A Versatile Approach for the Synthesis of Thiobarbiturate Analogues

Xiaokun Zhou, Ling-Yan Chen, and Zhihua Sun*

College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, Shanghai, 201620, China
*E-mail: sungaris@gmail.com

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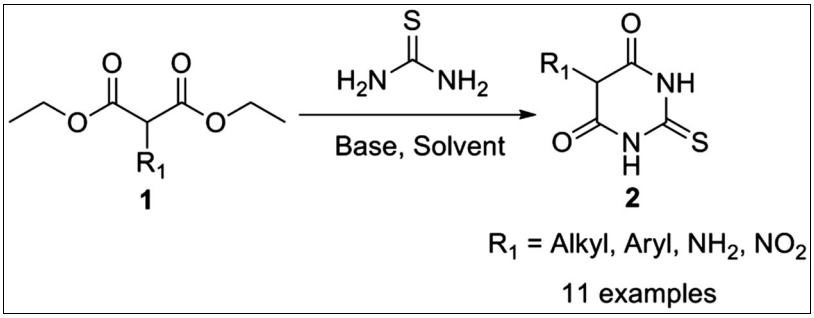

A variety of 5-substituted thiobarbiturates can be efficiently prepared in moderate to good yields. This protocol is broadly applicable and versatile, starting from substituted malonates and thiourea.

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INTRODUCTION

Thiobarbiturates and their derivatives **1-1** in Scheme 1, bearing urea or thiourea moiety, are structural scaffolds that are present in various important biologically active N-hetercyclic compounds. They could easily form tautomers. As shown in Figure 1, the first physiologically active drug (barbital or Veronal), 5,5-diethyl barbiturate **1-2**, was introduced in clinics in 1903 [1]. Thiobarbiturate 5-ethyl-5-(hexan-2-yl)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione **1-3** was applied as a local anesthetic [2], while thiobarbiturate **1-4** was proved to be a potent tyrosinase inhibitor exhibiting an IC50 of 0.05 m*M*/L [3]. Thiobarbiturates also could be used as anticonvulsants [4], immunotropic and anti-inflammatory compounds [5], antineoplastic agents [6], and as platforms in the synthesis of other biologically active compounds [7]. Besides, they are intermediates in the preparation of dyes [8]. Therefore, it is important to seek a versatile approach to synthesize thiobarbiturate derivatives for broad application in synthetic and medicinal chemistry.

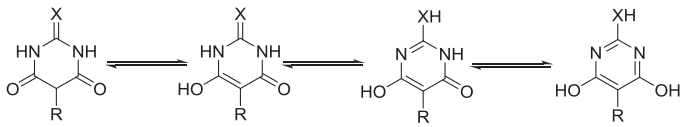
The most commonly used synthetic method for derivatives of thiobarbiturate started from thiobarbiturate without any substituents at the 5-position, obtained from condensation of malonate with thiourea. This thiobarbiturate could easily react with different alkyl halides via S_N2 to afford some derivatives under basic conditions, owing to the strong acidic protons at the 5-position ($pK_a = 4.01$). However, it is often hard to control the reaction to stop at 5-monoalkyl-substituted product when using this method. In addition, this method could not afford aryl-substituted compounds. Based on these limitations, we developed here a versatile approach for the synthesis of 5-mono-substituted thiobarbiturate analogues.

RESULTS AND DISCUSSION

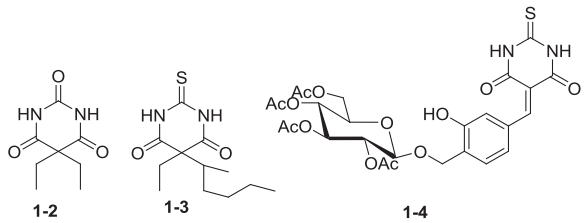
Our approach to the synthesis of thiobarbiturates started from different substituted diethyl malonates (Scheme 2). These substituted diethyl malonates often could be easily prepared. To illustrate, nitro-substituted diethyl malonates could be directly obtained from malonate and nitric acid. For aryl-substituted diethyl malonates, it could be prepared from the reaction between aryl iodides and malonates catalyzed by 2-picolinic acid and CuI [9]. For the barbiturate formation step, we first took methyl-substituted malonate for an initial study, using the classic condensation protocol with thiourea and sodium ethoxide in ethanol at 60°C. The reaction could not work well until it was under reflux because of the poor solubility of the substrates (64% yield). In order to improve the reaction, *t*-BuONa in THF or in *i*-PrOH was also examined. However, sodium ethoxide in EtOH at reflux gave the best performance.

