High Stereoselectivity in One-Pot Intramolecular Cycloadditions of Olefinic Silyl Nitronates

Qian Cheng,*[a] Takayuki Oritani,[a] Tohru Horiguchi,[a] and Qingwen Shi[a]

Keywords: Stereoselectivity / Michael additions / Cycloadditions / 1,3-Dipolar cycloaddition reactions / Silylation / Silyl nitronates

Intramolecular silyl nitronate olefin cycloaddition starting from nitro olefins **1** and leading to substituted tetrahydrofuran rings fused to isoxazolines **5** has been achieved in a one-pot protocol involving Michael addition, silylation, cycloaddition, and desilylation steps. The results show that unlike nitrile oxides, silyl nitronates undergo highly stereoselective intramolecular cycloadditions to produce functionalized heterocyclic rings.

Intramolecular 1,3-dipolar cycloaddition reactions have recently been of considerable synthetic and mechanistic interest.[1][2] Such reactions generate two new rings, one of which is a five-membered heterocyclic ring, and cleavage of the latter can lead to the stereospecific introduction of two functional groups. Intramolecular nitrile oxide olefin cycloadditions (INOC) have shown considerable synthetic utility in the synthesis of natural products.[3] These reactions proceed at room temperature, although with a variable degree of stereoselectivity. Nitrone olefin cycloadditions, including intramolecular oxime olefin cycloadditions (IOOC) proceeding via *H*-nitrones[4][5] as well as silyl nitronate olefin cycloadditions,[6] often require higher temperatures but are usually more stereoselective.[7] Silyl nitronates can be considered as synthetic equivalents of nitrile oxides in their reactions with alkenes. The resulting *N*-(silyloxy)isoxazolidines are readily transformed into isoxazolines upon treatment with acid or tetrabutylammonium fluoride (TBAF), although starting from nitro compounds this sequence requires several steps.

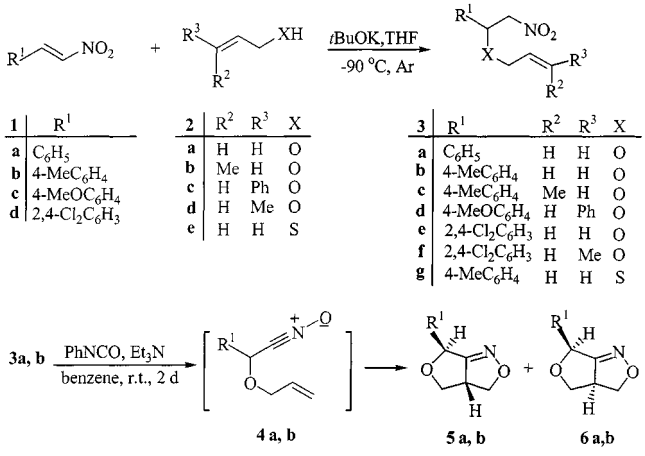
Tandem reactions have emerged in recent years as powerful tools in organic synthesis, due to their operational simplicity and frequently observed high selectivity.[8] Prominent in this family are Michael-initiated reactions, in which the enolate resulting from initial 1,4-addition can subsequently undergo a legion of other transformations in the same reaction vessel, including a facile intramolecular cyclization.[9a]

With this in mind, we have examined the possibility of performing a sequence of Michael addition, silylation, cycloaddition, and elimination of siloxane by using a one-pot protocol.

[a] Laboratory of Applied Bioorganic Chemistry, Division of Life Science, Graduate School of Agricultural Science, Tohoku University,
1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan
Fax: (internat.) + 81-22/717-8783
E-mail: chengq@biochem.tohoku.ac.jp

Results and Discussion

Recently, nitrile oxides have been shown to rank among the most reactive of dipoles, undergoing exclusive regioselective inter- or intramolecular dipolar cycloadditions with terminal olefins to afford isoxazolines. The latter are versatile intermediates for the synthesis of natural products.[3a,10] In most reported 1,3-dipolar cycloadditions, the nitrile oxides have been generated in situ either from hydroximyl halides[11] or from nitro compounds by treatment with Boc_2O (Boc = *tert*-butoxycarbonyl) and DMAP[9a] or phenyl isocyanate.[9b] In order to compare the stereoselectivities of INOC and intramolecular silyl nitronate olefin cycloaddition (ISOC), we first performed reactions of allyl alcohol **2a** with β-nitrostyrenes **1a** or **1b** with subsequent INOC, leading to isoxazolines **5a** and **6a** or **5b** and **6b** (Scheme 1).



