Research Article

Regioselective Synthesis of Some Pyrazole Scaffolds Attached to Benzothiazole and Benzimidazole Moieties

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Condensation of 2-(benzothiazol-2-yl)acetonitrile (1) or 2-(1-methyl-1H-benzimidazol-2-yl)acetonitrile (2) with thiophene-2-carbaldehyde afforded the corresponding acrylonitrile derivatives 3 or 4, respectively. The 1,3-dipolar cycloaddition reaction of the acrylonitrile 3 or 4 with nitrile-imine 6 gave novel pyrazole derivatives pendant to benzothiazole and benzimidazole. The pyrazoline derivative 7 was converted into the corresponding pyrazole derivative 11 via thermal elimination of hydrogen cyanide upon heating in sodium ethoxide solution. The structures of the synthesized products were confirmed by IR, 1H NMR, and mass spectral techniques.

1. Introduction

Benzothiazole derivatives have been reported to possess diverse biological properties [1, 2]. Benzimidazole is an interesting heterocyclic ring system because it is present in naturally occurring cyanocobalamin and several known commercialized drugs such as mebendazole, astemizole, and emedastine difumarate. Moreover, they have shown anthelmintic [3] and antimicrobial activities [4–6]. Also, many benzimidazole derivatives are used as inhibitors of HIV-1 that causes AIDS [7–9] as well as anticancer agents [10]. In addition, pyrazoline derivatives have been found antifungal [11], antidepressant [12–15], anticonvulsant [14, 15], anti-inflammatory [16], antibacterial [17], and antitumor [18] properties. Also, thiophene derivatives are important heterocycles found in several biologically active and natural compounds [19–21]. For example, 2-amino-3-aryli thiophene derivatives are reported as agonist allosteric enhancers at the A1 adenosine receptor [22, 23]. In view of the above-mentioned findings and in continuation of our previous work aimed at the synthesis of a variety of heterocyclic ring systems for biological and pharmacological evaluation [24–29], we report here an efficient method for the synthesis of some pyrazole derivatives attached to benzothiazole and benzimidazole moieties.

2. Experimental Section

2.1. Materials and Methods. All melting points were measured on a Gallenkamp melting point apparatus (Weiss-Gallenkamp, London, UK). The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3000 and Shimadzu FT-IR 8101 PC infrared spectrophotometers (Pye Unicam Ltd. Cambridge, England, and Shimadzu, Tokyo, Japan, resp.). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (Varian, Palo Alto, CA, USA). 1H spectra were run at 300 MHz in deuterated chloroform (CDCl3) or dimethyl sulphoxide (DMSO-d6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer (Shimadzu) at 70 eV. The starting materials 2-(benzothiazol-2-yl)acetonitrile (1) [30], 2-(1-methyl-1H-benzimidazol-2-yl)acetonitrile (2) [31, 32], and N’-phenylbenzohydrazonoyl chloride 5 [33] were prepared according to the reported literature procedures.
2.2. Synthesis

2.2.1. Synthesis of 2-(Benzothiazol-2-yl)-3-(thiophen-2-yl)acrylonitrile (3) and 2-(1-Methyl-1H-benzimidazol-2-yl)-3-(thiophen-2-yl)acrylonitrile (4)

General Procedure. To a mixture of acetonitrile 1 or 2 (10 mmol) and the thiophene 2-carbaldehyde (10 mmol) in ethanol (10 mL), piperidine (0.2 mL) was added, and the mixture was refluxed for 30 min. The formed coloured crystalline products were collected by filtration, washed with ethanol, and dried. Recrystallization from the appropriate solvent gave 3 or 4, respectively.

(1) 2-(Benzothiazol-2-yl)-3-(thiophen-2-yl)acrylonitrile (3), Yield (70%), mp 156–7 C; IR (KBr) ν 2211 (C≡N), 2956 (aliphatic CH), 3087 (aromatic CH) cm⁻¹; 1H NMR [DMSO-d₆] δ 8.04–8.18 (m, 4H), 8.68 (s, 1H); MS m/z (%) 268 (M⁺, 100.0), 242 (78.1), 134 (9.6), 83 (11.4). Anal. Calcd.: C, 71.70; H, 3.93; N, 9.65. Found: C, 71.79; H, 3.98; N, 9.60%.

