Radical cyclization in heterocycle synthesis. Part 14.[1] A simple and effective preparation of cyclic oxime ethers by photochemical radical addition–cyclization of acyclic oxime ethers

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Dedicated to Professor Keiichiro Fukumoto on his 70th birthday
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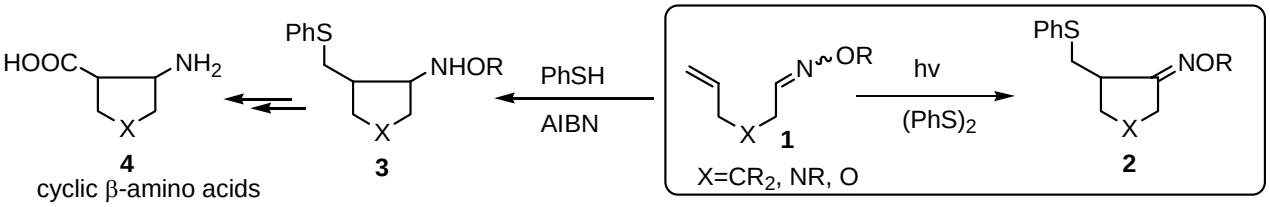
Abstract
The sulfanyl radical addition–cyclization of acyclic oxime ethers containing alkene groups proceeded smoothly under photochemical conditions to give the cyclic oxime ethers.

Keywords: Diphenyl disulfide, radical cyclization, oxime ether, photochemical reaction

Introduction

Free radical cyclization is an efficient method for synthesis of functionalized cyclic compounds, including biologically active natural products and medicinals.[2] In particular, the radical addition–cyclization using N-C multiple bonds as the radical acceptor has been studied extensively by several organic chemists,[3] including our own group[4] for the preparation of cyclic amine derivatives. Previously, we investigated the sulfanyl radical addition–cyclization of oxime ethers **1** with thiophenol in the presence of AIBN under thermal conditions, and found that the cyclic amine derivatives **3** having a phenylsulfanylmethyl group were obtained in excellent yield.[5] We have also applied this method to the synthesis of cyclic amino acids, **4**, (Scheme 1).[1,4f]

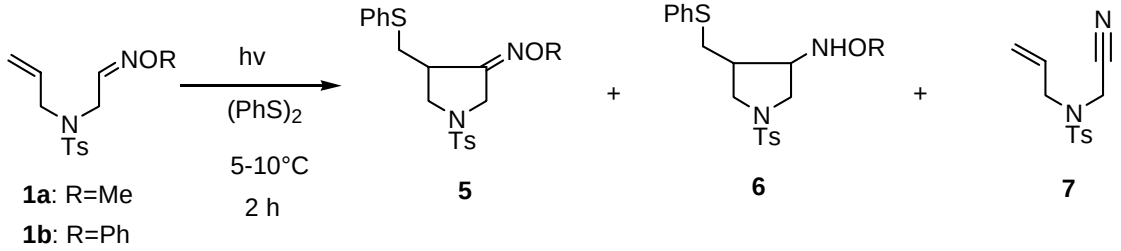
As an extension of our research on the sulfanyl radical addition–cyclization, we now report that the radical reaction of oxime ethers **1** with diphenyl disulfide under photochemical conditions provides direct routes to cyclic oxime ethers **2**. Although it is known[6] that the cyclic oxime ethers can be synthesized via radical addition–elimination reactions of *bis*-methanesulfonyl oxime ethers, the reaction requires one to employ as substrate imidate derivatives having a leaving group. In our newly found methods, one can use readily available aldoxime ethers as substrates.



Scheme 1

Results and Discussion

We first investigated the radical cyclization of *O*-methyl-[1] and *O*-phenyl-oxime ethers **1a**,**b** under photochemical conditions (Scheme 2, Table 1). The substrate **1b** was prepared from aminoacetaldehyde dimethyl acetal *via* tosylation, alkylation, deacetalization, and finally condensation with phenoxyamine, according to the reported procedure.[1]



Scheme 2

Table 1. Sulfanyl radical addition–cyclization of substrates **1a,b** under photochemical conditions[1]