1	R^1
a	C_6H_5
b	4-MeC_6H_4
c	4-MeOC_6H_4
d	2,4-$Cl_2C_6H_3$

2	R^2	R^3	X
a	H	H	O
b	Me	H	O
c	H	Ph	O
d	H	Me	O
e	H	H	S

3	R^1	R^2	R^3	X
a	C_6H_5	H	H	O
b	4-MeC_6H_4	H	H	O
c	4-MeC_6H_4	Me	H	O
d	4-MeOC_6H_4	H	Ph	O
e	2,4-$Cl_2C_6H_3$	H	H	O
f	2,4-$Cl_2C_6H_3$	H	Me	O
g	4-MeC_6H_4	H	H	S

Scheme 1. Michael additions of β-nitrostyrenes **1** to alcohols **2** and INOC of **3a**,**b** lead to isoxazolines **5a**,**b** and **6a**,**b**

The base-catalyzed Michael addition of alcohols **2** to β-nitrostyrenes **1** has previously been examined at −10 to −20°C, but in order to proceed in good yield the reaction required the use of 3 equivalents of both the alcohol and the base.[9b] Clearly, for less accessible alcohols a more ef-

  1434−193X/99/1010−2689 $ 17.50+.50/0

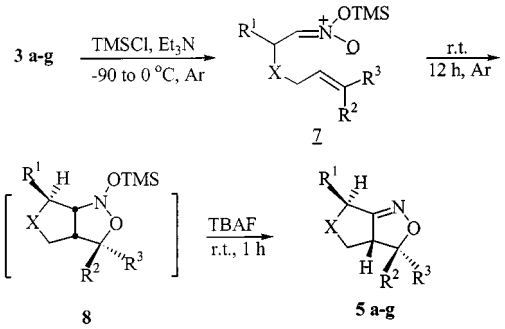
ficient reaction was desirable. We found that treatment of 1 equiv. of allyl alcohol **2a** with 2 equiv. of potassium *tert*-butoxide at −90°C increased the yields of the Michael addition products **3a** and **3b** to 89% and 83%, respectively. Reaction of **3a** with phenyl isocyanate in dry benzene containing a few drops of Et_3N at room temperature for 2 d produced a mixture of the separable diastereomers **5a** and **6a** in a 4:1 (*trans*/*cis*) ratio. The stereochemistry in **5a** and **6a** was confirmed by NOE experiments. Irradiation of the benzylic singlet had no effect on the bridgehead multiplet in the isolated *trans* isomer **5a**. On the other hand, a 3% enhancement of the bridgehead multiplet was observed upon irradiation of the benzylic singlet in the isolated *cis* isomer **6a**. These results are in agreement with a previous report.[12] An analogous INOC reaction of **3b** afforded the separable diastereomers **5b** and **6b** in a 4:1 (*trans*/*cis*) ratio (see Table 1).

Table 1. Michael additions of allyl alcohol **2a** to nitro olefins **1** and INOC of nitrile oxides **4**, generated from ω-nitroalkenes **3**, leading to isoxazolines **5** and **6** in a stepwise reaction

Entry	Nitro-olefin	Michael adduct	Yield (%)	Isoxazo-lines	*trans*/*cis*	Yield (%)
1	**1a**	**3a**	89	**5a** + **6a**	4:1	76
2	**1b**	**3b**	83	**5b** + **6b**	4:1	82

Although such INOC processes provide a useful access to stereoselectively functionalized heterocyclic rings, there is still room for improvement as far as the stereoselectivity is concerned. Recent investigations on intramolecular silyl nitronate olefin cycloadditions (ISOC) have indicated that these offer a highly stereoselective alternative to the analogous INOC reactions, as illustrated by applying this strategy to the synthesis of bicyclic isoxazolines.[7,9a,13] In the ISOC process, silyl nitronates can be generated from nitro compounds by treatment with TMSCl, and then the resulting *N*-(silyloxy)isoxazolidines are easily transformed into isoxazolines upon treatment with acid or TBAF. However, this sequence involves several steps. The aim of the present work was to investigate the viability of conducting Michael addition and ISOC in a consecutive one-pot protocol.[14] This approach has at least one precedent in the literature, though with a nitrogen-centered nucleophile.[9a,13] It involves quenching of the nitro olefins **3**, for example with TMSCl, to generate the silyl nitronates **7**, and then subjecting the latter to the ISOC reaction. Silyl nitronates (e.g. **7**) are regarded as synthetic equivalents of nitrile oxides (e.g. **4**) in their reactions with olefins[7,9b,13,15] since the resulting *N*-(silyloxy)isoxazolidines (e.g. **8**) undergo facile transformation to isoxazolines (e.g. **5**) upon treatment with acid or TBAF.

