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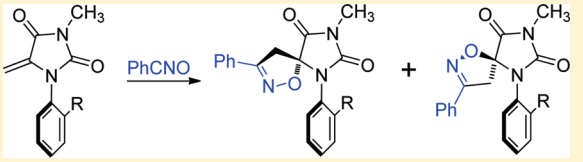
# Atropisomerism-Induced Facial Selectivity in Nitrile Oxide Cycloadditions with 5-Methylenehydantoins

Anna M. Said and G. Paul Savage*

CSIRO Materials Science and Engineering, Bag 10, Clayton South MDC, VIC 3169, Australia

Supporting Information

**ABSTRACT:** *N*-Aryl 5-methylenehydantoins underwent nitrile oxide cycloaddition with benzonitrile oxide to give 5-spiro isoxazoline adducts with complete regioselectivity. Atropisomerism around the *N*-aryl bond also led to facial selectivity in these cycloadditions.




The chemistry of hydantoin (imidazolidine-2,4-dione) dates back 150 years to Adolph von Baeyer,[1] but interest in this system has continued unabated. The ongoing interest in hydantoin is due in large part to the extensive biological activity associated with its derivatives.[2−4] Spiro hydantoin derivatives, such as the herbicidal (+)-hydantocidin from *Streptomyces hygroscopicus*[5] and the spiro hydantoin aldose reductase inhibitor Sorbinil,[6] have attracted strong interest from pharmaceutical companies (Figure 1). Diels−Alder and 1,3-dipolar cycloaddition reactions on 5-methylenehydantoins[7,8] have been successfully employed to access 5-spiro hydantoins.[9−14]

We have an ongoing interest in the construction of spiro isoxazolines using nitrile oxide cycloaddition (NOC) reactions on exocyclic methylene compounds.[15−19] NOC chemistry is reliable and predictable because the regiochemistry of cycloaddition is controlled to a great extent by steric influences. The oxygen of the nitrile oxide almost exclusively adds to the most hindered end of the dipolarophile, regardless of the polarity of the dipolarophile.[20−22] This characteristic of NOC reactions can be used to advantage in controlling the regiochemistry of cycloaddition to give a desired isomer.[23−26] In addition, subtle steric effects can control the facial selectivity of cycloaddition.[15] Recently we discovered that the exocyclic methylene dipolarophile in *N*-(2-methylphenyl)-5-methylene-1*H*-pyrrol-2(5*H*)-one underwent nitrile oxide cycloaddition with approximately a 4:1 facial selectivity as governed by atropisomerism along the aryl−nitrogen bond.[19] Such atroposelective nitrile oxide cycloaddition reactions are rare in the literature,[27−29] generally show poor selectivity, and are previously unknown for exocyclic methylene dipolarophiles. Some $\pi$-facial selectivity has been achieved in analogous open-chain systems.[30] Atropisomerism is a largely overlooked source of chirality, with important implications in the pharmaceutical industry.[31]

On the basis of the above findings, we anticipated that cycloadditions to *N*-aryl 5-methylenehydantoins might also show facial selectivity, controlled by the orientation of the atropisomers. However, despite several reports of 1,3-dipolar cycloadditions with *N*-substituted 5-methylenehydantoins, including

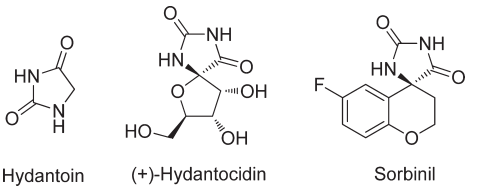
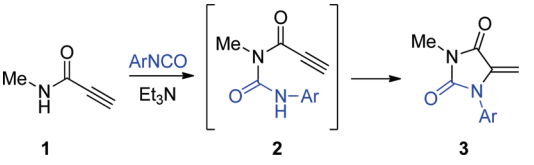



**Figure 1.** Structures of hydantoin, (+)-hydantocidin, and sorbinil.

**Scheme 1. Formation of 5-Methylenehydantoins**




one NOC reaction,[14] no such facial selectivity has been described. This is because in each reported case the *N*-substituent has been symmetrical and so the possibility of an asymmetric reaction due to atropisomerism has been overlooked. We herein report the formation of spiro hydantoins via benzonitrile oxide cycloaddition reactions with 5-methylenehydantoins bearing an unsymmetrical aryl group on N-1 and the facial selectivity engendered by atropisomeric control.

