Highly diastereoselective hetero-Diels–Alder reactions of alkenyldihydrooxazoles as an approach to novel pyrimidine derivatives

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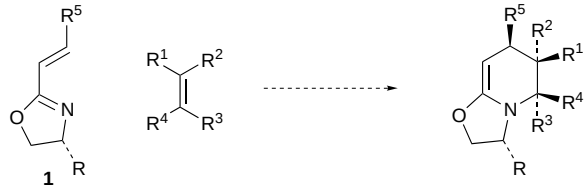
Chiral 2-alkenyldihydrooxazoles react with two equivalents of aryl and arylsulfonyl isocyanates to give chiral non-racemic dihydropyrimidone derivatives in high yield and with complete diastereocontrol.

Despite the proven synthetic utility of the all-carbon Diels–Alder reaction,[1] the aza analogue has been much less investigated.[2,3] It offers the opportunity to prepare a wide range of biologically interesting piperidines in a single step with control over three stereogenic centres. We considered the possibility that alkenyldihydrooxazoles **1** could act as aza-dienes,[4] and since these compounds are readily available in enantiopure form from amino alcohols, an asymmetric aza-Diels–Alder reaction as shown schematically in Scheme 1 is an attractive possibility. To the best of our knowledge there is only one example of the use of alkenyldihydrooxazoles as aza-dienes. However, the reported infrared stretching absorption of the product (1760 cm^{-1}) seems inconsistent with the assigned structure **2** (Scheme 2).[5] Since neither the yield nor reaction conditions were reported, we felt it would be useful to investigate the reactions of alkenyldihydrooxazoles with isocyanates as a prelude to a broader study.[6,7]

To this end, dihydrooxazoles **3**–**6** were prepared as shown in Scheme 3 from readily available (*R*)-2-aminobutan-1-ol.

When **3** was heated in a sealed tube (150 °C, 1 h) with 2 equiv. of phenyl isocyanate, an essentially pure 2 : 1 adduct was obtained to which structure **8a** was assigned on the basis of spectroscopic data.†,‡ In fact, this reaction proceeds at room temp. (24 h), and at either temperature only a *single diastereoisomer was observed* (Scheme 4). Presumably this reaction proceeds *via* addition of a second molecule of phenyl isocyanate to compound **7**. The absence of any other products in the ^1H and ^{13}C NMR spectra of the crude reaction mixture conducted under a wide range of stoichiometries lead us to conclude that this process is faster than the hetero-Diels–Alder reaction. For a such a small chiral directing group this selectivity is particularly impressive.

The reactions of **3**–**5** with five different isocyanates gave similar results as shown in Table 1. In each case only a single



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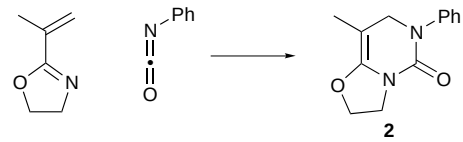
Scheme 1



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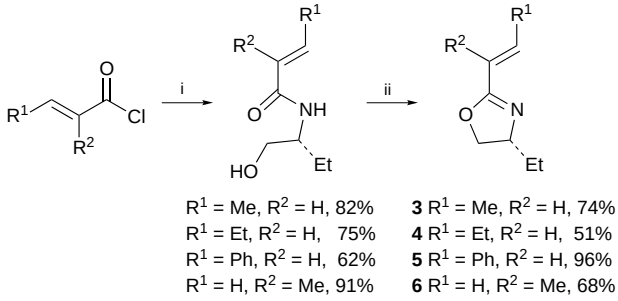
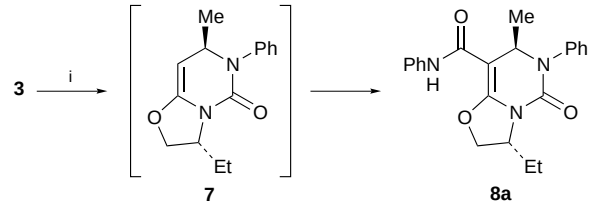
Scheme 2



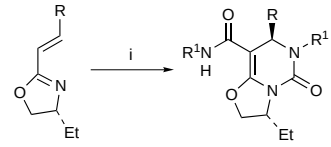
Scheme 3 *Reagents and conditions*: i, (*R*)-2-aminobutan-1-ol, Na_2CO_3, CH_2Cl_2; ii, $MeSO_2Cl$, Et_3N, CH_2Cl_2



7 **8a**

Scheme 4 *Reagents and conditions*: i, 2 equiv. PhNCO, 150 °C for 1 h or 25 °C for 24 h

