Pergamon

Tetrahedron Letters, Vol. 35, No. 4, pp. 595-598, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

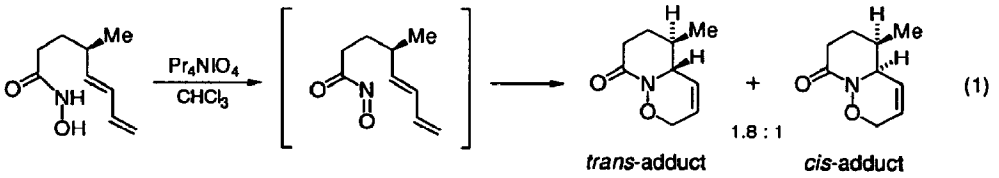
0040-4039(93)E0282-O

Enhanced Stereoselectivity in Aqueous Intramolecular Hetero Diels–Alder Cycloaddition of Chiral Acylnitroso Compounds

Masaichi Naruse, Sakae Aoyagi, and Chihiro Kibayashi*
Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract: In an aqueous medium, intramolecular hetero Diels–Alder cycloadditions of the chiral acylnitroso compounds, generated from the chiral hydroxamic acids by in situ periodate oxidation, shows a pronounced enhancement of the trans selectivity compared with the results obtained by employing nonaqueous conditions.

Hetero Diels–Alder cycloadditions with nitroso dienophiles have been the subject of increasing interest during the last two decades.[1] In our continuing efforts directed towards natural product syntheses utilizing the nitroso Diels–Alder approach,[2] we recently reported[2d, e] enantioselective preparation of alkaloids by intramolecular hetero Diels–Alder reaction using an optically active acylnitroso compound prepared by in situ oxidation of a hydroxamic acid, which preferentially provided the *trans*-1,2-oxazinolactam (eq 1). However,



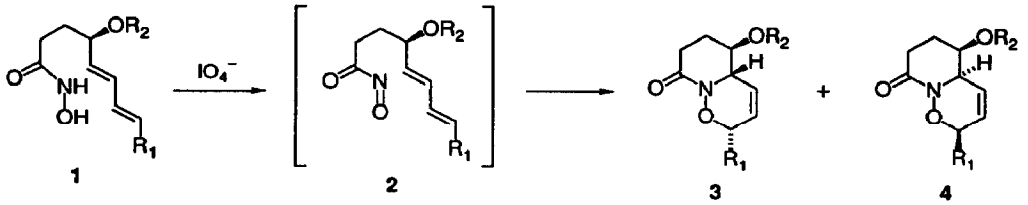
(1)

this sequence provided only poor stereoselectivity, which seemed to preclude its broad application to enantioselective total syntheses of natural products. In the case of the all-carbon Diels–Alder reaction, Breslow's group[3] postulated in a pioneering paper that water as solvent should have a hydrophobic accelerating influence. Subsequent investigations by this group[4] and Grieco et al.[5] demonstrated significant effects on the endo-exo selectivity as well as the reaction rate in some examples of intermolecular aqueous Diels–Alder reaction. However, water has never been considered as a solvent for the acylnitroso Diels–Alder reaction owing to the properties associated with RCO–N=O species, although not detected so far, namely, that they are short-lived and extremely reactive,[1a] and may undergo rapid solvolysis.[6] Nevertheless, considering the much more powerful dienophilic property of the acylnitroso group attributed to an extremely low LUMO energy and weak π bond,[7] it seemed likely that the acylnitroso Diels–Alder process would proceed in water by way of rapid trapping of the nitroso group with the diene, particularly in an intramolecular fashion.

In this communication we disclose a pronounced enhancement of the trans stereoselectivity for the intramolecular acylnitroso Diels–Alder cycloadditions, which are conducted in aqueous media.

With various 4-O-protected chiral hydroxamic acids **1a–d** in hand,[8] we undertook intramolecular [4 + 2] cycloaddition of the acylnitroso compounds, which were generated in situ from the hydroxamic acids by periodate oxidation in various solvents. All reactions were conducted at 0 °C using 10 mM solutions (or suspensions in some cases) of the substrates with vigorous stirring. In all cases, the reactions were very rapid and actually completed within 1 min though stirring was continued for 5–10 min.

