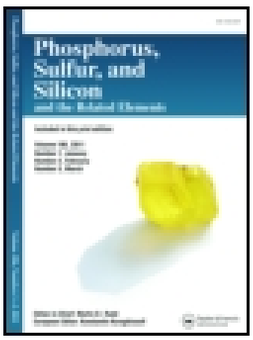


Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

Polystyrene-supported 2-bromoallyl sulfone as an efficient reagent for synthesis of 3,5-disubstituted isoxazoles

Liang Zhang, Xue-Chun Mao, Qiu-Ying Wang, Yang Pan & Jun-Min Chen

To cite this article: Liang Zhang, Xue-Chun Mao, Qiu-Ying Wang, Yang Pan & Jun-Min Chen (2019): Polystyrene-supported 2-bromoallyl sulfone as an efficient reagent for synthesis of 3,5-disubstituted isoxazoles, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2019.1655420

To link to this article: https://doi.org/10.1080/10426507.2019.1655420

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
https://doi.org/10.1080/10426507.2019.1655420

Polystyrene-supported 2-bromoallyl sulfone as an efficient reagent for synthesis of 3,5-disubstituted isoxazoles

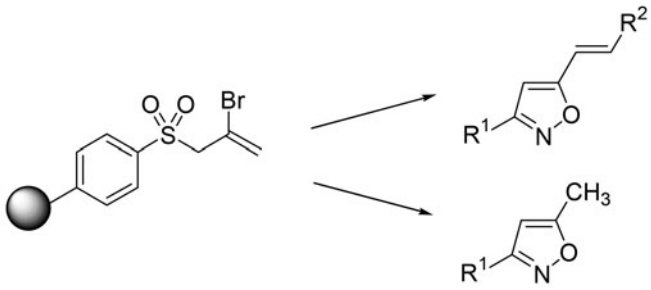
Liang Zhang, Xue-Chun Mao, Qiu-Ying Wang, Yang Pan, and Jun-Min Chen

Key Laboratory of Functional Small Organic Molecule of Ministry of Education, Jiangxi Normal University, Nanchang, China

ABSTRACT

A facile method has been developed for the solid-phase organic synthesis of 3,5-disubstituted isoxazoles from polystyrene-supported 2-bromoallyl sulfone. The advantages of this method include a straightforward and convenient procedure, high product yield, and good stability of this new polymeric reagent.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 6 June 2019
Accepted 9 August 2019

KEYWORDS
3,5-disubstituted isoxazole; solid-phase organic synthesis; polystyrene-supported 2-bromoallyl sulfone; 2-bromoallyl phenyl sulfone; nitrile oxides

Introduction

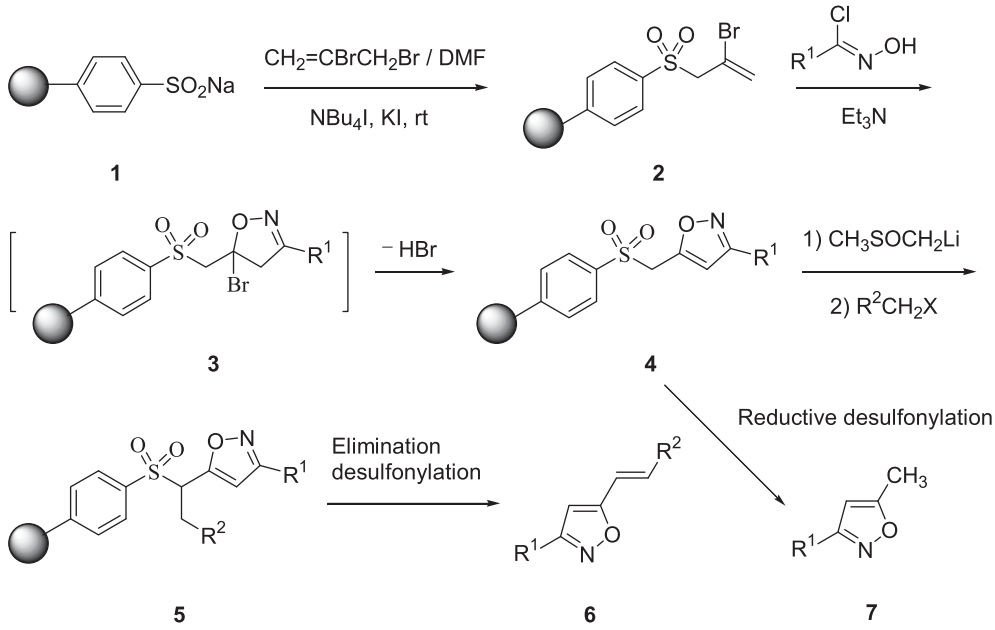
Isoxazole moieties are important constituents that commonly exist in biologically active natural products and synthetic compounds of medicinal interest.[1,2] Thus, it is not surprising that many methods have been developed for the construction of this useful scaffold.[3–5] Especially, many exciting advances in the synthesis and functionalization of isoxazoles have been reported in recent years.[6] It is well known that the major synthetic route towards the isoxazole nucleus is 1,3-dipolar cycoaddition.[7,8] For the synthesis of isoxazoles, alkynes are often used as the dipolarophile in the 1,3-dipolar cycloaddition reaction with nitrile oxides (1,3-dipoles generated *in situ* mainly from aldoximes, primary nitro compounds and hydroximinoyl chlorides), however, regioselectivity issues often arise.[9] Moreover, isoxazoles can be synthesized from simple alkenes, but an additional oxidation step is usually required.[10,11] On the other hand, geminally disubstituted alkenes with a bromine atom as one of the substituents have been shown to be effective alkyne surrogates that lead to the isolation of only one isoxazole regioisomer without the isolation of an isoxazoline intermediate.[11,12] However, these bromoalkenes need to be synthesized and isolated usually before they are incorporated into the cycloaddition process. Furthermore, some of them are unstable and quickly decompose after their isolation.