Methyl propiolate was treated with methylamine in 50% aqueous MeOH to form *N*-methylpropiolamide **1**.[32] Equimolar quantities of **1**, the appropriate isocyanate, and triethylamine were then reacted at room temperature, following the procedure of Coppola and Damon,[8] to give the 1-aryl-3-methyl hydantoins **3** (Scheme 1). This reaction presumably proceeds via the urea intermediate **2**, which is not isolated.

The methylenehydantoins **3** underwent NOC reactions with benzonitrile oxide to give spiro adducts **4**, (Table 1). Benzonitrile

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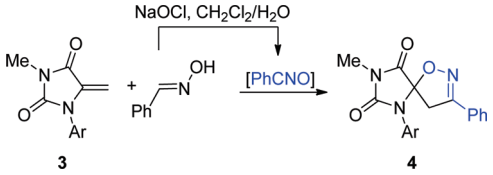
**Table 1. Atroposelectivity of Benzonitrile Oxide Cycloadditions with Methylenehydantoins 3**




| entry | *N*-aryl substituent | yield of **4** (%) | *anti*/*syn* ratio[a] |
|---|---|---|---|
| a | phenyl | 80 | N/A |
| b | 2-methylphenyl | 74 | 2.5:1 |
| c | 2,5-dimethylphenyl | 66 | 2.6:1 |
| d | 1-naphthyl | 71 | 4.7:1 |
| e | 2-nitrophenyl | 76 | >99:1[b] |
| f | 2-*tert*-butylphenyl | 45 | 30:1 |
| g | 2-phenylphenyl | 61 | 15:1 |

[a] See Scheme 2 [b] No *syn* isomer could be detected.

oxide was generated *in situ* by the action of 5% sodium hypochlorite on benzaldoxime using a water/$CH_2Cl_2$ biphasic system.[33] In each case, the cycloaddition was completely regioselective, in that the oxygen of the nitrile oxide became attached to the disubstituted end of the double bond. This regiochemical orientation was established from the $^1$H NMR chemical shifts for the methylene protons of the newly formed isoxazoline rings. The characteristic AB quartet system of these diastereotopic protons fell in the range of 3.0−3.5 ppm, which is indicative of protons on C-4 of the isoxazoline ring rather than C-5 (4.5−5.0 ppm),[34,35] hence establishing the regiochemistry of cycloaddition as shown.

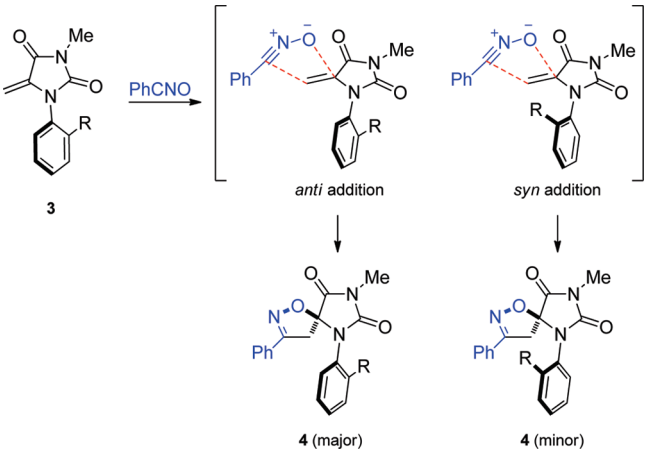
For some of the spiro heterocycles **4**, the $^1$H NMR featured a double set of resonances for all protons, which was consistent with atropisomeric mixtures. The diastereotopic protons on C-4 of the isoxazoline ring, at around 3.0−3.6 ppm, were especially diagnostic as the resonances for the two isomers were usually separated by approximately 0.4 ppm. The ratios of the atropisomeric products were conveniently determined by integrating these signals, and the ratios are reported in Table 1.

