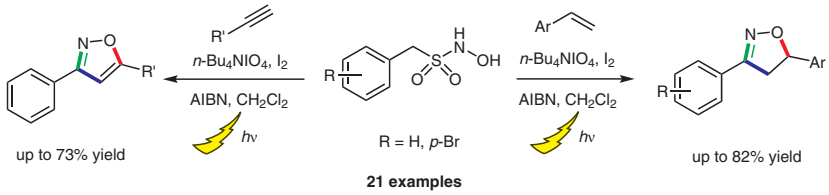
Synthesis J. Cheng et al. Paper

Synthesis of Isoxazolines and Isoxazoles via Metal-Free Desulfitative Cyclization

Jiaxin Cheng[a]
Ze Yang[a]
Yuansheng Li[a]
Yulan Xi[a]
Qiu Sun*[b]
Ling He*[a]

[a] Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu, Sichuan, 610041, P. R. of China
lhe2001@sina.com
[b] West China Medical Center of Sichuan University, Chengdu, Sichuan, 610041, P. R. of China
sunqiu@scu.edu.cn



Received: 03.02.2018
Accepted after revision: 09.03.2018
Published online: 14.05.2018
DOI: 10.1055/s-0037-1609480; Art ID: ss-2018-f0062-op

Abstract A novel, one-pot reaction for the synthesis of isoxazolines and isoxazoles is developed via a cascade process under metal-free conditions. The approach involves the formation of intramolecular C–N and C–O bonds and intermolecular C–C bonds from aromatic alkenes or alkynes and *N*-hydroxysulfonamides using hypervalent iodine(VII) and iodine as the oxidant. Activation of C–H and C–C bonds/construction of C–O bonds/elimination of SO_2/C–N bond formation is achieved in sequence in the reaction system.

Key words isoxazolines, isoxazoles, desulfurization, radical cyclization, tandem reaction

Compounds containing the isoxazoline and isoxazole moiety demonstrate a wide variety of biological activities and have been developed as human leukocyte elastase inhibitors,[1] herbicides,[2] and insecticides.[3] These compounds are also important synthetic intermediates for a variety of biological compounds[4] and serve as the building blocks or key structural units for the construction of asymmetric ligands in organic synthesis. Therefore, many methods for the synthesis of the isoxazoline and isoxazole skeleton have been developed. A broad literature survey revealed that isoxazolines and isoxazoles are usually prepared from oximes or nitro compounds.[5–8] These synthetic methods are shown in Figure 1. Among these methods, the [3+2] dipolar cycloaddition of olefins and nitrile oxides has historically been recognized as the most common approach.[9] In addition, both the reaction of α,β-unsaturated ketones with hydroxylamine[10] and the reaction of alkenes with ketones[11,12] resulted in the formation of isoxazolines. Isoxazolines have also been synthesized via the intramolecular cyclization of oximes[13] and hydroxylamines.[14] Alkynyl oxime ethers underwent a reaction sequence involving cyclization and subsequent Claisen-type rearrangement to afford trisubstituted isoxazoles.[15]

However, there is still a great need for new synthetic methods, particularly a simplified method with fewer reaction steps and a more easily available source for the starting material. The direct insertion of nitrogen groups into hydrocarbons, without relying on the prefunctionalization of simple compounds to the corresponding organic halides, has become an attractive synthetic strategy as an atom-economic and environmentally benign method for C–N bond formation. Although an approach based on nitrenoid transfer to C–H bonds by using Rh, Ru or Pd catalysts[16] has been investigated extensively, the oxidative amination of alkenes or (hetero)arenes has been explored only recently.[17,18] As part of our efforts to investigate the formation of

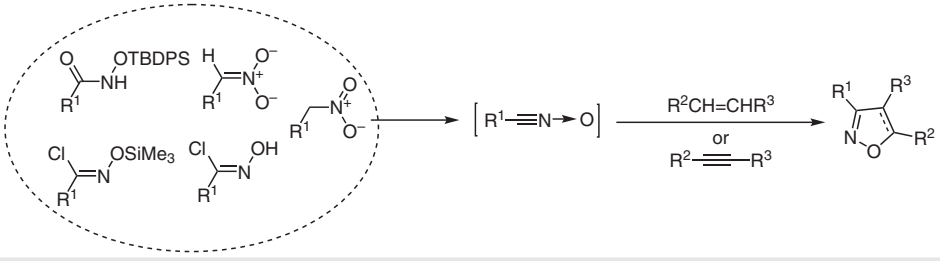
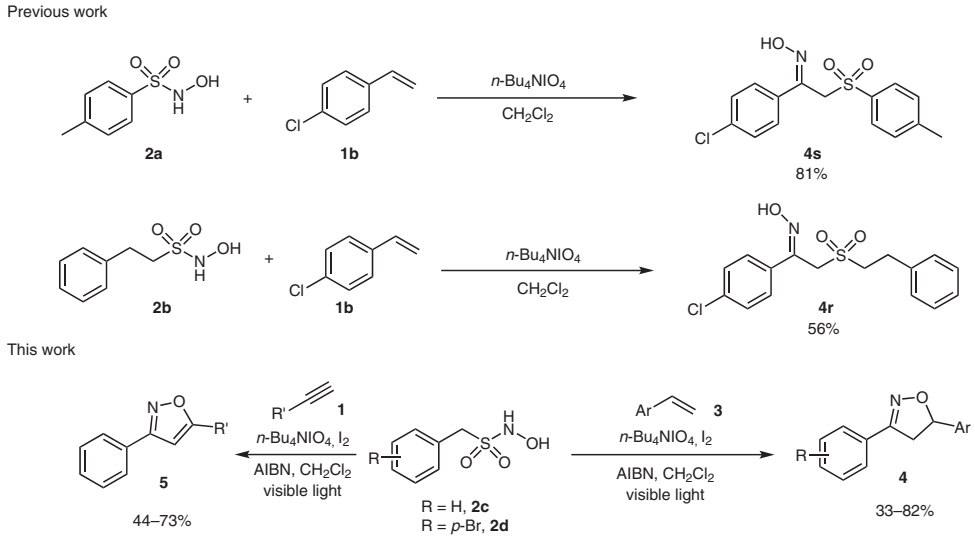


Figure 1 Synthesis of isoxazolines

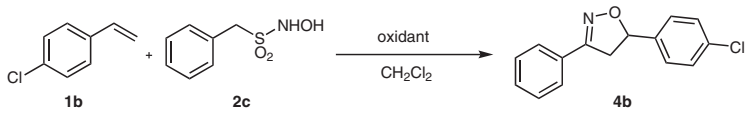


Scheme 1 Effect of the structure of the *N*-hydroxysulfonamide on the outcome of the reaction. *Reaction conditions*: **1b** (0.1 mmol), **2c** (0.1 mmol), *n*-Bu_4NIO_4 (0.1 mmol), CH_2Cl_2, 15 h, reflux.

