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Synthesis of Halomethyl Isoxazoles/Cyclic Nitrones via Cascade Sequence: 1,2-Halogen Radical Shift as a Key Link

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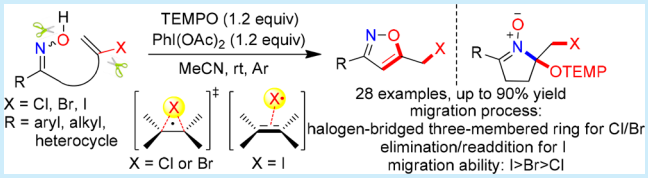
Supporting Information

ABSTRACT: A novel iminoxyl radical-promoted dichotomous regioselective 5-exo-trig cyclization onto vinylic halogen/1,2-halogen radical shift sequence is developed for the synthesis of halomethyl isoxazoles/cyclic nitrones using β-halo-β,γ- and γ-halo-γ,δ-unsaturated ketoximes as the substrates and $PhI(OAc)_2$/TEMPO as the oxidation system. DFT calculations reveal that a halogen-bridged three-membered ring transition state is involved in the 1,2-Cl-/Br-atom shift, while the 1,2-I atom migration can be taken into account with an elimination/readdition mechanism. The migration ability was indicated to be ranked in the following order: I > Br > Cl.



The 1,2-halogen radical shift is an important rearrangement reaction that was first reported by Urry and Nesmeyanov in 1951.[1] Later studies by Benson,[2] Skell,[3] and Urry[4] established the generality of this rearrangement in the reactions of 2-haloalkyl radicals. Although it is beyond doubt that this shift involves a radical process, the mechanistic details of this rearrangement have not been unambiguously elucidated. Both experimental[5] and theoretical[6] studies have been conducted to identify the species along the rearrangement pathway, on the basis of which two distinct mechanisms were proposed, as outlined in Figure 1. One is the elimination/readdition

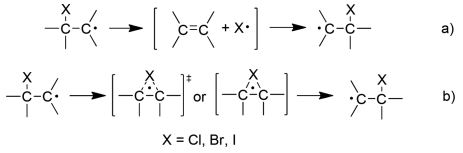
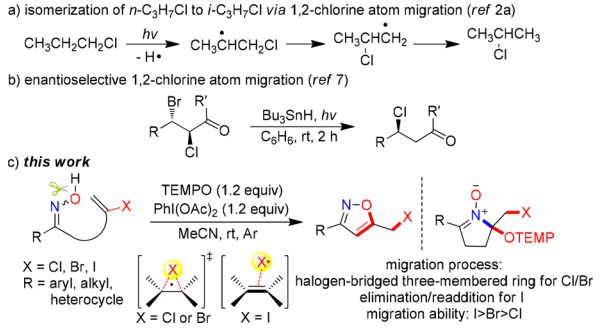


Figure 1. Plausible pathway for the 1,2-halogen radical shift.

sequence (Figure 1a),[5g,6b] the other involves the formation of a halogen radical-bridged three-membered ring as a transition state or an intermediate[5a−f,i] (Figure 1b). So far, there is no report to distinguish what type of halogen atom experiences which process, nor to reveal the migration ability of different halogen atoms. Apart from its mechanistic implications, the 1,2-halogen shift is expected to be synthetically useful, as demonstrated in the isomerization of n-C_3H_7Cl to i-C_3H_7Cl and enantioselective 1,2-Cl atom migration of β-bromo-α-chloro ketones under ultraviolet (UV)-light irradiation (see Schemes 1a and 1b).[2a,7] However, studies in this line have been rarely reported, despite the long-time interest in the free radical chemistry among synthetic chemists, and the synthetic powerfulness of 1,2-halogen radical shift has not been fully appreciated.

