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Diastereoselective Synthesis of Dispirobarbiturates through Et_3N-Catalyzed [3 + 2] Cycloaddition of Barbiturate-Based Olefins with 3-Isothiocyanato Oxindoles

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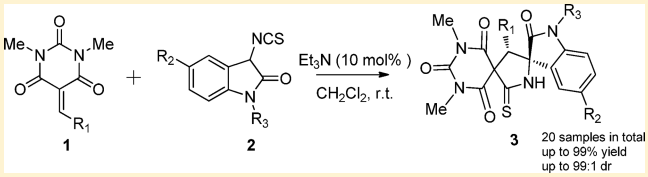
Supporting Information

ABSTRACT: Under catalysis of 10 mol % of Et_3N, the [3 + 2] cycloaddition of barbiturate-based olefins with 3-isothiocyanato oxindoles underwent smoothly and afforded the desired dispirobarbiturates in up to 99% yield with up to 99:1 dr. The relative configuration of the dispirobarbiturates was unambiguously determined by X-ray single-crystal structure analysis. The reaction mechanism was proposed to shed light on the diastereoselective formation of the dispirobarbiturates.



Spirobarbiturates constitute a class of biologically and medicinally important chemical entities, which have a wide range of biological activities, as shown in Figure 1.[1] Since

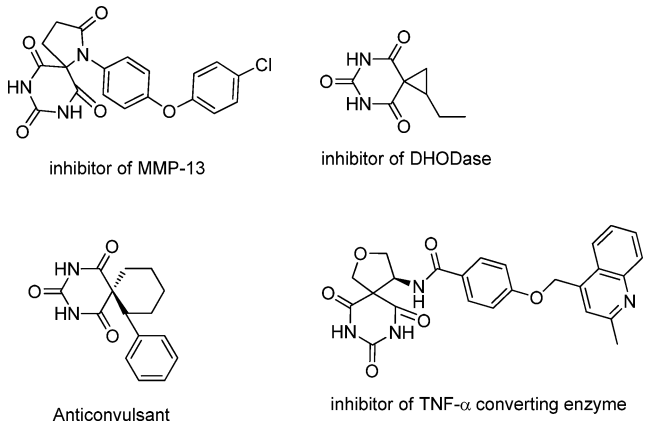
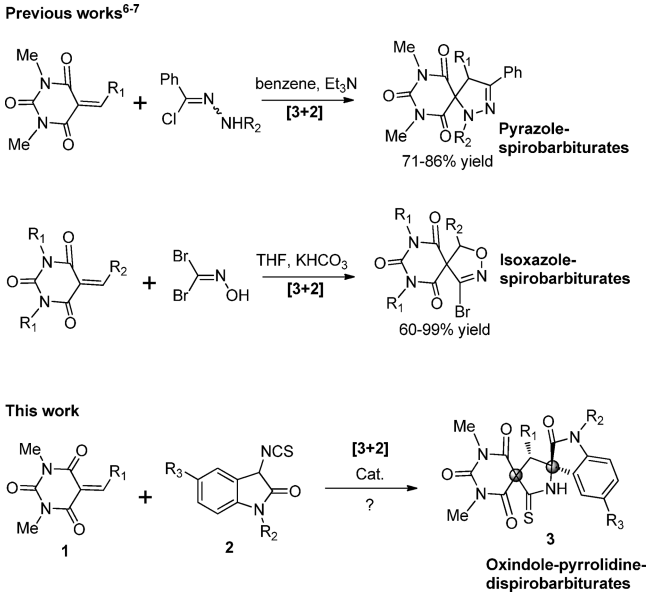


Figure 1. Representative bioactive spirobarbiturates.

the potential biological properties of the spirobarbiturates, many efforts were involved in the synthesis of a variety of structurally diverse spirobarbiturates.[2] For instances, Yoder and co-workers reported the first synthesis of cyclohexane-spirobarbiturates in 1921.[3] Since then, a number of synthetic methodologies have been developed for the synthesis of spirobarbiturates bearing various cyclic skeletons.[4] It was worthy to note that only a limited number of examples have been reported on the synthesis of dispirobarbiturates.[5] Moreover, the stereoselective construction of dispirobarbiturates has not been found in the literature works so far. Therefore, it is highly demanded to develop powerful and efficient protocols for the stereoselective construction of structurally and stereochemically diverse dispirobarbiturates.

By means of [3 + 2] cycloaddition, the Girgis[6] and Soleimani[7] groups accomplished the synthesis of pyrazole-spirobarbiturates and isoxazole-spirobarbiturates starting from barbiturate-based olefins, as depicted in Scheme 1, respectively. Moreover, pioneered by the Yuan group,[8a] 3-isothiocyanato oxindoles have found many applications in the diastereoselective and enantioselective synthesis of structurally and

Scheme 1. Synthesis of Spirobarbiturates via [3 + 2] Cycloadditions



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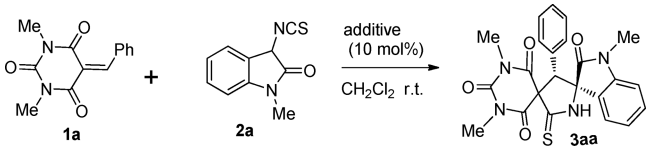
stereochemically diverse spirooxindoles.[8] In this work, we report the first diastereoselective synthesis of oxindole-pyrrolidine-dispirobarbiturates, as shown in Scheme 1. Under catalysis of 10 mol % of Et_3N, the [3 + 2] cycloaddition of barbiturate-based olefins with 3-isothiocyanato oxindoles proceeded readily, thus giving the desired dispirobarbiturates in excellent yields and diastereoselectivities. So far, there has been no such work in the literature.

