Enhancement of *endo* selectivity in Diels–Alder reactions of methyl (*E*)-3-nitroacrylate with (*E*)-1-oxybuta-1,3-dienes

Richard J. Stoodley* and Wai-Hung Yuen

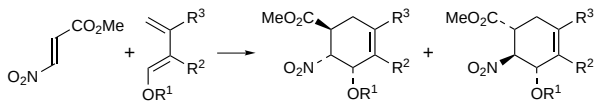
Department of Chemistry, UMIST, PO Box 88, Manchester, UK M60 1QD

(*E*)-1-Acetoxybuta-1,3-dienes show enhanced *endo* selectivity in Diels–Alder reactions with methyl (*E*)-3-nitroacrylate compared with (*E*)-1-methoxybuta-1,3-dienes and (*E*)-1-trimethylsilyloxybuta-1,3-dienes.

In foundation studies, Danishefsky[1] established that Diels–Alder reactions of the nitroacrylate **1** with 1-oxybuta-1,3-dienes are highly regioselective but poorly stereoselective. For example, the cycloaddition involving the diene **2a** (in PhH) led to a 50 : 50 mixture of the *endo*-nitro cycloadduct **3a** and the *exo*-nitro cycloadduct **4a**; mixtures of the cycloadducts **3b**/**4b** and **3d**/**4d** were also produced in the corresponding reactions of the dienes **2b** and **2d**, although the ratios were not specified. With the intention of utilising cycloadducts of types **3** and/or **4** for the synthesis of carbasugars (particularly, 4-aminocarbapyranoses), we have sought to control the stereochemical outcome of the cycloadditions. The results described herein illustrate a means of producing *endo*-nitro cycloadducts of type **3** in preference to their *exo*-nitro counterparts of type **4**.

Table 1 summarises the outcome of Diels–Alder reactions of the nitroacrylate **1**[2] with the 1-oxybuta-1,3-dienes **2a**,† **2b**,† **2c**,†‡ **2d**,† **2e**,[3]§ **2f**,¶ **2g**,[4] **2h**,[5] **2i**,[6] **2j**,[7] **2k**,[8] **2l**[9] and **2m**.‖ From the results, it is clear that the *O*-substituent plays a significant role in determining the *endo* : *exo* selectivity.** Thus, an *O*-acetyl substituent is considerately more effective than an *O*-methyl or *O*-trimethylsilyl group (which are comparable) in promoting the formation of *endo*-nitro cycloadducts. It is also evident that the 3-substituent is influential. Thus, for dienes with comparable *O*-substituents, *endo*-nitro group selectivity increases in the order H > Me > OAc > $OSiMe_2R$. Finally, it should be noted that dienes featuring a 2-methyl group generally show a higher *endo*-nitro group selectivity than their 2-unsubstituted counterparts.

Table 1 Selectivity of Diels–Alder reactions involving the nitroacrylate **1** and the dienes **2a**–**m**[a]

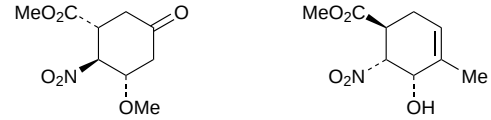


1 **2** **3** **4**

Diene **2**	R^1	R^2	R^3	Cyclo-adducts	Ratio[b]	Yield (%)[c]
a	Me	H	H	**3a/4a**	67 : 33	67
b	$SiMe_3$	H	H	**3b/4b**	68 : 32	—
c	Ac	H	H	**3c/4c**	> 95 : 5	71
d	Me	H	$OSiMe_3$	**3d/4d**	35 : 65	—
e	Me	H	$OSiMe_2Bu^t$	**3e/4e**	33 : 67	—
f	Ac	H	$OSiMe_2Bu^t$	**3f/4f**	74 : 26	73
g	Ac	H	OAc	**3g/4g**	82 : 18	57
h	$SiMe_3$	H	Me	**3h/4h**	50 : 50	—
i	Ac	H	Me	**3i/4i**	85 : 15	69
j	$SiMe_3$	Me	H	**3j/4j**	85 : 15	—
k	Ac	Me	H	**3k/4k**	92 : 8	64
l	Me	Me	$OSiMe_3$	**3l/4l**	52 : 48	—
m	Ac	Me	$OSiMe_2Bu^t$	**3m/4m**	83 : 17	71