Scheme 1. Radical-Promoted 1,2-Halogen Migration



Heterocycles are extremely important compounds, and efficient synthetic approaches toward heterocyclic structures have attracted the attention of chemists for years.[8] The cyclization of heteroatom-centered radicals onto alkenes play a remarkable role in the synthesis of heterocycles.[9] However, most of those reactions are focused on simple alkenes, and the cyclization involving vinylic halogen and its regioselectivity are rarely reported. Although Li reported elegant regiospecific 6-endo-trig cyclizations of a N-centered radical onto vinylic halogen via "lone pair−lone pair repulsion between the nitrogen radical and the vinylic halogen atom",[10] it is still unknown whether the 5-exo-trig cyclization of heteroatom-centered radical onto vinylic halogen and the subsequent 1,2-halogen radical shift can be realized. Iminoxyl radicals are attractive heteroatom-centered radicals that can be treated as the O-centered radical, as well as the N-centered radical, because the single electron spin is delocalized almost equally on both the O atom and the N atom.[11] Based on our continuous interest in the iminoxyl radical-involved cyclizations,[12] herein,

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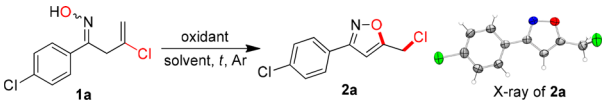
we wish to report an iminoxyl radical-facilitated regioselective cyclization/1,2-halogen shift sequence for the synthesis of structurally useful halomethyl isoxazoles/cyclic nitrones from β-halo-β,γ- and γ-halo-γ,δ-unsaturated ketoximes with $PhI(OAc)_2$ and TEMPO[13] (2,2,6,6-tetra-methylpiperidine-1-oxyl) as the oxidants (see Scheme 1c). Mechanistic study by DFT calculations reveal that the 1,2-Cl- and 1,2-Br-atom migration probably proceeds through a halogen-bridged three-membered ring transition state, while an elimination/readdition process is experienced in the 1,2-I atom migration. The migration ability of the halogen atom was found in the order of I > Br > Cl. This study not only provides new insight into the mechanism of the 1,2-halogen migration, but also constitutes the first example of 1,2-halogen migration-based radical cascade reactions of synthetic usefulness.

Initially, β-chloro-β,γ-unsaturated ketoxime **1a** was used as the model substrate to react with TEMPO (2.5 equiv) in CH_3CN under an Ar atmosphere at 80 °C. To our delight, the reaction proceeded smoothly and gave the desired tandem cyclization/1,2-Cl migration/aromatization product halomethyl isoxazole **2a** in 80% yield (Table 1, entry 1). The structure of

Table 1. Optimization of the Reaction Conditions[a]



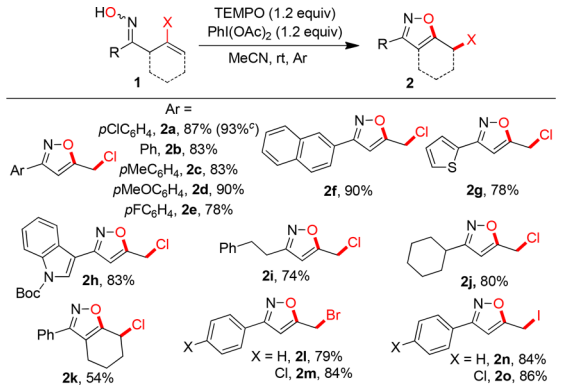
entry	oxidant (equiv)	solvent	t (°C)	yield[b] (%)
1	TEMPO (2.5)	MeCN	80	80
2	TBHP (3.0)/TBAI (0.2)	MeCN	80	11
3	$TEMPO^+BF_4^-$ (1.5)	MeCN	25	79
4	$PhI(OAc)_2$ (1.2)	MeCN	25	0
5	**$PhI(OAc)_2$ (1.2)/TEMPO (1.2)**	**MeCN**	**25**	**87**
6	$PhI(OAc)_2$ (1.2)/TEMPO (1.2)	DMSO	25	64
7	$PhI(OAc)_2$ (1.2)/TEMPO (1.2)	DMF	25	75
8	$PhI(OAc)_2$ (1.2)/TEMPO (1.2)	toluene	25	82

[a]Reaction conditions: **1a** (0.2 mmol), oxidant, solvent (2 mL), Ar, 5 h. [b]Yield of isolated product. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, TBHP = *tert*-butyl hydroperoxide, TBAI = tetrabutyl ammonium iodide.