It is well known that the use of polymer-supported reagents in solid-phase organic synthesis (SPOS) provides many advantages such as utilizing unstable or toxic intermediates conveniently by immobilization on the resin, driving the reaction to completion by the use of excess reagents, removing excessive or unconsumed reagents by a simple filtration workup operation, and isolating products easily by filtration from the solid support.[13] Therefore, the development of polymer-bound bromoalkenes reagents might be an ideal methodology for the construction of isoxazoles.

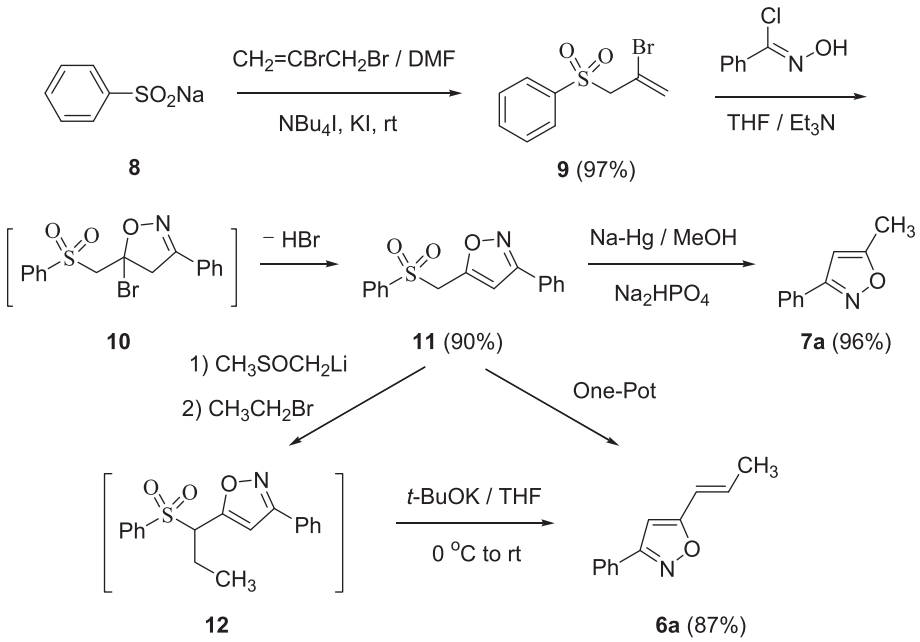
Sulfone is a vital functional group in organic chemistry, which has valuable synthetic capabilities due to its activating and electron-withdrawing effects.[14] Sulfinate-functionalized resin has been efficiently prepared and utilized in SPOS and the resulting sulfone linker has been found to be both a robust and a versatile traceless linker. Some research groups[15–24] have developed sulfone-linking strategies for SPOS method to explore sulfone-based chemical transformation. Among them, only 3-monosubstituted isoxazoles have been prepared through SPOS from polymer-supported vinyl sulfone.[25] Therefore, based on the importance of isoxazole molecules

CONTACT Yang Pan panyang@jxnu.edu.cn; Jun-Min Chen jxnuchenjm@163.com College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, 330022 P. R. China.

Supplemental data for this article is available online at https://doi.org/10.1080/10426507.2019.1655420.



Scheme 1. Sulfinate SPOS route to 3,5-disubstituted isoxazoles.



Scheme 2. Solution-phase pathway to 3,5-disubstituted isoxazoles.

and the advantages of polymeric regents in organic synthesis, we herein wish to report the application of polystyrene/1% divinylbenzene sodium sulfinate (**1**) for convenient traceless synthesis of 5-vinyl isoxazoles and 5-methyl isoxazoles, as outlined in Scheme 1. Key steps include (i) sulfinate *S*-alkylation, (ii) sequential [3 + 2] cycloaddition with nitrile oxides and elimination with a loss of HBr, (iii) α-sulfonyl carbanion monoalkylation with alkyl halides, and (iv) traceless product release by elimination or reductive desulfonylation reaction.

Results and discussion

Firstly, in order to find the most suitable SPOS reaction conditions for our purpose, preliminary solution-phase studies were undertaken as shown in Scheme 2. It was reported that 2-bromoallyl phenyl sulfone (**9**) could be obtained in 58% yield by equimolar reactions of sodium benzenesulfinate (**8**) and 2,3-dibromopropene in *N*,*N*-dimethylformamide (DMF) at room temperature.[26] Interestingly, **9** could be obtained in 97% yield by treating **8** with excess 2,3-dibromopropene in the presence of NBu_4I/KI/DMF at room temperature for 8 h. Subsequent tandem reaction afforded the 5-phenylsulfonylmethylisoxazole (**11**) in 93% yield, which involved [3 + 2] cycloaddition reaction of **9** with nitrile oxides generated *in situ* from *N*-hydroxybenzimidoyl chloride, 1,2-elimination reaction with a loss of HBr from the corresponding isoxazoline intermediates in the presence of Et_3N in THF at 60 °C. It should be pointed

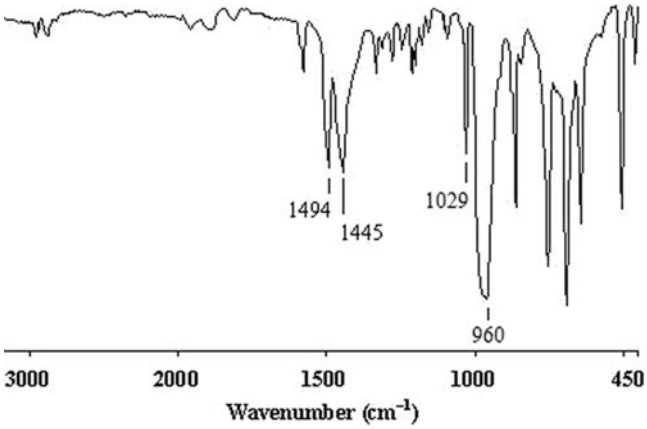


Figure 1. FTIR spectrum for the resin **1**.