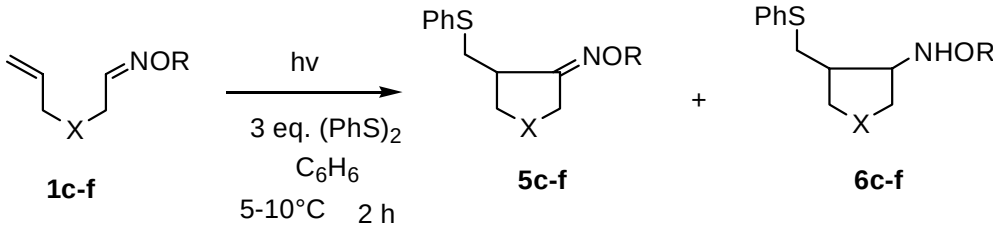
				Yield (%)		
Entry	Substrate	$(PhS)_2$ (eq.)	Solvent	**5** (*E*-**5A**:*Z*-**5B**)	**6** (*cis*:*trans*)	**7**
1	**1a**	0.5	C_6H_6	38 (1:2)	23 (2:1)	–
2	**1a**	1	C_6H_6	60 (1:4)	10 (2:1)	–
3	**1a**	3	C_6H_6	74 (1:4)	13 (2:1)	–
4	**1a**	3	MeOH		23 (2:1)	–
5	**1b**	3	C_6H_6		31 (2:1)	5

[1] The reaction was carried out under bubbling nitrogen.

A solution of diphenyl disulfide (0.5 equiv.) and the oxime ether **1a** in benzene was irradiated with a high-pressure mercury lamp through a Pyrex filter under N_2 bubbling at 5–10°C

for 2 h. The solution was concentrated and the resulting residue was purified by column chromatography to give the cyclic oxime ethers **5a** (*E*-**5aA**:*Z*-**5aB** = 1:2) and the cyclic amine **6a** (*cis*:*trans* = 2:1), both of which have a phenylsulfanylmethyl group (Entry 1). When 1- and 3 equiv. of diphenyl disulfide were used, **5a** was obtained in 60% and 74% yields, respectively (Entries 2 and 3). Interestingly, when methanol was used as solvent, the cyclic amine **6a** was obtained exclusively without formation of the cyclic oxime ether **5a** (Entry 4). The *O*-phenyloxime ether **1b** was subjected to the radical reaction under the photochemical conditions to give the cyclic amine **6b** in low yield, in addition to formation of the nitrile **7** which would be formed by elimination of phenol from the substrate **1b** (Entry 5).

We next investigated the radical reaction of various types of known oxime ethers **1c**–**f** [1] as shown in Scheme 3 and Table 2. The radical reaction of *N*-Boc-oxime ether **1c** with $(PhS)_2$ gave a mixture of cyclic oxime ether **5c** and amine **6c** (entry 1 in Table 2, Scheme 3). The oxime ether **1e** with a quaternary carbon was subjected to radical reaction with $(PhS)_2$ to give the cyclic oxime ether **5e** in improved yield (entry 3) while **1d,f** gave the cyclic oxime ethers **5d,f** in moderate or low yields (entries 2 and 4).



1c-f **5c-f** **6c-f**

Scheme 3

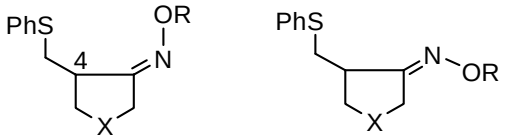
Table 2. Sulfanyl radical addition–cyclization of substrates **1c-f**

					Yield (%)	
Entry	Substrate	R	X	$(PhS)_2$ (eq.)	**5** (**5A**:**5B**)[1]	**6** (*cis*-:*trans*-)
1	**1c**	Me	NBoc	3	36 (1:2)	15 (3:1)
2	**1d**	Bn	O	3	30 (1:4)	7 (2:1)
3	**1e**	Me	$C(COOEt)_2$	3	64 (1:4)	8 (3:1)
4	**1f**	Me	CH_2	3	17 (1:2)	3 (2:1)

[1] The structures of **5A** and **5B** are;

The stereo-structures of the cyclic oxime ethers **5a,c–f** were established as follows (Figure 1, Table 3). The *E*/*Z*-geometries of the oxime ether **5a** were determined by ^{1}H NMR spectroscopy.

Karabatsos's group[7] reported that the oxime ethers which exhibit their hydrogen signals at lower field for the group on the same side as the N-OR group have *E*-geometries, while the oxime ethers showing these at higher field have *Z*-geometries. In our case, the signals for the hydrogen at the 4-position of the *E*-isomer, **5aA** (δ 3.20), appeared at lower field compared with that of the *Z*-isomer **5aB** (δ 2.97). Similarly, the stereo-structures of **5c–f** were established from their spectroscopic data. The cyclic amines **6a,c–f** were identical with authentic samples[1] prepared by the radical cyclization of the same substrates **1a,c–f** as used under the thermal conditions. The stereo-structure of **6b** was deduced by NOESY of the ^{1}H NMR spectrum.



