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Directed 1,3-dipolar cycloadditions of ylidene piperazine-2,5-diones

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Abstract—The reactivities and selectivities of 1,3-dipolar cycloaddition reactions of ylidene piperazine-2,5-diones with mesitonitrile oxide are reported. The stereoselectivities of reactions with chiral ylidene piperazine-2,5-diones can be directed by judicious choice of substituents on the *N*- and/or *C*-substituents of the piperazinedione ring.

1. Introduction

1,3-Dipolar cycloaddition (DPC) reactions of nitrile oxides and suitable alkenes are one of the most powerful methods for the generation of isoxazolines.[1] These heterocycles can be readily converted to a large range of compounds including γ-amino alcohols, β-hydroxy carbonyl compounds and derivatives.[2] Thus isoxazolines can be viewed as versatile synthetic precursors with masked functionalities which can be released upon hydrolysis of the isoxazoline ring.

Our interest in recent years has focussed on the use of ylidenepiperazinediones in synthesis.[3,4] Our studies have demonstrated that through a large repertoire of chemistry, the dehydro moiety of the piperazine-2,5-dione can be functionalised in a regio- and often, in a stereo-controlled fashion. As piperazine-2,5-diones are precursors to α-amino acids,[5] these studies have provided new asymmetric routes to novel non-proteinogenic amino acids and derivatives. Despite this, little has been reported on the 1,3-dipolar cycloaddition (1,3-DPC) reactions of ylidenepiperazinediones.[6] Isoxazolines derived from the 1,3-DPC of ylidenepiperazinediones and nitrile oxides can potentially give access to optically pure functionalised non-proteinogenic amino acids.

Our studies reported herein outline the synthesis of these isoxazolines with particular attention on the factors governing the reactivities as well as the regio- and stereoselectivities of the 1,3-DPC reactions.

Keywords: amino acids and derivatives; cycloadditions; nitrile oxides; X-ray crystal structures.
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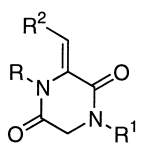
2. Results and discussion

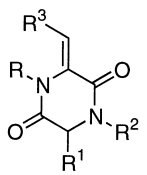
It is well established that the reactivities and selectivities of 1,3-DPC reactions are governed by steric and/or electronic effects.[1] Within the framework of our studies, a series of ylidenepiperazinediones were chosen as dipolarophiles in order to probe these effects in a systematic manner.

With the achiral systems, ylidenepiperazinediones **1a**, **1b**, **1e** were chosen in order to determine the effect of varying the *N*-substituents on the piperazinedione ring. On similar systems, the presence of a substituent on the β-carbon position of the olefin was also examined using piperazinediones **1c** and **1d**. As our previous studies have shown that chiral dehydropiperazinediones of type **2** are effective templates in asymmetric synthesis, dipolarophiles **2a**–**2f** were selected in order to assess the viability of these compounds in effecting regio- and stereo-controlled asymmetric 1,3-DPC.



(1)

1a R=H, R^1=Ac, R^2=H
1b R=Ac, R^1=Ac, R^2=H
1c R=H, R^1=Ac, R^2=Me
1d R=H, R^1=Ac, R^2=Ph
1e R=Me, R^1=Me, R^2=H



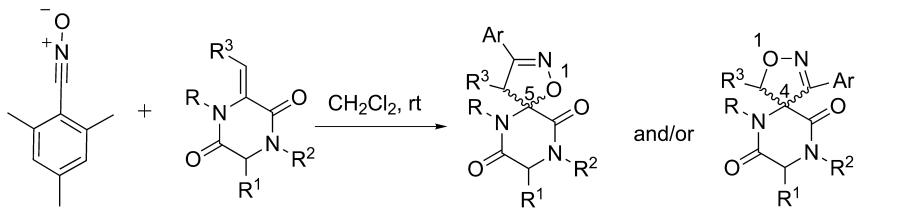
(2)

2a R=H, R^1=Me, R^2=Ac, R^3=H
2b R=Ac, R^1=Me, R^2=Ac, R^3=H
2c R=H, R^1=Me, R^2=Ac, R^3=Me
2d R=H, R^1=Me, R^2=Ac, R^3=Ph
2e R=H, R^1=*i*-Pr, R^2=Ac, R^3=H
2f R=Ac, R^1=*i*-Pr, R^2=Ac, R^3=H

Table 1. Reactions of achiral ylidene piperazinediones **1a**–**1e** with mesitonitrile oxide

Entries	Ylidene-piperazinediones	R	R^1	R^2	Cycloadducts	% Conversion (isolated yields)
1	**1a**	H	Ac	H	**3a**	89 (87)
2	**1b**	Ac	Ac	H	**3b**	93 (66)
3	**1c**	H	Ac	Me	**3c**	80 (78)
4	**1d**	H	Ac	Ph	**3d**	77 (53)
5	**1e**	Me	Me	H	**3e**	NR

% Conversion is obtained from accurate integration of relevant ^{1}H NMR signals of unreacted dipolarophile and cycloadduct in the crude reaction mixture. NR no reaction.



Scheme 1.

Access to these desired dipolarophiles required the installation of the α,β-unsaturation of the dehydropiperazinedione, which was accomplished in one of two ways, following literature procedures. The first of these, leading to the methylidene piperazinediones, involved the dehydration of the serinyl moiety of the appropriate piperazinedione precursor.[4a] The second method utilised aldol chemistry on appropriate piperazinedione precursors to install the ethylidene and benzylidene functionalities.[7]

2.1. 1,3-DPC of achiral ylidenepiperazine-2,5-diones

Cycloaddition reactions of mesitonitrile oxide and the dipolarophiles in a 1:1 ratio were carried out at room temperature in dichloromethane for seven days. The results reported in Table 1, as the percentage conversion as well as the isolated yields, give an indication of the reactivities of these systems towards 1,3-DPC with mesitonitrile oxide. These results indicate that, for an achiral, monoacetylated dehydropiperazinedione, the presence of a β-substituent has little or no effect on the reactivity in 1,3-dipolar cycloaddition reactions (Table 1, entries 1, 3, 4). Also, as the mono- and diacetylated methylidene piperazinediones (**1a**, **1b**) showed similar levels of conversion to the cycloadduct, the presence of the proximal *N*-acetyl substituent does not significantly affect the reactivity of the methylidene piperazinedione toward the 1,3-dipole (Table 1, entries 1, 2).

