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Synthesis of Tetramic Acid Derivatives via Intramolecular sp^3 C−H Amination Mediated by Hypervalent Iodine(III) Reagents/Brønsted Acids

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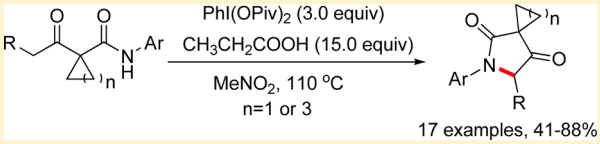
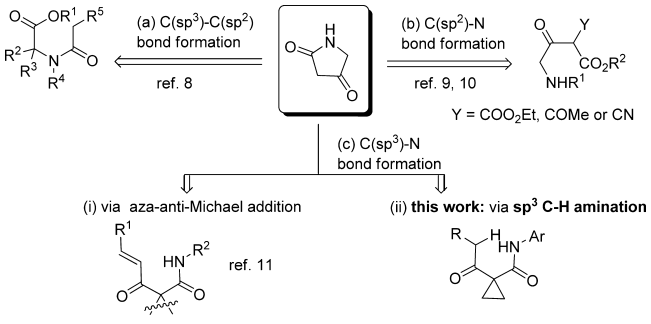
Supporting Information

ABSTRACT: An efficient synthesis of tetramic acid derivatives was developed via intramolecular sp^3 C−H aminations of 1-acetyl *N*-aryl cyclopropane/cyclopentanecarboxamides in the presence of $PhI(OPiv)_2$ and CH_3CH_2COOH.



Tetramic acid derivatives represent an important class of nitrogen-containing heterocycles with a pyrrolidine-2,4-dione moiety. They are core structural skeletons in a variety of natural products from terrestrial and marine origins exhibiting many biological activities such as antibiotic,[1] antiviral,[2] antifungal,[3] phytotoxic,[4] cytotoxic,[5] and enzyme inhibition against bacterial DNA-directed RNA polymerase.[6] Various synthetic paths to such five-membered nitrogen-containing heterocyles have been developed.[7−11] This structural core can be constructed either by $C(sp^3)-C(sp^2)$ bond formation via Dieckmann condensation of *N*-alkoxy-carbonylacetyl derivatives (Scheme 1a),[8] or by $C(sp^2)-N$ bond formation through

Scheme 1. Construction of the Tetramic Acid Skeleton



the condensation of α-amino keto ester derivatives (Scheme 1b).[9,10] Recently, Liu and co-workers synthesized tetramic acid derivatives by constructing the $C(sp^3)-N$ bond via aza-anti-Michael addition of α,β-unsaturated acetamides (Scheme 1c(i)).[11] Although a considerable amount of effort has been expended in the preparation of tetramic acid derivatives, new and straightforward methods to approach these heterocycles are still highly desirable.

The nitrogen functionality is prevalent in synthetic and natural small molecules possessing high levels of biological activity,[12] which motivates the development of methodologies to introduce nitrogen atoms into organic molecules. Among various C−N bond construction methods, the direct C−N bond formation reaction between C−H and N−H bonds is the most powerful strategy because it avoids prefunctionalization of the substrates, thus minimizing environmental impact and the number of synthetic steps.[13] Recently, intramolecular metal-free C−H amination has become an appealing strategy to directly construct aza-heterocycles due to its environmentally benign and atom-economic character.[14,15] Compared with sp^2 C−H amination,[14] sp^3 C−H amination reactions are rare.[15] Recently, Fan and co-workers synthesized azetidines[15b] and 3-oxyindoles[15c] via hypervalent iodine(III)[16]-mediated intramolecular α-amination of the sp^3 C−H bond of carbonyl compounds[17] under basic conditions. So far, to the best of our knowledge, the direct construction of the tetramic acid skeleton via intramolecular amination reaction between C−H and N−H bonds has never been realized. Herein, we present the first example for the synthesis of tetramic acids via metal-free intramolecular sp^3 C−H amination mediated by hypervalent iodine(III) reagents/Brønsted acids (Scheme 1c(ii)).