C–N bonds,[19] we found that *N*-hydroxysulfonamides were useful reagents for the preparation of sulfonylethanone oximes from aromatic alkenes using *n*-Bu_4NIO_4 as the oxidant (Scheme 1).[20] In continuation of our exploration of *N*-hydroxysulfonamides as a nitrogen source, we obtained an isoxazoline as an unexpected product from *N*-hydroxy-1-phenylmethanesulfonamide (**2c**) (Scheme 1). The difference in the reaction of *N*-hydroxy-1-phenylmethanesulfonamide (**2c**) relies on the activity of the allyl group and the stability of the allyl free radical. Herein, we report our preliminary results on this subject. The reaction of *N*-hydroxy-2-phenylethanesulfonamide (**2b**) with 1-chloro-4-vinylbenzene (**1b**) using *n*-Bu_4NIO_4 as the oxidant gave the α-sulfonylethanone oxime product **4r** in 56% yield. We also found that the reaction of *N*-hydroxy-4-methylbenzenesulfonamide (**2a**) with 1-chloro-4-vinylbenzene (**1b**) gave 1-*p*-chlorophenyl-2-tosylethanone oxime (**4s**) in a yield of 81%. However, only the reaction of *N*-hydroxy-1-phenylmethanesulfonamide (**2c**) with arylalkenes **3** under identical conditions led to the formation of isoxazolines **4**. Additionally, isoxazole derivatives were obtained under the same conditions when using alkynes **1** as the substrates.

The reaction of *N*-hydroxy-1-phenylmethanesulfonamide (**2c**) with 1-chloro-4-vinylbenzene (**1b**) was used to optimize the reaction conditions. First, we tested a variety of metal salts in the reaction, including Ru(TTP)CO, copper salts, iron salts, palladium salts, $ZnCl_2$ and $Rh_2(OAc)_4$, in addition to additives such as AcOH, Et_3N, pyridine, molecular sieves and activated carbon. The results showed that neither metal salts nor additives had an effect on the reaction. Solvent effects on the reaction were also investigated and indicated that dichloromethane was the most effective for the reaction; however, the reaction barely proceeded in THF, toluene, acetone, DME, 1,4-dioxane and cyclohexane. Reactions performed in $CHCl_3$, CCl_4 and MeCN resulted in the formation of trace amounts of products at approximately 40 °C. The temperature also affected the reaction and did not yield the corresponding products at lower temperatures, even after reaction times of more than 30 hours. Increasing the temperature (83 °C in 1,2-dichloroethane) decreased the reaction time from 18 hours to 3 hours with a similar yield (Table 1, entry 3). Next, we used oxidants other than *n*-Bu_4NIO_4 (Table 1, entries 4–7) and found that none of these were successful in the reaction. It is known that 2,2′-azobis(isobutyronitrile) (AIBN) is widely used in atom transfer radical polymerization reactions as an azo free-radical initiator.[21] In order to realize control of the radical polymerization reaction, AIBN was used as a free-radical initiator to improve the reaction yield under visible-light irradiation in this work (Table 1, entries 8,10–12). At the same time, we found that iodine was beneficial in promoting the reaction. Perhaps the color of iodine makes the reaction mixture absorb visible light more easily. Next, *n*-Bu_4NIO_4 and iodine were simultaneously used as oxidants in order to increase the oxidizing ability, and it was found that the reaction time was shortened and that the yield was increased (Table 1, entry 9–11).

Table 1 Optimization of the Reaction Conditions[a]



1b 2c 4b

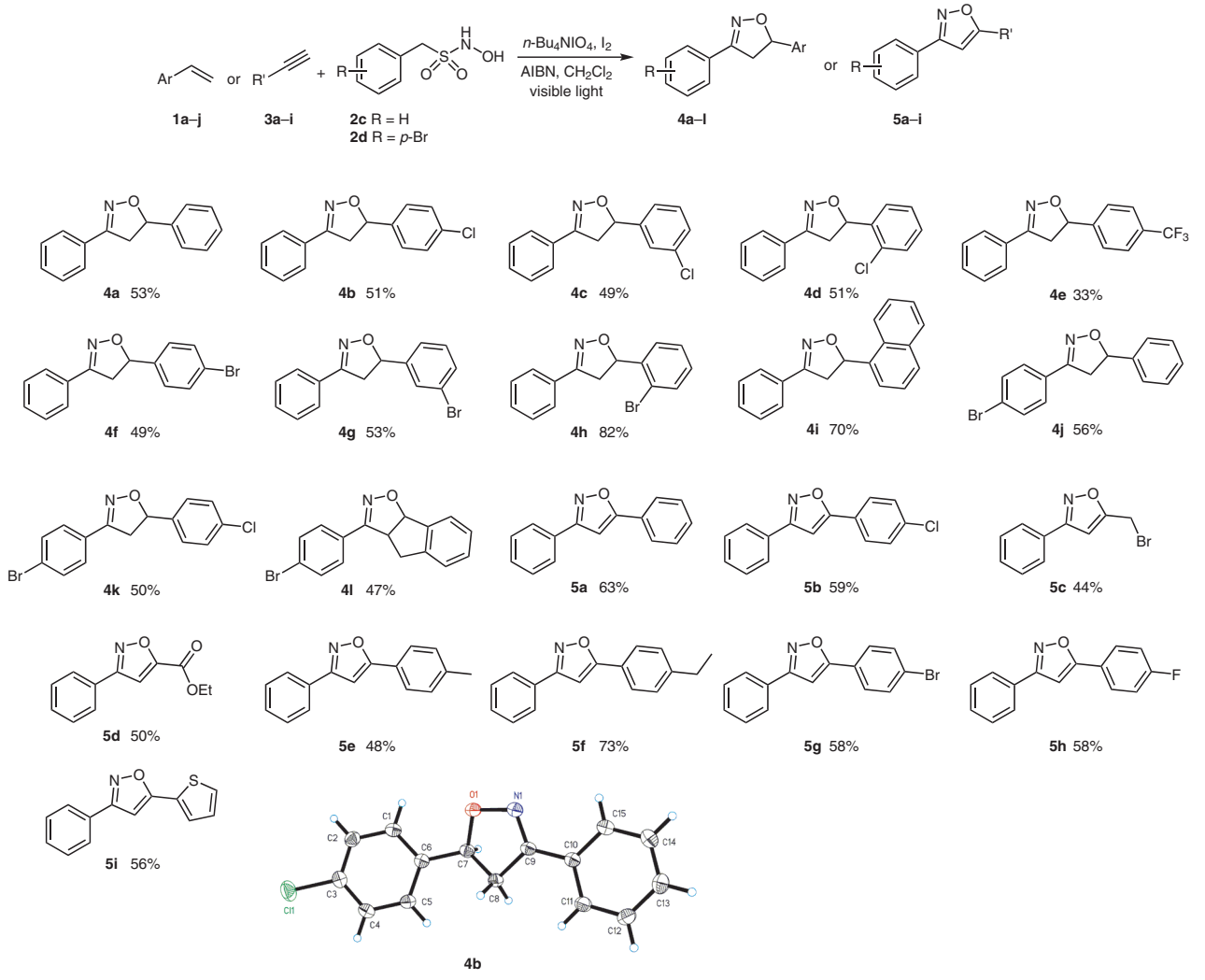
Entry	Oxidant	Temp	Time	Yield
1	*n*-Bu_4NIO_4	40 °C	15 h	22%
2	*n*-Bu_4NIO_4	r.t.	15 h	trace
3[b]	*n*-Bu_4NIO_4	83 °C	3 h	18%
4	*n*-Bu_4NClO_4	40 °C	18 h	0
5	$PhI(OAc)_2$	40 °C	18 h	0
6	PhI(OH)OTs	40 °C	18 h	0
7	PhI=O	40 °C	18 h	0
8	*n*-Bu_4NIO_4/AIBN	40 °C	15 h	24%
9[c]	*n*-Bu_4NIO_4/I_2	25 °C	10 h	34%
10[d]	*n*-Bu_4NIO_4/I_2/AIBN	25 °C	10 h	51%
11[e]	I_2/AIBN	25 °C	10 h	45%
12[f]	*n*-Bu_4NIO_4/AIBN	25 °C	10 h	25%