In contrast, no conversion to the cycloadduct was observed for the 1,3-dipolar cycloaddition reactions of the *N*,*N*′-dimethylated methylidene piperazinedione (**1e**) (Table 1, entry 5). The inert character of this piperazine-2,5-dione towards cycloaddition reactions has previously been documented.[4b]

2.2. Regioselectivity of 1,3-DPC reactions

Although two possible regioisomers of the cycloadduct can result (Scheme 1), i.e. the 5,5-disubstituted 2-isoxazoline or the 4,4-disubstituted 2-isoxazoline, only one product was obtained as is evident from the crude NMR (^{1}H and ^{13}C) spectra of the reaction mixtures. Comparison of the ^{13}C NMR data of the *N*-acetylated cycloadducts **3a**–**3d** suggests that these compounds possessed the same regiochemistry. In particular, the spiro carbon (90–93 ppm) and imino carbon (155–160 ppm) resonances, which would be expected to be significantly affected by the 4,4- or 5,5-substitution pattern of the isoxazoline ring, have very similar values for all the four cycloadducts.

A number of techniques were employed in attempts to determine the regiochemistry of the cycloadducts. The ^{1}H and ^{13}C NMR spectra of the cycloadducts derived from methylidene piperazinediones **1a** and **1b** were ambiguous, and did not permit the methylene group of the isoxazoline ring to be clearly distinguished from that of the glycyl protons of the piperazinedione. Thus, to simplify structural determination, in-depth NMR experiments were carried out on cycloadduct **3d**. From INEPT INADEQUATE experiments, the imino carbon atom (160 ppm) was observed to be adjacent to a tertiary carbon atom, thus confirming that the 5,5-disubstituted cycloadduct was formed. In addition a single crystal X-ray structure analysis for cycloadduct **3c** was also obtained. The structure clearly establishes the regiochemistry as the 5,5-disubstituted compound (Fig. 1).[†]

It can be seen from Figure 1 that the methyl substituent on the isoxazoline ring of **3c** is oriented towards the proximal nitrogen atom of the piperazinedione ring. This is the product that is predicted by the *cis* rule, as the dipolarophile was the (*Z*)-isomer of the ethylidene piperazinedione **1c**.

It is interesting to note that the crystal structure shows that the piperazinedione and isoxazoline rings are approximately perpendicular to one another. The piperazinedione ring

[†] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 212701, 212702 for compounds **3c** and **4a**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk)

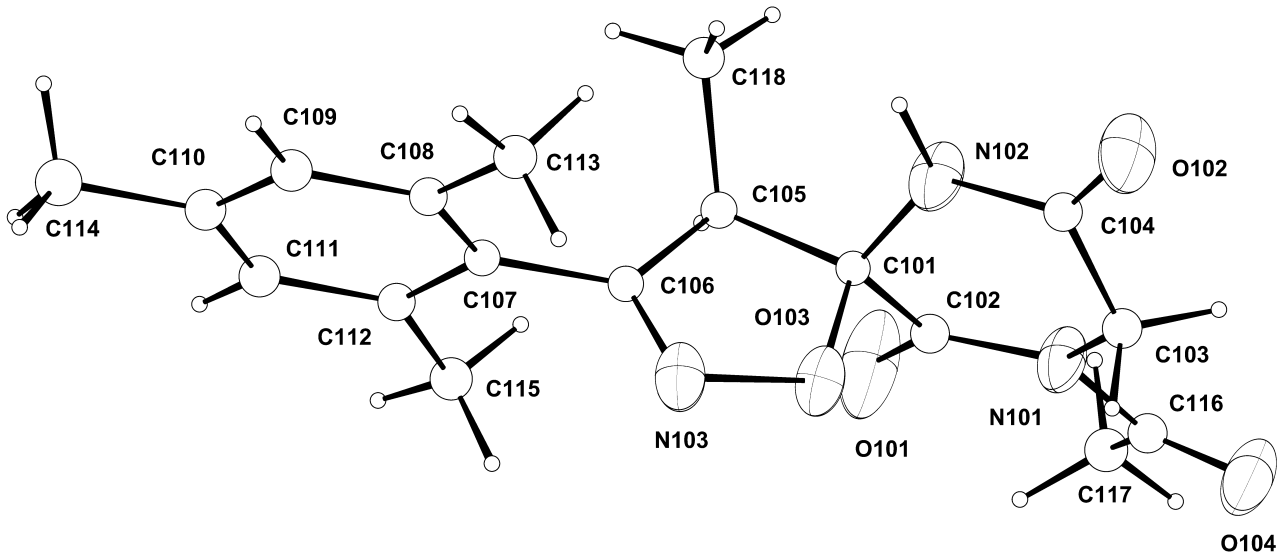


Figure 1. A molecule of cycloadduct **3c** as characterized in an X-ray diffraction study, establishing the regiochemistry of 1,3-DPC reaction.

adopts a boat-like conformation such that the degree of folding of the piperazinedione ring, as measured by the Hooker parameter,[8] is 53 degrees.

The cycloadducts obtained from the reactions of (*Z*)-ethylidene (**1c**) and benzylidene (**1d**) piperazinediones have thus been shown to be the 5,5-disubstituted isomer. By analogy, cycloadducts **3a** and **3b**, obtained from the reactions with the mono- and diacetylated methylidene piperazinediones, are also assigned as 5,5-disubstituted isoxazolines. Therefore, the 1,3-dipolar cycloaddition between mesitonitrile oxide and the mono- and diacetylated methylidene piperazinediones gave rise exclusively to the 5,5-disubstituted regioisomer (Scheme 2, Table 1).

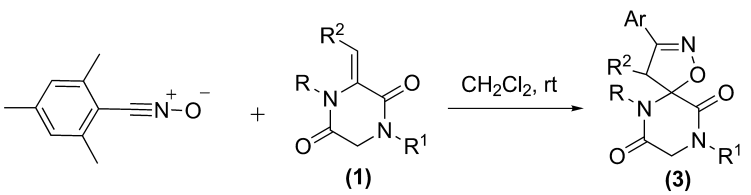
The exclusive formation of the 5,5-disubstituted regioisomer is in accord with the observations of Horikawa with *N*-acetyl dehydroalaninate.[9] In order to rationalise the origin of regioselectivity, semiempirical (AM1) calculations were performed on ylidene piperazinediones **1a**–**1d** and mesitonitrile oxide. From these calculations the electron densities at the α and β-carbon positions of the dipolarophile, as expressed by the orbital coefficients of these atoms, were determined.

From AM1 calculations, the 1,3-dipolar cycloaddition reactions between mesitonitrile oxide and the dipolarophiles **1a**–**d** are determined to be Type I reactions. Thus the LUMO orbital coefficients for the dipolarophiles were calculated. Our results indicate that β-carbon atoms of the ylidenepiperazinediones have larger orbital coefficients than α carbon atoms. Thus according to the FMO theory, the favoured product is predicted to be that which results from a transition state in which the β-carbon of the dipolarophile interacts with the oxygen atom of the dipole, leading to the 4,4-disubstituted regioisomer. This is clearly not in accordance with experimental observations, and hence suggests that other factors may be paramount in determining the regioselectivity of the 1,3-dipolar cycloaddition reaction.

