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Tandem 1,3-azaprotio cyclotransfer–cycloaddition reactions between aldoximes and divinyl ketone. The effect of oxime *E*/*Z*-isomerism on cycloaddition stereoselectivity

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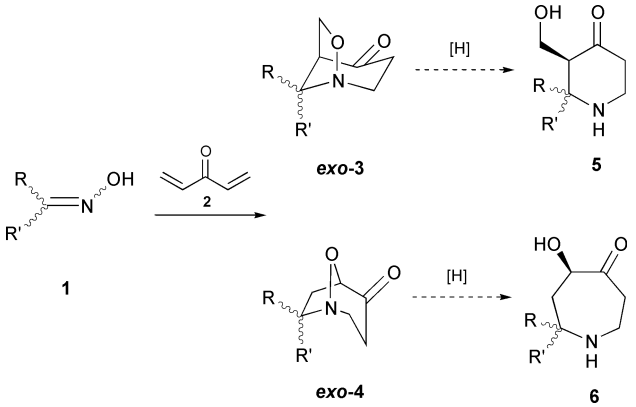
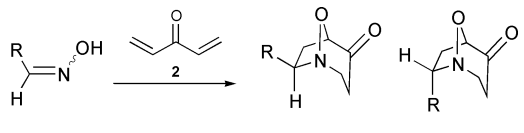
The tandem 1,3-azaprotiocyclotransfer–cycloaddition reaction between aldoximes and divinyl ketone affords mixtures of *exo*- and *endo*-isomers of substituted 1-aza-8-oxabicyclo[3.2.1]octan-4-ones, the ratio of which is dependent on the *E*/*Z* geometry of the starting oxime and its ability to isomerise under the thermal reaction conditions.

We recently reported that the tandem 1,3-azaprotio cyclotransfer–cycloaddition reaction between symmetrical ketoximes (R′ = R) and divinyl ketone **2** (or its equivalents) is selective for cycloadducts **3** or **4**, depending on solvent or additive.[1] Reductive cleavage of **3** and **4** can afford *piperidones* **5** and *perhydroazepinones* **6**, potentially making these Class 2 cascades viable routes to various alkaloids and other related natural products (Scheme 1).[2] We have been exploring the



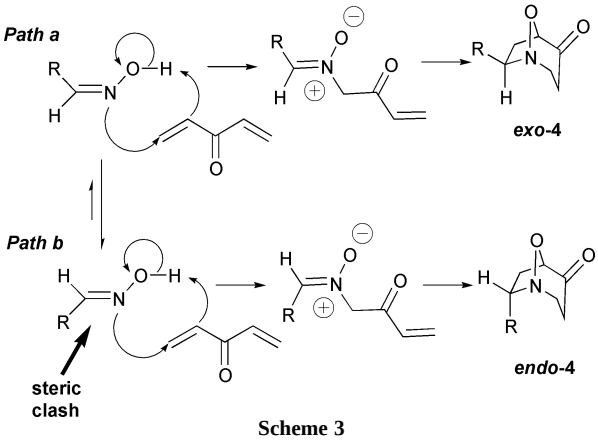
Scheme 1

scope of this reaction with aldoximes **1** (R or R′ = H). Under thermal reaction conditions (81 °C, acetonitrile) symmetrical ketoximes (R = R′) afford mixtures of **3** and **4**, whereas aldoximes (R or R′ = H) afford **4** only (as a mixture of *exo*- and *endo*-isomers) (Scheme 2).



Scheme 2

Under thermal reaction conditions aldoximes isomerise to a mixture of *E*- and *Z*-isomers. The rate of *E*/*Z* equilibration is dependent on temperature and the nature of the aldoxime R group. The desired 1,3-azaprotiocyclotransfer process (herein referred to as 1,3-APT) (Scheme 3) can occur between either *E*- or *Z*-oxime isomer and **2** to form respective *E*- and *Z*-nitrones. Nitrones are not expected to isomerise under the reaction conditions.[3] Intramolecular 1,3-dipolar cycloaddition then proceeds completely regioselectively from the *Z*-nitrone affording *exo*-**4** (*path a*) or the *E*-nitrone affording *endo*-**4** (*path b*).[4] A survey of aldoximes **1a**–**f** showed that the diastereoselectivity of the reaction is dependent on the size of the aldoxime R group (Table 1). Increasing the size of the R group (aldoximes **1b**–**d**) resulted in a decrease in *exo*-selectivity. However, the case of **1e** perturbed this trend, affording *exo*-**4e** as the sole product.