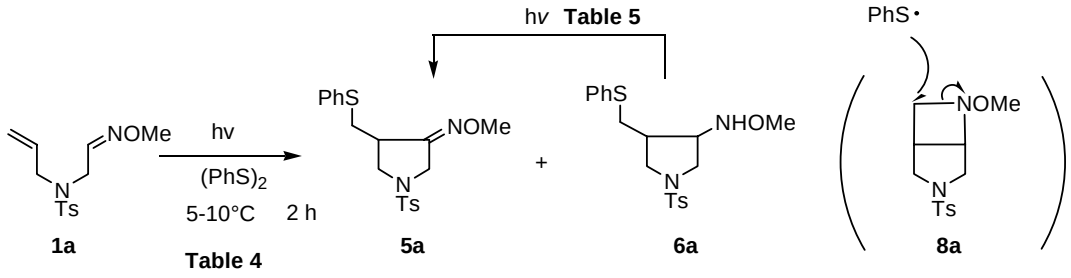
5A **5B**

Figure 1. Oxime ethers **5**.

Table 3. ^{1}H NMR Data of cyclic oxime ethers **5**

			5A δ (ppm)	**5B** δ (ppm)
5	R	X	4-H	4-H
a	Me	NTs	3.20	2.97
c	Me	NBoc	3.35-3.80	3.06
d	Bn	O	3.31	3.03
e	Me	$C(COOEt)_2$	3.30	2.96
f	Me	CH_2	3.14	2.75

In order to clarify the reaction pathway, we next investigated the radical reactions of **1a**,**g** and **6a** under various reaction conditions (Schemes 4 and 5, Tables 4 and 5). The sulfonamide **1a** was treated with 0.5 equiv. of $(PhS)_2$ through bubbling O_2 under the photochemical conditions to give a mixture of the cyclic oxime ether **5a** and the cyclic amine **6a** (entry 1, Table 4). This is similar to the result of the reaction using bubbling N_2, as shown in Table 1, Entry 1. Furthermore, the radical reaction of **1a** in the absence of $(PhS)_2$ gave neither the cyclic oxime ether **5a** nor the cyclic amine **6a**; the oxime ether **1a** was recovered (Entry 2). Since **1a** in the absence of $(PhS)_2$ did not give the azetidine derivative **8a** photochemically, which would be expected from its photochemical [2+2]-cycloaddition reaction, the cyclic compounds **5a** and **6a** could not be formed via [2+2]-cycloaddition followed by ring-opening reaction with attack of the phenylsulfanyl radical.



Scheme 4

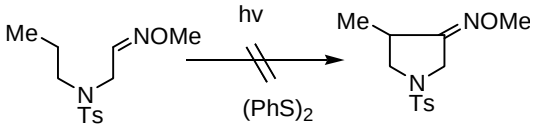
Table 4. Reaction of sulfonamide **1a**

			Yield (%)		
Entry	$(PhS)_2$ (eq.)	conditions	**1a**	**5a**	**6a**
1	0.5	bubbling O_2	18	30	5
2	---	bubbling N_2	100	0	0

Table 5. Reaction of cyclic amine **6a**

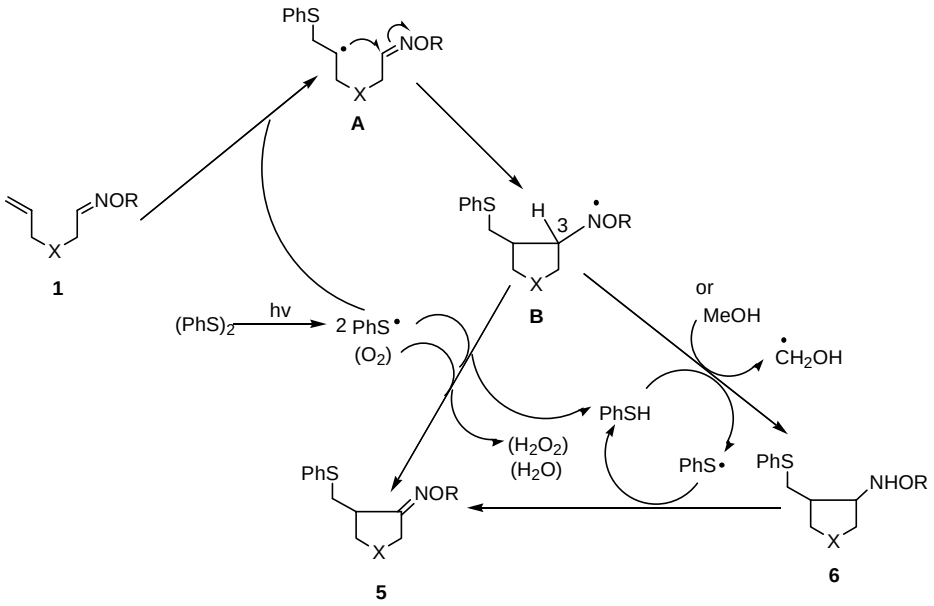
			Yield (%)	
Entry	$(PhS)_2$ (eq.)	Conditions	**5a**	**6a**
1	3	bubbling N_2	29	36
2	---	bubbling N_2	5	56
3	---	bubbling O_2	4	44

