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SHORT COMMUNICATION

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Preparation of α-Sulfonylethanone Oximes from Oxidized Hydroxylamine

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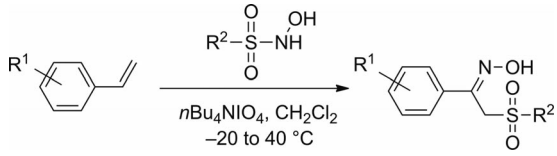
Alkenes react with substituted *N*-hydroxysulfonamides and tetrabutylammonium periodate under metal catalyst free conditions to give oximes in good to high yields. The reaction proceeds in a one-pot manner, giving rise to the formation of intermolecular C–N and C–S bonds simultaneously. The method is mild, highly efficient, and convenient.

Introduction

The formation of carbon–nitrogen bonds from olefins is considered to be an important strategy in organic synthesis that has found wide applications in the synthesis of many substances such as drugs, materials, natural products, and agrochemicals.[1] For some years, we have been interested in and have reported advancements in the construction of C–N bonds.[2] Recently, we found that NO is a practical amination reagent and can be used to react with olefins. On the basis of these former works, we wish to report a new method to synthesize oximes from olefins.

There are various ways to produce NO free radicals, for example, from organic nitrates and nitrites,[3] *N*-nitroso compounds,[4] metal–NO complexes,[5] *C*-nitroso compounds,[6] and *N*-hydroxyureas.[7] To date, there are few reported reactions that involve the release of NO for the synthesis of oximes from olefins.[8] In 2001, W. B. Motherwell and co-workers reported that thionitrites can be used as the nitrogen source in these reactions.[8d] Recently, Prateeptongkum and co-workers[8a] reported the first iron-catalyzed synthesis of oximes from styrenes. However, the methods described in these works have drawbacks, for example, low yields and limited varieties of nitrogen sources. Therefore, we wish to report a new NO-releasing reagent to improve this type of reaction. Due to the interest in the biological effects of nitric oxide and the chemical reactivity and biological activity of sulfonyl-containing compounds, we decided to use *N*-sulfonyl hydroxylamine as a novel NO-releasing reagent[9] to give rise to the formation of intermolecular C–N and C–S bonds simultaneously. In this paper, we report, for the first time, a practical process for synthesizing various sulfonylethanone oximes through a one-pot cascade oxidation–addition reaction of olefin derivatives by using *N*-hydroxysulfonamides as a nitrogen and sulfur source to give tosylethanone oximes in good yields (Scheme 1).



Scheme 1. The preparation of α-sulfonyl oximes by using oxidized hydroxylamine.

Results and Discussion

Initially, we carried out a set of experiments by using *N*-4-methylbenzenesulfonyl hydroxylamine[10] and styrene as model substrates and iodosylbenzene (PhI=O) as the oxidant to optimize the reaction conditions; the results are summarized in Table 1. In this reaction, the hydroxylamine was not stable in the presence of the oxidant; thus, a low temperature was selected. Considering previous reports,[8a–8c] a series of catalysts were tested, and a moderate amount of the expected product was formed when $Hg(OAc)_2$ was used as the catalyst (Table 1, Entries 1–4). We probed the solvent effect and found that dichloromethane was considerably superior to acetonitrile, tetrahydrofuran, and dichloroethane (Table 1, Entries 5–7). Subsequently, we attempted to identify the optimal oxidant, and the preliminary results showed that [hydroxy(tosyloxy)-iodo]benzene (HTIB) was more effective than PhI=O, $PhI(OAc)_2$, Dess–Martin periodinane, 2-iodoxybenzoic acid (IBX), and HTIB[11](Table 1, Entries 1, 8–12). However, we found that the temperature had a pronounced impact, and when tetrabutylammonium periodate (nBu_4NIO_4) was used as oxidant and the temperature ranged from –20 to 40 °C, there was a better yield than that obtained with

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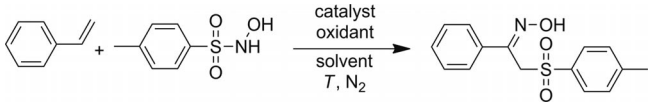
HTIB as oxidant (Table 1, Entries 13–19). Given the toxicity of mercuric acetate, we decided to use catalyst-free conditions and found that the reaction proceeded equally well without the catalyst (Table 1, Entries 18 and 19). Finally, the optimum results were obtained when hydroxylamine (1.2 equiv.), the oxidant (1.2 equiv.), and the alkene (1.0 equiv.) were allowed to react in dichloromethane at –20 °C for 1 h and then at reflux for 2 h.

