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Synthesis of novel thiazolo[2,3-*b*]quinazolines by cyclization reaction of octahydroquinazoline-2-thiones with α-bromoketones

Zheng-Jun Quan[1,2,*], Ying Wei[1,2] and Xi-Cun Wang[1,2,*]

[1] Key Laboratory of Eco-Environment-Related Polymer Materials, Ministry of Education, China, Gansu 730070, China

[2] Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Anning East Road 967#, Lanzhou, Gansu 730070, China

*Corresponding authors
e-mail: quanzhengjun@hotmail.com; wangxicun@nwnu.edu.cn

Abstract

Novel thiazolo[2,3-*b*]quinazolines were prepared by the cyclization reaction between octahydroquinazoline-2-thiones with α-bromoketones, which provides a readily accessible multifunctionalized quinazoline template for diversity-oriented synthesis.

Keywords: cyclization reaction; octahydroquinazoline-2-thiones; synthesis; thiazolo[2,3-*b*]quinazolines.

Introduction

3,4-Dihydropyrimidinone (DHPM) was first reported in 1893 (Biginelli, 1893). It has gained great therapeutic significance as a calcium-channel modulator in the treatment of cardiovascular diseases, such as hypertension, cardiac arrhythmias or angina (Janis et al., 1987). In recent years, interest has focused on Biginelli-like reactions in which open-chain β-dicarbonyl compounds have been extended to cyclic β-diketones, β-ketolactones, β-diamides, cyclic β-diesters and α-keto acids under a variety of conditions. The heterocycles thus obtained exhibit antiviral, antitumor, and antihypertensive activities, and neuropeptide Y (NPY) antagonism (Mokrosz et al., 1989; Byk et al., 2000; Abelman et al., 2003; Yarim et al., 2003; Prajapati et al., 2011). Among the synthetic products of the Biginelli reaction, the octahydroquinazolin-5-one derivatives are interesting compounds because of their potent antibacterial (Kidwai et al., 2005, 2010) and calcium antagonist activity (Sarac et al., 1998, 2001; Sabitha et al., 2003).

Other interesting derivatives are thiazolo[3,2-*a*]pyrimidines **1** (Figure 1) due to their calcium channel-blocking activity (Kappe, 2003). Few methods are known for the preparation of thiazolo[3,2-*a*]pyrimidine derivatives and the existing methodologies require prolonged reaction times and strict reaction conditions (Balkan et al., 1992).

Recently, we reported the synthesis of thiazolo[3,2-*a*]pyrimidines **1** (Figure 1) by the reaction of 2-thioxo-DHPMs with α-bromoacetone in aqueous media (Quan et al., 2008). More recently, these compounds were synthesized by the one-pot reaction between 2-thioxo-DHPMs, ketone, bromine and Et_3N (Singh et al., 2011). The structure between thiazolo[3,2-*a*]pyrimidines **1** and 5*H*-thiazolo[2,3-*b*]quinazolin-6-(7*H*)-ones **2** is similar (Figure 1), so we speculated that compound **2** could also be synthesized by the reaction of 2-thioxoquinazolin-6(7*H*)-one with α-bromoacetone. In the context of our interest in the synthesis of functionalized Biginelli compounds (Wang et al., 2006; Quan et al., 2011), we describe a general and comprehensive strategy for the preparation of 5*H*-thiazolo[2,3-*b*]quinazolines **2** by the direct cyclization reactions of octahydroquinazoline-2-thiones **3** with α-bromoketones **4** (Scheme 1).

Results and discussion

The reaction of octahydroquinazoline-2-thione **3** (R^2=H) with α-bromoacetone **4** (R^1=CH_3) was initially attempted using an aqueous medium but it failed to produce desired product **2** (R^1=CH_3, R^2=H). The reaction was, however, successful when it was carried out in tetrahydrofuran (THF) under reflux. It was also found that the one-pot reaction of 2-thioxoquinazolines, acetone and bromine in refluxing THF under base-free conditions proceeded smoothly to give the 5*H*-thiazolo[2,3-*b*]quinazoline products.

Using optimized conditions, the scope and versatility of this reaction was explored by conducting the reactions with various reactants, as depicted in Scheme 1. Specifically, various α-bromoketones **4** were allowed to react with 11 substituted 4-aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones **3**.

The structures of 5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-ones **2a–w** produced by these reactions are given in Scheme 1. Overall, the reaction proceeded smoothly and the products were isolated and purified by crystallization in high yields (73–87%). This method was further simplified by reacting methyl ketones with bromine and using the α-bromoketones thus generated *in situ* for the subsequent cyclization reaction.

In addition to high yields, this method benefits from having a short reaction time and the procedure is straightforward.

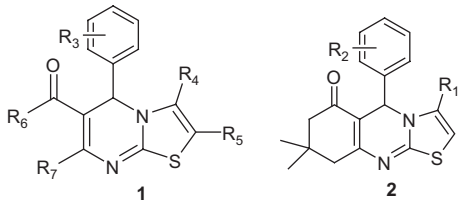


Figure 1 Thiazolo[3,2-*a*]pyrimidines **1** and thiazolo[2,3-*b*]quinazolines **2**.

