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PAPER

Facial selectivity induced by *N*-aryl atropisomerism in benzonitrile oxide cycloadditions with 4-methylene-2-oxazolidinones†

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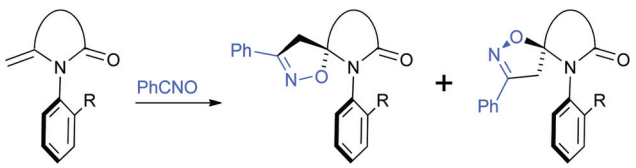
N-Aryl 4-methylene-2-oxazolidinones, prepared *via* the corresponding *O*-propargyl carbamates, underwent nitrile oxide cycloaddition with benzonitrile oxide to give 5-spiro isoxazoline adducts with complete regioselectivity. Steric hindrance by atropisomerism around the *N*-aryl bond induced facial selectivity in these cycloadditions.

Introduction

As part of an ongoing interest in drug discovery by fragment-based approaches,[1] we are interested in structurally novel small heterocycles to enrich our fragment library. Most commercial fragment libraries contain an abundance of flat, aromatic heterocycles and an underrepresentation of sp^3-rich compounds. This bias is inconsistent with the ligands typically found in nature, which tend to have more stereogenic centres and more architectural complexity.[2] A fragment library with high molecular shape diversity, especially one rich in three dimensional compounds, might be expected to display a broader range of biological activities.[3,4]

An expedient method for introducing three-dimensionality into small molecules is with spiro linkages, and to that end we have pursued the construction of spiro heterocycles using 1,3-dipolar nitrile oxide cycloaddition (NOC) reactions with exocyclic methylene compounds.[5–10] Nitrile oxides react readily with both electron-rich and electron-poor carbon–carbon double bonds to give isoxazolines.[11,12] Regardless of the polarity of the dipolarophile, the regiochemistry of NOC reactions is easily predictable because the cycloaddition orientation is dominated by steric influences. The oxygen of the nitrile oxide almost exclusively adds to the more hindered end of the dipolarophile.[13] This characteristic of NOC reactions has been used to control the regiochemistry of cycloaddition to give a desired isomer.[14–18] We were recently surprised to discover that the steric sensitivity of NOC reactions extended to facial selectivity of methylene pyrrolones[9] and methylene hydantoins[10] as controlled by atropisomerism due to remote, unsymmetrical *N*-aryl substituents (Scheme 1).



Scheme 1

Atropisomerism is a relatively overlooked source of asymmetry, with important implications in the pharmaceutical industry.[19] This phenomenon, in relation to facial selectivity of NOC reactions, had remained unnoticed in the field because previously reported NOC reactions on methylene N-substituted heterocycles,[20–23] including by us,[8] had all used symmetrical or non-hindered N-substituents.

The recent chemistry of 2-oxazolidinones is dominated by their use as chiral auxiliaries,[24,25] organocatalysts,[26] and ligands for asymmetric catalysis.[27] *N*-aryl 2-oxazolidinones also show activity against multi-resistant gram-positive bacteria,[28–30] cholesteryl ester transfer protein,[31,32] antagonists for the prostatic adrenoceptor,[33] and have applications for several other pharmaceutical purposes.[34] We now describe the nitrile oxide cycloaddition of *N*-aryl 4-methylene-2-oxazolidinones to generate 1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one systems, where the facial selectivity of cycloaddition is controlled by substituents on the *N*-aryl group through atropisomerism.

Results and discussion

Propargyl alcohols react readily with isocyanates to give *O*-propargyl carbamates, which in turn can undergo base-promoted cyclization to give 4-methylene-2-oxazolidinones.[35–37] Methods for improving the formation of carbamates from alcohols and isocyanates,[38] and for the subsequent cyclization to 4-methylene-2-oxazolidinones,[39,40] have recently been published. Using a previously described modification of these procedures,[8]

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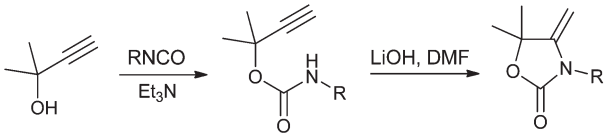
Table 1 Synthesis of carbamates **2** and oxazolidinones **3**, and the ^{1}H variable temperature NMR determined rotation barrier for the *N*-aryl bond



1 **2** **3**

Entry	R	Yields (%) **2**	Yields (%) **3**	Geminal methyl resonance difference at 25 °C (Hz)	Coalescence temperature[a] (°C)	Rotational barrier $\Delta G^{\neq}$ (kJ mol^{-1})
a	2-*t*-Butylphenyl	37	84	—	N/A	—
b	3,4-Dichlorophenyl	81	74	—	N/A	—
c	2,5-Dimethylphenyl	22	83	10.40	>150	>95.1
d	2-Methylphenyl	46	90	10.85	>150	>94.9
e	1-Naphthyl	91	79	32.20	>150	>91.0
f	2-Nitrophenyl	87	100	24.50	80–85	75.2–76.3
g	2-Phenylphenyl	51	69	170.50	>150	>85.1
h	2,4-Dichlorophenyl	92	81	16.60	125–150	86.5–92.1

[a] Measured at 500 MHz in DMSO-d_6.

carbamates **2a–h** were prepared by reacting dimethylpropargyl alcohol (2-methylbut-3-yn-2-ol) **1** with aryl isocyanates at room temperature in THF with an equivalent of triethylamine and a catalytic amount of DMAP. The yields were variable but generally satisfactory (Table 1), and in most cases the carbamates **2a–h** could be used for the next step without further purification. Cyclization of carbamates **2a–h** proceeded in good yields using a recently described, mild method (10 mol% LiOH in DMF)[41] to give the *N*-aryl oxazolidinones **3a–h**.