In keeping with our continuing interest for the construction of C−N bonds directly from C−H bonds,[18] we attempted to synthesize the tetramic acid skeleton from 1-acetyl *N*-aryl carboxamide derivatives[19] via cross coupling between sp^3 C−H and N−H bonds intramolecularly. Initially, we found that 1-acetyl-*N*-(4-chlorophenyl)cyclopropanecarboxamide (**1a**), a readily available acetoacetanilide derivative,[19] failed to undergo intramolecular sp^3 C−H bond amination reaction upon treatment with $PhI(OAc)_2$ (3 equiv) in anhydrous Ac_2O (distilled over CaH_2); only a trace amount of **2a** was observed (Table 1, entry 1). When 15.0 equiv of anhydrous CH_3CH_2COOH was added to the above reaction, **2a** was obtained in 54% yield (Table 1, entry 2), which showed the important role of the Brønsted acid additive. Next, other solvents were screened (Table 1, entries 4−6). DMF and 1,4-dioxane were not effective (Table 1, entries 4 and 5), while $MeNO_2$ gave **2a** in 69% yield (Table 1, entry 6). To our delight, when $PhI(OPiv)_2$ was used as the oxidant, **2a** was

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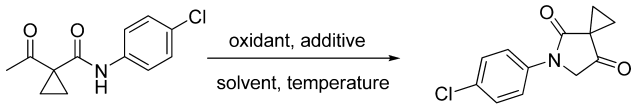
Table 1. Optimization of Reaction Conditions[a,j]



1a 2a

entry	oxidant	additive	solvent	temp (°C)	time (h)	yield (%)[b]
1	$PhI(OAc)_2$	none	Ac_2O	110	12.0	trace
2	$PhI(OAc)_2$	CH_3CH_2COOH[c]	Ac_2O	110	2.0	54
3	$PhI(OAc)_2$	CH_3CH_2COOH[d]	Ac_2O	110	2.0	54
4	$PhI(OAc)_2$	CH_3CH_2COOH	DMF	110	12.0	N.D.[e]
5	$PhI(OAc)_2$	CH_3CH_2COOH	1,4-dioxane	110	12.0	N.D.[e]
6	$PhI(OAc)_2$	CH_3CH_2COOH	$MeNO_2$	110	2.0	69
7	$PhI(OPiv)_2$	CH_3CH_2COOH	$MeNO_2$	110	2.0	85
8	PhI(OH)(OTs)	CH_3CH_2COOH	$MeNO_2$	110	12.0	N.D.[e]
9	$PhI(OOCCF_3)_2$	CH_3CH_2COOH	$MeNO_2$	110	12.0	N.D.[e]
10	$PhI(OPiv)_2$	$CH_3(CH_2)_2COOH$	$MeNO_2$	110	12.0	46
11	$PhI(OPiv)_2$	$CH_3(CH_2)_3COOH$	$MeNO_2$	110	12.0	35
12	$PhI(OPiv)_2$	PivOH	$MeNO_2$	110	12.0	23
13	$PhI(OPiv)_2$	CH_3CH_2COOH[f]	$MeNO_2$	110	2.0	67
14	$PhI(OPiv)_2$	CH_3CH_2COOH[g]	$MeNO_2$	110	3.0	44
15	$PhI(OPiv)_2$[h]	CH_3CH_2COOH	$MeNO_2$	110	12.0	31
16	$PhI(OPiv)_2$[i]	CH_3CH_2COOH	$MeNO_2$	110	1.5	62
17	$PhI(OPiv)_2$	CH_3CH_2COOH	$MeNO_2$	90	10.0	54
18	$PhI(OPiv)_2$	CH_3CH_2COOH	$MeNO_2$	130	1.0	57

[a]Reactions were carried out with **1a** (0.3 mmol), oxidant (3.0 equiv), and additive (15.0 equiv) in the solvent (1.8 mL). [b]Isolated yield. [c]CH_3CH_2COOH was dried with 4 Å MS. [d]Commercially available CH_3CH_2COOH was used in this and the following corresponding entries. [e]N.D. = not detected (monitored by TLC). [f]10.0 equiv of CH_3CH_2COOH was used. [g]20.0 equiv of CH_3CH_2COOH was used. [h]2.0 equiv of $PhI(OPiv)_2$ was used. [i]4.0 equiv of $PhI(OPiv)_2$ was used. [j]Caution: $MeNO_2$ is explosive at temperatures exceeding its boiling point!