Recent literature suggests that in some cases, the regioselectivity of a 1,3-dipolar cycloaddition may be under steric control.[10] In such cases, the stabilisation of the transition state that results from maximising the orbital overlap as predicted by FMO theory is insufficient to compensate for the steric repulsions. Thus to achieve the transition state leading to the 4,4-disubstituted regioisomer, a significant steric repulsion between the piperazinedione ring and the bulky mesityl system would be present as shown in Figure 2. These repulsions are minimised in the transition state leading to the 5,5-disubstituted cycloadduct. Thus, we suggest that steric effects outweigh the electronic considerations and the transition state that leads to the 5,5-disubstituted regioisomer is favoured.

2.3. 1,3-DPC of chiral ylidenepiperazine-2,5-diones

The cycloaddition reactions of ylidene piperazine-2,5-diones **2a**–**f** are summarized in Table 2, Scheme 3. Alanyl methylidene piperazinediones **2a** and **2b** exhibited a high degree of conversion to the cycloadducts whereas the (*Z*)-ethylidene and benzylidene piperazinediones **2c** and **2d** failed to react under the standard experimental conditions. This was unexpected in view of the reactivity trends observed in the analogous achiral systems **1c**, **1d** in which



Scheme 2.

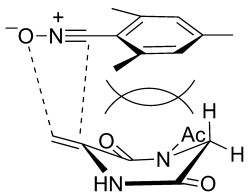


Figure 2. Proposed steric hindrance in the transition state leading to the 4,4-disubstituted cycloadduct.

the β-substituted systems also showed high degrees of conversion to the cycloadducts. As the HOMO/LUMO energies of the piperazinediones obtained from AM1 calculations had very similar values, the differences in reactivities cannot be easily attributed to the FMO energies.

One possible explanation for the lack of reactivity of the β-substituted systems (**2c** and **2d**) as compared to the methylidene derivatives **2a**, **2b** may relate to steric effects manifested in the transition states of the 1,3-dipolar cycloaddition reaction. It is conceivable that the presence of a β-substituent on the olefin of the piperazinedione hinders the approach of the dipole in the required orientation for reaction. This suggests that there is a fundamental difference between the conformations of the β-substituted alanyl- and glycyl-ylidene piperazinediones.

The conformations of the piperazinedione ring of the ylidene piperazinediones were modelled using AM1 semiempirical calculations. From molecular modeling, the piperazinedione rings of the achiral methylidene **1a** and ethylidene **1c** piperazinediones were found to be planar, that is with a Hooker value of β=0. In contrast, for the chiral monoacetylated ylidene piperazinediones **2a**, **2c** and **2d**, the Hooker values were approximately 22°, indicative of significant distortion of the ring system from planarity. The remote α-methyl substituent of the piperazinediones **2a**, **2c** and **2d** occupies the flagpole position, and as such the approach of the dipole to one face of the olefin may be impeded in the alanyl ylidene systems. In addition from modelling studies, the phenyl ring of the benzylidene piperazinedione (**2d**) was found to tilt by 47 degrees from the piperazinedione ring. This in turn may cause steric hindrance to the approach of the dipole to the double bond of the piperazinedione in addition to the steric congestion already present due to the remote α-methyl substituent of the piperazinedione ring. This is manifested in the lack of reactivity of **2d**. Similar and probably lesser effects may account for the lack of reactivity of the ethylidene piperazinedione **2c**.

2.4. Stereoselectivity of reactions

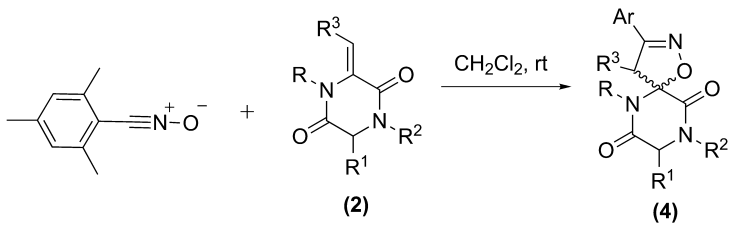
The 1,3-dipolar cycloaddition reactions of piperazinediones **2a** and **2b** proceeded to completion under the standard reaction conditions to give an approximately 5:1 mixture of isomers. The isomers were clearly distinguishable by ^{1}H NMR spectroscopy, but the ^{13}C NMR data for the isomers were very similar to each other. For example, for the *N*-monoacetylated cycloadduct **4a**, the spiro carbon signals of the two isomers were coincident, while the imino carbon atom signals differed by less than 0.2 ppm. This suggests that the two isomers are stereoisomeric rather than regioisomeric in nature. The ^{13}C NMR data of the major isomers of **4a** and **4b** show similar chemical shifts to those of **3a** and **3b** (obtained from the mono- (**1a**) and diacetylated (**1b**) achiral methylidene piperazinediones). This suggests that cycloadducts **4a** and **4b** are also 5,5-disubstituted regioisomers.

The reactions of the chiral mono- (**2a**) and diacetylated (**2b**) methylidene piperazinediones showed a high degree of stereoselectivity. From NOE studies, the stereochemistry of the major isomer of **4b** formed from the reaction of the diacetylated methylidene piperazinedione **2b** was found to result from the attack of the dipole onto the face of the dipolarophile opposite (*anti*) to the remote α-methyl group (Fig. 3). In contrast, X-ray structure analysis of a crystal of the major isomer of the monoacetylated cycloadduct **4a**

Table 2. Reactions of chiral ylidene piperazinediones **2a**–**2f** with mesitonitrile oxide

Entries	Ylidene-piperazinediones	R	R^1	R^2	R^3	Cycloadducts	% Conversion (isolated yields)
1	**2a**	H	Me	Ac	H	**4a**	>90 (72)
2	**2b**	Ac	Me	Ac	H	**4b**	>90 (62)
3	**2c**	H	Me	Ac	Me	**4c**	NR
4	**2d**	H	Me	Ac	Ph	**4d**	NR
5	**2e**	H	*i*-Pr	Ac	H	**4e**	80 (78%)
6	**2f**	Ac	*i*-Pr	Ac	H	**4f**	82 (66)

% Conversion is obtained from accurate integration of relevant ^{1}H NMR signals of unreacted dipolarophile and cycloadduct/s in the crude reaction mixture. NR no reaction.



Scheme 3.

