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Reversing the Regiochemical Course of 1,3-Dipolar Cycloaddition of Nitrile Oxides by Modification of Dipolarophiles

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Abstract The orientation of the cycloaddition of nitrile oxide to β-substituted-α,β-unsaturated aldehyde equivalents was directed by choice of the carbonyl protective group; both of the two possible regioisomers of 2-isoxazolines were selectively prepared. Cycloaddition to the acetal derivatives preferentially gave the regioisomer bearing acetal group on C(4) position. While the opposite regioselectivity was observed for the cycloaddition to dithioacetal derivatives, where the sulfur functional group was mainly located at C(5) position. Theoretical studies on these regiochemical courses showed the C(5) orientation of dithioacetal groups to be directed by steric control, whereas frontier orbital interaction controlled the C(4) orientation of the acetal groups.

The synthetic utility of the 1,3-dipolar cycloaddition of nitrile oxides has been well recognized recently.[1] The two stereogenic centers of 2-isoxazolines are well controlled by the choice of dipolarophile geometry, since the nitrile oxide cycloaddition usually occurs with high stereospecificity. The single regioisomers of 2-isoxazolines are usually formed *via* the cycloaddition to monosubstituted alkenes or 1,1-disubstituted alkenes, which afforded mainly the 5-substituted or 5,5-disubstituted-2-isoxazolines in high yields, respectively. Furthermore, reductive treatment of 2-isoxazolines leads to β-hydroxy ketones or γ-amino alcohols stereoselectively.[2,3] These features of the nitrile oxide cycloaddition provide a useful method for the stereoselective construction of acyclic carbon skeletons which have contiguous multi stereogenic centers.[4]

In contrast to these powerful points, however, very poor results have been known in the cycloaddition to 1,2-unsymmetrically substituted alkenes. Except for a few reported examples,[5,6] the reaction proceeds non-regioselectively to give a mixture of the two possible regioisomers. For example, the reaction between benzonitrile oxide and methyl crotonate gave a mixture of the two possible regioisomers in about a 2:1 ratio.[7] In addition, the yields of the cycloadducts are usually very low since the nitrile oxides prefer the formation of furazan 2-oxides, the nitrile oxide dimers, owing to the very low reactivity of these alkenes towards the cycloaddition process. As a result, this problem lowers the synthetic value of the nitrile oxide cycloaddition to unsymmetrically 1,2-disubstituted alkenes, and remains as the biggest hurdle to overcome.

Although the regiochemical course of the nitrile oxide cycloaddition is generally governed by frontier molecular orbital and/or steric interactions which vary according to the combination of the dipole and dipolarophile,[1b,1j] these factors have not been often used for the general regiochemical control. Recently, there have been several reports illustrating regiochemical control using hydrogen bonding or other factors which come from the allylic substituents of the dipolarophiles.[8,9] Additionally, Kanemasa and coworkers have

reported that the coordination of dipole and dipolarophile to magnesium ion dramatically improves regio- and stereoselectivity of the cycloaddition to crotyl alcohol derivatives.[10]

Although some useful methods exist to selectively prepare one of regioisomers of 2-isoxazolines, none of them are capable of preparing both regioisomers selectively. Both of regioisomers are equally useful as synthetic building blocks, and hence a selective route to both is desired. If a simple modification of either the dipolarophile or the dipole changes the regiochemical course of the cycloaddition, this would provide a convenient methodology for the preparation of 2-isoxazolines. To our knowledge, no methods based on this strategy have yet been reported. In this paper, we report that the choice of the carbonyl protecting group switches the orientation of the nitrile oxide cycloaddition to β-substituted-α,β-unsaturated aldehydes. The nitrile oxide cycloaddition with α,β-unsaturated acetals affords C(4) acetal substituted 2-isoxazolines. In contrast, C(5) dithioacetal substituted derivatives are prepared by cycloaddition with α,β-unsaturated dithioacetals. We also performed MNDO[11] calculations to help explain the regioselectivity of these reactions.

RESULTS AND DISCUSSION

1,3-Dipolar cycloaddition reactions of nitrile oxides were examined with various α,β-unsaturated acetals **2** (eq 1). The results are summarized in Table 1. Benzonitrile oxide **1a** and *p*-methoxybenzonitrile oxide **1c** were generated by treatment of the corresponding hydroximoyl chlorides with triethylamine, which was added very slowly over 12 hours *via* syringe pump (method A). This technique was found to be very important to obtain the cycloadducts in good yields and to avoid formation of the dimer of benzonitrile oxide. Phenylacetonitrile oxide **1b** was generated by treatment of 2-phenyl-1-nitroethane with phenyl isocyanate due to its convenience (method B).[12]

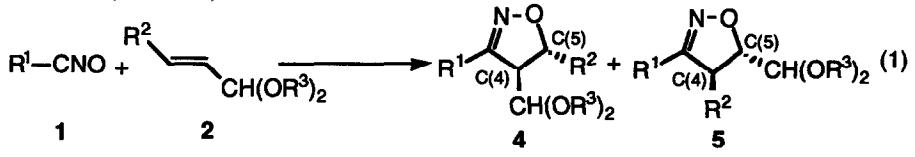


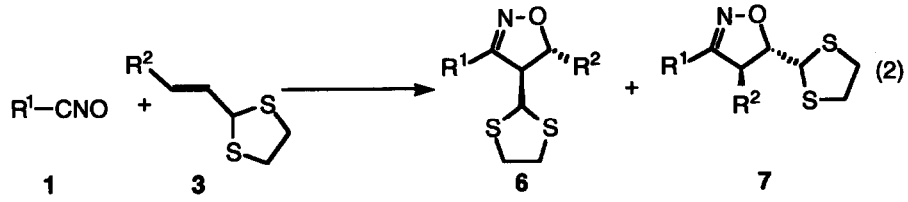
Table 1. 1,3-Dipolar cycloaddition to allylic acetals