Next, the conversion of the cyclic amine **6a** into the cyclic oxime ether **5a** was examined under our reaction conditions (Table 5). The radical reaction of cyclic amine **6a**, under nitrogen, both in the presence and absence of $(PhS)_2$, gave the cyclic oxime ether **5a**, in 29% and 5% yields, respectively. Under similar the reaction conditions, but with the solution of **6a** treated with bubbling O_2, **5a** was formed in 4% yield. These results suggest that **6a** is almost certainly not converted into **5a** by the reaction with O_2, but by the phenylsulfanyl radical. Furthermore, when the oxime ether **1g** having no alkenyl group was subjected to the radical reaction with $(PhS)_2$, no cyclic compound **5g** was found, and **1g** was recovered (Scheme 5). This result suggests that the radical reaction is initiated by addition of the phenylsulfanyl radical to the olefin in **1a**.



Scheme 5

Therefore, we propose the plausible reaction pathway shown in Scheme 6. The phenylsulfanyl radical formed from $(PhS)_2$ under the photochemical conditions would attack the olefin in the substrate **1**. The radical **A** then undergoes a 5-*exo*-*trig* cyclization to form the aminyl radical **B**. In the formation of oxime ether **5**, either the phenylsulfanyl radical or the dissolved O_2 in solvent would attack the hydrogen at the 3-position of radical **B** to afford the cyclic oxime ether **5**, which is also partially formed from the cyclic amine **6** under the photochemical conditions, by the action of the phenylsulfanyl radical. On the other hand, **6** is obtained by trapping radical **B** with thiophenol formed *in situ*. Furthermore, the fact that the cyclic amine **6a** was isolated exclusively, without the formation of cyclic oxime ether **5a**, in the radical reaction using methanol as solvent (Entry 4, Table 1) suggests that the aminyl radical **B** can be trapped with methanol to afford the cyclic amine **6** in preference to the cyclic oxime ether **5**.



Scheme 6

In conclusion, we have developed a method for the preparation of cyclic oxime ethers by phenylsulfanyl radical-mediated reaction of acyclic oxime ethers under photochemical conditions.

Experimental Section

General Procedures. RT denotes room temperature. Melting points are uncorrected. ^{1}H- and ^{13}C- NMR spectra were recorded at 200, 300, or 500 MHz, and at 50 MHz, respectively. IR spectra were recorded using FT-IR apparatus. Mass spectra were obtained by EI method. Flash

column chromatography (FCC) was performed using E. Merck Kieselgel 60 (230–400 mesh). Medium-pressure column chromatography (MPCC) was performed using Lobar größe B (E. Merck 310-25, Lichroprep Si60). Short column chromatography (SCC) was performed on a short glass filter using Silica gel 60F-254 (Merck) under reduced pressure. Preparative TLC (PTLC) was performed on pre-coated Silica gel 60F-254 plates (0.5 mm thick, Merck). The photochemical reactions were carried out by irradiation at 5–10°C with a high-pressure (300 W) mercury lamp (Eikosha PIH 300) through a Pyrex filter. The oxime ethers **1a,c–f** were prepared by reported procedure.[1]

(*E*/*Z*)-4-Methyl-*N*-[2-(phenoxyimino)ethyl]-*N*-(2-propenyl)benzenesulfonamide (1b). To a solution of 2-aminoacetaldehyde dimethyl acetal (3.15 g, 0.03 mol) in CH_2Cl_2 (50 mL) were added Et_3N (4.05 g, 0.04 mol) and then TsCl (7.63 g, 0.04 mol) in CH_2Cl_2 under a nitrogen atmosphere at 0°C. After being stirred at room temperature for 2 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude tosylate. To a suspension of the crude tosylate and K_2CO_3 (5.6 g, 0.04 mol) in acetone (55 mL) was added 3-bromo-1-propene (4.05 g, 0.03 mol) under a nitrogen atmosphere. After being heated at reflux for 5h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by MPCC (hexane/AcOEt 5:1) afforded *N*-(2,2-dimethoxy-ethyl)-4-methyl-*N*-(2-propenyl)-benzenesulfonamide (4.32 g, 46%) as a pale yellow oil. To a solution of the acetal (1.26 g, 4.2 mmol) in acetone (50 mL) was added 2M-HCl (25 mL) under a nitrogen atmosphere at room temperature. After being stirred a further 1 h, the reaction mixture was extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude aldehyde as yellow oil. To a solution of the crude aldehyde in CH_2Cl_2 (80 mL) was added AcONa (685 mg, 8.3 mmol) and $PhONH_2$[8] (458 mg, 4.2 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 2.5 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (hexane/AcOEt 1:1) to afford the oxime ether **1b** (577 mg, 40%) as a pale yellow oil and a 3:2 mixture of *E*- and *Z*- isomers; IR ($CHCl_3$) 1645 (C=N), 1354, 1161 (NSO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (9/5H, s), 2.44 (6/5H, s), 3.84 (4/5H, br. d, *J*=6.5 Hz), 3.86 (6/5H, br. d, *J*=6.5 Hz), 4.05 (6/5H, d, *J*=5.5 Hz), 4.21 (4/5H, d, *J*=4 Hz), 5.16–5.24 (2H, m), 5.59–5.76 (1H, m), 6.98 (2/5H, t, *J*=4 Hz), 7.00–7.34 (7H, m), 7.57 (3/5H, t, *J*=5.5 Hz), 7.69–7.74 (2H, m); HRMS (EI, *m/z*) calcd for $C_{18}H_{20}N_2O_3S$ (M^+) 344.1198, found : 344.1194.

