Communication

New Methodology for the Synthesis of Thiobarbiturates Mediated by Manganese(III) Acetate

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Abstract: A three step synthesis of various thiobarbiturate derivatives **17–24** was established. The first step is mediated by $Mn(OAc)_3$, in order to generate a carbon-carbon bond between a terminal alkene and malonate. Derivatives **1–8** were obtained in moderate to good yields under mild conditions. This key step allows synthesis of a wide variety of lipophilic thiobarbiturates, which could be tested for their anticonvulsive or anesthesic potential.

Keywords: manganese(III) acetate; barbiturates; radical

1. Introduction

Manganese(III) acetate has been extensively explored during the past decades, and it remains an useful tool for carbon-carbon bond formation [1,2]. Its specificity to carbonyl derivatives allows a wide variety of radical synthetic applications, as studied on acetoacetate [3], β-ketoesters [4], β-ketonitriles [5,6] and β-ketosulfones [7–9]. Malonate derivatives, key-step substrates for barbiturates synthesis [10,11], are also useful substrates for manganese(III) acetate-mediated reactions [12,13]. In continuation of our research program centered on the design and synthesis of original molecules with pharmacological properties [14–18], we propose herein a manganese(III) acetate-mediated multistep synthesis of new original barbiturates.

Barbiturate derivatives are a well-known pharmacological class with anticonvulsive, sedative and anesthetic properties [19]. Original barbiturates were also recently reported as matrix metalloproteinase inhibitors with potent pharmacological applications against focal cerebral ischemia after acute stroke [20] and cancer cells invasiveness inhibitors [21]. Barbiturate derivatives also show antitubercular [22], PPAR-γ agonist [23–25] and protein kinase C inhibitor [26] activities.

The lipophilicity of barbiturates is an important parameter which enhances anesthetic onset [27]. It can be improved by replacing oxygen by a sulfur [28], as seen with the very short acting barbiturate thiopenthal. Substituents on the carbons of the barbituric acid scaffold also have a great influence on the pharmacological activity [27,29]. Our methodology allows synthesis of a wide variety of substituted barbiturates, which could be tested for their anticonvulsive or anesthetic potentialities.

2. Results and Discussion

Starting from malonate barbiturate precursors, reproducible methodology for synthesis of various and highly functionalized derivatives was established. As reported in previously described mechanisms [30], $Mn(OAc)_3$ and malonates in acetic acid form a Mn^{3+}-enolate complex. Mn^{3+} is reduced in Mn^{2+}, generating a carbon centered radical between carbonyl groups. This radical reacts with terminal alkene, generating a carbon-carbon bond.

Depending on the malonate substituent, several reactions may occur and in order to investigate a larger variety of barbiturate synthesis possibilities, we have studied three of them. Results are reported in Scheme 1.

Scheme 1. $Mn(OAc)_3$ reactivity towards various malonate derivatives.
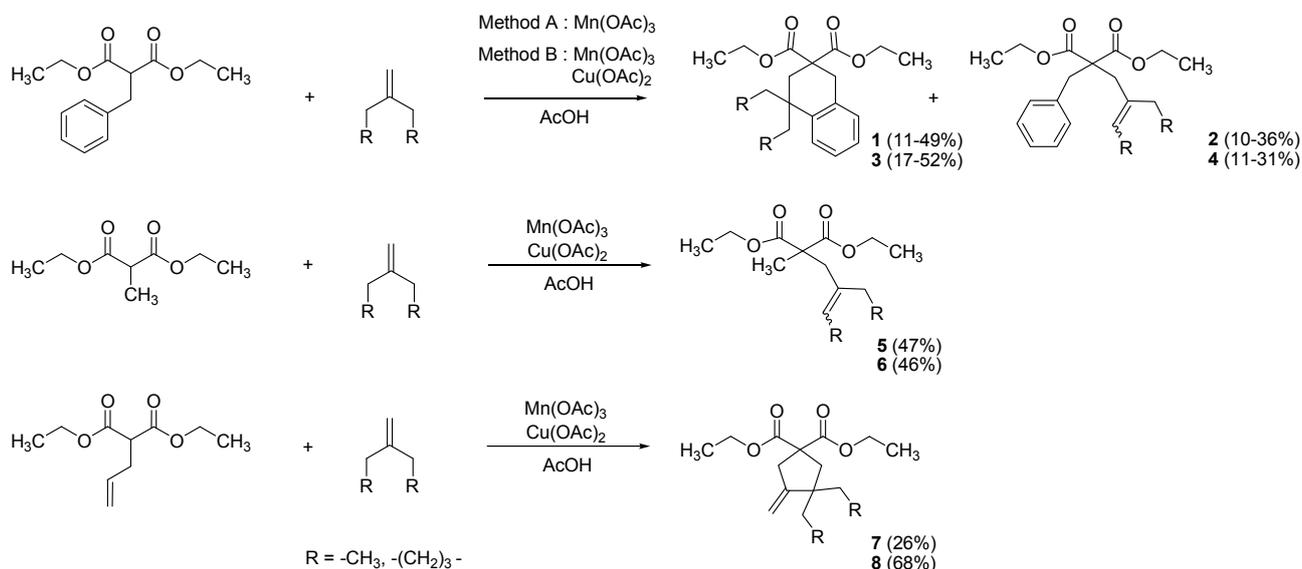
As reported by Citterio and coworkers [31–33], benzylmalonate allowed synthesis of two derivatives: Tetralines **1**,**3** from radical aromatic substitution, and elimination products **2**,**4**. We have previously reported different methods for optimizing yields of these two products [34]. For conditions favoring spirocyclic tetralin **1**,**3** formation, we divided up the $Mn(OAc)_3$ to ensure moderate oxidizing conditions (*method A*). Tetralins **1**,**3** were obtained as the major compound (49–52%) and alkenes **2**,**4** were observed as secondary products (10–11%). Stronger oxidative conditions [$Cu(OAc)_2$ + $Mn(OAc)_3$,

method B] afforded an increase in elimination products **2,4** (31–36%), while these conditions drastically decreased yields of tetralines **1,3** (11–17%).

