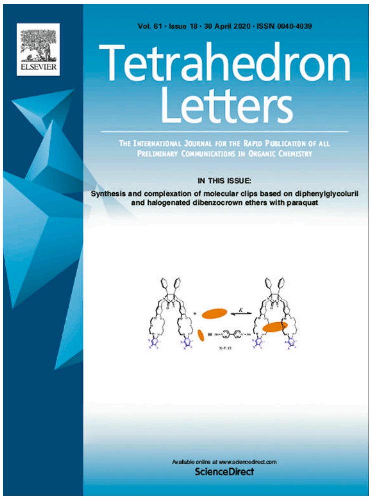

Cerium(IV) ammonium nitrate promoted synthesis of *O*-phthalimide oximes from vinyl azides and *N*-hydroxyphthalimide

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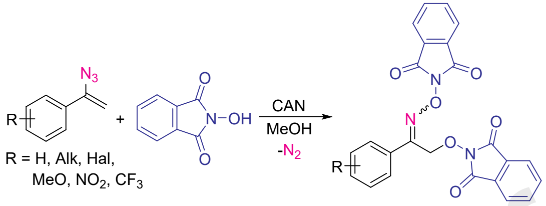

12 examples, 54-88% yield

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Cerium(IV) ammonium nitrate promoted synthesis of *O*-phthalimide oximes from vinyl azides and *N*-hydroxyphthalimide

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ABSTRACT

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O-Phthalimide oximes with an N-O-N fragment were synthesized in high yields *via* the reaction of vinyl azides with phthalimide-*N*-oxyl radicals derived from *N*-hydroxyphthalimide under the action of cerium(IV) ammonium nitrate. The disclosed process is based on the radical transformation of vinyl azides with the elimination of nitrogen and the formation of iminyl *N*-radicals. The developed approach exploited the dual reactivity of imide-*N*-oxyl radicals. They act as O-components for oxidative C-O coupling with vinyl azides and participate in subsequent formation of the N-O bond *via* their recombination with intermediate iminyl radicals.

1. Introduction

The present work lies at the intersection of important areas of organic chemistry, such as the chemistry of O-centered radicals, oxidative transformations under the action of cerium(IV) ammonium nitrate, and radical reactions involving C=C bonds.

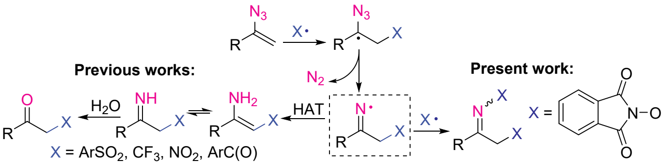
Radicals with an unpaired electron localized on an N-O fragment, namely, *N*-oxyl radicals are widely used in organic and biological chemistry, the development of organic radical batteries and material design.[1] In organic synthesis, more stable nitroxyl radicals are employed as free radical scavengers[1] and catalysts for the oxidation of alcohols.[2-7] Less stable imide-*N*-oxyl radicals have found application as mediators of hydrogen atom abstraction for the subsequent formation of C-C, C-O, C-S, and C-N bonds.[2, 6, 8-13] Phthalimide-*N*-oxyl (PINO) generated from inexpensive *N*-hydroxyphthalimide (NHPI) is widely employed in the aerobic oxidation of bulk chemicals.[8, 9, 14, 15]

The main approach for the generation of imide-*N*-oxyl radicals is the oxidation of *N*-hydroxyimides under the action of transition metal salts or hypervalent iodine compounds. Among the metal-based reagents, cerium(IV) ammonium nitrate (CAN) is widely used due to its commercial availability, ease of handling, low toxicity and high solubility in organic solvents. Using a combination of NHPI and CAN, a number of C-H functionalization[12, 16] and oxidation[17] processes have been developed.

