Research Article

Regioselective Syntheses of 3-Benzyl-Substituted 7H-Thiazolo[3,2-a]pyrimidine-7-ones through Palladium-Catalyzed Heteroannulation of Acetylenic Compounds

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An efficient synthesis of 3-benzyl-substituted 7H-thiazolo[3,2-a]pyrimidine-7-ones in acetonitrile is accomplished via Pd- and Cu-catalyzed reaction of 2-mercaptopropargylpyrimidone with various aryl iodides in the presence of triethylamine as the base.

1. Introduction

The Sonogashira reaction is one of the most widely used C–C bond formation ones [1, 2]. It provides an efficient route to aryl alkynes, which are interesting intermediates for the preparation of a variety of target compounds with applications ranging from natural products [3–7] and pharmaceuticals [8] to molecular organic materials [9]. Due to the utility of the products, development of new catalyst systems has received considerable attention. Palladium-catalyzed reactions have been immensely practical for both carboannulation [10, 11] and heteroannulation [12–16] processes.

Thiazole and pyrimidine nuclei are the active core of various bioactive molecules. In general, heterocycles encompassing a pyrimidine unit have found applications in a wide spectrum of biological and therapeutic areas [17, 18]. Thus, the heterocyclic system resulting from annulation of a pyrimidine ring on the biologically versatile thiazole nucleus is an attractive scaffold to be utilized for exploiting chemical diversity.

Continuing our efforts directed towards the straightforward preparation of biologically active target molecules through Sonogashira coupling reactions [19–22], we performed the synthesis of new derivatives of thiazolo[3,2-a]pyrimidones via Pd- and Cu-catalyzed Sonogashira coupling reaction.

2. Results and Discussion

In this communication, we wish to report that treatment of 2-thiouracil 1 with propargyl bromide in MeONa/MeOH affords 2-propargylmercaptouracil 2 in a good yield. The 1H NMR spectrum of 2 showed a CH proton at 2.17 ppm, CH2 protons at 3.92 ppm, and a single resonance for the NH group at 13.05 ppm that disappeared on deuteration (as shown in Scheme 1).

Reaction of compound 2 with various aryl iodides, 3a–f, in acetonitrile at room temperature led only to the formation of 3-benzyl-substituted 7H-thiazolo[3,2-a]pyrimidine-7-ones 4. The reactions were carried out under an argon atmosphere, and solvent was degassed prior to use. Presence of electron withdrawing groups such as NO2, Cl, and COMe on the aryl iodide seems to be essential. When iodobenzene was used as the aryl iodide, Sonogashira coupling could not be achieved. The results were tabulated in Table 1.

The following steps can be postulated for the mechanism of formation of either thiazolo[3,2-a]pyrimidine-7-ones 4 or thiazolo[3,2-a]pyrimidine-5-ones 5 (Scheme 2): (a) formation of ArPd(I) through oxidative addition of Pd(0) (I) to ArI [23]; (b) transmetallation with the Cu salt of the alkyne (III) to generate the alkynyl palladium complex (IV); (c) reductive elimination results in the extrusion of Pd(0) to yield the substituted alkyne (V); (d) finally, nucleophilic
attack of the nitrogen on the triple-bond intermediates (V) catalyzed by CuI led to product 4 or 5.

Structures 4 and 5 were characterized by comparing their spectra with those for the well-established compounds 6a [24], 6b [25], and 7 [25] (Scheme 3). The IR spectra for 4 or 5 were quite similar to that for 6. Therefore, we can conclude that the one-pot condensation, cyclization, and isomerization of acetylenic compounds regioselectively afford 4.

The $^1$H NMR spectrum of 4a exhibited an aromatic proton at 6.70 ppm, which was characteristic of a fused thiazole ring. The other four aromatic protons appeared at 8.10–8.40 ppm. In the aliphatic region, the singlet at 4.30 ppm was due to the benzylic protons.
In conclusion, we have described a palladium-catalyzed, one-pot reaction for the regioselective syntheses of 3-aryl-substituted 7H-thiazolo[3,2-a]pyrimidine-7-ones from readily available starting materials in moderate-to-good yields.

3. Experimental

Melting points were uncorrected. The $^1$H NMR spectra were recorded at 400 MHz, and the $^{13}$C NMR spectra were recorded at 100 MHz in DMSO-$d_6$. The $J$-coupling constants are reported in Hz.