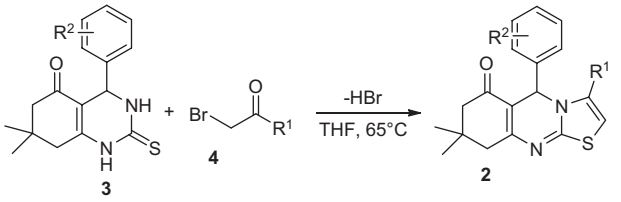
Experimental section

Commercially-available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. Melting points were determined on an XT-4 electrothermal micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using KBr pellets on a Digilab Merlin Fourier transform infrared (FT-IR) spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Varian Mercury plus-400 instrument. Electron-impact mass spectra were obtained on a Bruker Daltonics APEXII 47e Fourier transform ion cyclotron resonance spectrometer. Elemental analyses were performed on a Carlo-Erba 1106 elemental analysis instrument. The octahydroquinazoline-2-thiones were readily prepared according to the procedure described by Hassani et al. (2006).

General synthesis of 5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-ones 2a–w

Bromine (1 mmol) was added to a stirred sample of a methyl ketone (1 mmol). After the color of the mixture had faded, a solution of 4-aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione **3** (1 mmol) in THF (5 ml) was added and the mixture was stirred at 65°C for 4 h. Upon completion of the reaction as monitored by TLC, the mixture was cooled to room temperature. The precipitate was collected, dried and crystallized from ethanol to give pure product **2**.

3,8,8-Trimethyl-5-phenyl-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(*7H*)-one (2a) White solid; yield 87%; mp 293–295°C; IR: 3107, 3060, 1648, 1596, 1522, 1410 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.86 (3H, s), 1.06 (3H, s), 2.12–2.30 (2H, m), 2.18 (3H, s), 2.48–2.58 (2H, m), 6.48 (1H, s), 7.16 (1H, s), 7.32–7.40 (5H, m); ^{13}C NMR (DMSO-d_6): δ 12.9 (CH_3), 26.4 (CH_3), 28.2 (C), 32.5 (CH_2), 49.8 (CH_2), 56.9 (CH), 108.7 (CH), 108.8 (CH), 127.0 (CH), 128.9 (CH), 128.9 (C), 138.7 (C), 139.7 (C), 146.5 (C), 161.2 (C), 193.3 (C); MS: m/z 324 (M^+). Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.25; H, 6.13; N, 8.69.



Scheme 1 Synthesis of 5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-ones (**2**).

3,8,8-Trimethyl-5-(4-chlorophenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2b) White solid; yield 82%; mp 278–279°C; IR: 3111, 3062, 1650, 1599, 1521, 1411 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.87 (3H, s), 1.06 (3H, s), 2.12–2.30 (2H, m), 2.17 (3H, s), 2.48–2.59 (2H, m), 6.51 (1H, s), 7.18 (1H, s), 7.38 (2H, d, *J*=8.4 Hz), 7.45 (2H, d, *J*=8.4 Hz); ^{13}C NMR (DMSO-d_6): δ 12.9 (CH_3), 26.4 (CH_3), 28.1 (C), 32.5 (CH_2), 49.7 (CH_2), 56.3 (CH), 108.3 (CH), 109.0 (CH), 126.3 (CH), 128.9 (C), 129.1 (C), 133.4 (C), 138.3 (C), 138.5 (C), 161.1 (C), 193.2 (C); MS: m/z 358 (M^+). Anal. Calcd for $C_{19}H_{19}ClN_2OS$: C, 63.59; H, 5.34; N, 7.81. Found: C, 63.49; H, 5.39; N, 7.90.

3,8,8-Trimethyl-5-(4-nitrophenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2c) White solid; yield 79%; mp 279–281°C; IR: 3095, 3058, 1648, 1608, 1527, 1412 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.86 (3H, s), 1.07 (3H, s), 2.13–2.31 (2H, m), 2.16 (3H, s), 2.51–2.62 (2H, m), 6.69 (1H, s), 7.21 (1H, s), 7.67 (2H, d, *J*=8.4 Hz), 8.23 (2H, d, *J*=8 Hz); ^{13}C NMR (DMSO-d_6): δ 12.9 (CH_3), 26.6 (CH_3), 28.1 (C), 32.6 (CH_2), 49.7 (CH_2), 56.4 (CH), 107.7 (CH), 109.0 (CH), 124.2 (CH), 128.7 (C), 128.9 (C), 138.3 (C), 146.1 (C), 147.5 (C), 161.8 (C), 193.3 (C); MS: m/z 369 (M^+). Anal. Calcd for $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.69; H, 5.28; N, 11.30.