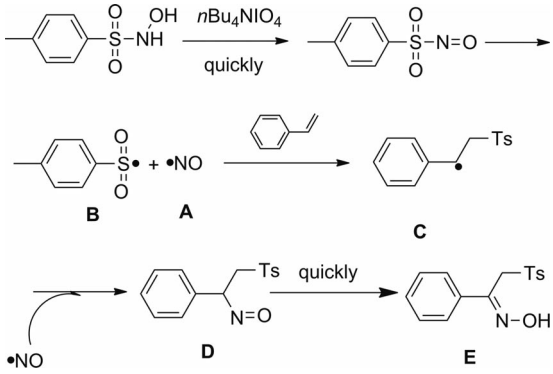
Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Oxidant	Solvent	Temperature [°C]	Yield [%][b]
1	$Hg(OAc)_2$	PhI=O	CH_2Cl_2	–40	40
2	AgOAc	PhI=O	CH_2Cl_2	–40	trace
3	$Cu(OAc)_2$	PhI=O	CH_2Cl_2	–40	0
4	$Cu(CF_3SO_3)_2$	PhI=O	CH_2Cl_2	–40	25
5	$Hg(OAc)_2$	PhI=O	CH_3CN	–40	trace
6	$Hg(OAc)_2$	PhI=O	THF	–40	trace
7	$Hg(OAc)_2$	PhI=O	DME	–40	37
8	$Hg(OAc)_2$	$PhI(OAc)_2$	CH_2Cl_2	–40	0
9	$Hg(OAc)_2$	nBu_4NIO_4	CH_2Cl_2	–40	20
10	$Hg(OAc)_2$	IBX	CH_2Cl_2	–40	0
11	$Hg(OAc)_2$	HITB	CH_2Cl_2	–40	52
12	$Hg(OAc)_2$	DMP	CH_2Cl_2	–40	0
13	$Hg(OAc)_2$	HITB	CH_2Cl_2	–20	50
14	$Hg(OAc)_2$	HITB	CH_2Cl_2	0	28
15	$Hg(OAc)_2$	HITB	CH_2Cl_2	–20 to 40	<10
16	$Hg(OAc)_2$	nBu_4NIO_4	CH_2Cl_2	–20	38
17	$Hg(OAc)_2$	nBu_4NIO_4	CH_2Cl_2	0	60
18[c]	$Hg(OAc)_2$	nBu_4NIO_4	CH_2Cl_2	–20 to 40	70
19[c]		nBu_4NIO_4	CH_2Cl_2	–20 to 40	70
20[d]	–	nBu_4NIO_4	CH_2Cl_2	–20 to 40	80
21[d,e]		nBu_4NIO_4	CH_2Cl_2	–20 to 40	80

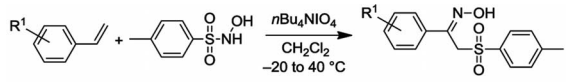
[a] Unless otherwise noted, all reactions were carried out by using the molar ratio of hydroxylamine/oxidant/substrate = 2:2:1. [b] Yield of isolated product. [c] –20 °C for 15 min and reflux for 1 h. [d] –20 °C for 1 h and reflux for 2 h. [e] Molar ratio of hydroxylamine/oxidant/substrate = 1.2:1.2:1.

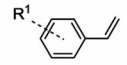
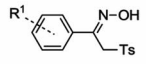
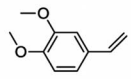
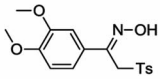
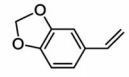
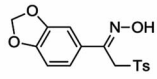
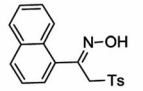
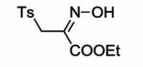
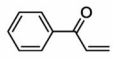
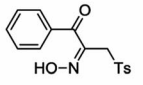
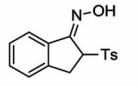
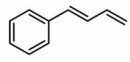
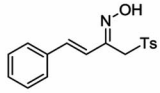
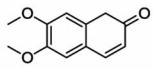
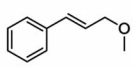
A probable mechanism for the formation of oximes is described in Scheme 2.[8d] First, hydroxylamine is oxidized by nBu_4NIO_4 at a low temperature to release NO free radical **A** and sulfonyl free radical **B**. Then, styrene first reacts



Scheme 2. Proposed mechanism.