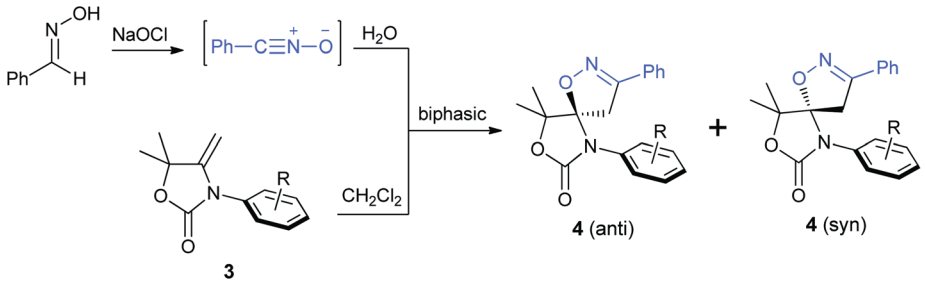
The ^{1}H NMR spectra of some of the oxazolidinones **3** showed clear evidence of atropisomerism, even at room temperature. For the symmetrical 5,5-dimethyl-4-methylene-3-phenyloxazolidin-2-one (**3**, R = Ph), the geminal methyl groups on C-5 appear as a single 6H resonance.[8] By contrast, in this study the geminal methyl groups on C-5 of 5,5-dimethyl-4-methylene-3-(2-nitrophenyl)oxazolidin-2-one **3f**, for example, appear as two separate, clearly resolved 3H singlets (see ESI†). This is obviously due to atropisomeric asymmetry along the *N*-aryl bond, which renders the methyl groups diastereotopic. Bertrand and co-workers recently reported data for some unsymmetrical *N*-aryl oxazolidinones, including the 2-nitrophenyl derivative **3f** and its C-5 monomethyl analogue.[42] They invoked the possibility of atropisomerism for the latter to account for complexity in the ^{1}H NMR spectrum of that compound, although the complexity was compounded by long-range allylic coupling. The separate methyl resonances for **3f** and other unsymmetrical *N*-aryl compounds were reported in the Experimental data, however the source of this magnetic inequivalence went without comment. Using variable temperature dynamic NMR we were able to determine the coalescence temperature for the atropisomers of **3f** and **3h** and thereby calculate the free energy barrier to rotation along the *N*-aryl bond for these examples (Table 1).[43] The measured rotation barriers in the order of 75–90 kJ mol^{-1} were consistent with those previously calculated at the B3LYP/6-31G* level for analogous *N*-aryl 5-methylenehydantoins.[10] The *N*-2,5-dimethylphenyl derivative **3c** formed crystals suitable for X-ray crystallography and in the obtained structure the dihedral angle between the oxazolidinone ring (itself virtually planar) and the *N*-aryl ring was 100.63° (see ESI†).

The methyl resonances for 5,5-dimethyl-4-methylene-3-(2-*t*-butylphenyl)oxazolidin-2-one (**3a**) and 5,5-dimethyl-4-methylene-3-(3,4-dichlorophenyl)oxazolidin-2-one (**3b**) were not resolved at 500 MHz. This is likely to be mere coincidental magnetic equivalence, certainly in the 2-*t*-butyl case (**3a**), rather than absence of atropisomerism.

Nitrile oxides are highly reactive intermediates that dimerize readily to furoxans so they are usually generated *in situ* and trapped in the presence of olefinic dipolarophiles. Alkyl nitrile oxides are typically prepared by the formal dehydration of primary nitro compounds.[44,45] The common precursors to aryl nitrile oxides are the corresponding hydroximoyl chlorides (prepared by chlorination of aldoximes), which eliminate HCl upon treatment with mild bases, such as triethylamine and sodium carbonate.[46] The chlorination and dehydrohalogenation steps can be combined in a one pot reaction where water-insoluble aldoximes are reacted under biphasic conditions with 5% sodium hypochlorite solution as both chlorinating agent and base.[47] An advantage of this method, apart from operational convenience, is that the slow formation of nitrile oxide at the biphasic interface leads to a low steady-state concentration of nitrile oxide compared to the dipolarophile, and hence increased cycloaddition product at the expense of the unwanted furoxane dimerization side-product.

Using this method, benzonitrile oxide was generated *in situ* by mixing commercially available benzaldehyde oxime in CH_2Cl_2 with a 5% aqueous NaOCl solution at 0 °C, in the presence of 4-methylene-2-oxazolidinones **3a–h**. The nitrile oxide was immediately trapped by the dipolarophile to give the corresponding spiro cycloadducts in moderate isolated yields (Table 2). In each case the cycloaddition was completely regioselective (to the limits of NMR detection), in that the oxygen of the nitrile oxide became attached to the oxazolidinone ring end of the

Table 2 Nitrile oxide cycloaddition reactions on oxazolidinones **3**



Entry	*N*-Aryl group	Cycloadduct **4** Yield[a] (%)	Anti : Syn ratio
a	2-*t*-Butylphenyl	46	>99 : 1
b	3,4-Dichlorophenyl	58	>99 : 1
c	2,5-Dimethylphenyl	50	4 : 1
d	2-Methylphenyl	61	4 : 1
e	1-Naphthyl	38	6 : 1
f	2-Nitrophenyl	47	>99 : 1
g	2-Phenylphenyl	45	>99 : 1
h	2,4-Dichlorophenyl	51	18 : 1

[a] Total isolated yield. Atropisomers were inseparable.

dipolarophile double bond, as expected.[13] The ^{1}H chemical shifts for the characteristic AB system of the diastereotopic methylene protons on the newly formed isoxazoline rings fell in the range of 3.0–3.5 ppm. This chemical shift is indicative of protons on C-4 of the isoxazoline ring rather than C-5 (4.5–5.0 ppm),[5] hence establishing the regiochemistry of cycloaddition as shown.