3,8,8-Trimethyl-5-(4-methoxyphenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2d) White solid; yield 86%; mp 294–296°C; IR: 3107, 3064, 1668, 1597, 1523, 1416 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.89 (3H, s), 1.07 (3H, s), 2.12–2.30 (2H, m), 2.20 (3H, s), 2.51–2.61 (2H, m), 3.73 (3H, s), 6.42 (1H, s), 6.92 (2H, d, *J*=8 Hz), 7.18 (1H, s), 7.27 (2H, d, *J*=8.4 Hz); ^{13}C NMR (DMSO-d_6): δ 12.9 (CH_3), 26.5 (CH_3), 28.3 (C), 32.5 (CH_2), 49.8 (CH_2), 55.2 (CH_3), 56.5 (CH), 108.7 (CH), 108.9 (CH), 114.2 (CH), 128.5 (C), 132.0 (C), 138.6 (C), 159.4 (C), 161.0 (C), 176.3 (C), 193.3 (C); MS: m/z 354 (M^+). Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.68; H, 6.34; N, 7.99.

3,8,8-Trimethyl-5-(3-nitrophenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2e) White solid; yield 81%; mp 281–282°C; IR: 3112, 3040, 1647, 1605, 1520, 1445 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.86 (3H, s), 1.07 (3H, s), 2.12–2.30 (2H, m), 2.15 (3H, s), 2.51–2.62 (2H, m), 6.67 (1H, s), 7.20 (1H, s), 7.57 (1H, t, *J*=8.4 Hz), 7.74 (1H, d, *J*=8 Hz), 8.09–8.22 (2H, m); ^{13}C NMR (DMSO-d_6): δ 12.9 (CH_3), 26.6 (CH_3), 28.2 (C), 32.6 (CH_2), 49.7 (CH_2), 56.5 (CH), 107.7 (CH), 109.0 (CH), 121.9 (CH), 124.2 (CH), 128.8 (C), 128.9 (CH), 131.8 (C), 138.3 (C), 146.1 (C), 147.5 (C), 161.8 (C), 193.3 (C); MS: m/z 369 (M^+). Anal. Calcd for $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.66; H, 5.26; N, 11.31.

3,8,8-Trimethyl-5-(2-methoxyphenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2f) White solid; yield 83%; mp 298–299°C; IR: 3169, 3049, 1646, 1601, 1514, 1440 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 0.86 (3H, s), 1.07 (3H, s), 2.12–2.31 (2H, m), 2.21 (3H, s), 2.51–2.60 (2H, m), 3.73 (3H, s), 6.40 (1H, s), 6.95 (1H, s), 6.97–7.54 (4H, m); ^{13}C NMR (DMSO-d_6): δ 12.9 (CH_3), 26.5 (CH_3), 28.3 (C), 32.5 (CH_2), 49.8 (CH), 55.2 (CH_2), 56.6 (CH_3), 108.6 (CH), 108.9 (CH), 114.2 (CH), 116.3 (C), 128.5 (CH), 130.0 (CH), 131.9 (C), 138.5 (C), 159.4 (C), 161.0 (C), 176.3 (C), 193.3

(C); MS: m/z 354 (M^+). Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.67; H, 6.32; N, 7.97.

3,8,8-Trimethyl-5-(4-bromophenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2g) White solid; yield 77%; mp 284–286°C; IR: 3114, 3054, 1650, 1599, 1519, 1408 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.85 (3H, s), 1.06 (3H, s), 2.12–2.31 (2H, m), 2.18 (3H, s), 2.48–2.59 (2H, m), 6.49 (1H, s), 7.19 (1H, s), 7.38 (2H, d, *J*=8 Hz), 7.52 (2H, d, *J*=8 Hz); ^{13}C NMR (DMSO-d_6): δ 13.0 (CH_3), 26.6 (CH_3), 28.1 (C), 32.6 (CH_2), 49.7 (CH_2), 56.4 (CH), 108.1 (CH), 109.3 (C), 121.8 (CH), 126.1 (C), 130.0 (CH), 131.8 (C), 138.3 (C), 142.1 (C), 161.5 (C), 193.3 (C); MS: m/z 402 (M^+). Anal. Calcd for $C_{19}H_{19}BrN_2OS$: C, 56.58; H, 4.75; N, 6.95. Found: C, 56.51; H, 4.85; N, 7.04.

3,8,8-Trimethyl-5-(4-methylphenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2h) White solid; yield 85%; mp 311–313°C; IR: 3119, 3065, 1652, 1601, 1527, 1416 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.86 (3H, s), 1.07 (3H, s), 2.12–2.30 (2H, m), 2.20 (6H, s), 2.48–2.59 (2H, m), 6.45 (1H, s), 6.88 (2H, d, *J*=8 Hz), 7.21 (1H, s), 7.25 (2H, d, *J*=8 Hz); ^{13}C NMR (DMSO-d_6): δ 12.9 (CH_3), 26.5 (CH_3), 28.3 (CH_3), 32.5 (C), 49.8 (CH_2), 55.1 (CH_2), 56.6 (CH), 108.6 (CH), 108.9 (CH), 114.2 (CH), 128.5 (C), 131.9 (C), 138.5 (C), 159.4 (C), 161.0 (C), 176.2 (C), 193.4 (C); MS: m/z 338 (M^+). Anal. Calcd for $C_{20}H_{22}N_2OS$: C, 70.97; H, 6.55; N, 8.28. Found: C, 70.87; H, 6.46; N, 8.36.