	R^1	R^2	R^3	Method[a]	temp (°C)	4 + 5	yield (%)[b]	4/5[c]
1	Ph	Me	$-(CH_2)_2-$	A	r.t.	**4a + 5a**	39	68/32
2	Ph	Me	$-(CH_2)_2-$	A	111	**4a + 5a**	46	62/38
3	Ph	Ph	$-(CH_2)_2-$	A	r.t.	**4b + 5b**	56	91/9
4	$PhCH_2$	Me	$-(CH_2)_2-$	B	80	**4c + 5c**	71	90/10
5	*p*-$MeOC_6H_4$	Me	$-(CH_2)_2-$	A	r.t.	**4d + 5d**	41	65/35
6	*p*-$MeOC_6H_4$	C_3H_7	$-(CH_2)_2-$	A	r.t.	**4e + 5e**	35	66/34
7	*p*-$MeOC_6H_4$	Ph	$-(CH_2)_2-$	A	r.t.	**4f + 5f**	62	85/15
8	*p*-$MeOC_6H_4$	Me	$-(CH_2)_3-$	A	r.t.	**4g + 5g**	44	71/29
9	*p*-$MeOC_6H_4$	Me	Me	A	r.t.	**4h + 5h**	33	71/29

a) A: Triethylamine (1.5 eq) was added to a solution of $R^1CCl{=}NOH$ and olefin (3 eq) in CH_2Cl_2 or toluene over 12 h at room temperature or 110 °C, and the mixture was stirred for an additional 12 h. B: Phenyl isocyanate (2.5 eq) was added to a solution of 1-nitro-2-phenylethane and olefin (3 eq) and triethylamine (2 drops) in refluxing benzene over 4 h, and the resulting solution was stirred for 20 h at 80 °C. b) Isolated yield. c) Determined by HPLC.

The reaction between **1a** and 2-[(*E*)-1-propenyl]-1,3-dioxolane **2a** in CH_2Cl_2 gave a mixture of two isomeric products, **4a** and **5a**, in 39% overall yield with the ratio of **4a**:**5a** of 68:32 as determined by HPLC (entry 1). The ^1H NMR spectrum of **4a** indicated that the carbon bearing the acetal functionality was attached to the C(4) carbon of the 2-isoxazoline (*vide infra*). Although the yield of the cycloadducts was improved when the reaction was performed in toluene heated to reflux, the selectivity of the reaction was lowered slightly (entry 2). A dimethylacetal group or 1,3-dioxane functionality in the dipolarophile did not change the regioselectivity in the reaction; thus the steric size of the acetal was not an influential factor (see Table 1, entry 8 and 9). The selective formation of the C(4) acetal isomer was enhanced by the presence of a phenyl group in the R^2 position; **4b** was obtained in 56% yield in a 91:9 ratio (entry 3). The cycloaddition of α-phenylacetonitrile oxide **1b** also proceeded regioselectively to give **4c** as a main product with a regioisomeric ratio of 90:10 (entry 4). Thus, the cycloaddition of nitrile oxides and α,β-unsaturated acetals **4** preferentially forms compound **4** in ratios varying from 2:1 to 9:1.

Table 2 summarizes the results of the cycloaddition to dithioacetal derivatives (eq 2).



1 3 6 7

Table 2. 1,3-Dipolar cycloaddition to allylic dithioacetals

	R^1	R^2	Method[a]	temp (°C)	6+7	yield (%)[b]	6/7[c]
1	Ph	Me	A	r.t.	**6a** + **7a**	32	17/83
2	Ph	Me	A	111	**6a** + **7a**	53	28/72
3	$PhCH_2$	Me	B	80	**6b** + **7b**	26	30/70
4	*p*-$MeOC_6H_4$	Me	A	r.t.	**6c** + **7c**	45	19/81
5	*p*-$MeOC_6H_4$	Ph	A	r.t.	**6d** + **7d**	43	27/73

a) A: Triethylamine (1.5 eq) was added to a solution of R^1CCl=NOH and olefin (3 eq) in CH_2Cl_2 or toluene over 12 h at room temperature or 110 °C, and the mixture was stirred for an additional 12 h. B: Phenyl isocyanate (2.5 eq) was added to a solution of 1-nitro-2-phenylethane, and olefin (3 eq) and triethylamine (2 drops) in refluxing benzene over 4 h and the resulting solution was stirred for 20 h at 80 °C. b) Isolated yield. c) Determined by HPLC.

The reaction of benzonitrile oxide with 2-[(*E*)-1-propenyl]-1,3-dithiolane preferentially gave **7a** (entry 1). The ratio of **7a** to **6a** was determined by HPLC and was shown to be 17:83. It is remarkable that the cycloaddition using dithioacetal derivative **3** led to the C(5) dithioacetal substituted 2-isoxazolines **7** predominantly, though the yield of the cycloadduct was moderate. This regioselectivity is opposite to that observed for the corresponding acetal derivatives **2**. The total yield of the cycloadducts was improved when the reaction was carried out in toluene heated to reflux, but this led to a lower selectivity in the reaction (entry 2). A similar result was observed with *p*-methoxybenzonitrile oxide (entry 4). Although preferential formation of C(5) dithioacetal isomer **7b** was observed in the reaction of aliphatic nitrile oxide **1b**, the **7b**:**6b** ratio was lower than that for aromatic nitrile oxides **1a** and **1c** (entry 3). Compared with the acetal reaction, use of dipolarophiles bearing phenyl group in R^2 was not as effective to obtain **7** selectively (see Table 1, entry 3 and

7 and Table 2, entry 5). All of these results reveal that the dithioacetal group furnishes a C(5)-dithioacetal orientation effect in nitrile oxide cycloaddition, the opposite regiocontrolling effect to the acetal group.

