DIASTEREOSELECTIVE [2+3]CYCLOADDITIONS OF NITRONES TO 2-OXAZOLONE HETEROCYCLES

Tadao Ishizuka, Hirofumi Matsunaga, Junji Iwashita, Takenori Arai, and Takehisa Kunieda*

Faculty of Pharmaceutical Sciences, Kumamoto University,
Oe-honmachi, Kumamoto 862, Japan

Abstract - Highly diastereoselective [2+3]cycloadditions of *N*-benzyl- and *N-tert*-butyl-α-phenylnitrones to 3-(2-substituted 7,7-dimethylbicyclo[2.2.1]heptane-1-carbonyl)-2-oxazolones are described.

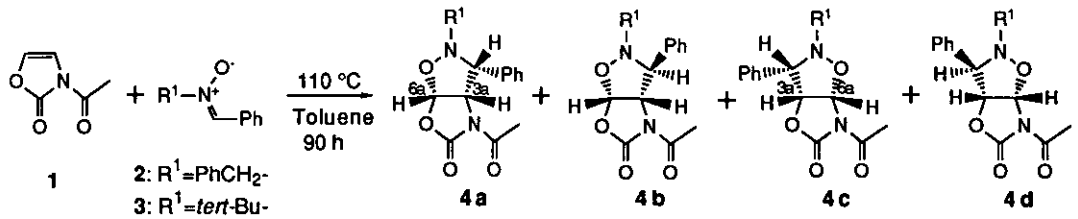
Nitrones are widely utilized as reactive 1,3-dipolar species in organic synthesis.[1] Among the possible reactions, the inter- and intramolecular [2+3]cycloadditions to olefins have been thoroughly studied and successfully applied to stereocontrolled syntheses of a number of polyfunctional natural products.[2] So far, the cycloaddition of nitrones to optically active olefins has received much less attention than those of the chiral nitrones widely explored.

We describe here the highly diastereoselective 1,3-dipolar cycloaddition of the nitrones to the 2-oxazolone olefinic skeleton[3] bearing optically active auxiliary groups on the nitrogen atom, which provides the facile route to optically active 2,3-diamino carboxylic acids of biological interest.[4] This is the first example of 2-oxazolone heterocycles as chiral 1,3-dipolarophile, though they serve as the reactive olefins in various kinds of addition reactions such as the Diels-Alder reactions,[5] photo [2+2]cycloaddition,[6] methoxybrominations,[7] methoxyselenylations[8] and telomerizations.[9]

N-Benzyl- and *N-tert*-butyl-α-phenylnitrones (**2** and **3**) reacted with 3-acetyl-2-oxazolone (**1**) at 110 °C to yield four isomeric isoxazolidine products including *regio*-isomers (**4a-d**). As shown in Table I, the cycloaddition proceeded with good regio- and diastereoselectivity and the major isomer proved to be the *syn*-acetal type adducts (**4a**) which would be formed *via* an *exo*-transition state. Stereostructures of these adducts are based on the ^{13}C-

* Dedicated to Prof. Alan R. Katritzky on the occasion of his 65th birthday.

Table I [2+3]Cycloadditions of Nitrones to 3-Acethyl-2-oxazolone



1

2: R^1=$PhCH_2$-
3: R^1=*tert*-Bu-

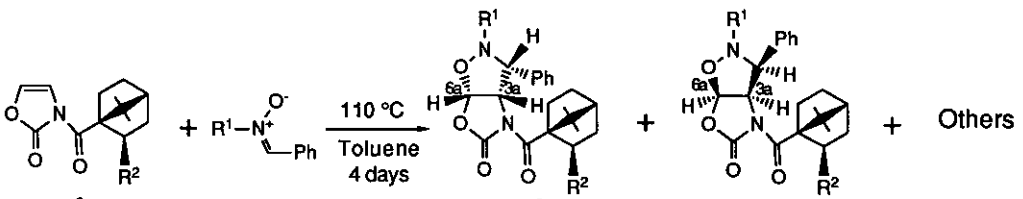
4a 4b 4c 4d

R^1	Yield (%)[a]	4a : 4b : 4c : 4d[b]
$PhCH_2$-	98	17 : 1 : 4 : 2
tert-Bu-	69	24 : 2 : 2 : 1

and ^{1}H-nmr spectral data[10] whose assignment is supported by good agreement with those of the cycloadducts, **6a** (R^1=*t*-Bu) and **6b** (R^1=$PhCH_2$-), determined by X-ray analysis.[11]

Diastereoselective cycloadditions were performed with the chiral 3-acyl-2-oxazolones (**5**) derived from the DPPOx[12] and (1*S*)-2-substituted 7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acids. The Table II shows the 2-alkoxy-1-apocamphanecarboxylic acids[13] appears to be a chiral auxiliary of choice. Formation of