3,8,8-Trimethyl-5-(2-chlorophenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2i) White solid; yield 84%; mp 301–302°C; IR: 3105, 3058, 1648, 1593, 1522, 1409 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.91 (3H, s), 1.07 (3H, s), 2.10–2.29 (2H, m), 2.12 (3H, s), 2.50–2.64 (2H, m), 6.78 (1H, s), 7.16 (1H, s), 7.37–7.69 (4H, m); ^{13}C NMR (DMSO-d_6): δ 13.3 (CH_3), 26.4 (CH_3), 28.3 (C), 32.4 (CH_2), 49.8 (CH), 56.8 (CH_2), 107.1 (CH), 108.3 (CH), 109.3 (CH), 121.8 (CH), 127.6 (CH), 130.4 (C), 130.9 (C), 132.0 (C), 138.9 (C), 146.5 (C), 161.8 (C), 193.2 (C); MS: m/z 358 (M^+). Anal. Calcd for $C_{19}H_{19}ClN_2OS$: C, 63.59; H, 5.34; N, 7.81. Found: C, 63.48; H, 5.39; N, 7.90.

3,8,8-Trimethyl-5-(3-bromophenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2j) White solid; yield 79%; mp 287–288°C; IR: 3106, 3055, 1647, 1591, 1524, 1418 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.88 (3H, s), 1.06 (3H, s), 2.15–2.30 (2H, m), 2.18 (3H, s), 2.56 (2H, s), 6.52 (1H, s), 7.20 (1H, s), 7.30–7.37 (2H, m), 7.55 (1H, d, *J*=7.6 Hz), 7.63 (1H, s); ^{13}C NMR (DMSO-d_6): δ 13.0 (CH_3), 26.5 (CH_3), 28.1 (C), 32.6 (CH_2), 49.8 (CH_2), 56.4 (CH), 108.1 (CH), 108.9 (C), 121.8 (CH), 124.1 (CH), 126.1 (C), 130.0 (CH), 131.3 (CH), 131.8 (C), 138.3 (C), 142.1 (C), 161.5 (C), 193.3 (C); MS: m/z 402 (M^+). Anal. Calcd for $C_{19}H_{19}BrN_2OS$: C, 56.58; H, 4.75; N, 6.95. Found: C, 56.50; H, 4.84; N, 7.04.

3,8,8-Trimethyl-5-(4-hydroxyphenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2k) White solid; yield 80%; mp 310–311°C; IR: 3124, 3068, 1650, 1599, 1527, 1422 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.89 (3H, s), 1.07 (3H, s), 2.12–2.30 (2H, m), 2.22 (3H, s), 2.51–2.63 (2H, m), 6.35 (1H, s), 6.74 (2H, d, *J*=8.4 Hz), 7.15 (2H, d, *J*=8.4 Hz), 7.20 (1H, s), 9.70 (1H, s); ^{13}C NMR (DMSO-d_6): δ 12.9 (CH_3), 26.5 (CH_3), 28.3 (C), 32.5 (CH_2), 49.8 (CH_2), 56.6 (CH), 108.9 (CH), 109.2 (CH), 115.6 (CH), 128.5 (C), 130.3 (C), 138.6 (C), 145.6 (C), 157.8 (C), 160.6 (C), 193.3 (C); MS: m/z 340 (M^+). Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.10; H, 5.83; N, 8.30.

8,8-Dimethyl-3,5-diphenyl-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2l) White solid; yield 82%; mp 287–289°C; IR: 3117, 3057, 1654, 1587, 1519, 1450 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.91 (3H, s), 1.10 (3H, s), 2.13–2.29 (2H, m), 2.63 (2H, s), 6.33 (1H, s), 6.64 (2H, d, *J*=8 Hz), 7.10 (2H, t, *J*=8 Hz), 7.17 (1H, t, *J*=8 Hz), 7.25 (2H, d, *J*=8 Hz), 7.47 (2H, t, *J*=8 Hz), 7.48 (1H, s), 7.58 (1H, t, *J*=8 Hz); ^{13}C NMR (DMSO-d_6): δ 26.7 (CH_3), 28.2 (C), 32.6 (CH_2), 49.8 (CH_2), 57.5 (CH), 108.9 (CH), 111.5 (CH), 126.5 (CH), 127.3 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 129.7 (C), 130.5 (C), 139.1 (C), 140.7 (C), 146.3 (C), 161.2 (C), 193.4 (C); MS: m/z 386 (M^+). Anal. Calcd for $C_{24}H_{22}N_2OS$: C, 74.58; H, 5.74; N, 7.25. Found: C, 74.67; H, 5.84; N, 7.33.

8,8-Dimethyl-3-phenyl-5-(4-chlorophenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2m) White solid; yield 74%; mp 304–306°C; IR: 3105, 3061, 1653, 1572, 1524, 1446 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.90 (3H, s), 1.09 (3H, s), 2.12–2.27 (2H, m), 2.59 (2H, s), 6.32 (1H, s), 6.66 (2H, d, *J*=8 Hz), 7.17 (2H, d, *J*=8 Hz), 7.27 (2H, d, *J*=8 Hz), 7.46 (1H, s), 7.49 (2H, t, *J*=8 Hz), 7.58 (1H, t, *J*=8 Hz); ^{13}C NMR (DMSO-d_6): δ 26.7 (CH_3), 28.0 (C), 32.5 (CH_2), 49.7 (CH_2), 56.9 (CH), 108.5 (CH), 111.1 (CH), 127.3 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 129.6 (C), 130.5 (C), 133.1 (C), 138.0 (C), 140.5 (C), 146.3 (C), 161.4 (C), 193.4 (C); MS: m/z 420 (M^+). Anal. Calcd for $C_{24}H_{21}ClN_2OS$: C, 68.48; H, 5.03; N, 6.65. Found: C, 68.41; H, 5.09; N, 6.55.