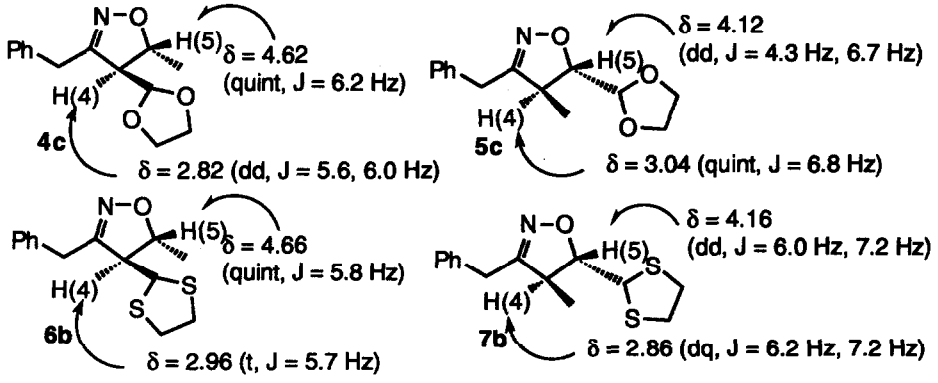
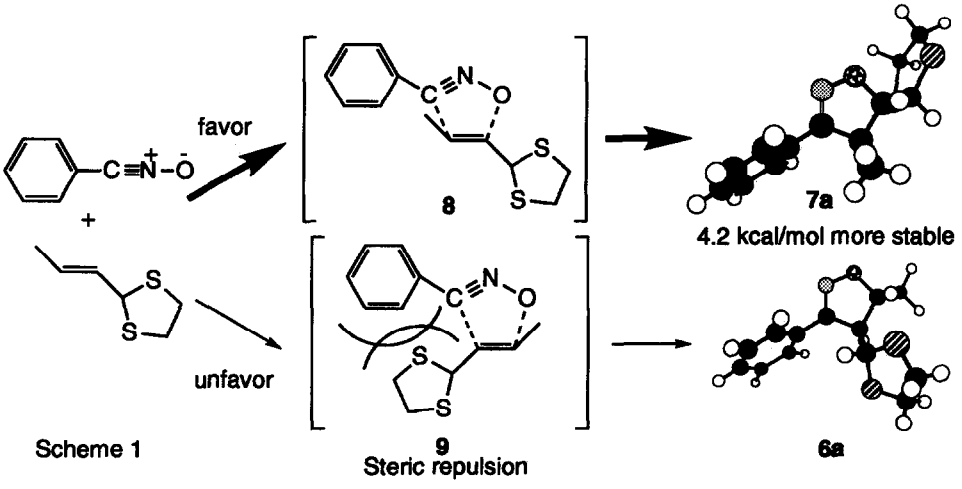


Figure 1

The structures of **4** - **7** were determined by their ^{1}H NMR spectra. For example, the two ring protons of **4c**, H(4) and H(5), appeared at δ = 2.82 ppm as a double doublet and δ = 4.62 ppm as a quintet, respectively, and the signals of **5c** were observed at δ = 3.04 ppm as a quintet and δ = 4.12 ppm as a double doublet, respectively. Since the signal of H(4) usually appears at higher field than that of H(5), the former signals were assigned to be H(4) of **4c** and **5c**.[13] The signal patterns indicated that a methine group was located adjacent to C(4) in **4c** but a methyl group was adjacent to C(4) in **5c**. Consequently, the structures of **4c** and **5c** were unambiguously determined as they are shown in Figure 1. The structures of **6b** and **7b** were determined analogously.

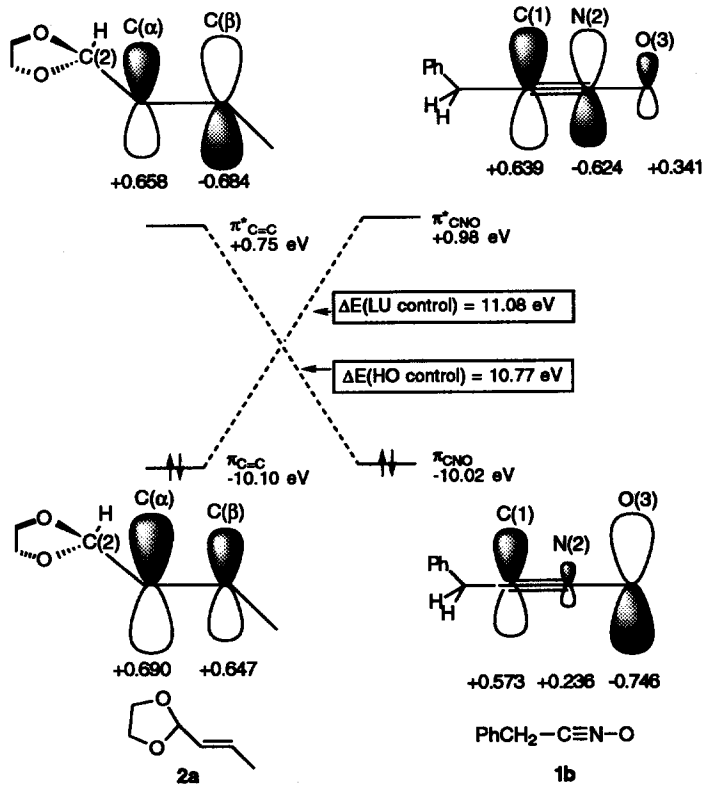


Scheme 1

In order to investigate the reason of the regiochemical differences directed by the acetal and dithioacetal in the reaction, MNDO calculations were performed. At first, the thermodynamic stability of the cycloadducts were calculated. Scheme 1 depicts the two possible reaction pathways for the reaction between α,β-unsaturated dithioacetals and nitrile oxides and gives the optimized structures for **6a** and **7a**. An almost planar structure