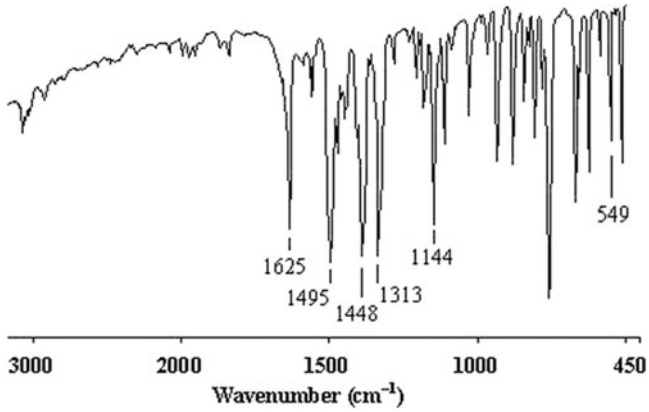


Figure 2. FTIR spectrum for the resin **2**.

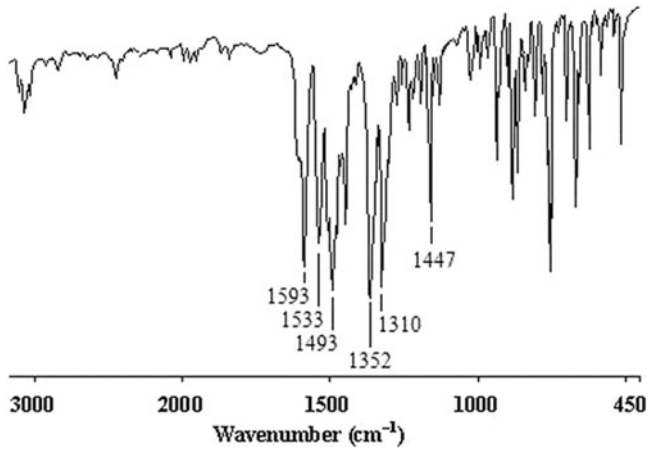


Figure 3. FTIR spectrum for the resin **4** (R^1 = 4-$NO_2C_6H_4$–).

out that compound **9** might produces a mixture of allenyl sulfone and propargyl sulfone[26] in the presence of Et_3N before its addition reaction with phenyl nitrile oxide in the process of conversion of compound **9** to **11**. Then, α-monoalkylation of **11** with ethyl bromide using the previously procedure[22] generated 3-phenyl-5-[(1-phenylsulfonyl)propyl]isoxazole (**12**) in 90% yield. After sulfinate β-elimination of **12** by treatment with potassium *tert*-butoxide formed the expected 3-phenyl-5-(1-*E*-propenyl)isoxazole (**6a**) in 95% yield. It should be noted that some other bases such as 8-diazabicyclo[5.4.0]undec-7-ene (DBU) and Et_3N could also be used for this reaction, but the yield of **6a** was relatively low. Further study indicated that in the course of the transformation of **12** into **6a**, one-pot procedure could be also carried out smoothly with good yield (87%). ^{1}H NMR analysis of **6a** indicates its only (*E*)-stereoisomer, as assigned from the coupling constant (J = 15.6 Hz) between the two of olefinic protons.

In addition, as a synthetic alternative, compound **11** was submitted to reductive desulfonation with Na-Hg/Na_2HPO_4 in MeOH at room temperature, yielding 3-phenyl-5-methylisoxazole (**7a**) in 96% yield using a similar procedure described in the literature.[27] It should be pointed out that some other reducing agents[28] such as Al/Hg, zinc-acetic acid and SmI_2 could also been used to transform **11** into **7a**, with moderate to good yields (70–84%).

Secondly, following the solution-phase pathway to isoxazoles established, treatment of a DMF-swollen suspension of polystyrene/1% divinylbenzene sodium sulfinate (**1**, 100-200 mesh) with 2,3-dibromopropene in the presence of NBu_4I/KI at room temperature generated in almost quantitative formation of polymer-supported 3-phenylsulfonyl-2-bromopropene (**2**) (elemental analysis Br, 1.60 mmol/g), which was easily monitored by FTIR spectroscopies for the disappearance of the sulfinate absorption at 1029 and 960 cm^{-1} for resin **1** (Figure 1), as well as the appearance of the sulfone stretches (ν_{asym} = 1313 cm^{-1} and ν_{sym} =1144 cm^{-1}), the expected new bands for C=C stretch at 1625 cm^{-1} and C–Br stretch at 549 cm^{-1} (Figure 2).

Thirdly, as described in Scheme 1, 1,3-dipolar cycloaddition of the resin **2** with nitrile oxides, generated *in situ* from hydroximinoyl chlorides, and subsequent 1,2-elimination reactions with loss of HBr in THF at 60 °C gave the resin **4**, which could not be reliably analyzed with FTIR. But, by employing *N*-hydroxy-4-nitrobenzimidoyl chloride as a potential 1,3-dipole, the corresponding conversion could be monitored by appearance of characteristic stretches at 1533 and 1352 cm^{-1} assigned to the asymmetric and symmetric stretching of the nitro group in the KBr FTIR (**4** where R^1 = 4-$NO_2C_6H_4$–), as shown in Figure 3. Furthermore, the transformation resulted in the complete disappearance of C–Br (549 cm^{-1}) absorption and found to have lost all its bromine from the resin **4** by elemental analysis except from the corresponding polymeric intermediates **4** (**4** where R^1 = 4-BrC_6H_4–).

Then, reaction of the resin **4** with dimsyl anion at room temperature generated the corresponding α-sulfonyl monocarbanion, followed by the monoalkylation reaction with alkyl halides furnished the resin **5**. Since this transformation exhibited no reliably diagnostic absorption peaks in the single bead FTIR spectrum, subsequent release the target molecules **6** from the resin support was undertaken by treated with potassium *tert*-butoxide *via* traceless linker sulfinate elimination cleavage as above solution-phase protocols. As illustrated in Table 1, various primary alkyl halides such as methyl iodide, ethyl bromide, benzyl chloride, allyl bromide and methyl bromoacetate were employed in the monoalkylation step, and the corresponding 3-substituted-5-vinylisoxazoles **6a**–**6l** were obtained in good overall yields (80–95%) from resin **2**. HPLC analysis of the crude products cleaved

from the resin directly indicated their high purities in all cases (90–98%).