Because the precursor methylene oxazolidinones **3** are atropisomeric, the faces of the dipolarophile are non-equivalent. Hence diastereomeric cycloadducts are possible due to either syn or anti addition with respect to the substituent on the *N*-aryl group. NMR spectra of the crude reaction mixtures, prior to purification, were recorded. In four cases (**4c–e** and **4h**) these diastereomers were evident in the ^{1}H NMR spectra and their ratios were measured (Table 2). In the other four cases (**4a,b** and **4f,g**) only a single diastereomer could be detected by NMR, which indicates a high degree of diastereoselectivity in the cycloaddition reaction. The least diastereoselectivity was observed where the substituent on the *N*-aryl group was methyl (4 : 1 for **4c** and **4d**). More sterically demanding substituents such as 1-naphthyl and 2,4-dichlorophenyl gave greater selectivity, whereas large substituents on the *N*-aryl group such as 2-*t*-butyl, 2-phenyl, and 2-nitro led to complete diastereoselectivity. Curiously, the 3,4-dichlorophenyl analogue **3b** also led to a completely diastereoselective cycloadduct **4b** even though it appears to be less sterically demanding; having no 2-substituent on the *N*-aryl ring.

Intuitively, the anti cycloaddition product is more likely to predominate because that face is less shielded than the *syn* face. The ^{1}H NMR data were consistent with this tentative assignment. When there was a mixture of diastereomers (**4c–e** and **4h**) the ^{1}H resonance for the isoxazoline ring methylene protons of the major isomer always appeared upfield from the analogous protons in the minor isomer. This observation is consistent with

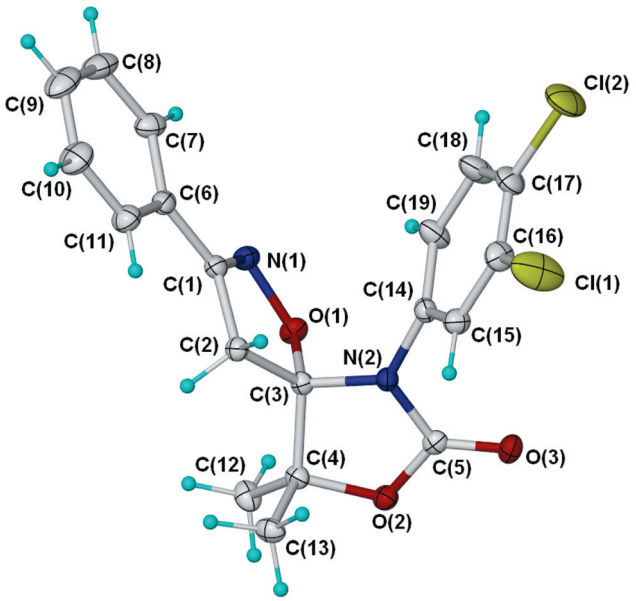


Fig. 1 Molecular diagram of **4b** with non-hydrogen atoms represented by 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size.

cycloaddition favouring the face opposite the substituent on the *N*-aryl group. The isoxazoline methylene protons of the resulting major products are shielded by the substituent on the *N*-aryl group, relative to the corresponding isoxazoline methylene protons of the minor isomer. For the *N*-2-*t*-butylphenyl cycloadduct **4a**, NOE correlations between the *t*-butyl group and the isoxazoline methylene protons further supported an assignment of the anti cycloadduct as the major product. Finally, crystals of cycloadduct **4b** were slowly grown from ethyl acetate and a single crystal X-ray structure was obtained (Fig. 1). From this

structure it can clearly be seen that the nitrile oxide has added to the dipolarophile C(2)–C(3) from the face opposite the substituents on the *N*-aryl group. All of these data are consistent with preferential cycloaddition to the anti face of the dipolarophile, controlled by atropisomeric induction.

Conclusion

Unsymmetrical *N*-aryl 4-methylene-2-oxazolidinones have been shown to readily undergo 1,3-dipolar cycloaddition reactions with benzonitrile oxide to give the corresponding 1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one systems with complete regioselectivity. Atropisomerism around the *N*-aryl bond led to facial selectivity in the cycloadditions for the less hindered face, varying from 4 : 1 to >99% selectivity. This finding demonstrates the significant sensitivity to steric influences that is inherent in nitrile oxide 1,3-dipolar cycloaddition reactions. Such sensitivity can be exploited to deliver facial selectivity in cycloaddition reactions.