for 2-isoxazoline rings was obtained through their optimization. This correlates closely to their X-ray structures.[4k] The MO calculations show that **7a** is more stable than **6a** by 4.2 kcal/mol. This difference seems to be attributed to the steric interaction between the phenyl group at C(3) and the 1,3-dithiolane ring at C(4) in **6a** (Scheme 1); these substituents occupy crowded positions in **6a**. In **7a**, the phenyl group and the dithioacetal group are separated so the steric repulsion between them is negligible. The relative reactivity of the cycloaddition process of **8** and **9** allows an analogous comparison to be made, showing pathway **9** to be less favorable than pathway **8**, and hence **7a** as generating the major isomer. Thus, the steric effect determines the C(5) orientation of the cycloaddition of dithioacetal derivatives. A similar discussion is also seen in the nitrile oxide cycloaddition to *cis*- and *trans*-4-methyl-2-pentene.[6a]

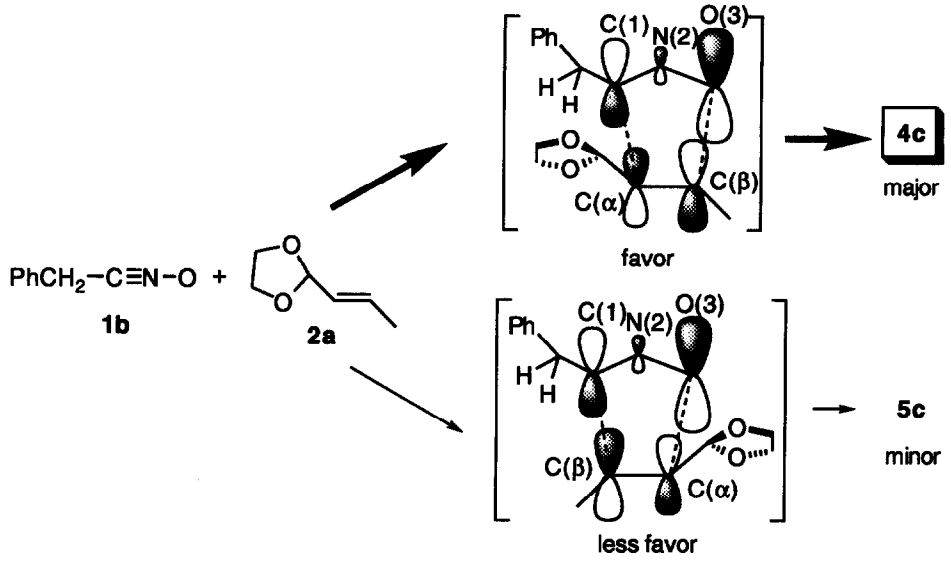
This discussion, however, cannot explain the regioselectivity of the acetal derivatives, which shows an opposite regioselctivity, though the steric bias of acetal group is similar to that of dithioacetal.[14] In order to explain this reversal of regiochemistry, we examined the frontier molecular orbitals (FMO's).[15,16] We optimized the geometries of a dipole, phenylacetonitrile oxide **1b**,[17] and the dipolarophiles, 2-[(*E*)-1-propenyl]-1,3-dioxolane **2a** and 2-[(*E*)-1-propenyl]-1,3-dithiolane **3a**. The results are depicted in Schemes 2-4.



Scheme 2

The interactions between π_{CNO} and $\pi^*_{C=C}$, and between π^*_{CNO} and $\pi_{C=C}$ are considered as possible interactions (Scheme 2). According to Sustman's classification,[18] we call them HO and LU control interactions, respectively.

The interaction with the smaller MO gap (ΔE) acts as the favorable interaction of the reaction. In this case, the ΔE's were estimated to be 10.77 eV for HO control and 11.08 eV for LU control, respectively. The difference between two ΔE's is not large, thus both interactions are almost equally favored.



