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Spiroheterocycles via Regioselective Cycloaddition Reactions of Nitrile Oxides with 5-Methylene-1*H*-pyrrol-2(5*H*)-ones

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Substituted 5-methylene-1*H*-pyrrol-2(5*H*)-ones underwent a 1,3-dipolar cycloaddition reaction with nitrile oxides to give the corresponding spiro heterocycles. Critical to this reaction was the development of a biphasic system for base-induced dehydrohalogenation of hydroximoyl chlorides, to give nitrile oxides, in the presence of a base-sensitive dipolarophile. A substituted *N*-tolyl 5-methylene-1*H*-pyrrol-2(5*H*)-one exhibited atropisomerism, which in turn led to a 4:1 facial selectivity during cycloaddition.

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Introduction

Despite their seemingly simple structure, 5-methylene-1*H*-pyrrol-2(5*H*)-ones **2** are quite uncommon in the literature. They have been patented as remedies for diseases caused by protein dephosphorylase,^[1] and as non-steroidal ligands for modulating ecdysone receptors.^[2] Pattenden and coworkers prepared 5-ylidenene-1*H*-pyrrol-2(5*H*)-ones by direct Wittig-type reactions of substituted maleimides with stabilized phosphoranes under forcing conditions.^[3] Demir and coworkers reported a synthesis of 5-methylene-1*H*-pyrrol-2(5*H*)-ones in two steps via initial singlet oxygen oxidation of 2-methylpyrroles to give 5-hydroxy- γ -lactams **1**, which eliminated water under acid conditions to give **2**.^[4] This method is limited by side reactions and over-oxidation.

More recently, Liepa and coworkers reported a convenient base-catalyzed condensation of 1,2-diketones with activated acetamides to give substituted 5-hydroxy- γ -lactams 1. Subsequent acid-catalyzed elimination of water from 1 gave 5-methylene-1*H*-pyrrol-2(5*H*)-ones 2 (Scheme 1).^[5]

The 1,3-dipolar cycloaddition reaction^[6] of nitrile oxides with carbon dipolarophiles has continued to attract attention as a versatile method to prepare Δ^2 -isoxazolines and isoxazoles.^[7] We have been interested in controlling the stereochemistry and regiochemistry of cycloaddition,^[8,9] inhibiting the competing side reaction of nitrile oxide dimerization,^[10,11] novel methods of ring-opening isoxazole cycloaddition products,^[12–14] and subsequent reactions of the ring-opened products.^[15] In particular, we have investigated nitrile oxide cycloaddition reactions with exocyclic methylene compounds, which lead to novel spiro heterocyclic systems.^[16–19]

The reactivity of 5-methylene-1*H*-pyrrol-2(5*H*)-ones towards nitrile oxides has not been reported. The related 3-methyleneisobenzofuranone **3a** and 3-methyleneisoindolinone **3b** react readily with aromatic nitrile oxides to give the corresponding spiroheterocycles **4a** and **4b**, respectively (Scheme 2).^[20,21] The spiro adducts **4a** were found to possess







Scheme 2.

activity as herbicides and plant growth regulators.^[22] The spiro adducts **4b** were sometimes accompanied by minor amounts of E and Z oximes **5**. The low solvent effects on reaction rates and product distribution led the authors to speculate that the oximes **5** were formed by a competitive stepwise biradical mechanism along with the 1,3-dipolar cycloaddition leading to spiro adducts **4b**.

Recently, the reaction mechanism for this cycloaddition and side reaction has been studied using density functional theory at the (U)B3LYP/6–31G* level.^[23] The latter analysis led to the conclusion that 1,3-dipolar cycloaddition reactions of benzonitrile oxides with 3-methyleneisoindolinones take place along concerted but highly asynchronous reaction pathways, while the formation of oximes occurs through a stepwise mechanism involving zwitterionic intermediates.

We now describe the nitrile oxide cycloaddition of some 5-methylene-1*H*-pyrrol-2(5H)-ones to generate 1-oxa-2,6-diazaspiro[4.4]nona-2,8-dien-7-one systems.





Results and Discussion

Convenient precursors to nitrile oxides are the corresponding hydroximoyl chlorides, which readily eliminate HCl on treatment with mild bases such as triethylamine or sodium carbonate.^[24] Thus, benzohydroximoyl chloride can be conveniently prepared from benzaldehyde oxime by treatment with *N*-chlorosuccinimide.^[25] Nitrile oxide generation can be carried out in THF, dichloromethane, diethyl ether, or other aprotic solvents.