In the last decade, the selective functionalization of alkenes with *N*-oxyl radicals has become a prominent area of modern organic chemistry. In the reactions of styrenes with NHPI, bifunctional products with C-O,[18-21] C-C,[22, 23] C-N[24, 25] and C-I[26, 27] bonds were obtained. Recently, we developed an approach for the selective radical difunctionalization of styrenes under the action of NHPI and CAN.[28]

Vinyl azides possess a rich spectrum of reactivity, and have therefore gained growing interest as versatile precursors for organic synthesis.[29-31] Reactions of $ArSO_2\cdot$,[32-34] $CF_3\cdot$,[35-39] $SCN\cdot$,[40] $NO_2\cdot$,[34] $ArC(O)\cdot$[34, 41] and various C-centered radicals[42-44] with vinyl azides have been reported. In general, such processes are accompanied by the addition of a radical species to the terminal atom of the C=C bond of vinyl azides with the release of nitrogen and the formation of an iminyl radical. Depending on the reaction conditions, the formation of ketones and enamines can occur. To date, no intermolecular addition reactions of such iminyl radicals have been reported.

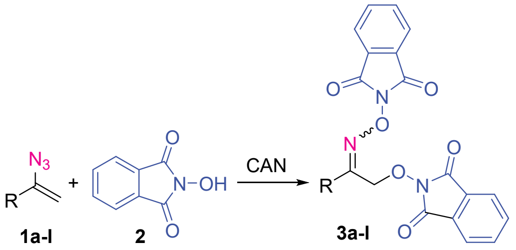
In the present work, the selective coupling of PINO radical with vinyl azides, followed by recombination with iminyl radicals was carried out to form *O*-substituted oximes containing two phthalimide-*N*-oxyl fragments (Scheme 1).



Scheme 1. The present work in the context of the iminyl radical mediated transformations of vinyl azides.

2.

In the present work we report the reaction of substituted vinyl azides **1a-l** and NHPI **2** under the action of CAN with the formation of *O*-phthalimide oximes **3a-l** (Scheme 2).



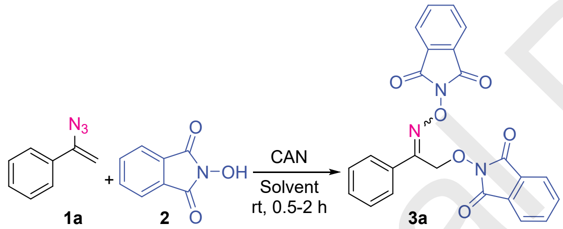
1a: R = C_6H_5
1b: R = 4-MeC_6H_4
1c: R = 4-*t*-BuC_6H_4
1d: R = 4-FC_6H_4
1e: R = 4-ClC_6H_4
1f: R = 4-$MeOC_6H_4$
1g: R = 4-$O_2NC_6H_4$
1h: R = 4-$F_3CC_6H_4$
1i: R = 3-MeC_6H_4
1j: R = 3-$MeOC_6H_4$
1k: R = 2-MeC_6H_4
1l: R = 2-$MeOC_6H_4$

Scheme 2. Reaction of vinyl azides **1a-l**, NHPI **2** and CAN to give *O*-phthalimide oximes **3a-l**.

An important feature of this work is that formation of the N-O-N fragment proceeds through the recombination of *N*-centered iminyl and *O*-centered PINO radicals.

Initially, we studied the model transformation of vinyl azide **1a** under the action of NHPI **2** and CAN (Table 1).

Table 1.
Optimization of the CAN-mediated reaction of vinyl azide **1a** with NHPI **2**.



Entry[a]	Molar ratio **1a**:**2**:CAN	Solvent	Time (h)	Yield **3a** (%)[b]
1	**1:2:2**	**MeOH**	**1**	**88 (85)**
2	1:2:2	CH_3CN	1	74
3	1:2:2	Acetone	1	70
4	1:2:2	THF	1	76
5	1:2:2	CH_2Cl_2/H_2O (3:2)	1	78
6	1:2:2	EtOAc/H_2O (3:2)	1	81
7	1:3:3	MeOH	1	85
8	1:2:3	MeOH	1	87
9	1:2:2	MeOH	0.5	80
10	1:2:2	MeOH	2	84