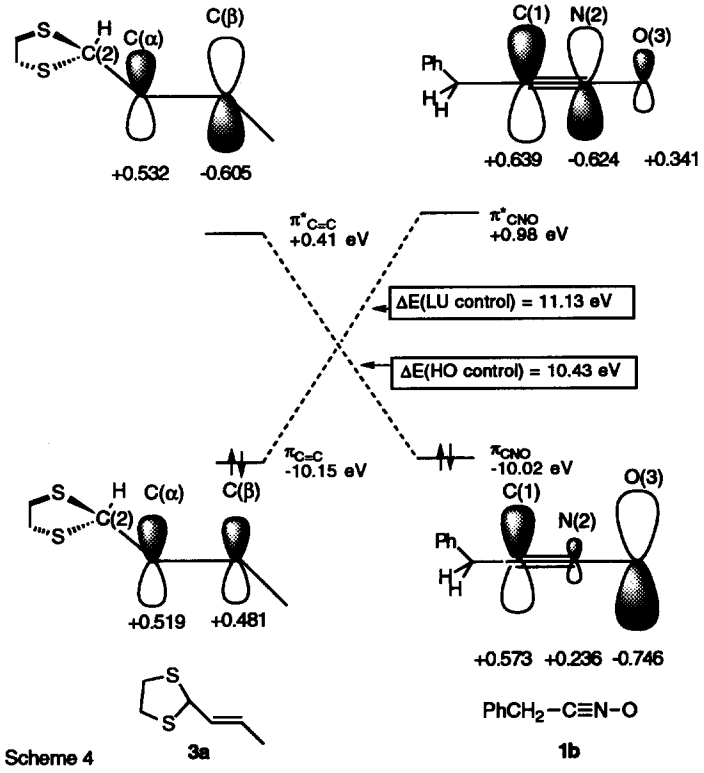
Scheme 3

We focused on the magnitude of their MO coefficients. In the dipole **1b**, the coefficients of C(1) and O(3) in π_{CNO} are +0.573 and -0.746, respectively. The absolute value for O(3) in π_{CNO} is larger than that for C(1). The coefficient of C(1) in π^*_{CNO} is +0.639, much larger than that of O(3), +0.341. In contrast, the absolute $\pi_{C=C}$ coefficient values of the of C(α) in the dipolarophile **2a** is larger than that of C(β), while in $\pi^*_{C=C}$ orbital, the value of C(β) is larger than that of C(α). Frontier orbital theory states that the interaction between the atoms which have larger MO coefficients occurs favorably.[16d,19] Therefore, O(3) in **1b** favors an interaction with C(β) in **2a**, and C(1) in **1b** prefers to form a new bond with C(α) in **2a** in HO control interaction shown in Scheme 3. The same discussion is applicable to LU control interaction. Hence, in both HO control and LU control interactions, the new bond formation occurrs preferentially between C(1)-C(α) and O(3)-C(β) bonds to give 4-acetal substituted 2-isoxazolines **4c** as the major product. We now conclude that the frontier orbitals govern the favorable regiochemical course of the cycloaddition to the acetal derivative **2a**.

MO relations between nitrile oxide **1b** and dithioacetal **3a** were also examined (Scheme 4). Since the MO gap for HO control (10.43 eV) is slightly smaller than that for LU control (11.13 ev), HO control is the most likely for this reaction. The frontier orbital coefficients of **3a** have a larger value for C(β) than C(α) in the π* orbital. This means that the frontier orbital interaction in HO control prefers to form **6b**. Therefore, it is impossible to predict the favorable product from FMO's. In this case, the steric interaction discussed above determines the regiochemistry of the cycloaddition to give **7** preferentially.

In conclusion, the regiochemical course of the 1,3-dipolar cycloaddition of nitrile oxides is reversed by the modification of α,β-unsaturated aldehydes to their acetal or dithioacetal derivatives. Selectivity of cycloaddition to the dithioacetal derivatives is determined by steric interactions, but FMO interactions control

cycloaddition to acetal derivatives. As these groups are frequently used as protecting groups for aldehydes and ketones, and readily removed under various conditions,[20] the methodology presented provides a new strategy for the selective preparation of the two regioisomers of nitrile oxide cycloaddition to the α,β-unsaturated aldehydes.



Scheme 4

EXPERIMENTAL

^{1}H NMR spectra were recorded on Hitachi R-250-H spectrometer at 250 MHz. $CDCl_3$ was used as the solvent with tetramethylsilane as a internal standard. Infrared spectra were measured by Hitachi-Nicolet I-5040 FTIR spectrometer. Mass spectra were recorded on Hitachi M-80B mass spectrometer at 70 eV (EI). Elemental analyses were performed by Advanced Instrumentation Center for Chemical Analysis, Ehime University. High performance liquid chromatography (HPLC) analyses were carried out on ODS-80T (4.6 mm i.d. x 15 cm, Tosoh Co. Ltd.) or Cosmosil 5-PYE (4.6 mm i.d. x 15 cm, Nacalai tesque Co. Ltd.) with Tosoh CCPE pump and UV 8000 UV detector or RI 8000 RI detector. Slow addition of reagent was carried out with Furue model JP-S syringe pump. Hydroximoyl chlorides were prepared by a previously reported method.[21]

1,3-Dipolar Cycloaddition of Nitrile Oxides 1 to Allylic Acetals 2 or Dithioacetals 3.

Preparation of 4a and 5a. Method A: To a solution of benzohydroximoyl chloride (0.751 g, 4.83 mmol) and 2-[(*E*)-1-propenyl]-1,3-dioxolane (1.716 g, 15.1 mmol) in CH_2Cl_2 (15 mL) was added triethylamine

(0.545 g, 5.45 mmol) in CH_2Cl_2 (5 mL) by syringe pump over 12 h at room temperature. The reaction mixture was stirred for additional 12 h. The mixture was poured into HCl (1 M, 20 mL) and extracted with ethyl acetate (3 x 50 mL), and the organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated. The crude product was subjected to flash column chromatography (silica gel 230-400 mesh/hexane-ethyl acetate 10:1 then 5:1 v/v) to give a mixture of **4a** and **5a** in 39% yield (0.426 g). Colorless oil. HPLC analysis showed that the ratio of **4a**:**5a** is 68:32. IR (neat) 1152 and 1045 cm^{-1}; Found: m/z 223.1079. Calcd for $C_{13}H_{15}NO_3$: M, 233.1052. **4a**: ^1H NMR ($CDCl_3$) δ 7.76-7.39 (5 H, m, *Ar*-), 5.11 (1 H, d, *J* = 3.0 Hz, O-CR*H*-O), 4.90 (1 H, qd, *J* = 6.7 and 4.9 Hz, *H*(5)), 3.72-4.06 (4 H, m, O-CH_2CH_2-O), 3.62 (1 H, dd, *J* = 3.6 Hz and 4.9 Hz, *H*(4)), 1.39 (3H, d, *J* = 6.1 Hz, CH_3). **5a**: ^1H NMR ($CDCl_3$) δ 7.76-7.39 (5 H, m, *Ar*-), 4.97 (1 H, d, *J* = 4.2 Hz, O-CR*H*-O), 4.33 (1 H, t, *J* = 4.8 Hz, *H*(5)), 3.72-4.06 (5 H, m, O-CH_2CH_2-O and *H*(4)), 1.35 (3 H, d, *J* = 7.3 Hz, CH_3).