Experimental section

General

Melting points were determined on a Büchi B-545 instrument and are uncorrected. Analytical thin layer chromatography (TLC) was carried out on Macherey–Nagel Polygram pre-coated plastic sheets (0.2 mm layer of silica gel with fluorescent indicator UV254). Developed plates were visualized with either UV light (254 nm) or $KMnO_4$ staining. 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 and ^{13}C NMR spectra were recorded on a Bruker AV400 spectrometer at 400 and 100 MHz, respectively, or a Bruker AV200 spectrometer at 200 and 50 MHz, respectively, using $CDCl_3$ as solvent and internal reference. Variable temperature ^1H NMR spectra were recorded on a Bruker DRX500 spectrometer operating at 500 MHz with toluene-D8 as solvent. FT-IR spectra were recorded on a Bruker Equinox 55/S FT-IR spectrometer with samples in KBr disks. Electron impact (EI) mass spectra were run on a ThermoQuest MAT95XP mass spectrometer using ionization energy of 70 eV. Accurate mass measurements were obtained on the same instrument with a resolution of 5000–10 000 using perfluorokerosene (PFK) as the reference compound.

General method of carbamate synthesis

The appropriate isocyanate (12 mmol) was added to a solution of 2-methyl-3-butyn-2-ol (0.84 g, 10 mmol), triethylamine (2.1 mL, 15 mmol) and *N*,*N*-dimethylaminopyridine (146 mg, 1.2 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred for 90 h before adding HCl (25 mL, 2 M) and extracting with EtOAc (3 × 20 mL). The combined organic phases were washed with saturated NaCl (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to return the crude product. The crude products were sufficiently pure for subsequent cyclization reactions, but they could be purified by either recrystallisation or flash column chromatography.

2-Methylbut-3-yn-2-yl (2-*t*-butylphenyl)carbamate, 2a

Carbamate **2a** was isolated as a white solid (37%), which was purified by flash chromatography (pet. ether to 5% EtOAc in pet. ether); mp 99.5–101.3 °C; ^1H NMR (200 MHz, $CDCl_3$) 7.63 (1H, br d, J = 7.6 Hz), 7.36 (1H, dd, J = 7.8, 1.7 Hz), 7.17 (2H, ddq, J = 13.9, 7.6, 1.7 Hz), 6.45 (1H, br s), 2.55 (1H, s), 1.75 (6H, s), 1.42 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 152.5, 135.2, 126.8, 126.3, 125.3, 85.1, 72.1, 34.5, 30.7, 29.3; HRMS (EI) found 259.1574, $C_{16}H_{21}NO_2$ requires 259.1567.

2-Methylbut-3-yn-2-yl (3,4-dichlorophenyl)carbamate, 2b

Carbamate **2b** was isolated as a white solid (81%), which was purified by flash chromatography (pet. ether to 10% EtOAc in pet. ether); mp 107.1–109.0 °C (lit.[48] 90–92 °C, lit.[49] 111–112 °C); ^1H NMR (200 MHz, $CDCl_3$) 7.68 (1H, br d, J = 2.5 Hz), 7.32 (1H, d, J = 8.7 Hz), 7.17 (1H, dd, J = 8.7, 2.5 Hz), 6.63 (1H, br s), 2.59 (1H, s), 1.74 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 151.3, 137.4, 132.9, 130.4, 126.5, 120.2, 117.7, 84.5, 72.9, 72.7, 29.1; HRMS (EI) [M^+] found 271.0160, $C_{12}H_{11}Cl_2NO_2$ requires 271.0161.

2-Methylbut-3-yn-2-yl (2,5-dimethylphenyl)carbamate, 2c

Carbamate **2c** was isolated as a white solid (22%) which was purified by flash chromatography (pet. ether to 15% EtOAc in pet. ether); mp 103.2–103.9 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.74 (1H, br s), 7.02 (1H, d, J = 7.6 Hz), 6.82 (1H, dd, J = 7.6, 1.0 Hz), 6.34 (1H, br s), 2.58 (1H, s), 2.31 (3H, s), 2.21 (3H, s), 1.76 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 152.1, 136.8, 135.8, 130.3, 124.8, 121.4, 85.2, 72.4, 72.4, 29.4, 21.3, 17.4; HRMS (EI) found 231.1248, $C_{14}H_{17}NO_2$ requires 231.1254.

2-Methylbut-3-yn-2-yl (2-methylphenyl)carbamate, 2d

Carbamate **2d** was isolated as a white solid (46%), which was purified by flash chromatography (pet. ether to 10% EtOAc in pet. ether); mp 79.4–79.5 °C; ^1H NMR (200 MHz, $CDCl_3$) 7.85 (1H, d, J = 8.3 Hz), 7.20 (2H, m), 7.01 (1H, m), 6.35 (1H, br s), 2.58 (1H, s), 2.26 (3H, s), 1.76 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 152.1, 136.0, 130.5, 127.0, 124.1, 85.1, 72.4, 29.4, 17.8; HRMS (EI) found 217.1097, $C_{13}H_{15}NO_2$ requires 217.1103.

2-Methylbut-3-yn-2-yl naphthalen-1-ylcarbamate, 2e

Carbamate **2e** was isolated as an off-white solid (91%), which was purified by flash chromatography (pet. ether to 10% EtOAc in pet. ether); mp 121.2–123.5 °C; ^1H NMR (200 MHz, $CDCl_3$) 8.00–7.82 (3H, m), 7.69–7.40 (4H, m), 6.94 (1H, br s), 2.60 (1H, s), 1.80 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 152.4, 134.0, 132.4, 128.8, 126.1, 125.9, 125.8, 124.7, 120.2, 84.9, 72.5, 72.4, 29.2; HRMS (EI) found 253.1099, $C_{16}H_{15}NO_2$ requires 253.1097.

