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RESEARCH ARTICLE

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Synthesis of 3,6-bisubstituted phenyl-bi-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives

Abstract 2,5-Bihydrazino-1,3,4-thiadiazole (**2**) was synthesized by condensation of 2,5-bimercapto-1,3,4-thiadiazole (**1**) with hydrazine hydrate, and compound **2** reacted with acyl chloride to give 2,5-biacylhydrazino-1,3,4-thiadiazole derivatives (**3a–3e**). Ring closure of compounds **3a–3e** was achieved with $POCl_3$ as the cyclization agent giving 3,6-bisubstituted phenyl-bi-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives (**4a–4e**), respectively. The novel compounds were identified by elemental analysis, and by infrared (IR), ^{1}H- nuclear magnetic resonance (NMR), and mass (MS) spectrometry. The mechanism of the cyclization is also discussed.

Keywords $POCl_3$, 2,5-bihydrazino-1,3,4-thiadiazol, triazolo-1,3,4-thiadiazole, mechanism

1 Introduction

As heterocycle compounds containing sulfur and nitrogen atoms, 1,3,4-thiadiazole derivatives are applied as bactericide and herbicide [1,2]. In recent years, their application has expanded into the pharmaceutical and petroleum industries [3], as additives in the latter. These additives can form a protective film over the tender metal surface to diminish the corrosion of metal caused by caustic substances in fuel oil, since 1,3,4-thiadiazole has antioxidation, anticorrosion, and antiwear properties [4]. It is known that triazoles are widely used as corrosion retardants for copper and alloy metals [5,6], and they even, to a certain extent, protect copper from being corroded [7]. We hypothesize that a new molecule containing two triazole units fused with one thiadizole unit should possess valuable properties of both the triazole and thiadiazole. The study on the new molecule will be important for the exploration of new corrosion retardants with high efficiency and low toxicity [8]. We report herewith the synthesis of these new molecules.

As shown in Scheme 1, 2,5-bihydrazino-1,3,4-thiadiazole (**2**) was synthesized by condensation of 2,5-bimercapto-1,3,4-thiadiazole (**1**) with hydrazine hydrate, and compound **2** reacted with acyl chloride to give 2,5-biacylhydrazino-1,3,4-thiadiazole derivatives (**3a–3e**). The ring closure of compounds **3a–3e** was carried out with $POCl_3$ as the cyclization agent giving the target compounds **4a–4e**, respectively, containing two triazole units fused with one thiadiazole unit. The novel compounds (**4a–4e**) were identified by elemental analysis, and by infrared (IR), ^{1}H- nuclear magnetic resonance (NMR), and mass (MS) spectrometry.

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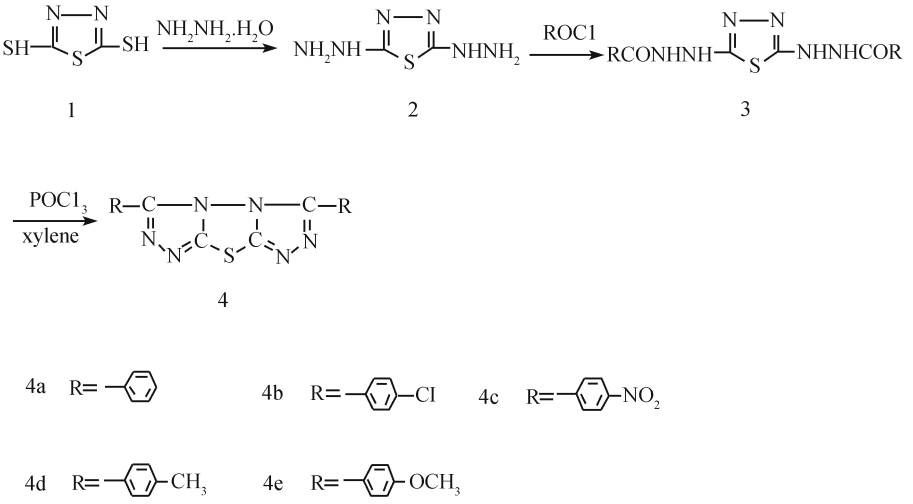
2 Experimental

Compounds **2** and **3** were synthesized according to the literature [9,10].

2.1 3,6-Biphenyl-bi-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (4a)

The reaction of 2,5-bibenzoyl hydrazino-1,3,4-thiadiazole (**3a**, 0.01 mol) with $POCl_3$ (0.03 mol) in anhydro xylene (25 mL) was carried out at the temperature of reflux for 5 h. This was followed by the condensation of the reaction mixture under diminished pressure, and hydrolysis of the residue with water followed by washing of the residue to neutral. The residue was recrystallized in ethanol and compound **4a** was obtained as light yellow solid. Yield: 65.2%; m.p. 178°C –179°C. ^{1}H-NMR (DMSO-d_6) δ: 7.4–8.1 (m, 10H, PhH); IR (KBr) ν: 1610(C=C) cm^{-1}, 1550 (C=C) cm^{-1}; MS *m/z* (%), 319 [$\overset{+}{M}$, 62], 105 [Ph–$\overset{+}{N}$≡N, 18], 77 [Ph$^+$, 15]. Anal. calcd for $C_{16}H_{10}N_6S$: C 60.37, H 3.15, N 26.42; found C 60.18, H 3.44, N 26.24.