5-Methylene-1*H*-pyrrol-2(5*H*)-ones **7a**–**d** were prepared according to the method of Liepa and coworkers.^[5] Hence, butadione was condensed with *N*-substituted cyanoacetamide or *N*,*N'*-disubstituted malonamide in DMF under base catalysis at room temperature. The reaction proved to be sluggish with the reported use of morpholine or piperidine as base, and instead a few drops of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave superior results. The intermediate hydroxy lactams **6** underwent acid-catalyzed elimination of water when treated with trifluoroacetic acid at room temperature to yield 5-methylene-1*H*-pyrrol-2(5*H*)-ones **7a–d** (Scheme 3).

Benzaldehyde oxime was converted to benzohydroximoyl chloride with *N*-chlorosuccinimide in DMF, according to the literature procedure.^[25] Benzonitrile oxide was generated in situ by treating benzohydroximoyl chloride with a slight excess of triethylamine in either THF or dichloromethane in the presence of the dipolarophile 5-methylene-1*H*-pyrrol-2(5*H*)-ones **7a–d** at 0°C. This standard nitrile oxide cycloaddition procedure caused the solution to immediately turn black. No cycloaddition products could be isolated and all of the pyrrolone starting materials had decomposed. We speculated that the 5-methylene-1*H*-pyrrol-2(5*H*)-ones were unstable to basic conditions and indeed, treating any these pyrrolones with triethylamine in organic solvents led to black solutions and extensive decomposition. Using more hindered bases such as Hünig's base also led to decomposition.

Nitrile oxides are usually generated in the presence of the dipolarophile to minimize the competing side reaction of dimerization.^[10] Nevertheless, separate generation of benzonitrile oxide (by treating benzohydroximoyl chloride with triethylamine, followed by careful neutralization or even slight acidification with HCl) and subsequent reaction with 5-methylene-1*H*-pyrrol-2(5*H*)-ones did lead to cycloadducts. The yields were poor and products were inevitably contaminated



with nitrile oxide dimerization products. The most convenient and effective method for cycloaddition was found to be in situ nitrile oxide generation in a biphasic reaction mixture. Thus, the 5-methylene-1*H*-pyrrol-2(5*H*)-one 7 was dissolved in ethyl acetate and mixed with an aqueous solution of sodium bicarbonate. Benzohydroximoyl chloride was added slowly to this two-phase system and moderate stirring allowed enough contact between the hydroximoyl chloride and the carbonate to achieve dehydrohalogenation to the nitrile oxide **8**. Cycloaddition then took place with the 5-methylene-1*H*-pyrrol-2(5*H*)-ones to afford spiro isoxazolines **9** without the associated complication of base-induced decomposition. Dichloromethane could be used as solvent in place of ethyl acetate with essentially the same results.

We further found that this two-phase system could also be used to conveniently generate the precursor hydroximoyl chlorides from the corresponding aldoximes using N-chlorosuccinimide, which could then be carried through to the cycloadducts **9** without any isolation of intermediates.

In each case, the cycloaddition only occurred on the exocyclic methylene group. Cycloaddition on the ring double bond of the pyrrolone was deemed unlikely as tetrasubstituted double bonds are known to react sluggishly with nitrile oxides, often to the point of there being no reaction occurring.^[7] NMR analysis of the products, specifically the total absence of the signals due to the exocyclic methylene protons, supported this contention. Furthermore, the cycloaddition was regioselective in orientation in that the oxygen of the nitrile oxide became attached to the disubstituted end of the double bond. This was established by observing the ¹H chemical shifts for the methylene protons of the newly formed isoxazoline rings. In each case, the characteristic AB system of these diastereotopic protons fell in the range of 3.2-3.6 ppm, which is indicative of protons on C4 of the isoxazoline ring rather than C5 (4.5–5.0 ppm), ^[17] hence establishing the regiochemistry of cycloaddition as shown (Scheme 4, Table 1).

In the cases of spiro isoxazolines **9a**, **9b**, **9d**, and **9e**, singlecrystal X-ray data were also obtained to confirm the structure of the cycloaddition adducts. Representative structures for spiro isoxazolines **9a** and **9e** are shown in Figs 1 and 2.

In each of the spiro heterocycles **9**, the diastereotopic protons on C4 of the isoxazoline ring appear as an AB quartet at \sim 3.0– 3.6 ppm. In the case of **9e**, an additional AB quartet could be observed for isoxazoline protons \sim 0.4 ppm downfield (the other resonances were also duplicated but not so clearly resolved). The additional isomeric spiro cycloadduct was attributed to atropisomerism,^[26] giving two rotational isomers in a ratio of 4:1. Restricted rotation around the N–tolyl bond makes this a stereogenic axis, which leads to substantially different magnetic environments for the isoxazoline protons depending on whether the tolyl methyl group is above or below the pyrrole plane and