With methyl malonate, only elimination products **5–6** were obtained with moderate yields (46–47%). With allyl malonate, cyclization generates a cyclopentane ring [35], and annulation products **7–8** were synthesized (26–68%). These three different reactivities depend on the malonate substituents, and allow access to a wide variety of substituted substrates for barbiturate synthesis.

C-Functionalized malonates **1–8** thus obtained reacted with thiourea [36], forming thiobarbituric scaffolds **9–16** in moderate to good yields (46–90%). Results are summarized in Scheme 2 and Table 1.

Scheme 2. Thiobarbituric acid synthesis from malonates **1–8**.
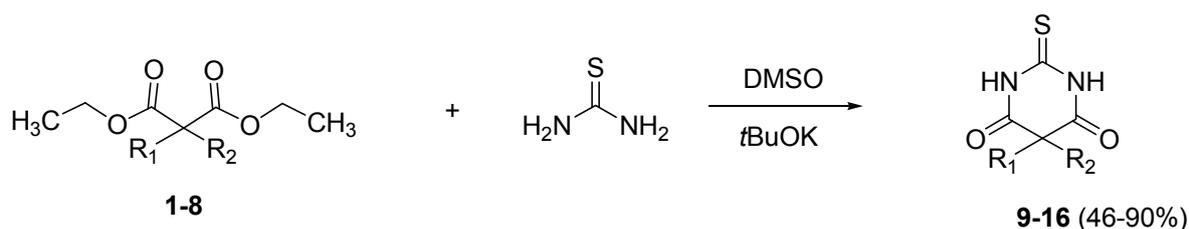
Table 1. Thiobarbituric acids **9–16** synthesis from malonates **1–8**.

Entry	R$_1$,R$_2$ (malonate)	Product	Yields
1	**1**	**9**	53%
2	**2a / 2b**	**10a / 10b**	46%
3	**3**	**11**	64%
4	**4**	**12**	88%
5	**5a / 5b**	**13a /13b**	75%

Table 1. *Cont.*

Entry	R1,R2 (malonate)	Product	Yields
6			90%
7			70%
8			54%
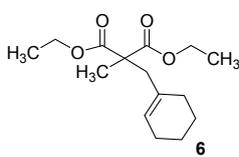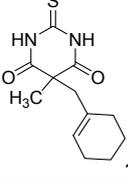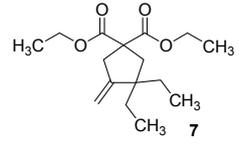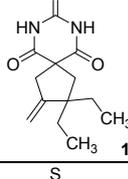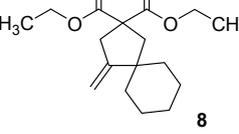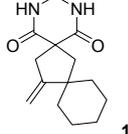
Finally, in order to synthesize intravenous administrable thiobarbiturates, each thiobarbituric acid was turned into the corresponding salt with potassium hydroxide in isopropanol [37], as reported in Scheme 3.

Scheme 3. Thiobarbituric acid to thiobarbiturate salt formation.
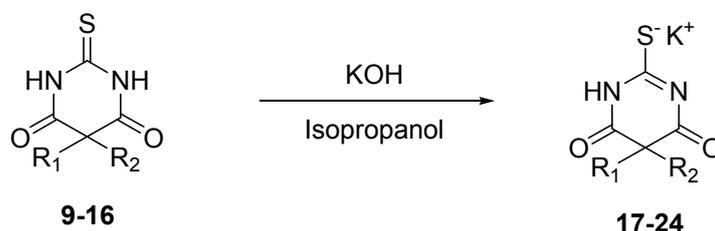
3. Experimental

3.1. General

Microwave-assisted reactions were performed in a multimode microwave oven (ETHOS Synth Lab Station, Ethos start, Milestone Inc., Shelton, CT, USA). Melting points were determined with a B-540 Büchi melting point apparatus. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on a Bruker ARX 200 spectrometer in CDCl$_3$ or D$_2$O at the Service interuniversitaire de RMN de la Faculté de Pharmacie de Marseille. The ^{1}H-NMR chemical shifts are reported as parts per million downfield from tetramethylsilane (Me$_4$Si), and the ^{13}C-NMR chemical shifts were referenced to the solvent peaks: CDCl$_3$ (76.9 ppm) or DMSO-d_6 (39.6 ppm). Absorptions are reported with the following notations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets. Elemental analysis and mass spectra which were run on an API-QqToF mass spectrometer were carried out at the Spectropole de la Faculté des Sciences Saint-Jérôme site. Silica gel 60 (Merck, particle size 0.040–0.063 nm, 70–230 mesh ASTM) was used

for flash column chromatography. TLC were performed on 5 cm × 10 cm aluminium plates coated with silica gel 60 F-254 (Merck, Gernsteim, Germany) in an appropriate solvent.