Table II Diastereoselective [2+3]Cycloadditions



5a : R^2= (=O)
5b : R^2=OMe
5c : R^2=OPr

2 : R^1=$PhCH_2$-
3 : R^1=*tert*-Bu-

6a : R^2= (=O)
6b : R^2=OMe
6c : R^2=OPr

7a : R^2= (=O)
7b : R^2=OMe
7c : R^2=OPr

Entry	R^2	R^1	Yield (%)[a]	6 : 7[b]
1	=O	$PhCH_2$-	51	95 : 5
2	OMe	$PhCH_2$-	55	>99 : 1
3	OPr	$PhCH_2$-	51	>99 : 1
4	=O	*tert*-Bu-	53	94 : 6
5	OMe	*tert*-Bu-	63	>99 : 1
6	OPr	*tert*-Bu-	64	>99 : 1

a) Corrected yields based on the consumed starting materials.
b) The ratios were determined based on ^{1}H-nmr (400 MHz) spectral data.

possible eight diastereomers was detected on the ^{1}H-nmr spectrum by the comparison with the authentic samples prepared from cycloadducts (**4**) and chiral auxiliaries.[14] The *syn*-acetal type adducts (**6a-c**) were obtained as purely isolable sole isomer by chromatographic separation on silica gel in moderate yields and the minor other isomers were too much scarce to be isolated. Table II shows excellent diastereofacial selectivity. The absolute stereostructures of the major isomers (**6a**) (R^1=*tert*-Bu-) and **6b** (R^1=$PhCH_2$-) were unequivocally determined by X-ray crystal analysis.[11]

The enantiomerically pure cycloadducts (**6a-c**) thus obtained could be deacylated by $PhCH_2SLi$ to yield the bicyclic 2-oxazolidinones whose both rings were stepwise cleaved under hydrolytic and reductive conditions to smoothly give (2*S*, 3*R*)-2,3-diamino-3-phenyl-1-propanols. The practical applications are now in progress.

REFERENCES AND NOTES

1. " Nitrones, nitonates and nitroxides " ed. by S. Patai and Z. Rappoport, John Wiley & Sons, Inc., **1989.**
2. " 1,3-Dipolar Cycloaddition Chemistry Vol. 1 and Vol. 2 " ed. by A. Padwa, John Wiley & Sons, Inc., **1984** ; P. N. Confalone, and E. M. Huie, ' Organic Reactions', John Wiley & Sons, Inc., **1988**, *36*, pp.1-73 ; W. Carruthers, ' Cycloaddition Reactions in Organic Synthesis ', Pergamon Press, **1990**, pp. 269-331.
3. K. Scholz, H. G. Heine, and W. Hartmann, *Liebigs Ann. Chem.*, **1976**, 1319.
4. P. J. Dunn, R. Häner, and H. Rapoport, *J. Org. Chem.*, **1990**, *55*, 5017, and references cited therein.
5. K. Scholz, H. G. Heine, and W. Hartmann, *Liebigs Ann. Chem.*, **1977**, 2027 ; J. A. Deyrup and H.L. Gingrich, *Tetrahedron Lett.*, **1977**, 3115 ; S. V. D'Andrea, J. P. Freeman, and J. Szmuszkovics, *J. Org. Chem.*, **1990**, *55*, 4356 ; H. Matsunaga, T. Ishizuka, N. Marubayashi, and T. Kunieda, *Chem. Pharm. Bull.*, **1992**, *40*, 1077.
6. K. H. Scholz, H. G. Heine, and W. Hartmann, *Tetrahedron Lett.*, **1978**, 1467 ; S. Sekretár, J. Kopecky, and M. Cerny, *Collect. Czech. Chem. Commun.*, **1986**, *51*, 899.
7. T. Kunieda, T. Ishizuka, T. Higuchi, and M. Hirobe, *J. Org. Chem.*, **1988**, *53*, 3381.
8. T. Ishizuka, S. Ishibuchi, and T. Kunieda, *Tetrahedron Lett.*, **1989**, *30*, 3449.
9. Y. Abe and T. Kunieda, *Tetrahedron Lett.*, **1979**, 5007 ; T. Kunieda, Y. Abe, Y. Iitaka, and M. Hirobe, *J. Org. Chem.*, **1982**, *47*, 4291 ; T. Ishizuka, M. Osaki, H. Ishihara, and T. Kunieda, *Heterocycles*, **1993**, *35*, 901 ; Y. Yamamoto, S. Ishibuchi, T. Ishizuka, M. Haratake, and T. Kunieda, *J. Org. Chem.*, **1993**, *58*, 1997.
10. Selected nmr spectral data for the adducts (**4a-4d**) are shown as follows.
^{13}C-Nmr (100 MHz ; δ / $CDCl_3$) :