Restricted rotation around the *N*-aryl bond of **4** leads to substantially different magnetic environments for the isoxazoline C-4 protons depending on whether the 2′-substituent on the aryl group is in close proximity to the isoxazoline protons, via *anti*-addition, or remote from the isoxazoline protons, via *syn*-addition (Scheme 2).

The ratios reported in Table 1 may conceivably represent either a thermodynamic equilibrium between the atropisomeric products or the kinetic atroposelectivity for the reaction. We reasoned that it was unlikely to be a thermodynamic equilibrium because the barrier to rotation in the products would be quite high and the reaction was carried out at 0 °C. As supporting evidence, the $^1$H NMR spectrum of the atropisomeric mixture of spiro-adduct **4c** remained unchanged upon heating to 100 °C in toluene-$d_8$. No coalescence of signals was observed at 100 °C, and after the temperature was held at 100 °C for 24 h, the atropisomeric ratio remained unchanged.

The dipolarophile precursors themselves may also experience restricted rotation around the *N*-aryl bond as, for example, the rotational barrier around the *N*-aryl single bond in 2′-substituted

**Scheme 2. Atropisometric Facial Selectivity in Benzonitrile Cycloaddition to 5-Methylenehydantoins 3**




*N*-arylimides ($\Delta G^{\ddagger}$ rotational barrier in toluene = 19.3 kcal/mol)[36] and 2-methyl-*N*-(4-methyl-3-(*o*-tolyl)thiazol-2(3*H*)-ylidene)aniline ($\Delta G^{\ddagger}$ rotational barrier in ethanol = 29 kcal/mol).[37] We explored the barrier to rotation of the dipolarophile methylenehydantoins **3a** and **3b** around the N−aryl torsional angle, locating energy minima using a Gaussian constrained optimization at each point (see Supporting Information). For unsubstituted phenyl derivative **3a**, the barrier to rotation was calculated to be approximately 4.2 kcal/mol. For the *N*-(2-methylphenyl) substituted methylenehydantoins **3b** and **3c** the barrier to rotation was calculated to be approximately 17.6 kcal/mol. For the more highly hindered compounds **3d**−**g** the barrier to rotation would be expected to be higher still. Hence, it is probable that torsional rotation around the N−aryl bond of the dipolarophiles at 0 °C is highly restricted.

As previously mentioned, nitrile oxide cycloadditions to exocyclic methylene groups are quite sensitive to steric control often displaying high levels of facial selectivity.[20] Cycloaddition to the atropisomeric dipolarophiles **3** is therefore more likely to occur on the face opposite to the aryl 2′-substituent leading to an uneven diastereomeric mix of atropisomers **4** (Scheme 2). In the $^1$H NMR spectra of the crude cycloadduct products, the isoxazoline protons of the major isomer appear upfield from the analogous protons in the minor isomer. This observation is consistent with preferential cycloaddition on the face opposite the aryl 2′-substituent, which would then result in the isoxazoline methylene protons being shielded by the 2′-substituent in product **4** (major) relative to the corresponding isoxazoline methylene protons of the minor isomer. In addition, resonances for the diastereomeric protons on the isoxazoline ring of the major isomer tended to be further apart than those for the corresponding protons on the minor isomer. Again, this is consistent with the stereochemistry of addition as shown in Scheme 2. The magnetic environment of these protons will be more differentially affected in **4** (major) by the adjacent 2′-substituent of the *N*-aryl ring, with one of the protons oriented toward, and the other pointing away from, the 2′-substituent. In the *syn*-cycloadduct, **4** (minor), both protons are remote from the 2′-substituent.