3.2. General Procedure for the Synthesis of Substituted Malonates 1–8

Method A: A solution of manganese(III) acetate dihydrate (1.68 mmol, 0.45 g) in glacial acetic acid (55 mL) was heated under microwave irradiation (200 W, 80 °C) for 15 min, until dissolution. Then, the reaction mixture was cooled down to 60 °C, and a solution of malonate (3.99 mmol, 1 equiv.) and alkene (11.97 mmol, 3 equiv.) in glacial acetic acid (5 mL) was added. The mixture was heated under microwave irradiation (200 W, 80 °C) for 20 min. Then, the reaction mixture was cooled down to 60 °C once more, and a second portion of manganese(III) acetate dihydrate (1.68 mmol, 0.45 g) was added. The mixture was heated under microwave irradiation (200 W, 80 °C) for 20 min. The addition of manganese(III) acetate dihydrate (1.68 mmol, 0.45 g) was repeated three times under the same conditions every 20 min. successively. The reaction mixture was poured into cold water (100 mL), and extracted with chloroform (3 × 70 mL). The organic extracts were collected, washed with saturated aqueous NaHCO$_3$ (3 × 50 mL) and brine (3 × 50 mL), dried over MgSO$_4$, filtrated, and concentrated under vacuum. The crude product was purified by silica gel chromatography with ethyl acetate/petroleum ether (0.5/9.5) to give corresponding compounds **1–4**.

Method B: A solution of manganese(III) acetate dihydrate (8.38 mmol, 2.24 g, 2.1 equiv.) and copper(II) acetate monohydrate (3.99 mmol, 0.80 g, 1 equiv.) in glacial acetic acid (55 mL) was heated under microwave irradiation (200 W, 80 °C) for 15 min, until dissolution. Then, the reaction mixture was cooled down to 60 °C, and a solution of malonate (3.99 mmol, 1 equiv.) and alkene (7.98 mmol, 3 equiv.) in glacial acetic acid (5 mL) was added. The mixture was heated under microwave irradiation (200 W, 80 °C) for 60 min. The reaction mixture was poured into cold water (100 mL), and extracted with chloroform (3 × 70 mL). The organic extracts were collected, washed with saturated aqueous NaHCO$_3$ (3 × 50 mL) and brine (3 × 50 mL), dried over MgSO$_4$, filtrated, and concentrated under vacuum. The crude product was purified by silica gel chromatography with ethyl acetate/petroleum ether (0.5/9.5) to give corresponding compounds **1–8**.

Diethyl 4,4-diethyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (**1**). Colorless oil; yields: 49% (*method A*), 11% (*method B*); ^{1}H-NMR (CDCl$_3$) δ_H 0.77 (t, *J* = 7.3, 6H, 2CH$_3$), 1.22 (t, *J* = 7.2, 6H, 2CH$_3$), 1.52–1.68 (m, 4H, 2CH$_2$), 2.32 (s, 2H, CH$_2$), 3.17 (s, 2H, CH$_2$), 4.08–4.21 (m, 4H, 2CH$_2$), 7.10–7.18 (m, 4H, 4CH). ^{13}C-NMR (CDCl$_3$) δ_C 8.3 (2CH$_3$), 13.8 (2CH$_3$), 33.1 (CH$_2$), 33.3 (2CH$_2$), 35.4 (CH$_2$), 40.2 (C), 52.5 (C), 61.2 (2CH$_2$), 125.5 (CH), 126.2 (CH), 126.5 (CH), 128.6 (CH), 134.2 (C), 141.5 (C), 172.9 (2C). HMRS (ESI): *m/z* calcd for C$_{20}$H$_{28}$O$_4$ [M+H$^+$]: 333.2060. Found: 333.2061.

Diethyl 2-benzyl-2-(2-ethylbut-2-enyl)malonate (**2a/2b**) (50:50 inseparable mixture of *Z/E* isomers). Colorless oil; yields: 10% (*method A*), 36% (*method B*); ^{1}H-NMR (CDCl$_3$) δ_H 0.89–0.99 (m, 3H, CH$_3$), 1.12–1.22 (m, 6H, 2CH$_3$), 1.54–1.64 (m, 3H, CH$_3$), 1.93–2.04 (m, 2H, CH$_2$), 2.63 and 2.80 (s, 2H, CH$_2$), 3.24 and 3.26 (s, 2H, CH$_2$), 4.03–4.15 (m, 4H, 2CH$_2$), 5.26–5.42 (m, 1H, CH), 7.11–7.36 (m, 5H, 5CH). ^{13}C-NMR (CDCl$_3$) δ_C 12.7 (CH$_3$), 12.8 and 13.2 (CH$_3$), 13.8 and 13.9 (2CH$_3$), 23.3 and 29.6 (CH$_2$), 33.5 and 40.6 (CH$_2$), 39.1 and 39.2 (CH$_2$), 58.9 and 59.0 (C), 61.1 (2CH$_2$), 122.2 and

123.0 (CH), 126.7 (CH), 128.0 (2CH), 130.1 (2CH), 130.2 (C), 136.8 and 137.3 (C), 171.5 and 171.6 (2C). HMRS (ESI): *m/z* calcd for $C_{20}H_{28}O_4$ [M+H$^+$]: 333.2060. Found: 333.2063.

Diethyl 2'H-spiro[cyclohexane-1,1'-naphtalene]-3',3'(4'H)-dicarboxylate (**3**). [34] Colorless oil; yields: 52% (*method A*), 17% (*method B*); ^{1}H-NMR (CDCl$_3$) δ_H 1.22 (t, *J* = 7.1, 6H, 2CH$_3$), 1.47–1.80 (m, 10H, 5CH$_2$), 2.46 (s, 2H, CH$_2$), 3.19 (s, 2H, CH$_2$), 4.14 (q, *J* = 7.1, 2H, CH$_2$), 4.15 (q, *J* = 7.1, 2H, CH$_2$), 7.10–7.23 (m, 3H, 3CH), 7.35–7.39 (m, 1H, 1CH). ^{13}C-NMR (CDCl$_3$) δ_C 13.9 (2CH$_3$), 21.9 (2CH$_2$), 25.9 (CH$_2$), 34.9 (CH$_2$), 35.6 (CH$_2$), 36.8 (C), 39.6 (2CH$_2$), 52.4 (C), 61.26 (2CH$_2$), 125.8 (CH), 126.1 (CH), 126.5 (CH), 128.7 (CH), 133.4 (C), 144.0 (C), 171.8 (2C). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.40; H, 8.50.