As outlined in Table 1, at the outset, we investigated the effect of basic additives on the chemical yield and

Table 1. Screening of Additives in the [3 + 2] Cycloaddition[a]



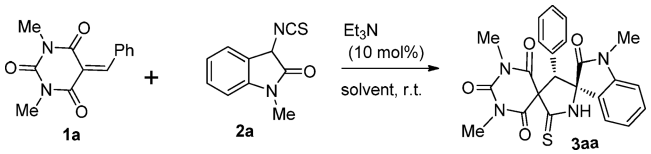
entry	additive	time (min)	yield (%)[b]	dr[c]
1	Et_3N	10	98	97:3
2	Na_2CO_3	1	84	97:3
3	DBU	13	98	97:3
4	DABCO	8	78	99:1
5	DIPEA	15	91	94:6
6	Na_2CO_3	10	40	97:3
7	DBU	10	75	97:3
8	DABCO	10	60	99:1
9	DIPEA	10	83	94:6

[a]Reactions were carried out with 0.1 mmol of **1a** and 0.1 mmol of **2a** in the presence of 10 mol % of additive in 1.0 mL of CH_2Cl_2 at room temperature. [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy.

diastereoselectivity of the [3 + 2] cycloaddition of **1a** and **2a** (entries 1−5). In all the cases, the [3 + 2] cycloaddition provided **3aa** with excellent diastereoselectivities. With respect to chemical yield, it was affected significantly by the basic additive used. For instance, using DABCO as an additive delivered **3aa** in 78% yield. Substitution of DABCO with Na_2CO_3 increased the chemical yield from 78% to 84% (entries 2 vs 4). In the cases of Et_3N, DBU, and DIPEA, all of them gave **3aa** in >90% chemical yield (entries 1, 3,and 5). Furthermore, we studied the effect of the bases on the [3 + 2] cycloaddition in the same reaction time (entries 1 and 6−9). As for Na_2CO_3 and DBU, they gave **3aa** in the same diastereoselectivities; however, the chemical yield of **3aa** differed drastically (entries 6 and 7). In regard to DABCO, it provided **3aa** in 60% yield with 99:1 dr (entry 8). In contrast with the former cases, the use of DIPEA increased the chemical yield and lowered the diastereoselectivity (entries 9 vs 6−8). Given the reaction rate, chemical yield, and diastereoselectivity, we chose Et_3N as the optimal base in the [3 + 2] cycloaddition (entry 1).

Next, in the presence of 10 mol % of Et_3N, we screened the solvent effect on the chemical yield and diastereoselectivity of the [3 + 2] cycloaddition of **1a** and **2a**, as summarized in Table 2 (entries 1−6). In all the cases, product **3aa** was obtained in excellent diastereoselectivities. In contrast, the chemical yield changed dramatically with the organic solvents examined. In the case of THF, the [3 + 2] cycloaddition gave **3aa** in 16% yield (entry 4). In comparison with THF, toluene produced a better yield (entries 2 vs 4). The significant increase in the chemical yield was observed with other solvents examined in contrast with the previous two cases (entries 1, 3, and 5 vs 2 and 4).

Table 2. Screening of Solvents in the [3 + 2] Cycloaddition[a]



entry	solvent	time (min)	yield (%)[b]	dr[c]
1	$CHCl_3$	25	>99	97:3
2	toluene	10	47	99:1
3	MeOH	2	88	97:3
4	THF	30	16	98:2
5	MTBE[d]	2	88	97:3
6	CH_2Cl_2	10	98	97:3
7	$CHCl_3$	10	65	97:3
8	MeOH	10	88	97:3
9	THF	10	95	98:2
10	MTBE[d]	10	88	97:3

[a]Reactions were carried out with 0.1 mmol of **1a**, and 0.1 mmol of **2a** in the presence of 10 mol % of Et_3N in 1.0 mL of solvent at room temperature. [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy. [d]Methyl *tert*-butyl ether.

Moreover, in the same reaction time, we examined the effect of the organic solvents on the chemical yield and diastereoselectivity of the [3 + 2] cycloaddition (entries 2 and 6−10). With respect to toluene, $CHCl_3$, MeOH, and MTBE as solvents, they furnished **3aa** in 47−88% yields with excellent diastereoselectivities (entries 2, 7−8, and 10). Satisfyingly, we found that using both CH_2Cl_2 and THF as solvent delivered **3aa** in excellent chemical yields and diastereoselectivities (entries 6 and 9). Even though THF could provide the excellent chemical yield and diastereoselectivity, it lowered the chemical yield of **3aa** dramatically as the reaction time prolonged because of the formation of some unidentified side products (entries 4 vs 9). After considering the reaction rate, chemical yield, and diastereoselectivity, we determined CH_2Cl_2 as the optimal reaction medium (entry 6).

