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Cycloadditions of 2-aza-1,3-dienes to aldehydes: a Diels–Alder strategy for the diastereoselective hydroxyalkylation of carboxylic acid derivatives

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Abstract

2-Aza-1,3-dienes **1** which are readily prepared from carboxylic acids cycloadd to aldehydes to give good yields of 1,3-oxazinones **3**. The cycloadditions were highly diastereoselective in favour of the *endo* adducts. Hydrolysis of 1,3-oxazinones **3** stereoselectively yielded the corresponding β-hydroxyamides **4**. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: 2-azadienes; Diels–Alder cycloadditions; hydroxyalkylations; aldehydes; 1,3-oxazinones; β-hydroxyamides.

Earlier studies from this laboratory have shown that a wide variety of 2-aza-1,3-dienes **1** could be prepared in a one-pot procedure from carboxylic acids and *N*-silylimines.[1] More recently our group described an efficient protocol which allowed the one-pot conversion of a carboxylic acid chloride, an iminoether and an acetylenic or nitrile dienophile into pyridones or pyrimidones.[2] The reaction of 2-aza-1,3-dienes **1** with electrophilic olefins provides a highly stereoselective route towards piperidones.[3] In the presence of a chiral copper(II) complex, the reaction gave substituted piperidones of high enantiomeric purities.[4]

We have also examined the possibility of using 2-aza-1,3-dienes **1** as reagents for the stereocontrolled functionalisation of the α-position of a carboxylic acid according to Scheme 1. This was first illustrated by a sequence involving the cycloaddition of **1** to nitroso compounds (X=Y: R^3-N=O) as key step.[5] The use of a chiral auxiliary on the nitroso compound led ultimately to amino acid derivatives of high enantiomeric purities.[6]

We now wish to report on the cycloaddition of **1** with aldehydes as a simple way to control the relative configurations of two contiguous stereogenic centres. The resulting adducts should be readily converted into the β-hydroxyamides.

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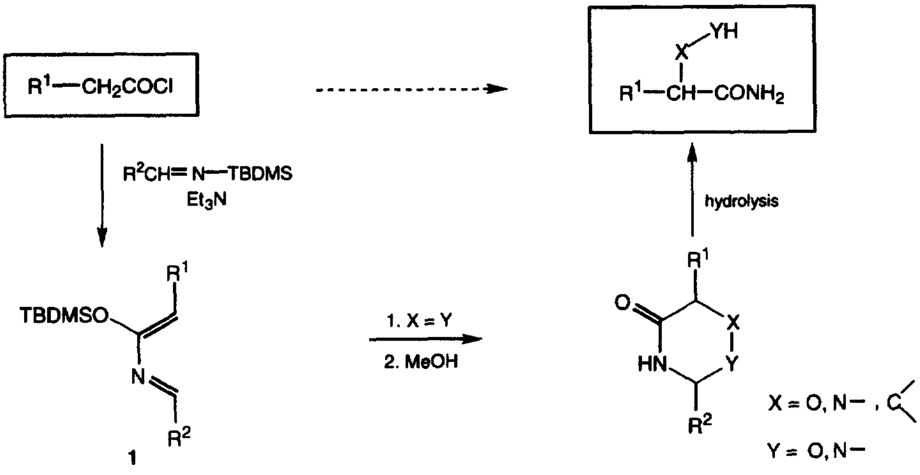
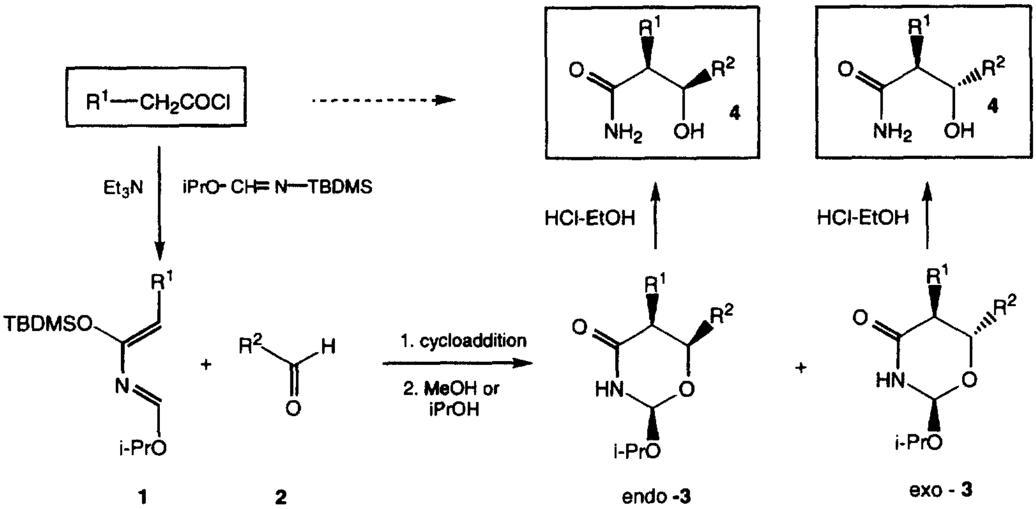


Scheme 1.

Azadienes **1a–e** were prepared by the described procedures.[1] In contrast with Danishefsky's dienes, they were sufficiently reactive to cycloadd to various aldehydes without Lewis acid catalysis (Scheme 2, Table 1).[7,8]



Scheme 2.

