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Metal-free carbonitration of alkenes using K₂S₂O₈+

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A novel metal-free oxidative carbonitration of alkenes by a nitration and C–H functionalization cascade process has been developed. This methodology provides an efficient way to construct valuable nitrocontaining oxindoles.

Nitro compounds are widely used in organic synthesis, the chemical industry, and pharmaceuticals. These important synthetic precursors can be easily transformed into various functional groups such as amines and ketones.¹ In general, electrophilic aromatic substitution that involves a nitrating agent has been the predominant synthetic approach for the preparation of nitroarenes.² Recently, transition-metal-catalyzed synthesis of nitroaromatics from aryl chlorides, triflates, and nonaflates has also been developed.³ For aliphatic nitro compounds, however, nucleophilic substitution reaction of an alkyl halide with the nitrite anion $(NO_2^{-})^4$ is the common method. Moreover, oxidation of amines and oximes also affords corresponding nitro compounds.⁵ These methods require large amounts of base or a specifically functionalized precursor, which significantly limits their application scope. Although direct addition of nitrogen dioxide to a C-C multiple bond provides the simplest pathway of affording aliphatic nitro compounds, the difficulty in handling NO2 gas and its toxicity dramatically decrease the overall reaction efficiency.^{1a} On the other hand, C-C bond-formation reactions involving nitroalkanes also promise alternative methods, including the Henry reaction,⁶ conjugate additions,⁷ alkylation of nitroalkanes with alkyl halides8 and Pd-catalyzed allylation,9 and arylation.¹⁰ Unfortunately, few substrates are compatible with nitro compounds, which further restricts availability. Therefore, the development of a more concise and efficient nitrating method for the preparation of aliphatic nitro compounds is highly desirable and presents a considerable challenge to research. Recently, transformations that result in the difunctionalization of alkenes have





become an active topic in organic synthesis.¹¹ In particular, transition-metal-catalyzed carbo-heterodifunctionalization of alkenes that leads to cyclization offers a new pathway for the synthesis of various functional oxindoles.¹² We envisioned direct installation of the nitro group into alkenes by carbonitration and conducted the necessary cyclization in order to afford the corresponding nitro-containing oxindoles. After great efforts, we report transition-metal free carbonitration-difunctionalization of arylacrylamides (Scheme 1).

Over the past several years, the development of transition-metalfree processes has become a topic of great interest in chemical synthesis.¹³ Such protocols are very valuable as attractive alternatives and beneficial complements to transition-metal-catalyzed transformations. In particular, the transition-metal-free C–H functionalization has attracted the most attention and achieved significant progress;¹⁴ indeed, this of all methods among the metal free processes that involve difunctionalization of alkenes appears particularly fascinating.¹⁵ Current reports mainly focus on the oxidative difunctionalization of alkenes; therefore, examples that involve the oxidative carbo–heterocascade cyclization of alkenes are very rare.¹⁶ Using the very cheapest NaNO₂ as a nitrogen source and $K_2S_2O_8$ as the oxidant, we first accomplished metal-free oxidative carbonitration of alkenes towards the nitro-containing oxindoles through a radical process.

In an initial study, we chose the *N*-methyl-*N*-arylacrylamide **1a** as the model substrate and NaNO₂ as a nitrating source to evaluate different oxidants in CH₃CN at 120 °C. To our delight, the carbonitration of alkenes could occur in the presence of 2.0 equiv. of oxidants such as Na₂S₂O₈, (NH₄)₂S₂O₈, K₂S₂O₈, and oxone, while the reactivity of K₂S₂O₈ was better than others to afford the desired

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 Table 1
 Carbonitration of different alkenes^{a,b}



^{*a*} All reactions were carried out in the presence of 0.4 mmol of **1a–1z**, NaNO₂ (2.0 equiv.), $K_2S_2O_8$ (2.0 equiv.) in 2 mL of CH₃CN at 120 °C. ^{*b*} Isolated yield.

product **2a** in 71% yield (see the ESI[†]). Besides NaNO₂, other nitrites could also be used to give good yields of **2a**: AgNO₂: 66%; KNO₂: 70%. The substrate concentration highly affected this transformation. When the substrate concentration was increased to 0.2 M, the yield of **2a** improved to 86%. Different solvents were screened, and among them CH_3CN exhibited unmatched efficacy for the transformation.