compound **2a** was verified by single-crystal X-ray diffraction (XRD) analysis. To further improve the yield of **2a**, other oxidants such as *tert*-butyl hydroperoxide (TBHP), 2,2,6,6-tetramethyl-1-oxopiperidin-1-ium tetrafluoroborate (TEMPO$^+BF_4^-$), and $PhI(OAc)_2$ were tested in the reaction, among which, however, only TEMPO$^+BF_4^-$ gave an acceptable yield. (Table 1, entries 2–4). When $PhI(OAc)_2$/TEMPO was used as the combined oxidant system, a satisfactory yield of **2a** in 87% was obtained (Table 1, entry 5). Acetonitrile proved to be an ideal solvent for this transformation. No better yield was obtained when other solvents such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and toluene were used as the reaction media (Table 1, entries 6–8).

To examine the applicability of this protocol, a diversity of β-halo-β,γ-unsaturated ketoximes were investigated under the optimal reaction conditions (Scheme 2). The chlorine-incorporating ketoximes were investigated first. It can be seen that 4-phenyl-substituted ketoximes of various electronic properties in this line reacted very well to give the corresponding chloromethyl isoxazoles **2a–2e** in good to excellent yields. Aryls and heteroaryls such as 2-naphthyl, 2-

Scheme 2. Scope of the Synthesis of Isoxazoles[a,b]



[a]Reaction conditions: oxime **1** (0.20 mmol), TEMPO (0.24 mmol, 1.2 equiv), $PhI(OAc)_2$ (0.24 mmol, 1.2 equiv) in MeCN (2.0 mL) at room temperature (rt) under Ar. [b]Isolated yields are shown. [c]**1a** (1 mmol) was used.

thienyl, and 3-indolyl substituted ketoximes also reacted smoothly, delivering the desired products **2f–2h** in excellent yields. Alkyl-substituted ketoximes, such as phenethyl and cyclohexyl, were also transformed swimmingly, as demonstrated in the case of **2i** and **2j**. Significantly, the cyclic chloroalkene-incorporated ketoxime **1k** was also compliable for this transformation to afford the corresponding chlorocyclohexyl-fused isoxazole **2k** in 54% yield, indicating that 1,2-halogen migration from a tertiary carbon atom to a secondary carbon was also quite facile under the current circumstances. Besides the 1,2-Cl migration, 1,2-Br and 1,2-I migrations also were realized using this strategy, as demonstrated by the reactions of **1l–1o**, which gave the corresponding products **2l–2o** in excellent yields. The structures of compounds **2m** and **2n** were confirmed by single-crystal XRD analysis.

Encouraged by the accomplishment of the O-centered radical-promoted cascade sequence of β-halo-β,γ-ketoximes, we shifted to extend this strategy to γ-halo-γ,δ-unsaturated counterparts to explore if the latter could experience a similar process of N-centered radical. Indeed, as illustrated in the Scheme 3, the expected N atom 5-exo-trig cyclization/1,2-halogen migration took place very well, with the TEMPO-trapped and halomethyl incorporated cyclic nitrones **4** being obtained in good to excellent yields. The trapping of the deuterogenic carbon radical derived from 1,2-halogen migration also confirmed that the 1,2-halogen migration was a radical process. In contrast to the formation of aromatic isoxazole as aforementioned, the TEMPO-trapped cyclic nitrone was obtained instead of the TEMPOH-eliminated one in all cases, because there is no driving force of aromatization in the present structure. This protocol is suitable for aryl-, heteroaryl-, and alkyl-substituted ketoximes, as demonstrated by the formation of **4a–4k** in excellent yields. The structure of compound **4a** was also verified by a single-crystal XRD study. Both the 1,2-Cl migration and 1,2-Br migration can be realized with this method. However, when γ-iodo-γ,δ-unsaturated ketoxime **3m** was subjected to the reaction, only a trace amount of the expected product **4m** was produced.

