

O-Alkylation of oxime with *N*-vinyl lactams induced by radical cationXiao-dong Jia^{a,*}, Yu-xia Da^a, Cai-xia Yang^a, Li Yang^b, Zhong-li Liu^b^a College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, PR China^b State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

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Abstract

Radical cation promoted O-alkylation of oxime with *N*-vinyl lactam was achieved under base free condition by using catalytic tris(4-bromophenyl)aminium cation radical (TBPA⁺SbCl₆[−]) as an initiator to produce the corresponding oxime ether in high yields.
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Oxime ethers are valuable nucleophilic reagents, with both nitrogen and oxygen atoms as the nucleophile. The addition of organometallic or radical species to oxime ethers becomes more and more important in organic syntheses.^{1,2} Recently, the utility of oximes in transition-metal-catalyzed allylic substitution³ and Michael addition⁴ has attracted more attention. Generally oxime ethers were prepared from *O*-alkyl hydroxylamine and the corresponding aldehyde. The direct preparation of oxime ethers from oximes has been commonly limited to the reaction of oximes with alkyl halides under basic conditions,⁵ while under acidic conditions byproducts of *N*-alkylation were inevitably produced.^{3b} Therefore, it is desirable to develop new synthetic protocol for the preparation of oxime ethers under neutral or acidic conditions.

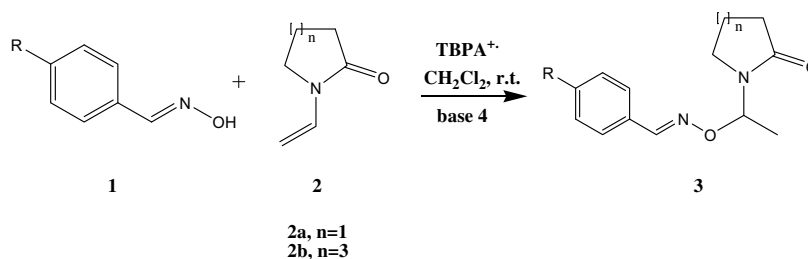
On our ongoing research program on synthetic potentials of cation radical induced reactions,⁶ we found recently that aza-Diels–Alder reactions could be efficiently induced by tris(4-bromophenyl)aminium cation radical (TBPA⁺SbCl₆[−]) to accomplish the [4+2] cycloaddition of aromatic imines with electron-rich olefins,^{6f,j} the [3+2] cycloaddition of chalcone epoxides with electron-rich olefins,^{6g} and [3+2] cycloaddition of chalcone epoxides with imines.^{6h} We report herein that TBPA⁺ can also efficiently initiate the

O-alkylation of oximes with *N*-vinyl lactams producing the corresponding oxime ethers in excellent yields.

An anhydrous CH₂Cl₂ solution (20 mL) of oxime (**1**, 1 mmol), *N*-vinyl lactam (**2**, 1 mmol), and 2,6-di-*tert*-butyl-pyridine (**4**, 0.1 mmol as base to inhibit acid-induced reactions.) was added dropwise to a stirred solution of a catalytic amount of tris(4-bromophenyl)aminium hexachloroantimonate (TBPA⁺SbCl₆[−], 0.05 mmol) suspended in anhydrous CH₂Cl₂ (20 mL) at ambient temperature. The reaction completed within 10–15 min, giving exclusively the corresponding oxime ethers **3** in excellent yield. In the reaction, the oxygen of oxime **1** was added regioselectively to the double bond of *N*-vinyl lactam **2**. Simple column chromatographic purification (silica gel, hexane/acetone 10:1) gave the pure products **3** (Scheme 1), which was fully identified by MS, ¹HNMR, ¹³CNMR, and HRMS.⁷ The results are listed in Table 1.

Diversified oximes **1** with either electron-withdrawing or electron-donating substituent were synthesized to test the generality of this methodology. It is seen from Table 1 that all the oximes reacted with **2** smoothly giving exclusively the corresponding *O*-alkyl oxime ethers in excellent yield, and no *N*-alkylation products were detected. Electron-donating groups (CH₃, CH₃O, entries 7–10) seem propitious to the addition giving extremely high yield, since they increase the nucleophilicity of the oxime, and hence facilitate its addition to the *N*-vinyl lactam radical cation (*vide infra*).