It is noteworthy that no significant difference in reactivity was observed for all examined hydroximyl chlorides. In general, aromatic hydroximyl chlorides bearing electron-withdrawing groups such as chloro, bromo, nitro, as well as electron-donating groups such as methyl and methoxy, and even *N*-hydroxy-2-chlorobenzimidoyl chloride bearing a *o*-chloro substituent (Table 1, entry 5) could afford the desired product in good yields. It was also observed that aliphatic hydroximyl chlorides like *N*-hydroxybutylimidoyl chloride (Table 1, entry 6) produced the corresponding compound **6f** in relatively low yield. Besides, for the examined primary alkyl halides, experiments were performed smoothly and the corresponding isoxazole derivatives were obtained. Furthermore, the stereochemistry of the final products **6a**–**6j** was determined by ^{1}H NMR spectroscopy. As expected, all the coupling constants ($J = 15.6$–16.0 Hz) of the two olefinic protons indicated the exclusive production of *E*-isomers.

On the other hand, the use of chloromethyltrimethylsilane as an alkylating agent instead of methyl iodide was further investigated. A typical example was shown in Scheme 3, the monoalkylation by treating monocarbanion of the resin **4a** with chloromethyltrimethylsilane yielded the resin **13**, which was treated with TBAF[29] in THF for 6 h delivered the target molecule 3-phenyl-5-ethenylisoxazole (**6k**) in high yield (89% yield).

Finally, cleavage of the immobilized intermediate **4** with Na(Hg)/Na_2HPO_4 in THF-MeOH at room temperature formed efficiently 3-aryl-5-methylisoxazoles **7** in excellent yields (91–94%), following the solution-phase conditions as described above. Several typical examples are listed in Table 2.

In summary, an efficient and convenient method for the synthesis of 3-vinyl-5-substituted-isoxazoles and 3-substituted-5-methyl-isoxazoles in good yields and purities has been developed based on a new polymer-supported 2-bromoallyl sulfone reagent. The use of a sulfone moiety as a traceless linker in the reaction benefits the solid-phase synthetic route as it not only makes isolation of the product easier but its chemical versatility also adds to the diversity of the isoxazole heterocycle library.

Table 1. Yields and purities of 3-substituted-5-vinylisoxazoles (**6a**–**6l**).

Entry	R^1	Reagent	Product (R^2)	Yield[a] (%)	Purity[b] (%)
1	C6H5	CH_3CH_2Br	**6a** (CH_3)	95	95
2	4-$CH_3C_6H_4$	CH_3CH_2Br	**6b** (CH_3)	94	98
3	4-$NO_2C_6H_4$	CH_3CH_2Br	**6c** (CH_3)	92	97
4	4-BrC_6H_4	CH_3CH_2Br	**6d** (CH_3)	92	97
5	2-ClC_6H_4	CH_3CH_2Br	**6e** (CH_3)	90	95
6	*n*-C_3H_7	CH_3CH_2Br	**6f** (CH_3)	80	90
7	4-$CH_3C_6H_4$	$C_6H_5CH_2Cl$	**6g** (C_6H_5)	90	92
8	4-$CH_3C_6H_4$	CH_3OOCH_2Br	**6h** (CH_3OO)	92	94
9	4-$CH_3OC_6H_4$	CH_2=$CHCH_2Br$	**6i** (CH_2=CH)	89	96
10	4-ClC_6H_4	CH_2=$CHCH_2Br$	**6j** (CH_2=CH)	88	94
11	C_6H_5	CH_3I	**6k** (H)	90	92
12	4-$CH_3OC_6H_4$	CH_3I	**6l** (H)	93	93

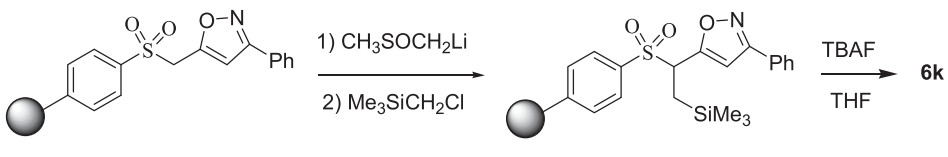
[a]Isolated yields based on the functional loading of resin **2** (1.60 mmol Br/g).
[b]Determined by HPLC of crude cleavage product.

Experimental

Melting points were measured with a Beijing-Taike X-4 apparatus without corrected. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as an internal standard. The FTIR spectra were measured with a Perkin-Elmer SP One FTIR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 Elemental Analyzer. Mass spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. High performance liquid chromatography (HPLC) analysis was performed with an Agilent 1100 automated system using a photodiode array (PDA) detector ($\lambda = 254$ nm). Polystyrene/1% divinylbenzene sodium sulfinate (2.0 mmol $-SO_2Na$/g) was purchased from Tianjin Nankai Hecheng Science and Technology Company of China (100–200 mesh). Hydroximyl chlorides were prepared from the corresponding readily available aldehydes through the reported method.[30] *N,N*-Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were freshly distilled from calcium hydride under reduced pressure. Triethylamine (TEA) was freshly distilled from calcium hydride, and tetrahydrofuran (THF) was freshly distilled from sodium-benzophenone before use. The other reagents and solvents were pure, analytical grade materials purchased from commercial sources and were used without further purification, unless otherwise stated. The Supplemental Materials contain sample NMR and HPLC spectra of the products.

Preparation of 2-bromoallyl phenyl sulfone (9)

Sodium benzenesulfinate **8** (410 mg, 2.5 mmol) was dissolved in DMF (10 mL), in which NBu_4I (90 mg, 0.25 mmol), KI (500 mg, 3.0 mmol) and 2,3-dibromopropene (600 mg, 3.0 mmol) were added. The mixture was stirred at room temperature for 8 h (by TLC). After which, the DMF was removed by vacuum distillation and a residual solid was purified by column chromatography on silica gel (25% EtOAc in petroleum ether as eluent) to afford **9** (633 mg, 97%) as a white crystal, mp = 80–81 °C (lit.[26] 77–79 °C).