Radical reaction of oxime ethers 1a and 1b under the photochemical conditions (Table 1, entry 3). A solution of oxime ether **1a** (197 mg, 0.7 mmol) and $(PhS)_2$ (458 mg, 2.1 mmol) in benzene (120 mL) was irradiated for 2 h, then concentrated under reduced pressure and the residue was purified by MCC (hexane/AcOEt 5:1) to afford *E*- oxime ether **5aA** (40 mg, 15%) as

a pale yellow oil, *Z*-**5aB** (162 mg, 59%) as a pale yellow oil, *cis*- amine **6a** (24 mg, 9%) and *trans*-**6a** (12 mg, 4%) as a pale yellow oil. The spectral data of *cis*- and *trans*-**6a** were identical with those reported in the literature,[1] respectively.

(*E*)-1-(4-Methylphenyl)sulfonyl-4-(phenylsulfanyl)methyl-3-pyrrolidinone *O*-methyloxime (5aA). IR ($CHCl_3$) 1600 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.43 (3H, s), 2.65 (1H, dd, *J*=14, 11 Hz), 3.20 (2H, m), 3.47 (1H, ddd, *J*=14, 3, 1 Hz), 3.63 (1H, m) 3.64 (1H, d, *J*=15 Hz), 3.97 (1H, dd, *J*=15, 1 Hz), 3.81 (3H, s), 7.18–7.35 (7H, m), 7.69 (2H, br. d, *J*=8.5 Hz); ^{13}C-NMR (50 MHz) δ 21.48, 32.21, 39.25, 49.50, 51.29, 62.06, 126.16, 127.94, 128.91, 129.78, 131.79, 134.88, 144.15, 157.60; HRMS (EI, *m/z*) calcd for $C_{19}H_{22}N_2O_3S_2$ (M^+) 390.1072, found: 390.1071.

(*Z*)-1-(4-Methylphenyl)sulfonyl-4-(phenylsulfanyl)methyl-3-pyrrolidinone *O*-methyloxime (5aB). IR ($CHCl_3$) 1599 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.43 (3H, s), 2.73 (1H, dd, *J*=13.5, 10.5 Hz), 2.97 (1H, m), 3.13 (1H, dd, *J*=9.5, 7 Hz), 3.33 (1H, dd, *J*=13.5, 3.5 Hz), 3.60 (1H, dd, *J*=9.5, 7 Hz), 3.80 (3H, s), 3.79 (1H, dd, *J*=17, 1.5 Hz), 3.95 (1H, d, *J*=17 Hz), 7.19–7.36 (7H, m), 7.68 (2H, br. d, *J*=8 Hz); ^{13}C NMR (50 MHz) δ 21.43, 34.86, 40.84, 47.86, 51.64, 62.09, 126.61, 127.74, 129.00, 129.77, 129.88, 131.68, 134.99, 144.01, 157.84; HRMS (EI, *m/z*) calcd for $C_{19}H_{22}N_2O_3S_2$ (M^+) 390.1072, found: 390.1070.

(Table 1, entry 5). According to the procedure given for the radical reaction of **1a**, a solution of oxime ether **1b** (241 mg, 0.7 mmol) and $(PhS)_2$ (458 mg, 2.1 mmol) in benzene (120 mL) was irradiated for 2 h, then concentrated under reduced pressure and the residue was purified by MCC (hexane/AcOEt, 5:1) to afford *cis*- amine **6b** (65 mg, 21%), *trans*- **6b** (32 mg, 10%) as a pale yellow oil, and nitrile **7** (9 mg, 5%) as a pale yellow oil.