obtained in 85% yield (Table 1, entry 7). Other hypervalent iodine(III) reagents, such as PhI(OH)(OTs) and $PhI(OOCCF_3)_2$, were not effective (Table 1, entries 8 and 9). In addition, Brønsted acids such as $CH_3(CH_2)_2COOH$, $CH_3(CH_2)_3COOH$, and PivOH were not as effective as CH_3CH_2COOH and gave **2a** in 46%, 35%, and 23% yields, respectively (Table 1, entries 10−12). When adding 10.0 or 20.0 equiv of CH_3CH_2COOH to the reaction, **2a** was obtained in 67% and 44% yields, respectively (Table 1, entries 13 and 14). When adding 2.0 or 4.0 equiv of $PhI(OPiv)_2$ to the reaction, **2a** was obtained in 31% and 62% yields, respectively (Table 1, entries 15 and 16). When the reaction temperature was decreased or increased, **2a** was formed in 54% and 57% yields, respectively (Table 1, entries 17 and 18). It should be noted that the transformation from **1a** to **2a** represents the first example for the synthesis of the tetramic acid skeleton via intramolecular sp^3 C−H amination.

Once the optimized conditions were established (Table 1, entry 7), we examined the scope of the intramolecular sp^3 C−H amination reaction. As shown in Table 2, substrates **1a−k** bearing electron-withdrawing groups or electron-donating groups on the benzene ring provided the corresponding tetramic acid derivatives **2a−k** in 47−88% yields. The tolerance of chloride or bromide on the aromatic ring in this transformation offers an opportunity for further functionalizations. Starting from the 4-methyl-substituted substrate **1l**, tetramic acid **2l** with a 2-$OOCCH_2CH_3$-substituted phenyl ring was obtained in 62% yield. When the substrate **1m** or **1n** with a 4-methoxy group on the phenyl ring, a strong electron-donating group, was used, an inseparable complex mixture[20] was generated and no desired tetramic acid **2m** or **2n** was detected. Gratefully, substrates **1o** and **1p** containing a methylene unit adjacent to the carbonyl group were viable for this amination reaction, and the desired products **2o** and **2p** were obtained in 72% and 41% yields, respectively. Nevertheless, **1q** with a 2-phenylacetyl group could not form **2q** and gave a complex mixture. For substrates **1m**, **1n**, and **1q**, even though lowering the reaction temperature or shortening the reaction time, no tetramic acid derivatives were generated. Additionally, the 2,6-disubstituted substrate **1r** failed to undergo the reaction, and **1r** was recovered completely. When the cyclopropanyl group in the substrates was changed to the cyclopentyl group, the tetramic acids **2q−s** were also formed in 65−87% yields. With *N*-benzylic-substituted substrate **1v**, no amination reaction occurred.

On the basis of all the results mentioned above, a possible mechanism for the formation of the tetramic acids **2** is depicted in Scheme 2. Under the acid conditions, the substrate **1** undergoes keto−enol tautomerism to form intermediate enol **I**. Then **I** reacts with $PhI(OPiv)_2$ to furnish a highly electrophilic *N*-(phenylpivalicoxyiodo)amide species **II** and its dissociated form **III**.[21] Alternatively, the *N*-iodane species **III** might form first and this step followed by enolization. Next, the intramolecular electrophilic amination of the *N*-iodo(III)-amide species **III** readily occurs to generate an oxonium intermediate **IV**. Subsequently, the proton elimination from **IV** provides the tetramic acids **2**. In contrast to Fan's previous report,[15c] during the formation of **2**, the substrates containing an acetyl group showed reactivity higher than those containing a methylene group adjacent to the carbonyl group (Table 2, **2a** and **2o**). Furthermore, starting from **1o** and **1p** but with $PhI(OPiv)_2$ as the oxidant, **2o** was obtained in 37% yield and **2p** was obtained in 21% yield. Also, the reaction of **1q** could not generate **2q**. These results could be attributed to bulky in