Using the optimal conditions, a series of 5-substituted thiobarbiturates (**2a–k**) were synthesized. The results were summarized in Table 1. The groups at the 5-position varied from alkyl to nitro, amino [10], and aryl. Based on the results displayed in Table 1, it showed that all the thiobarbiturates could be prepared in moderate to good yields. For the different aryl-substituted substrates, it showed some electronic effects. Electron-donating groups, like the methoxy group in the phenyl ring, improved the thiobarbiturate formation and resulted in 92% yield (Table 1, entry 6), while electron-withdrawing groups like fluoro or trifluoromethyl weakened the reaction rate and resulted in moderate yields (Table 1, entries 7 and 8). The pyridyl group showed the poorest reactivity in the cyclization (Table 1, entry 10).

Scheme 1



1-1 X=O or S



1-2 **1-3** **1-4**

Figure 1. Examples of bioactive thiobarbiturates.

For thiobarbiturate **2c**, it could lead to an important intermediate (4,6-dichloro-2-(propylthio)pyrimidin-5-amine) of the drug Ticagrelor in three steps (Scheme 3), which is an aplatelet aggregation inhibitor and an antagonist of the P2Y12 receptor [11].

CONCLUSIONS

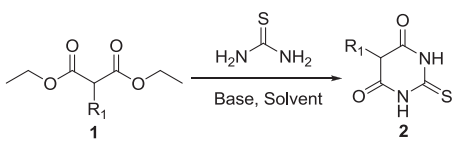
In summary, we reported here a versatile approach for the synthesis of thiobarbiturate analogues. A variety of 5-substituted thiobarbiturates can be efficiently prepared in moderate to good yields. The broad substitutions afforded at the 5-position of thiobarbiturates will provide important intermediates in medicinal chemistry.

EXPERIMENTAL

General information. Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Melting points were taken on a WRS-1B melting point apparatus (Shanghai, China). NMR spectra were recorded on a Bruker Avance II spectrometer (Billerica, MA, USA) at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR and 396 MHz for ^{19}F NMR. Chemical shifts were reported in δ (ppm) and spin-spin coupling constants as *J* (Hz) values. High resolution mass spectra (HRMS) were recorded on a Shimadzu High-Performance Liquid Chromatograph/Mass Spectrometer LCMS-IT-TOF (Kyoto, Japan).

General procedures for thiobarbiturate derivatives (2a–k). To a 100 mL round-bottomed flask with finely cut

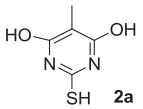
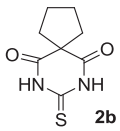
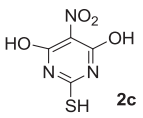
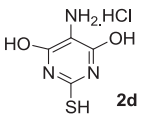
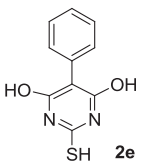
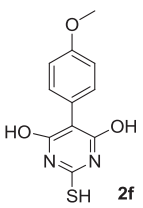
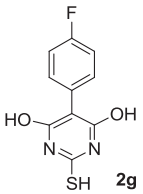
Scheme 2



1 **2**

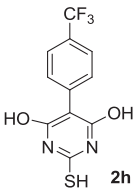
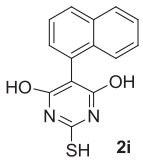
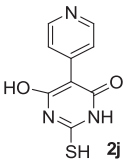
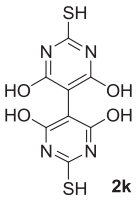
Table 1

Eleven examples for the series of thiobarbiturates.

Entry	R	Product	Yield (%)
1	Methyl	 **2a**	64
2	Spiro cyclopentyl	 **2b**	35
3	NO_2	 **2c**	90
4	NH_2	 **2d**	85
5	Phenyl	 **2e**	83
6	4-MeO-phenyl	 **2f**	92
7	4-F-phenyl	 **2g**	73

(*Continued*)

Table 1
(Continued)

Entry	R	Product	Yield (%)
8	4-CF_3-phenyl	 **2h**	35
9	1-Naphthyl	 **2i**	71
10	4-Pyridyl	 **2j**	14
11	Thiobarbiturate	 **2k**	65

sodium was added 25 mL anhydrous ethanol. When the sodium disappeared, thiourea and the corresponding 5-mono-substituted malonic diethyl ester were added and then the mixture was well stirred under reflux. After the corresponding malonic diethyl ester reacted completely, the mixture was acidified to pH = 1~2 with conc. HCl at room temperature. Compounds **2a**, **2c**, **2d**, **2e**, and **2h** were obtained by filtrating and washing with water and ethanol. Compounds **2b**, **2f**, **2g**, **2i**, and **2k** were obtained after silica gel chromatography.

2a: white solid, yield (73.7%). mp = 253.6–254.8°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.04 (s, 2H), 1.7 (s, 3H).^{13}C-NMR (100 MHz, DMSO-d_6) δ: 173.2, 160.7, 90.7, 7.8. HRMS (ESI): m/z calcd for $C_5H_6N_2O_2S$ [M-H]$^-$: 157.0066, found: 157.0063.