We were pleased to observe the formation of the desired isoxazolines fused to a substituted tetrahydrofuran ring under the following one-pot conditions (see Scheme 2 and the Experimental Section). The ω-nitro olefin **3a** formed by Michael addition of 1 equiv. of allyl alcohol (**2a**) to 1 equiv. of β-nitrostyrene (**1a**) in the presence of 2 equiv. of *t*BuOK



Scheme 2. One-pot ISOC of nitro olefins **3** leads to isoxazolines **5a**−**g** starting from β-nitrostyrenes **1** and alcohols **2**

Table 2. Michael addition of alcohols **2** to nitro olefins **1**, silylation of nitronates **3**, ISOC of the silyl nitronates **7**, and desilylation of *N*-(silyloxy)isoxazolidines **8** to give isoxazolines **5**, performed in a one-pot protocol

Entry	Nitro olefins **1**	Alcohols **2**	Isoxazolines **5**	Overall isolated yield (%)
1	**1a**	**2a**	**5a**	74
2	**1b**	**2a**	**5b**	80
3	**1b**	**2b**	**5c**	74
4	**1c**	**2c**	**5d**	60
5	**1d**	**2a**	**5e**	43
6	**1d**	**2d**	**5f**	39
7	**1b**	**2e**	**5g**	76

at −90°C was treated with TMSCl and then with Et_3N, and the mixture was slowly allowed to warm to 0°C to ensure complete silylation. The mixture was then stirred at room temperature for 12 h resulting in complete cyclization of the silyl nitronate **7a** to *N*-(silyloxy)isoxazolidine **8a**. Treatment of **8a** with TBAF afforded the desilylation product **5a** in 74% overall yield as a single *trans* isomer, as established by NOE experiments. Similarly, other isoxazolines **5b**−**g** were prepared in respectable overall yields from the corresponding nitrostyrenes and alcohols (entries 2−7, Table 2).

The *trans* stereochemistry in products **5** probably stems from a preference for transition state **A**[16] in the silyl nitronate olefin cycloadditions leading to **8**, in which the Ph substituent is pseudoequatorially orientated[9a,17] (Figure 1). The stereochemistry of **8a** was confirmed by NOE experiments. An ISOC reaction in $CDCl_3$ solution was followed by means of ^{1}H-NMR spectroscopy. Spectra were recorded at hourly intervals following the addition of Me_3SiCl and Et_3N to a $CDCl_3$ solution of **3a** at room temperature. No trace of the starting material **3a** or of silyl nitronate **7a** could still be detected after 2 h and only **8a** was detected after 8 h. A 10% NOE was observed between the two bridgehead protons of **8a**.

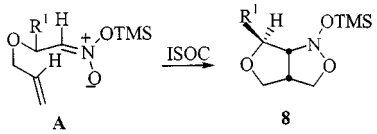


Figure 1. The transition state of ISOC leads to **8**

It is worthy of note that the isoxazolines **6c**, **6d** and **6f** were prepared from the nitro olefins **1b**, **1c** and **1d** and the alcohols (*Z*)-2-butenol (**2b**), (*E*)-3-phenyl-2-propen-1-ol (**2c**), and (*E*)-2-butenol (**2d**), respectively. Their stereochemistries were determined on the basis of NOE experiments (Figure 2). For example, a 7% enhancement of the bridgehead proton (3a-H) signal on irradiation of the C-3 Me group, a 2% NOE between 4α-H and the benzylic H, and a 3% NOE between the benzylic H and 3-H were observed in NOE experiments on **6f**. Three stereocenters were formed stereoselectively in the ISOC process. A similar ISOC reaction of allyl mercaptan (**2e**) with **1b** gave exclusively the *trans* isoxazoline **5g** in 76% overall yield.

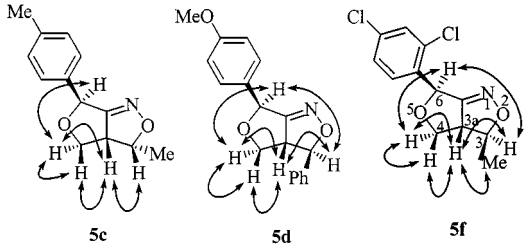


Figure 2. NOESY of **5c**, **5d** and **5f**

In conclusion, a convenient and stereoselective route to highly functionalized tetrahydrofuro[3,4-*c*]isoxazolidines **5** involving a one-pot sequence of Michael addition of alcohols to nitro olefins, silylation of the resulting nitronates, subsequent intramolecular 1,3-dipolar silyl nitronate cycloaddition, and desilylation has been developed. Furthermore, this intramolecular cycloaddition leading to five-membered rings fused to isoxazolines proceeds stereoselectively, furnishing preferentially the *trans* isomers.

Experimental Section

General: ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution with Bruker AM-300 or DMX 600 FT spectrometers with TMS as an internal standard. − MS data were recorded with a Finnigan 4021 spectrometer by CI with a beam energy of 60−70 eV. − HR MS/CI (methane) data were recorded at 60−70 eV with a Fisons VG Autospec spectrometer. − Chromatography was carried out on Merck silica gel 60 (230−240 mesh) eluting with petroleum ether (PE), diethyl ether (DE), and ethyl acetate (EA). − THF was distilled from sodium benzophenone ketyl under argon.

