JOC The Journal of Organic Chemistry

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Copper-Catalyzed C(sp^3)–S Bond and C(sp^2)–S Bond Cross-Coupling of 2-(2-Iodobenzoyl) Substituted or 2-(2-Iodobenzyl) Substituted 1,2,3,4-Tetrahydroisoquinolines with Potassium Sulfide: Synthesis of Isoquinoline-Fused 1,3-Benzothiazine Scaffolds

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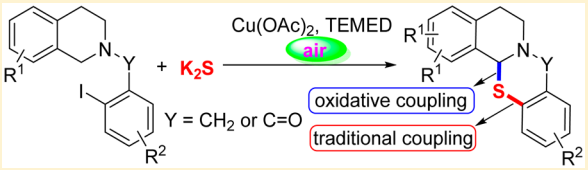
Supporting Information

ABSTRACT: The sulfuration reaction of 2-(2-iodobenzoyl) substituted, or 2-(2-iodobenzyl) substituted 1,2,3,4-tetrahydroisoquinolines with potassium sulfide proceeded in the presence of copper catalysts to give tetrahydroisoquinoline-fused 1,3-benzothiazine scaffolds in moderate to appropriate yields. This protocol provided an efficient and simple strategy to construct the corresponding benzothiazine derivatives via formation of C(sp^3)–S bond and C(sp^2)–S bond, which the C–S bonds formed via different routes in this reaction (traditional cross-coupling reaction via the cleavage of C–I bond and oxidative cross-coupling reaction via C(sp^3)–H bond functionalization).



Development of straightforward and efficient methods for rapid construct to nitrogen and sulfur-containing heterocyclic compounds is one of the central focuses in organic synthesis,[1−3] as well as applications in the pharmaceutical industry[4] and materials science.[5] 1,3-Benzothiazines[6−9] and 1,2,3,4-tetrahydroisoquinolines (THIQs),[10,11] in particular, are the core structural motifs of many biologically and pharmaceutically active molecules. Remarkably, 5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-*a*]isoquinolin-8(13a*H*)-one and 5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-*a*]-isoquinoline, which contain THIQ and 1,3-benzothiazine skeletons, are present as a key functional group in pharmacologically active compounds.[12] They have been investigated as sedatives (e.g., A, Figure 1),[13] cell growth

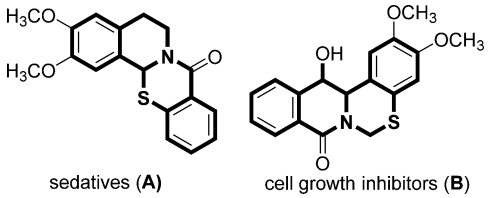
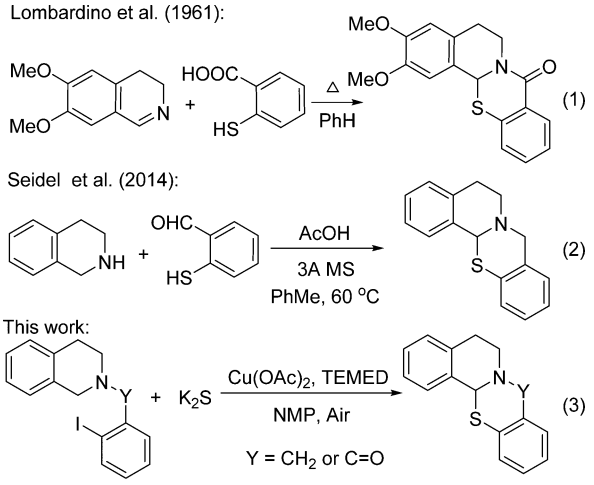


Figure 1. Examples of bioactive THIQ-fused 1,3-benzothiazines.

inhibitors (e.g., B, Figure 1).[12a,b] As a result, the design and development of a novel and straightforward route for the generation of isoquinoline-fused 1,3-benzothiazines are particularly valuable.

Conventional synthetic approaches for the construction of ring-fused 1,3-thiazine scaffolds focus on (1) direct imine acylation reaction of imines with thiosalicylic acid (Scheme 1, eq 1)[13,14] and (2) redox-neutral α-sulfenylation of secondary amine with thiosalicylaldehydes (Scheme 1, eq 2).[15] These reported routes are useful and interesting for the synthesis of ring-fused 1,3- benzothiazines. However, the sulfuration reagents of functional thiols have unpleasant odors, preparation difficulties, and easy oxidation during their entire processes, which impedes their applications. Recently, our group discovered that inorganic metal sulfides as a good coupling

Scheme 1. Selected Approaches to Ring-fused 1,3-Benzothiazine



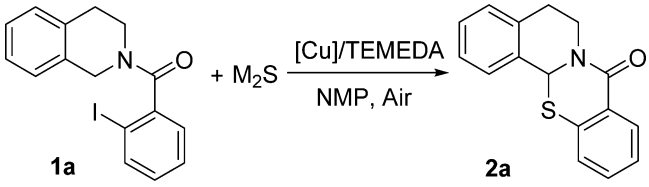
Received: December 7, 2016
Published: January 25, 2017