2b: white solid, yield (56.3%). mp =314.3–314.9°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.17 (s, 2H), 2.04 (t, J = 7.2 Hz, 4H), 1.75–1.71 (m, 4H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 180.0, 173.0, 57.0, 27.2. HRMS (ESI): m/z calcd for $C_8H_{10}N_2O_2S$ [M-H]$^-$: 197.0390, found: 197.0395.

2c: yellow solid, yield (90.8%). mp = 207.3–208.2°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.16 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 175.3, 157.6, 115.7. HRMS (ESI): m/z calcd for $C_4H_3N_3O_4S$ [M-H]$^-$: 187.9760, found: 187.9754.

2d: sandybrown solid, yield (80%). mp = 330.3–330.8°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.11 (s, 2H), 8.53 (s, 3H). HRMS (ESI): m/z calcd for $C_4H_6ClN_3O_2S$ [M-H]$^-$: 193.9785, found: 193.9788.

2e: white solid, yield (83.5%). mp = 277.3–278.2°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.84 (s, 2H), 7.40 (d, J = 6.8 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 7.21 (d, J = 6.8 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 173.5, 160.5, 132.5, 131.1, 128.0, 126.6, 96.8. HRMS (ESI): m/z calcd for $C_{10}H_8N_2O_2S$ [M-H]$^-$: 219.0224, found: 219.0230.

2f: white solid, yield (91.6%). mp = 287.1–289.0°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.79 (s, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 3.74 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 172.7, 160.5, 157.9, 124.7, 113.4, 55.5. HRMS (ESI): m/z calcd for $C_{11}H_{10}N_2O_3S$ [M-H]$^-$: 249.0339, found: 249.0332.

2g: white solid, yield (87.6%). mp = 285.4–287.0°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.96 (s,2H), 7.43–7.40 (m, 2H), 7.16–7.12 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 173.7, 162.6, 160.3, 160.2, 133.2, 133.1, 128.2, 115.0, 114.8, 96.3. ^{19}F-NMR (376 MHz) 115.8. HRMS (ESI): m/z calcd for $C_{10}H_7N_2O_2SF$ [M-H]$^-$: 237.0140, found: 237.0143.

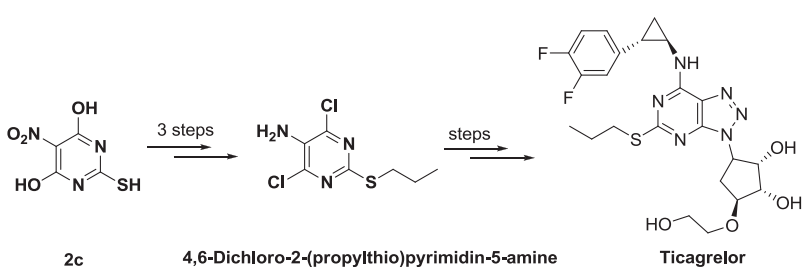
2h: red solid, yield (50.3%). mp = 270.3-272.0°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.51 (s,2H), 7.87 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 175.5, 166.4, 162.5, 131.2, 126.4, 124.5, 124.3, 82.5. HRMS (ESI): m/z calcd for $C_{11}H_7N_2O_2SF_3$ [M-H]$^-$: 287.0111, found: 287.0108.

2i: yellow solid, yield (81.2%). mp = 271.2–272.0°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.14 (s, 2H), 7.92 (q, J = 7.6 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.54–7.44 (m, 3H), 7.35 (d, J = 6.4 Hz, 2H).^{13}C-NMR (100 MHz, DMSO-d_6) δ: 174.4, 160.7, 133.9, 130.4, 129.6, 128.5, 128.3, 126.2, 126.1, 126.0, 95.2; HRMS (ESI): m/z calcd for $C_{14}H_{10}N_2O_2S$ [M-H]$^-$: 269.0390, found: 269.0394.

2j: yellow solid, yield (43.5%). mp = 263.5–267.0°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.47 (s,1H), 9.89 (s, 1H), 8.90 (d,146;J = 4.8 Hz, 2H), 7.91 (d, J = 5.6 Hz, 2H); ^{13}C-NMR (100MHz, DMSO-d_6) δ: 178.8, 166.9, 143.7, 127.9. HRMS (ESI): m/z calcd for $C_9H_7N_3O_2S$ [M-H]$^-$: 220.0186, found: 220.0183.

2k: yellow solid, yield (75.2%). mp = 265.7–266.0°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 11.83 (s, 4H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 173.6, 161.0, 88.4. HRMS (ESI): m/z calcd for $C_8H_6N_4O_4S_2$ [M-H]$^-$: 284.9758, found: 284.9762.

Scheme 3



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