	R ¹	R ²	R ³	Yield [%]
9a	CN	4-Chlorophenyl	Ph	43
9b	CN	2,4-Dichlorophenyl	Ph	49
9c	CN	4-Chlorophenyl	CO ₂ Et	49
9d	CN	2,4-Dichlorophenyl	CO ₂ Et	31
9e	CN	2-Methylphenyl	CO ₂ Et	79
9f	3-Chlorophenylcarbamoyl	3-Chlorophenyl	Ph	51
9g	3-Chlorophenylcarbamoyl	3-Chlorophenyl	COMe	45
9h	3-Chlorophenylcarbamoyl	3-Chlorophenyl	Thien-2-yl	76
9i	3-Chlorophenylcarbamoyl	3-Chlorophenyl	Pyridin-2-yl	89
9j	3-Chlorophenylcarbamoyl	3-Chlorophenyl	CO ₂ Et	35





Fig. 1. Molecular diagram of 6-(4-chlorophenyl)-9-methyl-7-oxo-3-phenyl-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-8-carbonitrile **9a**.



Fig. 2. Molecular diagram of ethyl 8-cyano-9-methyl-7-oxo-6-(2-methyl-phenyl)-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-3-carboxylate 9e.

hence adjacent to, or distant from, the isoxazoline C4 protons. The atropisomers were inseparable by TLC or HPLC under a variety of conditions.

Examining the structure of **9e** by molecular mechanics using the Sybyl force field with default parameters (under vacuum)





and Gasteiger Hückel charges, and by the semi-empirical AM1 method (under vacuum) gives two minimum energy conformations with N-tolyl torsion angles of 66° and 75° with the tolyl methyl above or below the pyrrole plane, which is consistent with the torsional angle of 71° observed in the solid-state crystal structure. The energy difference between these minimum energy conformations was only 2.5 kJ mol⁻¹. A dihedral driver was used to vary the N-tolyl dihedral angle, while minimizing the energy using the MM2 force field at each dihedral angle. Using this method, the barrier to rotation was estimated to be at least 200 kJ mol⁻¹ with the CH₃ eclipsing the pyrrole carbonyl. The high energy barrier to rotation and the small difference in the minimum energy conformations make it unlikely that the 4:1 ratio of atropisomers 9e represents a thermal equilibrium. To explore this, we examined the ¹H NMR spectra of the atropisomeric mixture 9e in [D8]toluene at various temperatures (25°C, 40°C, 55°C, 70°C, 85°C, and 100°C, and then at 25°C after cooling). The spectra in [D8]toluene at 25°C before and after heating were identical, including the ratio of atropisomers. As the sample was heated, the signals from the diastereotopic methylene protons, and the tolyl aromatic and methyl protons all became broader and the separation between the major and minor signals decreased. However, they did not coalesce even at 100°C, which is consistent with the high calculated barrier to rotation.

It is likely that the dipolarophile precursor, 4-methyl-5methylene-1-(2-methylphenyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile **7c** also experiences restricted rotation around the N-tolyl bond, similar to that reported for 3-(2-methylphenyl)-4methylthiazolin-2-one **10** (Scheme 5) ($\Delta G^{\neq} = 122 \text{ kJ mol}^{-1}$).^[27]

Nitrile oxide cycloadditions to exocyclic methylene groups are quite sensitive to steric control, often displaying high levels of facial selectivity.^[17,18] Cycloaddition to **7c** is therefore more likely to occur on the face opposite the methyl group, leading to an uneven diastereomeric mix of **9e** atropisomers (Scheme 6).

The crystal structure of 9e (major) is consistent with nitrile oxide addition to the face of the pyrrole on the opposite side to the tolyl methyl group. Furthermore, in the ¹H NMR spectra, the isoxazoline protons of the major isomer resonate upfield



Fig. 3. Nuclear Overhauser effect correlation spectroscopy (NOESY) correlations for major and minor rotational isomers of ethyl 8-cyano-9-methyl-7-oxo-6-(2-methylphenyl)-l-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-3-carboxylate 9e.

from the minor isomer. This is also consistent with preferential cycloaddition on the face opposite the tolyl methyl group, which would find the isoxazoline methylene protons relatively shielded by the tolyl methyl group in the product **9e** (major) in comparison with the corresponding isoxazoline methylene protons of the minor isomer.

Nuclear Overhauser effect correlation spectroscopy (NOESY) experiments were performed with the sample in both $CDCl_3$ and [D8]toluene. The results were similar for both solvents. The major and minor atropisomers both had correlations between one of the diastereotopic isoxazoline methylene protons and the lactam methyl group. The NOESY spectrum of the major isomer shows a correlation between the other diastereotopic methylene proton and the tolyl methyl protons, whereas the minor isomer exhibits a NOESY correlation between the other diastereotopic methylene proton and the tolyl ortho-aromatic proton (Fig. 3).