Table 1 Reactions of **3**, **4** and **5** with selected isocyanates



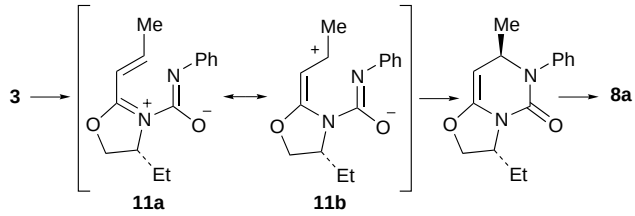
3 R = Me
4 R = Et
5 R = Ph

8 R = Me
9 R = Et
10 R = Ph

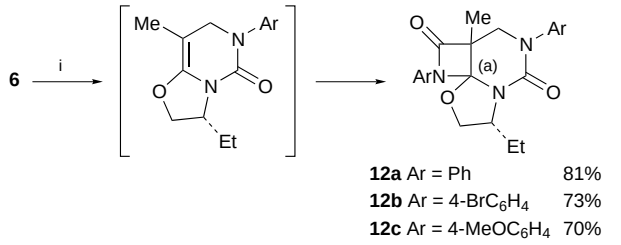
a R^1 = Ph
b R^1 = 4-BrC_6H_4
c R^1 = 4-$O_2NC_6H_4$
d R^1 = 4-$MeOC_6H_4$
e R^1 = 4-$MeC_6H_4SO_2$

R^1	R^2	*t*/h	*T*/°C	Compound (yield %)[a]
Me	Ph	48	25	**8a** (58)
Me	4-BrC_6H_4	24	25	**8b** (61)
Me	4-$O_2NC_6H_4$	21	25	**8c** (82)
Me	4-$MeOC_6H_4$	120	25	**8d** (65)
Me	4-$MeC_6H_4SO_2$	0.5	25	**8e** (59)
Et	Ph	1	150	**9a** (53)
Et	4-BrC_6H_4	1	150	**9b** (61)
Et	4-$O_2NC_6H_4$	1	150	**9c** (71)
Et	4-$MeOC_6H_4$	—	—	**9d** (0)[b]
Et	4-$MeC_6H_4SO_2$	0.5	25	**9e** (90)
Ph	Ph	1	150	**10a** (76)
Ph	4-BrC_6H_4	1	150	**10b** (59)
Ph	4-$O_2NC_6H_4$	1	150	**10c** (74)
Ph	4-$MeOC_6H_4$	1	150	**10d** (10)[c]
Ph	4-$MeC_6H_4SO_2$	0.5	25	**10e** (94)

[a] Yields refer to pure isolated compounds, and are not optimised. [b] The ^1H NMR spectrum of the crude reaction mixture shows a small amount of the desired product. No dihydrooxazole remains unreacted. [c] Not completely purified.



Scheme 5



12a Ar = Ph 81%
12b Ar = 4-BrC_6H_4 73%
12c Ar = 4-$MeOC_6H_4$ 70%

Scheme 6 *Reagents and conditions*: i, 2 equiv. ArNCO, 150 °C, 24 h

diastereoisomer was observed in the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture. The stereochemistry of **8c** and **10e** were determined by single crystal X-ray diffraction. All other compounds are assumed, on the basis of similar spectroscopic data, to have the same stereochemistry.

There has been much debate about the concerted nature, or lack thereof, in both normal[8] and hetero[9] Diels–Alder reactions. Given the highly polarised nature of the reacting partners, the initial interaction may be best represented as initial acylation of the dihydrooxazole nitrogen as shown in Scheme 5.[10] However, the present results do not rule out a concerted (although probably asynchronous) aza-Diels–Alder reaction.

The subsequent addition of the isocyanate may proceed either by a direct [2πs + 2πa] cycloaddition followed by cleavage of the β-lactam or by a stepwise enamine acylation.[11] In fact, when **6** was subjected to similar reaction conditions (2 equiv. phenyl isocyanate, 150 °C, 24 h) compound **12a** was obtained§ as a 1.7 : 1 mixture of diastereoisomers (Scheme 6). Similar reactions were observed with 4-bromophenyl and 4-methoxyphenyl isocyanates. No product could be isolated from the reaction with 4-nitrophenyl isocyanate, presumably due to the ease of hydrolysis of the corresponding β-lactam.