1-Allyloxy-2-nitro-1-phenylethane (3a): A solution of 116 mg (2 mmol) allyl alcohol (**2a**) in THF (30 mL) was injected at room temperature into a flame-dried flask under argon and cooled to −90°C, whereupon potassium *tert*-butoxide (448 mg, 4 mmol) was added. After stirring for 10 min, a solution of β-nitrostyrene (**1a**) (149 mg, 1 mmol) in THF (25 mL) was slowly injected, followed by glacial acetic acid (1.0 mL). The reaction mixture was allowed to warm to room temperature. Then it was filtered and the residual salt was rinsed with diethyl ether (20 mL). The combined organic phases were concentrated and chromatography of the residue (PE/DE, 4:1) gave 184 mg (89%) of **3a** as a colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.38 (ddt, *J* = 13, 6, 1.5 Hz, 1 H, CH_2O), 3.99 (ddt, *J* = 13, 6, 1.5 Hz, 1 H, CH_2O), 4.40 (dd, *J* = 13, 3.5 Hz, 1 H, CH_2NO_2), 4.64 (dd, *J* = 13, 10 Hz, 1 H, CH_2NO_2), 5.14 (dd, *J* = 10, 3.5 Hz, 1 H, CHO), 5.18 (dq, *J* = 10.5, 1 Hz, 1 H, C=CH_2), 5.20 (dq, *J* = 17.5, 1 Hz, 1 H, C=CH_2), 5.83 (dddd, *J* = 16.5, 11, 6, 5 Hz, 1 H, CH=), 7.35−7.44 (m, 5 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 69.86 (t, CH_2NO_2), 77.32 (d, CHO), 80.33 (t, OCH_2), 117.70 (t, =CH_2), 126.00 (d, Ph), 129.02 (d, Ph), 129.05 (d, Ph), 133.62 (d, CH=), 136.21 (s, Ph). − MS/CI (NH_3); *m*/*z* (%): 225 (100) [MNH_4^+], 208 (70) [MH^+], 147 (16). − HR MS/CI (CH_4); calcd. for $C_{11}H_{14}NO_3$ [MH^+] 208.0974, found 208.1033.

1-Allyloxy-1-(4-methylphenyl)-2-nitroethane (3b): Prepared in the same manner from 4-methyl-β-nitrostyrene (**1b**) and allyl alcohol (**2a**) in 83% yield; obtained as a light yellow oil following chromatography (PE/DE, 4:1). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3), 3.80 (ddt, *J* = 13, 6, 1.5 Hz, 1 H, CH_2O), 3.97 (ddt, *J* = 13, 5, 1.5 Hz, 1 H, CH_2O), 4.37 (dd, *J* = 13, 3.5 Hz, 1 H, CH_2NO_2), 4.62 (dd, *J* = 13, 10 Hz, 1 H, CH_2NO_2), 5.09 (dd, *J* = 10, 3.5 Hz, 1 H, CHO), 5.16 (dq, *J* = 10, 1.5 Hz, 1 H, C=CH_2), 5.19 (dq, *J* = 17, 1.5 Hz, 1 H, C=CH_2), 5.82 (dddd, *J* = 17, 11, 6, 5 Hz, 1 H, CH=), 7.21 (td, *J* = 8, 1.5 Hz, 2 H, ArH), 7.26 (td, *J* = 8, 1.5 Hz, 2 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.09 (t, CH_3), 69.65 (t, CH_2NO_2), 77.13 (d, CHO), 80.33 (t, OCH_2), 117.54 (t, =CH_2), 126.74 (d, Ph), 129.65 (d, Ph), 133.10 (s, Ph), 133.70 (d, CH=), 138.93 (s, Ph). − MS/CI (NH_3); *m*/*z* (%): 239 (100)[MNH_4^+]. − HR MS/CI (CH_4): calcd. for $C_{12}H_{16}NO_3$ [MH^+] 222.1130, found 222.1059.