4a **13**

Scheme 3. Solid-phase monoalkylation with $ClCH_2SiMe_3$.

Table 2. Yields and purities of 3-aryl-5-methylisoxazoles (**7a–7d**).

Entry	R[1]	Product	Yield[a] (%)	Purity[b] (%)
1	C_6H_5	**7a**	93	94
2	4-$CH_3C_6H_4$	**7b**	94	96
3	4-$CH_3OC_6H_4$	**7c**	94	97
4	4-ClC_6H_4	**7d**	91	95

[a]Isolated yields based on the functional loading of resin **2** (1.60 mmol Br/g).
[b]Determined by HPLC of crude cleavage product.

Preparation of 3-phenyl-5-(phenylsulfonylmethyl)isoxazole (11)

The *N*-hydroxybenzimidoyl chloride (460 mg, 3.0 mmol) and TEA (0.42 mL, 3.0 mmol) was added to a solution of **9** (652 mg, 2.5 mmol) in THF (10 mL), and the reaction mixture was then warmed up to 60 °C and stirred continuously at this temperature until the completion of the reaction (by TLC). After which, the resulting mixture was cooled to room temperature and diluted with water (5 mL), extracted with ethyl acetate (2 × 10 mL). The combined organic phase was washed with brine (5 mL), dried with anhydrous magnesium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (20% EtOAc in petroleum ether as eluent) to afford the compound **11** (673 mg, 90%) as a yellow solid, mp = 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.76 (m, 4 H, Ph-*H*), 7.68 (t, J = 7.6 Hz, 1 H), 7.55 (t, J = 7.8 Hz, 2 H, Ph-*H*), 7.47–7.45 (m, 3 H, Ph-*H*), 6.73 (s, 1 H, C*H*C = N), 4.60 (s, 2 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9 (*C*-5), 160.9 (*C*-3), 137.8 (Ph-*C*). 134.6 (Ph-*C*), 129.8 (Ph-*C*), 129.5 (Ph-*C*), 128.9 (Ph-*C*), 128.7 (Ph-*C*), 128.4 (Ph-*C*), 126.8 (Ph-*C*), 104.0 (*C*-4), 54.1 (CH_2). IR (KBr): ν = 3081, 2939, 2850, 1608, 1581, 1470, 1442, 1408, 1317, 1309, 1248, 1149, 1084, 833, 761, 688 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.20, H, 4.38, N, 4.68; found: C, 64.04, H, 4.52, N, 4.76. MS (EI, 70 eV): m/z = 299 (M^+).

One-pot preparation of 3-phenyl-5-(1-E-propenyl)isoxazole (6a)

BuLi (2.0 mmol, 1 mL, 2.0 M hexane solution) was added to DMSO (4.0 mmol, 310 mg) in THF (5 mL) at 0 °C and stirred for 5 min. The resulting dimsyl anion solution was transferred to a solution of **11** (1.0 mmol) in THF (5 mL) at room temperature. After stirring for 30 min, ethyl bromide (1.1 mmol) was added to this mixture. The reaction mixture was stirred for 1 h, then cooled to 0 °C, 1 M potassium *tert*-butoxide in THF (1 mL) was added subsequently, and stirred at the same temperature for 30 min. The reaction mixture was warmed to room temperature with stirring continuously for 30 min again, and then quenched with water (10 mL). After usual workup with EtOAc, the organic layer was evaporated, and the residue was subjected to column chromatography on silica gel (20% EtOAc in petroleum ether as eluent) to give **6a** (161 mg, 87%) as a pale yellow solid, mp = 64–65 °C. δ = 7.82 (d, J = 7.2 Hz, 2 H, Ph-*H*), 7.54–7.50 (m, 1 H, C*H*=CHCH$_3$), 7.43–7.35 (m, 3 H, Ph-*H*), 6.44 (d, J = 15.6 Hz, 1 H, CH = C*H*CH$_3$), 6.38 (s, 1 H, C*H*C = N), 1.97 (d, J = 7.2 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4 (*C*-5), 162.5 (*C*-3), 134.2 (*C*H = CHCH$_3$), 129.9 (Ph-*C*), 129.4 (Ph-*C*), 128.7 (Ph-*C*), 126.8 (Ph-*C*), 117.4 (CH=*C*HCH$_3$), 99.2 (*C*-4), 19.2 (*C*H$_3$). IR (KBr): ν = 3048, 2975, 1662, 1559, 1525, 1430, 1383, 965, 796, 695 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81, H, 6.00, N, 7.56; found: C, 77.72, H, 6.13, N, 7.77. MS (EI, 70 eV): m/z = 185 (M^+).

Preparation of 3-phenyl-5-methylisoxazole (7a)

To a stirred solution of sulfone **11** (1.0 mmol) and anhydrous disodium hydrogen phosphate (560 mg, 4.0 mmol) in 10 mL of dry methanol was added 1.5 g of pulverized 6% sodium amalgam (freshly prepared) at 0 °C. The reaction mixture was vigorously stirred until TLC showed complete conversion. The mixture was poured into water (30 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated, and the crude product was purified by flash chromatography to afford **7a** (153 mg, 96% yield) as a white solid, mp 40–42 °C (lit.[31] 41–42 °C).

Preparation of polymer-supported 3-phenylsulfonyl-2-bromopropene (2)

The resin **1** (1.0 g, 2.0 mmol/g) was swollen in DMF (15 mL) under nitrogen for 30 min. Then, 2,3-dibromopropene (5 mmol), KI (5 mmol) and tetrabutylammonium iodide (1 mmol) were added, and the mixture was shaken at room temperature for 12 h. The resin was filtered and washed sequentially with DMF (2 × 5 mL), H_2O (2 × 5 mL), ethanol (2 × 5 mL), CH_2Cl_2 (2 × 5 mL) and diethyl ether (2 × 5 mL), and dried overnight in a vacuum oven at 50 °C to produce the resin **2** in the form of yellow beads with a loading value of 1.60 Br mmol/g by bromine elementary analysis. IR (KBr): ν = 3038, 2923, 1625, 1495, 1448, 1313, 1144, 822, 754, 697, 549 cm^{-1}.