[a] Reaction conditions: **1b** (0.1 mmol), **2c** (0.1 mmol), oxidant (0.1 mmol), CH_2Cl_2.
[b] Reaction in 1,2-dichloroethane.
[c] Reaction conditions: **1b** (excess), **2c** (0.1 mmol), *n*-Bu_4NIO_4 (0.05 mmol), I_2 (0.05 mmol), CH_2Cl_2, 10 h, visible-light irradiation.
[d] Reaction conditions: **1b** (excess), **2c** (0.1 mmol), *n*-Bu_4NIO_4 (0.1 mmol), I_2 (0.05 mmol), AIBN (0.01 mmol), CH_2Cl_2, 10 h, visible-light irradiation.
[e] Reaction conditions: **1b** (excess), **2c** (0.1 mmol), I_2 (0.1 mmol), AIBN (0.01 mmol), CH_2Cl_2, 10 h, visible-light irradiation.
[f] Reaction conditions: **1b** (excess), **2c** (0.1 mmol), *n*-Bu_4NIO_4 (0.1 mmol), AIBN (0.01 mmol), CH_2Cl_2, 10 h, visible-light irradiation.

Furthermore, we examined the influence of the substrate and its substituent (Scheme 2). The reactions of olefins with electron-withdrawing substituents resulted in moderate yields; however, styrenes with electron-donating groups gave only trace amounts of the corresponding isoxazoline products. The negative result with cyclopentene implies that it is important for the reaction that the double bond conjugates directly with the aromatic ring. Meanwhile, the reaction was also applied to 1-vinylnaphthalene and phenylacetylene derivatives (Scheme 2). Under the optimized conditions, the reaction was extended to a variety of acetylenes to give the corresponding isoxazoles in 44–73% yield. We speculate that only moderate yields are obtained because of the possibility that the reactions undergo multiple reaction pathways, and also due to the oxidizing defects and deficiencies of the oxidants used.[20]

To gain further insight into the reaction mechanism, several mechanistic experiments were performed (Scheme 3). Initially, the possibility of benzaldehyde oxime as an intermediate could be ruled out, because benzaldehyde oxime reacted directly with phenylacetylene to form 3,5-diphenylisoxazole and 3,4-diphenylisoxazole in a molar ratio of about 6.5:1, while only 3,5-diphenylisoxazole was detected in the reaction of *N*-hydroxy-1-phenylmethanesulfonamide with phenylacetylene when using *n*-Bu_4NIO_4 and iodine as the oxidant and CH_2Cl_2 as the solvent (Scheme 3, b). Secondly, formation of 3-(4-chlorophenyl)-5-phenyl-4,5-dihydroisoxazole via benzyl radical addition to the alkene and subsequently with a NO free radical was not observed, which implies that the main reaction pathway was not that shown: homolysis of the presumed *N*-sulfonylnitroso intermediate and loss of SO_2 leads to a benzylic radical, which recombines with a NO free radical, ultimately yielding an oxime. The latter is then oxidized to a nitrile oxide by *n*-Bu_4NIO_4, and the nitrile oxide combines with 4-chlorostyrene to afford the product (Scheme 3, a). Furthermore, the reaction of *p*-methoxybenzeneacetylene with *N*-hydroxy-1-phenylmethanesulfonamide under identical conditions yielded *p*-methoxy-α-iodoacetophenone, but only trace amounts of the isoxazole. This result indicates that the main reaction pathway was also not the α-iodoacetophenone pathway (Scheme 3, c).

The suggested mechanism for the reaction based on the trapping of the intermediates and related literature reports[13,21,22] is depicted in Scheme 4. Initially, the *N*-hydroxysulfonamide is oxidized by *n*-Bu_4NIO_4 to give an *N*-sulfonylnitroso radical intermediate. Addition of the *N*-sulfonylnitroso radical intermediate to either 4-chlorostyrene or 4-chlorophenylacetylene yields the corresponding radical intermediate, which is further attacked by its own nitroso group. Finally, the loss of SO_2 ultimately leads to the formation of the isoxazolines and isoxazoles. Two effective radical scavengers, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) both halted