DOI: 10.1021/acs.joc.6b02943
J. Org. Chem. 2017, 82, 2263−2268

partner could be used to synthesize the five-members sulfur-containing heterocyclic compounds,[16−21] which are with the characteristics of low toxicity, low cost, readily available, relative stability, and operational simplicity. In continuation of our efforts on the synthesis of sulfur-containing compounds using simple and low-cost methods, we decided to explore the synthesis of six-members sulfur-containing heterocyclic compounds. We found that 2-(2-iodobenzoyl) substituted, or 2-(2-iodobenzyl) substituted THIQs could efficiently react with potassium sulfide to obtain isoquinoline-fused 1,3-benzothiazines in the presence of copper catalyst (Scheme 1, eq 3). Herein, we would introduced the details for constructing these *N*,*S*-heterocycles.

The initial evaluation was carried out with (3,4-dihydroisoquinolin-2(1H)-yl)(2-iodophenyl)methanone (**1a**) and K_2S as the model substrates to optimize the reaction conditions, and the results were summarized in Table 1. To our delight, the

Table 1. Optimization of Reaction Conditions[a]



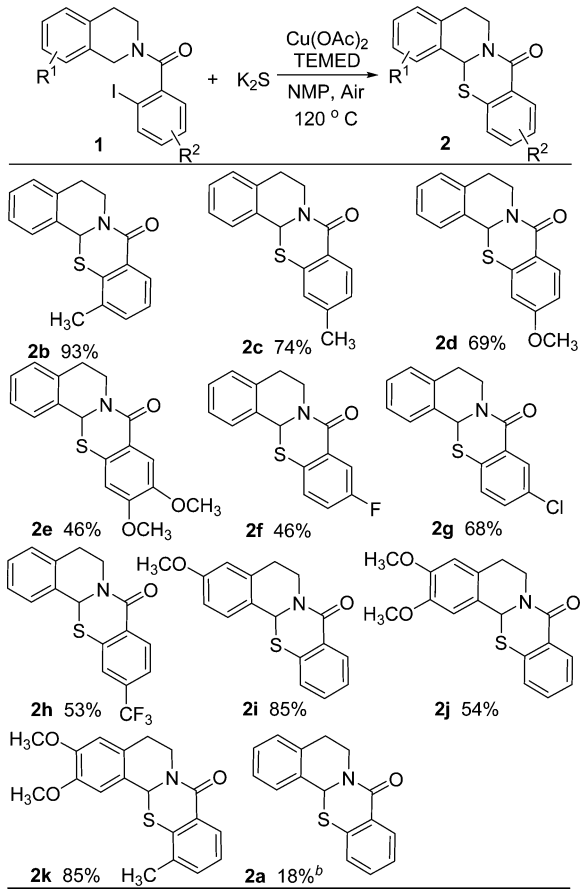
entry	catalyst	M_2S	temp(°C)[b]	yield(%)
1	CuBr	K_2S	120	70
2[c]	CuBr	K_2S	120	37
3[d]	CuBr	K_2S	120	58
4		K_2S	120	NR[e]
5	$Cu(OAc)_2$	K_2S	120	88
6	$Cu(OAc)_2$	K_2S	100	41
7	$Cu(OAc)_2$	K_2S	140	58
8	$Cu(OAc)_2$	Na_2S	120	trace
9	$Cu(OAc)_2$	Li_2S	120	trace

[a]Reaction conditions: **1a** (0.3 mmol), M_2S (0.9 mmol), Cu salt (20 mol%), TEMEDA (40 mol%), NMP (2 mL), under air atmosphere in sealed Schlenk tube, at 120 °C for 24 h. [b]Temp: temperature. [c]Under nitrogen atmosphere. [d]Under oxygen atmosphere. [e]NR: no reaction.

