

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

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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 skeleton³ 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 methoxy-selenylations⁸ 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 ¹³C-

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

1: 3-Acetyl-2-oxazolone
 2: R¹ = PhCH₂-
 3: R¹ = *tert*-Bu-

4a, 4b, 4c, 4d: Diastereomeric products

R ¹	Yield (%) ^a	4a : 4b : 4c : 4d ^b
PhCH ₂ -	98	17 : 1 : 4 : 2
<i>tert</i> -Bu-	69	24 : 2 : 2 : 1

and ¹H-nmr spectral data¹⁰ whose assignment is supported by good agreement with those of the cycloadducts, 6a (R¹=*t*-Bu) and 6b (R¹=PhCH₂-), determined by X-ray analysis.¹¹

Diastereoselective cycloadditions were performed with the chiral 3-acyl-2-oxazolones (5) derived from the DPPOx¹² and (1*S*)-2-substituted 7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acids. The Table II shows the 2-alkoxy-1-apocamphanecarboxylic acids¹³ appears to be a chiral auxiliary of choice. Formation of

Table II Diastereoselective [2+3]Cycloadditions

5a: R² = (=O)
 5b: R² = OMe
 5c: R² = OPr

2: R¹ = PhCH₂-
 3: R¹ = *tert*-Bu-

6a: R² = (=O)
 6b: R² = OMe
 6c: R² = OPr

7a: R² = (=O)
 7b: R² = OMe
 7c: R² = 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	<i>tert</i> -Bu-	53	94 : 6
5	OMe	<i>tert</i> -Bu-	63	>99 : 1
6	OPr	<i>tert</i> -Bu-	64	>99 : 1

a) Corrected yields based on the consumed starting materials.

b) The ratios were determined based on ¹H-nmr (400 MHz) spectral data.

possible eight diastereomers was detected on the ^1H -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) ($\text{R}^1=\text{tert-Bu-}$) and 6b ($\text{R}^1=\text{PhCH}_2\text{-}$) 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.

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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

¹H-Nmr (400 MHz; δ / CDCl₃) :

	R ¹	3-H	3a-H	6a-H
4a	PhCH ₂ -	4.17 (d, <i>J</i> =5.9 Hz)	5.30 (dd, <i>J</i> =5.9, 5.9 Hz)	6.08 (d, <i>J</i> =5.9 Hz)
4b	PhCH ₂ -	4.41 (s)	5.00 (d, <i>J</i> =5.9 Hz)	6.09 (d, <i>J</i> =5.9 Hz)
4c	PhCH ₂ -	3.71 (d, <i>J</i> =4.0 Hz)	4.95 (dd, <i>J</i> =4.0, 5.9 Hz)	6.18 (d, <i>J</i> =5.9 Hz)
4d	PhCH ₂ -	4.34 (s)	5.18 (d, <i>J</i> =5.9 Hz)	6.32 (d, <i>J</i> =5.9 Hz)
4a	<i>tert</i> -Bu-	4.27 (dd, <i>J</i> = 6.6 Hz)	5.30 (dd, <i>J</i> =6.6, 6.6 Hz)	6.09 (d, <i>J</i> = 6.6 Hz)
4b	<i>tert</i> -Bu-	4.38 (s)	4.90 (d, <i>J</i> =6.6 Hz)	6.10 (d, <i>J</i> =6.6 Hz)
4c	<i>tert</i> -Bu-	4.01 (d, <i>J</i> =4.8 Hz)	5.01 (dd, <i>J</i> =4.8, 6.2 Hz)	6.24 (d, <i>J</i> =6.2 Hz)
4d	<i>tert</i> -Bu-	4.36 (s)	5.01 (d, <i>J</i> =5.9 Hz)	6.27 (d, <i>J</i> =5.9 Hz)

11. The crystal data for **6a** and **6b** were as follows.

6a (R¹=*tert*-Bu) ; monoclinic, P2₁, *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** (R¹=PhCH₂-) ; orthorhombic, P2₁, *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.

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 14. Authentic samples were prepared by deacylation of the racemic adduct (**4a**) with catalytic amounts of Cs₂CO₃ 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, <i>J</i> =5.9 Hz)	5.38 (t, <i>J</i> =5.9 Hz)
7a	PhCH ₂ -	6.05 (d, <i>J</i> =6.2 Hz)	5.32 (t, <i>J</i> =6.2 Hz)
6a	<i>tert</i> -Bu	6.12 (d, <i>J</i> =6.6 Hz)	5.35 (t, <i>J</i> =6.6 Hz)
7a	<i>tert</i> -Bu	6.08 (d, <i>J</i> =6.6 Hz)	5.28 (t, <i>J</i> =6.6 Hz)
6b	PhCH ₂ -	6.02 (d, <i>J</i> =5.9 Hz)	5.46 (t, <i>J</i> =5.9 Hz)
7b	PhCH ₂ -	6.04 (d, <i>J</i> =5.9 Hz)	5.28 (t, <i>J</i> =5.9 Hz)
6b	<i>tert</i> -Bu	6.04 (d, <i>J</i> =6.2 Hz)	5.42 (dd, <i>J</i> =6.2, 7.3 Hz)
7b	<i>tert</i> -Bu	6.07 (d, <i>J</i> =6.2 Hz)	5.21 (t, <i>J</i> =6.2 Hz)
6c	PhCH ₂ -	5.98 (d, <i>J</i> =5.9 Hz)	5.40 (dd, <i>J</i> =6.2, 7.3 Hz)
7c	PhCH ₂ -	6.03 (d, <i>J</i> =5.9 Hz)	5.26 (dd, <i>J</i> =5.1, 5.9 Hz)
6c	<i>tert</i> -Bu	6.00 (d, <i>J</i> =5.9 Hz)	5.37 (dd, <i>J</i> =5.9, 7.3 Hz)
7c	<i>tert</i> -Bu	6.01 (d, <i>J</i> =5.9 Hz)	5.18 (t, <i>J</i> =5.9 Hz)

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