The atropisomeric cycloadduct mixtures **4b**−**d** could not be separated, but the major diastereomeric atropisomer of the *tert*-butyl-substituted cycloadduct **4f** and the biphenyl cycloadduct **4g** could be isolated by column chromatography. The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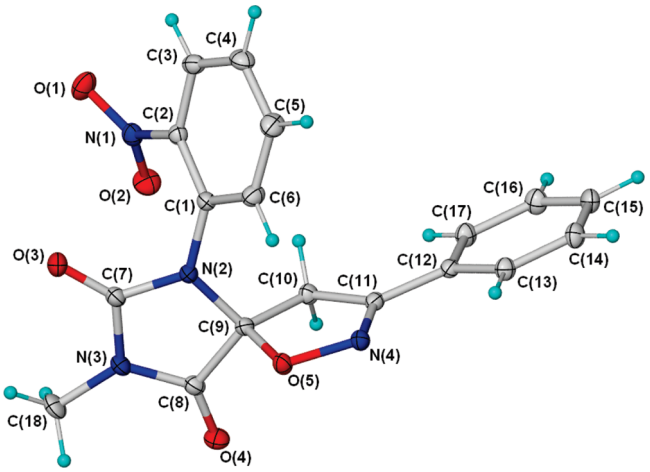


**Figure 2.** Molecular diagram of cycloadduct **4e** with 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size.

2′-nitro derivative **4e** only formed as a single atropisomer during the NOC reaction as far as we could detect. The greater facial selectivity in this system, as compared to the 2′-*tert*-butyl system, presumably reflects some additional electrostatic repulsion between the nitro group and the approaching nitrile oxide. Such electrostatic repulsion between nitrile oxides and fluorine has been postulated by Dolbier[38] and Houk[39] to explain facial selectivity in related systems. Crystals of cycloadduct **4e** grew slowly out of ethyl acetate/hexane and a single crystal X-ray structure was obtained (Figure 2). The molecule crystallized in the centrosymmetric orthorhombic space group *Pbca*, with both enantiomers present in the crystal (Supporting Information). A single diastereomer, where the cycloaddition had occurred on the face *anti* to the 2′-nitro substituent of the *N*-aryl ring, was observed. This observation is consistent with the NMR and computational data, and confirms the hypothesis that facial selectivity in these reactions is controlled by atropisomeric induction. We are currently examining additional methylene heterocyclic dipolarophiles to see if this finding holds across other systems.

## EXPERIMENTAL SECTION

General experimental methods have been previously described.[19]

**General Procedure for the Synthesis of 1-Aryl 3-Methyl-5-methyleneimidazolidine-2,4-diones (3).** Triethylamine (10 mmol) was cautiously added to an ice-cooled solution of *N*-methyl propiolamide[32] (10 mmol) and the appropriate aryl isocyanate (10 mmol) in anhydrous THF. The stirred mixture was allowed to warm to room temperature overnight. The solvent was evaporated, and the residue was recrystallized from chloroform/hexane unless otherwise stated.

**3-Methyl-5-methylene-1-phenylimidazolidine-2,4-dione (3a).** The product was isolated as a fine off-white powder (1.54 g, 76%) and recrystallized from EtOH. Mp 148−150 °C (lit.[8] 153−156 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.53−7.47 (2H, m, Ar), 7.43−7.38 (1H, m, Ar), 7.36−7.32 (2H, m, Ar), 5.50 (1H, d, $J$ = 2.2, $CH_2$), 4.86 (1H, d, $J$ = 2.2, $CH_2$), 3.19 (3H, s, NMe); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 162.3, 153.4, 136.9, 133.0, 129.7, 126.8, 95.8, 24.9.

**3-Methyl-5-methylene-1-(2-methylphenyl)imidazolidine-2,4-dione (3b).** The product was isolated as a white solid (1.90 g, 88%). Mp 81−82 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.29 (3H, m, Ar) 7.19 (1H, d, $J$ = 7.7, Ar), 5.43 (1H, d, $J$ = 2.0, $CH_2$), 4.49 (1H, d, $J$ = 2.0, $CH_2$), 3.19 (3H, s, NMe), 2.19 (3H, s, Me); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.5, 153.2, 137.1, 137.0, 131.6, 131.5, 129.6, 128.6, 127.4, 95.8, 25.0, 17.6. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.7; H, 5.6; N, 13.0; [$M^+$] 216.0893. Found: C, 66.8; H, 5.6; N, 13.0; [$M^+$] 216.0890.