SPOS of 3-substituted-5-vinyl isxoxazoles (6a–6l): general procedure

To a suspension of the swollen resin **2** (625 mg, 1.0 mmol) in THF (10 mL) was added hydroximyl chloride (2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol), and the resulting reaction mixture was shaken at 60 °C for 12 h. After filtration, the resin was washed successively with THF, MeOH, H_2O and CH_2Cl_2 (2 × 5 mL of each), and dried in vacuum to afford resin **4** as a pale yellow beads. Under nitrogen BuLi (2.0 mmol, 1 mL, 2.0 M) was added to DMSO (310 mg, 4.0 mmol) in THF (5 mL) at 0 °C and stirred for 5 min. The resulting dimsyl anion solution was transferred to a suspension of resin **4** pre-swollen in THF (10 mL). After shaking for 30 min, alkyl halide (2.0 mmol) was added to this mixture and shaken for 2 h, the color of the breads turned light orange. The reaction mixture was then cooled to 0 °C, 1 M potassium *tert*-butoxide in THF (4 mL) was added subsequently, and shaken at the same temperature for 30 min. The reaction mixture was warmed to room temperature with stirring for 30 min again, and then quenched with 10% HCl (aq.). The residual resin was collected by filtration and

washed with CH_2Cl_2 (3 × 5 mL), and the organic extracts were washed with water, dried over anhydrous $MgSO_4$ and concentrated to afford product **6** with 91–98% purity (determined by HPLC). The crude product was purified by flash chromatography for structural analysis. The compounds **6b**,[31] **6d**,[31] **6g**,[31] **6h**,[31] **6i**,[31] **6j**[31] and **6k**[32] are known, and our spectral data were in accordance with those in the literatures.

3-(4-Nitrophenyl)-5-(1-*E*-propenyl)isoxazole (6c). Yellow solid; mp = 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 8.8 Hz, 2 H, Ph-*H*), 7.96 (d, J = 8.8 Hz, 2 H, Ph-*H*), 7.64–7.60 (m, 1 H, C*H*=CHCH$_3$), 6.48 (d, J = 16.0 Hz, 1 H, CH = C*H*CH$_3$), 6.39 (s, 1 H, C*H*C = N), 1.93 (d, J = 6.4 Hz, 3 H, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9 (*C*-5), 160.0 (*C*-3), 148.5 (Ph-*C*), 135.4 (Ph-*C*), 134.1 (*C*H = CHCH$_3$), 127.3 (Ph-*C*), 124.8 (Ph-*C*), 117.3 (CH=*C*HCH$_3$), 99.8 (*C*-4), 19.2 (*C*H$_3$). IR (KBr): ν = 3048, 2975, 1662, 1559, 1525, 1430, 1383, 1350, 965, 825, 796, 692 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61, H, 4.38, N, 12.17; found: C, 62.73, H, 4.53, N, 12.25. MS (EI, 70 eV): m/z = 230 (M^+).

3-(2-Chlorophenyl)-5-(1-*E*-propenyl)isoxazole (6e). Pale yellow solid; mp = 68–69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.51 (m, 1 H, C*H*=CHCH$_3$), 7.16–7.13 (m, 2 H, Ph-*H*), 6.95–6.87 (m, 2 H, Ph-*H*), 6.47 (d, J = 15.6 Hz, 1 H, CH = C*H*CH$_3$), 6.34 (s, 1 H, C*H*C = N), 1.95 (d, J = 7.2 Hz, 3 H, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6 (*C*-5), 162.5 (*C*-3), 134.4 (*C*H = CHCH$_3$), 133.0 (Ph-*C*), 131.1 (Ph-*C*), 130.8 (Ph-*C*), 130.1 (Ph-*C*), 128.1 (Ph-*C*), 127.1 (Ph-*C*), 117.3 (CH=*C*HCH$_3$), 99.7 (*C*-4), 19.1 (*C*H$_3$). IR (KBr): ν = 3065, 2942, 1660, 1604, 1586, 1448, 1426, 1372, 971, 962, 836, 752 cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClNO$: C, 65.61, H, 4.59, N, 6.38; found: C, 65.74, H, 4.71, N, 6.47. MS (EI, 70 eV): m/z = 219 (M^+).

3-(*n*-Propyl)-5-(1-*E*-propenyl)isoxazole (6f). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.38 (m, 1 H, C*H*=CHCH$_3$), 6.47 (d, J = 16.0 Hz, 1 H, CH = C*H*CH$_3$), 6.33 (s, 1 H, C*H*C = N), 2.36 (t, J = 6.8 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$), 1.95 (d, J = 7.2 Hz, 3 H, C*H*$_3$), 1.67–1.64 (m, 2 H, CH$_2$*C*H$_2$CH$_3$), 1.11 (t, J = 7.2 Hz, 3 H, CH$_2$CH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5 (*C*-5), 157.2 (*C*-3), 133.6 (*C*H = CHCH$_3$), 115.9 (CH=*C*HCH$_3$), 98.5 (*C*-4), 29.9 (*C*H$_2$CH$_2$CH$_3$), 19.9 (CH$_2$*C*H$_2$CH$_3$), 19.0 (*C*H$_3$), 13.8 (CH$_2$CH$_2$*C*H$_3$). IR (neat): ν = 3045, 2971, 1655, 1450, 1386, 960, 832, 760, 696 cm^{-1}. Anal. Calcd for $C_9H_{13}NO$: C, 71.49, H, 8.67, N, 9.26; found: C, 71.36, H, 8.70, N, 9.35. MS (EI, 70 eV): m/z = 151 (M^+).