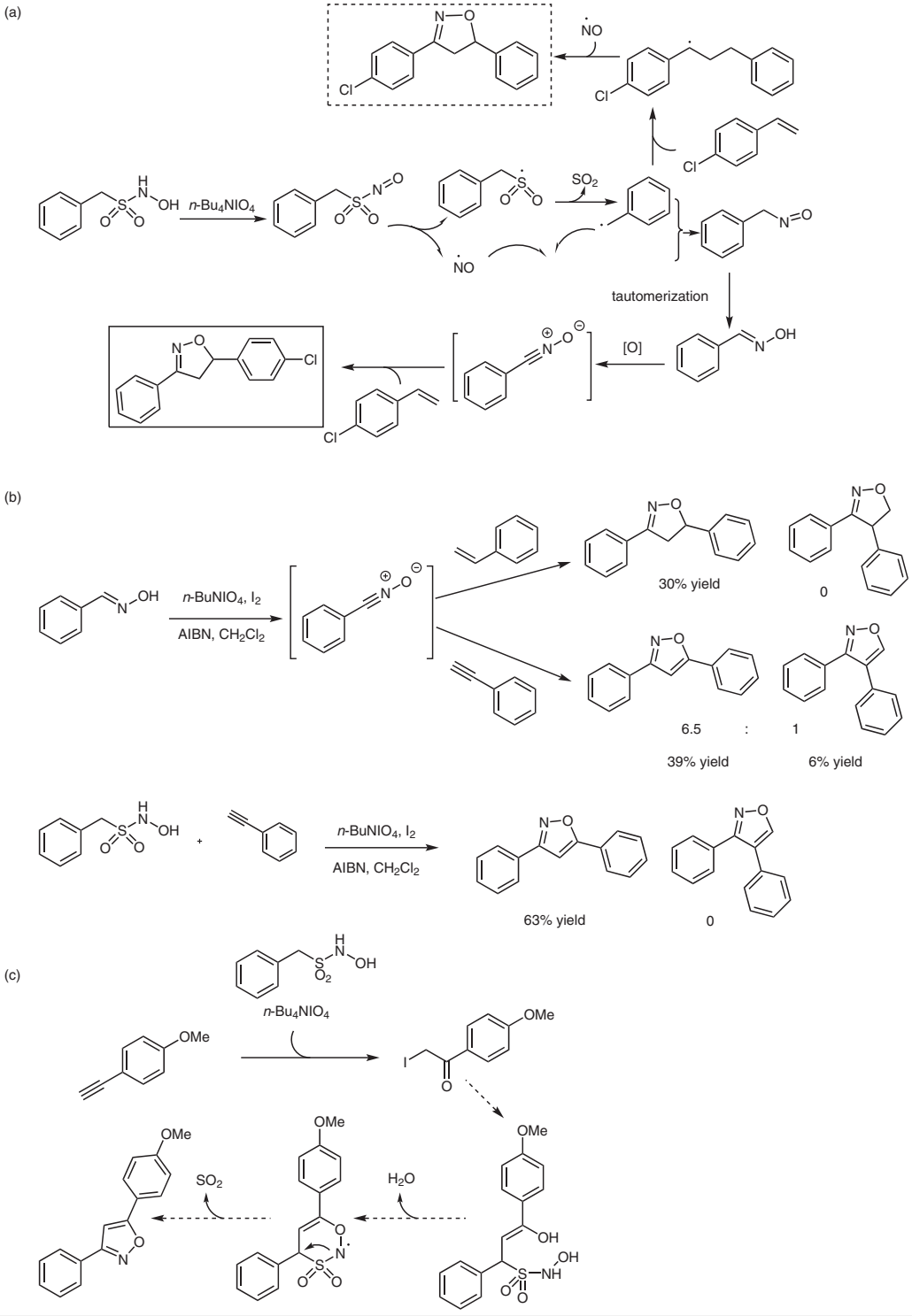
Scheme 2 Formation of isoxazolines **4** and isoxazoles **5**. *N*-hydroxy-1-phenylmethanesulfonamide **2**, *n*-Bu_4NIO_4, I_2, AIBN and CH_2Cl_2 were added to a flask and the resulting mixture was stirred under visible-light irradiation for about 10 h at r.t. Excess alkene (at least 3 equiv) was used. Molar ratio of alkyne/*N*-hydroxysulfonamide/*n*-Bu_4NIO_4/I_2/AIBN = 1.0:1.0:1.0:0.50:1.

the reactions, and no product was formed. Meanwhile, the radical-trapping products, 2,2,6,6-tetramethyl-1-[(nitrososulfonyl)(phenyl)methoxy]piperidine and 3,5-diphenyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]isoxazolidine were detected in the reaction by LCMS. Based on these results, we speculate that the reaction may involve a radical reaction process.

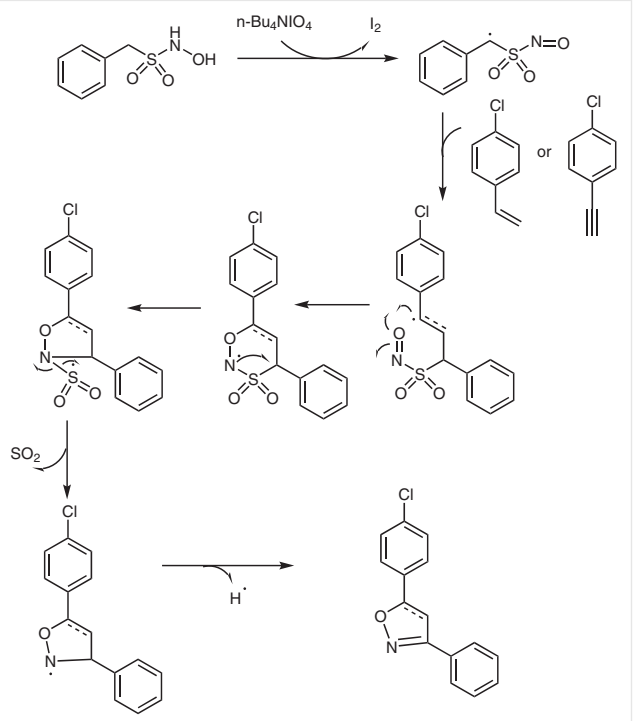
In summary, we have developed a new, one-pot procedure for the formation of isoxazolines and isoxazoles by a cascade of intermolecular C–C and intramolecular C–N and C–O bond-forming reactions under mild conditions. A variety of isoxazolines and isoxazoles have been prepared in yields of 33–82% and 44–73%, respectively. The reaction requires *n*-Bu_4NIO_4 and I_2 as the oxidant, AIBN as a free-radical initiator, but no metal salt catalysts or other additives. Further efforts are now underway to expand the scope of the substrates.

All reactions were performed under a N_2 atmosphere. Anhydrous solvents were purified according to standard procedures. Silica gel F_{254} plates were used for thin-layer chromatography (TLC) in which the spots were examined under UV light at 254 nm and then developed using iodine vapor. Flash chromatography was performed on silica gel H (300~400 mesh). Melting points were obtained using a YRT-3 melting Point instrument (Tianjin Tianda Fat Co., Ltd.) temperature uncorrected. IR spectra were recorded using a VECTOR 22 infrared spectrometer. NMR spectra were recorded on Varian Mercury spectrometers (400 MHz and 600 MHz), using $CDCl_3$ or DMSO-d_6 as the solvent. LRMS/HRMS were recorded on a Bruker Daltonics Data Analysis 3.4 mass spectrometer. High-performance liquid chromatography (HPLC)

was performed with a YoungLin instrument SP930D, equipped with Dikma C18 columns and using methanol as the eluent. X-ray data were collected on a Bruker APEX-II instrument, equipped with a CCD area detector, using Mo/Kα radiation. The structures were solved by direct methods using SHELXL-97.



