Heterocycl. Commun., Vol. 17(5-6), pp. 181–185, 2011 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/HC.2011.041

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

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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.

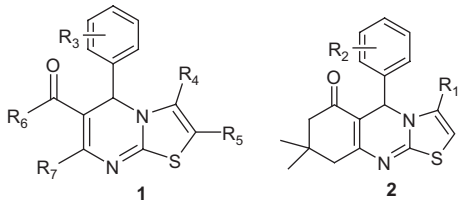


Figure 1 Thiazolo[3,2-*a*]pyrimidines **1** and thiazolo[2,3-*b*]quinazolines **2**.

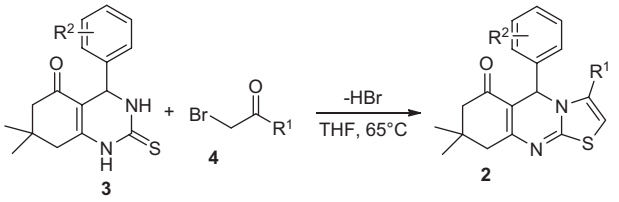
Experimental section

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.

Acknowledgments

We are thankful for financial support from the National Nature Science Foundation of China (No. 20902073 and 21062017), the Natural Science Foundation of Gansu Province (No. 096RJZA116), and the Scientific and Technological Innovation Engineering program of Northwest Normal University (nwnu-kjcxgc-03-64, nwnu-lkqn-10-15).

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Received August 9, 2011; accepted October 23, 2011