**3-Methyl-1-(2,5-dimethylphenyl)-5-methyleneimidazolidine-2,4-dione (3c).** The product was isolated as a pale yellow solid (1.95 g, 85%) and recrystallized from EtOH/water. Mp 85−86 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (1H, d, $J$ = 7.8, Ar), 7.16 (1H, d, $J$ = 7.9, Ar), 7.00 (1H, s, Ar), 5.42 (1H, d, $J$ = 2.0, $CH_2$), 4.48 (1H, d, $J$ = 2.0, $CH_2$), 3.18 (3H, s, NMe), 2.33 (3H, s, Me), 2.13 (3H, s, Me); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.5, 153.3, 137.3, 137.1, 133.5, 131.3, 131.2, 130.4, 129.0, 95.7, 24.9, 20.7, 17.1. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.8; H, 6.1; N, 12.2; [$M^+$] 230.1050. Found: C, 67.9; H, 6.1; N, 12.3; [$M^+$] 230.1061.

**3-Methyl-1-(naphthalen-1-yl)-5-methyleneimidazolidine-2,4-dione (3d).** The product was isolated as an off-white solid (1.54 g, 61%). Mp 147.5−148 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.80−7.93 (2H, m, Ar), 7.65−7.51 (4H, m, Ar), 7.47 (1H, dd, $J$ = 7.3 and 1.1, Ar), 5.46 (1H, d, $J$ = 2.2, $CH_2$), 4.44 (1H, d, $J$ = 2.2, $CH_2$), 3.26 (3H, s, NMe); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.5, 153.7, 137.7, 134.7, 130.1, 129.1, 128.7, 127.4, 127.0, 126.8, 125.7, 122.3, 96.6, 25.1. Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.4; H, 4.8; N, 11.1; [$M^+$] 252.0893. Found: C, 71.2; H, 4.9; N, 10.9; [$M^+$] 252.0891.

**3-Methyl-5-methylene-1-(2-nitrophenyl)imidazolidine-2,4-dione (3e).** The product was isolated as a yellow solid (1.38 g, 56%). Mp 110−111 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.19 (1H, dd, $J$ = 8.2 and 1.4, Ar), 7.82−7.76 (1H, m, Ar), 7.68−7.62 (1H, m, Ar), 7.50 (1H, dd, $J$ = 7.9 and 1.3, Ar), 5.52 (1H, d, $J$ = 2.6, $CH_2$), 4.68 (1H, d, $J$ = 2.6, $CH_2$), 3.19 (3H, s, NMe); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.9, 153.0, 145.8, 136.3, 134.5, 130.8, 130.2, 126.7, 126.3, 95.8, 25.1. Anal. Calcd for $C_{11}H_9N_3O_4$: C, 53.4; H, 3.7; N, 17.0. Found: C, 53.4; H, 3.5; N, 17.0. The sample did not give a molecular ion in the mass spectrum.

**3-Methyl-1-(2-*tert*-butylphenyl)-5-methyleneimidazolidine-2,4-dione (3f).** The product was isolated as off-white crystals (2.04 g, 79%). Mp 68−69 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (1H, dd, $J$ = 8.2 and 1.5, Ar), 7.44−7.39 (1H, m, Ar), 7.33−7.27 (1H, m, Ar), 6.99 (1H, dd, $J$ = 7.8 and 1.5, Ar), 5.49 (1H, d, $J$ = 2.0, $CH_2$), 4.39 (1H, d, $J$ = 2.0, $CH_2$), 3.19 (3H, s, NMe), 1.33 (9H, s, tBu); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.6, 154.3, 149.8, 139.6, 131.2, 131.0, 129.9, 129.0, 127.8, 97.4, 35.6, 31.5, 25.0. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.7; H, 7.0; N, 10.8; [$M^+$] 258.1363. Found: C, 69.9; H, 7.2; N, 11.0; [$M^+$] 258.1360.

**3-Methyl-5-methylene-1-(2-phenylphenyl)imidazolidine-2,4-dione (3g).** The product was isolated as a white solid (1.86 g, 67%). Mp 118−119 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.57−7.46 (3H, m, Ar), 7.37−7.28 (4H, m, Ar), 7.25−7.22 (2H, m, Ar), 5.29 (1H, d, $J$ = 2.1, $CH_2$), 4.49 (1H, d, $J$ = 2.1, $CH_2$), 3.05 (3H, s, NMe); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 162.2, 153.4, 141.7, 138.3, 137.2, 131.4, 130.2, 129.8, 129.3, 128.9, 128.5, 127.9, 127.8, 96.0. HRMS-EI calcd for $C_{17}H_{14}N_2O_2$: [$M^+$] 278.1050. Found: [$M^+$] 278.1058.