General Procedure for Stepwise INOC. − 3a,6-*trans*-6-Phenyl-3,3a,4,6-tetrahydrofuro[3,4-*c*]isoxazoline (5a) and 3a,6-*cis*-6-Phenyl-3,3a,4,6-tetrahydrofuro[3,4-*c*]isoxazoline (6a): To a solution of 104 mg (0.5 mmol) of **3a** in dry benzene (5 mL), containing a few drops of triethylamine, was added 177 mg (1.5 mmol) of phenyl isocyanate. The reaction mixture was allowed to stand at room temperature for 2 d, then filtered, and the solvent was evaporated. The residue was chromatographed (PE/EA, 3:1) to give 58 mg (61%) of **5a** as a solid; m.p. 77−78°C. − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.82 (dd, *J* = 9.5, 8 Hz, 1 H, OCH_2), 4.07 (dd, *J* = 12.5, 8 Hz, 1 H, CH_2O), 4.24 (ddddd, *J* = 12.5, 9.5, 9, 8, 1.5 Hz, 1 H, CH), 4.43 (td, *J* = 8, 0.5 Hz, 1 H, OCH_2), 4.59 (dd, *J* = 9, 8 Hz, 1 H, CH_2O), 5.61 (s, 1 H, CH), 7.29−7.44 (m, 5 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.47 (d, CH), 69.93 (t, CH_2O), 72.92 (d, CH), 73.66 (t, CH_2O), 125.65 (d), 128.43 (d), 128.68 (d), 137.31 (s), 170.27 (s, C=N). − MS/CI (NH_3); *m*/*z*(%): 190 (100) [MH^+], 174 (22), 162 (14). − HR MS/CI (CH_4): calcd. for $C_{11}H_{12}NO_2$ [MH^+] 190.0868, found 190.0872. − Further elution afforded 14 mg (15%) of **6a** as a solid; m.p. 90−92°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.91 (m, 1 H, OCH_2), 4.06 (m, 1 H, CH_2O), 4.40 (m, 2 H, CH, OCH_2), 4.62 (m, 1 H, CH_2O), 5.61 (s, 1 H, CH), 7.30−7.43 (m, 5 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.08 (d, CH), 69.31 (t, CH_2O), 73.11 (d, CH), 73.98 (t, CH_2O), 126.40 (d), 128.45 (d), 128.74 (d), 137.31 (s), 170.64 (s, C=N). − MS/CI (NH_3); *m*/*z* (%): 207 (100) [MNH_4^+], 189 (46) [M^+], 159 (19). − HR MS/CI (CH_4): calcd. for $C_{11}H_{12}NO_2$ [MH^+] 190.0868, found 190.0871.

3a,6-*trans*-6-(4-Methylphenyl)-3,3a,4,6-tetrahydrofuro[3,4-*c*]-isoxazoline (5b) and 3a,6-*cis*-6-(4-Methylphenyl)-3,3a,4,6-tetrahydrofuro[3,4-*c*]isoxazoline (6b): Prepared according to the general procedure by using **3b** (110 mg, 0.5 mmol) and phenyl isocyanate (177 mg, 1.5 mmol). Chromatography (PE/EA, 3:1) gave 67 mg (66%) of **5b** as a solid; m.p. 55−57°C. − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3), 3.81 (dd, *J* = 9.5, 8.5 Hz, 1 H, OCH_2), 4.07 (dd, *J* = 12.5, 8.5 Hz, 1 H, CH_2O), 4.25 (ddddd, *J* = 12.5, 9.5, 9.5, 8.5, 1.5 Hz, 1 H, CH), 4.42 (td, *J* = 8.5, 1 Hz, 1 H, OCH_2), 4.59 (dd, *J* = 9.5, 8.5 Hz, 1 H, CH_2O), 5.57 (br. s, 1 H,

CH), 7.20 (td, J = 8, 2 Hz, 2 H, ArH), 7.30 (td, J = 8, 2 Hz, 2 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.13 (q, CH_3), 54.62 (d, CH), 69.87 (t, CH_2O), 72.92 (d, CH), 73.65 (t, CH_2O), 125.67 (d), 129.38 (d), 134.39 (s), 138.32 (s), 170.42 (s, C=N). − MS/CI (NH_3); *m/z* (%): 221 (51) [MNH_4^+], 204 (100) [MH^+], 188 (8). − HR MS/CI (CH_4): calcd. for $C_{12}H_{14}NO_2$ [MH^+] 204.1024, found 204.1025. − $C_{12}H_{13}NO_2$ (203.1): calcd. C 70.90, H 6.45, N 6.89; found C 70.95, H 6.46, N 6.83. − Further elution afforded 17 mg (16%) of **6b** as an oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, CH_3), 3.88 (dd, J = 8, 6 Hz, 1 H, OCH_2), 4.05 (dd, J = 12.5, 8 Hz, 1 H, CH_2O), 4.38 (m, 2 H, CH, OCH_2), 4.61 (dd, J = 9, 8 Hz, 1 H, CH_2O), 5.57 (s, 1 H, CH), 7.19 (td, J = 8, 1.5 Hz, 2 H, ArH), 7.33 (td, J = 8, 1.5 Hz, 2 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.14 (q, CH_3), 56.02 (d, CH), 69.18 (t, CH_2O), 73.05 (d, CH), 74.01 (t, CH_2O), 126.39 (d), 129.28 (d), 134.26 (s), 138.26 (s), 170.81 (s, C=N). − MS/CI (NH_3); *m/z* (%): 204 (23) [MH^+], 189 (22) [MH^+ − Me], 119 (100). − HR MS/CI (CH_4): calcd. for $C_{12}H_{14}NO_2$ [MH^+] 204.1024, found 204.1070. − $C_{12}H_{13}NO_2$ (203.1): calcd. C 70.90, H 6.45, N 6.89; found C 71.06, H 6.47, N 6.74.