desired product **2a** was obtained in 70% yield by employing CuBr as catalyst and TEMED (tetramethylethylenediamine) as ligand in NMP (*N*-methyl-2-pyrrolidone) at 120 °C under air atmosphere (entry 1). When the reaction was performed under oxygen atmosphere or nitrogen atmosphere, the yields of product **2a** are all decreased obviously (entries 2 and 3). Control experiment revealed that the use of copper salt was imperative (entry 4). In order to achieve the best result, a series of copper catalysts and nitrogen-ligands are screened (entry 5, see the Supporting Information for more details). Among the comparison of copper catalysts, monovalent copper salts (CuCl, CuI, Cu_2O) were inferior to bivalent copper salts (CuF_2, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, $Cu(OTf)_2$), and $Cu(OAc)_2$ showed the best catalytic efficiency. No ligand and the other ligands, such as DMEDA (*N*,*N*′-dimethylethylenediamine), L-proline, DMAP (4-dimethylaminopyridine), and 1,10-phenanthroline, all gave lower yields than TEMED. Subsequently, several polar solvents (dimethylformamide, dimethyl sulfoxide, dimethylacetamide, and acetonitrile) were evaluated as potential alternatives to NMP, but the desired product all gave rise in lower yields (see the Supporting Information for more details). Finally, it is found that both decreasing and increasing the temperature could not improve the yields (entries 6 and 7). In order to improve the yield, the other metal sulfides, such as Na_2S and Li_2S, were used to displace K_2S. Regrettably, they are not efficient sulfur reagents for the reaction, and no product **2a** was obtained under the identical conditions (entries 8 and 9). Thus, the use of 20 mol% of $Cu(OAc)_2$ and 40 mol% of TEMED, in NMP at 120 °C for 24 h was found to be optimal reaction conditions (88%, entry 5).

With the optimal reaction conditions in hand, the scope of the substituents on the aromatic ring of 2-iodobenzoyl group was tested initially (Scheme 2, **2b**−**2h**). Both electron-donating

Scheme 2. Synthesis of 5,6-Dihydrobenzo[5,6][1,3]thiazino[2,3-*a*]isoquinolin-8(13aH)-ones[a]



[a]Reaction conditions: **1** (0.3 mmol), K_2S (0.9 mmol), $Cu(OAc)_2$ (20 mol%), TEMED (40 mol%), NMP (2 mL), under air atmosphere in sealed Schlenk tube, at 120 ° C for 24 h. [b](2-Bromophenyl)(3,4-dihydroisoquinolin-2(1H)-yl)methanone was applied.

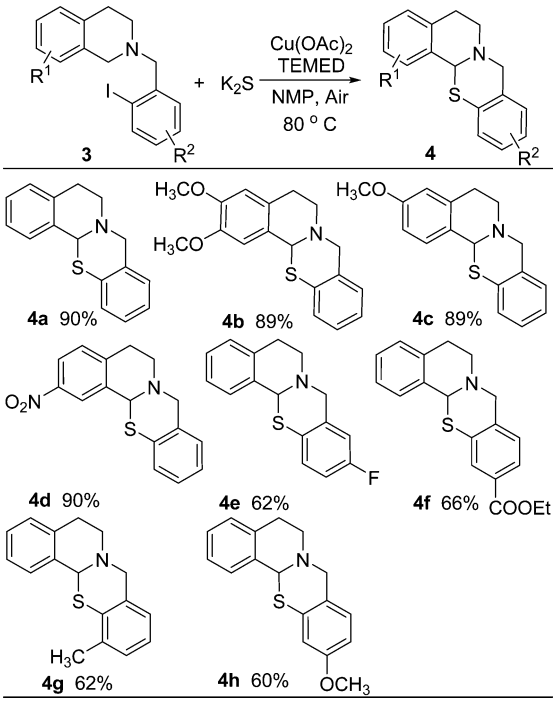
groups (CH_3 and OCH_3) and electron-withdrawing groups (F, Cl, and CF_3) were tolerated, and could smoothly transform into the desired isoquinoline-fused 1,3-benzothiazines under the optimized conditions. For example, the *N*,*S*-heterocycle **2b** was afforded in 93% yield. Due to the biological activity of bearing of methoxyl group on the isoquinoline-fused 1,3-benzothiazines, the methoxyl group on the isoquinoline ring were evaluated (Scheme 2, **2i**−**2k**). Luckily, the desired products **2i** and **2k** all were obtained in 85% yield. Importantly, the isoquinoline-fused 1,3-benzothiazine **2j** could be gained in 54% yield which has been investigated as sedatives. Finally, the reactivity of (2-bromophenyl)(3,4-dihydroisoquinolin-2(1H)-

DOI: 10.1021/acs.joc.6b02943
J. Org. Chem. 2017, 82, 2263−2268

yl)methanone was investigated (Scheme 2, **2a**). Unfortunately, it could not efficiently react with K_2S, and low yield of product **2a** was afforded in the standard reaction conditions.