Diethyl 2-benzyl-2-(cyclohexenylmethyl)malonate (**4**). [34] Colorless oil; yields: 11% (*method A*), 31% (*method B*); ^{1}H-NMR (CDCl$_3$) δ_H 1.20 (t, *J* = 7.1, 6H, 2CH$_3$), 1.55–1.59 (m, 4H, 2CH$_2$), 1.90–2.00 (m, 4H, 2CH$_2$), 2.58 (s, 2H, CH$_2$), 3.26 (s, 2H, CH$_2$), 4.12 (q, *J* = 7.1, 4H, 2CH$_2$), 5.52 (s, 1H, 1CH), 7.11–7.24 (m, 5H, 5CH). ^{13}C-NMR (CDCl$_3$) δ_C 13.9 (2CH$_3$), 22.1 (CH$_2$), 23.0 (CH$_2$), 25.5 (CH$_2$), 29.2 (CH$_2$), 39.0 (CH$_2$), 41.4 (CH$_2$), 58.7 (C), 61.0 (2CH$_2$), 126.4 (CH), 126.7 (CH), 128.0 (2CH), 130.1 (2CH), 133.1 (C), 136.7 (C), 171.4 (2C). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.95; H, 8.35.

Diethyl 2-(2-ethylbut-2-enyl)-2-methylmalonate (**5a/5b**) (50:50 inseparable mixture of *Z/E* isomers). Colorless oil; yields: 47% (*method B*); ^{1}H-NMR (CDCl$_3$) δ_H 0.81–0.93 (m, 3H, CH$_3$), 1.14–1.21 (m, 6H, 2CH$_3$), 1.27 (s, 3H, CH$_3$), 1.48–1.53 (m, 3H, CH$_3$), 1.65–1.96 (m, 2H, CH$_2$), 2.57 and 2.71 (s, 2H, CH$_2$), 4.04–4.15 (m; 4H, 2CH$_2$), 5.13 and 5.34 (m, 1H, 1CH). ^{13}C-NMR (CDCl$_3$) δ_C 12.4 (CH$_3$), 12.6 and 12.9 (CH$_3$), 13.7 and 13.8 (CH$_3$), 19.2 and 19.7 (CH$_3$), 22.9 and 29.7 (CH$_2$), 33.6 and 40.8 (CH$_2$), 53.2 and 53.4 (C), 60.9 and 61.0 (2CH$_2$), 122.4 and 123.4 (CH), 136.6 and 136.8 (C), 172.3 and 172.5 (2C). HMRS (ESI): *m/z* calcd for $C_{14}H_{24}O_4$ [M+H$^+$]: 257.1747. Found: 257.1743.

Diethyl 2-(cyclohexenylmethyl)-2-methylmalonate (**6**). Colorless oil; yields: 46% (*method B*); ^{1}H-NMR (CDCl$_3$) δ_H 1.23 (t, *J* = 7.1 Hz, 6H, 2CH$_3$), 1.34 (s, 3H, CH$_3$), 1.44–1.58 (m, 4H, 2CH$_2$), 1.73–2.03 (m, 4H, 2CH$_2$), 2.58 (s, 2H, CH$_2$), 4.15 (q, *J* = 7.1, 2CH$_2$), 5.43 (s, 1H, 1CH). ^{13}C-NMR (CDCl$_3$) δ_C 14.0 (2CH$_3$), 19.9 (CH$_3$), 22.0 (CH$_2$), 22.9 (CH$_2$), 25.4 (CH$_2$), 29.2 (CH$_2$), 43.7 (CH$_2$), 53.3 (C), 61.1 (2CH$_2$), 126.6 (CH), 132.9 (C), 172.6 (2C). HMRS (ESI): *m/z* calcd for $C_{15}H_{24}O_4$ [M+H$^+$]: 269.1747. Found: 269.1754.

Diethyl 3,3-diethyl-4-methylenecyclopentane-1,1-dicarboxylate (**7**). Colorless oil; yields: 26% (*method B*); ^{1}H-NMR (CDCl$_3$) δ_H 0.79 (t, *J* = 7.3, 6H, 2CH$_3$), 1.24 (t, *J* = 7.1, 6H, 2CH$_3$), 1.33–1.41 (m, 4H, 2CH$_2$), 2.29 (s, 2H, CH$_2$), 2.98–3.00 (m, 2H, CH$_2$), 4.17 (q, *J* = 7.1, 4H, 2CH$_2$), 4.65 (bs, 1H, CH), 4.95 (bs, 1H, CH). ^{13}C-NMR (CDCl$_3$) δ_C 8.6 (2CH$_3$), 14.0 (2CH$_3$), 29.9 (2CH$_2$), 41.8 (CH$_2$), 43.3 (CH$_2$), 48.5 (C), 57.3 (C), 61.4 (2CH$_2$), 106.0 (CH$_2$), 154.8 (C), 172.3 (2C). HMRS (ESI): *m/z* calcd for $C_{16}H_{26}O_4$ [M+H$^+$]: 283.1904. Found: 283.1906.