Preparation of 4c and 5c: **Method B**. To a solution of 2-nitro-1-phenylethane (0.652 g, 4.31 mmol) and 2-[(*E*)-1-propenyl]-1,3-dioxolane (1.944 g, 17.1 mmol) in benzene (30 mL) was added phenyl isocyanate (1.096 g, 9.21 mmol) and triethylamine (0.092 g, 0.91 mmol) and the reaction mixture was heated to reflux for 12 h. After completion of the reaction, the reaction mixture was filtrated through a glassfilter. The solution was evaporated and subjected to column chromatography (silica gel 230-400 mesh/ hexane-ethyl acetate 20:1 then 5:1 v/v) to give the cycloadducts **4c** and **5c** in 71% yield (0.753 g). Colorless oil. **4c**:**5c** = 90:10 (HPLC). IR (neat) 1157 and 1053 cm^{-1}; Found: C, 68.34; H, 6.74. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. **4c**: ^1H NMR ($CDCl_3$) δ 7.20-7.48 (5 H, m, *Ar*-), 4.91 (1 H, d, *J* = 4.9 Hz, O-CR*H*-O), 4.62 (1 H, quint, *J* = 6.1 Hz, *H*(5)), 3.82-4.00 (5 H, m, O-CH_2CH_2-O and one of PhCH_2-), 3.59 (1 H, d, *J* = 14.7 Hz, the other of PhCH_2-), 2.82 (1 H, t, *J* = 5.6 and 6.0 Hz, *H*(4)), 1.22 (3 H, d, *J* = 6.7 Hz, CH_3). **5c**: ^1H NMR ($CDCl_3$) δ 7.20-7.53 (5 H, m, *Ar*-), 4.88 (1 H, d, *J* = 4.3 Hz, O-CR*H*-O), 4.12 (1 H, dd, *J* = 4.3 and 6.1 Hz, *H*(5)), 3.82-4.00 (5 H, m, O-CH_2CH_2-O and one of PhCH_2-), 3.49 (1 H, d, *J* = 15.2 Hz, the other of PhCH_2-), 3.04 (1 H, quint, *J* = 6.7 Hz, *H*(4)), 1.16, (3 H, d, *J* = 7.3 Hz, CH_3).

The other cycloadducts **4**, **5**, **6**, and **7** were obtained with a similar procedure. Their physical data are shown below:

4b:**5b** = 91:9 (HPLC). IR (nujor) 1157, 1080, and 764 cm^{-1}. **4b**: mp 165-166 °C (from hexane-ethyl acetate 3:1); Found: C, 73.15; H, 5.86; N, 4.73. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74; ^1H NMR ($CDCl_3$) δ 7.07-7.75 (10 H, m, *Ar*-), 5.80 (1 H, d, *J* = 4.9 Hz, *H*(5)), 5.24 (1 H, d, *J* = 3.0 Hz, O-CR*H*-O), 3.84-4.16 (5 H, m, O-CH_2CH_2-O and *H*(4)). **5b**: ^1H NMR ($CDCl_3$) δ 7.07-7.75 (10 H, m, *Ar*-), 5.09 (1 H, d, *J* = 4.3 Hz, O-CR*H*-O), 4.76 (1 H, d, *J* = 4.9 Hz, *H*(4)), 4.54 (1 H, t, *J* = 4.5 Hz, *H*(5)), 3.84-4.16 (4 H, m, O-CH_2CH_2-O).

4d:**5d** = 65:35 (HPLC). IR (neat) 1261, 1183, and 1030 cm^{-1}; Found: m/z 263.1139. Calcd for $C_{14}H_{17}NO_4$: M, 263.1158. **4d**: ^1H NMR ($CDCl_3$) δ 7.68 (2 H, d, *J* = 9.2 Hz, *Ar*-), 6.92 (2 H, d, *J* = 9.1 Hz, *Ar*-), 5.10 (1 H, d, *J* = 3.0 Hz, O-CR*H*-O), 4.87 (1 H, dq, *J* = 4.9 and 6.1 Hz, *H*(5)), 3.83-4.14 (4 H, m, O-CH_2CH_2-O), 3.84 (3 H, s, O*Me*), 3.57 (1 H, dd, *J* = 3.6 and 4.3 Hz, *H*(4)), 1.37 (3 H, d, *J* = 6.7 Hz, CH_3). **5d**: ^1H NMR ($CDCl_3$) δ 7.63 (2 H, d, *J* = 9.1 Hz, *Ar*-), 6.92 (2 H, d, *J* = 9.1 Hz, *Ar*-), 4.95 (1 H, d, *J* = 4.2 Hz, O-CR*H*-O), 4.29 (1 H, t, *J* = 4.3 Hz, *H*(5)), 3.83-4.14 (5 H, m, O-CH_2CH_2-O and *H*(4)), 3.84 (3 H, s, O*Me*), 1.33 (3 H, d, *J* = 8.0 Hz, CH_3).

4e:**5e** = 66:34. IR (neat) 1261, 1184, and 1032 cm^{-1}; Found: m/z 291.1485. Calcd for $C_{16}H_{21}NO_4$: M, 291.1471. **4e**: ^1H NMR ($CDCl_3$) δ 7.69 (2 H, d, *J* = 8.6 Hz, *Ar*-), 6.91 (2 H, d, *J* = 8.6 Hz, *Ar*-), 5.10 (1 H, d,

J = 3.6 Hz, O-CR*H*-O), 4.74 (1 H, dt, *J* = 3.0 and 4.2 Hz, *H*(5)), 3.79-4.14 (4 H, m, O-C*H*$_2$C*H*$_2$-O), 3.84 (3 H, s, O*Me*), 3.61 (1 H, t, *J* = 3.6 Hz, *H*(4)), 1.34-1.74 (4 H, m, -(C*H*$_2$)$_2$-), 0.96 (3 H, t, *J* = 6.7 Hz, C*H*$_3$). **5e**: ^{1}H NMR ($CDCl_3$) δ 7.62 (2 H, d, *J* = 8.6 Hz, *Ar*-), 6.92 (2 H, d, *J* = 9.1 Hz, *Ar*-), 4.92 (1 H, d, *J* = 3.7 Hz, O-CR*H*-O), 4.40 (1 H, t, *J* = 4.2 Hz, *H*(5)), 3.79-4.14 (5 H, m, O-C*H*$_2$C*H*$_2$-O and *H*(4)), 3.84 (3 H, s, O*Me*), 1.34-1.74 (4 H, m, -(C*H*$_2$)$_2$-), 0.96 (3 H, t, *J* = 6.7 Hz, C*H*$_3$).