Encouraged by the success in the coupling reaction of (3,4-dihydroisoquinolin-2(1H)-yl)(2-iodophenyl)methanones **1** with K_2S, we next attempted to examine the substrate scope to 2-(2-iodobenzyl)-THIQs **3** (Scheme 3). However, it

Scheme 3. Synthesis of 5,6,8,13a-Tetrahydrobenzo[5,6][1,3]thiazino[2,3-*a*]isoquinolines[a]

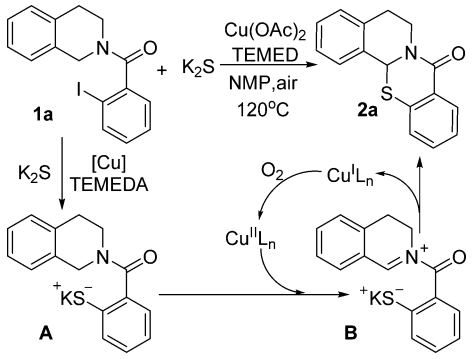


[a]Reaction conditions: 3 (0.3 mmol), K_2S (0.9 mmol), $Cu(OAc)_2$ (20 mol %), TEMED (40 mol%), NMP (2 mL), under air atmosphere in sealed Schlenk tube, at 80 °C for 4 h.

revealed that the reaction of 2-(2-iodobenzyl)-THIQ **3a** with potassium sulfide is sluggish under the standard conditions. Fortunately, **3a** was found to be a suitable substrate and achieved isoquinoline-fused 1,3-benzothiazines in 90% yield, when the reaction temperature was lowered to 80 °C. Subsequently, the electronic effect of the substituents on the aromatic ring of isoquinoline was investigated. We were pleased to find that the reactions of isoquinoline bearing both electron-donating groups and electron-withdrawing groups worked well and afforded the corresponding products in good yields (Schemes 3 and 4b–d). Among them, the products **4b** and **4c** were both attained in 89% yields. To our delight, electron-withdrawing group NO_2 of isoquinoline ring system gave compound **4d** in 90% yield. Finally, a wide range of 2-iodobenzyl-substituted THIQs were examined. It was observed that bearing either electron-donating groups (CH_3, OCH_3) or electron-withdrawing groups (F, COOEt) on the phenyl ring of **3** proceeded smoothly, and obtained the desired products **4** in 60–66% yields (Schemes 3 and 4e–h).

Based on the reported literatures[1,22,23] and previous works, a plausible mechanism of this coupling reaction was proposed in Scheme 4. First, intermediate **A** is formed from (3,4-dihydroisoquinolin-2(1H)-yl)(2-iodophenyl)methanone **1a** and K_2S via the copper-catalyzed traditional coupling reaction.

Scheme 4. Possible Reaction Mechanism



Subsequently, the intermediate **A** undergoes a copper-promoted single-electron transfer process to provide the iminium intermediate **B**, which can effectively undergo an intramolecular nucleophilic attack to give the desired cross-coupling product **2a**.

In conclusion, we have developed an efficient and straightforward method for the synthesis of isoquinoline-fused 1,3-benzothiazines via copper-catalyzed cross-coupling of 2-(2-iodobenzoyl) substituted, or 2-(2-iodobenzyl) substituted 1,2,3,4-THIQs with potassium sulfide. The main features of this new methodology are (1) this reaction provides an efficient protocol for the construction $C(sp^3)$-S bond and $C(sp^2)$-S bond in a step; (2) the low cost, low toxicity, odorless, and readily available potassium sulfide should be desired sulfuration reagent for the coupling partner; and (3) the isoquinoline-fused 1,3-benzothiazine derivatives have biological and pharmaceutical activity, which are easily prepared using this synthetic strategy.

EXPERIMENTAL SECTION

General Information. NMR spectra of the products **2a–2k**, **4a–4h** were recorded using 500 MHz NMR spectrometer. The chemical shifts were calibrated to TMS (^{1}H NMR spectra) and $CD(H)Cl_3$ (^{13}C NMR spectra) as the internal reference (0.00 ppm for ^{1}H NMR spectra and 77.00 ppm for ^{13}C NMR spectra). High-resolution mass spectra (HRMS) were recorded with an ESI-Obitrap mass spectrometer. Reactions were monitored by thin-layer chromatography, and column chromatography (petroleum ether/ethyl acetate) was performed on silica gel (200–300 mesh). All reagents were used without further purification as received from commercial suppliers unless otherwise noted. All solvents were dried and distilled prior to use according to the standard protocols.

General Procedure for the Preparation of Starting Materials (1). A solution sodium nitrite (703.8 mg, 10.2 mmol) in water (2 mL) was added slowly to a cold (0 °C) stirred solution of substituted 2-aminobenzoic acid (10 mmol) in water (25 mL) and concentrated hydrochloric acid (7.5 mL). On completion of the addition the solution was stirred for 5–10 min until complete consumption of starting material was indicated by TLC. Then, a solution of the potassium iodide (1693.2 mg, 10.2 mmol) in water (2.5 mL) was slowly added. The cooling bath was removed and the mixture stirred for a further 30 min before carefully heating the suspension to 90 °C for 30 min. The mixture was cooled to room temperature and the precipitated solid was collected and washed with water. The crude product was recrystallized from ethanol and water to afford the pure substituted-2-iodobenzoic acids.

The substituted-2-iodobenzoic acids (3 mmol), thionyl chloride (3.0 mL), and one drop of *N*,*N*-dimethylformamide were heated under reflux for 4 h. The mixture was cooled to room temperature. The excess thionyl chloride was removed from the cooled reaction mixture and the remaining acid chloride was dissolved in dichloromethane.