(2) 2-(1-Methyl-1H-benzimidazol-2-yl)-3-(thiophen-2-yl)acrylonitrile (4). Yield (75%), mp. 100°C (methanol); IR (KBr) ν 1609 (C≡N), 2956 (aliphatic CH), 3087 (aromatic CH) cm⁻¹; 1H NMR [DMSO-d₆] δ 4.0 (s, 3H, CH₃), 7.25–7.36 (m, 3H), 7.63–7.70 (m, 2H), 7.95 (d, 1H), 8.08 (d, 1H), 8.47 (s, 1H); MS m/z (%) 267 (5.96), 265 (M⁺, 100.0), 131 (23.95), 83 (4.47). Anal. Calcd for C₁₅H₁₁N₃S₂: C, 76.90; H, 4.18; N, 15.84. Found: C, 76.82; H, 4.25; N, 15.77%.

2.2.2. Synthesis of 5-Cyanopyrazole Derivatives 7 and 9

General Procedure. Equimolar quantities of the appropriate acrylonitrile 3 or 4 (5 mmol) and N'-phenylbenzhydrazonoyl chloride 5 (5 mmol) were dissolved in dry benzene (20 mL). To the resulting solution, triethylamine (0.5 mL, 5 mmol) was added and the reaction mixture was stirred for 12 h, and then the solvent was distilled under reduced pressure. The oil residue was triturated with MeOH and the solid product was collected by filtration, washed with methanol, and recrystallized from the suitable solvent to afford the corresponding pyrazole derivatives 7 and 9, respectively.

(1) 5-(Benzothiazol-2-yl)-1,3-diphenyl-4-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-5-carbonitrile (7). Yield (56%), mp. 190–1°C; IR (KBr) ν 1600 (C≡N) cm⁻¹; 1H NMR [CDCl₃] δ 5.68 (s, 1H, Pyrazole-H), 7.02–8.18 (m, 17H, ArH); MS m/z (%) 465 (2.1), 464 (8.1), 463 (M⁺, 14.4). Anal. Calcd for C₃₀H₂₀N₅S: C, 70.10; H, 3.92; N, 12.11. Found: C, 70.05; H, 3.85; N, 12.17%.

(2) 5-(1-Methyl-1H-benzimidazol-2-yl)-1,3-diphenyl-4-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-5-carbonitrile (9). Yield (45%), mp. 176–7°C (ethanol); IR (KBr) ν 1600 (C≡N) cm⁻¹; 1H NMR [CDCl₃] δ 3.71 (s, 3H, CH₃), 5.66 (s, 1H, Pyrazole-H), 6.95–7.96 (m, 17H, ArH). For C₂₆H₂₁N₅S Calcd.: C, 73.18; H, 4.61; N, 15.24. Found: C, 73.09; H, 4.66; N, 15.18%.

(3) Synthesis of 2-(1,3-diphenyl-4-(thiophen-2-yl)-1H-pyrazol-5-yl)benzothiazole (11). A mixture of 5-cyanopyrazole 7 (1.38 g, 3 mmol) and sodium ethoxide (prepared from sodium metal (0.07 g, 3 mmol) in EtOH (15 mL)) was heated under reflux for 1 h and then left to cool. The precipitated solid was collected by filtration, washed with water, and recrystallized from ethanol to give compound 11 in 75% yield, mp. 178–9°C (ethanol); IR (KBr) ν 1600 (C≡N) cm⁻¹; 1H NMR [CDCl₃] δ 7.04–7.99 (m, ArH); MS m/z (%) 438 (1.6), 437 (8.1), 436 (M⁺, 25.4), 352 (1.3), 134 (2.8), 83 (1.6), 77 (100.0). For C₂₆H₁₇N₅S₂ Calcd.: C, 71.70; H, 3.93; N, 9.65. Found: C, 71.79; H, 3.98; N, 9.60%.