Table 2. Scope and limitations.[a]



Entry	Substrate	Product	Yield [%][c]
1		**3a** R^1 = H	80
2		**3b** R^1 = *p*-Cl	81
3		**3c** R^1 = *m*-Cl	78
4		**3d** R^1 = *o*-Cl	78
5		**3e** R^1 = *p*-Br	85
6		 **3f** R^1 = *p*-F	79
7		**3g** R^1 = *o*-F	85
8		**3h** R^1 = *p*-CF_3	85
9		**3i** R^1 = *p*-CN	79
10		**3j** R^1 = *p*-NO_2	78
11		**3k** R^1 = *p*-OCH_3	88
12		**3l** R^1 = *o*-OH	59
13		 **3m**	91
14		 **3n**	82
15		 **3o**	75
16		 **3p**	54
17		 **3q**	68
18[b]		 **3r**	94
19[b]		 **3s**	90
20		–	**3t**	–
21		–	**3u**	–
22		–	**3v**	–
23		–	**3w**	–

[a] All reactions were carried out with molar ratio hydroxylamine/oxidant/substrate = 1.2:1.2:1, –20 °C for 1 h to reflux for 2 h. [b] *E*/*Z* = 1:1. [c] Yield of isolated product.

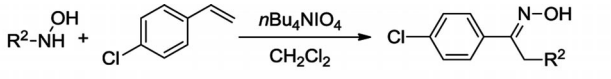
with **B** and subsequent capture of **A** by the carbon-centered radical gives intermediate **D**, which can afford the product through quick intramolecular hydrogen transfer. This mechanism is supported by successful capture of NO free radicals by using morpholine as a capturing reagent (see the Supporting Information). Moreover, when oxygen was present, a red-brown gas was obtained, and if this gas was allowed to flow through the tube into an aqueous solution of $FeSO_4$, the solution color changed from light green to brown, which proves the presence of NO free radicals.

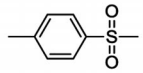
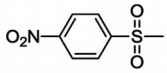
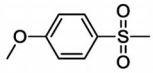
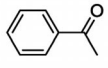
Having determined the optimized conditions, we explored the scope of this NO free radical addition by utilizing a variety of alkenes as substrates (Table 2). Different *para*-, *meta*-, and *ortho*-substituted styrene derivatives gave the desired products in good yields (Table 2, Entries 1–15). In general, no significant electronic effects were observed for electron-rich and electron-poor styrenes. On the other hand, the reactivity of the substrates suffered significantly from steric hindrance; for instance, 2,6-disubstituted and multisubstituted alkenes (Table 2, Entries 20–23) did not afford the corresponding oximes under identical conditions. However, cyclic alkenes could afford excellent yields, and the stereoconfiguration of the corresponding oximes had a *Z*/*E* ratio of 1:1 (Table 2, Entry 18). In addition, ethyl acrylate and 1-phenylpropenone afforded moderate yields of the target products (Table 2, Entries 16 and 17). It is possible that the steric hindrance and electronic effects of the carbonyl group makes the reactions with these compounds more sluggish than the reactions with styrene derivatives.

Remarkably, conjugated diene compounds were converted into the corresponding oximes in good yields (Table 2, Entry 19); however, the 1,4-addition compound was not formed; only the reaction with the unhindered double bond was observed.

Finally, we investigated the scope of the use of sulfonyl hydroxylamine (Table 3, Entries 1–6) under the optimized reaction conditions with *p*-chlorostyrene as the model alkene. As expected, the corresponding oximes were obtained in low to excellent yields. Different substituted benzenesulfonyl hydroxylamines were more reactive than alkyl-substituted sulfonyl hydroxylamines and gave the corresponding addition products in higher yields (Table 3, Entries 1–4). Possibly, the instabilities of the alkyl-substituted nitrogen sources resulted in lower yields of the oximes. Hydroxylamine lacking the sulfonyl group (Table 3, Entries 5 and 6) did not afford the corresponding oximes.

Table 3. Effect of hydroxylamine in the reaction.[a]



Entry	R^2	Yield [%][b]
1		81
2		77
3		66
4		27
5		–
6		–

[a] All reactions were carried out with a molar ratio of hydroxylamine/oxidant/substrate = 1.2:1.2:1 at –20 °C for 1 h and then at reflux for 2 h. [b] Yield of isolated product.

Conclusions

In summary, we have developed an efficient procedure for the addition of NO free radicals through the oxidation of hydroxylamine to form the corresponding oximes. These α-sulfonylethanone oximes are prepared from a cheap and environmentally friendly TsNHOH reagent and a mild oxidant, nBu_4NIO_4. The versatility, convenient operation, low cost, and environmental friendliness of this method, in addition to the high yields, make it viable for use both in laboratory research and in industrial production. Currently, we are exploring the scope of this reaction and the application of this free radical addition reaction with regard to the synthesis of pharmaceutical compounds.

Supporting Information (see footnote on the first page of this article) General procedure for the imidation of tertiary amines; characterization data, including ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

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