Scheme 3 Mechanistic studies



Scheme 4 Proposed mechanism for the formation of isoxazolines and isoxazoles

Isoxazolines and Isoxazoles; General Procedure

N-Hydroxy-1-phenylmethanesulfonamide (0.2 mmol), *n*-Bu_4NIO_4 (0.2 mmol), I_2 (0.1 mmol) and AIBN (10%) were added to a 25 mL round-bottom flask. A solution of the alkene (excess) or alkyne (0.2 mmol) in anhydrous CH_2Cl_2 (2 mL) was injected via a syringe and the mixture was stirred under visible-light irradiation for 10 h at r.t. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous NaCl (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by column chromatography on silica gel H with petroleum ether/ethyl acetate (20:1) as the eluent to give the pure product.

3,5-Diphenyl-4,5-dihydroisoxazole (4a)

Yield: 24 mg (53%); white solid; mp 75–76 °C (Lit.[23] 73–74 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.42 (m, 10 H, Ph-H), 5.77–5.73 (m, 1 H, 5-H), 3.83–3.76 (m, 1 H, 4-H), 3.39–3.32 (m, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 140.9, 130.1, 129.4, 128.7, 128.2, 126.7, 125.9, 82.5, 43.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}NO$: 224.1070; found: 224.1068.

5-(4-Chlorophenyl)-3-phenyl-4,5-dihydroisoxazole (4b)

Yield: 26 mg (51%); pale yellow solid; mp 111–112 °C (Lit.[24] 111–112 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.73–7.70 (m, 2 H, Ph-H), 7.48–7.42 (m, 7 H, Ph-H), 5.78–5.74 (m, 1 H, 5-H), 3.93–3.86 (m, 1 H, 4-H), 3.43–3.37 (m, 1 H, 4-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.7, 140.2, 132.8, 130.4, 129.3, 129.0, 128.8, 128.3, 127.0, 126.9, 81.4, 42.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{12}NOClNa$: 280.0500; found: 280.0492.

5-(3-Chlorophenyl)-3-phenyl-4,5-dihydroisoxazole (4c)

Yield: 25 mg (49%); white solid; mp 82–85 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.67 (m, 2 H, Ph-H), 7.42–7.39 (m, 4 H, Ph-H), 7.31–7.28 (m, 3 H, Ph-H), 5.74–5.69 (m, 1 H, 5-H), 3.84–3.77 (m, 1 H, 4-H), 3.35–3.29 (m, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 138.2, 129.8, 125.4, 125.2, 124.2, 123.9, 123.4, 121.9, 121.1, 119.0, 76.7, 38.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}NOCl$: 258.0679; found: 258.0680.

5-(2-Chlorophenyl)-3-phenyl-4,5-dihydroisoxazole (4d)

Yield: 26 mg (51%); white solid; mp 76–78 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 2 H, Ph-H), 7.43–7.39 (m, 4 H, Ph-H), 7.31–7.28 (m, 3 H, Ph-H), 5.74–5.69 (m, 1 H, 5-H), 3.84–3.77 (m, 1 H, 4-H), 3.35–3.29 (m, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 138.2, 129.8, 125.4, 125.2, 124.2, 123.9, 123.4, 121.9, 121.1, 119.0, 76.7, 38.4.

LRMS (ESI): *m*/*z* = 258 [M + H]$^+$.

3-Phenyl-5-[4-(trifluoromethyl)phenyl]-4,5-dihydroisoxazole (4e)

Yield: 19 mg (33%); white solid; mp 142–143 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.68 (m, 2 H, Ph-H), 7.64 (d, *J* = 8.0 Hz, 2 H, Ph-H), 7.52 (d, *J* = 8.0 Hz, 2 H, Ph-H), 7.43–7.42 (m, 3 H, Ph-H), 5.83–5.78 (m, 1 H, 5-H), 3.89–3.82 (m, 1 H, 4-H), 3.35–3.29 (m, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 145.0, 130.4, 129.0, 128.8, 126.8, 126.0, 125.8, 81.6, 43.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{12}F_3NNaO$: 314.0763; found: 314.0753.

5-(4-Bromophenyl)-3-phenyl-4,5-dihydroisoxazole (4f)

Yield: 29 mg (49%); white solid; mp 130–131 °C (Lit.[25] 130.5–131.5 °C).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.70–7.68 (m, 2 H, Ph-H), 7.51 (d, *J* = 8.4 Hz, 2 H, Ph-H), 7.43–7.42 (m, 3 H, Ph-H), 7.28 (d, *J* = 8.4 Hz, 2 H, Ph-H), 5.73–5.70 (m, 1 H, 5-H), 3.82–3.78 (m, 1 H, 4-H), 3.32–3.28 (m, 1 H, 4-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.0, 140.0, 131.9, 130.3, 129.2, 128.8, 127.6, 126.7, 122.1, 81.8, 43.2.

LRMS (ESI): *m*/*z* = 302 [M + H]$^+$.

5-(3-Bromophenyl)-3-phenyl-4,5-dihydroisoxazole (4g)

Yield: 32 mg (53%); white solid; mp 97–98 °C (Lit.[26] 97.5–98.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.68 (m, 2 H, Ph-H), 7.55 (s, 1 H, Ph-H), 7.46–7.40 (m, 4 H, Ph-H), 7.33 (d, *J* = 7.6 Hz, 1 H, Ph-H), 7.25–7.23 (m, 1 H, Ph-H), 5.74–5.69 (m, 1 H, 5-H), 3.84–3.77 (m, 1 H, 4-H), 3.35–3.29 (m, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 143.3, 131.2, 130.3, 130.3, 129.1, 128.8, 126.7, 124.4, 122.8, 81.5, 43.2.

LRMS (ESI): *m*/*z* = 302 [M + H]$^+$.

5-(2-Bromophenyl)-3-phenyl-4,5-dihydroisoxazole (4h)

Yield: 49 mg (82%); white solid; mp 66–67 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 2 H, Ph-H), 7.59–7.55 (m, 2 H, Ph-H), 7.41–7.35 (m, 5 H, Ph-H), 6.02–5.98 (m, 1 H, 5-H), 4.01–3.94 (m, 1 H, 4-H), 3.24–3.18 (m, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 140.6, 132.7, 130.2, 129.3, 129.1, 128.7, 127.8, 126.8, 126.7, 120.8, 81.4, 42.9.

LRMS (ESI): *m*/*z* = 302 $[M + H]^+$.