The cycloaddition reactions proceeded faster in acetonitrile than in a less polar solvent such as toluene (entry a). Yields were usually good except for the reaction of a diene bearing a phenyl group at C-4 (entry b). Substituents such as fluorine, chlorine, *N*-phthalimido at C-4 of the diene were tolerated (entries c, d, e, h, i). However the reaction of the halogen-bearing dienes with benzaldehyde required high pressure conditions (entries c, d). As expected, cycloadditions of ethyl glyoxylate were faster (entries g, h, i, j). Hydrolysis of oxazinones **3** took place readily to yield the corresponding β-hydroxyamides **4**.[9]

The *endo*-selectivity observed in most cases is in accordance with earlier cycloadditions involving aldehyde dienophiles.[10] Also calculations on a related model have shown that these cycloadditions could be considered as concerted and that an *endo*-approach of the reactants leads to a more stable transition state[11] (Scheme 3).

The kinetic *exo*-preference observed with the *N*-phthalimido substituted azadiene (entries e, i) probab-

Table 1
Results of Scheme 2

entry	R^1	R^2	Conditions	endo : exo[a]	yield (%)[b,c]		yield (%)[b,d]
					endo-3	exo-3	4
a.	Me	Ph	toluene, Δ, 14 h.	9 : 1	83	8	74
			MeCN, Δ, 8 h.	9 : 1	80	8	
b.	Ph	Ph	MeCN, Δ, 24 h.	9 : 1	35	-	84
c.	Cl	Ph	toluene, Δ, 14 h.	no reaction			-
			toluene, 10 kbars, 40° C, 3 days	16 : 1	79	-	75
d.	F	Ph	toluene, 10 kbars, 40° C, 3 days	-	63	-	84
e.	FtN	Ph	MeCN, Δ, 12 h.	-	-	60	88
f.	Me	i-butyl	MeCN, Δ, 8 h.	11.5 : 1	84	8	83
g.	Me	CO_2Et	MeCN, Δ, 30 min.	9 : 1	82	-	85
h.	Cl	CO_2Et	MeCN, Δ, 1 h.	-	63	-	92
i.	FtN	CO_2Et	MeCN, Δ, 1 h.	1 : 14	-	83	70
j.	Ph	CO_2Et	MeCN, Δ, 1 h.	1.2 : 1	35	40	-

[a] Determined on the crude mixture by ^1H NMR spectroscopy. [b] All products have been fully characterised by ^1H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis; stereochemical assignments were confirmed by an X-ray diffraction of the crystalline endo-3j. [c] After separation of the two isomers by flash chromatography. [d] Pure products after flash chromatography or recrystallisation.

endo - approach

exo - approach

Scheme 3.

ly results from steric repulsions between this large substituent and the aldehyde R^2 group. These should be larger in the *endo*-TS than in the *exo*-TS.

The Diels–Alder reaction of 2-azadienes with aldehydes followed by the hydrolysis of the resulting adducts represents a highly stereoselective route for the α-hydroxyalkylation and α-hydroxyacylation of carboxylic acids. Of particular interest is the compatibility of the reaction conditions with the presence of fluorine, chlorine and protected amino substituents. Further studies are planned in order to extend the scope of the reaction and to develop an asymmetric version of the sequence.

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8. Synthesis of oxazinone *endo*-**3a**: 0.59 ml (1 equiv.) of freshly distilled benzaldehyde was added to a solution of 3 g (2 equiv.) of 2-azadiene **1a** in dry toluene. The mixture was heated at 90°C for 14 h. Addition of 4 ml of MeOH followed by flash chromatography on silica gel (AcOEt:cyclohexane 4:1) gave crystalline *endo*-**3a** (83%). Recrystallisation in ether gave analytically pure *endo*-**3a**, mp 104–105°C. ^{1}H NMR (300 MHz, CDCl$_3$, TMS, ppm) δ 7.43–7.30 (m, 5H), 6.35 (s, 1H), 5.85 (s, 1H), 5.08 (d, 1H, 3J=3.0 Hz), 4.22 (sept, 1H, 3J=6.3 Hz), 2.68 (qxd, 1H, 3J=3.0 Hz; 3J=7.2 Hz), 1.33 (t, 6H, 3J=6.3 Hz), 1.02 (d, 3H, 3J=7.2 Hz); ^{13}C NMR (50 MHz, CDCl$_3$, TMS, ppm) δ 174.5, 137.3, 128.2, 127.3, 125.1, 99.8, 74.3, 69.3, 41.4, 23.5, 22.9, 11.9; IR (KBr, cm^{-1}): 3400, 3092, 1694; MS (EI) 234 (1%), 190 (11%), 145 (26%), 117 (100%), 91 (26%), 77 (16%), 44 (6%). Anal. calcd for C$_{14}$H$_{19}$NO$_3$: C: 67.44%, H: 7.68%, N: 5.61%. Found: C: 67.24%, H: 7.47%, N: 5.59%.
9. Hydrolysis of **3a**: a mixture of 0.5 g (1 equiv.) of **3a** in THF and 4 ml of a 3 M solution of HCl in ethanol was allowed to stay at room temperature for 16 h. Evaporation of the solvents gave an oily residue which was purified by flash chromatography on silica gel (AcOEt:cyclohexane 4:1). The crystalline compound **4a** was identical with an authentic sample RN: 29478-52-2.
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