**General Procedure for Benzonitrile Oxide Cycloadditions with 1-Aryl 3-Methyl-5-methyleneimidazolidine-2,4-diones.** A solution of benzaldehyde oxime (12 mmol) and the appropriate 1-aryl-3-methyl-5-methyleneimidazolidine-2,4-dione **3** (4 mmol) in $CH_2Cl_2$ was cooled to 0 °C and treated with aqueous NaOCl (5%, 24 mmol) added in portions over 30 min. The vigorously stirred mixture was allowed to warm to room temperature overnight. The layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$. The solvent was removed under reduced pressure. The crude reaction mixture was analyzed by $^1$H NMR, and the product was purified as stated.

**8-Methyl-3,6-diphenyl-1-oxa-2,6,8-triazaspiro[4.4]non-2-ene-7,9-dione (4a).** The product was isolated as a pale yellow solid (1.03 g, 80%) and recrystallized from isopropyl alcohol. Mp 128−129 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.53−7.49 (2H, m, Ar),

7.44−7.33 (7H, m, Ar), 7.33−7.27 (1H, m, Ar), 3.85 (1H, d, $J$ = 17.8, C4-H$^a$), 3.34 (1H, d, $J$ = 17.8, C4-H$^b$), 3.21 (3H, s, NMe); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.1, 156.6, 153.9, 132.9, 130.9, 129.6, 128.8, 128.4, 127.7, 126.8, 126.5, 96.0, 39.4, 25.4. Anal. Calcd for $C_{18}H_{15}N_3O_3$: C, 67.3; H, 4.7; N, 13.1; [M$^+$] 321.1108. Found: C, 67.1; H, 4.7; N, 13.2; [M$^+$] 321.1098.

**8-Methyl-6-(2-methylphenyl)-3-phenyl-1-oxa-2,6,8-triazaspiro[4.4]non-2-ene-7,9-dione (4b).** The residue was purified by column chromatography (4% MeOH in $CH_2Cl_2$) to give an off-white solid (0.99 g, 74%). Mp 73−74 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ [major atropisomer] 7.53 (1H, d, $J$ = 7.6, Ar), 7.49−7.43 (2H, m, Ar), 7.42−7.30 (3H, m, Ar), 7.29−7.12 (3H, m, Ar), 3.84 (1H, d, $J$ = 17.6, C4-H$^a$), 3.21 (3H, s, NMe), 3.11 (1H, d, $J$ = 17.6, C4-H$^b$), 2.24 (3H, s, Me); [minor atropisomer] 7.49−7.43 (2H, m, Ar), 7.42−7.30 (4H, m, Ar), 7.29−7.12 (2H, m, Ar), 7.08 (1H, d, $J$ = 7.3, Ar), 3.94 (1H, d, $J$ = 17.6, C4-H$^a$), 3.65 (1H, d, $J$ = 17.6, C4-H$^b$), 3.22 (3H, s, NMe), 2.43 (3H, s, Me); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ [major atropisomer] 169.5, 156.1, 153.4, 139.5, 136.6, 132.2, 130.8, 129.6, 129.3, 128.8, 127.9, 127.8, 127.6, 96.1, 38.5, 25.3, 18.2; [minor atropisomer] 169.5, 155.8, 154.1, 139.5, 136.6, 132.2, 131.0, 129.8, 129.2, 128.8, 127.7, 127.6, 126.8, 96.4, 40.0, 25.4. Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.1; N, 12.5; [M$^+$] 335.1264. Found: C, 68.8; H, 5.2; N, 12.0; [M$^+$] 335.1253.