At last, under the optimal reaction conditions (1:1 molar ratio of **1** to **2**, 10 mol % of Et_3N, CH_2Cl_2, r.t.), we extended the reaction scope of the [3 + 2] cycloaddition by using structurally diverse barbiturate-based olefins **1** and 3-isothiocyanato oxindoles **2**, as presented in Table 3. In most cases, the [3 + 2] cycloaddition processed smoothly and yielded oxindole-pyrrolidine-spirobarbiturates **3** in excellent chemical yields and diastereoselectivities (entries 1−2, 4−5, 8−14, 16−17, and 20). As for the other cases, the chemical yields ranged from 53% to 89%, and diastereoselectivities changed from 91:9 to 98:2 (entries 3, 6−7, 15, and 18−19). The relative configuration of **3fa** was determined by the single-crystal X-ray analysis (see details in the Supporting Information).[9] On the basis of the determined relative stereochemistry of **3fa**, the relative configuration of the other oxindole-pyrrolidine-spirobarbiturates **3** was also assigned similarly, as shown in Table 3. Moreover, with a purpose to gain potentially biologically active new homodimers,[10] we designed and synthesized disulfide-linked homodimer **4** in 60% yield by treating **3aa** with DDQ in CH_2Cl_2 at 0 °C, as shown in Scheme 2. Simultaneously, the relative configuration of **4** was also characterized by its single-crystal X-ray analysis (see details in the Supporting Information).[11]

To interpret the diastereoselective formation of **3fa**, the reaction mechanism of the [3 + 2] cycloaddition of **1f** and **2a**

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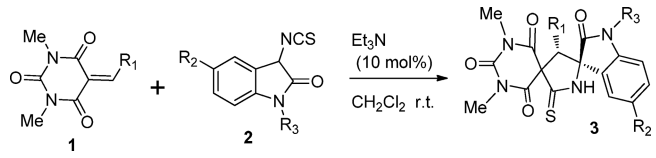
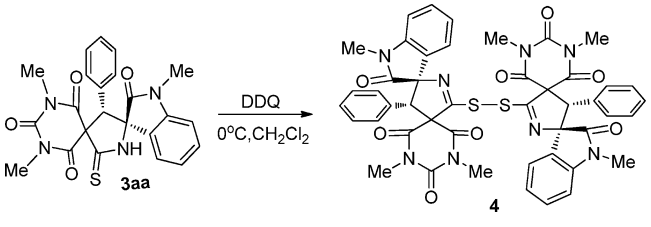
Table 3. Extension of the Reaction Scope of the [3 + 2] Cycloaddition[a]



Entry	**1** (R_1)	**2** (R_2, R_3)	**3**	Time (min)	Yield (%) [b]	dr [c]
1	**1a** (C_6H_5)	**2a** (H, Me)	**3aa**	10	98	97:3
2	**1a** (C_6H_5)	**2b** (Me, Me)	**3ab**	1	91	99:1
3	**1b** (4-MeC_6H_4)	**2b** (Me, Me)	**3bb**	1	53	95:5
4	**1c**(4-FC_6H_4)	**2b** (Me, Me)	**3cb**	1	90	94:6
5	**1a** (C_6H_5)	**2c** (F, Me)	**3ac**	1	94	90:10
6	**1a** (C_6H_5)	**2d** (H, Bn)	**3ad**	1	83	96:4
7	**1d** (2-Thienyl)	**2d** (H, Bn)	**3dd**	3	82	98:2
8	**1d** (2-Thienyl)	**2a** (H, Me)	**3da**	3	97	98:2
9	**1e** (4-BrC_6H_4)	**2a** (H, Me)	**3ea**	2	99	97:3
10	**1f** (4-$MeOC_6H_4$)	**2a** (H, Me)	**3fa**	2	99	96:4
11	**1g** (4-ClC_6H_4)	**2a** (H, Me)	**3ga**	2	99	98:2
12	**1h** 	**2a** (H, Me)	**3ha**	2	98	98:2
13	**1i** (4-$CF_3C_6H_4$)	**2a** (H, Me)	**3ia**	2	99	99:1
14	**1j** (4-FC_6H_4)	**2a** (H, Me)	**3ja**	2	99	96:4
15	**1k** (2-BrC_6H_4)	**2a** (H, Me)	**3ka**	5	89	91:9
16	**1l**(3,4,5-*tri*-$MeOC_6H_2$)	**2a** (H, Me)	**3la**	5	93	97:3
17	**1m** (3-ClC_6H_4)	**2a** (H, Me)	**3ma**	3	94	97:3
18	**1n** (3-$NO_2C_6H_4$)	**2a** (H, Me)	**3na**	3	86	97:3
19	**1o** (3,4-*di*-$MeOC_6H_3$)	**2a** (H, Me)	**3oa**	1	83	98:2
20	**1p** (4-$NO_2C_6H_4$)	**2a** (H, Me)	**3pa**	3	99	94:6

[a]Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2** in the presence of 10 mol % of Et_3N in 1.0 mL of CH_2Cl_2 at room temperature. [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy.