Scheme 3

It is proposed that *path a* and *path b* can have different rate determining steps. In *path a*, oxime isomerism can become the rate determining step when the steric clash resulting from the *cis*-relationship of the R and hydroxy moieties in the *Z*-oxime is severe or due to the electronic properties of R (*vide infra*). In contrast, 1,3-APT is rate determining in *path b* because the R group impedes the reactivity of the lone pair. The ratio of *exo*- and *endo*-products is determined by the relative rates of these steps and this is determined by the nature of R. Predominant formation of *exo*-**4** (*e.g.* for aldoximes **1a**,**b**) indicates that oxime *E*/*Z*-isomerism is faster than *E*-oxime 1,3-APT.

Though an increase in the size of the R group will decrease both the rate of oxime isomerism and *E*-oxime 1,3-APT, we propose that the effect is more pronounced on the oxime isomerism step due to the increased steric clash between the R and hydroxy moieties. The *E*-oxime 1,3-APT step can occur

Table 1[a]

Oxime **1**	R	Conv. (%)[b]	*exo*-**4**:*endo*-**4**[b]	Yield (%)[c]
a	Bn	> 95	3:1	65
b	Me	> 95	3.4:1	59
c	Et	> 95	2:1	41
d	Pr^{i}	90	1.5:1	34
e	Bu^{t}	25	*exo*-**4e** only	11
f	Ph	10	*endo*-**4f** only	—

[a] Reaction conditions: divinyl ketone (1.2 eq.), acetonitrile, 48 h, carried out in a STEM block at 80 °C. [b] Determined by ^{1}H NMR. [c] Combined yield isolated by column chromatography.

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Table 2

X	Isomer	Conv. (%)[a]	*exo*-**4**[b]	*endo*-**4**[b]	Yield (%)[c]
H	*E*-	10	1	> 20	—
H	*Z*-	> 95	> 20	1	79
CF_3	*E*-	< 5	—	—	—
CF_3	*Z*-	> 95	> 20	1	76
CN	*E*-	< 5	—	—	—
CN	*Z*-	90	> 20	1	44
NO_2	*E*-	< 5	—	—	—
NO_2	*Z*-	55	> 20	1	19
MeO	*E*-	80	4	1	55
MeO	*Z*-	> 95	7	1	78
Cl	*E*-	> 95	10	1	61
Cl	*Z*-	> 95	8	1	76
F	*E*-	> 95	8	1	72
F	*Z*-	> 95	12	1	70

[a] Reaction conditions: Divinyl ketone (1.2 eq.), acetonitrile, 80 °C, 48 h. [b] Determined by ^{1}H NMR. Where the ratio of isomers is > 20 : 1 no trace of the minor isomer was detected. [c] Yield isolated by column chromatography.

provided the oxime R substituent contains an α-hydrogen (as in **1a**–**d**). This allows conformations where a C–H bond, as opposed to a C–R′ bond, impedes the reactivity of the lone pair. As the size of R increases, the increasingly sluggish nature of the *E*-oxime 1,3-APT step is reflected in the lower yields and conversions (Table 1). Where the oxime contains no α-hydrogens (**1e**) severe impediment of the lone pair's reactivity is unavoidable and 1,3-APT can only proceed *via* the *Z*-oxime (*path a*). The sluggish nature of the oxime isomerism step for **1e** is reflected in the low conversion (25% after 48 h) and yield (11%).