8,8-Dimethyl-3-phenyl-5-(2-methoxyphenyl)-8,9-dihydro-*5H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2n) White solid; yield 80%; mp 272–274°C; IR: 3116, 3059, 1658, 1583, 1518, 1452 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (3H, s), 1.13 (3H, s), 2.13–2.29 (2H, m), 2.73–2.84 (2H, m), 3.76 (3H, s), 6.33 (1H, d, *J*=8 Hz), 6.35 (1H, s), 6.49 (1H, t, *J*=8 Hz), 6.76 (1H, d, *J*=8 Hz), 7.01 (2H, d, *J*=8 Hz), 7.13 (1H, d, *J*=8 Hz), 7.15 (1H, s), 7.36 (2H, t, *J*=8 Hz), 7.50 (1H, t, *J*=8 Hz); ^{13}C NMR ($CDCl_3$): δ 26.7 (CH_3), 28.0 (C), 32.5 (CH_2), 49.7 (CH), 51.4 (CH_2), 56.9 (CH_3), 108.5 (CH), 109.6 (CH), 111.1 (CH), 127.3 (C), 128.3 (CH), 128.5 (CH), 128.7 (CH), 129.6 (CH), 130.5 (CH), 131.2 (C), 133.1 (C), 138.0 (C), 140.5 (C), 146.3 (C), 161.4 (C), 193.4 (C); MS: m/z 416 (M^+). Anal. Calcd for $C_{25}H_{24}N_2O_2S$: C, 72.09; H, 5.81; N, 6.73. Found: C, 72.18; H, 5.89; N, 6.63.

8,8-Dimethyl-3-phenyl-5-(4-methylphenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2o) White solid; yield 77%; mp 270–271°C; IR: 3115, 3055, 1653, 1583, 1519, 1450 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.91 (3H, s), 1.10 (3H, s), 2.13–2.29 (2H, m), 2.34 (3H, s), 2.57 (2H, s), 6.25 (1H, s), 6.54 (2H, d, *J*=8 Hz), 6.64 (2H, d, *J*=8 Hz), 7.27 (2H, d, *J*=8 Hz), 7.42 (1H, s), 7.51 (2H, t, *J*=8 Hz), 7.59 (1H, t, *J*=8 Hz); ^{13}C NMR (DMSO-d_6): δ 26.7 (CH_3), 28.2 (CH_3), 32.6 (C), 45.3 (CH_2), 49.8 (CH_2), 56.9 (CH), 109.1 (CH), 111.2 (CH), 113.7 (CH), 127.5 (CH), 128.0 (CH), 128.7 (CH), 129.6 (C), 130.5 (C), 131.3 (C), 140.7 (C), 146.1 (C), 159.2 (C), 161.1 (C), 193.5 (C); MS: m/z 400 (M^+). Anal. Calcd for $C_{25}H_{24}N_2OS$: C, 74.97; H, 6.04; N, 6.99. Found: C, 74.88; H, 6.13; N, 6.87.

8,8-Dimethyl-3-phenyl-5-(4-bromophenyl)-8,9-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-one (2p) White solid; yield 75%; mp 282–284°C; IR: 3117, 3056, 1653, 1589, 1523, 1450 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.90 (3H, s), 1.09 (3H, s), 2.12–2.27 (2H, m), 2.59 (2H, s), 6.31 (1H, s), 6.60 (2H, d, *J*=8 Hz), 7.28 (2H, d, *J*=8 Hz, 2H), 7.30 (2H, d, *J*=8 Hz), 7.47 (1H, s), 7.49 (2H, t, *J*=8 Hz), 7.58 (1H, t, *J*=8 Hz); ^{13}C NMR (DMSO-d_6): δ 26.7 (CH_3), 28.0 (C), 32.5 (CH_2), 49.6 (CH_2), 56.9 (CH), 108.5 (CH), 111.1 (C), 127.2

(CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 129.6 (C), 130.4 (CH), 133.1 (C), 138.0 (C), 140.5 (C), 146.3 (C), 161.4 (C), 193.4 (C); MS: m/z 464 (M^+). Anal. Calcd for $C_{24}H_{21}BrN_2OS$: C, 61.94; H, 4.55; N, 6.02. Found: C, 61.86; H, 4.49; N, 6.11.