***cis*-1-(4-Methylphenyl)sulfonyl-*N*-phenoxy-4-(phenylsulfanyl)methyl-3-pyrrolidineamine (6b).** IR ($CHCl_3$) 3556 (NH), 1347, 1161 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.40 (3H, s), 2.43–2.49 (1H, m), 2.78 (1H, dd, *J*=13, 8.5 Hz), 3.05 (1H, dd, *J*=13, 7.5 Hz), 3.12 (1H, t, *J*=9.5 Hz), 3.45 (1H, dd, *J*=11, 3 Hz), 3.50 (1H, dd, *J*=11, 5.5 Hz), 3.59 (1H, dd, *J*=9.5, 7.5 Hz), 3.83 (1H, m), 5.72 (1H, d, *J*=5.5 Hz), 6.84 (2H, br. d, *J*=8 Hz), 7.17–7.28 (10H, m), 7.67 (2H, br. d, *J*=8 Hz). NOE was observed between NH (δ 5.72) and C*H*$_2$SPh (δ 2.78, 3.05) in NOESY spectroscopy. ^{13}C-NMR (125 MHz) δ 21.54, 31.55, 41.41, 51.18, 51.25, 60.73, 113.40, 121.40, 126.67, 127.50, 129.12, 129.21, 129.72, 129.79, 133.43, 134.98, 143.57, 159.85; HRMS (EI, *m/z*) calcd for $C_{24}H_{26}N_2O_3S_2$ (M^+) 454.1385, found: 454.1383.

***trans*-1-(4-Methylphenyl)sulfonyl-*N*-phenoxy-4-(phenylsulfanyl)methyl-3-pyrrolidineamine (6b).** IR ($CHCl_3$) 3555 (NH), 1349, 1161 (NSO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.29 (1H, m), 2.42 (3H, s), 2.74 (1H, dd, *J*=13, 9 Hz), 2.94 (1H, dd, *J*=13, 7 Hz), 3.11 (1H, dd, *J*=10, 5.5 Hz), 3.27 (1H, dd, *J*=10, 4 Hz), 3.47 (2H, m), 3.68 (1H, m), 5.71 (1H, d, *J*=7 Hz), 6.87 (2H, br. d, *J*=8 Hz), 7.17–7.28 (10H, m), 7.67 (2H, br. d, *J*=8 Hz); HRMS (EI, *m/z*) calcd for $C_{24}H_{26}N_2O_3S_2$ (M^+) 454.1385, found: 454.1383.

***N*-Cyanomethyl *N*-2-propenyl-4-methylbenzenesulfonamide (7).** IR ($CHCl_3$) 2270 (CN), 1356, 1165 (NSO_2) cm^{-1}; ^1H-NMR (200 MHz, $CDCl_3$) δ 2.45 (3H, s), 3.82 (2H, d, *J*=6.5 Hz),

4.22 (2H, s), 5.33–5.39 (2H, m), 5.66–5.80 (1H, m), 7.38 (2H, br. d, *J*=8 Hz), 7.74 (2H, br. d, *J*=8 Hz); HRMS (EI, *m/z*) calcd for $C_{12}H_{14}N_2O_2S$ (M^+) 250.0789, found: 250.0775.

Radical reaction of oxime ethers 1c–f under the photochemical conditions (Table 2) According to the procedure given for the radical reaction of **1a**, a solution of oxime ether **1c–f** (0.7 mmol) and $(PhS)_2$ (2.1 mmol) in benzene (120 mL) was irradiated for 2 h, then concentrated under reduced pressure and the residue was purified by MCC (hexane/AcOEt 5:1) to afford **5c–f** and **6c–f** as shown in Table 2. The spectral data of c*is*- and *trans*- **6c–f** were identical with those reported in the literature.[1]

1,1-Dimethylethyl-(*E*)-3-(methoxyimino)-4-(phenylsulfanyl)methyl-1-pyrrolidinecarboxylate (5cA). Pale yellow oil; IR ($CHCl_3$) 1693 (NCOO) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.47 (9H, s), 2.79 (1H, br. dd, *J*=13, 10 Hz), 3.35–3.80 (4H, m), 3.97 (1H, br. d, *J*=16 Hz), 4.14 (1H, m), 3.86 (3H, s), 7.16–7.41 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.36, 33.48, 38.57, 47.59, 49.27, 61.95, 80.08, 124.04, 126.13, 128.90, 129.00, 129.34, 135.32, 154.33, 159.38; HRMS (EI, *m/z*) calcd for $C_{17}H_{24}N_2O_3S$ (M^+) 336.1508, found: 336.1506.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