Diethyl 4-methylenespiro[4.5]decane-2,2-dicarboxylate (**8**). Colorless oil; yields: 68% (*method B*); ^{1}H-NMR (CDCl$_3$) δ_H 1.22 (t, *J* = 7.2, 6H, 2CH$_3$), 1.33–1.66 (m, 10H, 5CH$_2$), 2.33 (s, 2H, CH$_2$), 3.01

(bs, 2H, CH$_2$), 4.15 (q, J = 7.1, 4H, 2CH$_2$), 4.77 (bs, 1H, CH), 4.87 (bs, 1H, CH). ^{13}C-NMR (CDCl$_3$) δ_C 13.9 (2CH$_3$), 23.2 (2CH$_2$), 25.8 (CH$_2$), 38.0 (2CH$_2$), 40.8 (CH$_2$), 42.6 (CH$_2$), 45.6 (C), 57.9 (C), 61.4 (2CH$_2$), 104.6 (CH$_2$), 158.4 (C), 172.1 (2C). HMRS (ESI): *m/z* calcd for C$_{17}$H$_{26}$O$_4$ [M+H$^+$]: 295.1904. Found: 295.1903.

3.3. General Procedure for the Synthesis of Thiobarbituric Acids **9–16**

Thiourea (1.25 g, 16.38 mmol, 6 equiv.) was added to a solution of malonate **1–8** (2.73 mmol, 1 equiv.) in dry DMSO (3 mL). Then, a solution 1M of potassium *tert*-butoxide (0.67 g, 6.0 mmol, 2.2 equiv.) was added dropwise. The solution was stirred for 4 h under inert atmosphere and at rt (starting from malonates **1**, **3**, **7**, **8**) or at 50 °C (starting from malonates **2**, **4**, **5**, **6**). The solution was diluted with ethyl acetate (15 mL) and washed with a solution of 1 N hydrochloric acid. The layers were separated and the aqueous phase was extracted with ethyl acetate. The collected organic phase was washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and the solvent was removed *in vacuo*. The residue was purified with column chromatography (CH$_2$Cl$_2$/petroleum ether, 8:2), affording the corresponding thiobarbituric acids **9–16**.

4,4-Diethyl-2'-thioxo-3,4-dihydro-1H,2'H-spiro[naphthalene-2,5'-pyrimidine]-4',6'(1'H,3'H)-dione (**9**). White solid; m.p. 151 °C (cyclohexane); yields: 53% ^{1}H-NMR (CDCl$_3$) δ_H 0.76 (t, J = 7.4, 6H, 2CH$_3$), 1.67–1.80 (m, 4H, 2CH$_2$), 2.23 (s, 2H, CH$_2$), 3.28 (s, 2H, CH$_2$), 7.12–7.36 (m, 4H, 4CH), 8.99 (bs, 2H). ^{13}C-NMR (CDCl$_3$) δ_C 8.4 (2CH$_3$), 31.5 (2CH$_2$), 34.3 (CH$_2$), 38.2 (CH$_2$), 52.2 (C), 53.4 (C), 126.0 (CH), 126.2 (CH), 126.8 (CH), 128.5 (CH), 132.4 (C), 140.9 (C), 170.4 (2C), 176.0 (C). HMRS (ESI): *m/z* calcd for C$_{17}$H$_{20}$N$_2$O$_2$S [M+H$^+$]: 317.1318. Found: 317.1317.

5-Benzyl-5-(2-ethylbut-2-enyl)-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione (**10a/10b**) (50:50 inseparable mixture of *Z/E* isomers). White solid; m.p. 182 °C (cyclohexane); yields: 46% ^{1}H-NMR (CDCl$_3$) δ_H 0.90–0.99 (m, 3H, CH$_3$), 1.53–1.66 (m, 3H, CH$_3$), 1.85–2.02 (m, 2H, CH$_2$), 2.87 and 3.00 (s, 2H, CH$_2$), 3.30 and 3.38 (s, 2H, CH$_2$), 5.19–5.30 and 5.41–5.52 (m, 1H, CH), 7.07–7.24 (m, 5H, 5CH), 8.84 (bs, 2H). ^{13}C-NMR (CDCl$_3$) δ_C 12.6 and 13.0 (CH$_3$), 13.4 and 13.7 (CH$_3$), 23.4 and 29.9 (CH$_2$), 39.1 and 44.9 (CH$_2$), 45.0 and 45.2 (CH$_2$), 58.0 and 59.0 (C), 124.6 and 124.8 (CH), 127.9 (CH), 128.9 (2CH), 129.5 and 129.6 (2CH), 134.2 and 134.3 (C), 134.7 and 135.7 (C), 169.6 (2C), 175.3 (C). *m/z* calcd for C$_{17}$H$_{20}$N$_2$O$_2$S [M+H$^+$]: 317.1318. Found: 317.1323.

2"-Thioxo-2"H,4'H-dispiro[cyclohexane-1,1'-naphtalene-3',5"-pyrimidine]-4",6"(1"H,3"H)-dione (**11**). White solid; m.p. 200–202 °C (ethyl alcohol); yields: 64% ^{1}H-NMR (CDCl$_3$) δ_H 1.49–1.84 (m, 10H, 5CH$_2$), 2.35 (s, 2H, CH$_2$), 3.31 (s, 2H, CH$_2$), 7.12–7.41 (m, 4H, 4CH), 9.33 (bs, 2H, 2NH). ^{13}C-NMR (CDCl$_3$) δ_C 22.0 (2CH$_2$), 25.7 (CH$_2$), 33.6 (CH$_2$), 37.8 (C), 38.1 (2CH$_2$), 38.3 (CH$_2$), 52.2 (C), 125.1 (CH), 126.1 (CH), 127.2 (CH), 128.5 (CH), 132.1 (C), 143.8 (C), 170.2 (2C), 176.0 (C). HMRS (ESI): *m/z* calcd for C$_{18}$H$_{20}$N$_2$O$_2$S [M+H$^+$]: 329.1318. Found: 329.1317.

