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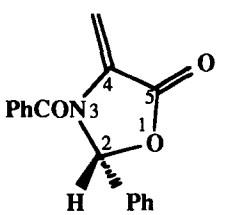
Exo-Diastereoselective 1,3-Dipolar Cycloadditions of Azomethine Ylides to (2*R*)-3-Benzoyl-4-methylene-2-phenyloxazolidin-5-one.

Stephen G. Pyne*, Javad Safaei-G. and Fiona Koller (in part)

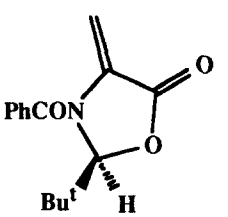
Department of Chemistry, University of Wollongong, Wollongong, NSW, 2522, Australia

Abstract: *Exo*-diastereoselective 1,3-dipolar cycloadditions of azomethine ylides derived from α-amino acid esters to (2*R*)-3-Benzoyl-4-methylene-2-phenyloxazolidin-5-one (1) are reported. The cycloaddition products are conveniently converted to polyfunctional prolines in high enantiomeric purity.

The 1,3-diploar cycloaddition reactions of azomethine ylides derived from *N*-alkylidene α-amino acid esters to electron deficient alkenes is an extremely powerful method for the synthesis of polyfunctional prolines.[1-5] The asymmetric version of these reactions has been realised by employing a chiral auxiliary attached to either the dipolarophile[3] or the azomethine ylide[4] or the use of a chiral metal complex catalyst.[5] As part of a continuing program we have been interested in the asymmetric synthesis of novel non-proteinogenic amino acids using the chiral oxazolindinones (1)[6] and (2).[6-8] We have recently reported that (1) and (2) undergo highly *exo*-diastereoselective Diels-Alder reaction with dienes to give chiral carbocyclic amino acid derivatives in high enantiomeric purities.[6,9] Other workers have demonstrated that (2) undergoes diastereoselective 1,2-addition reactions with alkyl radicals[10] and nitronate anions[11] and cyclopropanation reactions.[12] We now report that (1) undergoes highly regioselective and *exo*-diastereoselective 1,3-diploar cycloaddition reactions with azomethine ylides derived from *N*-benzylidene α-amino acid esters. The cycloaddition products are conveniently converted to polyfunctional prolines in high enantiomeric purity.



(1)

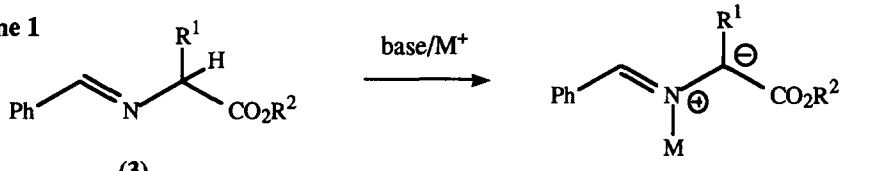


(2)

It is well documented that azomethine ylides can be prepared *in situ* from the reaction of *N*-alkylidene α-amino acid esters and a variety of metal cations in the presence of a base.[2,3(a-f)] In this study with (1) and imines (3), we found that the metal salt/base/solvent combination of LiBr/DBU/THF[2(a,b,e,g),3(a-e)] was far superior to AgOAc/DBU/THF[2(b,d-g),3(b,f)] or LiBr/Et_3N/MeCN[2(a,b,e,g),3(a-e)] in terms of chemical reactivity and product diastereoselectivity. The results of this study are summarised in Table 1. The azomethine ylides

(4) were generated *in situ* from (3) in the presence of (1) by treating a THF or MeCN solution of (1), (3) and the metal salt with base (DBU or Et_3N) at -78°C. The reaction mixtures were maintained at -78°C for several hours or warmed to the temperatures specified in Table 1 before being quenched with saturated aqueous NH_4Cl solution. In each case the diastereoselectivities of these reactions were measured on the crude reaction products by ^1H NMR analysis (Typically H2 in (5) (δ 5.76–5.88, s) was observed upfield of H2 in (6) (δ 6.04–6.35, s)). In each case a mixture of *exo*-(5) and *endo*-(6) products were formed and these could be conveniently separated by column chromatography. The yields in Table 1 refer to the combined yield of (5) and (6) after chromatographic separation.