	4a	**4b**	**4c**	**4d**
3a-C	64.7	70.0	84.6	81.4
6a-C	97.8	98.7	85.8	84.0

^{1}H-Nmr (400 MHz ; δ / $CDCl_3$) :

	R^1	3-H	3a-H	6a-H
4a	$PhCH_2$-	4.17 (d, *J*=5.9 Hz)	5.30 (dd, *J*=5.9, 5.9 Hz)	6.08 (d, *J*=5.9 Hz)
4b	$PhCH_2$-	4.41 (s)	5.00 (d, *J*=5.9 Hz)	6.09 (d, *J*=5.9 Hz)
4c	$PhCH_2$-	3.71 (d, *J*=4.0 Hz)	4.95 (dd, *J*=4.0, 5.9 Hz)	6.18 (d, *J*=5.9 Hz)
4d	$PhCH_2$-	4.34 (s)	5.18 (d, *J*=5.9 Hz)	6.32 (d, *J*=5.9 Hz)
4a	*tert*-Bu-	4.27 (dd, *J*= 6.6 Hz)	5.30 (dd, *J*=6.6, 6.6 Hz)	6.09 (d, *J*= 6.6 Hz)
4b	*tert*-Bu-	4.38 (s)	4.90 (d, *J*=6.6 Hz)	6.10 (d, *J*=6.6 Hz)
4c	*tert*-Bu-	4.01 (d, *J*=4.8 Hz)	5.01 (dd, *J*=4.8, 6.2 Hz)	6.24 (d, *J*=6.2 Hz)
4d	*tert*-Bu-	4.36 (s)	5.01 (d, *J*=5.9 Hz)	6.27 (d, *J*=5.9 Hz)

11. The crystal data for **6a** and **6b** were as follows. **6a** (R^1=*tert*-Bu) ; monoclinic, $P2_1$, a=11.456(2)Å, b=14.423(3)Å, c=6.908(1)Å, α=90.00(2)°, β=94.29(1)°, γ=90.00(1)°, z=2. The structure was refined to the R-value of 4.0 %. **6b** (R^1=$PhCH_2$-) ; orthorhombic, $P2_1$, a=15.386(3)Å, b=24.022(3)Å, c=6.858(1)Å, α=90.00(2)°, β=90.00(1)°, γ=90.00(2)°, z=4. The structure was refined to the R-value of 4.5 %. We are indebted to Drs. N. Marubayashi and M. Haratake of Yoshitomi Research Laboratories (Fukuoka, Japan) for these X-ray analysis. The author has deposited atomic coordinates of the adducts with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
12. T. Kunieda, Y. Abe, T. Higuchi, and M. Hirobe, *Tetrahedron Lett.*, **1981**, *22*, 1257.
13. T. Ishizuka, K. Kimura, S. Ishibuchi, and T. Kunieda, *Chem. Pharm. Bull.*, **1990**, *38*, 1717.
14. Authentic samples were prepared by deacylation of the racemic adduct (**4a**) with catalytic amounts of Cs_2CO_3 in MeOH followed by *N*-acylation with the chiral auxiliary acid chloride. Chemical shifts of 6a-H and 3a-H for the diastereomers were showed in the table.

Product	R^1	6a-H	3a-H
6a	$PhCH_2$-	6.08 (d, *J*=5.9 Hz)	5.38 (t, *J*=5.9 Hz)
7a	$PhCH_2$-	6.05 (d, *J*=6.2 Hz)	5.32 (t, *J*=6.2 Hz)
6a	*tert*-Bu	6.12 (d, *J*=6.6 Hz)	5.35 (t, *J*=6.6 Hz)
7a	*tert*-Bu	6.08 (d, *J*=6.6 Hz)	5.28 (t, *J*=6.6 Hz)
6b	$PhCH_2$-	6.02 (d, *J*=5.9 Hz)	5.46 (t, *J*=5.9 Hz)
7b	$PhCH_2$-	6.04 (d, *J*=5.9 Hz)	5.28 (t, *J*=5.9 Hz)
6b	*tert*-Bu	6.04 (d, *J*=6.2 Hz)	5.42 (dd, *J*=6.2, 7.3 Hz)
7b	*tert*-Bu	6.07 (d, *J*=6.2 Hz)	5.21 (t, *J*=6.2 Hz)
6c	$PhCH_2$-	5.98 (d, *J*=5.9 Hz)	5.40 (dd, *J*=6.2, 7.3 Hz)
7c	$PhCH_2$-	6.03 (d, *J*=5.9 Hz)	5.26 (dd, *J*=5.1, 5.9 Hz)
6c	*tert*-Bu	6.00 (d, *J*=5.9 Hz)	5.37 (dd, *J*=5.9, 7.3 Hz)
7c	*tert*-Bu	6.01 (d, *J*=5.9 Hz)	5.18 (t, *J*=5.9 Hz)

Received, 29th September, 1993