The diastereotopic methylene proton closer to the tolyl methyl group resonates significantly upfield in the major isomer compared with the minor isomer, suggesting shielding of the methylene proton by the tolyl methyl group. All of these data are consistent with an atropisomeric mixture of dipolarophile **7c** undergoing nitrile oxide cycloaddition preferentially from the least hindered face to give rise to a 4:1 diastereomeric mixture of atropisomers **9e**.

Conclusion

Substituted 5-methylene-1*H*-pyrrol-2(5*H*)-ones have been shown to readily undergo 1,3-dipolar cycloaddition reactions with nitrile oxides to give the corresponding 9-methyl-7-oxo-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene systems

with complete regioselectivity. Cycloaddition to the atropisomers of 4-methyl-5-methylene-1-(2-methylphenyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile **7c** gave a 4:1 facial selectivity leading to spiro adduct **9e**, which itself exhibited atropisomerism such that diastereomers could be clearly distinguished in the ¹H NMR spectrum. To our knowledge, this is the first reported example of atropisomeric induction of diastereoselectivity in nitrile oxide cycloadditions.

Experimental

General

Ethyl 2-chloro-2-(hydroxyimino)acetate was purchased from the Aldrich Chemical Co. Melting points were determined on a Buchi B-545 instrument and are uncorrected. Analytical TLC was carried out on Macherey-Nagel Polygram precoated plastic sheets (0.2 mm layer of silica gel with fluorescent indicator UV254). Developed plates were visualized with either UV light (254 nm) or a solution of 10% (w/v) phosphomolybdic acid in ethanol followed by heating. Radial chromatography was performed on a Harrison Research Chromatotron (Model 7924T) using 1-, 2-, or 4-mm thick silica plates (Merck silica gel 60 PF254 containing gypsum). ¹H NMR spectra were recorded at room temperature on a Bruker AV400 spectrometer operating at 400 MHz, using CDCl3 as solvent and internal reference unless otherwise specified. ¹³C NMR spectra were recorded at room temperature on a Bruker AV400 spectrometer operating at 100.6 MHz, using CDCl₃ as solvent and internal reference unless otherwise specified. Variable-temperature ¹H NMR spectra were recorded on a Bruker DRX500 spectrometer operating at 500 MHz with [D8]toluene as solvent. Electronimpact (EI) mass spectra were run on a ThermoQuest MAT95XP

mass spectrometer using an ionization energy of 70 eV. Accurate mass measurements were obtained on the same instrument with a resolution of 5000-10000 using perfluorokerosene as the reference compound. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago. All other starting materials, reagents, and solvents were obtained from commercial sources and used as supplied unless otherwise noted. The Cambridge Crystallographic Data Centre contains the supplementary crystallographic data for this paper. Molecular diagrams are shown with 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size. These data for 6-(4-chlorophenyl)-9-methyl-7-oxo-3-phenyl-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-8-carbonitrile 9a (CCDC 746208), 6-(2,4-dichlorophenyl)-9-methyl-7-oxo-3-phenyl-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-8-carbonitrile 9b (CCDC 746209), ethyl 8-cyano-6-(2,4-dichlorophenyl)-9-methyl-7-oxo-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-3-carboxylate 9d (CCDC 746210), and ethyl 8-cyano-9-methyl-7-oxo-6-(2-methylphenyl)-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-3carboxylate 9e (CCDC 746211) can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk.

General Procedure for the Preparation of 5-Methylene-1H-pyrrol-2(5H)-ones 7

Butadione (0.81 g, 10 mmol) was added to a solution of the appropriate cyanoacetamide (10 mmol) in DMF (6 mL) at room temperature. A few drops of DBU were added and this initiated a rise in temperature. The reaction was stirred overnight at room temperature and then diluted with water (50 mL). The mixture was extracted with dichloromethane (3×40 mL), and the combined extracts were dried (MgSO₄) and concentrated to ~20 mL. The resulting dichloromethane solution of hydroxy lactam **6** was treated with trifluoroacetic acid (2 mL), left to stand for 24 h, and then evaporated to dryness. The residue was recrystallized as stated to give 5-methylene-1*H*-pyrrol-2(5*H*)-ones **7**.

1-(4-Chlorophenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile **7a**

Prepared from *N*-(4-chlorophenyl)-2-cyanoacetamide, isolated as a pale yellow powder and recrystallized from acetic acid to give pale yellow plates in 77% yield over two steps, mp 182– 184° C (lit.^[5] 182–184°C).