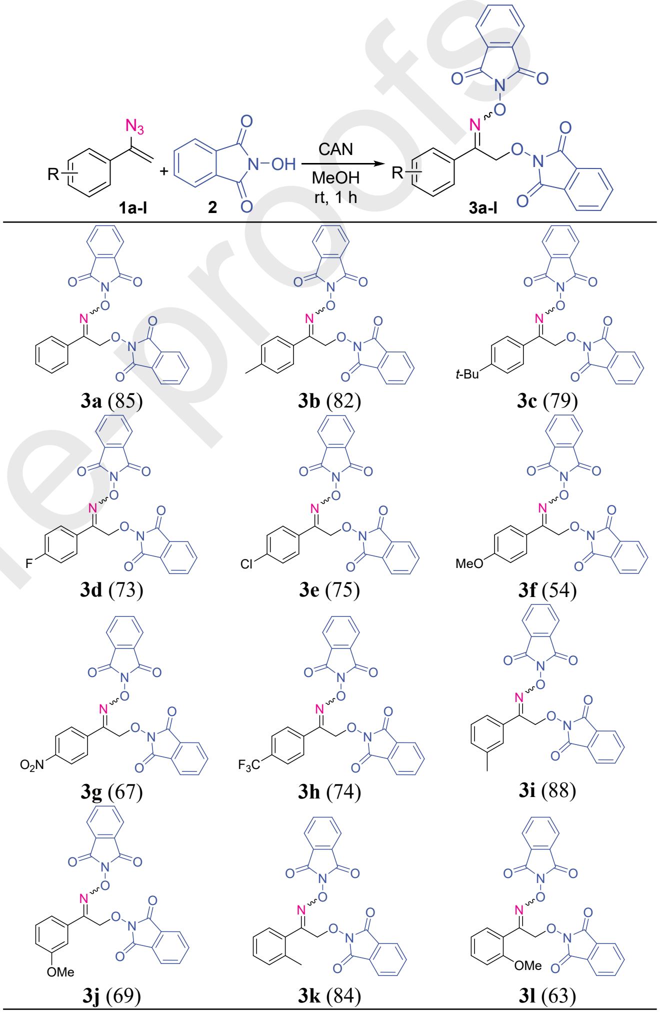
[a] Reagents and conditions: CAN (1.0-1.5 mmol) was added to a mixture of vinyl azide **1a** (0.5 mmol) and NHPI **2** (1.0 mmol) in solvent (5 mL), and stirred at 20-25 °C for 0.5-2 h under an air atmosphere. For entries with a mixture of solvents, the v/v ratio is in parentheses. [b] NMR yields; isolated yields are given in parentheses.

The effect of the solvent nature on the yield of *O*-phthalimide oxime **3a** was evaluated in Entries 1-6. In an initial experiment using MeOH as the solvent, target product **3a** was obtained in 88% yield. Carrying out the reaction in CH_3CN, acetone or THF, as well as in two-phase systems (CH_2Cl_2/H_2O, EtOAc/H_2O) led to a decrease in the yield of **3a** (Entries 2-6, 70-81%). Therefore, MeOH proved to be the best solvent for the process under study, and was chosen for further optimization.

Increasing the amount of NHPI **2** and CAN led to a slight decrease in the yield of **3a** (Entry 7, 85%). The increase in the yield of the target product (Entry 8, 87%). The optimal reaction time was 1 h, since carrying out the reaction for 30 min resulted in decrease in the yield of the imide oxime **3a** (Entry 9, 80%). Prolonging the reaction time to 2 h reduced the yield of **3a** (Entry 10, 84%).

With the optimized conditions (Table 1, Entry 1) in hand, the synthesis of *O*-phthalimide oximes **3a-l** from various vinyl azides **1a-l** was performed in order to study the scope of the discovered process (Table 2).

Table 2.
Scope of *O*-phthalimide oximes **3a-l** synthesized from vinyl azides **1a-l** and NHPI **2**.[a]

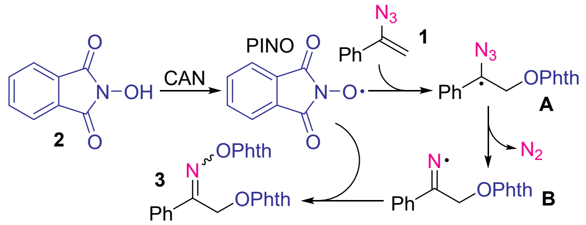


3a (85) **3b** (82) **3c** (79)
3d (73) **3e** (75) **3f** (54)
3g (67) **3h** (74) **3i** (88)
3j (69) **3k** (84) **3l** (63)

[a] Reagents and conditions: CAN (1.0 mmol, 548 mg) was added to a mixture of vinyl azide **1a-l** (0.5 mmol, 73-107 mg) and NHPI **2** (1.0 mmol, 163 mg) in MeOH (5 mL), and stirred at 20-25 °C for 1 h under an air atmosphere; isolated yields.