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Scheme 1.

Table 1
 TBPA⁺SbCl₆[−] initiated addition of oxime **1** with *N*-vinyl lactam **2**

Entry	Substrates		Products		Yield ^a (%)
	R	2			
1	1a	H	2a	3a	84
2	1a	H	2b	3b	82
3	1b	NO ₂	2a	3c	84
4	1b	NO ₂	2b	3d	87
5	1c	Cl	2a	3e	89
6	1c	Cl	2b	3f	85
7	1d	CH ₃	2a	3g	96
8	1d	CH ₃	2b	3h	98
9	1e	CH ₃ O	2a	3i	94
10	1e	CH ₃ O	2b	3j	92

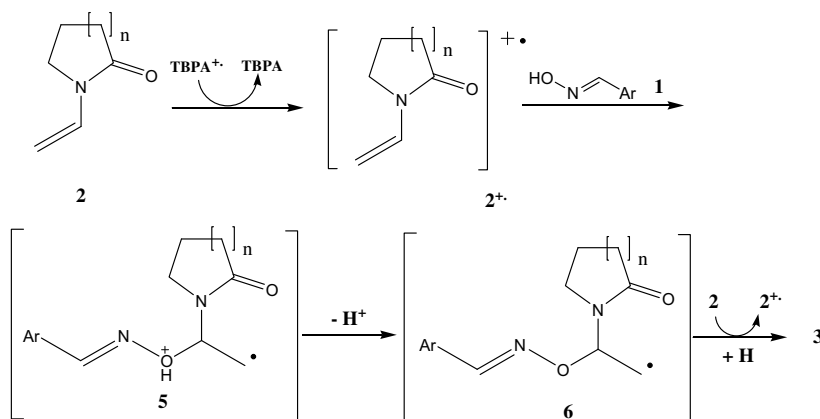
^a Isolated yields based on **1**.

We have reported previously that the oxidation potential of the substrates exerts remarkable effect on the radical cation reaction.^{6f,j} The smooth reaction of **1** with **2** again supports this criterion because the oxidation potential of **2** (~1.12 V vs SCE)⁶ⁱ is significantly lower than the oximes (1.77–2.14 V vs Ag/AgCl electrode).⁸ We also tried the reaction of **1** with other alkenes, such as α -methylstyrene ($E^{\text{ox}} = 1.72$ V vs SCE)^{6f} and cyclohexene,⁹ whose oxidation potentials are significantly higher than **2**. No reaction took place but a little bit of decomposition products of **1** were isolated. In case excessive *N*-vinyl lactam **2** was used, small amount of the dimer of **2** would be isolated. Therefore, this reaction can be rationalized as a cation radical

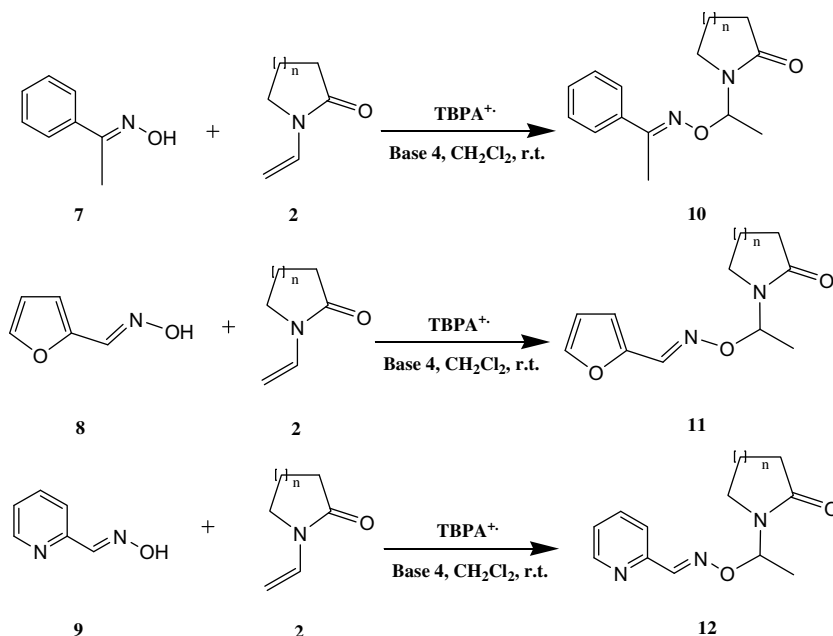
chain addition with **2** as the electrophile and the cationogen¹⁰ as depicted in Scheme 2. In Scheme 2, **2** is preferentially oxidized by TBPA⁺ giving the corresponding cation radical **2⁺**. The oxygen of **1** adds regioselectively to the α -carbon of the C=N bond of **2⁺**, affording a distonic cation radical adduct **5**. Cation radical **6** undergoes the second electron transfer with **2** to produce product **3**. This second electron transfer produces a new **2⁺** to propagate the radical chain reaction.

