Research Article

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

Mohammad Bakherad and Farzaneh Gholipoor

School of Chemistry, Shahrood University of Technology, Shahrood 3619995161, Iran

Correspondence should be addressed to Mohammad Bakherad, m.bakherad@yahoo.com

Received 8 June 2012; Revised 2 August 2012; Accepted 5 August 2012

Academic Editor: Dipakranjan Mal

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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 ArPdI (**II**) through oxidative addition of Pd(0) (**I**) to ArI [23]; (b) transmetalation 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

SCHEME 1

TABLE 1: Melting points and yields of 3-aryl-substituted 7H-thiazolo[3,2-*a*]pyrimidine-7-ones.

Entry	Ar	m.p. (°C)	Yield (%)
4a		253–255	85
4b		228–230	78
4c		250–252	86
4d		269–271	75
4e		277–279	88
4f		265–267	90

^a Reaction reagents and conditions: **2** (1.3 mmol), **2a–f** (1 mmol), Et_3N (2 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.03 mmol), CuI (0.06 mmol), and CH_3CN (5 mL), room temperature, 24 h.

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 ^1H 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.

SCHEME 2: Proposed mechanism for the formation of either 3-aryl-substituted 7H-thiazolo[3,2-*a*]pyrimidine-7-ones 4 or 3-aryl-substituted 5H-thiazolo[3,2-*a*]pyrimidine-5-ones 5 at room temperature. Reagents and conditions: (a) reduction of Pd(II) to Pd(0) with alkyne and Et_3N ; (b) CuI , Et_3N ; (c) nucleophilic attack on the triple bond (V) catalyzed by CuI , Et_3N to generate the product 4 or 5.

SCHEME 3

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 ^1H NMR spectra were recorded at 400 MHz, and the ^{13}C NMR spectra were

recorded at 100 MHz in $\text{DMSO}-d_6$. The J -coupling constants are reported in Hz.

3.1. Synthesis of 2-Propargylmercaptouracil 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, $\nu_{\max}$ cm⁻¹): 3200, 2100, 1645. ¹H NMR (400 MHz, DMSO-*d*₆ 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), Cul (0.06 mmol), and triethylamine (2.0 mmol) was stirred in acetonitrile (5 mL) under an argon atmosphere. 2-Propargylmercaptouracil 2 (1.3 mmol) was then added, and the mixture was stirred 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, $\nu_{\max}$ cm⁻¹): 1645, 1510, 1345. ¹H NMR (400 MHz, DMSO-*d*₆ 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): 287.010.

3.2.2. 3-(3-Nitrobenzyl)-7H-thiazolo[3,2-*a*]pyrimidine-7-one 4b. IR (KBr, $\nu_{\max}$ cm⁻¹): 1645, 1520, 1330. ¹H NMR (400 MHz, DMSO-*d*₆ 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, $\nu_{\max}$ cm⁻¹): 1645, 1510, 1345. ¹H NMR (400 MHz, DMSO-*d*₆ 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): 287.018.

3.2.4. 3-(4-Chloro-2-nitrobenzyl)-7H-thiazolo[3,2-*a*]pyrimidine-7-one 4d. IR (KBr, $\nu_{\max}$ cm⁻¹): 1640, 1530, 1340; ¹H NMR (400 MHz, DMSO-*d*₆ 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, $\nu_{\max}$ cm⁻¹): 1640, 1520, 1345; ¹H NMR (400 MHz, DMSO-*d*₆ 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, $\nu_{\max}$ cm⁻¹): 1680, 1645; ¹H NMR (400 MHz, DMSO-*d*₆ 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.

Acknowledgment

The authors would like to thank the Research Council of Shahrood University of Technology for the support of this work.

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