5-(Naphthalen-1-yl)-3-phenyl-4,5-dihydroisoxazole (4i)

Yield: 38 mg (70%); white solid; mp 62–63 °C(Lit.[27] 62.5–63.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.90 (m, 2 H, Ph-H), 7.82 (d, *J* = 4.0 Hz, 1 H, Ph-H), 7.71–7.68 (m, 3 H, Ph-H), 7.58–7.46 (m, 3 H, Ph-H), 7.40–7.39 (m, 3 H, Ph-H), 6.45–6.40 (m, 1 H, 5-H), 4.03–3.96 (m, 1 H, 4-H), 3.43–3.37 (m, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 136.1, 133.9, 130.1, 129.6, 129.4, 129.1, 128.7, 128.5, 126.7, 126.3, 125.7, 125.5, 122.9, 122.9, 80.2, 42.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{15}NNaO$: 296.1046; found: 296.1040.

3-(4-Bromophenyl)-5-phenyl-4,5-dihydroisoxazole (4j)

Yield: 33 mg (56%); pale yellow solid; mp 140–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 4 H, Ph-H), 7.39–7.32 (m, 5 H, Ph-H), 5.78–5.73 (m, 1 H, 5-H), 3.79–3.72 (m, 1 H, 4-H), 3.35–3.28 (m, 1 H, 4-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.2, 140.6, 131.9, 128.8, 128.35, 128.29, 128.1, 125.8, 124.4, 82.8, 42.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}BrNO$: 302.0175; found: 302.0181.

3-(4-Bromophenyl)-5-(4-chlorophenyl)-4,5-dihydroisoxazole (4k)

Yield: 33 mg (50%); white solid; mp 119–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 4 H, Ph-H), 7.34 (q, *J* = 15.8 Hz, 4 H, Ph-H), 5.75–5.71 (m, 1 H, 5-H), 3.80–3.73 (m, 1 H, 4-H), 3.30–3.24 (m, 1 H, 4-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.2, 139.1, 134.1, 132.0, 129.0, 128.1, 127.2, 124.5, 82.0, 42.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}BrClNO$: 335.9785; found: 335.9792.

3-(4-Bromophenyl)-3a,8b-dihydro-4*H*-indeno[2,1-*d*]isoxazole (4l)

Yield: 29 mg (47%); pale yellow solid; mp 152–155 °C.

IR (KBr): 2955 (w), 2921(s), 2851 (w), 1244 (w), 1586 (w, C=N) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (s, 5 H, Ph-H), 7.33–7.31 (m, 2 H, Ph-H), 7.22–7.20 (m, 1 H, Ph-H), 6.24 (d, *J* = 9.6 Hz, 1 H, 5-H), 4.52–4.49 (m, 1 H, 4-H), 3.50–3.46 (m, 1 H, CH_2CH-4), 3.21–3.18 (m, 1 H, CH_2CH-4).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.8, 140.5, 140.4, 132.0, 129.7, 128.5, 127.7, 125.8, 124.8, 124.1, 89.8, 31.9, 29.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}BrNO$: 314.0175; found: 314.0185.

3,5-Diphenylisoxazole (5a)

Yield: 27 mg (63%); white solid; mp 140 °C (Lit.[28] 141–142 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.85 (m, 4 H, Ph-H), 7.51–7.46 (m, 6 H, Ph-H), 6.84 (s, 1 H, 4-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.4, 163.0, 130.2, 130.0, 129.2, 128.9, 127.5, 126.9, 125.8, 97.6.

LRMS (ESI): *m*/*z* = 222.2 $[M + H]^+$.

5-(4-Chlorophenyl)-3-phenylisoxazole (5b)

Yield: 30 mg (59%); pale yellow solid; mp 178–179 °C (Lit.[29] 178–179 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.86 (m, 2 H, Ph-H), 7.80–7.77 (m, 2 H, Ph-H), 7.55–7.49 (m, 5 H, Ph-H), 6.83 (s, 1 H, 4-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.4, 162.9, 130.2, 130.0, 129.1, 129.0, 128.9, 127.4, 126.8, 125.8.

LRMS (ESI): *m*/*z* = 255.9 $[M + H]^+$.

5-(Bromomethyl)-3-phenylisoxazole (5c)

Yield: 20 mg (44%); white solid; mp 85–86 °C (Lit.[30] 85–86 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.78 (m, 2 H, Ph-H), 7.47–7.45 (m, 3 H, Ph-H), 6.64 (s, 1 H, 4-H), 4.52 (s, 2 H, CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 146.3, 136.0, 129.0, 128.7, 128.5, 128.1, 103.1, 20.9.

LRMS (ESI): *m*/*z* = 237.8 $[M + H]^+$.

Ethyl 3-Phenylisoxazole-5-carboxylate (5d)

Yield: 21 mg (50%); white solid; mp 47 °C (Lit.[31] 45–46 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.843–7.839 (m, 2 H, Ph-H), 7.60–7.62 (s, 1 H, 4-H), 7.52–7.48 (m, 3 H, Ph-H), 4.47 (q, *J* = 7.2 Hz, 2 H, CH_2OCO) 1.38 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.1, 162.8, 156.7, 130.4, 129.3, 128.9, 126.7, 107.2, 62.2, 14.0.

LRMS (ESI): *m*/*z* = 217.9 $[M + H]^+$.

3-Phenyl-5-(*p*-tolyl)isoxazole (5e)

Yield: 22 mg (48%); white solid; mp 138–138.5 °C (Lit.[32] 137 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.92 (m, 4 H, Ph-H), 7.31–7.27 (m, 5 H, Ph-H), 6.51 (s, 1 H, 3-H), 2.44 (s, 3 H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 187.9, 145.4, 129.6, 129.6, 128.5, 128.5, 128.3, 128.1, 127.6, 126.8, 125.9, 125.8, 125.7, 96.8, 21.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{14}NO$: 236.1070; found: 236.1070.

5-(4-Ethylphenyl)-3-phenylisoxazole (5f)

Yield: 36 mg (73%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.86 (m, 4 H, Ph-H), 7.36–7.28 (m, 5 H, Ph-H), 6.50 (s, 1 H, 3-H), 2.73 (q, *J* = 7.6 Hz, 2 H, CH_2CH_3), 1.26 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 188.0, 175.1, 151.5, 129.7, 128.9, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 126.8, 126.0, 96.9, 29.0, 15.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{16}NO$: 250.1226; found: 250.1226.

5-(4-Bromophenyl)-3-phenylisoxazole (5g)

Yield: 34 mg (58%); white solid; mp 178–179 °C (Lit.[33] 180.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, 2 H, *J* = 8.4, Ph-H), 7.90–7.87 (m, 2 H,Ph-H), 7.85–7.64 (m, 2 H, Ph-H), 7.62 (d, *J* = 8.4, 2 H, Ph-H), 7.48–7.48 (m, 1 H, Ph-H), 6.42 (s, 1 H, 3-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.2, 163.0, 132.3, 130.9, 130.1, 129.4, 128.9, 127.2, 126.7, 97.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}ONBr$: 300.0019; found: 300.0019.