DOI: 10.1021/acs.joc.6b02943
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A solution *o*-iodoebenzoyl chlorides (3 mmol) in CH_2Cl_2 (3 mL) was added slowly to a cold (0 °C) stirred solution of isoquinoline (2.5 mmol) and triethylamine (0.84 mL, 6 mmol) in dichloromethane (5 mL). The mixture was stirred until complete consumption of starting material was indicated by TLC. The mixture was quenched with water and the organic layer extracted with dichloromethane. The combined extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography to afford the pure product **1**.

Typical Experimental Procedure for the Synthesis of 5,6-Dihydrobenzo[5,6][1,3]thiazino[2,3-*a*]isoquinolin-8(13aH)-ones (Scheme 2). The sealed Schlenk tube was charged with (3,4-dihydroisoquinolin-2(1H)-yl)(2-iodophenyl)methanone derivatives **1** (0.3 mmol), K_2S (99 mg, 3 equiv, 0.9 mmol), $Cu(OAc)_2$ (10.9 mg, 20 mol%, 0.06 mmol), TEMED (13.9 mg, 40 mol%, 0.12 mmol), and NMP (2 mL). Then the mixture was stirred at 120 °C (oil bath temperature). After the reaction was finished, the reaction mixture was cooled to room temperature, quenched by water, and extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over Na_2SO_4, and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to afford ring-fused 1,3-benzothiazine heterocycles **2**.

Typical Experimental Procedure for the Synthesis of 5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-*a*]-isoquinolines (Scheme 3). The sealed Schlenk tube was charged with 2-(2-iodobenzyl)-1,2,3,4-tetrahydroisoquinoline derivatives **3** (0.3 mmol), K_2S (99 mg, 3equiv, 0.9 mmol), $Cu(OAc)_2$ (10.9 mg, 20 mol %, 0.06 mmol), TEMED (13.9 mg, 40 mol%, 0.12 mmol), and NMP (2 mL). Then the mixture was stirred at 80 °C for 4 h (oil bath temperature). After the reaction was finished, the reaction mixture was cooled to room temperature, quenched by water, and extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over Na_2SO_4, and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to afford ring-fused 1,3-benzothiazine heterocycles **4**.

*5,6-Dihydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinolin-8(13aH)-one (**2a**):*[14b] White solid (70 mg, 88%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.92−2.96 (m, 1H), 3.11−3.22 (m, 2H), 4.78−4.81 (m, 1H), 6.22 (s, 1H), 7.24−7.26 (m, 1H), 7.29−7.34 (m, 4H), 7.38−7.42 (m, 2H), 8.19 (d, J = 8.0 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 29.4, 39.8, 60.5, 126.1, 126.8, 127.1, 127.5, 128.4, 128.7, 128.9, 130.6, 131.0, 131.7, 136.2, 137.6, 164.8.

*12-Methyl-5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinolin-8(13aH)-one (**2b**).* Pale yellow solid (78 mg, 93%); mp: 79.9−81.3 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.33 (s, 3H), 2.94 (d, J = 14.5 Hz, 1H), 3.11−3.22 (m, 2H), 4.77−4.80 (m, 1H), 6.13 (s, 1H), 7.20−7.31 (m, 5H), 7.41 (t, J = 5.5 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 19.8, 29.4, 39.7, 59.8, 125.3, 127.0, 127.6, 128.4, 128.6, 128.7, 128.9, 130.8, 132.8, 134.6, 136.3, 137.4, 165.1. HRMS (ESI, m/z) calcd for $[C_{17}H_{15}NOS]H^+$: 282.0947; found 282.0942.

*11-Methyl-5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinolin-8(13aH)-one (**2c**).* Pale yellow oil (62 mg, 74%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.37 (s, 3H), 2.90−2.94 (m, 1H), 3.09−3.20 (m, 2H), 4.76−4.79 (m, 1H), 6.20 (s, 1H), 7.12 (t, J = 8.0 Hz, 2H), 7.23−7.25 (m, 1H), 7.28 (t, J = 4.5 Hz, 2H), 7.36−7.38 (m, 1H), 8.07 (d, J = 8.0 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 21.3, 29.4, 39.7, 60.4, 126.3, 127.0, 127.1, 127.2, 127.5, 128.3, 128.6, 130.7, 130.9, 136.2, 137.4, 142.4, 164.8. HRMS (ESI, m/z) calcd for $[C_{17}H_{15}NOS]H^+$: 282.0947; found 282.0943.