To gain insight into the observed iminoxyl radical-triggered regioselective cyclization/1,2-halogen radical migration, the density functional theory (DFT) calculations (Gaussian 09, at the M06-2X/6-311+G (d,p) level and Def2-TZVPD basis set for halogen atoms) were carried out next (see Figure 2).[14] The

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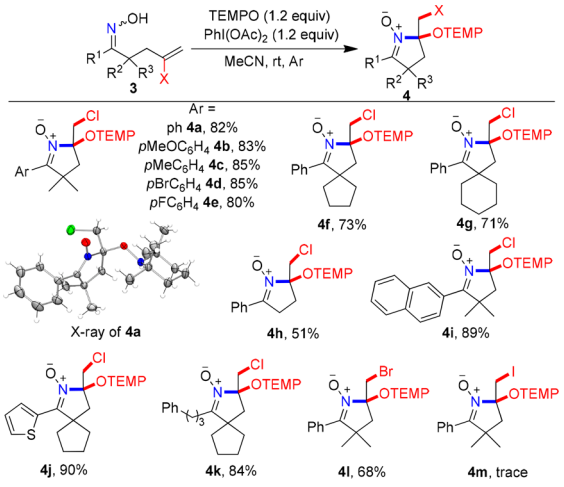
Scheme 3. Scope of the Synthesis of Cyclic Nitrones[a,b]



[a]Reaction conditions: oxime **3** (0.20 mmol), TEMPO (0.24 mmol, 1.2 equiv), $PhI(OAc)_2$ (0.24 mmol, 1.2 equiv) in MeCN (2.0 mL) at rt under Ar. [b]Isolated yields are shown.

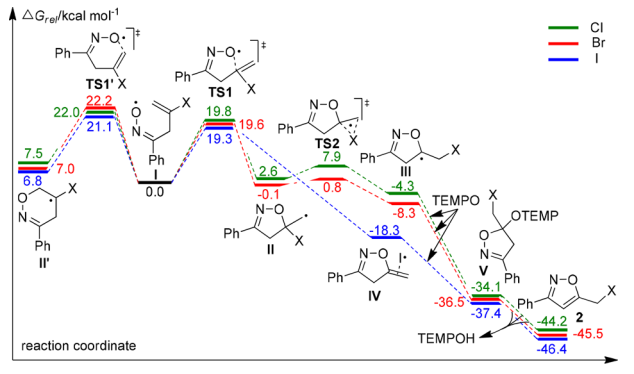


Figure 2. Energy profiles for the O atom regioselective cyclization of iminoxyl radical **I** and the 1,2-halogen migration.

calculated energy profile for the O-centered radical cyclization processes of iminoxyl radicals **I** indicates that the 5-*exo*-trig mode via **TS1** is favored than the 6-*endo*-trig mode via **TS1′** by 2.2, 2.6, and 1.8 kcal/mol for Cl-, Br-, and I-substituted **I**, in terms of the free energy of activation, respectively. Such energy differences explain well why the products derived from the 6-endo pattern were not observed. The energy profile also discloses that the 1,2-Cl and 1,2-Br migration proceeds through carbon-centered intermediates **II** and **III** connected with a halogen-bridged three-membered transition state **TS2**, whereas a different pathway is followed in the 1,2-I migration. For the latter process, the initial radical cyclization through transition state **TS1** would result in I-atom elimination to afford intermediate **IV**. The elimination of I atom is barrierless, as confirmed by the intrinsic reaction coordinate (IRC) of the transition state **TS1** (see the Supporting Information (SI)), indicating that the O−C 5-*exo*-trig cyclization and the elimination of the I atom represent a concerted step. It can be seen from the free energy of activation that the 1,2-halogen migration ability is ranked in the following order: I > Br > Cl. This order is consistent with the strength of the C−halogen bonds. Subsequent trapping of the intermediate **IV** by TEMPO, which is barrierless and exothermic, realizing the readdition of I atom to produce the intermediate **V**. Trapping of intermediate **III** by TEMPO to yield the intermediate **V** in the cases of 1,2-Cl and 1,2-Br migration is also barrierless and exothermic. Finally, the product halomethyl isoxazoles are formed from the intermediate **V** via the elimination of TEMPOH, because of the strong driving force of aromatization.