Scheme 2. Dimerization of 3aa via Oxidation Reaction



was predicted as presented in Scheme 3. Deprotonation of **2a** with Et_3N led to the formation of enolate **5**. Then, the resultant **5** underwent [3 + 2] cycloaddition with **1f** through the transition state **TS**, thus furnishing the intermediate **6**. Finally, the protonation of **6** delivered the diastereoselective formation of **3fa**.

In conclusion, we first developed the novel [3 + 2] cycloaddition of barbiturate-based olefins with 3-isothiocyanato oxindoles. The [3 + 2] cycloaddition proceeded readily, thus producing the desired oxindole-pyrrolidine-dispirobarbiturates in excellent chemical yields and diastereoselectivities.

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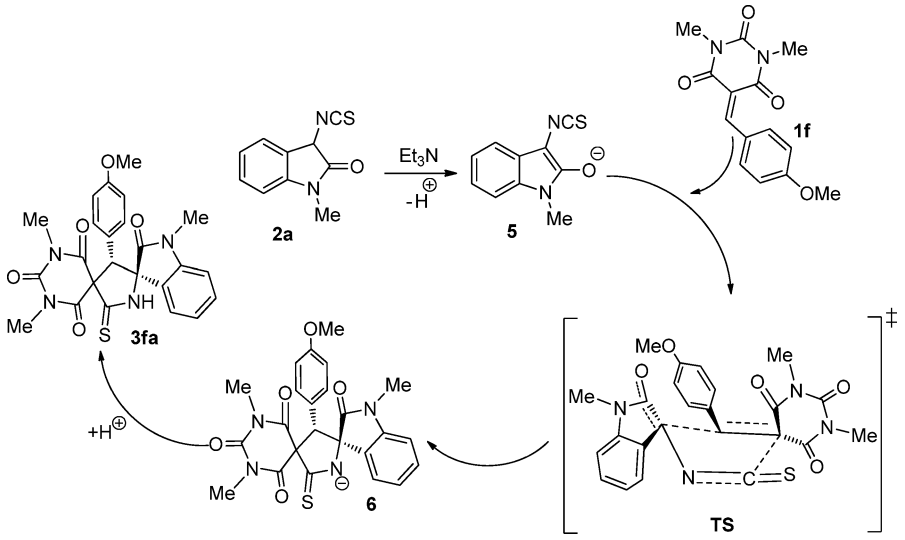
Scheme 3. Proposed Mechanism for the [3 + 2] Cycloaddition



EXPERIMENTAL SECTION

General Information. Unless noted otherwise, all reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before use. Reactions were monitored by TLC carried out on 0.25 mm SDS silica gel coated glass plates (60F254), and compounds were detected with UV light. The melting point of compounds was determined by a melting point instrument. NMR spectra were recorded on a 400 MHz instrument and calibrated using tetramethylsilane (TMS) as internal reference. IR spectra were monitored with an FT-IR spectrometer using KBr pellets (4000−400 cm^{-1}), and only major peaks were reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI) conditions on an Orbitrap mass analyzer.

Typical Procedure for the Diastereoselective Synthesis of Dispirobarbiturates 3. Triethylamine (0.01 mmol) was added to a mixture of barbiturate-based olefins **1** (0.1 mmol), and 3-isothiocyanato oxindoles **2** (0.1 mmol) in anhydrous CH_2Cl_2 (1.0 mL). The reaction was stirred at room temperature for 1−10 min. The reaction was quenched with 2.0 mL of saturated aqueous NH_4Cl solution, followed by diluting with 2.0 mL of CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1−2:1) to afford the pure products **3** as a white powder (53%−99% yield; 90:10−99:1 dr).

3aa. White powder; yield 98% (43.9 mg); mp = 210−211 °C; dr 97:3; ^{1}H NMR (400 MHz, DMSO): δ 11.54 (s, 1H), 8.26 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 6.8 Hz, 1H), 7.09−7.06 (m, 3H), 6.76 (d, J = 7.6 Hz, 2H), 5.39 (s, 1H), 3.27 (s, 3H), 3.17 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.1, 174.5, 166.6, 165.4, 150.4, 144.2, 131.8, 131.3, 129.0, 129.0, 128.6, 128.5, 125.8, 123.4, 109.9, 75.0, 74.3, 57.7, 29.9, 29.4, 27.4; HRMS (ESI) calculated for $C_{23}H_{20}N_4O_4S$ (M + H^+): 449.12780, found 449.12741; IR (KBr) 3342, 2961, 1730, 1681, 1605, 1491, 1371, 1103, 745 cm^{-1}.