Upon optimization of the reaction conditions, we turned our attention to the scope of substrates. As shown in Table 1, an investigation into different N-protection groups showed that the electron-donating groups such as methyl and benzyl are suitable for this reaction (2a-2b). However, replacement of the methyl substituent with a hydrogen atom failed to produce corresponding products. N-Arylacrylamides bearing electron-donating or electron-withdrawing substituents on aniline moieties could be successfully converted into the desired products in moderateto-good yields (2d-2m). Cyclization of a tetrahydroquinoline derivative furnished tricyclic oxindole 2d with moderate yield. Notably, Cl, Br, and I groups were also well tolerated, thereby facilitating possible additional modifications at halogenated positions (2i-2k). Next, we evaluated various alkene substituent groups. A series of α -substituted olefines bearing different functional groups, such as benzyl (2n), acetoxymethyl (2o), phthalimide (2p), and azidoethyl (2q), still provided the desired products in moderate to good yields. It is worth noting that unactivated alkenes can also undergo carbonitration smoothly, generating corresponding products in moderate yields (2r-2x). Finally, the polycyclic aromatic hydrocarbon such as naphthalene was compatible with this reaction and the desired product 2y was obtained in 71% yield. But pyridineacrylamide produced only a trace amount of the product 2z.



Nitro groups feature facile transformation into various functional groups, a versatility that has broadened their importance in the synthesis of complex molecules.¹ On the other hand, 3-substituted oxindoles are ubiquitous heterocycles found in a wide range of natural products, pharmaceuticals, and agrochemicals.¹⁷ We demonstrate herein the postsynthetic transformations of nitro-containing oxindoles (Scheme 2). Compound 2a can be further transformed into 1,3-dimethylindolin-2-one (3a) in moderate yield using the oxone–NaOH system. Moreover, KMnO₄-oxidized reaction conditions were employed to obtain 3-hydroxyoxindole 3b in good yield from 2a. Finally, compound 2a was also reduced with ammonium formate and Pd/C to give the primary amine 3c. These representative transformations clearly demonstrate that the presented methodology provides an efficient and atom economical access to various valuable 3-substituted oxindoles.

To probe the mechanism of the carbonitration process, substrate $[D_1]$ -**1a** was used to determine the intramolecular isotope effect, and a mixture of substrates **1a** and $[D_5]$ -**1a** in a 1:1 ratio was used to determine the intermolecular isotope effect (see the ESI[†]). Two secondary kinetic isotope effects were observed (the intramolecular $k_{\rm H}/k_{\rm D} = 0.9$, intermolecular $k_{\rm H}/k_{\rm D} = 0.8$). These findings suggested that this transformation reaction might involve a free-radical process similar to mechanisms proposed in previously reports. ^{12e}, f.¹⁶ In addition, control experiments support the free-radical mechanism in the presence of radical inhibitors. Addition of 2.0 equivalents of TEMPO or 1,1-diphenylethylene would led the carbonitration process remarkably suppressed.

Based on the above experiments and previous mechanistic studies,^{12*d*-*g*,16} we propose a tentative pathway of this transformation described in Scheme 3. Initially, potassium peroxydisulphate may decompose to the sulfate radical anion upon heating.¹⁸ Then, NaNO₂ reacts with the sulfate radical anion to form a nitrogen dioxide radical, followed by addition to the carbon–carbon double bond of amide **1a**, thus affording radical intermediate **2A**.¹⁹ The resulting alkyl radical **2A** participates in an intramolecular radical substitution reaction. Addition of a radical to the aromatic ring led to the generation of intermediate **2B**, followed by oxidation of **2B** into the corresponding carbocation, which loses H⁺ to produce the oxindole **2a**.

In summary, we have developed a novel metal-free oxidative carbonitration of alkenes by a nitration and C–H functionalization cascade process using the $K_2S_2O_8$ as oxidant. This methodology provides the most efficient way to construct nitro-containing oxindoles, which are important synthetic intermediates. Further applications of this new transformation to other substrates and



Scheme 3 Proposed mechanisms for carbonitration of alkenes.

the synthesis of more valuable compounds are underway in our group.

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