General Procedure for One-Pot ISOC. − 3a,6-*trans*-6-Phenyl-3,3a,4,6-tetrahydrofuro[3,4-*c*]isoxazoline (5a): A solution of allyl alcohol (**2a**) (58 mg, 1 mmol) in THF (25 mL) was placed in a flame-dried flask under argon and cooled to −90°C, whereupon 224 mg (2 mmol) of potassium *tert*-butoxide was added. After stirring for 10 min, a solution of 149 mg (1 mmol) of β-nitrostyrene (**1a**) in THF (20 mL) was slowly injected, followed by 0.38 mL (3 mmol) of TMSCl. After 1 h at −90°C, stirring was continued at room temperature for a further 12 h and then 3 mL of a TBAF solution (1.0 M in THF) was slowly injected. After a further 1 h, the mixture was filtered, the filtrate was concentrated, and the residue was chromatographed (PE/EA, 3:1) to afford 140 mg (74%) of **5a**, which proved to be identical to the previously described compound.

6-Phenyl-*N*-(trimethylsilyloxy)-3a,4,6,7-tetrahydrofuro[3,4-*c*]-isoxazolidine (8a): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.80 (dd, J = 9, 8 Hz, 1 H, OCH_2), 4.03 (dd, J = 11, 8 Hz, 1 H, CH_2O), 4.10 (ddddd, J = 11, 9.5, 9, 9, 7.5 Hz, 1 H, CH), 4.23 (dd, J = 9.5, 6.5 Hz, 1 H, CH), 4.40 (dd, J = 8, 7.5 Hz, 1 H, OCH_2), 4.55 (dd, J = 9, 8 Hz, 1 H, CH_2O), 5.63 (d, J = 6.5 Hz, 1 H, CH), 7.24−7.41 (m, 5 H, ArH).

3a,6-*trans*-6-(4-Methylphenyl)-3,3a,4,6-tetrahydrofuro[3,4-*c*]-isoxazoline (5b): Following the general procedure for one-pot ISOC with **2a** and **1b**, 163 mg (80%) of **5b** was obtained, which proved to be identical to the previously described compound.

3a,6-*trans*-3,3a-*cis*-3-Methyl-6-(4-methylphenyl)-3,3a,4,6-tetrahydrofuro[3,4-*c*]isoxazoline (5c): Following the general procedure for one-pot ISOC with (*Z*)-2-buten-1-ol (**2b**) and **1b**, 151 mg (74%) of **5c** was obtained as a solid; m.p. 75−76°C. − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.26 (d, J = 7 Hz, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 3.95 (m, 1 H, OCH_2), 4.23 (m, 1 H, CHMe), 4.26 (td, J = 9, 1 Hz, 1 H, CH_2O), 4.91 (dddd, J = 9, 7.5, 6.5, 1 Hz, 1 H, CH), 5.55 (br. s, 1 H, CH), 7.18 (td, J = 8, 2 Hz, 2 H, ArH), 7.30 (td, J = 8, 2 Hz, 2 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.42 (q, CH_3), 21.24 (q, CH_3), 56.45 (d, CH), 65.06 (t, CH_2O), 73.39 (d, CH), 79.68 (d, OCHMe), 125.80 (d), 129.37 (d), 134.28 (s), 138.28 (s), 169.35 (s, C=N). − MS/CI (NH_3); *m/z* (%): 218 (100) [MH^+], 194 (14), 176 (45). − HR MS/CI (CH_4): calcd. for $C_{13}H_{16}NO_2$ [MH^+] 218.1181, found 218.1163. − $C_{13}H_{15}NO_2$ (217.1): calcd. C 71.85, H 6.03, N 6.45; found C 71.94, H 5.92, N 6.37.