5-(4-Fluorophenyl)-3-phenylisoxazole (5h)

Yield: 27 mg (58%); white solid; mp 130–132 °C (Lit.[34] 131 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.07 (m, 2 H, Ph-H), 7.88–7.83 (m, 2 H, Ph-H), 7.49–748 (m, 2 H, Ph-H), 7.18–7.14 (m, 3 H, Ph-H), 6.45 (s, 1 H, 3-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 186.8, 166.9, 165.2, 132.4, 132.3, 130.1, 128.9, 126.8, 116.3, 116.2, 116.1, 97.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}ONF$: 240.0819; found: 240.0819.

3-Phenyl-5-(thiophen-2-yl)isoxazole (5i)

Yield: 25 mg (56%); white solid; mp 96–97 °C (Lit.[35] 95.5 °C).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.3, 162.9, 133.9, 130.1, 128.9, 127.0, 126.8, 124.4, 123.9, 97.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}ONS$: 228.0478; found: 228.0478.

Funding Information

We gratefully acknowledge the financial support from the National Science Foundation of China (No. 21072131) and Sichuan University–Lu Zhou Strategic Cooperation Projects (No. 2013 CDLZ-S18).

Acknowledgment

We sincerely thank Prof. Dr. Burkhard Koenig (Institut für Organische Chemie, Universität Regensburg, Germany) for his revisions and suggestions on the work reported in this paper.

References

(1) Groutas, W. C.; Venkataman, R.; Chong, L. S.; Yoder, J. E.; Epp, J. B.; Stanga, M. A.; Kim, E. *Bioorg. Med. Chem.* **1995**, *3*, 125.
(2) Fan, Y. J.; He, T.T.; Yang, J.C.; Liu, C.L. *Agrochem. Res. Appl.* **2010**, *14*, 1.
(3) (a) Zhao, C.; Casida, J. E. *J. Agric. Food Chem.* **2014**, *62*, 1019. (b) Lahm, G. P.; Cordova, D.; Barry, J. D.; Pahutski, T. F. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3001. (c) Ozoe, Y.; Asahi, M.; Ozoe, F. *Biochem. Biophys. Res. Commun.* **2010**, *391*, 744.
(4) (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (b) Zaki, M.; Oukhrib, A.; Akssira, M.; Berteina-Raboin, S. *RSC Adv.* **2017**, *7*, 6523.
(5) Gao, M. C.; Li, Y. Y.; Gan, Y. S.; Xu, B. *Angew. Chem.* **2015**, *127*, 8919.
(6) Li, C. L.; Deng, H. M.; Li, C. J.; Jia, X. S.; Li, J. *Org. Lett.* **2015**, *17*, 5718.
(7) (a) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (b) Cecchi, L.; De Sarlo, F.; Machetti, F. *Chem. Eur. J.* **2008**, *14*, 7903. (c) Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.; Maskaev, A. V.; Zhdankin, V. V. *Org. Lett.* **2013**, *15*, 4010. (d) Minakata S., Okumura S., Nagamachi, T.; Takeda, Y. *Org. Lett.*, **2011**, *13*, 2966; (e) Jia, Q-f.; Benjamin, P. M. S.; Huang, J.; Du, Z.; Zheng, X.; Zhang, K.; Conney, A. H.; Wang, J. *Synlett* **2013**, *24*, 79. (f) Grecian, S.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2008**, *47*, 8285. (g) Nishiwaki N., Kobiro K., Kiyoto, H.; Hirao, S.; Sawayama, J.; Saigo, K.; Okajima, Y.; Uehara, T.; Maki, A.; Ariga, M. *Org. Biomol. Chem.*, **2011**, *9*, 2832 (h) Trogu, E.; Vinattieri, C.; De Sarlo, F.; Machetti, F. *Chem. Eur. J.* **2012**, *18*, 2081. (i) Svejstrup, T. D.; Zawodny, W.; Douglas, J. J.; Bidgeli, D.; Sheikh, N. S.; Leonori, D. *Chem. Commun.* **2016**, *52*, 12302. (j) Zhang W., Su, Y.; Wang, K.-H.; Wu, L.; Chang, B.; Shi, Y.; Huang, D.; Hu, Y. *Org. Lett.*, **2017**, *19*, 376. (k) Triandafillidi, I.; Kokotos, C. G. *Org. Lett.* **2017**, *19*, 106. (l) Maestri G., Cañeque, T.; Della Ca', N.; Derat, E.; Catellani, M.; Chiusoli, G. P.; Malacria, M. *Org. Lett.*, **2016**, *18*, 6108. (m) Chandrasekhar, B.; Ahn, S.; Ryu, J-S. *J. Org. Chem.* **2016**, *81*, 6740. (n) Rouf, A.; Şahin, E.; Tanyeli, C. *Tetrahedron* **2017**, *73*, 331. (o) Bhosale S., Kurhade, S.; Prasad, U. V.; Palle, V. P.; Bhuniya, D. *Tetrahedron*, **2009**, *50*, 3948. (p) Wang, L-J.; Chen, M.; Qi, L.; Xu, Z.; Li, W. *Chem. Commun.* **2017**, *53*, 2056. (q) Han, B.; Yang, X. L.; Fang, R.; Yu, W.; Wang, C.; Duan, X. Y.; Liu, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 8816.
(8) Ibrar, A.; Khan, I.; Abbas, N.; Farooq, U.; Khan, A. *RSC Adv.* **2016**, *6*, 93016.
(9) (a) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (b) CecchI, L.; De Sarlo, F.; Machetti, F. *Chem. Eur. J.* **2008**, *14*, 7903. (c) Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.; Maskaev, A. V.; Zhdankin, V. V. *Org. Lett.* **2013**, *15*, 4010. (d) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. *Org. Lett.* **2011**, *13*, 2966. (e) Jia, Q. F.; Benjamin, P. M. S.; Huang, J. *Synlett* **2013**, *24*, 79. (f) Grecian, S.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2008**, *47*, 8285. (g) Nishiwaki, N.; Kobiro, K.; Kiyoto, H.; Hirao, S.; Sawayama, J.; Saigo, K.; Okajima, Y.; Uehara, T.; Maki, A.; Ariga, M. *Org. Biomol. Chem.* **2011**, *9*, 2832. (h) Trogu, E.; Vinattieri, C.; De Sarlo, F.; Machetti, F. *Chem. Eur. J.* **2012**, *18*, 2081. (i) Svejstrup, T. D.; Zawodny, W.; Douglas, J. J.; Bidgeli, D.; Sheikh, N. S.; Leonori, D. *Chem. Commun.* **2016**, *52*, 12302. (j) Zhang, W.; Su, Y.; Wang, K. H.; Wu, L.; Chang, B.; Shi, Y.; Huang, D. F.; Hu, Y. L. *Org. Lett.* **2017**, *19*, 376. (k) Triandafillidi, I.; Kokotos, C. *Org. Lett.* **2017**, *19*, 106. (l) Maestri, G.; Cañeque, T.; DellaCa', N.; Derat, E.; Catellani, M.; Chiusoli, G. P.; Malacria, M. *Org. Lett.* **2016**, *18*, 6108. (m) Chandrasekhar, B.; Ahn, S.; Ryu, J. *J. Org. Chem.* **2016**, *81*, 6740. (n) Rouf, A.; Sahin, E.; Tanyeli, C. *Tetrahedron* **2017**, *73*, 331. (o) Bhosale, S.; Kurhade, S.; Prasad, U. V.; Palle, V. P.; Bhuniya, D. *Tetrahedron* **2009**, *50*, 3948. (p) Wang, L. J.; Chen, M.; Qi, L.; Xu, Z.; Li, W. *Chem. Commun.* **2017**, *53*, 2056. (q) Han, B.; Yang, X. L.; Fang, R.; Yu, W.; Wang, C.; Duan, X. Y.; Liu, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 8816.
(10) Tang, S.; He, J.; Sun, Y.; He, L.; She, X. *J. Org. Chem.* **2010**, *75*, 1961.
(11) Itoh, K. I.; Sakamaki, H.; Nakazato, N. *Synthesis* **2005**, 3541.
(12) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023.
(13) Zhu, X.; Wang, Y. F.; Ren, W. *Org. Lett.* **2013**, *15*, 3214.
(14) (a) Knight, D. W.; Proctor, A. J.; Clough, J. M. *Synlett* **2010**, *4*, 628. (b) Pennicott, L.; Lindell, S. *Synlett* **2006**, 463.
(15) Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. *Org. Lett.* **2010**, *12*, 2594.
(16) (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (c) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562. (d) Davies, H. M. L.; Manning, J.