3-(4-Methoxyphenyl)-5-ethenylisoxazole (6l). Pale yellow solid; mp = 44–45 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.0 Hz, 2 H, Ph-*H*), 6.99 (d, J = 8.0 Hz, 2 H, Ph-*H*), 6.93 (s, 1 H, C*H*C = N), 6.75–6.67 (m, 1 H, C*H*=CH$_2$), 5.93 (d, J = 18.4 Hz, 1 H, *trans*-CH = C*H*$_2$), 5.43 (d, J = 11.2 Hz, 1 H, *cis*-CH = C*H*$_2$), 3.85 (s, 3 H, OC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2 (*C*-5), 161.4 (*C*-3), 158.7 (Ph-*C*), 148.9 (*C*H = CH$_2$), 128.1 (Ph-*C*), 121.2 (Ph-*C*), 117.1 (CH=*C*H$_2$), 114.3 (Ph-*C*), 104.4 (*C*-4), 55.3 (O*C*H$_3$). IR (KBr): ν = 3055, 1646, 1497, 1452, 1382, 1245, 991, 916, 765, 690 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63, H, 5.51, N, 9.96; found: C, 71.56, H, 5.75, N, 9.90. MS (EI, 70 eV): m/z = 201 (M^+).

SPOS of 3-Aryl-5-methylisoxazoles (7a–7d): general procedure

To a suspension of the swollen resin **4**, derived from the resin **2** (1.0 mmol) in THF-MeOH (1:1, 20 mL) was added anhydrous Na_2HPO_4 (4.0 mmol) and 1.5 g of pulverized 6% sodium amalgam (freshly prepared) at 0 °C, and the resulting reaction mixture was vigorously stirred for 2 h. The residual resin was collected by filtration and successively with THF, MeOH, H_2O and CH_2Cl_2 (2 × 5 mL of each), and the organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated to afford product **7** with 94–97% purity (determined by HPLC). Further purification was carried out through flash chromatography their structural analyses. Structures of compounds **7a**,[32] **7b**,[31] **7c**[31] and **7d**[31] have been already described, our characterization data were in accordance with those in the literatures.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

National Natural Science Foundation of China (No. 21762022), the Opening Foundation of National Research Center for Carbohydrate Synthesis (No. GJDTZX-KF-201414) and the Opening Foundation of Key Laboratory of Functional Small Organic Molecule of Ministry of Education (No. KLFS-KF-201411, KLFS-KF-201706) is gratefully acknowledged.

ORCID

Yang Pan http://orcid.org/0000-0002-9429-1296

References

[1] Lakhvich, F. A.; Koroleva, E. V.; Akhrem, A. A. Synthesis, Chemical Transformation, and Application of Isoxazole Derivatives in the Total Chemical Synthesis of Natural Compounds (Review). *Chem. Heterocycl. Compd.* **1989**, *25*, 359–372. DOI: 10.1007/BF00480746.

[2] Taylor, R. D.; MacCoss, M.; Lawson, D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845–5859. DOI: 10.1021/jm4017625.

[3] Pinho, e. M.; Teresa, M. V. D. Recent Advances on the Synthesis and Reactivity of Isoxazoles. *Curr. Org. Chem.* **2005**, *9*, 925–958. DOI: 10.2174/1385272054368420.

[4] Hu, F.; Szostak, M. Recent Developments in the Synthesis and Reactivity of Isoxazoles: Metal Catalysis and beyond. *Adv. Synth. Catal.* **2015**, *357*, 2583–2614. DOI: 10.1002/adsc.201500319.

[5] Singh, M. S.; Chowdhury, S.; Koley, S. Progress in 1,3-Dipolar Cycloadditions in the Recent Decade: An Update to Strategic Development towards the Arsenal of Organic Synthesis. *Tetrahedron* **2016**, *72*, 1603–1644. DOI: 10.1016/j.tet.2016.02.031.

[6] Morita, T.; Yugandar, S.; Fuse, S.; Nakamura, H. Recent Progresses in the Synthesis of Functionalized Isoxazoles.

Tetrahedron Lett. **2018**, *59*, 1159–1171. DOI: 10.1016/j.tetlet.2018.02.020.

[7] Caramella, P.; Grunanger, P. *1,3-Dipolar Cycloaddition Chemistry* (Ed.: Padwa, A.), Wiley, New York, NY, **1984**.

[8] Grünanger, P.; Vita-Finzi, P. Isoxazoles In *The Chemistry of Heterocyclic Compounds*, John Wiley: New York, **1991**.

[9] Heaney, F. Nitrile Oxide/Alkyne Cycloadditions–a Credible Platform for Synthesis of Bioinspired Molecules by Metal-Free Molecular Clicking. *Eur. J. Org. Chem.* **2012**, *2012*, 3043–3058. DOI: 10.1002/ejoc.201101823.

[10] Simoni, D.; Grisolia, G.; Giannini, G.; Roberti, M.; Rondanin, R.; Piccagli, L.; Baruchello, R.; Rossi, M.; Romagnoli, R.; Invidiata, F. P.; et al. Heterocyclic and Phenyl Double-Bond-Locked Combretastatin Analogues Possessing Potent Apoptosis-Inducing Activity in HL60 and in MDR Cell Lines. *J. Med. Chem.* **2005**, *48*, 723–736. DOI: 10.1021/jm049622b.

[11] Easton, C. J.; Heath, G. A.; Hughes, C. M. M.; Lee, C. K. Y.; Savage, G. P.; Simpson, G. W.; Tiekink, E. R. T.; Vuckovic, G. J.; Webster, R. D. Electrochemical and Yeast-Catalysed Ring-Opening of Isoxazoles in the Synthesis of Analogues of the Herbicide Grasp®. *J. Chem. Soc, Perkin Trans.* **2001**, *1*, 1168–1174. DOI: 10.1039/b008081k.

[12] Dadiboyena, S.; Xu, J. P.; Hamme, A. T. II. Isoxazoles from 1,1-Disubstituted Bromoalkenes. *Tetrahedron Lett.* **2007**, *48*, 1295–1298. DOI: 10.1016/j.tetlet.2006.12.005.

[13] Young, D. D.; Deiters, A. *Solid-Phase Organic Synthesis: Concepts, Strategies, and Applications*; Toy, P. H.; Lam, Y. Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, **2012**.

[14] Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, **1993**.

[15] Huang, W. Q.; Cheng, S. L.; Sun, W. M. 2-Polystyrylsulfonyl Ethanol Supports for the Solid-Phase Syntheses of Hydantoins and Ureas. *Tetrahedron Lett.* **2001**, *42*, 1973–1974. DOI: 10.1016/S0040-4039(01)00057-0.