Unlike aliphatic oximes (*E*)-benzaldoxime **1f** does not isomerise at 81 °C. Both *E*- and *Z*-isomers can be prepared and stored separately.[5,6] The observation that (*E*)-**1f** forms *endo*-**4f** exclusively while (*Z*)-**1f** affords *exo*-**4f** exclusively (Table 2) supports our hypothesis. In order to determine the effect of the electronic nature of the aryl ring on oxime isomerism we carried out the cascade with both *E*- and *Z*-isomers of *para*-substituted benzaldoximes (Table 2). We observed that the presence of electron donating groups promotes oxime isomerism, affording mixtures of *exo*- and *endo*-isomers. The presence of electron withdrawing groups in the aromatic ring does not promote oxime isomerism and instead 'switches off' the 1,3-APT step for *E*-oxime isomers. Switching to the *Z*-isomers in the case of these electron deficient benzaldoximes allows the reactions to proceed, leading to *exo*-**4** exclusively.

Increasing the reaction temperature from 80 to 95 °C (closed system) resulted in an increase in the propensity of aliphatic aldoximes to form the *exo*-isomer (Table 3). We were able to utilise this effect in the case of phenyl acetaldehyde oxime (**1a**), attaining *exo*-selectivity of 8 : 1 (81%) when the reaction temperature was 120 °C (closed system) (Table 3). Similarly, **1b** afforded an 8 : 1 ratio of *exo*-**4b** and *endo*-**4b** (65%). Increasing the temperature of the system further (150 °C) resulted in identical *exo*-selectivity, however. It is proposed that high temperatures facilitate higher rates of *E*/*Z*-oxime equilibration, leading to enhanced *exo*-selectivity.[7]

In conclusion we have demonstrated that this tandem 1,3-APT-cycloaddition cascade between aldoximes and divinyl ketone can afford single diastereomers with predictable *exo*- or *endo*-stereochemistry by a correct choice of conditions: high temperatures for aliphatic aldoximes and correct choice of starting oxime for aromatic aldoximes.

Table 3[a]

Oxime **1**	R	Temp/°C	Conv. (%)[d]	*exo*-**4** : *endo*-**4**[d]	Yield (%)[e]
a	Bn	95[b]	> 95	4.3 : 1	57
a	Bn	120[c]	> 95	8 : 1	81
b	Me	95[b]	> 95	5.6 : 1	59
b	Me	120[c]	> 95	8 : 1	65
c	Et	95[b]	> 95	2.7 : 1	53
d	Pr^i	95[b]	90	2 : 1	54
e	Bu^t	95[b]	45	*exo*-**4e** only	37
f	Ph	95[b]	30	*endo*-**4f** only	14

[a] Reaction conditions: Divinyl ketone (1.2 eq.), acetonitrile, STEM block at 95 °C, 48 h. [b] Temperature of STEM block. [c] Temperature of closed system. [d] Determined by ^{1}H NMR. [e] Combined yield of *exo*-**4** and *endo*-**4** isolated by column chromatography.

Notes and References

1 I. S. Saba, M. Frederickson, R. Grigg P. Dunn and P. Levett, *Tetrahedron Lett.*, 1997, **38**, 6099.
2 I. S. Saba, PhD Thesis, 1997, University of Leeds.
3 R. Grigg, F. Heaney, S. Surendrakumer and W. Warnock, *Tetrahedron*, 1991, **47**, 4477.
4 The reasons for this regioselective formation of **4** are discussed in the proceeding communication.
5 R. Grigg, F. Heaney, S. Surendrakumar and W. Warnock, *Tetrahedron*, 1991, **47**, 4477.
6 R. Grigg, M. Dorrity, F. Heaney, J. Malone, S. Rajviroongit, V. Sridharan and S. Surendrakumar, *Tetrahedron*, 1991, **47**, 8297.
7 A mixture of *exo*-**3b** and *endo*-**3b** was recovered unchanged, in good recovery after heating in a closed system at 120 °C. Thus proving that a cycloreversion–cycloaddition is not responsible for the increased *exo*-selectivity.