3. Results and Discussion

The key starting materials 2-(benzothiazol-2-yl)acetonitrile (1) [30] and 2-(1-methyl-1H-benzimidazol-2-yl)acetonitrile (2) [31, 32] are characterized by the presence of an active methylene as well as nitrile function which makes them active so they can be used as a precursor for the synthesis of biologically and chemically active compounds. In the present work, the synthetic potential of the acrylonitriles 3 and 4 has been explored.

The usual method for the synthesis of acrylonitrile 3 or 4 employs condensation of 2-(benzothiazol-2-yl)acetonitrile (1) or 2-(1-methyl-1H-benzimidazol-2-yl)acetonitrile (2) with thiophene-2-carbaldehyde in refluxing ethanol containing a catalytic amount of piperidine (Scheme 1). The analytical and spectroscopic data were consistent with the final products 3 and 4 (see Section 2).

Treatment of compound 3 with nitrile imine 6 (generated in situ from N'-phenylbenzhydrazonoyl chloride 5 [33] by the action of triethylamine in benzene) afforded only one cycloadduct as deduced from TLC and 1H NMR analysis of the crude reaction product (Scheme 2). The structure of the isolated cycloadduct was assigned as 5-(benzothiazol-2-yl)-1,3-diphenyl-4-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-5-carbonitrile (7) based on its elemental analysis and its spectroscopic data. The distinction between the two possible regioisomeric cycloadducts 7 and 8 (Figure 1) was made on the basis of the IR and 1H NMR spectra of the isolated product.

The structure of the product 7 was in agreement with its elemental analysis and spectroscopic data. Although compound 7 bears a nitrile function, its IR spectrum did not afford nitrile absorption band similar to the case of aliphatic nitriles activated by a nitrogen or oxygen atom in the α-position [34, 35]. This similarity of the absence of the nitrile absorption in the IR spectrum excludes the possibility of the other regioisomer 8 for the isolated product. This is because compound of type 8 is expected to exhibit strong nitrile absorption in their IR spectra [36].
Scheme 1

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{N} & \quad \text{Ph} \\
\text{Cl} & & & \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{N} & \quad \text{Ph} \\
\text{TEA} & & & \text{−HCl} \\
\end{align*}
\]

Scheme 2

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{N} & \quad \text{Ph} \\
\text{NC} & & & \text{S} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{N} & \quad \text{Ph} \\
\text{−HCl} & & & \text{−} \\
\end{align*}
\]

Figure 1: The two possible regioisomeric cycloadducts 7 and 8.
In analogous manner, the nitrile imine 6 added regioselectively to the carbon-carbon double bond of 2-(1-methyl-1H-benzimidazol-2-yl)-3-(thiophen-2-yl)acrylonitrile (4) in benzene at room temperature to afford 5-(1-methyl-1H-benzimidazol-2-yl)-1,3-diphenyl-4-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-5-carbonitrile (9) (Scheme 2). The structure of the latter product was assigned on the basis of its elemental analysis and spectral data. For example, its IR spectrum revealed no nitrile absorption band. Moreover, elemental analysis and spectral data. For example, its IR spectrum revealed no nitrile absorption band. Moreover, structure 9 was confirmed by $^{1}H$ NMR spectrum which revealed a sharp singlet signal at δ 5.66 assignable to the proton at C-4 of the pyrazoline ring. This chemical shift is very similar to those reported for the C-4 proton of 4,5-dihydro-1H-pyrazole derivatives [37].

When compound 7 was heated in ethanolic sodium ethoxide solution, it afforded the pyrazole derivative 11 in high yield (Scheme 3). The structure of the product was confirmed by $^{1}H$ NMR spectra, which revealed the disappearance of the proton signal at C-4.

4. Conclusion

We have successfully synthesized some pyrazole derivatives attached to benzothiazole and benzimidazole moieties of biological and pharmacological interest, via 1,3-dipolar cycloaddition reaction.

Conflict of Interests

The authors declare that there is no conflict of interests.

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