1,1-Dimethylethyl-(*Z*)-3-(methoxyimino)-4-(phenylsulfanyl)methyl-1-pyrrolidinecarboxylate (5cB). Pale yellow oil; IR ($CHCl_3$) 1694 (NCOO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (9H, s), 2.87 (1H, br. dd, *J*=13, 10 Hz), 3.06 (1H, m), 3.41 (2H, m), 3.81 (1H, m), 3.86 (3H, s), 4.07 (2H, br. s) 7.18-7.43 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.34, 35.80, 40.48, 46.19, 49.36, 62.03, 77.21, 79.96, 126.52, 128.25, 129.00, 129.95, 135.18, 154.20, 159.67; HRMS (EI, *m/z*) calcd for $C_{17}H_{24}N_2O_3S$ (M^+) 336.1508, found: 336.1506.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

(*E*)-Dihydro-4-(phenylsulfanyl)methyl-3(2*H*)-furanone *O*-phenylmethyloxime (5dA). A pale yellow oil; IR ($CHCl_3$) 1602 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (1H, dd, *J*=14, 11 Hz), 3.31 (1H, m), 3.64 (1H, ddd, *J*=14, 4, 1 Hz), 3.91 (1H, ddd, *J*=9, 6, 1 Hz), 4.11 (1H, br. dd, *J*=9, 3 Hz), 4.21 (1H, br. d, *J*=14 Hz), 4.40 (1H, br. dd, *J*=14, 1 Hz), 5.09 (2H, s), 7.08–7.39 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.41, 40.58, 68.20, 72.39, 76.53, 125.76, 128.16, 128.36, 128.51, 128.54, 128.90, 135.11, 137.08, 162.12; HRMS (EI, *m/z*) calcd for $C_{18}H_{19}NO_2S$ (M^+) 313.1136; found 313.1136.

(Z)-Dihydro-4-(phenylsulfanyl)methyl-3-(2H)-furanone O-phenylmethyloxime (5dB). A pale yellow oil; IR ($CHCl_3$) 1604 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (1H, dd, *J*=13, 10.5 Hz), 3.03 (1H, m), 3.36 (1H, dd, *J*=13, 4 Hz), 3.83 (1H, dd, *J*=9, 6.5 Hz), 4.09 (1H, dd, *J*=9, 6.5 Hz), 4.42 (2H, s), 5.08 (2H, br. s), 7.18–7.39 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.93, 41.74, 67.17, 72.47, 76.29, 126.55, 127.90, 128.07, 128.36, 129.06, 129.89, 135.21, 137.53, 163.41; HRMS (EI, *m/z*) calcd for $C_{18}H_{19}NO_2S$ (M^+) 313.1136, found 313.1135.

Diethyl (*Z*)-3-(methoxyimino)-4-(phenylsulfanyl)methyl-1,1-cyclopentanedicarboxylate (5eA). A pale yellow oil; IR ($CHCl_3$) 1728 (COO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, t, *J*=7 Hz), 1.26 (3H, t, *J*=7 Hz), 2.24 (1H, dd, *J*=13.5, 8 Hz), 2.72 (1H, dd, *J*=13.5, 8.5 Hz), 2.84 (1H, dd, *J*=13, 10 Hz), 2.93 (1H, dd, *J*=16.5, 1.5 Hz), 3.10 (1H, dd, *J*=16.5, 1.5 Hz), 3.30 (1H, m), 3.64 (1H, dd, *J*=13, 3 Hz), 3.81 (3H, s), 4.19 (4H, m), 7.12–7.40 (5H, m); ^{13}C NMR (50 MHz,

$CDCl_3$) δ13.90, 13.96, 34.65, 37.55, 38.58, 38.84, 57.28, 61.71, 61.79, 61.86, 125.99, 128.84, 129.13, 135.81, 161.38, 170.66, 170.71; HRMS (EI, *m/z*) calcd for $C_{19}H_{25}NO_5S$ (M^+) 379.1453, found 379.1452.

Diethyl (*E*)-3-(methoxyimino)-4-(phenylsulfanyl)methyl-1,1-cyclopentanedicarboxylate (5eB). A pale yellow oil; IR ($CHCl_3$) 1728 (COO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, t, *J*=7 Hz), 1.24 (3H, t, *J*=7 Hz), 2.06 (1H, dd, *J*=13, 11 Hz), 2.77 (1H, ddd, *J*=13, 7, 1.5 Hz), 2.84 (1H, dd, *J*=13, 10 Hz), 2.96 (1H, m), 2.98 (1H, dd, *J*=19, 1.5 Hz), 3.20 (1H, dd, *J*=19, 1.5 Hz), 3.48 (1H, dd, *J*=13, 3.6 Hz), 3.84 (3H, s), 4.16 (2H, q, *J*=7 Hz), 4.19 (2H, q, *J*=7 Hz), 7.15–7.39 (5H, m); ^{13}C-NMR (50 MHz) δ 13.30, 13.36, 34.93, 35.56, 37.44, 40.67, 56.33, 61.09, 125.64, 128.36, 129.04, 135.47, 160.85, 169.92, 170.13; HRMS (EI, *m/z*) calcd for $C_{19}H_{25}NO_5S$ (M^+) 379.1453, found 379.1452.

