Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Oxycyanation of Vinyl Ethers with 2,2,6,6-Tetramethyl-*N*-oxopiperidinium Enabled by Electron Donor−Acceptor Complex

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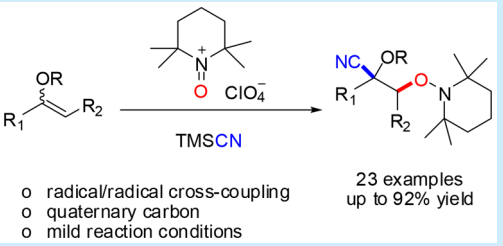
Supporting Information

ABSTRACT: An efficient and mild oxycyanation of vinyl ethers with 2,2,6,6-tetramethyl-*N*-oxopiperidinium and TMSCN is described. The mechanistic studies indicated that the formation of an electron donor−acceptor complex and subsequent single-electron-transfer process could be involved in the reaction.

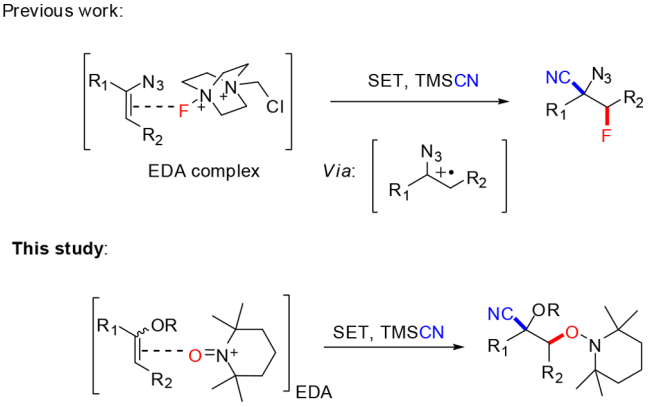


Nitrile compounds not only can serve as synthons for preparation of carboxylic acids, amides, amines, aldehydes and ketones[1] but also prevail in bioactive natural products and pharmaceutical agents.[2] Therefore, the development of efficient cyanation methods has been of considerable significance.[3] While olefins are a class of versatile building blocks in organic synthesis, direct cyanation of alkenes toward functionalized nitriles still remains underexplored.[4] Among these methods, the vicinal oxycyanation of alkenes represents a notable approach to introduce a cyano group as well as an oxygen atom.[4h−k] Despite the utility of these protocols to achieve oxycyanation, the development of new methods to meet various synthetic demands is still of great interest.

Alkene radical cations, as an open-shell species, show a combination of free-radical and cation properties that would deliver an attractive manner of reactivity and selectivity.[5] Recent efforts from our laboratory have demonstrated that vinyl azide could interact with 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) to form an electron donor−acceptor (EDA) complex,[6] followed by single-electron transfer (SET) to generate an alkene radical cation intermediate and subsequent fluorine atom transfer and nucleophilic cyanation (Scheme 1).[7b] On the other hand, the use of EDA complex strategy in synthetic chemistry is relatively less studied,[6] while the physicochemical properties of EDA complexes have been extensively investigated since the 1950s.[8] Due to the mild and sustainable properties of EDA complex-enabled reactions, the design and development of novel methods for the synthesis of useful molecules is highly desirable, and many groups have been devoted to finding new reactions in recent years.[9]

Inspired by the concept that the "F^+" could form EDA aggregate with electron-rich vinyl azide (Scheme 1), we wondered that whether "O^+" species would interact with electron-rich vinyl ether to give an EDA complex as well.

Scheme 1. EDA Complex-Enabled Vicinal Difunctionalization of Electron-Rich Alkenes



2,2,6,6-Tetramethyl-*N*-oxopiperidinium ($TEMPO^+$), as one of the oxoammonium salts which are widely used for the oxidation of alcohols,[10] might act as the "O^+" source. Recently, a charge-transfer (CT) complex TEMPO−ClO_2 was identified by Yamamoto and co-workers.[11] In continuation of our research interest in the transformation of electron-rich alkenes via alkene radical cations,[7] herein we report a novel and efficient protocol for the oxycyanation of vinyl ethers by using $TEMPO^+$ as the electron acceptor and TMSCN as the cyanating reagent, obtaining TEMPO-trapped 2-alkoxynitriles as the products which are difficult to access by existing methods (Scheme 1).