3a,6-*trans*-3,3a-*trans*-3-Phenyl-6-(4-methoxyphenyl)-3,3a,4,6-tetrahydrofuro[3,4-*c*]isoxazoline (5d): Following the general procedure for one-pot ISOC with (*E*)-3-phenyl-2-propen-1-ol (**2c**) and **1c**, 177 mg (60%) of **5d** was obtained as an oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, CH_3), 3.97 (dd, J = 9.5, 8.5 Hz, 1 H, OCH_2), 4.24 (dddd, J = 11.5, 9.5, 8.5, 1.5 Hz, 1 H, CH), 4.42 (td, J = 8.5, 0.5 Hz, 1 H, CH_2O), 5.52 (d, J = 6.5 Hz, 1 H, CH), 5.59 (d, J = 0.5 Hz, 1 H, CH), 6.91 (td, J = 8.5, 2 Hz, 2 H, ArH), 7.33−7.40 (m, 7 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.23 (d, CH), 60.56 (q, OCH_3), 69.41 (t, CH_2O), 73.06 (d, CH), 89.15 (d, OCHAr), 114.24 (d), 126.73 (d), 127.21 (d), 128.86 (d), 129.43 (s), 136.93 (s), 159.88 (s), 171.27 (s, C=N). − MS/CI (NH_3); *m/z* (%): 296 (100) [MH^+], 280 (19), 255 (9), 192 (62). − HR MS/CI (CH_4): calcd. for $C_{18}H_{18}NO_3$ [MH^+] 296.1286, found 296.1320. − $C_{18}H_{17}NO_3$ (295.1): calcd. C 73.19, H 5.80, N 4.74; found C 73.30, H 5.76, N 4.68.

3a,6-*trans*-6-(2,4-Dichlorophenyl)-3,3a,4,6-tetrahydrofuro[3,4-*c*]-isoxazoline (5e): Following the general procedure for one-pot ISOC with allyl alcohol (**2a**) and **1d**, 110 mg (43%) of **5e** was obtained as a yellow solid; m.p. 63−65°C. − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.85 (dd, J = 9.5, 8.5 Hz, 1 H, OCH_2), 4.10 (dd, J = 12, 8 Hz, 1 H, CH_2O), 4.25 (ddddd, J = 12, 9.5, 9.5, 8, 1.5 Hz, 1 H, CH), 4.50 (dd, J = 8.5, 8 Hz, 1 H, OCH_2), 4.60 (dd, J = 9.5, 8 Hz, 1 H, CH_2O), 5.88 (br. s, 1 H, CH), 7.27−7.31 (m, 1 H, ArH), 7.43−7.46 (m, 2 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.14 (d, CH), 70.25 (t, CH_2O), 70.27 (d, CH), 73.58 (t, CH_2O), 127.35 (d), 128.13 (d), 129.74 (d), 133.43 (s), 133.71 (s), 134.96 (s), 168.92 (s, C=N). − MS/CI (NH_3); *m/z* (%): 275, 277, 279 [MNH_4^+] (100, 65, 11), 258, 260, 262 [MH^+] (30, 22, 6). − HR MS/CI (CH_4): calcd. for $C_{11}H_{10}Cl_2NO_2$ [MH^+] 258.0088, found 258.0094. − $C_{11}H_9Cl_2NO_2$ (257.0): calcd. C 51.36, H 3.53, N 5.45; found C 51.47, H 3.58, N 5.37.

3a,6-*trans*-3,3a-*trans*-3-Methyl-6-(2,4-dichlorophenyl)-3,3a,4,6--tetrahydrofuro[3,4-*c*]isoxazoline (5f): Following the general procedure for one-pot ISOC with (*E*)-2-buten-1-ol (**2d**) and **1d**, 106 mg (39%) of **5f** was obtained as an oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (d, J = 6 Hz, 3 H, CH_3), 3.81 (m, 1 H, CH), 3.87 (dd, J = 10, 8 Hz, 1 H, CH_2O), 4.44 (dd, J = 10, 7.5 Hz, 1 H, CH_2O), 4.67 (m, 1 H, CHMe), 5.84 (s, 1 H, CH), 7.27−7.31 (m, 1 H, ArH), 7.43−7.46 (m, 2 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.31 (q, CH_3), 59.09 (d, CH), 69.54 (t, CH_2O), 70.55 (d, CH), 83.87 (d, OCHMe), 127.28 (d), 128.06 (d), 129 (d), 133.41 (s), 133.79 (s), 134.87 (s), 169.97 (s, C=N). − MS/CI (NH_3); *m/z* (%): 289, 291, 293 [MNH_4^+] (100, 78, 14), 272, 274, 276 [MH^+] (99, 78, 14), 256 (15), 230 (25). − HR MS/CI (CH_4): calcd. for $C_{12}H_{12}Cl_2NO_2$ [MH^+] 272.0245, found 272.0244. − $C_{12}H_{11}Cl_2NO_2$ (271.0): calcd. C 53.13, H 4.09, N 5.17; found C 53.22, H 4.13, N 5.12.