**6-(2,5-Dimethylphenyl)-8-methyl-3-phenyl-1-oxa-2,6,8-triazaspiro[4.4]non-2-ene-7,9-dione (4c).** The solid residue was recrystallized from hexane/ethyl acetate (2:1) to give the product as a white powder (0.92 g, 66%). Mp 123−124 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ [major atropisomer] 7.51−7.45 (2H, m, Ar), 7.43−7.31 (4H, m, Ar), 7.14 (1H, d, $J$ = 7.8, Ar), 7.06 (1H, d, $J$ = 7.8, Ar), 3.82 (1H, d, $J$ = 17.6, C4-H$^a$), 3.20 (3H, s, NMe), 3.11 (1H, d, $J$ = 17.6, C4-H$^b$), 2.26 (3H, s, Me), 2.18 (3H, s, Me); [minor atropisomer] 7.51−7.45 (2H, m, Ar), 7.43−7.31 (3H, m, Ar), 7.18 (1H, d, $J$ = 7.8, Ar), 7.06 (1H, d, $J$ = 7.8, Ar), 6.88 (1H, s, Ar) 3.91 (1H, d, $J$ = 17.6, C4-H$^a$), 3.64 (1H, d, $J$ = 17.6, C4-H$^b$), 3.21 (3H, s, NMe), 2.37 (3H, s, Me), 2.21 (3H, s, Me); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ [major atropisomer] 169.6, 156.1, 130.5, 129.8, 127.9, 96.2, 38.3, 25.4, 20.8, 17.8; [minor atropisomer] 169.5, 155.9, 130.7, 130.5, 129.7, 127.9, 96.5, 39.9, 25.4, 20.7, 17.9; signals that cannot be assigned to one atropisomer or the other: 153.5, 137.5, 136.5, 136.2, 133.3, 132.0, 130.8, 128.8, 126.7. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.5; N, 12.0; [M$^+$] 349.1421. Found: C, 68.8; H, 5.45; N, 12.1; [M$^+$] 349.1411.

**8-Methyl-6-(1-naphthalenyl)-3-phenyl-1-oxa-2,6,8-triazaspiro[4.4]non-2-ene-7,9-dione (4d).** The crude residue was recrystallized from hexane/ethyl acetate (2:1) to give the product as a white solid (1.05 g, 71%). Mp 191−192 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ [major atropisomer] 7.92−7.77 (3H, m, Ar), 7.69−7.39 (4H, m, Ar), 7.38−7.27 (4H, m, Ar), 7.25−7.20 (1H, m, Ar), 3.85 (1H, d, $J$ = 17.8, C4-H$^a$), 3.28 (3H, s, NMe), 3.21 (1H, d, $J$ = 17.8, C4-H$^b$); [minor atropisomer] 8.20 (1H, d, $J$ = 8.6, Ar), 7.92−7.77 (2H, m, Ar), 7.69−7.39 (4H, m, Ar), 7.38−7.27 (4H, m, Ar), 7.25−7.20 (1H, m, Ar), 3.97 (1H, d, $J$ = 17.6, C4-H$^a$), 3.73 (1H, d, $J$ = 17.6, C4-H$^b$), 3.28 (3H, s, NMe); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ [major atropisomer] 169.5, 156.3, 154.2, 130.7, 127.6, 96.5, 38.7, 25.5; [minor atropisomer] 169.5, 156.3, 154.2, 130.7, 127.6, 96.5, 39.7, 25.5; signals that cannot be assigned to one atropisomer or the other: 134.4, 131.0, 130.2, 129.0, 128.7, 128.3, 128.2, 128.0, 127.5, 127.0, 126.7, 126.5, 126.0, 124.9, 123.9, 121.7. Anal. Calcd for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.6; N, 11.3; [M$^+$] 371.1264. Found: C, 71.15; H, 4.6; N, 11.3; [M$^+$] 371.1261.