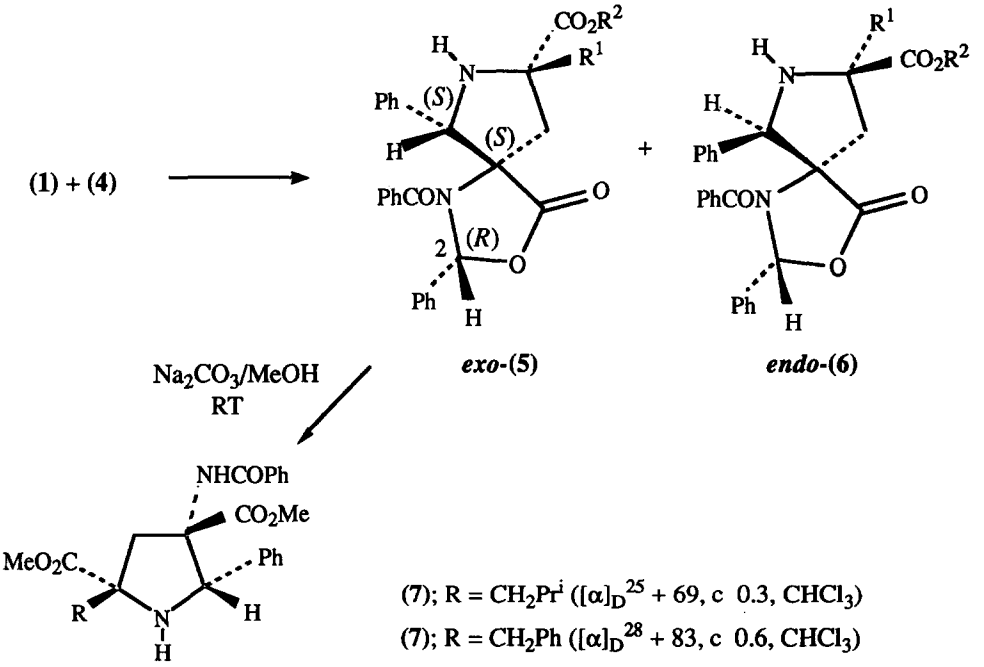
Scheme 1



(3)

method a: LiBr/DBU/THF
method b: LiBr/Et_3N/MeCN
method c: AgOAc/DBU/THF

(4); M = Li, Ag



exo-(5)

endo-(6)

(7); R = CH_2Pr^i ($[\alpha]_D^{25}$ + 69, c 0.3, $CHCl_3$)

(7); R = CH_2Ph ($[\alpha]_D^{28}$ + 83, c 0.6, $CHCl_3$)

In all but one case (Table 1, entry 6) the reactions were completely regioselective and showed good to high diastereoselectivity in favour of the *exo*-diastereoiomer (5) over the *endo*-diastereoiomer (6). The structures of (5) (R^1 = CH_2Pr^i) and (6) (R^1 = CH_2Pr^i and CH_2Ph) were determined by single-crystal X-ray structural analysis and the structural assignments of the other adducts (5) and (6) (R^1 = H, Me, Ph and CH_2Ph) were

based on the similarity of their ^1H NMR spectra to those of (5) ($R^1 = CH_2Pr^i$) and (6) ($R^1 = CH_2Pr^i$). When LiBr/Et_3N/MeCN was used the diastereoselectivities were generally lower except in the case of (3) (R^1 = Ph) (Table 1, entry 8) where an enhanced *exo*-diastereoselectivity (93 : 7) was realized. When AgOAc/DBU in THF was employed the diastereoselectivity was in general much lower (64-55 : 36-45) and the reactions did not proceed at an appreciable rate below 0^0C. In the case of the glycine derivative (3) (R^1 = H) (Table 1, entry 12), the LiBr/Et_3N or DBU method gave two as yet unknown structures, while a 43 : 57 mixture of (5) (R^1 = H) and (6) (R^1 = H) resulted when AgOAc/DBU in THF was used.

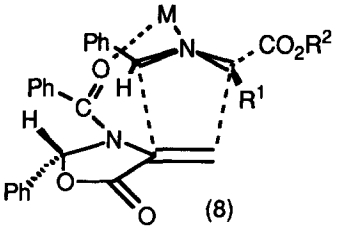
The adducts (5) ($R^1 = CH_2Pr^i$, CH_2Ph) were converted to the highly functionalised proline derivatives (7) (R = CH_2Pr^i, CH_2Ph) upon mild treatment with sodium carbonate in methanol. The enantiomeric purity of (7) (R = CH_2Pr^i) was determined to be 92% based on ^1H NMR analysis of its diastereomeric carbamate derivatives from treatment with (S)-(+)1-phenylethylisocyanate.

Table 1. 1,3-Dipolar cycloaddition products from azomethine ylides (4) and (1).

Entry	Imine (2) R^1	R^2	Method	Time(h)/Temp.(^0C)	Yield(%)	Diastereoselectivity (5) : (6)
1	Me	Me	a	6/-78	52	82 : 18
2	Me	Me	b	8/0	69	76 : 24
3	Me	Me	c	20/RT	83	58 : 42
4	CH_2Pr^i	Me	a	30/-20	61	94 : 6
5	CH_2Pr^i	Me	b	10/0	62	82 : 18
6	CH_2Pr^i	Me	c	30/RT	67	57 : 37 : 6
7	Ph	Me	a	20/-78	50	83 : 17
8	Ph	Me	b	20/0	59	93 : 7
9	CH_2Ph	Et	a	9/-78	45	85 : 15
10	CH_2Ph	Et	b	3/0	51	78 : 22
11	CH_2Ph	Et	c	30/RT	51	64 : 36
12	H	Et	c	6/RT	88	43 : 57

In summary, we report that the 1,3-dipolar cycloaddition reactions of (1) and the azomethine ylides (4) proceed with good to high *exo*-diastereoselectivity and that the cycloaddition adducts can be converted to highly functionalised prolines in high enantiomeric purity. The preference for *exo*-cycloaddition adducts can be rationalised by assuming chelation between the lithium cation and the *N*-benzoyl carbonyl group and the azomethine ylide (4), as shown in the possible transition state structure (8). While *endo*-cycloaddition adducts

are generally favoured in these types of reactions,[1,2(a,e,g),3(a,c-e,g),4(b,c,g,h)] *exo*-diastereoselective azomethine ylide cycloadditions are not uncommon.[4(e),13]



(8)

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