8,8-Dimethyl-3-phenyl-5-(4-methoxyphenyl)-8,9-dihydro-*5H*-thiazolo[*2,3-b*]quinazolin-6(7*H*)-one (2q) White solid; yield 81%; mp 276–277°C; IR: 3119, 3056, 1658, 1589, 1515, 1453 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.92 (3H, s), 1.10 (3H, s), 2.11–2.28 (2H, m), 2.59 (2H, s), 3.64 (3H, s), 6.26 (1H, s), 6.53 (2H, d, *J*=8 Hz, 2H), 6.64 (2H, d, *J*=8 Hz), 7.28 (2H, d, *J*=8 Hz), 7.43 (1H, s), 7.51 (2H, t, *J*=8 Hz), 7.59 (1H, t, *J*=8 Hz); ^{13}C NMR (DMSO-d_6) δ 26.7 (CH_3), 28.2 (C), 32.6 (CH_2), 45.3 (CH_2), 49.8 (CH_3), 57.0 (CH), 109.1 (CH), 111.2 (CH), 113.7 (CH), 127.4 (CH), 128.0 (CH), 128.7 (CH), 129.6 (C), 130.5 (C), 131.3 (C), 140.7 (C), 146.1 (C), 159.2 (C), 161.0 (C), 193.4 (C); MS: m/z 416 (M^+). Anal. Calcd for $C_{25}H_{24}N_2O_2S$: C, 72.09; H, 5.81; N, 6.73. Found: C, 72.16; H, 5.90; N, 6.67.

8,8-Dimethyl-3-phenyl-5-(2-chlorophenyl)-8,9-dihydro-*5H*-thiazolo[*2,3-b*]quinazolin-6(7*H*)-one (2r) White solid; yield 76%; mp 275–276°C; IR: 3120, 3054, 1657, 1589, 1518, 1454 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (3H, s), 1.14 (3H, s), 2.16–2.30 (2H, m), 2.82 (2H, s), 6.55 (1H, s), 6.64 (1H, d, *J*=8 Hz), 6.82 (1H, t, *J*=8 Hz), 7.01 (2H, d, *J*=8 Hz), 7.09 (1H, t, *J*=8 Hz), 7.14 (1H, s), 7.18 (1H, d, *J*=8 Hz), 7.31 (2H, t, *J*=8 Hz), 7.47 (1H, t, *J*=8 Hz); ^{13}C NMR ($CDCl_3$): δ 27.1 (CH_3), 28.9 (C), 32.7 (CH_2), 50.6 (CH), 59.1 (CH_2), 107.2 (CH), 112.2 (CH), 126.3 (CH), 126.9 (CH), 128.9 (CH), 129.5 (CH), 130.1 (CH), 130.4 (CH), 130.7 (C), 132.5 (C), 133.2 (C), 134.3 (C), 141.2 (C), 146.7 (C), 161.4 (C), 194.0 (C); MS: m/z 420 (M^+). Anal. Calcd for $C_{24}H_{21}ClN_2OS$: C, 68.48; H, 5.03; N, 6.65. Found: C, 68.37; H, 5.12; N, 6.56.

8,8-Dimethyl-3-phenyl-5-(4-nitrophenyl)-8,9-dihydro-*5H*-thiazolo[*2,3-b*]quinazolin-6(7*H*)-one (2s) White solid; yield 73%; mp 281–283°C; IR: 3108, 3051, 1656, 1588, 1516, 1448 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.88 (3H, s), 1.08 (3H, s), 2.10–2.26 (2H, m), 2.56 (2H, s), 6.42 (1H, s), 6.95 (2H, d, *J*=8 Hz), 7.22 (2H, d, *J*=8 Hz), 7.41 (1H, s), 7.44 (2H, t, *J*=8 Hz), 7.55 (1H, t, *J*=8 Hz), 7.95 (2H, d, *J*=8 Hz); ^{13}C NMR (DMSO-d_6): δ 26.8 (CH_3), 28.2 (C), 32.5 (CH_2), 49.8 (CH_2), 56.9 (CH), 107.8 (CH), 109.3 (CH), 123.4 (CH), 127.4 (CH), 128.1 (CH), 128.7 (CH), 129.6 (C), 130.5 (C), 139.1 (C), 140.4 (C), 146.2 (C), 147.0 (C), 161.4 (C), 193.4 (C); MS: m/z 431 (M^+). Anal. Calcd for $C_{24}H_{21}N_3O_3S$: C, 66.80; H, 4.91; N, 9.74. Found: C, 66.88; H, 4.83; N, 9.65.

8,8-Dimethyl-3-phenyl-5-(3-nitrophenyl)-8,9-dihydro-*5H*-thiazolo[*2,3-b*]quinazolin-6(7*H*)-one (2t) White solid; yield 75%; mp 293–294°C; IR: 3119, 3058, 1650, 1581, 1520, 1445 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.91 (3H, s), 1.09 (3H, s), 2.10–2.26 (2H, m), 2.58 (2H, s), 6.41 (1H, s), 7.19 (1H, s), 7.22 (2H, d, *J*=8 Hz), 7.31 (1H, d, *J*=8 Hz), 7.40 (1H, d, *J*=8 Hz), 7.43 (1H, s), 7.46 (2H, t, *J*=8 Hz), 7.53 (1H, t, *J*=8 Hz), 8.02 (1H, d, *J*=8 Hz); ^{13}C NMR (DMSO-d_6): δ 26.8 (CH_3), 28.2 (C), 32.6 (CH_2), 49.7 (CH_2), 57.1 (CH), 107.8 (CH), 109.8 (CH), 121.7 (CH), 123.3 (CH), 127.6 (CH), 128.6 (CH), 129.6 (CH), 130.3 (C), 130.4 (CH), 133.4 (C), 138.1 (C), 140.4 (C), 141.5 (C), 146.9 (C), 161.4 (C), 193.5 (C); MS: m/z 431 (M^+). Anal. Calcd for $C_{24}H_{21}N_3O_3S$: C, 66.80; H, 4.91; N, 9.74. Found: C, 66.91; H, 4.83; N, 9.63.

