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Synthesis of α-nitro ketoximes from styrenes and *tert*-butyl nitrite

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Abstract

We have discovered that various α -nitro ketoximes can be synthesized in good yields starting from styrenes and *tert*-butyl nitrite. It was found that the success of the reaction was critically dependent on the use of a mixture solvent of DMSO and water. The reaction can tolerate a wide variety of substituents including electron-withdrawing and electron-donating groups.



 $R^2 = H \text{ or } Me.$

KEYWORDS: α-nitro ketoxime, styrene, tert-butyl nitrite, free radical, NO

INTRODUCTION

The synthesis of nitro-substituted compounds is particularly important because they can not only serve as valuable intermediates for polymers, dyes, but also for pharmaceuticals and agrochemicals.^{[1],[2]} They are frequently transformed into the corresponding amines and carbonyl compounds via reduction and Nef reaction.^{[1],[2]} Consequently, the development of new and improved methods for the synthesis of nitro-compounds has always attracted the attention of synthetic chemists.^[1-4] For the synthesis of nitroalkanes, the classical nucleophilic substitution reaction ($S_N 2$ type reaction) of an alkyl halide with a nitrate salt as the nucleophilic reagent is the bench mark method. As for the synthesis of nitroarenes, the classical electrophilic aromatic nitration using a cationic nitronium species is the method of choice in cases where it is applicable.^[5] Though these methods are efficient, they do suffer from problems such as lack of regioselectivity or having to employ strong acidic reaction conditions. As a result, chemists are seeking other alternative methods for the synthesis of nitro compounds.^[6]

RESULTS AND DISCUSSION

One of the most straightforward ways to synthesize nitroalkanes would be from an olefin and a nitro group donor. Indeed, the reaction of an olefin with a nitro donor has been studied extensively. Up to now, a number of reagents such as $NaNO_2$,^[7] RONO₂,^[8] $(NO_2)_4$,^[9] CeNH₄ $(NO_3)_4$,^[10] N_2O_4 ,^[11] NO_2 ,^[12] HNO₃^[13] and $NO^{[14]}$ have been utilized for the nitration of olefins. However, the products derived from the nitration of olefin can be

rather diverse. Sometimes, nitroalkenes are produced instead of the desired nitroalkanes, other times oximes are obtained as well. Among the nitrating reagents utilized, the use of alkyl nitrite, especially tert-butyl nitrite (TBN) has attracted considerable attention because TBN is a relatively stable liquid and its reaction usually does not employ strongly acidic condition. For example, Maiti has shown that in the presence of stoichiometric amount of TEMPO, the reaction of tert-butyl nitrite with olefins can give rise to nitroalkenes.^[15] Okamoto and Tanimoto have shown that using a Co complex as the catalyst, and BH₄⁻ as the hydrogen donor, the reaction of ethyl nitrite with styrenes can produce oximes as the exclusive product.^[16] In 1998, Sugamoto was able to effect the same transformation using Et₃SiH as the hydride donor employing Co^{II}(tpp) as the catalyst.^[17] This was later extended by Beller to use Fe(pc) as the catalyst.^[18] On the other hand, Ishibashi has tested the reaction of tert-butyl nitrite with styrenes under oxygen in a mixture solvent of hexane and water. They have found that α -nitro nitrate ester was formed as the major product.^[19] From all these studies, we can see that the chemistry of tert-butyl nitrite with olefins is very rich and can furnish all kinds of products depending on the reaction conditions. In this paper, we would like to report by running the reaction in DMSO and water under air, α -nitro ketoximes can be efficiently synthesized in good yields from *tert*-butyl nitrite and styrenes (Scheme 1, Eq.1).

The synthesis of α -nitro ketoximes from styrene is actually known. In 2001, Grossi and co-workers reported the radical nitration of styrene using peroxynitrite to give 2-nitro-1-phenylethyl nitrite along with 2-nitro-1-phenylethyl nitrate, benzaldehyde and α -nitro acetophenone and the combined yield is only 57% (**Scheme 1**, Eq. 2).^[20] Shaabani and coworkers have studied the reaction of styrene with sodium nitrite in the presence of a cationic exchange resin (Rexyn 101H) under solvent free condition. Surprisingly, they have discovered that the product they have obtained is the tautomeric isomer of α -nitro ketoxime, i.e., 2-nitro-1-nitrosoethylbenzene instead of α -nitro ketoxime.^[21] They also found that 2-nitro-1-nitrosoethylbenzene can readily undergo tautomerization to form the more stable α -nitro ketoxime (**Scheme 1**, Eq.3).