4f:**5f** = 85:15 (HPLC). IR (nujor) 1251 and 1145 cm^{-1}; Found: C, 69.82; H, 5.89; N, 4.30. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. **4f**: mp 174-176 °C; ^{1}H NMR ($CDCl_3$) δ 7.67 (2 H, d, *J* = 8.5 Hz, *Ar*-), 7.26-7.41 (5 H, m, *Ph*-), 6.90 (2 H, d, *J* = 8.6 Hz, *Ar*-), 5.77 (1 H, d, *J* = 4.9 Hz, *H*(5)), 5.22 (1 H, d, *J* = 3.1 Hz, O-CR*H*-O), 3.86-4.13 (5 H, m, O-C*H*$_2$C*H*$_2$-O and *H*(4)), 3.82 (3 H, s, O*Me*). **5f**: ^{1}H NMR ($CDCl_3$) δ 7.55 (2 H, d, *J* = 8.6 Hz, *Ar*-), 7.26-7.41 (5 H, m, *Ph*-), 6.79 (2 H, d, *J* = 8.6 Hz, *Ar*-), 5.06 (1 H, d, *J* = 4.3 Hz, O-CR*H*-O), 4.72 (1 H, d, *J* = 4.9 Hz, *H*(4)), 4.49 (1 H, t, *J* = 4.2 Hz, *H*(5)), 3.86-4.13 (4 H, m, O-C*H*$_2$C*H*$_2$-O), 3.82 (3 H, s, O*Me*).

4g:**5g** = 71:29 (HPLC). IR (neat) 1261, 1183, and 1030 cm^{-1}; Found: m/z 277.1299. Calcd for $C_{15}H_{19}NO_4$: M, 277.1314. **4g**: ^{1}H NMR ($CDCl_3$) δ 7.67 (2 H, d, *J* = 8.5 Hz, *Ar*-), 6.91 (2 H, d, *J* = 8.0 Hz, *Ar*-), 5.06 (1 H, dq, *J* = 4.3 and 6.1 Hz, *H*(5)), 4.78 (1 H, d, *J* = 3.5 Hz, O-CR*H*-O), 3.57-4.20 (4 H, m, O-C*H*$_2$), 3.84 (3 H, s, O*Me*), 3.39 (1 H, t, *J* = 4.1 Hz, *H*(4)), 1.97-2.14 (2 H, m, -C*H*$_2$-), 1.33 (3 H, d, *J* = 6.1 Hz, C*H*$_3$-). **5g**: ^{1}H NMR ($CDCl_3$) δ 7.64 (2 H, d, *J* = 8.5 H, *Ar*-), 6.91 (2 H, d, *J* = 8.0 Hz, *Ar*-), 4.60 (1 H, d, *J* = 4.2 Hz, O-CR*H*-O), 4.24 (1 H, t, *J* = 4.9 Hz, *H*(5)), 3.57-4.20 (4 H, m, O-C*H*$_2$), 3.84 (3 H, s, O*Me*), 3.28 -3.40 (1 H, m, *H*(4)), 1.97-2.14 (2 H, m, -C*H*$_2$-), 1.33 (3 H, d, *J* = 6.1 Hz, C*H*$_3$).

4h:**5h** = 71:29 (HPLC). IR (neat) 1257, 1182, and 1074 cm^{-1}; Found: m/z 265.1309. Calcd for $C_{14}H_{19}NO_4$: M, 265.1314. **4h**: ^{1}H NMR ($CDCl_3$) δ 7.68 (2 H, d, *J* = 8.9 Hz, *Ar*-), 6.92 (2 H, d, *J* = 7.9 Hz, *Ar*-), 4.94 (1 H, dq, *J* = 4.3 and 6.7 Hz, *H*(5)), 4.43 (1 H, d, *J* = 4.9 Hz, O-CR*H*-O), 3.84 (3 H, s, O*Me*), 3.40-3.60 (1 H, m, *H*(4)), 3.32 (3 H, s, O*Me*), 3.31 (3 H, s, O*Me*), 1.33 (3 H, d, *J* = 6.8 Hz, C*H*$_3$). **5h**: ^{1}H NMR ($CDCl_3$) δ 7.63 (2 H, d, *J* = 7.4 Hz, *Ar*-), 6.92 (2 H, d, *J* = 7.9 Hz, *Ar*-), 4.43 (1 H, d, *J* = 2.4 Hz, O-CR*H*-O), 4.14 (1 H, t, *J* = 6.7 Hz, *H*(5)), 3.84 (3 H, s, O*Me*), 3.49 (3 H, s, O*Me*), 3.45 (3 H, s, O*Me*), 3.40-3.60 (1 H, m, *H*(4)), 1.33 (3 H, d, *J* = 6.8 Hz, C*H*$_3$).