8,8-Dimethyl-3-phenyl-5-(3-bromophenyl)-8,9-dihydro-*5H*-thiazolo[*2,3-b*]quinazolin-6(7*H*)-one (2u) White solid; yield 79%; mp 278–279°C; IR: 3115, 3056, 1655, 1589, 1517, 1450 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.92 (3H, s), 1.09 (3H, s), 2.12–2.28 (2H, m), 2.55 (2H, s), 6.27 (1H, s), 6.53 (1H, s), 6.82 (1H, d, *J*=8 Hz), 7.12 (1H, t, *J*=8 Hz), 7.25 (2H, d, *J*=8 Hz), 7.37 (1H, d, *J*=8 Hz), 7.43 (1H, s), 7.50 (2H, t, *J*=8 Hz), 7.60 (1H, t, *J*=8 Hz); ^{13}C NMR (DMSO-d_6) δ 26.7 (CH_3), 28.0 (C), 32.5 (CH_2), 49.6 (CH_2), 56.9 (CH), 108.5 (CH), 109.2 (C), 111.1 (CH), 127.2 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 129.6 (C), 130.4 (CH), 131.3 (CH), 133.1 (C), 138.0 (C), 140.5 (C), 146.3 (C), 161.4 (C), 193.4 (C); MS: m/z 464 (M^+). Anal. Calcd for $C_{24}H_{21}BrN_2OS$: C, 61.94; H, 4.55; N, 6.02. Found: C, 61.86; H, 4.49; N, 6.11.

8,8-Dimethyl-3-(4-methylphenyl)-5-phenyl-8,9-dihydro-*5H*-thiazolo[*2,3-b*]quinazolin-6(7*H*)-one (2v) White solid; yield 74%; mp 230–232°C; IR: 3113, 3052, 1658, 1584, 1519, 1453 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.94 (3H, s), 1.14 (3H, s), 2.19–2.32 (2H, m), 2.44 (3H, s), 2.83 (2H, s), 6.34 (1H, s), 6.73 (2H, d, *J*=8 Hz), 6.93 (2H, d, *J*=8 Hz), 7.07 (1H, d, *J*=8 Hz), 7.14 (2H, t, *J*=8 Hz), 7.22 (2H, d, *J*=8 Hz), 7.27 (1H, s); ^{13}C NMR ($CDCl_3$): δ 26.9 (CH_3), 29.1 (CH_3), 33.0 (C), 39.0 (CH_2), 50.5 (CH_2), 58.0 (CH), 109.5 (CH), 111.4 (CH), 123.5 (CH), 126.4 (CH), 128.9 (CH), 129.3 (CH), 129.6 (C), 129.7 (C), 138.4 (C), 141.5 (C), 141.6 (C), 146.2 (C), 160.7 (C), 194.1 (C); MS: m/z 400 (M^+). Anal. Calcd for $C_{25}H_{24}N_2OS$: C, 74.97; H, 6.04; N, 6.99. Found: C, 74.87; H, 6.12; N, 6.88.

8,8-Dimethyl-3-(4-chlorophenyl)-5-phenyl-8,9-dihydro-*5H*-thiazolo[*2,3-b*]quinazolin-6(7*H*)-one (2w) White solid; yield 73%; mp 268–270°C; IR: 3102, 3060, 1654, 1576, 1522, 1446 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.94 (3H, s), 1.15 (3H, s), 2.18–2.35 (2H, m), 2.77 (2H, s), 6.30 (1H, s), 6.75 (2H, d, *J*=8 Hz), 6.92 (1H, d, *J*=8 Hz), 7.00 (1H, t, *J*=8 Hz), 7.05 (1H, d, *J*=8 Hz), 7.15 (2H, t, *J*=8 Hz), 7.36 (2H, d, *J*=8 Hz), 7.48 (1H, s); ^{13}C NMR ($CDCl_3$): δ 29.0 (CH_3), 32.9 (C), 38.9 (CH_2), 50.3 (CH_2), 58.2 (CH), 109.5 (CH), 113.0 (CH), 125.0 (CH), 126.4 (CH), 127.9 (CH), 128.9 (CH), 129.1 (C), 129.2 (C), 131.1 (C), 135.4 (C), 137.2 (C), 145.1 (C), 160.4 (C), 194.0 (C); MS: m/z 420 (M^+). Anal. Calcd for $C_{24}H_{21}ClN_2OS$: C, 68.48; H, 5.03; N, 6.65. Found: C, 68.40; H, 5.08; N, 6.57.