3ab. White powder; yield 91% (42.0 mg); mp = 210 °C; dr 99:1; ^{1}H NMR (400 MHz, DMSO): δ 11.53 (s, 1H), 8.08 (s, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.14−7.07 (m, 3H), 6.96 (d, J = 8 Hz, 1H), 6.76 (d, J = 7.6 Hz, 2H), 5.42 (s, 1H), 3.28 (s, 3H), 3.15 (s, 6H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 194.9, 174.4, 166.6, 165.3, 150.5, 141.9, 132.3, 132.0, 131.4, 129.2, 129.0, 128.8, 128.4, 125.9, 109.6, 75.0, 74.4, 67.5, 57.3, 30.0, 29.4, 27.4, 25.6, 21.5; HRMS (ESI) calculated for $C_{24}H_{22}N_4O_4S$ (M + H^+): 463.14345, found 463.14218; IR (KBr) 3327, 2961, 1730, 1676, 1616, 1501, 1360, 1125, 750 cm^{-1}.

3bb. White powder; yield 53% (25.2 mg); mp = 194−194.7 °C; dr 95:5; ^{1}H NMR (400 MHz, DMSO): δ 11.49 (s, 1H), 8.11 (s, 1H), 7.23 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 8.0 Hz, 2H), 5.33 (s, 1H), 3.26 (s, 3H), 3.15 (s, 3H), 3.13 (s, 3H), 2.34 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.2, 174.5,166.7, 165.5, 150.4, 141.9, 137.9, 132.2, 131.3, 129.5, 129.2, 129.0, 128.6, 126.0, 109.5, 75.1, 74.6, 57.7, 29.9, 29.4, 27.4, 21.5, 20.9; HRMS (ESI) calculated for $C_{25}H_{24}N_4O_4S$ (M + H^+): 477.15910, found 477.15814; IR (KBr) 3305, 2918, 1725, 1670, 1621, 1496, 1355, 1120, 755 cm^{-1}.

3cb. White powder; yield 90% (43.2 mg); mp = 209−209.6 °C; dr 94:6; ^{1}H NMR (400 MHz, DMSO): δ 11.53 (s, 1H), 8.08 (s, 1H), 7.24 (d, J = 7.2 Hz, 1H), 6.96−6.86 (m, 5H), 5.42 (s, 1H), 3.27 (s, 3H), 3.17 (s, 3H), 3.13 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 194.9, 174.4, 166.4, 165.2, 150.5, 141.9, 132.3, 131.5, 131.4, 129.1, 128.0, 125.7, 115.9, 115.7, 109.6, 75.1, 74.4, 56.5, 30.0, 29.5, 27.4, 21.5; HRMS (ESI) calculated for $C_{24}H_{21}FN_4O_4S$ (M + H^+): 481.13403, found 481.13293; IR (KBr) 3327, 2934, 1735, 1665, 1605, 1496, 1360, 1125, 750 cm^{-1}.

3ac. White powder; yield 94% (43.8 mg); mp = 210−210.3 °C; dr 90:10; ^{1}H NMR (400 MHz, DMSO): δ 11.59 (s, 1H), 8.12−8.09 (m, 1H), 7.34−7.29 (m, 1H), 7.14−7.11 (m, 4H), 6.73 (d, J = 6.4 Hz, 2H), 5.47 (s, 1H), 3.29 (s, 3H), 3.20 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.1, 174.3, 166.3, 165.5, 150.5, 140.6, 131.7, 129.1, 129.0, 128.9, 128.6, 128.4, 117.7, 117.5, 116.3, 116.0, 74.8, 74.2, 56.9, 30.0, 29.5, 27.6; HRMS (ESI) calculated for $C_{23}H_{19}FN_4O_4S$ (M + H^+): 467.11838, found 467.11758; IR (KBr) 3283, 2967, 1735, 1681, 1616, 1491, 1382, 1103, 755 cm^{-1}.

3ad. White powder; yield 83% (43.5 mg); mp = 213−214 °C; dr 96:4; ^{1}H NMR (400 MHz, DMSO): δ 11.75 (s, 1H), 8.28 (d, J = 7.2 Hz, 1H), 7.33−7.29 (m, 1H), 7.20−7.15 (m, 5H), 7.08−7.03 (m, 4H), 6.86 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 7.6 Hz, 2H), 5.40 (s, 1H), 5.02 (d, J = 16.0 Hz, 1H), 4.83 (d, J = 16.0 Hz, 1H), 3.27 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.7, 174.9, 166.6, 165.4, 150.4, 143.0, 135.5, 131.3, 131.2, 129.6, 129.0, 128.9, 128.8, 128.7, 127.9, 127.3, 126.0, 123.4, 110.4, 75.0, 74.7, 58.8, 55.3, 43.7, 29.9, 29.4; HRMS (ESI) calculated for $C_{29}H_{24}N_4O_4S$ (M + H^+): 525.15910, found 525.15826; IR (KBr) 3348, 3060, 1740, 1676, 1611, 1483, 1367, 1153, 742 cm^{-1}.