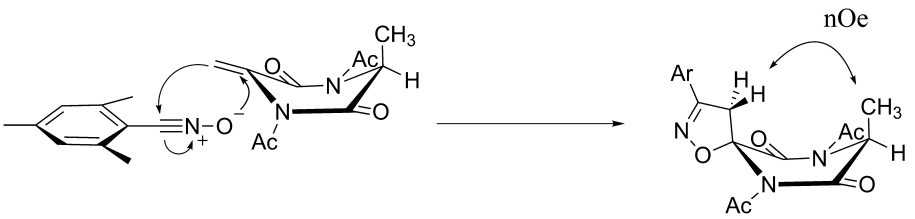


Figure 3. The 1,3-DPC reaction of *N*,*N*-diacetyl alanyl methylidene piperazinedione (**2b**) with mesitonitrile oxide.

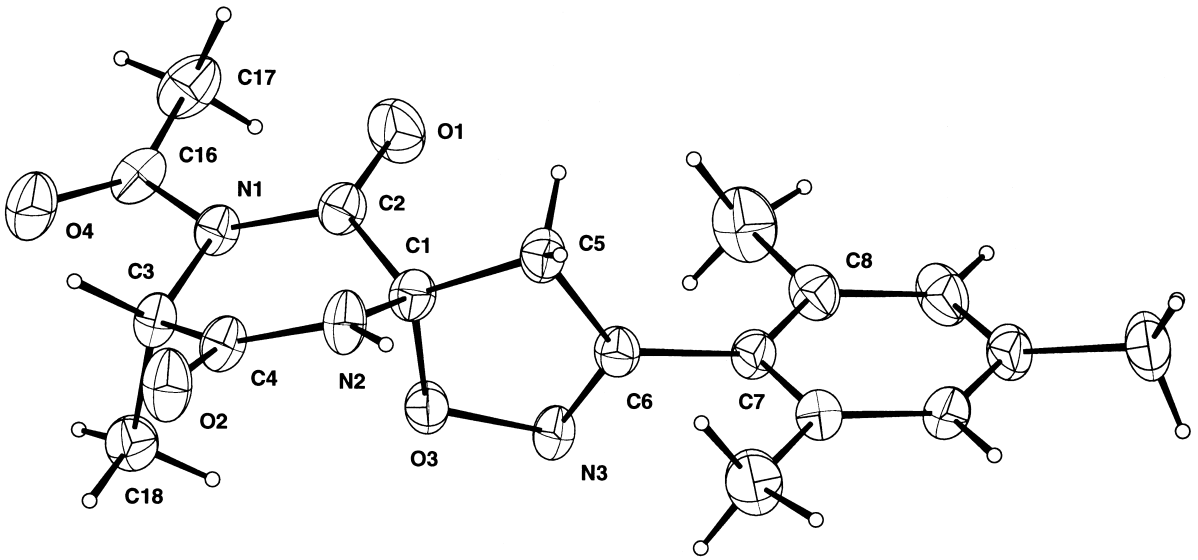
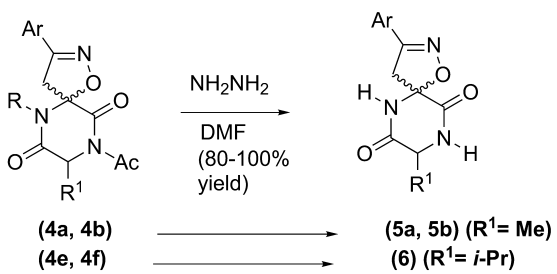


Figure 4. A molecule of cycloadduct **4a** as characterized in an X-ray diffraction study, establishing the regiochemistry and relative stereochemistry of 1,3-DPC reaction.

showed the opposite stereochemical outcome in which the attack of the dipole occurred *syn* to the remote α-methyl substituent (Fig. 4).

In order to firmly establish the two opposing stereochemical outcomes, deacetylation of each of the major isomers with hydrazine hydrate was undertaken (Scheme 4). The ^{1}H NMR data of the resulting derivatives **5a** and **5b** indicated that they were indeed different isomers. This was confirmed using HPLC analysis (conditions: 35% MeOH, 65% H_2O, Waters reversed phase C18 column) of the deacetylated cycloadducts (**5a** and **5b**) in which the two stereoisomers have different retention times.

This study suggests that, for a constant remote α-substituent and distal *N*-substituent, the nature of the proximal *N*-substituent could affect the stereoselectivity of the 1,3-DPC reaction. Specifically, for the *N*,*N*′-diacetylated piperazinedione **2b**, the attack of the dipole is directed preferentially to the *Re* face of the olefin, which gives rise to the *anti* cycloadduct **4b**. In contrast, the attack of the dipole is directed to the *Si* face of the monoacetylated piperazinedione **2a**, giving rise preferentially to the *syn* cycloadduct **4a**.



Scheme 4.

The greater susceptibility of the *Re* face to attack by mesitonitrile oxide for the *N*,*N*′-diacetylated piperazinedione is not unexpected, due to shielding of the *Si* face by the remote α-methyl substituent. In addition, molecular modelling studies suggest that the piperazinedione ring of the diacetylated dipolarophile **2b** is more puckered than that of the monoacetylated methylidene piperazinedione **2a** (β=36° as opposed to β=23°). Thus, the *N*,*N*′-diacetylated compound **2b** would be predicted to show greater facial selectivity as compared to the monoacetylated piperazinedione **2a**.

However, this does not account for the reversal in facial selectivity of the latter case with monoacetylated methylidene piperazinedione **2b**. In this case, despite the shielding of the *Si* face by the remote α-methyl substituent, the attack of the dipole occurs predominantly from the *Si* face of the piperazinedione.

A possible explanation for this may relate to hydrogen bonding effects.[11] For example, if the hydrogen atom on the proximal nitrogen atom of the monoacetylated

piperazinedione resides above the plane of the piperazinedione ring (i.e. towards the *Si* face of the olefin) hydrogen bonding between the proximal NH group of the piperazinedione and the oxygen atom of the dipole may be present. This would facilitate the approach of the dipole to the *Si* face of the piperazinedione, giving rise to the observed *Si* selectivity. In order to assess the viability of this proposal, the 1,3-DPC reaction was carried out in a number of solvents and the diastereomeric ratios of **4a** were measured using ^{1}H NMR spectroscopy. Within the errors of measurements, it was found that 1,3-DPC cycloadditions carried out in diethyl ether, *N*,*N*-dimethylformamide gave very similar ratios to that carried out in dichloromethane.