5-Benzyl-5-(cyclohexenylmethyl)-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione (**12**). Colorless oil; yields: 88% ^{1}H-NMR (CDCl$_3$) δ_H 1.35–2.04 (m, 8H, 4CH$_2$), 2.82 (s, 2H, CH$_2$), 3.31 (s, 2H, CH$_2$), 5.50 (s, 1H, 1CH), 7.13–7.26 (m, 5H, 5CH), 8.98 (bs, 2H, 2NH). ^{13}C-NMR (CDCl$_3$) δ_C 21.9 (CH$_2$), 22.8

(CH$_2$), 23.6 (CH$_2$), 29.8 (CH$_2$), 44.5 (CH$_2$), 47.6 (CH$_2$), 58.9 (C), 127.7 (CH), 127.8 (CH), 128.8 (2CH), 129.5 (2CH), 131.5 (C), 134.3 (C), 169.7 (2C), 175.4 (C). HMRS (ESI): *m/z* calcd for C$_{18}$H$_{20}$N$_2$O$_2$S [M+NH$_4^+$]: 346.1584. Found: 346.1579.

5-(2-Ethylbut-2-enyl)-5-methyl-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione (**13a/13b**) (50:50 inseparable mixture of *Z/E* isomers). Colorless oil; yields: 75% ^{1}H-NMR (CDCl$_3$) δ_H 0.87–0.97 (m, 3H, CH$_3$), 1.54–1.61 (m, 3H, CH$_3$), 1.57 (s, 3H, CH$_3$), 1.80–2.01 (m, 2H, CH$_2$), 2.70 and 2.82 (s, 2H, CH$_2$), 5.18 and 5.47 (m, 1H, CH), 9.05 (bs, 2H, 2NH). ^{13}C-NMR (CDCl$_3$) δ_C 12.6 and 13.0 (CH$_3$), 13.3 and 13.9 (CH$_3$), 23.1 and 23.3 (CH$_3$), 23.5 and 29.9 (CH$_2$), 40.4 and 46.2 (CH$_2$), 51.0 and 51.9 (C), 124.5 and 125.0 (CH), 134.8 and 135.9 (C), 170.5 and 170.6 (2C), 176.0 (C). Anal. Calcd for C$_{11}$H$_{16}$N$_2$O$_2$S: C, 54.98; H, 6.71; N, 11.66. Found: C, 55.15; H, 6.86; N, 11.63.

5-(Cyclohexenylmethyl)-5-methyl-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione (**14**). White solid; m.p. 160–164 °C (ethyl alcohol); yields: 90% ^{1}H-NMR (CDCl$_3$) δ_H 1.37–1.52 (m, 4H, 2CH$_2$), 1.57 (s, 3H, CH$_3$), 1.76–1.98 (m, 4H, 2CH$_2$), 2.65 (s, 2H, CH$_2$), 5.44 (s, 1H, 1CH), 9.61 (bs, 2H, 2NH). ^{13}C-NMR (CDCl$_3$) δ_C 21.8 (CH$_2$), 22.8 (CH$_2$), 23.0 (CH$_3$), 25.4 (CH$_2$), 29.7 (CH$_2$), 48.5 (CH$_2$), 51.8 (C), 127.5 (CH), 131.6 (C), 170.9 (2C), 176.2 (C). HMRS (ESI): *m/z* calcd for C$_{12}$H$_{16}$N$_2$O$_2$S [M+H$^+$]: 253.1005. Found: 253.1007.

2,2-Diethyl-3-methylene-8-thioxo-7,9-diazaspiro[4.5]decane-6,10-dione (**15**). White solid; m.p. 194–196 °C (cyclohexane); yields: 70% ^{1}H-NMR (CDCl$_3$) δ_H 0.83 (t, *J* = 7.4, 6H, 2CH$_3$), 1.43–1.70 (m, 4H, 2CH$_2$), 2.27 (s, 2H, CH$_2$), 3.03 (bs, 2H, CH$_2$), 4.77 (bs, 1H, CH), 5.01 (bs, 1H, CH), 8.96 (bs, 2H, 2NH). ^{13}C-NMR (CDCl$_3$) δ_C 8.7 (2CH$_3$), 29.0 (2CH$_2$), 44.4 (CH$_2$), 47.2 (CH$_2$), 49.9 (C), 54.3 (C), 107.4 (CH$_2$), 153.4 (C), 170.7 (2C), 176.1 (C). HMRS (ESI): *m/z* calcd for C$_{13}$H$_{18}$N$_2$O$_2$S [M+NH$_4^+$]: 284.1427. Found: 284.1434.

14-Methylene-3-thioxo-2,4-diazadispiro[5.1.5.2]pentadecane-1,5-dione (**16**). White solid; m.p. 177 °C (isopropanol); yields: 54% ^{1}H-NMR (CDCl$_3$) δ_H 1.22–1.47 (m, 6H, 2CH$_3$), 1.66–1.77 (m, 4H, 2CH$_2$), 2.33 (s, 2H, CH$_2$), 3.06 (s, 2H, CH$_2$), 4.89–4.93 (m, 2H, CH$_2$), 9.09 (bs, 2H, 2NH). ^{13}C-NMR (CDCl$_3$) δ_C 23.2 (2CH$_2$), 25.7 (CH$_2$), 37.5 (2CH$_2$), 44.0 (CH$_2$), 45.2 (CH$_2$), 46.8 (C), 55.0 (C), 105.4 (CH$_2$), 157.4 (C), 170.7 (2C), 176.2 (C). HMRS (ESI): *m/z* calcd for C$_{14}$H$_{18}$N$_2$O$_2$S [M+NH$_4^+$]: 296.1427. Found: 296.1422.