*11-Methoxy-5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-a]-isoquinolin-8(13aH)-one (**2d**).* Pale yellow solid (60 mg, 69%); mp: 142.3−143.8 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.90−2.93 (m, 1H), 3.08−3.19 (m, 2H), 3.84 (s, 3H), 4.74−4.77 (m, 1H), 6.23 (s, 1H), 6.79−6.84 (m, 2H), 7.23−7.25 (m, 1H), 7.29 (t, J = 4.5 Hz, 2H), 7.36−7.38 (m, 1H), 8.12 (d, J = 9.0 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 29.4, 39.6, 55.4, 60.5, 110.8, 112.8, 121.7, 127.0, 127.5, 128.3, 128.6, 130.6, 132.8, 136.2, 139.4, 161.9, 164.7. HRMS (ESI, m/z) calcd for $[C_{17}H_{15}NO_2S]H^+$: 298.0896; found 298.0896.

*10,11-Dimethoxy-5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-a]-isoquinolin-8(13aH)-one (**2e**).* Yellow oil (45 mg, 46%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.92−2.97 (m, 1H), 3.10−3.20 (m, 2H), 3.91 (s, 3H), 3.95 (s, 3H), 4.75−4.79 (m, 1H), 6.20 (s, 1H), 6.76 (s, 1H), 7.25 (t, J = 3.5 Hz, 1H), 7.30 (t, J = 5.0 Hz, 2H), 7.39 (t, J = 5.5 Hz, 1H), 7.69 (s, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 29.4, 39.7, 56.0, 56.1, 60.8, 108.7, 112.9, 121.4, 127.0, 127.5, 128.3, 128.7, 130.3, 130.7, 136.2, 147.7, 151.9, 164.8. HRMS (ESI, m/z) calcd for $[C_{18}H_{17}NO_3S]H^+$: 328.1002; found 328.1001.

*10-Fluoro-5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinolin-8(13aH)-one (**2f**).* Yellow oil (40 mg, 46%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.92−2.96 (m, 1H), 3.10−3.24 (m, 2H), 4.76−4.80 (m, 1H), 6.20 (s, 1H), 7.14 (td, J = 8.5 Hz, 2.5 Hz, 1H), 7.25−7.27 (m, 1H), 7.29−7.33 (m, 3H), 7.38−7.40 (m, 1H), 7.89 (dd, J = 9.5 Hz, 3.0 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 29.4, 40.0, 60.7, 117.6 (d, J = 23.5 Hz), 119.3 (d, J = 22.6 Hz), 127.2, 127.6, 128.4 (d, J = 7.2 Hz), 128.5, 128.8, 130.3, 130.6 (d, J = 7.2 Hz), 132.7 (d, J = 3.2 Hz), 136.1, 161.2 (d, J = 244.7 Hz), 163.8. HRMS (ESI, m/z) calcd for $[C_{16}H_{12}NOSF]H^+$: 286.0696; found 286.0697.

*10-Chloro-5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinolin-8(13aH)-one (**2g**).* Yellow oil (60 mg, 68%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.91−2.95 (m, 1H), 3.09−3.22 (m, 2H), 4.74−4.78 (m, 1H), 6.19 (s, 1H), 7.24−7.27 (m, 2H), 7.29−7.31 (m, 2H), 7.35−7.38 (m, 2H), 8.15 (d, J = 2.5 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 29.3, 39.9, 60.5, 127.2, 127.5, 128.0, 128.5, 128.7, 130.1, 130.2, 130.8, 131.7, 132.1, 135.9, 136.1, 163.6. HRMS (ESI, m/z) calcd for $[C_{16}H_{12}ClNOS]H^+$: 302.0401; found 302.0399.

*11-(Trifluoromethyl)-5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-a]-isoquinolin-8(13aH)-one (**2h**).* Pale yellow solid (53 mg, 53%); mp: 78.7−80.4 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.94−2.99 (m, 1H), 3.12−3.25 (m, 2H), 4.77−4.81 (m, 1H), 6.25 (s, 1H), 7.26−7.29 (m, 1H), 7.32 (t, J = 4.0 Hz, 2H), 7.38−7.40 (m, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 8.29 (d, J = 8.5 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 29.3, 40.0, 60.7, 122.7 (q, J = 3.5 Hz), 123.2 (q, J = 271.2 Hz), 123.9 (q, J = 3.75 Hz), 127.3, 127.5, 128.7, 128.8, 129.9, 131.5, 131.6, 133.5 (q, J = 32.4 Hz), 136.1, 138.8, 163.7. HRMS (ESI, m/z) calcd for $[C_{17}H_{12}NOSF_3]H^+$: 336.0665; found 336.0660.

*3-Methoxy-5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinolin-8(13aH)-one (**2i**).* Yellow oil (77 mg, 85%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.86−2.90 (m, 1H), 3.07−3.20 (m, 2H), 3.81 (s, 3H), 4.74−4.78 (m, 1H), 6.16 (s, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.83 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 7.28−7.31 (m, 3H), 7.38 (td, J = 7.5 Hz, 1.5 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 29.6, 39.7, 55.2, 60.3, 113.2, 113.3, 122.5, 125.9, 126.7, 128.7, 128.9, 130.9, 131.5, 137.6, 137.7, 159.3, 164.7. HRMS (ESI, m/z) calcd for $[C_{17}H_{15}NO_2S]H^+$: 298.0896; found 298.0896.