We became our study by using the reaction of styrene **1a** with *tert*-butyl nitrite **2** as the model reaction. When **1a** was treated with 0.5 equiv of TBN in DMSO under air at 50 °C, we were able to isolate a major product in 20% yield. Originally, we thought the product was α -nitro acetophenone. However, analysis of the isolated product's mass spectrum revealed that it was in fact α -nitro ketoximes **3a**. Next we tried to optimize the reaction conditions to increase the product yield and the results are shown in **Table 1**. We were pleased to find the yield can be increased to 26% if a small amount of water was added to the reaction mixture. The yield could be further increased to 38% if the solvent consists of a 2:1 mixture of DMSO and water. Disappointedly, running the reaction at higher

temperature actually had a detrimental effect on the product yield. However, lowering the reaction temperature to room temperature did benefit the reaction and a 46% yield could be achieved. Further lowering temperature to 0 $^{\circ}$ C slowed down the reaction considerably. Switching the solvent from DMSO to acetonitrile or toluene did not help either. In the end, we were delighted to find that an 84% yield could be achieved if two equiv of TBN was added. Test also indicated that though the reaction still proceeded under N₂, the yield was much lower. On the basis of the above results, we decided to set running the reaction of **1a** (1 equiv) with TBN (2 equiv) in a mixture of DMSO/water (2/1) at room temperature for 12 hours as our standard procedure.

With the optimized protocol in hand, we next turned our attention to explore the scope of the reaction. Starting from diversely substituted styrenes, a series of α -nitro ketoximes were synthesized in good yields and the results were summarized in **Table 2**. From **Table 2**, we could see that a wide variety of functional groups could be tolerated on the phenyl ring. Styrenes with substituents such as methyl, *tert*-butyl, methoxy, ethoxy, chloro, cyano as well as nitro group reacted smoothly under the standard reaction conditions to give the corresponding ketoximes in 40-82% yields. Substrates with electron donating groups tend to furnish the desired products in higher yields than styrenes with electron withdrawing groups. For example, styrene **1k** with a nitro group on the 4-position of the phenyl only produced the desired ketoxime **3k** in 51% yield whereas styrenes with

4-ethoxy or 4-methoxy groups generated the desired products in yields higher than 70%. It is worthwhile to point out that even a benzyl chloride functional group can survive in our reaction as in the case of 3e, highlighting the mildness of our reaction condition. We also noticed that substituents on the *ortho*-position of the styrene did have a negative impact on the product yield. For example, substrate 1c with a methyl group on the 2-position reacted with TBN to give product 3c in 46% while substrate 1n with a chloro group on the 2-position afforded the corresponding ketoxime 3n in only 40% yield. These results indicated that the reaction was sensitive to steric hindrance. We were pleased to find that a disubstituted styrene such as 1q could also participate in the reaction, affording the desired ketoxime 3q in 75% yield. Unfortunately, aliphatic alkenes such as 1-octene gave a complex mixture. It should be mentioned that some ketoximes did exist as an Z/E mixture.

Though the exact mechanism is still unknown at present, a plausible mechanism based on literature precedents^[19,20] is proposed and depicted in **Scheme 2**. First, TBN reacted with water to generate nitrous acid and two molecules of nitrous acid disproportionate to give nitrogen monoxide and dioxide. In air, nitrogen monoxide would be oxidized to nitrogen dioxide as well. Nitrogen dioxide would subsequently react with the double bond of styrene to generate the benzyl radical **A**. Next intermediate **A** would be captured by another molecule of nitrogen monoxide to give intermediate **B**. Finally, the α -nitro

ketoxime was produced after tautomerization. Alternatively, nitrogen monoxide could be formed directly from *tert*-butyl nitrite as depicted in the alternative pathway.

In summary, we have discovered that under suitable reaction conditions, styrenes can react with *tert*-butyl nitrite to give α -nitro keoximes as the major product. We found that the use of a mixture solvent of DMSO and water is critical for the success of the reaction. The reaction was found to tolerate a variety of functional groups including electron withdrawing and electron donating groups on the phenyl ring of styrene.

EXPERIMENTAL

All solvents and reagents were purchased from the suppliers and used without further purification. ¹H NMR and ¹³C NMR were recorded in CDCl₃ or d_6 -DMSO at room temperature on the Varian INOVA-400 spectrometer (400 MHz ¹H) and Bruker spectrometer (400 MHz ¹H). The chemical-shifts scale is based on internal TMS. All reactions were carried out in the air atmosphere.

General Reaction Procedure

To a 25 mL round bottom flask charged with a magnetic stir-bar was added H_2O (0.5 mL), Styrene (0.5 mmol), *tert*-butyl nitrite (1 mmol) and DMSO (1 mL). Then the reaction mixture was stirred at room temperature for 12 h. After the reaction was finished,

the mixture was diluted with CH_2Cl_2 , washed with brine and extracted with CH_2Cl_2 . The combined organic extracts were dried over Na_2SO_4 , concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=5:1) to afford the desired product (**3a**).