3.4. General Procedure for Salification of Barbituric Acids to Barbiturate Potassium Salts **17–24**

A suspension of potassium hydroxide (0.02 g, 0.36 mmol, 1 equiv.) in isopropanol (5 mL) was stirred under inert atmosphere. The corresponding barbituric acid **9–16** (0.36 mmol, 1 equiv.) was added, and reaction was monitored by TLC until the barbituric acid disappeared. Isopropanol was removed *in vacuo*, and corresponding barbiturates **17–24** were obtained without further purification.

Potassium 4,4-diethyl-4',6'-dioxo-1',3,4,6'-tetrahydro-1H,4'H-spiro[naphthalene-2,5'-pyrimidine]-2'-thiolate (**17**). White solid; m.p. 161–163 °C (isopropanol); yields: 77%; ^{1}H-NMR (D$_2$O) δ_H 0.72 (s, 3H, CH$_3$), 0.99 (s, 3H, CH$_3$), 1.42–1.79 (m, 4H, 2CH$_2$), 2.38 (d, *J* = 15.4, 1H, CH$_2$), 2.53 (d, *J* = 15.4, 1H, CH$_2$), 3.13 (d, *J* = 16.4, 1H, CH$_2$), 3.40 (d, *J* = 16.4, 1H, CH$_2$), 7.35–7.41 (m, 4H, 4CH). ^{13}C-NMR

(D$_2$O) δ_C 8.4 (CH$_3$), 8.5 (CH$_3$), 32.9 (CH$_2$), 35.1 (CH$_2$), 35.2 (CH$_2$), 35.8 (CH$_2$), 41.2 (C), 57.2 (C), 126.5 (CH), 127.0 (CH), 127.9 (CH), 129.1 (CH), 136.2 (C), 142.8 (C), 177.0 (2C), 178.9 (C). HMRS (ESI): *m/z* calcd for C$_{17}$H$_{19}$N$_2$O$_2$S$^-$ M: 315.1173. Found: 315.1183.

Potassium 5-benzyl-5-[2-ethylbut-2-en-1-yl]-4,6-thioxo-1,4,5,6-tetrahydropyrimidine-2-thiolate (**18a**/ **18b**) (50:50 inseparable mixture of *Z/E* isomers). White solid; m.p. 142–144 °C (isopropanol); yields: 78%; ^{1}H-NMR (D$_2$O) δ_H 0.98–1.05 (m, 3H, CH$_3$), 1.61–1.73 (m, 3H, CH$_2$), 1.93–2.12 (m, 2H, CH$_2$), 2.89 and 3.01 (s, 2H, CH$_2$), 3.28 and 3.38 (s, 2H, CH$_2$), 5.11 and 5.51 (bs, 1H, 1CH), 7.22–7.39 (m, 5H, 5CH). ^{13}C-NMR (D$_2$O) δ_C 12.6 and 12.7 (CH$_3$), 13.2 and 13.3 (CH$_3$), 23.6 and 29.8 (CH$_2$), 39.3 and 44.8 (CH$_2$), 45.0 and 45.9 (CH$_2$), 57.6 (C), 122.7 and 123.8 (CH), 128.0 (CH), 129.1 (2CH), 129.9 (2CH), 135.9 (C), 138.0 (C), 172.9 (C), 179.6 (2C). HMRS (ESI): *m/z* calcd for C$_{17}$H$_{19}$N$_2$O$_2$S$^-$ M: 315.1173. Found: 315.1180.

Potassium 4",6"-dioxo-1",6"-dihydro-4'H,4"H-dispiro[cyclohexane-1,1'-naphtalene-3',5"-pyrimidine]-2"-thiolate (**19**). White solid; m.p. 216–218 °C (isopropanol); yields: 70%; ^{1}H-NMR (D$_2$O) δ_H 1.38–2.25 (m, 10H, 5CH$_2$), 2.40 (bs, 1H, CH$_2$), 3.08–3.68 (m, 3H, CH$_2$), 7.40–7.58 (m, 3H, 3CH), 7.72–7.78 (m, 1H, 1CH). ^{13}C-NMR (D$_2$O) δ_C 22.1 (CH$_2$), 22.4 (CH$_2$), 26.0 (CH$_2$), 35.8 (CH$_2$), 37.6 (CH$_2$), 37.7 (C), 38.2 (CH$_2$), 42.0 (CH$_2$), 56.9 (C), 126.8 (CH), 127.2 (CH), 127.3 (CH), 129.3 (CH), 135.3 (C), 144.7 (C), 176.5 (C), 178.8 (C), 181.5 (C). HMRS (ESI): *m/z* calcd for C$_{18}$H$_{19}$N$_2$O$_2$S$^-$ M: 327.1173. Found: 327.1184.

Potassium 5-benzyl-5-(cyclohex-1-en-1-ylmethyl)-4,6-dioxo-1,4,5,6-tetrahydropyrimidine-2-thiolate (**20**). White solid; m.p. 143 °C (isopropanol); yields: 84% ^{1}H-NMR (D$_2$O) δ_H 1.36–1.60 (m, 4H, 2CH$_2$), 1.74–2.00 (m, 4H, 2CH$_2$), 2.70 (s, 2H, CH$_2$), 3.18 (s, 2H, CH$_2$), 5.39 (s, 1H, 1CH), 7.06–7.11 (m, 2H, 2CH), 7.26–7.30 (m, 3H, 3CH). ^{13}C-NMR (D$_2$O) δ_C 22.3 (CH$_2$), 23.3 (CH$_2$), 25.7 (CH$_2$), 29.8 (CH$_2$), 45.5 (CH$_2$), 47.6 (CH$_2$), 57.3 (C), 126.2 (CH), 127.8 (CH), 129.1 (2CH), 129.9 (2CH), 134.0 (C), 136.6 (C), 181.5 (2C), 192.6 (C). HMRS (ESI): *m/z* calcd for C$_{18}$H$_{19}$N$_2$O$_2$S$^-$ M: 327.1173. Found: 327.1173.