1,3-DPC reactions with valyl methylidene piperazinediones **2e** and **2f** were also carried out with mesitonitrile oxide under the standard conditions (Table 2, entries 5, 6). Only a single cycloadduct was obtained in each case. From NOE studies, it was shown that the stereoisomer formed is that resulting from attack of the dipole from the opposite face to the remote α-isopropyl substituent on the piperazine-2,5-dione ring. The similarities in the stereochemical outcomes for the reactions with the *N*,*N*′-diacetylated methylidene piperazinedione **2f** and monoacetylated piperazine-2,5-dione **2e** was confirmed by treating each cycloadduct **4e** and **4f** with hydrazine hydrate. The resulting deacetylated product **6** have identical spectroscopic properties. The stereochemical outcome for the cycloaddition with monoacetylated valyl methylidene piperazine-2,5-dione **2e** contrasts with that for the alanyl methylidene piperazine-2,5-dione **2a**. This is presumably because steric factors outweighs other factors (e.g. H-bonding) in affecting the facial selectivity of 1,3-DPC reactions.

3. Conclusion

Our studies above show that the success of 1,3-DPC reactions of ylidenepiperazinediones is governed by a number of factors. The reactions to form isoxazolines are highly directed, and only one regioisomer is formed. The stereoselectivity of reaction is primarily controlled by steric effects such that the favoured direction of attack is that opposite to the remote α-carbon substituent on the piperazine-2,5-dione ring. In the case with piperazinedione **2a**, the major diastereomer results from *syn* addition to the remote α-carbon substituent of **2a**. In this system, H-bonding effects presumably predominates over steric effects in affecting facial selectivity.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Gemini II 300 MHz spectrometer, operating at 300 MHz for proton and 75 MHz for carbon spectroscopy. Double quantum ^{1}H–^{1}H correlation spectroscopy (DQCOSY) NMR experiments were carried out on a Varian Inova 500 spectrometer (500 MHz). All 1D and 2D ^{1}H NMR spectra were recorded in $CDCl_3$, CD_2Cl_2 or CD_3OD as stated, using the residual solvent peaks at 7.26 ppm ($CHCl_3$), 5.32 ppm ($CHDCl_2$) and 3.30 ppm (CD_2HOD) as internal references. ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 as stated, using the respective residual solvent peaks at 77 ppm ($CDCl_3$) and 53.8 ppm ($CHDCl_2$) as internal references. All chemical shifts are reported as δ values in parts per million (ppm).

Infrared spectra were recorded on a Perkin–Elmer Spectrum One spectrophotometer and samples were analysed as KBr discs. Microanalyses and mass spectra were performed by the Analytical Facility of the Australian National University. Melting points were recorded on an Electrothermal melting point apparatus and Leica MV TG micro hot stage apparatus and are uncorrected.

Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 GF_{254} (supplied by Merck) and the chromatograms were visualised under a 254 nm UV lamp and by treatment with a developing solution [ammonium molybdate/ceric(IV) ammonium sulfate/sulfuric acid/water (10 g:0.4 g:5.6 mL:200 mL) dip] followed by heating. Column chromatography was conducted using Merck silica gel 60 (230–400 mesh ASTM) and analytical reagent (AR) grade solvents. Analytical grade solvents (AR) were used as received or purified before use according to Armarego and Perrin.[12]

Mesitonitrile oxide[13] and the ylidene piperazinediones[4,7] **1a**–**1e**, **2a**–**2f** were synthesised following literature procedures.

4.2. General procedure for 1,3-dipolar cycloaddition reactions

To a stirred solution of the dipolarophile in dichloromethane (15 mL/mmol dipolarophile, typical scale 0.5 mmol) was added mesitonitrile oxide (1 equiv.). The mixture was stirred under N_2 for 7 days, following which the solvent was removed under reduced pressure to yield the crude cycloadduct, which was subsequently purified by flash column chromatography.

4.2.1. 9-Acetyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (3a). The title compound was synthesised from piperazinedione **1a** in 87% yield. The product is insoluble in dichloromethane, and precipitated from the reaction mixture as a white solid.

Mp 221–224°C. IR (KBr) 1720 (s, C═O), 1697 (s, C═O), 1413 (s), 1376 (s), 1296 (s), 1244 (m), 1220 (s), 801 (m). ^{1}H NMR δ (DMSO) 2.27 (s, 6H, 2×ArCH_3), 2.28 (s, 3H, ArCH_3), 2.54 (s, 3H, C(═O)CH_3), 3.42 (d, J=18 Hz, 1H, isoxazoline CH_aH$_b$ or glycyl CH_aH$_b$), 4.13 (d, J=18 Hz, 1H, isoxazoline CH$_a$$H_b$ or glycyl CH$_a$$H_b$), 4.22 (d, J=18 Hz, 1H, isoxazoline CH_aH$_b$ or glycyl CH_aH$_b$), 4.59 (d, J=18 Hz, 1H, isoxazoline CH$_a$$H_b$ or glycyl CH$_a$$H_b$), 6.96 (s, 2H, 2×Ar$H$), 10.07 (s, 1H, N$H$). ^{13}C NMR (DMSO) δ 19.3 (ArCH$_3$), 20.7 (ArCH$_3$), 26.9 (C(═O)CH$_3$), 44.7 (glycyl or isoxazoline CH$_2$), 46.0 (glycyl or isoxazoline CH$_2$), 92.5 (spiro carbon), 124.7 (aromatic), 128.3 (aromatic), 136.4 (aromatic), 138.7 (aromatic), 157.6 (N═CAr), 163.7 (ring C═O), 166.8 (ring C═O), 171.4 (exocyclic C═O); m/z (EI) 329 ($M^{+\cdot}$, 67%),

286 ($M^{+\cdot}-Ac$, 4%), 270 (33%), 244 (30%), 229 (57%), 186 (84%), 161 ([ArCNO]$^{+\cdot}$, 100%). HRMS Mol. wt. Found: 329.1377. Calcd for $C_{17}H_{19}N_3O_4$: 329.1376. Microanalysis calcd for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 61.95; H, 5.59; N, 12.67.

4.2.2. 6,9-Diacetyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (3b). The title compound was prepared from piperazinedione **1b** according to the general procedure outlined above and purified by recrystallisation from ethyl acetate/hexane in 66% yield.