6a:**7a** = 17:83 (HPLC). IR (neat) 914, 885, and 767 cm^{-1}; Found: C, 58.72; H, 5.72; N, 5.20. Calcd for $C_{13}H_{15}NOS_2$: C, 58.84; H, 5.70; N, 5.28. **6a**: ^{1}H NMR ($CDCl_3$) δ 7.40-7.71 (5 H, m, *Ar*-), 4.99 (1 H, d, *J* = 4.3 Hz, S-CR*H*-S), 4.97 (1 H, dq, *J* = 4.9 and 6.7 Hz, *H*(5)), 3.77 (1 H, t, *J* = 4.3 Hz, *H*(4)), 3.21-3.33 (4 H, m, S-C*H*$_2$C*H*$_2$-S), 1.44 (3 H, d, *J* = 6.7 Hz, C*H*$_3$). **7a**: ^{1}H NMR ($CDCl_3$) δ 7.40-7.71 (5 H, m, *Ar*-), 4.57 (1 H, d, *J* = 8.0 Hz, S-CR*H*-S), 4.31 (1 H, dd, *J* = 3.7 and 8.0 Hz, *H*(5)), 3.58 (1 H, dq, *J* = 3.6 and 7.3 Hz, *H*(4)), 3.21-3.33 (4 H, m, S-C*H*$_2$C*H*$_2$-S), 1.37 (3 H, d, *J* = 7.3 Hz, C*H*$_3$).

6b:**7b** = 30:70 (HPLC). IR (neat) 910, 866, and 704 cm^{-1}; Found: C, 60.16; H, 6.23; N, 5.20. Calcd for $C_{14}H_{17}NOS_2$: C, 60.18; H, 6.13; N, 5.01. **6b**: ^{1}H NMR ($CDCl_3$) δ 7.16-7.37 (5 H, m, *Ar*-), 4.75 (1 H, d, *J* = 5.7 Hz, S-CR*H*-S), 4.66 (1 H, quint, *J* = 5.8 Hz, *H*(5)), 3.94 (1 H, d, *J* = 15.2 Hz, PhC*H*$_2$-), 3.62 (1 H, d, *J* = 15.1 Hz, PhC*H*$_2$-), 3.21-3.27 (4 H, m, S-C*H*$_2$C*H*$_2$-S), 2.96 (1 H, t, *J* = 5.7 Hz, *H*(4)), 1.24 (3 H, d, *J* = 6.7 Hz, C*H*$_3$). **7b**: ^{1}H NMR ($CDCl_3$) δ 7.16-7.37 (5 H, m, *Ar*-), 4.50 (1 H, d, *J* = 7.2 Hz, S-CR*H*-S), 4.16 (1 H, dd, *J* = 6.0 and 7.2 Hz, *H*(5)), 3.83 (1 H, d, *J* = 15.3 Hz, PhC*H*$_2$-), 3.47 (1 H, d, *J* = 15.3 Hz, PhC*H*$_2$-), 3.10-3.20 (4 H, m, S-C*H*$_2$C*H*$_2$-S), 2.87 (1 H, dq, *J* = 6.2 and 7.2 Hz, *H*(4)), 1.19 (3 H, d, *J* = 7.2 Hz, C*H*$_3$).

6c:**7c** = 19:81 (HPLC). IR (neat) 1256, 1030, 914, and 839 cm^{-1}; Found: m/z 295.0713. Calcd for $C_{14}H_{17}NO_2S_2$: M, 295.0701. **6c**: ^{1}H NMR ($CDCl_3$) δ 7.60 (2 H, d, *J* = 6.1 Hz, *Ar*-), 6.93 (2 H, d, *J* = 8.6 Hz,

Ar-), 4.98 (1 H, d, *J* = 3.6 Hz, S-CR*H*-S), 4.93 (1 H, dq, *J* = 4.9 and 6.7 Hz, *H*(5)), 3.86 (3 H, s, O*Me*), 3.72 (1 H, t, *J* = 4.3 Hz, *H*(4)), 3.17-3.32 (4 H, m, S-CH_2CH_2-S), 1.42 (3 H, d, *J* = 6.7 Hz, CH_3). **7c**: ^{1}H NMR ($CDCl_3$) δ 7.63 (2 H, d, *J* = 8.5 Hz, *Ar*-), 6.93 (2 H, d, *J* = 8.6 Hz, *Ar*-), 4.56 (1 H, d, *J* = 8.5 Hz, S-CR*H*-S), 4.27 (1 H, dd, *J* = 3.6 and 7.9 Hz, *H*(5)), 3.84 (3 H, s, O*Me*), 3.51 (1 H, dq, *J* = 3.7 and 7.3 Hz, *H*(4)), 3.17-3.32 (4 H, m, S-CH_2CH_2-S), 1.36 (3 H, d, *J* = 7.3 Hz, CH_3).

6d:**7d** = 27:73 (HPLC). IR (nujor) 1253, 1177, and 837 cm^{-1}; Found: C, 63.25; H, 5.33; N, 3.86. Calcd for $C_{19}H_{19}NO_2S_2$: C, 63.84; H, 5.36; N, 3.92. **6d**: ^{1}H NMR ($CDCl_3$) δ 7.60 (2 H, d, *J* = 8.5 Hz, *Ar*-), 7.26-7.39 (5 H, m, *Ph*-), 6.92 (2 H, d, *J* = 8.5 Hz, *Ar*-), 5.85 (1 H, d, *J* = 4.3 Hz, *H*(5)), 5.06 (1 H, d, *J* = 4.3 Hz, S-CR*H*-S), 4.07 (1 H, t, *J* = 4.3 Hz, *H*(4)), 3.83 (3 H, s, O*Me*), 3.20-3.43 (4 H, m, S-CH_2CH_2-S). **7d**: mp 164-166 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (2 H, d, *J* = 8.5 Hz, *Ar*-), 7.26-7.39 (5 H, m, *Ph*-), 6.80 (2 H, d, *J* = 8.5 Hz, *Ar*-), 4.65 (1 H, d, *J* = 8.5 Hz, *H*(4)), 4.56 (1 H, d, *J* = 3.7 Hz, S-CR*H*-S), 4.45 (1 H, dd, *J* = 3.7 and 8.0 Hz, *H*(5)), 3.76 (3 H, s, O*Me*), 3.20-3.43 (4 H, m, S-CH_2CH_2-S).

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