Potassium 5-[2-ethylbut-2-en-1-yl]-5-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidine-2-thiolate (**21a**/ **21b**) (50:50 inseparable mixture of *Z/E* isomers). White solid; m.p. 174–176 °C (isopropanol); yields: 28% ^{1}H-NMR (D$_2$O) δ_H 0.82–0.98 (m, 3H, CH$_3$), 1.32–1.42 (m, 3H, CH$_3$), 1.49–1.56 (m, 3H, CH$_3$), 1.76–2.05 (m, 2H, CH$_2$), 2.54–2.69 (m, 2H, CH$_2$), 5.01 and 5.45 (bs, 1H, 1CH). ^{13}C-NMR (D$_2$O) δ_C 12.8 and 13.0 (CH$_3$), 13.2 and 14.0 (CH$_3$), 21.0 and 22.7 (CH$_3$), 23.7 and 30.2 (CH$_2$), 38.5 and 44.8 (CH$_2$), 56.7 and 57.0 (C), 123.1 and 123.8 (CH), 138.3 and 139.1 (C), 177.8 and 177.9 (C), 180.0 and 180.1 (C), 181.5 and 181.6 (C). HMRS (ESI): *m/z* calcd for C$_{11}$H$_{15}$N$_2$O$_2$S$^-$ M: 239.0860. Found: 239.0857.

Potassium 5-(cyclohex-1-en-1-ylmethyl)-5-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidine-2-thiolate (**22**). White solid; m.p. 177 °C (isopropanol); yields: 69% ^{1}H-NMR (D$_2$O) δ_H 1.47 (s, 3H, CH$_3$), 1.45–1.61 (m, 4H, 2CH$_2$), 1.84–2.09 (m, 4H, 2CH$_2$), 2.55 (s, 2H, CH$_2$), 5.41 (s, 1H, 1CH). ^{13}C-NMR (D$_2$O) δ_C 22.4 (CH$_2$), 22.5 (CH$_3$), 23.3 (CH$_2$), 25.7 (CH$_2$), 29.6 (CH$_2$), 47.4 (CH$_2$), 56.8 (C), 126.7

(CH), 134.9 (C), 177.9 (2C), 181.6 (C). HMRS (ESI): *m/z* calcd for $C_{12}H_{15}N_2O_2S^-$ M: 251.0860. Found: 251.0859.

Potassium 2,2-diethyl-3-methylene-6,10-dioxo-7,9-diazaspiro[4.5]dec-7-ene-8-thiolate (**23**). White solid; decomp. 270 °C (isopropanol); yields: 88% ¹H-NMR (D₂O) δ_H 0.72–0.83 (m, 6H, 2CH₃), 1.14–1.53 (m, 4H, 2CH₂), 2.27 (s, 2H, CH₂), 2.84 (d, *J* = 16.3, 1H, CH₂), 3.04 (d, *J* = 16.3, 1H, CH₂), 4.72 (bs, 1H, CH), 5.01 (bs, 1H, CH). ¹³C-NMR (D₂O) δ_C 8.6 (CH₃), 8.7 (CH₃), 30.5 (CH₂), 31.0 (CH₂), 41.7 (CH₂), 45.0 (CH₂), 49.1 (C), 62.5 (C), 105.8 (CH₂), 157.2 (C), 176.7 (C), 179.1 (C), 182.1 (C). HMRS (ESI): *m/z* calcd for $C_{13}H_{17}N_2O_2S^-$ M: 265.1016. Found: 265.1025.

Potassium 14-methylene-1,5-dioxo-2,4-diazaspiro[5.1.5.2]pentadec-2-ene-3-thiolate (**24**). White solid; m.p. 174–176 °C (isopropanol); yields: 53% ¹H-NMR (D₂O) δ_H 1.13–1.65 (m, 10H, 5CH₂), 2.25 (d, *J* = 14.0, 1H, CH₂), 2.40 (d, *J* = 14.0, 1H, CH₂), 2.88 (d, *J* = 16.4, 1H, CH₂), 3.04 (d, *J* = 16.4, 1H, CH₂), 4.86 (bs, CH), 4.96 (bs, CH). ¹³C-NMR (D₂O) δ_C 22.8 (CH₂), 22.9 (CH₂), 37.6 (CH₂), 38.6 (CH₂), 40.1 (CH₂), 44.0 (CH₂), 45.7 (C), 62.3 (C), 104.0 (CH₂), 160.7 (C), 175.9 (C), 178.3 (C). 1C not observed in these conditions. HMRS (ESI): *m/z* calcd for $C_{14}H_{17}N_2O_2S^-$ M: 277.1016. Found: 277.1009.

4. Conclusions

We have synthesized eight new functionalized thiobarbiturates by a three steps synthesis, thanks to Mn(OAc)₃ radical reactivity. This methodology allows *C*-functionalization of barbituric acid with a wide variety of scaffolds, such as aromatic, aliphatic and spirocyclic moieties. Derivatives thus obtained could be tested for their anesthetic potentialities, but also for targeting anticonvulsive leads.

Acknowledgements

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Sample Availability: Samples of the compounds **6**, **8**, **10**, **15**, **17**–**24** are available from the authors.