Conclusion

In summary, a method for the synthesis of 5*H*-thiazolo[2,3-*b*]quinazolin-6(7*H*)-ones from the cyclization of octahydroquinazoline-2-thiones, α-*H*-ketones, and bromine is described. In addition to high yields, this method benefits from having a short reaction time and it is base-free, and the procedure is straightforward.

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References

Abelman, M. M.; Smith, S. C.; James, D. R. Cyclic ketones and substituted α-keto acids as alternative substrates for novel Biginelli-like scaffold synthesis. *Tetrahed. Lett.* **2003**, *44*, 4559–4562.

Balkan, A.; Uma, S.; Ertan, M.; Wiegrebe, W. Thiazolo[3,2-*a*]pyrimidine derivatives as calcium antagonists. *Pharmazie*. **1992**, *47*, 687–688.

Biginelli, P. Aldehyde-urea derivatives of aceto- and oxaloacetic acids. *Gazz. Chim. Ital.* **1893**, *23*, 360–413.

Byk, G.; Gettlieb, H. E.; Herscovici. J.; Mirkin, F. New regioselective multicomponent reaction: one pot synthesis of spiro heterobicyclic aliphatic rings. *J. Comb. Chem*. **2000**, *2*, 732–735.

Hassani, Z.; Islami, M. R.; Kalantari, M. An efficient one-pot synthesis of octahydroquinazolinone derivatives using catalytic amount of H_2SO_4 in water. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 4479–4482.

Janis, R. A.; Silver, P. J.; Triggle, D. J. Drug action and cellular calcium regulation. *Adv. Drug Res.* **1987**, *16*, 309–591.

Kappe, C. O. The generation of dihydropyrimidine libraries utilizing Biginelli multicomponent chemistry. *QSAR Comb. Sci.* **2003**, *22*, 630–645.

Kidwai, M.; Saxena, S.; Khalilur Rahman Khan, M.; Thukral, S. S. Synthesis of 4-aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2-one/thione-5-one derivatives and evaluation as antibacterials. *Eur. J. Med. Chem.* **2005**, *40*, 816–819.

Kidwai, M.; Bhatnagar, D.; Kumar, R.; Luthra, P. M. Synthesis of 2-oxo/thioxooctahydroquinazolin-5-one derivatives and their evaluation as anticancer agents. *Chem. Pharm. Bull*. **2010**, *58*, 1320–1323.

Mokrosz, J. L.; Paluchowska, M. H.; Szneler, E.; Drozdz, B. The effect of aryl substituents in some spiro[2-oxo-4,6-bis(aryl) hexahydropyrimidine-5,5′-barbituric acids. *Arch. Chem (Weinheim, Germany)*. **1989**, *322*, 231–235.

Prajapati, D.; Bhuyan, D.; Gohain, M.; Hu, W. H. Green chemistry approaches to the regioselective synthesis of spiro heterobicyclic rings using iodine as a new and efficient catalyst under solvent-free conditions. *Mol Divers.* **2011**, *15*, 257–261.

Quan, Z.-J.; Zhang, Z.; Wang, J.-K.; Wang, X.-C.; Liu, Y.-J.; Ji, P.-Y. Efficient synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidines from reactions of 3,4-dihydropyrimidine-thiones with α-bromoacetone in aqueous media. *Heteroatom Chem.* **2008**, *19*, 149–153.

Quan, Z.-J.; Ren, R.-G.; Jia, X.-D.; Da, Y.-X.; Zhang, Z.; Wang, X.-C. *N*-Alkoxymethylation of heterocyclic compounds with diethyl phosphite via cleavage of P-O bond. *Tetrahedron*. **2011**, *67*, 2462–2467.

Sabitha, G.; Reddy, G. S. K. K; Reddy, K. B.; Yadav, J. S. Vanadium(III) chloride catalyzed Biginelli condensation: solution phase library generation of dihydropyrimidin-(2*H*)-ones. *Tetrehedron Lett*. **2003**, *44*, 6497–6499.

Sarac, S.; Yarim, M.; Ertan, M.; Boydag, S.; Erol, K. Synthesis, chemical and pharmacological properties of some 4-aryl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones. *Pharmazie*. **1998**, *53*, 91–94.

Sarac, S.; Yarim, M.; Ertan, M.; Kilic, F. S.; Erol, K. 4-Aryl-6,6-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones: synthesis, chromatographic resolution and pharmacological activity. *Pharmazie.* **2001**, *56*, 298–302.

Singh, S.; Schober, A.; Gebinoga, M.; Groß, G. A. Convenient method for synthesis of thiazolo[3,2-*a*]pyrimidine derivatives in a one-pot procedure. *Tetrahed. Lett*. **2011**, *52*, 3814–3817.

Wang, X.-C.; Quan, Z.-J.; Wang, J.-K.; Zhang, Z.; Wang, M.-G. A practical and green approach toward synthesis of *N3*-substituted dihydropyrimidinones: using Aza-Michael addition reaction catalyzed by KF/Al_2O_3. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4592–4595.

Yarim, M.; Sarac, S.; Kilic, F. S.; Erol, K. Synthesis and in vitro calcium antagonist activity of 4-aryl-7,7-dimethyl/1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives. *Il Farmaco*. **2003**, *58*, 17–24.

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