[16] D'herde, J. N. P.; De Clercq, P. J. Carbon-Carbon Bond Formation on Solid Support. Application of the Classical Julia–Lythgoe Olefination. *Tetrahedron Lett.* **2003**, *44*, 6657–6659. DOI: 10.1016/S0040-4039(03)01637-X.

[17] Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Gong, Y.-D. Solid-Phase Synthesis of 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Derivatives via Selective, Reagent-Based Cyclization of Acyldithiocarbazate Resins. *J. Comb. Chem.* **2005**, *7*, 816–819. DOI: 10.1021/cc0500957.

[18] McAllister, L. A.; Turner, K. L.; Brand, S.; Stefaniak, M.; Procter, D. J. Solid Phase Approaches to *N*-Heterocycles Using a Sulfur Linker Cleaved by SmI_2. *J. Org. Chem.* **2006**, *71*, 6497–6507. DOI: 10.1021/jo060940n.

[19] Gao, Y.-N.; Lam, Y.-L. [3 + 2] Cycloaddition Reactions in the Solid-Phase Synthesis of 1,2,3-Triazoles. *Org. Lett.* **2006**, *8*, 3283–3285. DOI: 10.1021/ol0611494.

[20] Xie, J. W.; Sun, J.; Zhang, G. L.; Houghten, R. A.; Yu, Y. P. A Traceless Approach for the Solid-Phase Parallel Synthesis of Trisubstituted Oxindoles. *J. Comb. Chem.* **2007**, *9*, 566–568. DOI: 10.1021/cc070010x.

[21] Chang, Y.-F.; Jiang, Y.-R.; Cheng, W.-C. Traceless Sulfone Linker Cleavage Triggered by Ozonolysis: Solid-Phase Synthesis of Diverse α,β-Unsaturated Carbonyl Compounds. *Tetrahedron Lett.* **2008**, *49*, 543–547. DOI: 10.1016/j.tetlet.2007.11.064.

[22] Li, X.; Sheng, S.-R.; Su, H.-Y.; Liu, L.; Liu, X.-L. Polymer-Bound Phenylselenenylmethyl Sulfone as an Efficient Reagent for the Solid-Phase Synthesis of (*E*)-Vinyl Phenyl Selenides. *React. Funct. Polym.* **2014**, *77*, 18–22. DOI: 10.1016/j.reactfunctpolym.2014.02.001.

[23] He, A.-Y.; Sheng, S.-R.; Huang, Z.-Z.; Li, L.; Cai, M.-Z. Solid-Phase Organic Synthesis of 1,4-*N*-Vinyl- and 1,4-*N*-Allyl-Triazoles with the Sulfonate Linker. *J. Hetercyclic. Chem.* **2014**, *51*, 1862–1965. DOI: 10.1002/jhet.1857.

[24] Wang, Z.; Sheng, S.-R.; Wei, M.-H.; Liu, X.-L. Simple Synthesis of 1-Substituted-4-Vinyl-1,2,3-Triazoles Based on Polystyrene-Supported Sulfonyl Chloride. *Synth. Commun.* **2016**, *46*, 226–231. DOI: 10.1080/00397911.2015.1130228.

[25] Wu, G.-J.; Sheng, S.-R.; Li, D.; Xu, L.-F.; Huang, Z.-Z. Polymer-Supported Vinyl Sulfone as an Efficient Reagent for the Synthesis of 3-Monosubstituted Isoxazoles. *Synth. Commun.* **2013**, *43*, 3034–3043. 18 DOI: 10.1080/00397911.2012.7627.

[26] Undeela, S.; Thadkapally, S.; Nanubolu, J. B.; Singarapu, K. K.; Menon, R. S. Catalyst-Controlled Divergence in Cycloisomerisation Reactions of *N*-propargyl-*N*-Vinyl Sulfonamides: Gold-Catalysed Synthesis of 2-Sulfonylmethyl Pyrroles and Dihydropyridines. *Chem. Commun.* **2015**, *51*, 13748–13751. DOI: 10.1039/C5CC04871K.

[27] Martín, T.; Rodríguez, C. M.; Martín, V. S. A New Approach to Functionalized Cyclobutanes: Stereoselective Synthesis of the Enantiomers of Grandisol and Fraganol. *Tetrahedron: Asymmetry* **1995**, *6*, 1151–1164. DOI: 10.1016/0957-4166(95)00141-B.

[28] Nájera, C.; Yus, M. Desulfonylation Reactions: Recent Developments. *Tetrahedron* **1999**, *55*, 10547–10658. DOI: 10.1016/S0040-4020(99)00600-6.

[29] Kim, S. H.; Jin, Z. D.; Ma, S.; Fuchs, P. L. Conversion of Vinyl Sulfones to Regiospecifically Functionalized Trisubstituted Olefins. *Tetrahedron Lett.* **1995**, *36*, 4013–4014. DOI: 10.1016/0040-4039(95)00701-D.

[30] Dubrovskiy, A. V.; Larock, R. C. Synthesis of Benzisoxazoles by the [3 + 2] Cycloaddition of *in Situ* Generated Nitrile Oxides and Arynes. *Org. Lett.* **2010**, *12*, 1180–1183. DOI: 10.1021/ol902921s.

[31] Xu, W. M.; Tang, E.; Huang, X. Preparation of Isoxazol(in)yl Substituted Selenides and Their Further Deselenenylation Reaction to Synthesize 3,5-Disubstituted Isoxazoles. *Tetrahedron* **2005**, *61*, 501–506. DOI: 10.1016/j.tet.2004.10.071.

[32] Hwang, S. H.; Kurth, M. J. 1,3-Dipolar Cycloaddition of Nitrile Oxides to 1-Phenylsulfonyl-1,3-Butadienes: synthesis of 3-(4,5-Dihydroisoxazol-5-yl)Pyrroles. *Tetrahedron Lett.* **2002**, *43*, 53–56. DOI: 10.1016/S0040-4039(01)02069-X.