2-Methylbut-3-yn-2-yl (2-nitrophenyl)carbamate, 2f

Carbamate **2f** was isolated as a yellow solid (87%), which was purified by flash chromatography (10% EtOAc in pet. ether); mp 118.1–119.5 °C (lit.[42] 108 °C); ^{1}H NMR (400 MHz, $CDCl_3$) 9.81 (1H, br s), 8.62 (1H, dd, J = 8.6, 1.2 Hz), 8.21 (1H, dd, J = 8.5, 1.6 Hz), 7.62 (1H, ddd, J = 8.5, 7.2, 1.6 Hz), 7.12 (1H, ddd, J = 8.5, 7.2, 1.3 Hz), 2.61 (1H, s), 1.78 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 151.2, 135.8, 135.3, 125.8, 122.3, 120.8, 84.3, 73.1, 72.8, 29.1; HRMS (EI) found 248.0804, $C_{12}H_{12}N_2O_4$ requires 248.0805.

2-Methylbut-3-yn-2-yl [1,1′-biphenyl]-2-ylcarbamate, 2g

Carbamate **2g** was isolated as a white solid (51%), which was purified by flash chromatography (pet. ether to 10% EtOAc in pet. ether); mp 122.1–123.9 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.20 (1H, d, J = 8.2 Hz), 7.55–7.29 (6H, m), 7.24–7.06 (2H, m), 6.61 (1H, br s), 2.56 (1H, s), 1.69 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 151.7, 138.2, 134.7, 131.3, 130.1, 129.3, 129.1, 128.4, 127.8, 123.3, 119.7, 84.9, 72.3, 72.2, 29.2; HRMS (EI) found 279.1247, $C_{18}H_{17}NO_2$ requires 279.1254.

2-Methylbut-3-yn-2-yl (2,4-dichlorophenyl)carbamate, 2h

Carbamate **2h** was isolated as a white solid (92%), which was purified by flash chromatography (5% EtOAc in pet. ether); mp 86.1–89.4 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.19 (1H, d, J = 8.9 Hz), 7.35 (1H, d, J = 2.4 Hz), 7.23 (1H, dd, J = 6.6, 2.3 Hz), 7.05 (1H, br s), 2.60 (1H, s), 1.76 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 151.1, 133.5, 128.6, 128.1, 127.8, 122.3, 120.6, 84.5, 72.9, 72.7, 29.1; HRMS (EI) found 271.0181, $C_{12}H_{11}Cl_2NO_2$ requires 271.0161.

General method for cyclization to oxazolidinones 3

Lithium hydroxide monohydrate (21 mg, 0.5 mmol) was added to a solution of the appropriate carbamate **2a–h** (5.0 mmol) in DMF (5 mL) at room temperature and the reaction stirred for 1 h (unless otherwise stated). The reaction was diluted with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were then washed with water (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the oxazolidinones **3a–h**. The isolated products were usually of sufficient purity to perform nitrile oxide cycloaddition reactions without further purification.

3-(2-(*Tert*-butyl)phenyl)-5,5-dimethyl-4-methyleneoxazolidin-2-one, 3a

Oxazolidinone **3a** was isolated as a white solid (84%) and purified by flash chromatography (20% EtOAc in pet. ether, R_f 0.69); mp 105.7–106.7 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 7.56 (1H, dd, J = 7.9, 1.6 Hz), 7.33 (2H, ddt, J = 17.7, 7.3, 1.7 Hz), 6.99 (1H, dd, J = 7.4, 1.8 Hz), 4.09 (1H, d, J = 2.6 Hz), 3.68 (1H, d, J = 2.6 Hz), 1.64 (6H, s), 1.37 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 154.16, 149.2, 132.4, 131.2, 129.5, 128.9, 127.8, 82.8, 82.6, 35.7, 31.5, 28.1, 28.0; IR (KBr) ν/cm^{-1} 1755 (st), 1654 (m), 1486 (m), 1441 (m), 1393 (m); HRMS (EI) found 259.1546, $C_{16}H_{21}NO_2$ requires 259.1572.

3-(3,4-Dichlorophenyl)-5,5-dimethyl-4-methyleneoxazolidin-2-one, 3b

Oxazolidinone **3b** was isolated as a cream solid (74%) and purified by flash chromatography (50% EtOAc in pet. ether, R_f 0.55); mp: 134.0–134.8 °C (lit.[50] 134.0–134.7 °C); ^{1}H NMR (200 MHz, $CDCl_3$) 7.51 (2H, m), 7.22 (1H, dd, J = 8.6, 2.3 Hz), 4.18 (1H, d, J = 3.0 Hz), 4.11 (1H, d, J = 3.0 Hz), 1.61 (6H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 153.8, 150.9, 133.4, 133.4, 132.4, 131.2, 128.9, 126.3, 82.9, 81.8, 28.0; IR (KBr) ν/cm^{-1} 1758 (st), 1652 (m), 1507 (w), 1427 (m), 1386 (m); HRMS (EI) found 271.0161, $C_{12}H_{11}Cl_2NO_2$ requires 271.0167.

3-(2,5-Dimethylphenyl)-5,5-dimethyl-4-methyleneoxazolidin-2-one, 3c

Oxazolidinone **3c** was isolated as a white solid (0.33 g; 83%) and purified by flash chromatography (20% EtOAc in pet. ether, R_f 0.28); mp: 106.3–110.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.21 (1H, dd, J = 7.8 Hz), 7.14 (1H, dd, J = 7.7, 1.5 Hz), 7.01 (1H, br s), 3.99 (1H, d, J = 2.6 Hz), 3.76 (1H, d, J = 2.6 Hz), 2.34 (3H, s), 2.16 (3H, s), 1.65 (3H, s), 1.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 154.6, 152.0, 137.3, 133.4, 132.2, 131.4, 130.3, 129.1, 82.8, 80.9, 28.6, 28.0, 20.9, 16.9; HRMS (EI) found 231.1264, $C_{14}H_{17}NO_2$ requires 231.1259.