*2,3-Dimethoxy-5,6-dihydrobenzo[5,6][1,3]thiazino[2,3-a]-isoquinolin-8(13aH)-one (**2j**):*[13] White solid (53 mg, 54%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.83−2.86 (m, 1H), 3.03−3.10 (m, 1H), 3.15−3.18 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 4.74−4.78 (m, 1H), 6.15 (s, 1H), 6.72 (s, 1H), 6.86 (s, 1H), 7.29−7.33 (m, 2H), 7.40 (t, J = 7.5 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 28.7, 39.7, 55.8, 55.9, 60.5, 109.9, 111.1, 122.0, 126.0, 126.7, 128.6, 128.9, 130.9, 131.6, 137.5, 148.1, 148.9, 164.8.

*2,3-Dimethoxy-12-methyl-5,6-dihydrobenzo[5,6][1,3]thiazino-[2,3-a]isoquinolin-8(13aH)-one (**2k**).* Pale yellow solid (87 mg, 85%); mp: 142.1−143.3 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.34 (s, 3H), 2.84−2.87 (m, 1H), 3.04−3.10 (m, 1H), 3.15−3.21 (m, 1H), 3.89 (s, 3H), 3.91 (s, 3H), 4.73−4.77 (m, 1H), 6.06 (s, 1H), 6.73 (s, 1H), 6.88 (s, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 7.0 Hz, 1H), 8.04 (d, J = 7.5 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 19.9, 28.8, 39.7, 55.9, 56.0, 59.8, 110.1, 111.1, 122.2, 125.3, 128.5, 128.7, 128.9, 132.8, 134.5, 137.4, 148.1, 149.0, 165.2. HRMS (ESI, m/z) calcd for $[C_{19}H_{19}NO_3S]H^+$: 342.1158; found 342.1158.

*5,6,8,13a-Tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (**4a**):*[15] White solid (68 mg, 90%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.84 (d, J = 12.0 Hz, 2H), 3.16−3.30 (m, 2H), 3.96 (d, J = 16.5 Hz, 1H), 4.55 (d, J = 17.0 Hz, 1H), 6.18 (s, 1H), 7.00−7.06 (m, 3H), 7.11 (td, J = 8.5 Hz, 2.0 Hz, 1H), 7.16−7.25 (m, 4H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 28.7, 43.6, 57.7, 67.0, 124.1, 126.0, 126.2, 126.4, 126.5, 127.0, 127.8, 128.0, 129.2, 133.0, 134.7, 134.8.

DOI: 10.1021/acs.joc.6b02943
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*2,3-Dimethoxy-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (**4b**):*[15] Pale yellow solid (84 mg, 89%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.81 (d, J = 7.5 Hz, 2H), 3.15 (d, J = 50.5 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.00 (s, 1H), 4.51 (s, 1H), 6.01 (s, 1H), 6.64 (s, 2H), 6.99−7.09 (m, 4H). ^{1}H NMR ($CDCl_3$, 500 MHz, −60 °C) δ 2.76 (d, J = 15.5 Hz, 1H), 2.83−2.86 (m, 1H), 3.07−3.20 (m, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 3.98 (d, J = 16.5 Hz, 1H), 4.53 (d, J = 16.5 Hz, 1H), 6.14 (s, 1H), 6.65 (d, J = 21.5 Hz, 2H), 6.99 (d, J = 8.0 Hz, 1H), 7.04−7.09 (m, 2H), 7.13 (t, J = 7.0 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 28.4, 43.7, 55.8, 55.9, 57.8, 67.1, 108.9, 111.6, 124.1, 125.2, 126.5, 126.6, 126.7, 126.9, 127.9, 134.9, 147.4, 148.6.

*3-Methoxy-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (**4c**):*[15] Pale yellow solid (81 mg, 90%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.85 (s, 2H), 3.15 (s, 2H), 3.80 (s, 3H), 3.98 (s, 1H), 4.51 (s, 1H), 6.14 (s, 1H), 6.71 (s, 1H), 6.76 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 6.99−7.05 (m, 3H), 7.09−7.11 (m, 2H). ^{1}H NMR ($CDCl_3$, 500 MHz, −60 °C) δ 2.84 (d, J = 15.0 Hz, 2H), 3.19−3.26 (m, 2H), 3.82 (s, 3H), 4.00 (d, J = 17.0 Hz, 1H), 4.54 (d, J = 17.0 Hz, 1H), 6.17 (s, 1H), 6.74 (s, 1H), 6.80 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.06−7.16 (m, 4H). ^{13}C{H} NMR ($CDCl_3$,125 MHz) δ 28.9, 43.5, 55.1, 57.7, 66.8, 112.2, 113.8, 124.0, 126.4, 126.5, 126.8, 127.2, 127.3, 127.8, 134.5, 134.9, 158.9.