R. *Nature* **2008**, *451*, 417. (e) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (f) Li, Z.; Capretto, D. A.; Rahaman, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 5184.

(17) (a) Brice, J. L.; Harang, J. E.; Timokhin, V. I. *J. Am. Chem. Soc.* **2005**, *127*, 2868. (b) Inamoto, K.; Saito, T.; Katsuno, M. *Org. Lett.* **2007**, *9*, 2931. (c) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274. (d) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (e) Liu, G.; Yin, G.; Wu, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 4733.

(18) (a) Lee, J. M.; Ahn, D. S.; Jung, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 12954. (b) Cho, S. H.; Kim, J. Y.; Lee, S. Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 9127. (c) Kim, J. Y.; Cho, S. H.; Joseph, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 9899.

(19) (a) He, L.; Chan, P. W. H.; Tsui, W. M.; Yu, W. Y.; Che, C. M. *Org. Lett.* **2004**, *6*, 2405. (b) He, L.; Yu, J.; Zhang, J.; Yu, X. Q. *Org. Lett.* **2007**, *9*, 2277. (c) Jiang, Y.; Zhou, G. C.; He, G. L.; He, L. *Synthesis* **2007**, 1459. (d) Liu, N.; Tang, B. Y.; He, L. *Eur. J. Org. Chem.* **2009**, 2059. (e) Yin, P.; Ma, W. B.; Chen, Y. *Org. Lett.* **2009**, *11*, 5482.

(20) Feuer, H. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*; John Wiley & Sons: Hoboken, **2008**.

(21) (a) Al-Majid, A. M.; Shamsan, W. S.; Al-Odayn, A.-B. M.; Nahra, F.; Aouak, T.; Nolan, S. P. *Des. Monomers Polym.* **2017**, *20*, 167. (b) Paulus, R. M.; Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Aust. J. Chem.* **2009**, *62*, 254. (c) Zhang, H. *Eur. Polym. J* **2013**, *49*, 579. (d) Narasimhan, N. S.; Aidhen, I. S. *Tetrahedron Lett.* **1988**, *29*, 2987. (e) Huang, N.-J.; Sundberg, D. C. *J. Polym. Sci., Part A: Polym. Chem* **1995**, *33*, 2571.

(22) (a) Cavero, M.; Motherwell, W. B.; Potier, P. *Tetrahedron Lett.* **2001**, *42*, 4377. (b) Turner, C. D.; Ciufolini, M. A. *ARKIVOC* **2011**, *(i)*, 410. (c) Santra, S.; Kundu, S. K.; Ghosal, N. C.; Chatterjee, R.; Mahato, S.; Khalymbadzha, I. A.; Zyryanov, G. V.; Hajra, A.; Majee, A. *ARKIVOC* **2016**, *(v)*, 416. (d) Li, W.; Zhou, X.; Shi, Z.; Liu, Y.; Liu, Z.; Gao, H. *Org. Biomol. Chem.* **2016**, *14*, 9985.

(23) Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. *Org. Lett.* **2011**, *13*, 2966.

(24) Grunanger, P.; Finzi, P. V. *Gazz. Chim. Ital.* **1959**, *89*, 1771.

(25) Barnes, R. P.; Pinkney, G. E.; Phillips, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 276.

(26) Yuzuri, S.; Chandrasekaran, P. C.; Vasquez, T.; Baumstark, A. L. *Heterocycl. Commun.* **2006**, *12*, 7.

(27) Bianchi, G.; Gruenanger, P. *Tetrahedron* **1965**, *21*, 817.

(28) Lee, G. A. *Synthesis* **1982**, 508.

(29) Kidwai, M.; Kukreja, S.; Thakur, R. *Lett. Org. Chem.* **2006**, *3*, 135.

(30) Aliev, A. G. *Russ. J. Org. Chem.* **2005**, *41*, 1192.

(31) Bhosale, S.; Kurhade, S.; Vyas, S.; Palle, V. P.; Bhuniya, D. *Tetrahedron* **2010**, *66*, 9582.

(32) Jose, B.; Jesus, J.; Victor, R.; Vicente, G. *J. Org. Chem.* **1983**, *48*, 1379.

(33) Barnes, R. P.; Dodson, L. B. *J. Am. Chem. Soc.* **1945**, *64*, 132.

(34) Lokesh, B.; Tomar, S. S. *Pestic. Res. J.* **2005**, *17*, 1.

(35) Mitchell, A. D.; Nonhebel, D. C. *Tetrahedron* **1976**, *32*, 2437.