(*Z*)-2-(Phenylsulfanyl)methylcyclopentanone O-methyloxime (5fA). A pale yellow oil; IR ($CHCl_3$) 1650 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (1H) and 1.89 (3H) and 2.40 (2H) (each m), 2.72 (1H, dd, *J*=13, 10.5 Hz), 3.14 (1H, m), 3.64 (1H, dd, *J*=13, 3 Hz), 3.83 (3H, s), 7.12–7.40 (5H, m); HRMS (EI, *m/z*) calcd for $C_{13}H_{17}NOS$ (M^+) 235.1031, found 235.1030.

(*E*)-2-(Phenylsulfanyl)methylcyclopentanone *O*-methyloxime (5fB). A pale yellow oil; IR ($CHCl_3$) 1650 (C=N) cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 1.58 (2H) and 1.87 (1H) and 2.09 (1H) and 2.42 (2H) (each m), 2.75 (1H, m), 2.83 (1H, dd, *J*=12, 10 Hz), 3.46 (1H, dd, *J*=12, 3 Hz), 3.85 (3H, s), 7.12–7.38 (5H, m); HRMS (EI, *m/z*) calcd for $C_{13}H_{17}NOS$ (M^+) 235.1031; found 235.1030.

Radical reaction of 1a through O_2 bubbling (Table 4, entry 1). According to the procedure given for radical reaction of **1a**, a solution of oxime ether **1a** (198 mg, 0.7 mmol) and $(PhS)_2$ (76.3 mg, 0.35 mmol) in benzene (120 mL) was stirred through O_2 bubbling at 0°C for 10 min. The reaction mixture was irradiated under atmosphere for 2 h, then concentrated under reduced pressure and the residue was purified by MCC (hexane/AcOEt 5:1) to afford **5a** and **6a** as shown in Table 4, Entry 1.

Conversion of cyclic amine 6a into cyclic oxime ether (5a). According to the procedure given for radical reaction of **1a**, a solution of the cyclic methoxyamine **6a** (274 mg, 0.7 mmol) and $(PhS)_2$ (458 mg, 2.1 mmol) in benzene (120 mL) was irradiated for 2 h, then concentrated under reduced pressure and the residue was purified by MCC (hexane/AcOEt 5:1) to afford **5a** and **6a** as shown in Table 5, Entry 1.

1,1-Dimethylethyl (*E/Z*)-*N*-[2-(methoxyimino)ethyl]-*N*-(2-propenyl)carbamate (1g). To a stirred solution of *n*-propylamine (3 g, 51 mmol) in benzene (34 mL) was added a solution of chloroacetaldehyde *O*-methyloxime (1.8 g, 17 mmol) in benzene (8.6 mL) at room temperature under a nitrogen atmosphere. After being stirred at 80 °C for 5 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by SCC (AcOEt) to afford (*E/Z*)-(1-propylamino)- acetaldehyde O-methyloxime (1.3 g, 59%) as a pale yellow oil. To a solution of the oxime ether (1.3 g, 10 mmol) in CH_2Cl_2 (23 mL) were added Et_3N (1.7 mL, 12 mmol) and TsCl (2.28 g, 12 mmol) at room temperature under a nitrogen atmosphere. After being stirred at

room temperature for 24 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by FCC (hexane/AcOEt 5:1) to afford **1g** (2.55 g, 90%) as a pale yellow oil and a 1:1 mixture of *E*- and *Z*- isomers; IR ($CHCl_3$) 1340, 1159 (NSO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3/2H, t, *J*=7.5 Hz), 0.90 (3/2H, t, *J*=7.5 Hz), 1.55 (2H, m), 2.43 (3H, s), 3.09 (2H, br. t, *J*=7.5 Hz), 3.80 (3/2H, s), 3.86 (3/2H, s), 3.87 (2/2H, d, *J*=6 Hz), 4.01 (2/2H, d, *J*=4 Hz), 6.62 (1/2H, t, *J*=4 Hz), 7.18 (1/2H, t, *J*=6 Hz), 7.31 (2H, m), 7.69 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 10.75, 10.82, 21.19, 21.22, 43.27, 46.29, 49.53, 50.88, 61.44, 61.82, 77.20, 126.74, 126.88, 129.56, 129.62, 130.06, 135.94, 136.36, 143.27, 143.36, 145.53, 148.05; HRMS (EI, *m/z*) calcd for $C_{13}H_{21}N_2O_3S$ $(M+H)^+$ 285.1273, found 285.1272.

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