*2-Nitro-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (**4d**).* Pale yellow solid (80 mg, 90%); mp: 169.5−170.9 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.86−2.96 (m, 2H), 3.20−3.32 (m, 2H), 3.96 (d, J = 16.5 Hz, 1H), 4.56 (d, J = 16.5 Hz, 1H), 6.18 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.06 (s, 2H), 7.10−7.13 (m, 1H), 7.33 (d, J = 8.5 Hz, 1H), 8.15 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 29.1, 43.0, 57.4, 66.0, 121.4, 122.7, 124.7, 125.9, 126.6, 127.2, 128.0, 130.2, 133.6, 136.2, 141.4, 146.2. HRMS (ESI) m/z calcd for $[C_{16}H_{15}N_2O_2S]H^+$: 299.0849, found 299.0849.

*10-Fluoro-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (**4e**).* Pale yellow solid (50 mg, 62%); mp: 138.5−139.8 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.79−2.82 (m, 2H), 3.12−3.23 (m, 2H), 3.89 (d, J = 16.5 Hz, 1H), 4.48 (d, J = 17.0 Hz, 1H), 6.09 (s, 1H), 6.77−6.84 (m, 2H), 6.91−6.94 (m, 1H), 7.12−7.18 (m, 3H), 7.19−7.23 (m, 1H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 28.7, 43.6, 57.6, 66.9, 114.5 (q, J = 21.5 Hz), 126.1, 126.2, 127.6, 127.7, 127.9, 128.0 (d, J = 5.75 Hz), 129.2, 129.5 (d, J = 2.8 Hz), 132.9, 134.5, 159.7 (d, J = 242.75 Hz). HRMS (ESI, m/z) calcd for $[C_{16}H_{14}NSF]H^+$: 272.0904; found 272.0905.

*5,6,8,13a-Tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline-11-carboxylate Ethyl (**4f**).* White solid (64 mg, 66%); mp: 120.5−121.8 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.36 (t, J = 7.0 Hz, 3H), 2.79−2.81 (m, 2H), 3.16−3.19 (m, 2H), 3.97 (d, J = 17.0 Hz, 1H), 4.33 (q, J = 7.0 Hz, 2H), 4.52 (d, J = 16.5 Hz, 1H), 6.15 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.13−7.24 (m, 4H), 7.65−7.76 (m, 2H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 14.2, 28.7, 43.7, 57.6, 60.9, 67.2, 124.9, 126.1, 126.2, 127.7, 127.8, 127.9, 129.1, 129.2, 131.3, 132.9, 134.4, 135.5, 166.0. HRMS (ESI, m/z) calcd for $[C_{19}H_{19}NO_2S]H^+$: 326.1209; found 326.1209.

*12-Methyl-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (**4g**).* Yellow solid (50 mg, 62%); mp: 140.3−141.8 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (d, J = 6.0 Hz, 3H), 2.82 (d, J = 15 Hz, 2H), 3.15−3.26 (m, 2H), 3.95 (d, J = 16.5 Hz, 1H), 4.54 (d, J = 16.5 Hz, 1H), 6.13 (s, 1H), 6.90−6.95 (m, 2H), 7.01 (t, J = 5.5 Hz, 1H), 7.17−7.23 (m, 4H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 19.1, 28.7, 43.5, 58.1, 67.0, 123.0, 125.3, 125.9, 126.0, 126.2, 127.9, 128.2, 129.2, 133.1, 133.9, 134.2, 135.0. HRMS (ESI) m/z calcd for $[C_{17}H_{18}NS]H^+$ 268.1155, found 268.1155.

*11-Methoxy-5,6,8,13a-tetrahydrobenzo[5,6][1,3]thiazino[2,3-a]isoquinoline (**4h**):*[15] Yellow solid (50 mg, 60%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.81 (s, 2H), 3.20 (d, J = 19.5 Hz, 2H), 3.75 (s, 3H), 3.90 (d, J = 13.0 Hz, 1H), 4.48 (d, J = 15.0 Hz, 1H), 6.15 (s, 1H), 6.55 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 7.14−7.24 (m, 4H). ^{13}C{H} NMR ($CDCl_3$, 125 MHz) δ 28.7, 43.5, 55.2, 57.2, 67.1, 110.8, 110.9, 118.4, 126.0, 126.2, 127.8, 128.8, 129.2, 133.0, 134.7, 135.8, 158.2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02943.

Copies of ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of China (21572051), Ministry of Education of the People's Republic of China (213027A), Education Department of Hunan Province (15A109) for financial support.

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DOI: 10.1021/acs.joc.6b02943
J. Org. Chem. 2017, 82, 2263−2268