We commenced our investigation on the reaction of the substrate **1a** with $TEMPO^+ClO_4^-$ and TMSCN using dichloromethane (DCM) as the solvent. To our delight, the TEMPO-

Received: December 11, 2017

DOI: 10.1021/acs.orglett.7b03858
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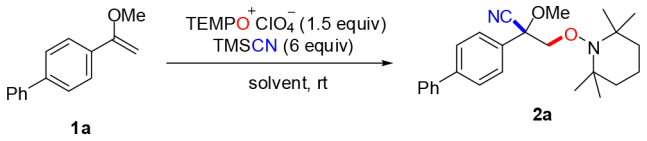
trapped nitrile **2a** was obtained in 53% yield (Table 1, entry 1). An increase of the loading of TMSCN up to 6 equiv led to a

Table 1. Optimization of Reaction Conditions[a]



1a **2a**

entry	solvent	additive	time (h)	yield[b] (%)
1[c]	DCM		1	53
2	DCM		1	62
3	CH_3CN		1	53
4	$PhCH_3$		1	42
5	DMF		12	<5
6	DCE		1	76
7	$CHCl_3$		1	10
8	PhCl		1	46
9	THF		1	28
10[d]	DCE	4 Å MS	1	56
11	DCE	Na_2CO_3 (2 equiv)	1	73
12	DCE	Na_3PO_4 (2 equiv)	1	75
13	**DCE**	**K_3PO_4 (2 equiv)**	**1**	**78**
14	DCE	K_2CO_3 (2 equiv)	1	75
15[e]	DCE	K_3PO_4 (2 equiv)	1.5	74

[a]**1a** (0.20 mmol), $TEMPO^+ClO_4^-$ (030 mmol), TMSCN (1.2 mmol), solvent (2 mL). [b]Isolated yield. [c]TMSCN (4 equiv, 0.80 mmol). [d]Powdered molecular sieves (4 Å, 50 mg). [e]In the dark.

higher chemical yield (entry 2 vs entry 1). A survey of organic solvents revealed that 1,2-dichloroethane (DCE) was the best one (entries 2–9). To inhibit the formation of hydrolysis byproduct ketone, molecular sieves were added but did not provide a better result (entry 10). Although the addition of an inorganic base could not significantly improve the chemical yield (entries 11–14), the TLC analysis showed that it was cleaner (or had fewer byproducts) compared to the neutral conditions (entry 6). It should be noted that the reaction proceeded smoothly in the dark as well though the yield dropped (entry 15).

In general, the EDA complex exhibits a charge-transfer (CT) band, the bathochromic shift band, which lies within the visible region in many cases.[8] We performed UV–vis spectroscopic measurements on **1a**, $TEMPO^+$, and a combination of these two components (Figure 1a). A noticeable absorption shift which could be attributed to the formation of an EDA complex was observed. Moreover, a Job's plot was constructed to evaluate the stoichiometry of the EDA complex between **1a** and $TEMPO^+$ in solution (Figure 1b).[12] The maximum absorbance was obtained at a ratio of 1:1. These results indicate that vinyl ether and $TEMPO^+$ can form the CT complex through single-electron transfer. To gain more insights about the mechanism of this reaction, control experiments were conducted (Scheme 2, eqs 1 and 2). In the presence of radical scavenger 4-oxo-TEMPO, we detected the formation of 4-oxo-TEMPO-trapped cyanation product **3** (Scheme 2, eq 1). To rule out the possibility that 4-oxo-TEMPO could be involved in the initiation step, the reaction of **1a** without $TEMPO^+$ was carried out. As might be expected, 4-oxo-TEMPO only acted as the radical scavenger (Scheme 2, eq 2). These results could support the involvement of radical process in the EDA complex-enabled oxycyanation.