Table I. Intramolecular [4 + 2] Cycloaddition of Acylnitroso Compounds[a]



1 2 3 4

entry	substrate	R_1	R_2	periodate	solvent[b]	trans:cis (3:4)[c]	yield,%[d]
1	**1a**	H	Bn	Pr_4NIO_4	$CHCl_3$	1.3:1	76
2[e]	**1a**	H	Bn	$NaIO_4$	H_2O	4.0:1	89
3[e]	**1a**	H	Bn	Pr_4NIO_4	H_2O	4.1:1	87
4[e]	**1a**	H	Bn	Pr_4NIO_4	H_2O + β-CD	2.8:1	93
5[e]	**1a**	H	Bn	Pr_4NIO_4	H_2O + γ-CD	1.7:1	86
6	**1b**	H	MOM	Pr_4NIO_4	$CHCl_3$	1.7:1	75
7	**1b**	H	MOM	$NaIO_4$	H_2O	4.4:1	97
8	**1b**	H	MOM	Pr_4NIO_4	H_2O	4.4:1	93
9	**1b**	H	MOM	Pr_4NIO_4	H_2O + β-CD	3.1:1	91
10	**1b**	H	MOM	Pr_4NIO_4	H_2O + γ-CD	3.4:1	74
11	**1c**	Et	Bn	Pr_4NIO_4	$CHCl_3$	1.4:1	87
12	**1c**	Et	Bn	$NaIO_4$	H_2O–DMSO (5:1)	4.2:1	77
13	**1c**	Et	Bn	Pr_4NIO_4	H_2O–MeOH (6:1)	4.5:1	73
14	**1c**	Et	Bn	Pr_4NIO_4	H_2O–DMSO (5:1) + α-CD	4.1:1	80
15	**1c**	Et	Bn	Pr_4NIO_4	H_2O–DMSO (5:1) + β-CD	2.7:1	75
16	**1d**	Et	MOM	Pr_4NIO_4	$CHCl_3$	1.9:1	86
17	**1d**	Et	MOM	Bu_4NIO_4	H_2O	5.0:1	83

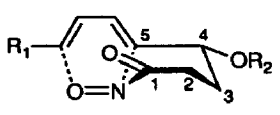
[a]All reactions were homogeneous at 10 mM in substrates **1** unless otherwise noted, and were performed using 1.5 equiv of periodate as an oxidant. [b]For cyclodextrin (CD) an equimolar amount was used. [c]Determined by ^1H NMR. [d]Isolated yield of diastereomeric mixture. [e]Reaction carried out in heterogeneous suspended phase.

First we conducted oxidation of **1a** with Pr_4NIO_4 under conventional nonaqueous conditions using $CHCl_3$ as a solvent to generate the intermediacy acylnitroso compound **2a**, which cyclizes spontaneously to give a chromatographically separable mixture of the *trans*- and *cis*-1,2-oxazinolactams **3a** and **4a** with a low diastereoselection of 1.3:1 in 76% combined yield (Table I, entry 1). The corresponding reaction of **1a** was performed in water under heterogeneous conditions (a part of oily **1a** is suspended in the aqueous solution), thereby providing improved trans/cis ratio of 4.0–4.1:1 as well as yield (89–87%) (entries 2 and 3). Breslow[3] and subsequently Sternbach[9] have suggested that β-cyclodextrin accelerates some aqueous Diels–Alder reactions by including both the diene and the olefin into the cyclodextrin cavity. Accordingly, the aqueous cycloaddition of **1a** was performed in the presence of cyclodextrins. Although the yields were significantly improved relative to the yield in the organic solvent, neither β- nor γ-cyclodextrin markedly enhanced the selectivity compared to the cycloaddition conducted in water alone (entries 4 and 5).

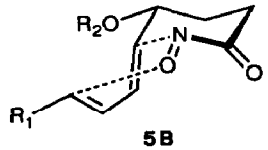
Significant increases in trans selectivity from 1.7:1 to 4.4:1 and in yield were also observed in the cycloaddition of **1b** by switching the solvent from $CHCl_3$ to water (entries 7 and 8). However, as in the former case, marked effectiveness of cyclodextrins likewise was not recognized in this aqueous reaction (entries 9 and 10).