5,5-Dimethyl-4-methylene-3-(2-methylphenyl)oxazolidin-2-one, 3d

Oxazolidinone **3d** was isolated as an off-white solid (90%) and purified by flash chromatography (10% EtOAc in pet. ether, R_f 0.08); mp 114.0–114.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.35–7.27 (3H, m), 7.23–7.16 (1H, m), 4.00 (1H, d, J = 2.7 Hz), 3.76 (1H, d, J = 2.6 Hz), 2.23 (3H, s), 1.65 (6H, apparent d, J = 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 151.8, 136.6, 131.4, 129.3, 128.6, 127.3, 82.7, 80.9, 28.4, 27.9, 17.2; IR (KBr) ν/cm^{-1} 1748 (st), 1654 (m), 1494 (w), 1398 (m), 1303 (m); HRMS (EI) found 217.1098, $C_{13}H_{15}NO_2$ requires 217.1103.

5,5-Dimethyl-4-methylene-3-(naphthalen-1-yl)oxazolidin-2-one, 3e

Oxazolidinone **3e** was isolated as a pale pink solid (79%) and purified by flash chromatography (50% EtOAc in pet. ether, R_f 0.55); mp: 143.2–143.3 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.00–7.42 (7H, m), 4.03 (1H, d, J = 2.8 Hz), 3.74 (1H, d, J = 2.7 Hz), 1.79 (3H, s), 1.72 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 154.9, 152.4, 134.7, 130.1, 129.8, 129.7, 128.7, 127.2, 126.9, 126.6, 125.7, 122.1, 83.0, 81.9, 28.6, 28.0; IR (KBr) ν/cm^{-1} 1759 (st), 1678 (m), 1637 (m), 1409 (st), 1370 (m); HRMS (EI) found 253.1089, $C_{16}H_{15}NO_2$ requires 253.1097.

5,5-Dimethyl-4-methylene-3-(2-nitrophenyl)oxazolidin-2-one, 3f

Oxazolidinone **3f** was isolated as a yellow solid (100%) and purified by flash chromatography (10% EtOAc in pet. ether, R_f

0.05); mp 121.5–121.6 °C (lit.[42] 92 °C); ^{1}H NMR (200 MHz, $CDCl_3$) 8.17 (1H, dd, J = 8.1, 1.5 Hz), 7.77 (1H, dt, J = 7.6, 1.6 Hz), 7.62 (1H, m), 7.51 (1H, dd, J = 7.7, 1.6 Hz), 4.06 (1H, d, J = 3.3 Hz), 3.90 (1H, d, J = 3.3 Hz), 1.69 (3H, s), 1.66 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 150.9, 134.4, 131.2, 130.0, 127.6, 126.2, 83.8, 81.0, 27.9, 27.8; IR (KBr) ν/cm^{-1}: 1758 (st), 1654 (m), 1609 (m), 1525 (st), 1401 (st); HRMS (EI) found 248.0804, $C_{12}H_{12}N_2O_4$ requires 248.0797.

3-([1,1′-Biphenyl]-2-yl)-5,5-dimethyl-4-methyleneoxazolidin-2-one, 3g

Oxazolidinone **3g** was isolated as an orange solid (69%) and purified by flash column chromatography (10% EtOAc in pet. ether, R_f 0.11); mp 154.5–155.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 7.52–7.44 (3H, m), 7.38–7.30 (6H, m), 3.82 (1H, d, J = 2.7 Hz), 3.71 (1H, d, J = 2.7 Hz), 1.53 (3H, s), 1.16 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 154.8, 152.1, 141.8, 138.3, 131.2, 129.5, 129.3, 128.9, 128.4, 128.2, 127.7, 82.7, 81.0, 27.9, 27.6; IR (KBr) ν/cm^{-1} 1752 (st), 1653 (m), 1483 (w), 1400 (m), 1304 (m); HRMS (EI) found 279.1250, $C_{18}H_{17}NO_2$ requires 279.1259.

3-(2,4-Dichlorophenyl)-5,5-dimethyl-4-methyleneoxazolidin-2-one, 3h

Oxazolidinone **3h** was isolated as a pale orange solid (81%) and purified by flash chromatography (50% EtOAc in pet. ether, R_f 0.63); mp 121.5–124.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.57 (1H, dd, J = 2.2 Hz), 7.37 (1H, dd, J = 2.2 Hz), 7.32 (1H, s), 4.07 (1H, d, J = 3.0 Hz), 3.79 (1H, d, J = 3.0 Hz), 1.66 (3H, s), 1.65 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 153.6, 150.1, 136.0, 134.3, 131.4, 130.8, 129.9, 128.5, 83.5, 81.5, 28.4, 27.6; IR (KBr) ν/cm^{-1} 1755 (st), 1647 (st), 1587 (m), 1486 (st), 1407 (st); HRMS (EI) found 271.0158, $C_{12}H_{11}Cl_2NO_2$ requires 271.0167.

General method for benzonitrile oxide cycloaddition reactions

A solution of benzaldehyde oxime (12 mmol) and the appropriate *N*-aryl-5,5-dimethyl-4-methyleneoxazolidin-2-one, **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 analysed by ^{1}H NMR for evidence of diastereomers and the product was purified as stated.