Mp 179–181°C. IR (KBr) 1728 (s, C═O), 1325 (m), 1210 (m). ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H, ArCH_3), 2.40 (s, 6H, 2×ArCH_3), 2.56 (s, 3H, C(═O)CH_3), 2.67 (s, 3H, C(═O)CH_3), 3.73 (d, J=18 Hz, 1H, glycyl or isoxazoline CH_aCH$_b$), 4.40 (d, J=18 Hz, 1H, glycyl or isoxazoline CH_aCH$_b$), 4.43 (d, J=18 Hz, 1H, glycyl or isoxazoline CH$_a$$H_b$), 5.04 (d, J=18 Hz, 1H, glycyl or isoxazoline CH$_a$CH_b), 6.94 (s, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ 19.9 (ArCH$_3$), 21.1 (ArCH$_3$), 27.1 (C(═O)CH$_3$), 28.7 (C(═O)CH$_3$) 44.0 (glycyl or isoxazoline CH$_2$), 46.0 (glycyl or isoxazoline CH$_2$), 95.1 (spiro carbon), 124.0 (aromatic), 128.7 (aromatic), 137.3 (aromatic), 139.5 (aromatic), 159.1 (N═CAr), 162.8 (ring C═O), 166.9 (ring C═O), 171.2 (exocyclic C═O), 174.2 (exocyclic C═O); m/z (EI) 371 ($M^{+\cdot}$, 27%), 328 ($M^{+\cdot}-Ac$, 2%), 286 ($M^{+\cdot}-2Ac+1$, 4%), 270 (12%), 244 (14%), 186 (100%), 159 ([ArCNO]$^{+\cdot}$, 62%), 130 (25%). HRMS Mol. wt. Found: 371.1475. Calcd for $C_{19}H_{21}N_3O_5$: 371.1481. Microanalysis calcd for $C_{19}H_{21}N_3O_5$: C, 61.45; H, 5.70; N, 11.31. Found: C, 61.35; H, 5.84; N, 11.52.

4.2.3. 9-Acetyl-4-methyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (3c). This was prepared from (*Z*)-piperazinedione **1c** and the product was purified by flash column chromatography (1:2 ethyl acetate/pet spirits, R_f=0.77) to yield the pure product as a white solid in 78% yield.

Mp 206–207°C. IR (KBr) 1729 (m, C═O), 1700 (s, C═O), 1366 (m), 1201 (m). ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J=8 Hz, 3H, CHCH_3), 2.23 (s, 9H, 3×ArCH_3), 2.57 (s, 3H, C(═O)CH_3), 4.17 (d, J=18 Hz, 1H, glycyl CH_aCH$_b$), 4.75 (q, J=8 Hz, 1H, CHCH$_3$), 4.80 (d, J=18 Hz, 1H, glycyl CH$_a$CH_b), 6.86 (s, 2H, ArH), 8.84 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 8.9 (CHCH$_3$), 20.1 (ArCH$_3$), 21.1 (ArCH$_3$), 27.2 (C(═O)CH$_3$), 45.9 (glycyl CH$_2$ or CHCH$_3$), 48.4 (glycyl CH$_2$ or CHCH$_3$), 93.2 (spiro carbon), 123.5 (aromatic), 128.8 (aromatic), 137.1 (aromatic), 139.5 (aromatic), 161.9 (N═CAr), 162.9 (C═O), 169.0 (C═O), 171.6 (C═O); m/z (EI) 343 ($M^{+\cdot}$, 30%), 300 ($M^{+\cdot}-Ac$, 4%), 243 (63%), 200 (48%), 172 (46%), 161 ([ArCNO]$^{+\cdot}$, 100%). HRMS Mol. wt. Found: 343.1527. Calcd for $C_{18}H_{21}N_3O_4$: 343.1532.

4.2.4. 9-Acetyl-4-phenyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (3d). The title compound was prepared from (*Z*)-piperazinedione **1d** and isolated by flash column chromatography (2:1 hexane/ethyl acetate R_f=0.61) to give **3d** as a white solid in 53% yield.

Mp 73–76°C. IR (KBr) 1709 (s, C═O), 1365 (m), 1256 (m), 1204 (m), 736 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H, ArCH_3), 2.44 (s, 6H, ArCH_3), 2.68 (s, 3H, C(═O)CH_3), 4.25 (d, J=18 Hz, 1H, glycyl CH_aH$_b$), 4.90 (d, J=18 Hz, 1H, glycyl CH$_a$$H_b$), 6.11 (s, 1H, C$H$Ph), 6.25 (br s, 1H, N$H$), 6.82 (s, 2H, Ar$H$), 7.1 (m, 2H, Ar$H$), 7.3 (m, 3H, Ar$H$). ^{13}C NMR ($CDCl_3$) δ 20.9 (ArCH$_3$), 21.3 (ArCH$_3$), 27.2 (C(═O)CH$_3$), 45.9 (CH$_2$), 59.2 (CHPh), 92.7 (spiro carbon), 123.5 (aromatic), 129.1 (aromatic), 129.4 (aromatic), 129.5 (aromatic), 129.9 (aromatic), 137.2 (aromatic), 139.5 (aromatic), 159.7 (N═CAr), 163.2 (C═O), 166.3 (C═O), 171.3 (C═O); m/z (EI) 405 ($M^{+\cdot}$, 55%), 362 ($M^{+\cdot}-Ac$, 7%), 305 ([M−C(═O)CH$_2$NAc−1]$^{+\cdot}$, 100%), 262 (87%), 244 (98%), 161 ([ArCNO]$^{+\cdot}$, 59%). HRMS Mol. wt. Found: 405.1692. Calcd for $C_{23}H_{23}N_3O_4$: 405.1689.

4.2.5. 9-Acetyl-8-methyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (4a). The title compound was prepared from piperazinedione **2a** and purified by flash column chromatography (2:1 hexane/ethyl acetate, R_f=0.6) to yield a 4.8:1 mixture of isomers in 72% yield. The major isomer was isolated by recrystallisation from ethyl acetate.

Mp (major) 218–220°C. IR (KBr) (major) 1702 (s, C═O), 1384 (s), 1339 (m), 1308 (m), 1221 (s), 828 (m), 740 (m) cm^{-1}. ^{1}H NMR major isomer ($CDCl_3$) δ 1.75 (d, J=7 Hz, 3H, CHCH_3), 2.32 (s, 9H, 3×ArCH_3), 2.65 (s, 3H, C(═O)CH_3), 3.19 (d, J=18 Hz, 1H, CH_aH$_b$), 4.38 (d, J=18 Hz, 1H, CH$_a$$H_b$), 5.09 (q, J=7 Hz, 1H, CHCH$_3$), 6.94 (s, 2H, 2×ArH), 8.82 (br d, 1H, NH). Minor isomer ($CDCl_3$) δ 1.57 (d, J=7 Hz, 1H, CHCH_3), 2.32 (s, 9H, 3×ArCH_3), 2.57 (s, 3H, C(═O)CH_3), 3.28 (d, J=18 Hz, 1H, CH_aH$_b$), 4.09 (d, J=18 Hz, 1H, CH$_a$$H_b$), 4.94 (q, J=7 Hz, 1H, CHCH$_3$), 6.94 (s, 2H, 2×ArH), 9.21 (br d, 1H, NH). ^{13}C NMR major isomer ($CDCl_3$) δ 19.7 (ArCH$_3$), 19.9 (ArCH$_3$), 21.1 (CHCH$_3$), 27.8 (C(═O)CH$_3$), 47.1 (CH$_2$), 54.0 (CHCH$_3$), 91.8 (spiro carbon), 124.0 (aromatic), 128.6 (aromatic), 136.8 (aromatic), 139.7 (aromatic), 157.5 (N═CAr), 163.6 (C═O), 171.8 (C═O), 172.5 (C═O). Minor isomer ($CDCl_3$) δ 19.6 (ArCH$_3$), 19.8 (ArCH$_3$), 21.3 (CHCH$_3$), 26.2 (C(═O)CH$_3$), 47.4 (CH$_2$), 53.8 (CHCH$_3$), 91.7 (spiro carbon), 124.0 (aromatic), 128.5 (aromatic), 136.9 (aromatic), 139.5 (aromatic), 157.3 (N═CAr), 165.3 (C═O), 169.7 (C═O), 171.3 (C═O). $[\alpha]_D^{20}$ (major, 5*S*,8*S*)+5.0 (1 mg/mL, CH_2Cl_2); m/z (EI) 343 ($M^{+\cdot}$, 46%), 284 (23%), 258 (21%), 186 (42%), 161 ([ArCNO]$^{+\cdot}$, 100%). HRMS Mol. wt. Found: 343.1535. Calcd for $C_{18}H_{21}N_3O_4$ 343.1532. Microanalysis calcd for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 63.02; H, 6.21; N, 12.20.