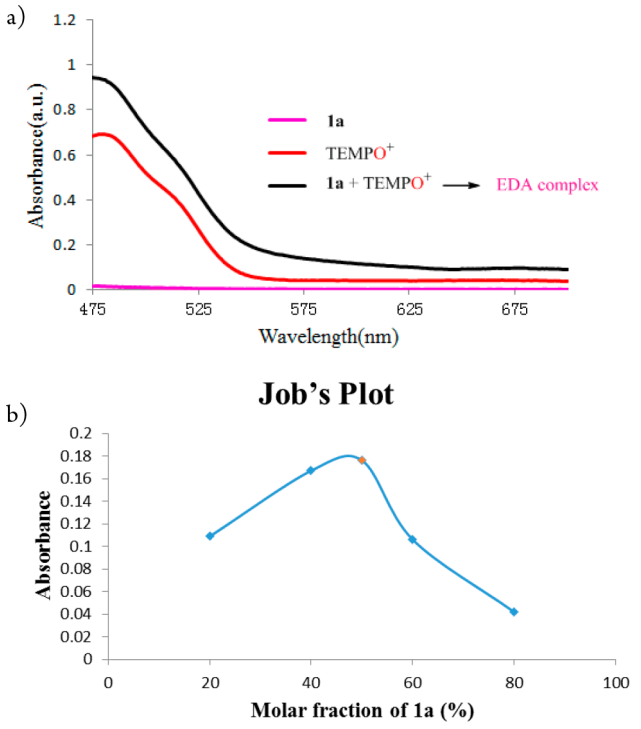
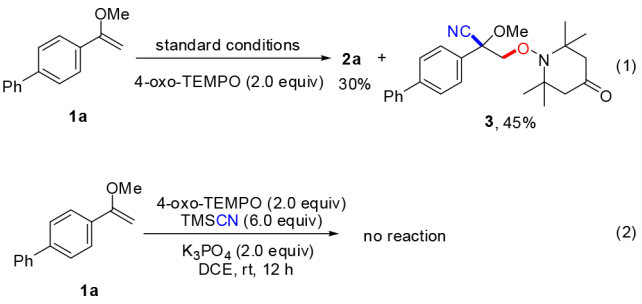


Figure 1. Optical absorption spectra recorded in acetonitrile in a 1 cm path quartz cuvettes using a Shimadzu UV-2600 UV–vis spectrophotometer. (a) [**1a**] = 0.1 M, [$TEMPO^+$] = 0.15 M. The combination of **1a** with $TEMPO^+$ leads to absorption shift. (b) Stoichiometry of the EDA complex in solution determined at 480 nm. The acetonitrile solutions of **1a** and $TEMPO^+$ have a constant total concentration of 0.02 M but different donor/acceptor ratios.

Scheme 2. Control Experiments



Having established the above optimal reaction conditions, we aimed to explore the scope of this mild oxycyanation protocol. As shown in Figure 2, a series of differentially substituted TEMPO-trapped nitriles were readily obtained in moderate to excellent yields (**2a–w**). In most cases, conversion of vinyl ether was completed within 2 h. This protocol could accommodate a wide range of substituents on arenes regardless of their electronic and/or steric properties (**2a–n**). For example, the reactions of the substrates bearing electron-withdrawing and electron-donating groups at the *para* positions on the phenyl rings proceeded nicely, giving the corresponding products in good yields (**2c–i**). In the examples of **2d** and **2e**, the survived bromo and iodo atoms reserved the options for further cross-coupling. It is of note that vinyl ethers containing alkynyl (**2p**) or thienyl (**2q**) moiety were compatible with the reaction conditions, providing the desired nitriles in satisfied yields. This protocol could also be extended to nonterminal vinyl ethers (**2r,s**), including cyclic substrate (**2r**), readily