3dd. White powder; yield 82% (43.5 mg); mp = 201−201.9 °C; dr 98:2; ^{1}H NMR (400 MHz, DMSO): δ 11.79 (s, 1H), 8.31 (d, J = 7.6 Hz, 1H), 7.35−7.31 (m, 2H), 7.21−7.18 (m, 4H), 7.04−7.02 (m, 2H), 6.84−6.80 (m, 2H), 6.69 (d, J = 3.2 Hz, 1H), 5.73 (s, 1H), 5.00(d, J = 16.4 Hz, 1H), 4.83 (d, J = 16.4 Hz, 1H), 3.28 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.6, 174.8, 166.3, 165.0, 150.5, 143.3, 135.5, 132.0, 131.5, 129.9, 129.1, 128.9, 128.4, 127.8, 127.2, 126.8, 125.7, 123.3, 110.3, 75.4, 74.7, 55.3, 54.7, 43.6, 30.0, 29.4;

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HRMS (ESI) calculated for $C_{27}H_{22}N_4O_4S_2$ (M + H^+): 531.11552, found 531.11438; IR (KBr) 3321, 3076, 1735, 1670, 1611, 1496, 1371, 1103, 750 cm^{-1}.

3da. White powder; yield 97% (44.0 mg); mp = 205 °C; dr 98:2; ^{1}H NMR (400 MHz, DMSO): δ 11.58 (s, 1H), 8.32−8.30 (m, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 5.2 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.77 (t, J = 4.4 Hz, 1H), 6.64 (d, J = 3.2 Hz, 1H), 5.64 (s, 1H), 3.28 (s, 3H), 3.14 (s, 6H); ^{13}C NMR (100 MHz, DMSO): δ 195.2, 174.4, 166.3, 165.1, 150.4, 144.4, 132.4, 131.6, 129.3, 129.0, 128.1, 126.9, 125.4, 123.3, 109.7, 75.5, 74.4, 54.2, 31.1, 30.0, 29.4, 27.3; HRMS (ESI) calculated for $C_{21}H_{18}N_4O_4S_2$ (M + H^+): 455.08422, found 455.08365; IR (KBr) 3354, 3086, 1730, 1676, 1611, 1491, 1371, 1147, 739 cm^{-1}.

3ea. White powder; yield 99% (52.1 mg); mp = 196−196.4 °C; dr 97:3; ^{1}H NMR (400 MHz, DMSO): δ 11.57 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 7.46−7.42 (m, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.8 Hz, 2H), 5.43 (s, 1H), 3.27 (s, 3H), 3.18 (s, 3H), 3.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 194.7, 174.5, 166.2, 165.1, 150.6, 144.2, 131.8, 131.5, 131.4, 131.3, 128.5, 125.5, 123.4, 121.9, 109.9, 74.9, 74.1, 56.1, 30.0, 29.5, 27.4; HRMS (ESI) calculated for $C_{23}H_{19}BrN_4O_4S$ (M + H^+): 527.03831, found 527.03790; IR (KBr) 3354, 3174, 1725, 1681, 1611, 1485, 1377, 1103, 750 cm^{-1}.

3fa. White powder; yield 99% (47.3 mg); mp = 192−192.7 °C; dr 96:4; ^{1}H NMR (400 MHz, DMSO): δ 11.49 (s, 1H), 8.30 (d, J = 7.6 Hz, 1H), 7.44−7.40 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 5.21 (s, 1H), 3.60 (s, 3H), 3.24 (s, 3H), 3.12 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.7, 174.6, 166.8, 165.7, 159.5, 150.3, 144.1, 131.2, 130.8, 128.5, 125.9, 123.3, 122.9, 114.3, 109.8, 75.3, 74.7, 66.8, 58.6, 55.4, 29.8, 29.3, 27.3; HRMS (ESI) calculated for $C_{24}H_{22}N_4O_5S$ (M + H^+): 479.13837, found 479.13745; IR (KBr) 3179, 2972, 1705, 1703, 1611, 1513, 1371, 1093, 755 cm^{-1}.

3ga. White powder; yield 99% (47.7 mg); mp = 205 °C; dr 98:2; ^{1}H NMR (400 MHz, DMSO): δ 11.56 (s, 1H), 8.24 (d, J = 7.2 Hz, 1H), 7.46−7.42 (m, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 7.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 5.45 (s, 1H), 3.28 (s, 3H), 3.18 (s, 3H), 3.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 194.8, 174.5, 166.2, 165.1, 150.5, 144.2, 133.3, 131.4, 131.2, 130.8, 128.8, 128.5, 125.6, 123.4, 109.9, 75.0, 74.2, 56.2, 30.0, 29.5, 27.4; HRMS (ESI) calculated for $C_{23}H_{19}ClN_4O_4S$ (M + H^+): 483.08883, found 483.08813; IR (KBr) 3354, 2923, 1725, 1681, 1611, 1491, 1371, 1088, 750 cm^{-1}.