4.2.6. 6,9-Diacetyl-8-methyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (4b). Following the general procedure outlined above, the title compound was prepared from mesitonitrile oxide and piperazinedione **2b** and obtained as a 5:1 mixture of isomers. These were purified by flash column chromatography (1:2 ethyl acetate/petroleum spirits, R_f=0.73) to yield the product as a white solid in 62% overall yield. Data presented is for the major isomer only.

Mp 114–115°C. IR (KBr) 1720 (s, C═O), 1368 (m), 1336

(m), 1297 (m), 1215 (s), 1146 (m), 887 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.52 (d, J=7 Hz, 3H, CHCH_3), 2.31 (s, 3H, ArCH_3), 2.43 (s, 6H, 2×ArCH_3), 2.61 (s, 3H, C(=O)CH_3), 2.63 (s, 3H, C(=O)CH_3), 3.57 (d, J=17 Hz, 1H, CH_aH_b), 3.94 (d, J=17 Hz, 1H, CH_aH_b), 5.18 (q, J=7 Hz, 1H, CHCH$_3$), 6.93 (s, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ 19.6 (ArCH$_3$), 20.9 (ArCH$_3$), 21.0 (CHCH$_3$), 26.5 (C(=O)CH$_3$), 28.5 (C(=O)CH$_3$), 49.9 (CH$_2$), 52.6 (CHCH$_3$), 94.1 (spiro carbon), 123.8 (aromatic), 128.6 (aromatic), 137.5 (aromatic), 139.3 (aromatic), 157.3 (N=CAr), 167.4 (C=O), 167.8 (C=O), 170.9 (C=O), 174.1 (C=O); m/z (EI) 385 ($M^{+\cdot}$, 42%), 284 (15%), 258 (15%), 186 (100%), 159 (76%), 145 (34%). $[\alpha]_D^{20}$ for the 5R,8S isomer+14.0 (1 mg/mL, CH_2Cl_2) HRMS Mol. wt. Found: 385.1642. Calcd for $C_{20}H_{23}N_3O_5$ 385.1638. Microanalysis calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.01; N, 10.90. Found: C, 62.31; H, 5.64; N, 10.94.

4.2.7. 9-Acetyl-8-isopropyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (4e). Following the general procedure outlined above, the title compound was prepared from mesitonitrile oxide and piperazinedione **2e**. This was purified by flash column chromatography (1:4 ethyl acetate/petroleum spirits, R_f=0.23) to yield the product as a white solid in 78% overall yield.

Mp 182–183°C. IR (KBr) 3104 (s), 2972 (s), 1695 (s, C=O), 1691 (s, C=O), 1610 (m), 1465 (s), 1417 (s), 1380 (s), 1332 (s), 1290 (s), 1222 (s), 1078 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.89 (d, J=7 Hz, 3H, CH(CH_3)$_2$), 1.09 (d, J=7 Hz, 3H, CH(CH_3)$_2$), 2.16 (m, 1H, CH(CH$_3$)$_2$, 2.30 (s, 3H, ArCH_3), 2.33 (s, 6H, 2×ArCH_3), 2.55 (s, 3H, C(=O)CH_3), 3.23 (d, J=18 Hz, 1H, CH_aH_b), 4.03 (d, J=18 Hz, 1H, CH_aH_b), 4.94 (d, J=7 Hz, 1H, ring methine), 6.91 (s, 2H, 2×ArH), 8.45 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 17.5 ((CH_3)$_2$CH), 19.2 ((CH_3)$_2$CH), 19.6 (2×ArCH$_3$), 21.1 (ArCH$_3$), 25.6 ((C=O)CH$_3$), 34.1 ((CH$_3$)$_2$$C$H), 48.4 ($CH_2$), 61.8 (piperazinedione CH), 92.1 (spiro carbon), 124.1 (aromatic), 128.5 (aromatic), 136.9 (aromatic), 139.5 (aromatic), 157.2 (N=CAr), 166.4 (C=O), 167.2 (C=O), 171.0 (C=O); m/z (EI) 371 ($M^{+\cdot}$, 50%), 354 (34%), 328 (4%), 312 (42%), 286 (33%), 186 (55%), 161 ([ArCNO]$^{+\cdot}$, 100%). $[\alpha]_D^{20}$ for the 5R,8S isomer+32.4 (c 0.01, CH_2Cl_2). Microanalysis calcd for $C_{20}H_{25}N_3O_4$: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.58; H, 7.30; N, 11.32.

4.2.8. 6,9-Diacetyl-8-isopropyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (4f). Following the general procedure outlined above, the title compound was prepared from mesitonitrile oxide and piperazinedione **2f**. This was purified by flash column chromatography (1:4 ethyl acetate/petroleum spirits, R_f=0.29) to yield the product as a white solid in 66% overall yield.