6-(2-*t*-Butylphenyl)-9,9-dimethyl-3-phenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one, 4a

Flash column chromatography (20%–30% Et_2O in pet. ether, R_f 0.33, 50% EtOAc in pet. ether) afforded the title compound **4a** as a white solid (0.054 g, 46%); mp 159.6–160.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.63 (1H, dd, J = 7.9, 1.6 Hz), 7.46 (3H, m), 7.37–7.25 (4H, m), 7. 19 (1H, m), 3.35 (2H, s), 1.67 (3H, s), 1.60 (3H, s), 1.42 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 156.3, 156.1, 148.6, 133.4, 131.9, 130.8, 129.6, 129.2, 129.0, 128.6, 127.9, 126.4, 106.5, 85.0, 36.4, 36.2, 32.7, 25.3, 22.3; HRMS (EI) found 378.1931, $C_{23}H_{26}N_2O_3$ requires 378.1938.

6-(3,4-Dichlorophenyl)-9,9-dimethyl-3-phenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one, 4b

Flash column chromatography (pet. ether to 30% EtOAc in pet. ether, R_f 0.37, 50% EtOAc in pet. ether) afforded the title compound **4b** as a white solid (0.26 g; 58%); mp 168.5–168.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.52–7.47 (3H, m), 7.44–7.34 (4H, m), 7.21 (1H, dd, J = 8.6, 2.4 Hz), 3.45 (1H, d, J = 18.5 Hz), 3.25 (1H, d, J = 18.5 Hz), 1.66 (6H, apparent d, J = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 156.2, 154.2, 133.6, 133.4, 132.9, 131.2, 131.0, 129.6, 129.0, 127.8, 126.6, 126.4, 104.4, 84.8, 37.2, 25.5, 21.0; IR (KBr) ν/cm^{-1} 1744 (st), 1472 (w), 1397 (m), 1377 (m), 1367 (m); HRMS (EI) found 390.0519, $C_{19}H_{16}Cl_2N_2O_3$ requires 390.0532.

6-(2,5-Dimethylphenyl)-9,9-dimethyl-3-phenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one, 4c

Flash column chromatography (20% Et_2O in pet. ether; R_f 0.16, 50% EtOAc in pet. ether) afforded the title compound **4c** as a white solid (0.035 g; 50%); mp 157.4–158.1 °C; isolated as an inseparable 4 : 1 ratio of atropisomeric diastereomers ^{1}H NMR (400 MHz, $CDCl_3$) * indicates minor isomer peaks, † indicates major and minor isomer peaks 7.47–7.43 (1.50H, m), 7.40–7.26 (4.50H, m), 7.12* (0.25H, d, J = 7.9 Hz), 7.09 (1H, d, J = 7.8 Hz), 6.99† (1.25H, m), 6.82* (0.25H, br s), 3.50* (0.25H, d, J = 17.8Hz), 3.36† (1.25H, m apparent d), 2.99 (1H, d, J = 18.2 Hz), 2.40* (0.75H, s), 2.25 (3H, s), 2.23 (3H, s), 2.21 (0.75H, s), 1.67† (3.75H, s), 1.65* (0.75H, s), 1.63 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) * indicates minor isomer peaks, † indicates major and minor isomer peaks 155.9†, 154.6*, 154.5, 137.6, 136.3*, 136.3*, 133.7, 132.4, 132.0, 131.9*, 130.8, 130.8, 130.7*, 130.5*, 130.4, 129.9*, 129.7, 129.0, 128.8*, 128.6*, 128.5*, 126.5, 105.3*, 105.2, 85.0, 84.2, 37.6*, 36.4, 26.0*, 25.9, 21.5*, 21.4, 20.9, 20.8*, 18.1*, 17.9; IR (KBr) ν/cm^{-1} 1763 (st), 1503 (w), 1419 (w), 1366 (m), 1292 (w); HRMS (EI) found 350.1619, $C_{21}H_{22}N_2O_3$ requires 350.1625.

9,9-Dimethyl-3-phenyl-6-(2-methylphenyl)-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one, 4d

Flash column chromatography (10%–30% EtOAc in pet. ether, R_f 0.43, 50% EtOAc in pet. ether) afforded the title compound **4d** as a peach solid (0.41 g; 61%); mp 151.3–154.6 °C; isolated as an inseparable 4 : 1 ratio of atropisomeric diastereomers ^{1}H NMR (400 MHz, $CDCl_3$) * indicates minor isomer peaks, † indicates major and minor isomer peaks 7.47–7.42† (3H, m), 7.39–7.27† (4H, m), 7.25–7.07† (4H, m), 7.03* (0.25H, dd, J = 7.7, 1.3 Hz), 3.50* (0.25H, d, J = 17.9 Hz), 3.41† (1.25H, m), 3.00 (1H, d, J = 18.2 Hz), 2.44* (0.75H, s), 2.28 (3H, s), 1.65† (3.75H, br s), 1.62 (0.75H, s), 1.60 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) * indicates minor isomer peaks, † indicates major and minor isomer peaks 155.7†, 154.4*, 154.2, 139.4*,

136.8, 132.3*, 132.1, 131.9*, 130.9†, 130.6, 130.5*, 129.4*, 129.3, 128.8, 128.7†, 128.2, 128.1*, 127.5†, 126.3†, 126.2*, 105.0†, 84.8, 84.0*, 37.4*, 36.3, 25.7†, 21.2*, 21.1, 18.3*, 18.1; IR (KBr) ν/cm^{-1}: 1747 (st), 1495 (w), 1447 (w), 1374(st), 1303 (w); HRMS (EI) found 336.1473; $C_{20}H_{20}N_2O_3$ requires 336.1468.