**8-Methyl-6-(2-nitrophenyl)-3-phenyl-1-oxa-2,6,8-triazaspiro-[4.4]non-2-ene-7,9-dione (4e).** The crude residue was recrystallized from isopropyl alcohol to give the product as light yellow crystals (1.11 g, 76%). Mp 148−149 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (1H, dd, $J$ = 8.2 and 1.4, Ar), 7.72 (1H, d, $J$ = 8.0, Ar), 7.64−7.59 (1H, m, Ar), 7.53−7.47 (3H, m, Ar), 7.43−7.31 (3H, m, Ar), 3.94 (1H, d, $J$ = 18.4, C4-H$^a$), 3.49 (1H, d, $J$ = 18.4, C4-H$^b$), 3.17 (3H, s, NMe); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.9, 157.0, 153.3, 134.6, 131.1, 130.2, 129.8, 128.9, 127.4, 126.9, 126.4, 125.6, 96.1, 77.2, 39.6, 25.6. Anal. Calcd for $C_{18}H_{14}N_4O_5$: C, 59.0; H, 3.85; N, 15.3; [M$^+$] 366.0959. Found: C, 58.8; H, 3.8; N, 15.2; [M$^+$] 366.0951.

**6-(2-*tert*-Butylphenyl)-8-methyl-3-phenyl-1-oxa-2,6,8-triazaspiro[4.4]non-2-ene-7,9-dione (4f).** The residue was purified by column chromatography (2% MeOH in $CH_2Cl_2$) to give a white solid (0.68 g, 45%). Mp 157−159 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ [major atropisomer] 7.53−7.48 (4H, m, Ar), 7.40−7.30 (4H, m, Ar), 7.23−7.17 (1H, m, Ar), 3.86 (1H, d, $J$ = 17.5, C4-H$^a$), 3.38 (1H, d, $J$ = 17.5, C4-H$^b$), 3.20 (3H, s, NMe), 1.37 (9H, s, tBu); [minor atropisomer] 7.64−7.60, (1H, m, Ar), 7.49−7.47 (2H, m, Ar), 7.42−7.28 (4H, m, Ar), 7.22−7.14 (1H, m, Ar), 6.92 (1H, dd, $J$ = 7.8 and 1.4, Ar), 3.80 (1H, d, $J$ = 17.6, C4-H$^a$), 3.69 (1H, d, $J$ = 17.6, C4-H$^b$), 3.21 (3H, s, NMe), 1.48 (9H, s, tBu); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ [major atropisomer] 169.2, 156.0, 155.5, 148.4, 132.3, 130.8, 130.3, 129.8, 128.8, 128.3, 128.0, 127.5, 126.6, 97.1, 36.8, 36.5, 32.5, 25.3; [minor atropisomer] 170.0, 155.7, 154.8, 151.7, 132.2, 131.3, 130.8, 129.7, 129.1, 128.8, 127.8, 126.7, 126.6, 96.7, 39.9, 36.8, 31.9, 25.4. Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.0; H, 6.1; N, 11.1; [M$^+$] 377.1734. Found: C, 69.9; H, 6.3; N, 10.85; [M$^+$] 377.1730.

**6-([1,1′-Biphenyl]-2-yl)-8-methyl-3-phenyl-1-oxa-2,6,8-triazaspiro[4.4]non-2-ene-7,9-dione (4g).** The residue was purified by column chromatography (2% MeOH in $CH_2Cl_2$) to give a white powder (0.97 g, 61%). Mp 163−165 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ [major atropisomer] 7.56−7.50 (1H, m, Ar), 7.48−7.27 (13H, m, Ar), 3.38 (1H, d, $J$ = 17.8, C4-H$^a$), 3.18 (3H, s, NMe), 2.68 (1H, d, $J$ = 17.8, C4-H$^b$); [minor atropisomer] 7.48−7.27 (12H, m, Ar), 7.20 (2H, d, $J$ = 7.7, Ar), 3.81 (1H, d, $J$ = 17.7, C4-H$^a$), 3.51 (1H, d, $J$ = 17.7, C4-H$^b$), 3.11 (3H, s, NMe); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.1, 156.0, 155.6, 141.9, 139.1, 131.9, 131.0, 129.6, 129.1, 128.7, 128.1, 127.6, 126.7, 96.1, 38.5, 25.5. Anal. Calcd for $C_{24}H_{19}N_3O_3$: C, 72.5; H, 4.8; N, 10.6; [M$^+$] 397.1426. Found: C, 72.7; H, 4.9; N, 10.3; [M$^+$] 397.1415.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Copies of NMR spectra, X-ray structure data and CIF file, and molecular simulation data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

**Corresponding Author**

*E-mail: paul.savage@csiro.au.

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