Mp 148–150°C. IR (KBr) cm^{-1} 2968 (m), 1726 (C=O, s), 1413 (s), 1387 (s), 1334 (s), 1276 (s), 1136 (s), 1136 (s), 1074 (s), 890 (s), 857 (s), 847 (s). ^1H NMR ($CDCl_3$) δ 0.97 (d, J=7 Hz, 3H, CH(CH_3)$_2$), 1.01 (d, J=7 Hz, 3H, CH(CH_3)$_2$), 2.05 (m, 1H, CH(CH$_3$)$_2$, 2.30 (s, 3H, ArCH_3), 2.44 (s, 6H, 2×ArCH_3), 2.58 (s, 3H, C(=O)CH_3), 2.59 (s, 3H, C(=O)CH_3), 3.36 (d, J=18 Hz, 1H, CH_aH_b), 3.92 (d, J=18 Hz, 1H, CH_aH_b), 5.16 (d, J=7 Hz, 1H, ring methine), 6.91 (s, 2H, 2×ArH). ^{13}C NMR ($CDCl_3$) δ 18.5 ((CH_3)$_2$CH), 19.0 ((CH_3)$_2$CH), 19.7 (2×ArCH$_3$), 21.0 (ArCH$_3$), 25.5 ((C=O)CH$_3$), 28.6 ((C=O)CH$_3$), 34.5 ((CH$_3$)$_2$$C$H), 49.7 ($CH_2$), 60.8 (piperazinedione CH), 94.8 (spiro carbon), 124.0 (aromatic), 128.6 (aromatic), 137.6 (aromatic), 139.2 (aromatic), 158.0 (N=CAr), 165.9 (C=O), 169.1 (C=O), 170.4 (C=O), 174.0 (C=O); m/z (EI) 413 ($M^{+\cdot}$, 68%), 371 (7%), 354 (20%), 328 (16%), 310 (39%), 268 (33%), 186 (100%), 161 ([ArCNO]$^{+\cdot}$, 82%). $[\alpha]_D^{20}$ for the 5R,8S isomer+6.4 (c 0.01, CH_2Cl_2). Microanalysis calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.82; H, 6.32; N, 10.16.

4.3. General procedure for deacetylation reactions

To a stirred solution of the cycloadduct in *N*,*N*,-dimethylformamide (1 mL per 0.2 mmol of cycloadduct) was added hydrazine hydrate (1 mol equiv. per *N*-acetyl group present). The reaction mixture was stirred at room temperature for 16 h, following which the reaction mixture was concentrated under high vacuum. The resulting residue was triturated with diethyl ether and the resulting solid was filtered.

4.3.1. 8-Methyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (5a). IR (KBr) cm^{-1} 3204 (m), 3086 (m), 2971 (m), 1706 (C=O, s), 1483 (m), 1338 (m), 1313 (m). ^1H NMR (d_6-DMSO) δ 1.42 (d, J=7 Hz, 3H, CH_3), 2.18 (s, 6H, ArCH_3), 2.20 (s, 3H, ArCH_3), 3.15 (d, J=18 Hz, 1H, CH_aH_b), 3.90 (d, J=18 Hz, 1H, CH_aH_b), 3.90 (m, 1H, CHCH$_3$), 6.89 (m, 2H, ArH), 8.65 (s, 1H, NH), 9.10 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 19.4 (2×ArCH$_3$), 20.7 (ArCH$_3$), 21.9 (CH$_3$CH), 45.1 (CH$_2$), 51.6 (piperazinedione CH), 90.9 (spiro carbon), 125.2 (aromatic), 128.2 (aromatic), 136.6 (aromatic), 138.5 (aromatic), 156.9 (N=CAr), 163.1 (C=O), 170.8 (C=O); m/z (EI) 301 ($M^{+\cdot}$, 25%), 284 (38%), 258 (17%), 186 (27%), 161 ([ArCNO]$^{+\cdot}$, 100%), 144 (23%), 130% (26%), 91 (27%).

4.3.2. 8-Methyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (5b). IR (KBr) cm^{-1} 3204 (m), 3086 (m), 2971 (m), 1706 (C=O, s), 1483 (m), 1338 (m), 1313 (m). ^1H NMR (d_6-DMSO) δ 1.29 (d, J=7 Hz, 3H, CH_3), 2.22 (s, 3H, ArCH_3), 2.24 (s, 6H, ArCH_3), 3.19 (d, J=18 Hz, 1H, CH_aH_b), 3.96 (d, J=18 Hz, 1H, CH_aH_b), 4.21 (m, 1H, CHCH$_3$), 6.91 (m, 2H, ArH), 8.67 (s, 1H, NH), 9.66 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 16.6 (CH$_3$CH), 19.4 (2×ArCH$_3$), 20.7 (ArCH$_3$), 44.5 (CH$_2$), 49.7 (piperazinedione CH), 91.5 (spiro carbon), 125.2 (aromatic), 128.2 (aromatic), 136.6 (aromatic), 138.5 (aromatic), 156.9 (N=CAr), 163.7 (C=O), 170.9 (C=O); m/z (EI) 301 ($M^{+\cdot}$, 23%), 284 (38%), 258 (17%), 186 (26%), 161 ([ArCNO]$^{+\cdot}$, 100%), 144 (23%), 130% (26%), 91 (25%).

4.3.3. 8-Isopropyl-3-(2,4,6-trimethylphenyl)-1-oxa-2,6,9-triaza-spiro[4.5]dec-2-ene-7,10-dione (6). Mp 245–250°C (dec.). IR (KBr) cm^{-1} 3206 (m), 3110 (m), 2968 (m), 1688 (C=O, s), 1410 (m), 1383 (m), 1329 (m). ^1H NMR (d_6-DMSO) δ 1.17 (d, J=7 Hz, 3H, CH(CH_3)$_2$), 1.33 (d,

J=7 Hz, 3H, CH(CH_3)$_2$), 2.60 (m, 1H, CH(CH$_3$)$_2$, 2.81 (s, 3H, ArCH_3), 3.49 (d, J=18 Hz, 1H, CH_aH$_b$), 3.65 (s, 6H, 2×ArCH_3), 4.23 (d, J=18 Hz, 1H, CH$_a$$H_b$), 4.35 (br s, 1H, ring methine), 7.22 (s, 2H, 2×ArH), 8.68 (s, 1H, NH), 9.98 (s, 1H, NH). ^{13}C NMR (CDCl$_3$) δ 16.4 ((*C*H$_3$)$_2$CH), 17.8 ((*C*H$_3$)$_2$CH), 19.4 (2×Ar*C*H$_3$), 20.7 (Ar*C*H$_3$), 29.7 ((CH$_3$)$_2$*C*H), 44.9 (*C*H$_2$), 59.1 (piperazinedione *C*H), 91.1 (spiro carbon), 125.3 (aromatic), 128.2 (aromatic), 136.6 (aromatic), 138.5 (aromatic), 156.9 (N=*C*Ar), 164.7 (*C*=O), 169.3 (*C*=O); *m/z* (EI) 329 ($M^{+\cdot}$, 21%), 312 (44%), 286 (11%), 186 (36%), 161 ([ArCNO]$^{+\cdot}$, 100%). $[\alpha]_D^{20}$=−130 (*c* 0.4 mg/mL, DMSO). HRMS Mol. wt. Found: 329.1744. Calcd for $C_{18}H_{23}N_3O_3$ 329.1739.

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