The structures of compounds **12** were assigned by analogy with compounds **8**–**10**, and are supported by extensive NOE studies. Unfortunately we have been unable to assign the stereochemistry of the major isomer. Furthermore, the quaternary carbon (a) in Scheme 6 is significantly deshielded (^{13}C resonance in **12**, 152.6 ppm), which could be explained by the contribution of a zwitterionic resonance form **13** to the overall structure (Fig. 1). The existence of **12** as a full zwitterion seems unlikely on the grounds of polarity. Rigorous purification of **12a**–**c** proved difficult due to the lability of these compounds. Chromatography over neutral alumina gave essentially pure compounds, although traces of the diaryl urea, derived from the isocyanate, could not be completely removed. To the best of our knowledge this work represents the first synthesis of the azeto[3′,2′ : 5,6]pyrimido[6,1-*b*]oxazole ring system. We are unable to consolidate our data with that of Seeliger *et al.*[5]

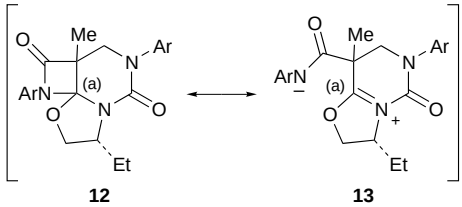


Fig. 1

This new variation on the Diels–Alder reaction has considerable potential in the provision of novel chiral nonracemic compounds. This is, as far as we are aware, only the second report of an asymmetric aza-Diels–Alder reaction of a chiral 1-azadiene.[3] Detailed experimental and computational studies are in progress to determine the mechanism and origin of stereoselectivity with a view to realising the potential of this reaction.

We thank the University of Wales, Cardiff for financial support of this research, Mrs A. Dams for microanalytical data and Mr R. Jenkins for mass spectrometric data. The X-ray crystallographic study of compounds **8c** and **10e** was carried out by Professor M. B. Hursthouse, Mr D. E. Hibbs and Mr D. S. Hughes of this department. Full details will be published elsewhere.

Footnotes and References

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† All compounds exhibit satisfactory spectroscopic and analytical data.

‡ *Selected data* for **8a**: δ_H(400 MHz; $CDCl_3$; *J*/Hz) 8.32 (1 H, s, N*H*), 7.47 (2 H, d, *J* 7.9, Ar-H), 7.33 (2 H, d, *J* 7.5, Ar-H), 7.28–7.20 (5 H, m, Ar-H), 7.00 (1 H, t, *J* 7.4, Ar-H), 4.89 (1 H, q, *J* 6.2, Me-C*H*), 4.60 (1 H, app. t, *J* 8.1, O-C*H*), 4.48 (1 H, dd, *J* 8.4 and 1.6, O-C*H*), 4.31 (1 H, m, *H*C-Et), 1.99–1.93 (1 H, m, one of CH_2), 1.90–1.83 (1 H, m, one of CH_2), 1.22 (3 H, d, *J* 6.2, CH_3), 0.87 (3 H, t, *J* 7.4, CH_3); δ_C(100 MHz; $CDCl_3$) 162.6 (C=O), 152.1 (C=O), 150.4 (C=C), 140.3 (C), 139.0 (C), 129.6 (CH), 129.3 (CH), 128.3 (CH), 127.0 (CH), 123.9 (CH), 120.2 (CH), 83.8 (C=C), 74.1 (O-CH_2), 57.3 (CH), 56.2 (CH), 23.7 (CH_2), 21.2 (CH_3), 9.0 (CH_3); ν_{max}($CHCl_3$)/cm^{-1} 3424, 1686, 1649, 1595, 1535.

§ *Selected data* for **12a** (mixture of stereoisomers): δ_H(400 MHz; $CDCl_3$; *J*/Hz) 7.7–6.9 (10 H, m, aromatic H), 4.40–4.20 (1 H, m) 4.14–4.04 (2 H, m), 3.95–3.85 (2 H, m), 1.58–1.46 (5 H, m, CH_2 and CH_3), 0.90 (3 H of major isomer, t, *J* 7.4, CH_3), 0.85 (3 H of minor isomer, t, *J* 7.5, CH_3); δ_C(100 MHz; [$^2H_6$]DMSO) 170.1 (C=O), 165.2 (C=O), 165.2 (C=O), 152.6 (C), 152.6 (C), 142.9 (C), 142.7 (C), 137.7 (C), 137.6 (C), 129.8 (CH), 129.7 (CH), 129.6 (CH), 129.5 (CH), 128.7 (CH), 127.3 (CH), 127.1 (CH), 126.3 (CH), 126.0 (CH), 73.1 (CH_2), 72.9 (CH_2), 67.7 (CH), 67.7 (CH), 53.6 (CH_2), 53.1 (CH_2), 45.1 (C), 45.1 (C), 29.1 (CH_2), 28.6 (CH_2), 18.4 (CH_3), 18.0 (CH_3), 10.6 (CH_3), 10.2 (CH_3); ν_{max}($CHCl_3$)/cm^{-1} 3012, 2970, 1729, 1686 and 1498.

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