1-(2,4-Dichlorophenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile **7b**

Prepared from *N*-(2,4-dichlorophenyl)-2-cyanoacetamide, isolated as a fawn powder (75%), mp 176–177°C. (Found: C 55.6, H 2.7, N 9.8; [M^{+*}] 278.0006. C₁₃H₈Cl₂N₂O requires C 55.9, H 2.9, N 10.0%; [M^{+*}] 278.0008). $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.58 (1H, d, 2.0, Ar–H), 7.39 (1H, d, 8.5, Ar), 7.25 (1H, dd, 8.5 and 2.2, Ar), 5.24 (1H, d, 2.6, =CH₂), 4.77 (1H, d, 2.6, =CH₂), 2.48 (3H, s, CH₃). $\delta_{\rm C}$ (100 MHz, CDCl₃) 162.9, 158.1, 144.3, 136.3, 134.6, 131.7, 130.8, 129.7, 128.5, 111.4, 108.2, 100.4, 12.5.

4-Methyl-5-methylene-1-(2-methylphenyl)-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile **7c**

Prepared from N-(2-methylphenyl)-2-cyanoacetamide, isolated as a dark green-grey solid, which was recrystallized from isopropanol to give pale olive crystals (72%), mp 154–159°C. (Found: C 74.5, H 5.5, N 12.6; $[M^{+*}]$ 224.0943. $C_{14}H_{12}N_2O$ requires C 74.9, H 5.4, N 12.5%; $[M^{+*}]$ 224.0944). δ_H (400 MHz, CDCl₃) 7.37–7.25 (3H, m, Ar), 7.13 (1H, d, 8.5, Ar), 5.21 (1H, d, 2.7, =CH₂), 4.78 (1H, d, 2.7, =CH₂), 2.48 (3H, s, CH₃), 2.12 (3H, s, CH₃). δ_C (100 MHz, CDCl₃) 163.0, 157.5, 145.5, 137.1, 132.1, 131.4, 129.5, 129.0, 127.2, 111.8, 108.0, 100.3, 17.6, 12.4.

N,1-Bis(3-chlorophenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxamide **7d**

Prepared from N^1 , N^3 -bis(4-chlorophenyl)malonamide, isolated as a yellow powder and recrystallized from methanol to give pale yellow needles (65%), mp 164–165°C. (Found: C 60.9, H 3.6, N 7.3; [M⁺⁺] 372.0413. C₁₉H₁₄Cl₂N₂O₂ requires C 61.1, H 3.8, N 7.5%; [M⁺⁺] 372.0427). $\delta_{\rm H}$ (400 MHz, CDCl₃) 10.57 (1H, s, NH), 7.88 (1H, t, 2.0, Ar–H), 7.38–7.48 (3H, m, Ar–H), 7.33 (1H, t, 1.8, Ar–H), 7.20–7.25 (2H, m, Ar–H), 7.07 (1H, m, Ar–H), 5.39 (1H, d, 2.6, =CH₂), 5.15 (1H, d, 2.6, =CH₂), 2.70 (3H, s, CH₃). $\delta_{\rm C}$ (100 MHz, CDCl₃) 168.3, 160.0, 154.6, 145.9, 139.0, 135.1, 134.63, 134.61, 130.5, 129.9, 128.8, 128.0, 125.9, 124.4, 120.5, 120.1, 117.9, 100.8, 11.5.

General Method for Nitrile Oxide Cycloadditions

A solution of sodium hydrogen carbonate (0.67 g, 7.9 mmol) in water (10 mL) was added to a solution of the appropriate 5-methylene-1*H*-pyrrol-2(5*H*)-one 7 (1.1 mmol) in ethyl acetate (10 mL) at room temperature. The two-phase mixture was cooled to 0°C and the appropriate hydroximoyl chloride (2.5 mmol) was added portionwise over 15 min with stirring. The mixture was stirred for 3 h and allowed to warm to room temperature. The organic phase was washed with water (3 × 20 mL), dried (MgSO₄), and evaporated using reduced pressure. The residue was triturated with Et₂O, collected by filtration, and the crude product was recrystallized from the solvent stated.

6-(4-Chlorophenyl)-9-methyl-7-oxo-3-phenyl-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-8-carbonitrile **9a**

Prepared on a 1.6-mmol scale to give the spiro heterocycle **9a** (0.25 g, 43%) as a white fluffy solid, mp 179–180°C. (Found: C 65.8, H 3.7, N 11.5; $[M^{+*}]$ 363.0759. C₂₀H₁₄ClN₃O₂ requires C 66.0, H 3.9, N 11.5%; $[M^{+*}]$ 363.0769). $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.54–7.35 (9H, m, Ar), 3.59 (1H, d, 18.4, H4), 3.37 (1H, d, 18.4, H4), 2.37 (3H, s, CH₃). $\delta_{\rm C}$ (100 MHz, CDCl₃) 168.0, 161.9, 157.4, 134.2, 131.9, 131.4, 129.9, 129.1, 128.0, 127.3, 126.7, 110.8, 110.7, 102.0, 39.6, 12.7.