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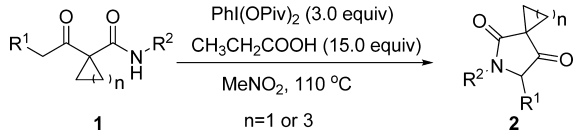
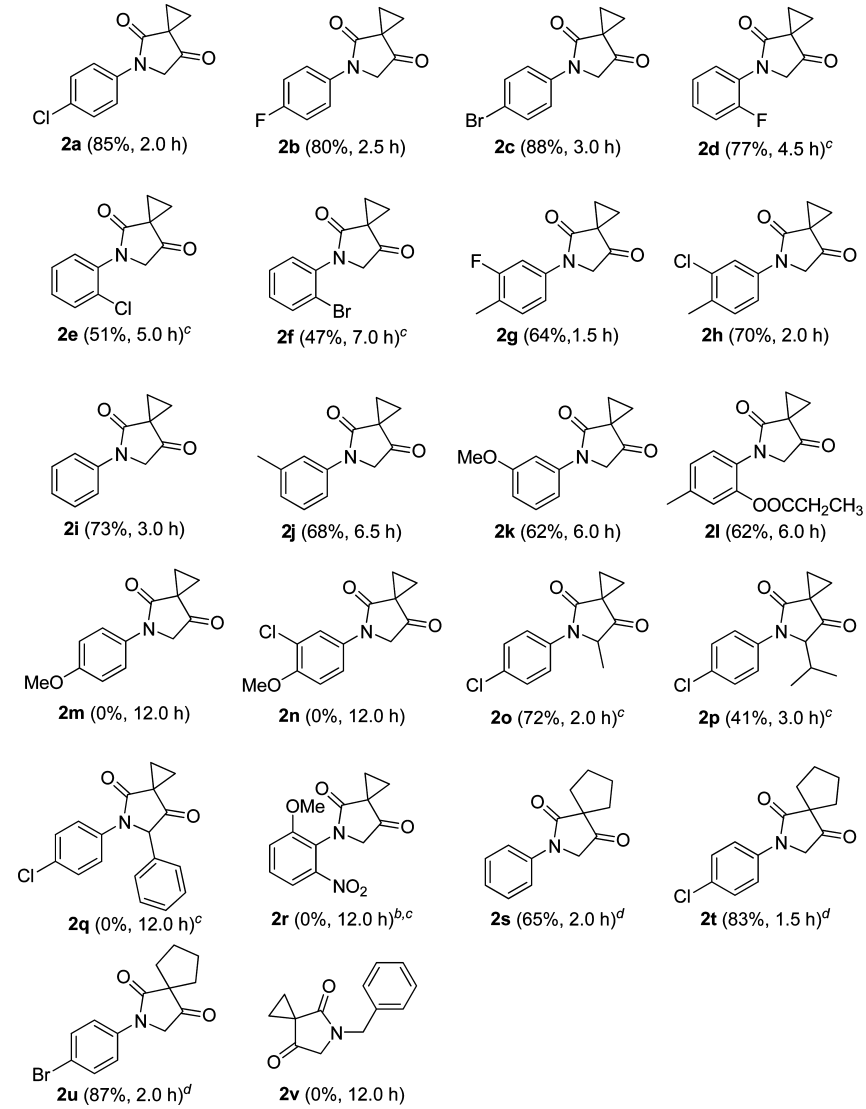
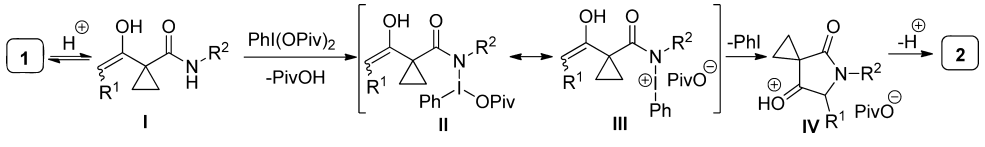
Table 2. Synthesis of Tetramic Acid Deveritives 2[a,b]





[a]Isolated yield. [b]Reactions were carried out with **1** (0.3 mmol), PhI(OPiv)2 (3.0 equiv), and CH_3CH_2COOH (15.0 equiv) in $MeNO_2$ (1.8 mL) at 110 °C. [c]3.0 equiv of $PhI(OAc)_2$ was used as the oxidant, and Ac_2O (1.8 mL) was used as the solvent. [d]10.0 equiv of CH_3CH_2COOH was used as the additive.

Scheme 2. Proposed Mechanism for the Formation of 2



situ-generated amide species[18e] **II** or **III** (Scheme 2). From **1v**, no desired annulation product was observed, which might be attributed to the unstable *N*-iodane species **III** formed.