3ha. White powder; yield 98% (49.6 mg); mp = 199−199.6 °C; dr 98:2; ^{1}H NMR (400 MHz, DMSO): δ 11.49 (s, 1H), 8.29 (d, J = 7.2 Hz, 1H), 7.46−7.42 (m, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.58−6.56 (m, 1H), 6.31−6.30 (m, 2H), 5.19 (s, 1H), 4.08−4.07 (m, 4H), 3.25 (s, 3H), 3.14 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.4, 174.5, 166.7, 165.5, 150.4, 144.2, 143.8, 143.3, 131.3, 128.5, 125.9, 124.0, 123.3, 122.8, 118.0, 117.4, 109.9, 75.3, 74.5, 64.4, 64.3, 57.8, 29.9, 29.3, 27.4; HRMS (ESI) calculated for $C_{25}H_{22}N_4O_6S$ (M + H^+): 507.13328, found 507.13257; IR (KBr) 3288, 2929, 1730, 1670, 1605, 1507, 1377, 1125, 755 cm^{-1}.

3ia. White powder; yield 99% (51.1 mg); mp = 189 °C; dr 99:1; ^{1}H NMR (400 MHz, DMSO): δ 11.62 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.47−7.42 (m, 3H), 7.19−7.11 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 5.65 (s, 1H), 3.30 (s, 3H), 3.21 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 194.1, 174.4, 165.9, 164.8, 150.7, 144.3, 137.1, 131.5, 129.9, 128.5, 125.6, 125.6, 125.4, 123.5, 110.0, 74.9, 73.8, 55.1, 30.1, 29.5, 27.5; HRMS (ESI) calculated for $C_{24}H_{19}F_3N_4O_4S$ (M + H^+): 517.11519, found 517.11414; IR (KBr) 3179, 2956, 1733, 1698, 1611, 1469, 1327, 1118, 752 cm^{-1}.

3ja. White powder; yield 99% (46.1 mg); mp = 209−209.7 °C; dr 96:4; ^{1}H NMR (400 MHz, DMSO): δ 11.55 (s, 1H), 8.26 (d, J = 7.6 Hz, 1H), 7.46−7.41 (m, 1H), 7.22−7.18 (m, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.94−6.84 (m, 4H), 5.40 (s, 1H), 3.27 (s, 3H), 3.16 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.1, 174.5, 166.4, 165.3, 150.5, 144.2, 131.6, 131.5, 131.4, 128.5, 127.9, 127.8, 125.7, 123.4, 115.9, 115.6, 109.9, 75.1, 74.4, 56.7, 30.0, 29.4, 27.4; HRMS (ESI) calculated for $C_{23}H_{19}FN_4O_4S$ (M + H^+): 467.11838, found 467.11728; IR (KBr) 3305, 2967, 1730, 1681, 1605, 1474, 1371, 1229, 750 cm^{-1}.

3ka. White powder; yield 89% (46.8 mg); mp = 203 °C; dr = 91:9; ^{1}H NMR (400 MHz, DMSO): δ 11.51 (s, 1H), 8.28 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.12−7.08 (m, 1H), 7.02 (d, J = 4.4 Hz, 2H), 6.95 (d, J = 7.6 Hz, 1H), 5.70 (s, 1H), 3.19 (s, 3H), 3.05 (s, 3H), 2.95 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 196.8, 174.0, 166.7, 166.6, 149.9, 144.0, 133.8, 131.5, 131.5, 131.2, 129.4, 128.4, 127.5, 126.6, 125.3, 123.2, 109.9, 109.7, 75.1, 74.3, 58.6, 29.8, 29.1, 27.3; HRMS (ESI) calculated for $C_{23}H_{19}BrN_4O_4S$ (M + H^+): 527.03831, found 527.03748; IR (KBr) 3261, 2939, 1735, 1681, 1611, 1469, 1377, 1098, 760 cm^{-1}.

3la. White powder; yield 93% (50.0 mg); mp = 206−206.5 °C; dr 97:3; ^{1}H NMR (400 MHz, DMSO): δ 11.51 (s, 1H), 8.34 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.07 (s, 2H), 5.14 (s, 1H), 3.52 (s, 3H), 3.44 (s, 6H), 3.29 (s, 3H), 3.15 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.7, 174.6, 166.9, 165.7, 152.8, 150.3, 144.2, 137.7, 131.3, 128.5, 126.7, 126.2, 123.2, 110.0, 106.7, 75.3, 74.5, 60.4, 59.1, 56.5, 56.1, 29.9, 29.3, 27.4, 19.0; HRMS (ESI) calculated for $C_{26}H_{26}N_4O_7S$ (M + H^+): 539.15950, found 539.15863; IR (KBr) 3337, 2956, 1735, 1681, 1583, 1463, 1377, 1125, 755 cm^{-1}.

3ma. White powder; yield 94% (45.3 mg); mp = 192−193 °C; dr 97:3; ^{1}H NMR (400 MHz, DMSO): δ 11.59 (s, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.24−7.19 (m, 2H), 7.15−7.07 (m, 2H), 6.85−6.80 (m, 2H), 5.44 (s, 1H), 3.27 (s, 3H), 3.17 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 194.7, 174.5, 166.1, 165.0, 150.5, 144.2, 134.1, 133.3, 131.5, 130.7, 129.2, 128.6, 128.5, 125.6, 123.4, 110.0, 75.0, 74.1, 56.1, 30.1, 29.4, 27.4; HRMS (ESI) calculated for $C_{23}H_{19}ClN_4O_4S$ (M + H^+): 483.08883, found 483.08774; IR (KBr) 3299, 2961, 1741, 1676, 1611, 1469, 1371, 1109, 745 cm^{-1}.

