: C, 50.28; H, 2.11; N, 18.32%. Found: C, 50.26; H, 2.13; N, 18.30%.

2-(*p*-Tolyl)-1-thia-3,3a,4,9,10-pentazopentaleno[1,2-b]naphthalene (5d)

Mp: 242-244⁰C; IR (KBr): ν (cm⁻¹) 1610 (C=N); ¹H NMR (300 MHz, DMSO-*d*₆): 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. Calcd 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 activity¹⁹ was assayed by sabouraud dextrose agar media plate disc diffusion method at the concentration of 50 μ g per disk. All the synthesized compounds were tested in vitro for their antifungal activity against microorganisms such as *Candida albicans*, *Microsporium gypsum* and *microsporium 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 μ L of each test solution to get 50 μ g/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 22⁰C for 48 h and the inhibition zones were

measured in mm. Discs impregnated with DMSO were used as a control and fluconazole 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-methylimidazolium cations 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 liquids²⁰. They are nonvolatile, recyclable, non explosive, easily operable, and thermally robust²¹. 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-thia-tetrazopentaleno-[1,2-b]-naphthalene **4(a-d)** and 2-substituted phenyl-1-thia-pentazopentaleno-[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*, *Microsporium gypsum*, and *Microsporium canis*, using fluconazole 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 1. Results of anti-fungal activity.

Compounds	Zone of Inhibition		
	C.albicans	M.gypsum	M.canis
4a	-	-	-
4b	+++	+++	+++
4c	++	++	++
4d	++	++	++
5a	-	-	-
5b	+++	+++	+++
5c	++	++	++
5d	++	++	++
Fluconazole	+++	+++	+++

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)**.

Entry	R	Yield, %/Time, h	
		^a [bmim]VBF ₄	^b AcOH
4a	H	92/1.8	62/16
4b	Cl	93/1.5	65/14
4c	Br	95/1.5	67/14
4d	Me	89/2.2	58/17
5a	H	91/2.1	60/15
5b	Cl	93/2	62/14
5c	Br	94/2	64/15
5d	Me	90/2.5	57/16

^a reaction temperature at 80°C, ^b 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]BF₄ 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 Flucanazole as standard antifungal agent.

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