6-(2,4-Dichlorophenyl)-9-methyl-7-oxo-3-phenyl-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-8-carbonitrile **9b**

Prepared on a 1.4-mmol scale to give spiro heterocycle **9b** (0.28 g, 49%) as a pale orange solid, which was purified by recrystallization from isopropanol to give a pale yellow solid, mp 211–213°C. (Found: C 60.3, H 3.3, N 10.4; [M^{+*}] 397.0374. C₂₀H₁₃Cl₂N₃O₂ requires C 60.3, H 3.3, N 10.6%; [M^{+*}] 397.0379). $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.48 (3H, dd, 6.7 and 1.3, Ar), 7.43 (2H, dd, 5.7 and 2.5, Ar), 7.39 (1H, dd, 5.8 and 1.3, Ar), 7.30 (1H, d, 2.2, Ar), 7.28 (1H, d, 2.2, Ar), 3.60 (1H, d, 18.4, H4), 3.44 (1H, d, 18.4, H4), 2.39 (3H, s, CH₃). $\delta_{\rm C}$ (100 MHz, CDCl₃) 168.2, 161.1, 157.1, 136.5, 134.5, 132.6, 131.4, 130.4, 129.1, 128.8, 127.3, 126.7, 110.9, 110.6, 101.6, 38.7, 12.9.

Ethyl 6-(4-Chlorophenyl)-8-cyano-9-methyl-7-oxo-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-3-carboxylate **9c**

Prepared on a 2.1-mmol scale to give carboxylate **9c** (0.37 g, 49%) as a pale orange solid, which was purified by recrystallization from isopropanol to give colourless needles, mp 184–185°C. (Found: C 56.9, H 3.8, N 11.5; $[M^{+*}]$ 359.0660. C₁₇H₁₄ClN₃O₄ requires C 56.8, H 3.9, N 11.7%; $[M^{+*}]$ 359.0667). $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.41 (2H, dd, 6.6 and 2.0, Ar), 7.25 (2H, dd, 6.6 and 2.0, Ar), 4.32 (2H, q, 7.1, CH₃CH₂O), 3.41 (1H, d, 19.5, H4), 3.21 (1H, d, 19.5, H4), 2.34 (3H, s, CH₃), 1.35 (3H, t, 7.1, CH₃CH₂O). $\delta_{\rm C}$ (100 MHz, CDCl₃) 166.5, 161.7, 158.6, 152.0, 134.9, 131.2, 131.1, 128.5, 111.3, 110.3, 103.3, 63.0, 37.8, 13.9, 12.6.

Ethyl 8-Cyano-6-(2,4-dichlorophenyl)-9-methyl-7-oxo-1oxa-2,6-diazaspiro[4.4]nona-2,8-diene-3-carboxylate **9d**

Prepared on a 1.3-mmol scale to give spiro heterocycle **9d** (0.17 g, 31%) as a green-grey solid, which was recrystallized from isopropanol to an off-white solid, mp 185–186°C. (Found: C 52.0, H 3.5, N 10.4; [M^{+•}] 393.0293. C₁₇H₁₃Cl₂N₃O₄ requires C 51.8, H 3.3, N 10.7%; [M^{+•}] 393.0278). $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.56 (1H, d, 2.2, Ar), 7.38 (1H, d, 8.5, Ar), 7.33 (1H, dd, 8.5 and 2.2, Ar), 4.30 (2H, q, 7.1, CH₃CH₂O), 3.43 (1H, d, 19.7, H4), 3.25 (1H, d, 19.7, H4), 2.35 (3H, s, CH₃), 1.33 (3H, t, 7.1, CH₃CH₂O). $\delta_{\rm C}$ (100 MHz, CDCl₃) 166.9, 160.8, 158.5, 151.8, 136.8, 134.7, 132.3, 130.6, 129.0, 128.5, 111.1, 110.2, 103.1, 62.9, 36.9, 13.9, 12.8.