2-Nitro-1-phenyl-ethanone oxime (**3a**): Yield: 84%; Yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 9.01 (s, 1H), 7.55-7.53 (m, 2H), 7.38-7.33 (m, 3H), 5.57 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 148.6, 132.8, 130.5, 129.0, 126.1, 68.4; HRMS (ESI) calcd for C₈H₈N₂O₃K (M+K)⁺ 219.0172, found 219.0165.

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SUPPORTING INFORMATION:

Full experimental detail, ¹H NMR and ¹³C NMR spectra and references for all the products can be accessed on the publisher's website.

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Table 1. Reaction condition optimization

	+ t-BuONODMSO	, H ₂ O ► N ¹ OH	O ₂		
1a	2	~	3a		
Entry	1a:2	Atmosphere	Solvent(mL)	Temperature	Yield
				(°C)	(%) ^a
1	2:1	air	DMSO(1)	50	20
2	2:1	air	DMSO(1):H ₂ O(0.05)	50	26
3	2:1	air	DMSO(1):H ₂ O(0.5)	50	38
4	2:1	air	DMSO(1):H ₂ O(0.5)	75	34
5	2:1	air	DMSO(1):H ₂ O(0.5)	r.t.	46
6	2:1	air	DMSO(1):H ₂ O(0.5)	0	28
7	2:1	air	CH ₃ CN(1):H ₂ O(0.5)	r.t.	27
8	2:1	air	Toluene(1): $H_2O(0.5)$	r.t.	14
9	1:2	air	DMSO(1):H ₂ O(0.5)	r.t.	84
10	1:2	N ₂	DMSO(1):H ₂ O(0.5)	r.t.	36
11	1:2	air	CH ₃ CN(1):H ₂ O(0.5)	r.t.	37

^aIsolated yields.

$R^{1} \stackrel{ }{\underset{i}{\overset{i}{\overset{i}{\overset{i}{\overset{i}{\overset{i}{\overset{i}{i$							
Entry	Substrate	Product	Yield $(\%)^{b}(Z/E)^{c}$	Entry	Substrate	Product	Yield (%) ^{b,} (Z/E) ^c
1	$R^1 = 4-CH_3$	3b		9	$\mathbf{R}^1 =$	3ј	64(>20:1)
	$\mathbf{R}^2 = \mathbf{H} (\mathbf{1b})$		64(13.4:1)		4-CN		
					$\mathbf{R}^2 = \mathbf{H}$		
					(1 j)		
2	$R^1 = 2,5-CH_3$	3c		10	$\mathbf{R}^1 =$	3k	51(>20:1)
	$\mathbf{R}^2 = \mathbf{H} \left(\mathbf{1c} \right)$		46(7.0:1)		4-NO ₂		
		0	5		$R^2 = H$		
	, Ç				(1k)		
3	$\mathbf{R}^1 = 4 - t - \mathbf{B} \mathbf{u}$	3d	82(>	11	$\mathbf{R}^1 = 4 - \mathbf{C} \mathbf{l}$	31	69(>20:1)
	$\mathbf{R}^2 = \mathbf{H} (\mathbf{1d})$		20:1)		$R^2 = H$		
					(11)		
4	$R^1 = 4$ -CH ₂ Cl	3e	73(>	12	$R^1 = 3-Cl$	3m	
	$R^2 = H (1e)$		20:1)		$R^2 = H$		50(9.5:1)
					(1m)		

Table 2. Synthesis of α -nitro ketoximes from styrenes and *tert*-butyl nitrite^a

5	$R^1 = 4$ -MeO	3f		13	$R^1 = 2 - C1$	3n	
	$R^2 = H (1f)$		76(12.5:1)		$R^2 = H$		40(1.7:1)
					(1n)		
6	R ¹ =2-MeO	3g		14	$R^1 = 4-Br$	30	62(>20:1)
	$\mathbf{R}^2 = \mathbf{H} (\mathbf{1g})$		59(4.9:1)		$R^2 = H$		Q.
					(10)	\mathbf{G}	
7	$\mathbf{R}^1 = 4$ -EtO	3h	71(>	15	$R^1 = 3-Br$	3р	52(>20:1)
	$R^2 = H (\mathbf{1h})$		20:1)		$\mathbf{R}^2 = \mathbf{H}$		
				2	(1 p)		
8	R ¹ =4-CH ₃ COO	3i	61(>	16	$R^1 =$	3q	75(1.8:1)
	$\mathbf{R}^2 = \mathbf{H} (1\mathbf{i})$		20:1)		4-CH ₃ O		
		.0	5		$R^2 = CH_3$		
	, C				(1q)		

^aAll reactions were carried out by treating styrene (1 equiv.) with *tert*-butyl nitrite (2

equiv.) in DMSO (1 mL) and H_2O (0.5 mL) at room temperature for 12 h.

^bIsolated yields.

^cThe Z/E ratios were determined from the ¹H NMR spectra of the isolated product

mixtures.

Scheme 1.