The reaction proceeded in high yields with vinyl azides **1b,c,i,k**, containing weakly electron-donating alkyl substituents on the aromatic ring (**3b,c,i,k,** 79-88%). The reactions with vinyl azides **2d,e,h** possessing moderately electron-withdrawing groups (F, Cl, CF_3) yielded *O*-phthalimide oximes **3d,e,h** with slightly diminished yields (73-75%). Vinyl azides bearing strongly electron-donating (MeO) or -withdrawing (NO_2) substituents gave products **3f,g,j,l** with the lowest yields of 54-69%.

Based on the literature data concerning the generation of PINO radicals from NHPI under the action of CAN[45] and the addition of radical species to vinyl azides,[29-31] we proposed a mec azides under the action of NHPI and CAN (Scheme 3).



Scheme 3. Proposed mechanism for the CAN-mediated synthesis of *O*-phthalimide oxime **3** from vinyl azide **1** and NHPI **2**.

The reaction begins with the formation of PINO radical from NHPI **2** under the action of CAN, followed by addition to the terminal carbon atom of the C=C bond of vinyl azide **1**. Nitrogen elimination from the resulting radical **A** occurs with the formation of iminyl radical **B**. At the last stage radical **B** is intercepted by the PINO radical to form product **3**.

3. Conclusion

In summary, we have disclosed the reaction between various vinyl azides and *N*-hydroxyphthalimide resulting in the formation of *O*-phthalimide oximes with an N-O-N fragment. The reaction proceeds under the action of cerium(IV) ammonium nitrate which acts as an oxidizing agent for the formation of the phthalimide-*N*-oxyl radical from NHPI. The radical pathway starts with the addition of the PINO radical to the C=C bond of the vinyl azide which triggers a cascade of radical transformations, including generation of the iminyl radical and its recombination with the PINO radical. The developed approach was successfully extended to various substituted vinyl azides. As a result, a wide range of *O*-phthalimide oximes was obtained with the yields ranging from 54-88%.

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Supplementary data

Supplementary data (experimental procedures, spectroscopic data for all of the synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/xxxx.

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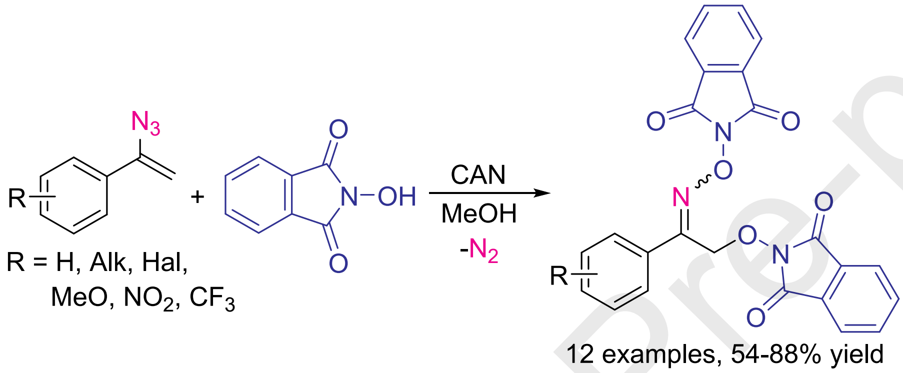
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐

interests/personal relationships which may be considered as potential competing interests:



- Cerium(IV) ammonium nitrate as a reagent for radical oxidative transformations.
- Preparative generation of imide-N-oxyl radicals from N-hydroxyphthalimide.
- Addition of O-centered imide-N-oxyl radicals to double carbon-carbon bonds.
- Reactions involving vinyl azides with the formation of iminyl radicals.
- Formation of N-O bond through the recombination of N- and O-centered radicals.