Ethyl 8-Cyano-9-methyl-7-oxo-6-(2-methylphenyl)-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-3-carboxylate **9e**

Prepared on a 1.6-mmol scale to give spiro heterocycle **9e** (0.43 g, 79%) as an off-white solid, which was recrystallized from isopropanol to give white needles, mp 159–160°C. (Found: C 63.8, H 5.2, N 12.4; [M^{+•}] 339.1210. C₁₈H₁₇N₃O₄ requires C 63.7, H 5.1, N 12.4%; [M^{+•}] 339.1214). Major atropisomer: $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.34–7.25 (4H, m, Ar), 4.30 (2H, q, 7.1, CH₃CH₂O), 3.37 (1H, d, 19.5, H4), 3.04 (1H, d, 19.5, H4), 2.35 (3H, s, lactam CH₃), 2.16 (3H, s, tolyl CH₃), 1.31 (3H, t, 7.1, CH₃CH₂O). $\delta_{\rm C}$ (100 MHz, CDCl₃) 166.6, 159.7, 157.6, 151.5, 136.9, 131.4, 129.8, 129.2, 127.7, 127.0, 111.1, 110.5, 103.5, 62.8, 36.5, 18.2, 12.9, 12.8. Minor atropisomer: $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.4–7.3 (3H, m, Ar), 7.01 (1H, d, 7.7, tolyl H6), 4.3–4.25 (2H, m, CH₃CH₂O), 3.65 (1H, d, 19.2, H4), 3.46 (1H, d, 19.2, H4), 2.35 (3H s, lactam CH₃), 2.29 (3H, s, tolyl CH₃), 1.30 (3H, t, 7.1, CH₃CH₂O).

N,6-Bis(3-chlorophenyl)-9-methyl-7-oxo-3-phenyl-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-8-carboxamide **9f**

Prepared on a 1.1-mmol scale to give spiro heterocycle **9f** as a white fluffy solid, which was purified by recrystallization from isopropanol (0.275 g, 51%), mp 247–248.5°C. (Found: C 63.1, H 3.9, N 8.5; [M^{+•}] 491.0792. C₂₆H₁₉Cl₂N₃O₃ requires C 63.4, H 3.9, N 8.5%; [M^{+•}] 491.0798). $\delta_{\rm H}$ (400 MHz, CDCl₃) 10.56 (1H, s, NH), 7.88 (1H, m, Ar), 7.54–7.25 (11H, m, Ar), 7.13 (1H, m, Ar), 3.64 (1H, d, 18.3, H4), 3.37 (1H, d, 18.3, H4), 2.62 (3H, s, CH₃). $\delta_{\rm C}$ (100 MHz, CDCl₃) 167.8, 165.2, 158.9, 157.3, 138.6, 135.1, 134.7, 131.2, 130.5, 129.9, 129.0, 128.7, 127.6, 127.1, 126.7, 124.7, 122.5, 120.2, 118.0, 101.8, 39.6, 11.9.

3-Acetyl-N,6-bis(3-chlorophenyl)-9-methyl-7-oxo-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-8-carboxamide **9g**

Prepared on a 1.3-mmol scale using pyruvohydroximoyl chloride^[28] to give carboxamide 9g (0.276 g, 45%), which was

purified by recrystallization from dichloromethane/ethanol to give colourless microcrystals, mp 206–207°C. (Found: C 57.6, H 3.8, N 9.3; [M^{+•}] 457.0584. C₂₂H₁₇Cl₂N₃O₄ requires C 57.7, H 3.7, N 9.2%; [M^{+•}] 457.0591). $\delta_{\rm H}$ (400 MHz, CDCl₃) 10.43 (1H, s, NH), 7.83 (2H, s, Ar), 7.41–7.32 (3H, m, Ar), 7.28–7.22 (3H, m, Ar), 3.48 (1H, d, 19.8, H4), 3.12 (1H, d, 19.8, H4), 2.51 (3H, s, CH₃), 2.44 (3H, s, CH₃). $\delta_{\rm C}$ (100 MHz, CDCl₃) 191.3, 167.8, 163.7, 158.5, 158.3, 138.5, 135.4, 134.7, 134.2, 130.7, 130.0, 129.2, 127.5, 125.2, 124.8, 122.9, 120.3, 118.1, 103.7, 36.5, 26.6, 11.9.

N,6-Bis(3-chlorophenyl)-9-methyl-7-oxo-3-(thiophen-2-yl)-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-8-carboxamide **9h**