The maps of spin density and SOMO orbit of **TS2** further manifest that the Cl-/Br-bridged three-membered ring is formed in the migration process as a transition state (Figure 3). Calculation indicates that conspicuous spin populations are

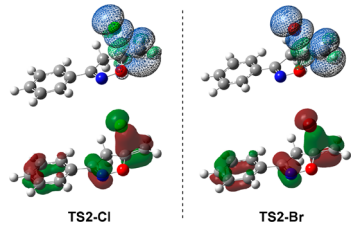


Figure 3. Calculated spin density map (top) and the SOMO-3 orbital map (bottom) of the transition state **TS2-Cl** and **TS2-Br**.

located on Cl/Br, C^1, and C^2 atoms of **TS2** (see Table S1 in the SI). For the 1,2-I atom migration, the spin population was calculated to be mostly located on the I atom (0.88) in intermediate **IV**, suggesting that the I atom is eliminated from the molecule. This point can be further verified by the breaking of C^1−I bond (3.25 Å), the long distance of the C^2−I bond (3.05 Å), and the double-bond character between C^1 and C^2 (1.34 Å) of the intermediate **IV** (see Figure S7 in the SI). In addition, it can be seen that, in the transition from **TS1** to intermediate **IV**, the spin population on the I atom increases monotonously from 0.03 to 0.88 and then maintains at this level, while it sharply decreases on the C^2 atom from 0.69 to −0.06. On the other hand, the spin population on the C^1 atom is not noticeably altered during the process. This tendency is totally different from that observed for the 1,2-Cl or 1,2-Br migration where the spin population increases remarkably on C^1 atoms, decreases obviously on C^2 atoms, and fluctuates on the halogen atom (see the SI). These results clearly demonstrate that I-atom migration experiences an elimination/readdition process, rather than a transition state such as **TS2**.

Based on the experimental results and theoretical calculations, a proposed mechanism for these reactions is shown in Figure 4. The reaction is initiated by $PhI(OAc)_2$ via a single-electron oxidation of vinylic halogen-substituted ketoximes **1** or **3** to the corresponding iminoxyl radicals **I**, which immediately undergo O- or N-atom 5-exo-trig cyclization, based on the

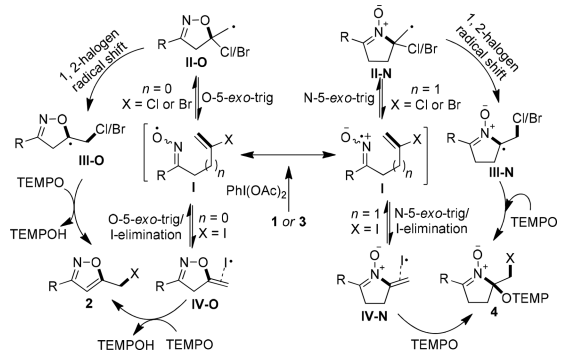


Figure 4. Proposed mechanism.

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position of the tethered alkenes. When the halogen atom is Cl or Br, intermediates **II−O** and **II−N** are generated in the cyclization step, from which the C-centered radicals **III−O** and **III−N** are formed, as a result of the 1,2-halogen radical migration. Finally, TEMPO-promoted aromatization of **III−O** occurs to give isoxazole **2**, while cyclic nitrone **4** is generated from **III−N** via radical trapping by TEMPO. When the halogen atom is iodine, on the other hand, radical **I** experiences a concerted O-atom/N-atom 5-exo-trig cyclization/I atom elimination process to deliver intermediates **IV−O** and **IV−N** directly. The latter species then react with TEMPO to afford isoxazole **2** and cyclic nitrone **4**, respectively.

In summary, a novel, efficient, and metal-free approach has been developed for the synthesis of halomethyl isoxazoles/cyclic nitrones by using vinylic halogen-tethered ketoximes as the substrates and $PhI(OAc)_2$/TEMPO as the oxidation system. The reaction involves the initiation of iminoxyl radicals from the oxidation of β-halo-β,γ- and γ-halo-γ,δ-unsaturated ketoximes by $PhI(OAc)_2$, followed by a cascade regioselective radical cyclization/1,2-halogen shift/aromatization or TEMPO-trapping sequence. DFT calculations reveal that the Cl- and Br-atom shift passes through a transition state of halogen-bridged three-membered ring, but the I atom migration follows an elimination/readdition process. The migration ability was found to be in the order of I > Br > Cl. Further studies on new 1,2-halogen radical shift-involved reactions, for synthetic purposes, are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00967.

Detailed experimental procedures and spectral data for all products (PDF)

Accession Codes

CCDC 1522036, 1522038, 1522039, and 1561740 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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