Scheme 1 Synthesis of 3,6-bisubstituted phenyl-bi-1,2,4-triazolo[3,4-*b*]-1,3,4- thiadiazole derivatives

2.2 3,6-Bi-*p*-chloro-phenyl-bi-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (4b)

A mixture of *p*-chloro-benzoyl chloride (0.01 mol) and 2,5-bihydrazino-1,3,4-thiadiazole (**2**, 0.01 mol) in anhydropyridine was stirred for 25 min at 50°C, and then stirred at room temperature for 2 h. The resulting mixture was poured into ice-water, then filtrated and recrystallized in ethanol to give 2,5-bi-*p*-chlorobenzoylhydrazino-1,3,4-thiadiazole (**3b**). Reaction of **3b** (0.01 mol) with $POCl_3$ (0.03 mol) in anhydro xylene (25 mL) was carried out at the temperature of reflux for 6 h. This was followed by the condensation of the reaction mixture under diminished pressure and hydrolysis of the residue with water followed by washing to neutral. The residue was recrystallized in ethanol and product **4b** was obtained as light yellow solid. Yield: 68.2%; m.p. 186–188°C. ^{1}H-NMR (DMSO-d_6) δ: 7.6–8.3 (m, 8H, PhH); IR (KBr) ν: 1620 (C=C) cm^{-1}, 1540(C=C) cm^{-1}; MS *m/z* (%): 387 [$\overset{+}{M}$, 71], 139.5 [*P*–ClC_6H_4–$\overset{+}{N}$≡N]. Anal. calcd for $C_{16}N_6SH_8Cl_2$: C 49.61, H 2.0, N 21.71; found C 49.51, H 2.06, N 21.45.

2.3 3,6-Bi-*p*-nitrophenyl-bi-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (4c)

Compound **4c** was synthesized from **3c** as pale yellow crystals by the same procedure described in the preparation of **4b**. Yield: 70.1%; m.p. 189–190°C. ^{1}H-NMR (DMSO-d_6) δ: 7.5–8.2 (m, 8H, PhH); IR (KBr) ν: 1492(C=N) cm^{-1}, 1610(C=C) cm^{-1}; MS *m/z* (%): 408 [$\overset{+}{M}$, 56], 150[*P*–$NO_2C_6H_4$–$\overset{+}{N}$≡N, 27]. Anal. calcd for $C_{16}N_8SH_8O_4$: C 47.06, H 1.46, N 27.45; found C 47.01, H 1.01, N 27.41.

2.4 3,6-Bi-*p*-methylphenyl-bi-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (4d)

Compound **4d** was synthesized from **3d** as pale yellow crystals by the same procedure described in the preparation of **4b**. Yield: 61.2%; m.p. 172–174°C. ^{1}H-NMR (DMSO-d_6) δ: 2.6 (S, 3H, Me), 7.3–8.1 (m, 8H, Ar–H); IR (KBr) ν: 1481 (C=N) cm^{-1}, 1603 (C=C) cm^{-1}; MS *m/z* (%): 346 [$\overset{+}{M}$, 42], 119 [*P*–$CH_3C_6H_4$–$\overset{+}{N}$≡N, 28]. Anal. calcd for $C_{18}N_6SH_{14}$: C 62.42, H 4.05, N 24.28; found C 62.39, H 4.08, N 24.21.

2.5 3,6-Bi-*p*-methoxylphenyl-bi-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (4e)

Compound **4e** was synthesized from **3e** as pale yellow crystals by the same procedure described in the preparation of **4b**. Yield: 57.2%; m.p. 168–170°C. ^{1}H-NMR (DMSO-d_6) δ: 4.2 (S, 3H, MeO), 7.0–8.1 (m, 8H, Ar-H); IR (KBr) ν: 1547 (C=N) cm^{-1}, 1671 (C=C) cm^{-1}; MS *m/z* (%): 378 [$\overset{+}{M}$, 74], 135 [*P*–$MeoC_6H_4$–$\overset{+}{N}$≡N, 17], Anal. calcd for $C_{18}H_{14}N_6O_2S$: C 57.14, H 3.70, N 22.22; found C 57.29, H 3.78, N 22.27.

3 Ring closure reaction mechanism with $POCl_3$ as the cyclization agent to synthesize 3,6-bisubstituted phenyl-bi-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives

The ring closure reaction with $POCl_3$ as the cyclization agent might be as follows: a tetrahedron intermediate could be formed by the addition reaction of $POCl_3$ with the carbonyl group of compound **3**. Subsequently, as the chloro-phosphate proved to be a good leaving group, its cleavage gave a carbonium ion intermediate and consequent electron transfer and elimination reaction gave the ring closure product.

Infrared spectra of compounds **3a–3e** and **4a–4e**, the ones obtained before and after the ring closure, were in accordance with our hypothesis: compounds **3a–3e** had strong absorptions in their IR spectra at 3190, 3006, and 1627 cm^{-1}, while in the IR spectra of **4a–4e** those signals vanished, but new signals at 1600–1400 cm^{-1} such as a strong signal at 1550 cm^{-1} for C=N vibration appeared. This was attributed

to cycle-skeletal vibrations. Besides, the ^{1}H-NMR spectra of **4a–4e** showed only signals for protons on benzene ring and no signals for the ones on nitrogen.

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