A solution of thiophene 2-aldoxime (0.42 g, 33 mmol) in dichloromethane (6 mL) containing one drop of concentrated hydrochloric acid was cooled to 0°C and treated with N-chlorosuccinimide (0.44 g, 33 mmol) added in portions over 15 min, and then stirred for 1.5 h. Dichloromethane (10 mL) followed by water (10 mL), N,1-bis(3-chlorophenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxamide 7e (0.6 g, 1.6 mmol), and sodium bicarbonate (0.6 g, 71 mmol) were added and the whole stirred at 0°C for 4 h, then at room temperature for 3 h. The precipitate was collected by filtration and washed with a little dichloromethane and water to give the spiro heterocycle 9h (0.62 g, 76%). A portion was crystallized from dichloromethane/isopropanol to give colourless microneedles, mp 252–253°C. (Found: C 57.5, H 3.3, N 8.3; [M+•] 497.0360. C₂₄H₁₇Cl₂N₃O₃S requires C 57.8, H 3.4, N 8.4%; [M^{+•}] 497.0362). δ_H (400 MHz, CDCl₃) 10.58 (1H, s, NH), 7.64 (2H, m, Ar), 7.49-7.06 (9H, m, Ar), 3.78 (1H, d, 21.5, H4), 3.49 (1H, d, 21.5, H4), 2.61 (3H, s, CH₃). δ_C (100 MHz, CDCl₃) 168.8, 167.7, 161.8, 161.5, 154.0, 136.5, 136.0, 135.3, 133.1, 130.6, 128.3, 128.0, 127.3, 126.1, 122.6, 122.55, 120.5, 118.7, 115.9, 113.1, 110.2, 102.1, 40.9, 12.6.

N,6-Bis(3-chlorophenyl)-9-methyl-7-oxo-3-(pyridin-2-yl)-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-8-carboxamide **9i**

One drop of concentrated hydrochloric acid was added to a mixture of picolinaldehyde oxime (0.61 g, 5 mmol) and N-chlorosuccinimide (0.67 g, 5 mmol) in dichloromethane (8 mL) and the whole was stirred overnight. N,1-bis (3-chlorophenyl)-4-methyl-5-methylene-2-oxo-2,5-dihydro-1Hpyrrole-3-carboxamide 7e (0.93 g, 2.5 mmol) and water (5 mL) were added followed by sodium bicarbonate (1 g), which was added in four portions over 30 min. After 3 h, benzene (10 mL) and water (20 mL) were added and the mixture was stirred for 1 h, and then filtered to give the product (0.74 g) as fine, colourless needles. The organic phase from the filtrate was evaporated and the residue was briefly boiled with isopropanol (10 mL). Cooling to room temperature followed by filtration afforded an additional 0.27 g of spiro heterocycle 9i (combined weight 1.01 g, 89%). A portion was crystallized from dichloromethane/isopropanol to give colourless woolly needles, mp 224-225°C. (Found: C 60.8, H 3.8, N 11.4; [M^{+•}] 492.0750. C₂₅H₁₈Cl₂N₄O₃ requires C 60.9, H 3.7, N 11.4%; $[M^{+\bullet}]$ 492.0750). $\delta_{\rm H}$ (400 MHz, CDCl₃) 10.57 (1H, s, NH), 8.53 (1H, m, Py-H6), 7.97–7.87 (2H, m, Ar), 7.76–7.68 (1H, m, Ar), 7.48–7.05 (8H, m, Ar), 3.81 (1H, d, 19.6, H4), 3.53 (1H, d, 19.6, H4), 2.61 (3H, s, CH₃). δ_C (100 MHz, CDCl₃) 168.0, 165.2, 159.3, 159.0, 149.5, 147.5, 138.7, 136.7, 135.1, 134.7, 130.5, 130.0, 128.7, 127.3, 125.1, 125.0, 124.6, 122.4, 121.7, 120.3, 118.1, 102.2, 38.3, 12.0.

Ethyl 6-(3-Chlorophenyl)-8-(3-chlorophenylcarbamoyl)-9-methyl-7-oxo-1-oxa-2,6-diazaspiro[4.4]nona-2,8-diene-3-carboxylate **9j**

Prepared on a 1.1-mmol scale to give carboxylate **9j** (0.18 g, 35%) as a white fluffy solid, which was purified by recrystallization from isopropanol, mp 219–221°C. (Found: C 56.9, H 4.1, N 8.6; [M^{+*}] 487.0694. C₂₃H₁₉Cl₂N₃O₅ requires C 56.6, H 3.9, N 8.6%; [M^{+*}] 487.0696). $\delta_{\rm H}$ (400 MHz, CDCl₃) 10.44 (1H, s, NH), 7.85 (1H, dd, 3.9 and 1.9, Ar), 7.43–7.38 (3H, m, Ar), 7.28–7.24 (3H, m, Ar), 7.12 (1H, m, Ar), 4.33 (2H, q, 7.1, CH₃CH₂O), 3.48 (1H, d, 19.4, CH), 3.24 (1H, d, 19.4, CH), 2.58 (3H, s, CH₃), 1.36 (3H, t, 7.1, CH₃CH₂O). $\delta_{\rm C}$ (100 MHz, CDCl₃) 167.8, 163.8, 158.8, 158.5, 152.0, 138.5, 135.4, 134.7, 134.1, 130.9, 129.9, 129.2, 127.5, 125.1, 124.8, 122.8, 120.2, 118.0, 103.4, 62.9, 37.8, 13.9, 11.9.

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451

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