[a] The reactions were performed in dry dichloromethane (*ca*. 5 cm^3) using the nitroacrylate (1 mmol) and the diene (1 mmol). [b] The cycloadduct ratio was determined by 300 MHz ^1H NMR spectroscopic analysis of the crude product. [c] The yield refers to the purified cycloadduct mixture (the ratio was unaltered) isolated after silica gel column chromatography.

From a preparative context, the following points are of note. It was possible to isolate the ensuing cycloadducts in a pure state by crystallisation: **3a**†† (17% yield), mp 68–70 °C; **3c**†† (68% yield), mp 88–90 °C; **3i**†† (54% yield), mp 118–120 °C; and **3k**†† (60% yield), mp 88–90 °C. When the crude silylated cycloadduct mixtures **3d**/**4d** and **3j**/**4j** were subjected to hydrolysis, crystallisation of the products gave compound **5** (34% yield), mp 110–112 °C (lit.,[1] 110–112 °C), and compound **6**†† (42% yield), mp 108–110 °C, in pure states.



5 **6**

The results reported are of both synthetic and mechanistic interest. In a synthetic context, they illustrate that *O*-substituent tuning can have a notable impact on *endo* : *exo* selectivity in cycloaddition reactions involving (*E*)-1-oxybuta-1,3-dienes of type **2** and the nitroacrylate **1**. Specifically, *O*-acetyl substituents are more effective than *O*-methyl/silyl groups in promoting the formation of *endo*-nitro cycloadducts of type **3**. From a mechanistic standpoint, the results suggest that the degree of 'electron richness' of a diene is an important consideration in *endo* : *exo* selectivity issues. In particular, electron-rich dienes favour the formation of *exo*-nitro cycloadducts of type **4**. Recently, Node and co-workers have noted[10] that *exo*-nitro group selectivity is a feature of Diels–Alder reactions of Danishefsky's diene **2d** and (*E*)-nitroalkenes (bearing alkyl or aryl groups) but they suggest that the *endo* transition state is destabilised by electrostatic repulsion between the silyloxy group of the diene and the nitro group of the dienophile.

Footnotes

* E-mail: richard.stoodley@umist.ac.uk

† The dienes **2a**–**d** were purchased from Aldrich.

‡ The reaction of the diene **2c** with the ethyl ester counterpart of the nitroacrylate **1** has been studied by Shin and co-workers (ref. 11). Although the cycloadduct ratio was not specified, the ethyl ester analogue of the *endo*-nitro cycloadduct **3c** was isolated in 57% yield.

§ The diene **2e** was prepared by a modification of the literature route (ref. 3) in which (*E*)-4-methoxybut-3-en-2-one was treated with *tert*-butyldimethylsilyl triflate and triethylamine (ref. 12).

¶ The diene **2f** was prepared from (*E*)-4-acetoxybut-3-en-2-one (ref. 4) in a manner analogous to that employed in the synthesis of the diene **2e**.

‖ The diene **2m** was prepared from (*E*)-4-acetoxy-3-methylbut-3-en-2-one [obtained by acetylation (ref. 4) of the sodium salt of (*E*)-4-hydroxy-3-methylbut-3-en-2-one (ref. 13)] in a manner similar to that used in the synthesis of the diene **2e**.

** In general, the cycloadducts were differentiated by the appearance in the NMR spectrum of the double doublet at *ca*. δ 4.90, attributed to the nitro-bearing methine proton; coupling constants (*J*) of *ca*. 4 and 12 Hz were

observed for *endo*-nitro cycloadducts of type **3** and of *ca*. 8 and 11 Hz for *exo*-nitro cycloadducts of type **4**.

†† All new compounds displayed analytical and spectral properties that supported their assigned structures.

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