In conclusion, we have developed a new, straightforward, and efficient method for the synthesis of tetramic acid derivatives from 1-acetyl *N*-aryl carboxamide derivatives in the presence of hypervalent iodine(III) reagents/Brønsted acids. This method would offer a complementary approach to α-amination of carbonyl compounds.

EXPERIMENTAL SECTION

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a 500 and 125 MHz, respectively,

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using TMS as internal standard. High-resolution mass spectra (ESI/HRMS) were recorded on a mass spectrometer. Melting points were uncorrected. All reactions were monitored by TLC with GF254 silica gel-coated plates. Chromatography was carried out on flash silica gel (300−400 mesh). The synthesis of $PhI(OPiv)_2$,[22] $PhI(OH)(OTs)$,[23] and 1-acetyl *N*-aryl cyclopropane-/cyclopentanecarboxamides **1**[19,24] followed the literature methods.

General Procedure for Synthesis of 2 (2a as an example). Compound **1a** (0.3 mmol, 71 mg) and $PhI(OPiv)_2$ (0.9 mmol, 366 mg) were dissolved in $MeNO_2$ (1.80 mL), and then propanoic acid (4.5 mmol, 0.34 mL) was added to the mixture and stirred at 110 °C until the reaction was completed (monitored by TLC). After the mixture was cooled, it was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (petroleum ether/acetic ether = 15/1, v/v) to give **2a** as a white solid (60 mg, 85%).

*5-(4-Chlorophenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2a**).* white solid (60 mg, 85%); mp 204−206 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76−1.78 (m, 2H), 1.83−1.85 (m, 2H), 4.35 (s, 2H), 7.37−7.39 (m, 2H), 7.64−7.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 33.2, 56.5, 120.9, 129.2, 130.1, 137.0, 171.4, 204.2; HRMS (ESI-TOF) calcd for $C_{12}H_{11}ClNO_2^+$ ($[M + H]^+$) 236.0473, found 236.0481.

*5-(4-Fluorophenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2b**).* white solid (53 mg, 80%); mp 171−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75−1.77 (m, 2H), 1.83−1.85 (m, 2H), 4.36 (s, 2H), 7.11 (t, J = 9.0 Hz, 2H), 7.64−7.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.3, 33.1, 56.8, 115.9 (d, J = 22.5 Hz), 121.7 (d, J = 8.0 Hz), 134.5, 159.7 (d, J = 244.1 Hz), 171.3, 204.6; HRMS (ESI-TOF) calcd for $C_{12}H_{11}FNO_2^+$ ($[M + H]^+$) 220.0768, found 220.0777.

*5-(4-Bromophenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2c**).* white solid (74 mg, 88%); mp 214−216 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76−1.79 (m, 2H), 1.84−1.86 (m, 2H), 4.35 (s, 2H), 7.52−7.54 (m, 2H), 7.58−7.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 33.2, 56.4, 117.8, 121.1, 132.2, 137.5, 171.4, 204.2; HRMS (ESI-TOF) calcd for $C_{12}H_{11}BrNO_2^+$ ($[M + H]^+$) 279.9968, found 279.9979.

*5-(2-Fluorophenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2d**).* white solid (48 mg, 73%); mp 163−165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76−1.81 (m, 2H), 1.81−1.86 (m, 2H), 4.40 (s, 2H), 7.17−7.23 (m, 2H), 7.29−7.34 (m, 1H), 7.51−7.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 31.9, 58.1 (d, J = 4.3 Hz), 116.8 (d, J = 19.6 Hz), 124.7 (d, J = 3.4 Hz), 124.8 (d, J = 11.5 Hz), 128.1, 129.0 (d, J = 8.1 Hz), 157.0 (d, J = 249.0 Hz), 171.8, 205.5; HRMS (ESI-TOF) calcd for $C_{12}H_{11}FNO_2^+$ ($[M + H]^+$) 220.0768, found 220.0773.

*5-(2-Chlorophenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2e**).* white solid (36 mg, 51%); mp 181−183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74−1.79 (m, 2H), 1.82−1.84 (m, 2H), 4.34 (s, 2H), 7.31−7.37 (m, 2H), 7.39−7.40 (m, 1H), 7.50−7.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 31.7, 57.9, 127.9, 129.5, 129.6, 130.6, 132.1, 134.7, 171.8, 205.4; HRMS (ESI-TOF) calcd for $C_{12}H_{11}ClNO_2^+$ ($[M + H]^+$) 236.0473, found 236.0474.