3na. White powder; yield 86% (42.4 mg); mp = 167 °C; dr 97:3; ^{1}H NMR (400 MHz, DMSO): δ 11.66 (s, 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.47−7.34 (m, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 5.66 (s, 1H), 3.29 (s, 3H), 3.19 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 194.4, 174.5, 165.8, 164.8, 150.7, 147.7, 144.2, 136.7, 134.0, 131.6, 130.3, 128.5, 125.3, 124.2, 123.5, 123.3, 110.0, 75.0, 74.0, 55.1, 30.2, 29.5, 27.4; HRMS (ESI) calculated for $C_{23}H_{19}N_5O_6S$ (M + H^+): 494.11288, found 494.11188; IR (KBr) 3218, 2956, 1710, 1681, 1611, 1529, 1349, 1103, 750 cm^{-1}.

3oa. White powder; yield 83% (42.2 mg); mp = 206−207 °C; dr 98:2; ^{1}H NMR (400 MHz, DMSO): δ 11.51 (s, 1H), 8.35 (d, J = 7.6 Hz, 1H), 7.46−7.42 (m, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.42−6.40 (m, 1H), 6.34 (s, 1H), 5.15 (s, 1H), 3.61 (s, 3H), 3.33 (s, 3H), 3.25 (s, 3H), 3.12 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 196.0, 174.7, 166.9, 165.8, 150.3, 149.1, 148.4, 144.2, 131.3, 128.5, 126.2, 123.2, 123.0, 122.6, 112.3, 111.7, 109.9, 75.3, 74.7, 59.2, 55.7, 55.4, 29.8, 29.3, 27.3; HRMS (ESI) calculated for $C_{25}H_{24}N_4O_6S$ (M + H^+): 509.14893, found 509.14767; IR (KBr) 3342, 2956, 1735, 1677, 1611, 1485, 1371, 1147, 755 cm^{-1}.

3pa. White powder; yield 99% (48.8 mg); mp = 198 °C; dr 94:6; ^{1}H NMR (400 MHz, DMSO): δ 11.66 (s, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.18−7.13 (m, 2H), 7.01 (d, J = 8.4 Hz, 2H), 5.71 (s, 1H), 3.31 (s, 3H), 3.23 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 193.8, 174.3, 165.7, 164.7, 150.7, 147.1, 144.3, 140.0, 131.6, 130.2, 128.4, 125.2, 123.7, 123.6, 110.1, 74.9, 73.7, 54.7, 30.2, 29.6, 27.5; HRMS (ESI) calculated for $C_{23}H_{19}N_5O_6S$ (M + H^+): 494.11288, found 494.11169; IR (KBr) 3152, 2961, 1707, 1681, 1611, 1529, 1349, 1120, 750 cm^{-1}.

Typical Procedure for the Synthesis of Compound 4. DDQ (0.1 mmol) was added to the solution of dispirobarbiturate **3aa** (0.1 mmol) in CH_2Cl_2 (1.0 mL). The reaction was stirred at 0 °C for 2 h. The reaction was quenched with 2.0 mL of saturated aqueous $NaHSO_3$ solution, followed by diluting with 2.0 mL of CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were washed with brine (3 × 10 mL) and dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulted residue was

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purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) to afford **4** as a white powder; yield 60% (53.6 mg); mp = 220 °C; ^{1}H NMR (400 MHz, DMSO): δ 8.27−7.94 (m, 1H), 7.43−7.34 (m, 1H), 7.21−7.11 (m, 4H), 6.96−6.75 (m, 3H), 5.38−4.48 (m, 1H), 3.27−2.84 (m, 9H); ^{13}C NMR (100 MHz, DMSO): δ 174.5, 174.3, 174.2, 169.1, 168.8, 167.9, 167.5, 166.4, 165.9, 150.3, 144.0, 130.9, 130.4, 130.4, 130.2, 129.8, 128.9, 128.6, 126.2, 126.1, 123.0, 109.7, 85.7, 85.5, 75.0, 74.3, 74.3, 67.3, 67.2, 29.9, 29.4, 29.3, 29.2, 29.0, 28.9, 27.4; HRMS (ESI) calculated for $C_{46}H_{38}N_8O_8S_2$ ($M + H^+$): 895.23268, found 895.23175; IR (KBr) 2961, 1730, 1682, 1599, 1447, 1371, 1093, 750 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01810.

Crystallographic data for **3fa** (CIF)

Crystallographic data for **4** (CIF)

Copies of NMR for dispirobarbiturates **3** and **4**; X-ray single-crystal structure analysis data for **3fa** and **4** (PDF)

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1416436 contains the supplementary crystallographic data for compound **4**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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