The beneficial effect of water as a reaction medium on an enhancement of the trans selectivity was also observed when the hydroxamic acids **1c** and **1d** bearing an ethyl group at C-8 were used for the same cycloaddition. Upon intramolecular cycloaddition of **1c** (sparingly soluble in water alone), changing the medium from $CHCl_3$ to a mixture of water and MeOH (6:1) led to a significant enhancement in the trans selectivity from 1.4:1 up to 4.5:1 (entry 13). A pronounced increase of the trans selectivity of 5.0:1 was also observed on the aqueous cycloaddition of **1d** (entry 17).[10]

The trans stereoselectivity enhancement observed in these aqueous intramolecular reactions would be explained by considering the boat-like and chair-like transition states **5A** and **5B**, respectively, both of which have the carbonyl group in the endo orientation and the oxygen functional group in the connecting chain



5A



5B

adopting a quasi-equatorial position. The increased preference for the endo transition states in a water solvent has been justified by producing some extra charge separation resulting from secondary orbital interaction and hydrophobic packing of reactants.[11] For the all-carbon decatrienone system, rationalization of the preference of chair-like or boat-like transition states has been argued by Roush,[12] which seemed applicable to the rationalization for the observed stereochemical outcome. Accordingly, in the chair-like conformation **5B**, leading to the cis cycloadducts **4**, the C-4/C-5 and C-1/C-2 units exist in high-energy gauche butene and gauche ethanone conformations, respectively. These rotamers exist in favorable skew butene and eclipsed

ethanone alignments, respectively, in the alternative boat-like conformation **5A** giving rise to the trans adducts **3**. The "hydrophobic packing effect"[13] in aqueous media may have served to stabilize the more compact transition state **5A** rather than **5B**.

In conclusion, our studies demonstrated the pronounced advantages of aqueous media on the trans stereoselectivity of intramolecular hetero Diels–Alder reactions of chiral acylnitroso dienes. Our findings would be quite useful for chiral synthesis of natural products, and applications of this protocol to alkaloid syntheses are in progress.

References and Notes

1. For reviews, see: (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1. (b) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. (c) Boger, D. L.; Weinreb, S. M. In *Hetero Diels–Alder Methodololgy in Organic Synthesis*; Academic Press: New York, 1987; Chapter 3.
2. (a) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5513. (c) Watanabe, Y.; Iida, H. Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088. (d) Aoyagi, S.; Shishido, Y.; Kibayashi, C. *Tetrahedron Lett.* **1991**, *32*, 4325. (e) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876.
3. Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
4. Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901. (b) Breslow, R.; Maitra, U. *ibid.* **1984**, *25*, 1239.
5. (a) Grieco, P. A.; Garner, P.; He, Z.-m. *Tetrahedron Lett.* **1983**, *24*, 1897. (b) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137.
6. Corrie, J. E. T.; Kirby, G. W.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 883.
7. McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330.
8. These chiral hydroxamic acids **1a–d** were prepared in several steps from (2*R*,4*R*)-2-phenyl-4-formyl-1,3-dioxane (i), which was prepared from D-malic acid in 3 steps according to following references: (a) Herradon, B. *Tetrahedron Asymmetry* **1991**, *2*, 191. (b) Synthesis of the (2*S*,4*S*)-enantiomer of i: Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 2101. Thiam, M.; Slassi, A.; Chastrette, F.; Amouroux, R. *Synth. Commun.* **1992**, *22*, 83. Detailed preparation of **1** will be reported elsewhere.
9. Sternbach, D. D.; Rossana, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 5853.
10. When the aqueous cycloadditions of **1d** were conducted using $Pb(OAc)_4$ (0 °C, 10 min) and HgO (100 °C, 1 h) as oxidants, modest and low trans selectivities (and yields) of 3.5:1 (78%) and 1.8:1 (29%), respectively, were obtained.
11. Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.
12. Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915.
13. Kool, E. T.; Breslow, R. *J. Am. Chem. Soc.* **1988**, *110*, 1596.

(*Received in Japan* 14 *September* 1993; *accepted* 17 *November* 1993)