*5-(2-Bromophenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2f**).* white solid (39 mg, 47%); mp 177−179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75−1.77 (m, 2H), 1.83−1.86 (m, 2H), 4.35 (s, 2H), 7.26−7.29 (m, 1H), 7.37−7.43 (m, 2H), 7.68−7.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 31.9, 58.1, 122.3, 128.7, 129.8, 130.1, 133.8, 136.4, 171.8, 205.6; HRMS (ESI-TOF) calcd for $C_{12}H_{11}BrNO_2^+$ ($[M + H]^+$) 279.9968, found 279.9965.

*5-(3-Fluoro-4-methylphenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2g**).* white solid (45 mg, 64%); mp 179−180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76−1.78 (m, 2H), 1.84−1.86 (m, 2H), 2.27 (d, J = 1.5 Hz, 3H), 4.35 (s, 2H), 7.21 (t, J = 8.5 Hz, 1H), 7.24−7.25 (m, 1H), 7.56−7.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (d, J = 3.4 Hz), 22.4, 33.3, 56.5, 107.1 (d, J = 27.6 Hz), 114.4 (d, J = 3.3 Hz), 121.3 (d, J = 17.6 Hz), 131.5 (d, J = 6.3 Hz), 137.4 (d, J = 10.5 Hz), 161.1 (d, J = 243.1 Hz), 171.3, 204.5; HRMS (ESI-TOF) calcd for $C_{13}H_{13}FNO_2^+$ ($[M + H]^+$) 234.0925, found 234.0925.

*5-(3-Chloro-4-methylphenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2h**).* white solid (52 mg, 70%); mp 179−181 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75−1.78 (m, 2H), 1.83−1.85 (m, 2H), 2.37 (s, 3H), 4.34 (s, 2H), 7.25 (d, J = 9.0 Hz, 1H), 7.48 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz 1H), 7.74 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 22.4, 33.2, 56.5, 117.8, 120.2, 131.1, 132.6, 134.7, 137.1, 171.3, 204.4; HRMS (ESI-TOF) calcd for $C_{13}H_{13}ClNO_2^+$ ($[M + H]^+$) 250.0629, found 250.0633.

*5-Phenyl-5-azaspiro[2.4]heptane-4,7-dione (**2i**).* white solid (44 mg, 73%); mp 209−212 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75−1.77 (m, 2H), 1.83−1.86 (m, 2H), 4.39 (s, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.69 (t, J = 7.5 Hz 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.3, 33.3, 56.6, 119.8, 125.0, 129.2, 138.4, 171.3, 204.9; HRMS (ESI-TOF) calcd for $C_{12}H_{12}NO_2^+$ ($[M + H]^+$) 202.0863, found 202.0862.

*5-(m-Tolyl)-5-azaspiro[2.4]heptane-4,7-dione (**2j**).* white solid (44 mg, 68%); mp 183−185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (dd, J_1 = 4.5 Hz, J_2 = 3.0 Hz, 2H), 1.84 (dd, J_1 = 4.5 Hz, J_2 = 3.0 Hz, 2H), 2.39 (s, 3H), 4.38 (s, 2H), 7.02 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 22.3, 33.3, 56.8, 116.9, 120.7, 125.9, 128.9, 138.3, 139.2, 171.3, 205.2; HRMS (ESI-TOF) calcd for $C_{13}H_{14}NO_2^+$ ($[M + H]^+$) 216.1019, found 216.1017.

*5-(3-Methoxyphenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2k**).* white solid (43 mg, 62%); mp 169−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75−1.79 (m, 2H), 1.83−1.85 (m, 2H), 3.83 (s, 3H), 4.37 (s, 2H), 6.75 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.14 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.31 (t, J = 8.5 Hz, 1H), 7.47 (t, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 33.4, 55.3, 56.7, 105.9, 110.7, 111.6, 129.9, 139.6, 160.2, 171.4, 204.9; HRMS (ESI-TOF) calcd for $C_{13}H_{14}NO_3^+$ ($[M + H]^+$) 232.0968, found 232.0968.