3.1. Synthesis of 2-Propargymercaptouracil 2. A mixture of sodium (1.2 mmol) and 2-thiouracil 1 (1 mmol) was stirred in methanol (5 mL). Propargyl bromide (1.2 mmol) was then added, and the mixture was stirred at room temperature for 24 h. The solid substance formed was filtered, washed with water, and recrystallized from water to afford the title compound.
Yield, 78%; m.p., 152–153 °C; IR (KBr, ν max cm⁻¹): 3200, 2100, 1645. ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 2.10 (s, 1H, CH), 3.90 (s, 2H, CH₂), 6.10 (d, J = 6.4 Hz, 1H, CH of pyrimidine), 7.80 (d, J = 6.4 Hz, 1H, CH of pyrimidine), 13.05 (s, 1H, NH).

3.2. Syntheses of 3-Aryl-Substituted 7H-Thiazolo[3,2-a]pyrimidine-7-ones 4a–f. A mixture of aryl iodide (1 mmol), PdCl₂(PPh₃)₂ (0.03 mmol), CuI (0.06 mmol), and triethylamine (2 mmol) was stirred in acetonitrile (5 mL) under argon atmosphere. 2-Propargylmercaptouracil ethylamine (2.0 mmol) was stirred in acetonitrile (5 mL) at room temperature for 12 h. The solid substance formed was filtered, washed with water, and recrystallized from acetonitrile (Table 1).

3.2.1. 3-(2-Nitrobenzyl)-7H-thiazolo[3,2-a]pyrimidine-7-one 4a. IR (KBr, ν max cm⁻¹): 1645, 1510, 1345. ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 4.30 (s, 2H, CH₂), 6.20 (d, J = 8.0 Hz, 1H, CH of pyrimidine), 6.70 (s, 1H, CH of thiazole), 7.84 (d, J = 8.0 Hz, 1H, CH of pyrimidine), 8.10–8.40 (m, 4H, ArH); HRMS (ESI): 287.018.

3.2.2. 3-(3-Nitrobenzyl)-7H-thiazolo[3,2-a]pyrimidine-7-one 4b. IR (KBr, ν max cm⁻¹): 1620, 1590, 1300. ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 4.36 (s, 2H, CH₂), 5.72 (d, J = 8.0 Hz, 1H, CH of pyrimidine), 6.55 (s, 1H, CH of thiazole), 7.20 (d, J = 8.0 Hz, 1H, CH of pyrimidine), 7.80–8.10 (m, 4H, ArH); HRMS (ESI): 287.053.

3.2.3. 3-(4-Nitrobenzyl)-7H-thiazolo[3,2-a]pyrimidine-7-one 4c. IR (KBr, ν max cm⁻¹): 1645, 1510, 1345. ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 4.07 (s, 2H, CH₂), 6.30 (d, J = 8.0 Hz, 1H, CH of pyrimidine), 6.35 (s, 1H, CH of thiazole), 7.45 (dd, J = 8.0, 1.6 Hz, 2H, ArH), 7.53 (d, J = 8.0 Hz, 1H, CH of pyrimidine), 8.2 (dd, J = 8.0, 1.6 Hz, 2H, ArH); HRMS (ESI): 320.966.

3.2.4. 3-(4-Chloro-2-nitrobenzyl)-7H-thiazolo[3,2-a]pyrimidine-7-one 4d. IR (KBr, ν max cm⁻¹): 1640, 1530, 1340; ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 4.27 (s, 2H, CH₂), 6.20 (s, 1H, CH of thiazole), 6.34 (d, J = 8.0 Hz, 1H, CH of pyrimidine), 7.58 (dd, J = 8.0, 2.0 Hz, 1H, ArH), 7.65 (d, J = 8.0 Hz, 2H, CH of pyrimidine and ArH), 8.10 (d, J = 2.0 Hz, 1H, ArH); HRMS (ESI): 320.966.

3.2.5. 3-(2-Methyl-4-nitrobenzyl)-7H-thiazolo[3,2-a]pyrimidine-7-one 4e. IR (KBr, ν max cm⁻¹): 1640, 1520, 1345; ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 2.40 (s, 3H, CH₃), 3.97 (s, 2H, CH₂), 6.10 (s, 1H, CH of thiazole), 6.35 (d, J = 8.0 Hz, 1H, CH of pyrimidine), 7.60 (d, J = 8.0, 1H, CH of pyrimidine), 7.95–8.20 (m, 3H, ArH); HRMS (ESI): 301.352.

3.2.6. 3-(4-Acetylbenzyl)-7H-thiazolo[3,2-a]pyrimidine-7-one 4f. IR (KBr, ν max cm⁻¹): 1680, 1645; ¹H NMR (400 MHz, DMSO-d₆, δ ppm): 2.64 (s, 3H, CH₃), 4.10 (s, 2H, CH₂), 6.35 (d, J = 8.0 Hz, 1H, CH of pyrimidine), 6.45 (s, 1H, CH of thiazole), 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.62 (d, J = 8.0, 1H, CH of pyrimidine), 8.02 (d, J = 8.0 Hz, 2H, ArH); HRMS (ESI): 284.302.

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