DOI: 10.1021/acs.orglett.7b03858
Org. Lett. XXXX, XXX, XXX–XXX

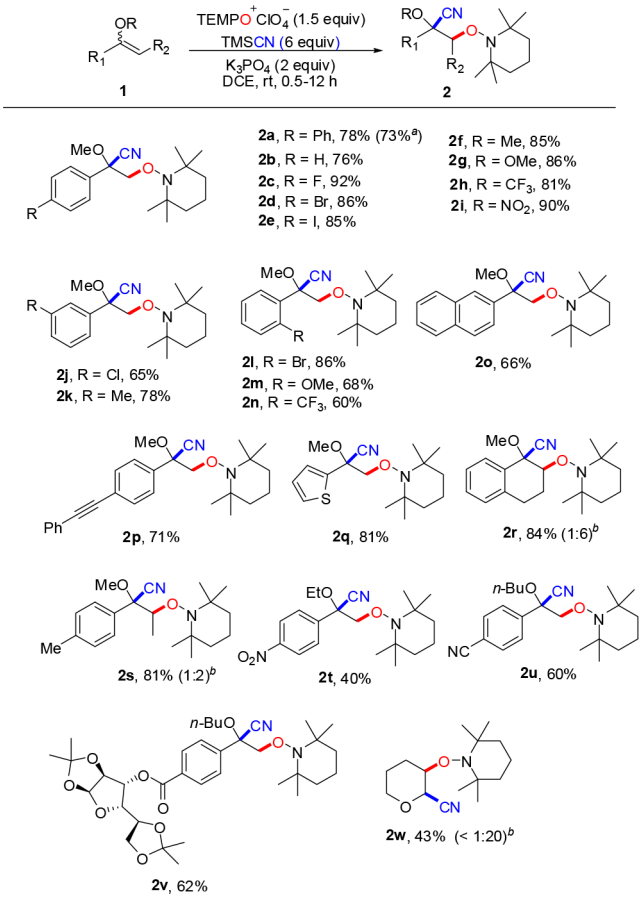


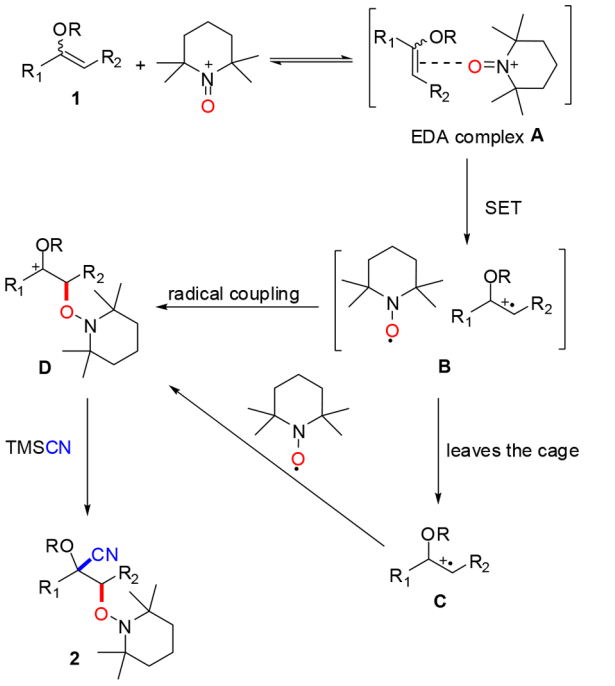
Figure 2. Scope of vinyl ethers. (a) 5 mmol scale. (b) The dr value was determined by ^{1}H NMR spectroscopy of the crude product.

furnishing the desired products in high yields. Ethyl (**2t**) and butyl (**2u**,**v**) ethers were also applicable for the oxycyanation. Inparticular, the chemical yield was not compromised when a sugar (diacetone-D-glucose) moiety was installed (**2v** vs **2u**). The reaction of alkyl vinyl ether also proceeded smoothly, affording the desired product with excellent stereoselectivity in acceptable yield (**2w**). Importantly, the reaction can be readily scaled up without compromising the chemical yield, for instance, affording **2a** in 73% yield (5 mmol scale).

The proposed mechanistic details of the transformation are depicted in Scheme 3.[7] At first, an EDA aggregate **A** can be formed between vinyl ether **1** and TEMPO$^+$ on the basis of the aforementioned experimental phenomena. The subsequent single-electron transfer (SET) is activated thermally, providing an alkene radical cation **C** within **B**, followed by a fast radical−radical cross-coupling to form a C−O bond in solvent cage. The final step involves a nucleophilic cyanation of carbocation intermediate **D**, giving the desired oxycyanation product. Alternatively, out-of-cage diffusion and following a radical coupling pathway cannot be excluded.

In conclusion, we have described the first example of an operationally simple protocol for the synthesis of TEMPO-trapped 2-alkoxynitriles under transition-metal-free conditions. The investigations indicated that an EDA complex-enabled generation of open-shell radical cation and subsequent radical/radical cross-coupling and nucleophilic cyanation could be involved in the reaction. Moreover, this mechanistically interesting reaction is efficient and widely applicable to a range of vinyl ethers. This transformation also demonstrated

Scheme 3. Proposed Mechanism



excellent functional group tolerance. Further applications of radical cations in organic synthesis are still ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03858.

Experimental details, characterizations, and ^{1}H, ^{19}F, and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (Grant No. 21302134) is acknowledged.

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DOI: 10.1021/acs.orglett.7b03858
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