9,9-Dimethyl-6-(naphthalen-1-yl)-3-phenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one, 4e

Flash column chromatography (pet. ether to 30% EtOAc in pet. ether; R_f 0.54, 50% EtOAc in pet. ether) afforded the title compound **4** as a pink solid (0.28 g; 38%); mp 200 °C (dec); isolated as an inseparable 6 : 1 ratio of atropisomeric diastereomers ^{1}H NMR (400 MHz, $CDCl_3$) * indicates minor isomer peaks, † indicates major and minor isomer peaks 8.30* (0.15H, d, J = 8.8 Hz), 7.89–7.81† (3.30H, m), 7.77 (1H, dd, J = 7.4, 1.1 Hz), 7.60† (1.15H, m), 7.53† (1.15H, dt, J = 7.0, 1.2 Hz), 7.46 (1.15H, dd, J = 8.2, 7.5 Hz), 7.39* (0.15H, dd, J = 8.1, 7.3 Hz), 7.38† (3.30H, m), 7.25† (12.60H, m), 3.60* (0.15H, d, J = 17.8 Hz), 3.46* (0.15H, d, J = 17.8 Hz), 3.38 (1H, d, J = 18.4 Hz), 3.09 (1H, d, J = 18.4 Hz), 1.86 (3H, s), 1.75 (0.60H, s), 1.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) * indicates minor isomer peaks, † indicates major and minor isomer peaks 156.1, 155.5*, 155.0, 134.9*, 134.5*, 134.3, 131.4, 130.6, 130.5*, 130.4*, 130.3*, 129.8, 129.6, 128.9, 128.7, 128.6*, 128.1, 127.9*, 127.9, 127.7*, 127.6*, 127.5, 127.3*, 126.8*, 126.6*, 126.4, 126.3, 126.0, 125.4*, 124.7*, 124.3*, 121.6, 121.1*, 120.8*, 105.5, 105.0*, 85.0, 84.5*, 37.3*, 36.6, 26.1, 25.8*, 21.3, 14.2*; HRMS (EI) found 372.1455, $C_{23}H_{20}N_2O_3$ requires 372.1468.

9,9-Dimethyl-6-(2-nitrophenyl)-3-phenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one, 4f

Flash column chromatography (pet. ether to EtOAc; R_f 0.49, 50% EtOAc in pet. ether) afforded the title compound **4f** as a yellow solid (0.30 g; 47%); mp 168.9–170.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.95 (1H, dd, J = 7.9, 1.6 Hz), 7.72 (1H, dd, J = 8.0, 1.5 Hz), 7.62 (1H, dd, J = 7.5, 1.6 Hz), 7.57–7.31 (6H, m), 3.57 (1H, d, J = 18.9 Hz), 3.41 (1H, d, J = 18.9 Hz), 1.73 (3H, s), 1.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 156.6, 153.6, 134.1, 130.9, 130.5, 129.8, 128.9, 127.9, 127.9, 127.5, 126.4, 125.3, 104.7, 85.8, 37.1, 25.4, 21.6; IR (KBr) ν/cm^{-1}: 1752 (st), 1605 (w), 1524 (st), 1393 (st), 1380 (st); HRMS (EI) found 367.1151, $C_{19}H_{17}N_3O_5$ requires 367.1149.

6-([1,1′-Biphenyl]-2-yl)-9,9-dimethyl-3-phenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one, 4g

Flash column chromatography (pet. ether to 15% EtOAc in pet. ether; R_f 0.17, 20% EtOAc in pet. ether) afforded the title compound **4g** as a white solid (0.25 g; 45%); mp 148.5–150.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60 (1H, m), 7.49–7.28 (13H, m), 2.85 (1H, d, J = 18.1 Hz), 2.78 (1H, d, J = 18.1 Hz), 1.51 (3H, s), 1.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 156.5, 155.5, 142.1, 139.3, 131.9, 131.1, 130.7, 130.7, 130.0, 129.4, 129.3, 128.9, 128.8, 128.4, 128.1, 126.3, 105.3, 84.1, 36.0, 24.9, 21.1; IR (KBr) ν/cm^{-1} 1753 (st), 1480 (w), 1437 (w), 1368 (m), 1302 (w); HRMS (EI) found 398.1620, $C_{25}H_{22}N_2O_3$ requires 398.1625.

6-(2,4-Dichlorophenyl)-9,9-dimethyl-3-phenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one, 4h

Flash column chromatography (10%–30% EtOAc in pet. ether; R_f 0.58, 50% EtOAc in pet. ether) afforded the title compound **4h** (major isomer) as a white solid (0.40 g; 51%); mp 137.6–138.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.57–7.32 (7H, m), 7.26 (1H, dd, J = 8.5, 2.3 Hz), 3.45 (1H, d, J = 18.6 Hz), 3.21 (1H, d, J = 18.5 Hz), 1.73 (3H, s), 1.63 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 155.9, 153.7, 136.2, 135.0, 132.3, 130.9, 130.1, 129.7, 128.9, 128.8, 127.9, 126.4, 104.7, 85.2, 36.6, 25.6, 21.0; IR(KBr) ν/cm^{-1} 1765 (st), 1485 (m), 1397 (m), 1367 (st), 1265 (m); HRMS (EI) found 390.0519, $C_{19}H_{16}Cl_2N_2O_3$ requires 390.0532.

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