*5-(4-Methyl-2-(prop-1-en-2-ylperoxy)phenyl)-5-azaspiro[2.4]heptane-4,7-dione (**2l**).* red solid (66 mg, 76%); mp 163−166 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 1.17 (t, J = 7.5 Hz, 3H), 1.53−1.58 (m, 4H), 2.08 (s, 3H), 2.59 (q, J = 7.5 Hz, 2H), 4.43 (s, 2H), 7.24 (d, J = 8.5 Hz, 1H), 7.45 (q, J = 8.5 Hz, 1H), 7.67 (d, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 8.8, 15.0, 20.8, 27.1, 32.7, 56.6, 113.8, 116.6, 126.2, 131.0, 138.4, 149.9, 171.5, 172.1, 204.6; HRMS (ESI-TOF) calcd for $C_{16}H_{18}NO_4^+$ ($[M + H]^+$) 288.1230, found 288.1237.

*5-(4-Chlorophenyl)-6-methyl-5-azaspiro[2.4]heptane-4,7-dione (**2o**).* white solid (54 mg, 72%); mp 180−182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (d, J = 7.0 Hz, 3H), 1.73−1.76 (m, 2H), 1.78−1.87 (m, 2H), 4.60 (q, J = 7.0 Hz, 1H), 7.39−7.41 (m, 2H), 7.43−7.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.8, 21.8, 22.3, 31.5, 62.3, 124.3, 129.3, 131.3, 134.9, 170.9, 208.3; HRMS (ESI-TOF) calcd for $C_{13}H_{13}ClNO_2^+$ ($[M + H]^+$) 250.0629, found 250.0629.

*5-(4-Chlorophenyl)-6-isopropyl-5-azaspiro[2.4]heptane-4,7-dione (**2p**).* white solid (35 mg, 41%); mp 109−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 1.61−1.64 (m, 1H), 1.74−1.80 (m, 3H), 2.14−2.18 (m, 1H), 4.48 (d, J = 3.5 Hz, 1H), 7.38−7.41 (m, 2H), 7.41−7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 17.9, 21.1, 22.6, 32.9, 71.1, 124.9, 129.4, 131.5, 135.2, 171.5, 207.6; HRMS (ESI-TOF) calcd for $C_{15}H_{17}ClNO_2^+$ ($[M + H]^+$) 278.0942, found 278.0956.

*2-Phenyl-2-azaspiro[4.4]nonane-1,4-dione (**2s**).* white solid (45 mg, 65%); mp 124−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87−1.92 (m, 2H), 1.94−2.01 (m, 4H), 2.08−2.13 (m, 2H), 4.29 (s, 2H), 7.20 (t, J = 7.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.69 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.1, 35.9, 55.7, 58.4, 120.1, 125.1, 129.1, 138.2, 175.4, 210.0; HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_2^+$ ($[M + H]^+$) 230.1176, found 230.1180.

*2-(4-Chlorophenyl)-2-azaspiro[4.4]nonane-1,4-dione (**2t**).* white solid (66 mg, 83%); mp 149−151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.88−1.92 (m, 2H), 1.94−2.01 (m, 4H), 2.07−2.11 (m, 2H), 4.26 (s, 2H), 7.37 (dd, J_1 = 6.5 Hz, J_2 = 1.5 Hz 2H), 7.65 (dd, J = 7.0 Hz, J_2 = 2.0 Hz 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 35.9, 55.5, 58.3, 121.2, 129.1, 130.3, 136.8, 175.5, 209.3; HRMS (ESI-TOF) calcd for $C_{14}H_{15}ClNO_2^+$ ($[M + H]^+$) 264.0786, found 264.0787.

*2-(4-Bromophenyl)-2-azaspiro[4.4]nonane-1,4-dione (**2u**).* white solid (80 mg, 87%); mp 157−159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87−1.91 (m, 2H), 1.92−1.96 (m, 2H), 1.97−2.01 (m, 2H), 2.07−2.12 (m, 2H), 4.26 (s, 2H), 7.52 (t, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.1, 35.9, 55.5, 58.4, 117.9,

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121.5, 132.1, 137.3, 175.6, 209.3; HRMS (ESI-TOF) calcd for $C_{14}H_{15}BrNO_2^+$ ([M + H]$^+$) 308.0281, found 308.0263.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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