To extend the generality of this reaction, ketone oxime **7**, 2-furaldehyde oxime **8**, and 2-pyridinecarboxaldehyde oxime **9** were chosen to react with **2** (Scheme 3, Table 2). It was found that acetophenone and 2-furaldehyde oximes could smoothly react with *N*-vinyl lactams **2a** and **2b**, but the reaction of 2-pyridinecarboxaldehyde oxime (**9**) with **2** was relatively slow and the yield was lower. It is because of the fact that the presence of the pyridine ring can accelerate the rate of decomposition of TBPA⁺SbCl₆[−], presumably by removing protons from cation radicals generated in the reaction of **9** and **2**.¹¹

In conclusion, TBPA⁺SbCl₆[−] can effectively initiate the addition of oxime with *N*-vinyl lactams, producing the corresponding oxime ethers in excellent yield. In comparison with the previously reported methods, this approach is superior in terms of using catalytic amount of initiator (5 mol %), mild reaction conditions (ambient temperature and completed within 10–15 min), high yields, and especially avoiding the use of strong base. Further extension of this protocol is in progress.



Scheme 2.



Scheme 3.

Table 2

TBPA⁺SbCl₆[−] initiated addition of ketone and hetero-aromatic aldehyde oxime 7–9 with *N*-vinyl lactam 2

Entry	Substrates	2	Products	Yield ^a (%)
1	7	2a	10a	87
2	7	2b	10b	81
3	8	2a	11a	90
4	8	2b	11b	92
5	9	2a	12a	82
6	9	2b	12b	61

^a Isolated yields based on 1.

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- General procedure for TBPA⁺ induced reaction of oximes 1 and *N*-vinyl lactams 2: An anhydrous CH₂Cl₂ solution (20 mL) of oxime (1, 1 mmol), *N*-vinyl lactam (2, 1 mmol) and 2,6-di-*tert*-butylpyridine (4, 0.1 mmol) was added dropwise to a CH₂Cl₂ solution (20 mL) of a catalytic amount of tris-(4-bromophenyl)aminium hexachloroantimonate (TBPA⁺SbCl₆[−], 0.05 mmol) at ambient temperature under stirring. After completion of the reaction as monitored by TLC (10 min), the reaction was quenched with sodium carbonate methanol solution. The mixture was poured into a separator funnel with the addition of excess methylene chloride, and then the crude organic solution was extracted three times with water to remove inorganic salts. The organic phase was then dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure and the products were separated by silica gel column chromatography eluted with hexane/acetone (v/v 10:1) to afford the pure oxime ether as the unique product. Representative spectral data of the products (*E*)-*O*-1-(2-Oxopyrrolidin-1-yl)-ethyl-4-methyl-benzaldehyde oxime (3g): Colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 1.35 (d, *J* = 6.3 Hz, 3H), 1.82–1.92 (m, 2H), 2.23 (s, 3H),

2.27–2.32 (m, 2H), 3.30–3.34 (m, 2H), 6.02 (q, $J = 6.3$ Hz, 1H), 7.04 (d, $J = 7.5$ Hz, 2H), 7.36 (d, $J = 7.5$ Hz, 2H), 7.92 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 16.7, 17.8, 21.2, 31.4, 41.3, 80.0, 126.9, 128.9, 129.1, 140.0, 149.2, 175.3. EI-MS m/z (rel. int., %): 135 (4.4), 113 (7.9), 112 (100). HR-ESI-MS: Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2\text{H}^+$: 247.1441; found: 247.1439.

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