3a,6-*trans*-6-(2,4-Dichlorophenyl)-5-oxy-3,3a,4,6-tetrahydrothiopheno[3,4-*c*]isoxazoline (5g): Following the general procedure for one-pot ISOC with allyl mercaptan (80%) (**2e**) and **1b**, 166 mg (76%) of **5g** was obtained as an oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, CH_3), 2.84 (dd, J = 10, 9.5 Hz, 1 H, SCH_2), 3.16 (dd, J = 10, 8.5 Hz, 1 H, SCH_2), 4.09 (dd, J = 10.5, 8.5 Hz, 1 H, OCH_2), 4.27 (ddddd, J = 10.5, 10, 9.5, 8.5, 1 Hz, 1 H, CH), 4.54 (dd, J = 10, 8.5 Hz, 1 H, CH_2O), 5.18 (s, 1 H, CH), 7.16 (td, J = 8, 1.5 Hz, 2 H, ArH), 7.33 (td, J = 8, 1.5 Hz, 2 H, ArH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.98 (q, CH_3), 31.60 (t, SCH_2), 43.05 (d, SCH), 55.12 (d, CH), 74.66 (t, CH_2O), 127.06 (d), 129.41 (d), 135.89 (s), 137.68 (s), 168.02 (s, C=N). − MS/CI (NH_3); *m/z* (%): 237 (6) [MNH_4^+], 220 (100) [MH^+]. − HR MS/CI (CH_4): calcd. for $C_{12}H_{14}NOS$ [MH^+] 220.0796, found 220.0822. − $C_{12}H_{13}NOS$ (219.1): calcd. C 65.37, H 5.98, N 6.39; found C 65.23, H 5.94, N 6.30.

Acknowledgments

The authors are grateful to Professor X. T. Liang and A. Hassner for useful discussions and to the Japanese Society for the Promotion of Science for a research fellowship to Dr. Q. Cheng.

[1] [1a] N. A. LeBel, *J. Am. Chem. Soc*. **1959**, *81*, 6334−6335. − [1b] W. Oppolzer, K. Keller, *Tetrahedron Lett*. **1970**, *11*, 117−1120.
[2] J. J. Tufariello, *Acc. Chem. Res.* **1979**, *12*, 396−403.
[3] For instance: [3a] A. Padwa (Ed.), in *1,3-Dipolar Cycloaddition Chemistry*, J. Wiley and Sons, New York, **1984**, vol. 2. − [3b] A. P. Kozikowski, C. S. Li, *J. Org. Chem*. **1987**, *52*, 3541−3552. − [3c] R. Annunziata, M. Cinquini, F. Cozzi, C. Gennari, L. Raimondi, *J. Org. Chem*. **1987**, *52*, 4674−4681. − [3d] A. Hassner, K. S. K. Murthy, A. Padwa, W. H. Bullock, P. D. Stull, *J. Org. Chem*. **1988**, *53*, 5063−5069.
[4] M. H. Norman, C. H. Heathcock, *J. Org. Chem*. **1987**, *52*, 226−235.
[5] [5a] A. Hassner, R. Maurya, E. Mesko, *Tetrahedron Lett*. **1988**, *29*, 5313−5316. − [5b] A. Hassner, R. Maurya, *Tetrahedron Lett*. **1989**, *30*, 2289−2291.
[6] [6a] K. B. G. Torssell, S. C. Sharma, *Acta Chem. Scand. B* **1979**, *33*, 379−383. − [6b] K. B. G. Torssell, *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, New York, **1988**.
[7] A. Hassner, W. Dehaen, *Tetrahedron Lett*. **1990**, *31*, 743−746.
[8] [8a] T. L. Ho, *Tandem Organic Reactions*, J. Wiley and Sons, New York, **1992**. − [8b] R. A. Bunce, *Tetrahedron Lett*. **1995**, *51*, 13103−13159.
[9] [9a] I. N. N. Namboothiri, A. Hassner, H. E. Gottlieb, *J. Org. Chem*. **1997**, *62*, 485−492. − [9b] A. Hassner, W. Dehaen, *Chem. Ber*. **1991**, *124*, 1181−1186.
[10] W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1990**, p. 285−297.
[11] S. Kanemasa, K. Onimura, *Tetrahedron* **1992**, *48*, 8645−8658.
[12] A. Hassner, K. S. K. Murthy, A. Padwa, U. Chiacchio, D. C. Dean, A. M. Schoffstall, *J. Org. Chem*. **1989**, *54*, 5277−5286.
[13] L. Gottlieb, A. Hassner, *J. Org. Chem*. **1995**, *60*, 3759−3763.
[14] S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137−165.
[15] [15a] K. B. G. Torssell, O. Zeuthen, *Acta Chem. Scand. B* **1978**, *32*, 118−123. − [15b] S. H. Andersen, N. B. Das, R. D. Joergensen, G. Kjeldsen, J. S. Knudsen, S. C. Sharma, K. B. G. Torssell, *Acta Chem. Scand. B* **1982**, *36*, 1−5.
[16] P. Armstrong, R. Grigg, F. Heaney, S. Surendrakumer, W. J. Warnock, *Tetrahedron* **1991**, *47*, 4495−4518.
[17] A. Hassner, R. Maurya, O. Friedman, H. E. Gottlieb, A. Padwa, D. Austin, *J. Org. Chem*. **1993**, *58*, 4539−4546.

Received January 14, 1999
[O99013]