

This article was downloaded by:

On: 29 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713618290>

## Organic Synthesis Using Organosulfur-Nitrites and -Nitrates

Yong Hae Kim<sup>a</sup>

<sup>a</sup> Korea Advanced Institute of Science and Technology, Taejeon, Korea

**To cite this Article** Kim, Yong Hae(1993) 'Organic Synthesis Using Organosulfur-Nitrites and -Nitrates', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 74: 1, 249 — 260

**To link to this Article:** DOI: 10.1080/10426509308038111

**URL:** <http://dx.doi.org/10.1080/10426509308038111>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

## ORGANIC SYNTHESIS USING ORGANOSULFUR - NITRITES AND - NITRATES

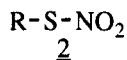
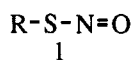
YONG HAE KIM

Korea Advanced Institute of Science and Technology, Yusung-Ku, Taejon, 305-701, Korea

**Abstract** Thionitrites or thionitrates have been considered to be unstable. However, bulky groups' thio- $\text{NO}_n$  such as *t*-butylthio-nitrites and -nitrates have been readily synthesized and found to be stable enough for the use of the useful organic syntheses as an excellent nitrosation and diazotization reagents under mild conditions. Direct conversion of amines to the corresponding halides in the presence of copper halides (II), fluorination of heterocyclic amines in the presence of sodium tetrafluoroborate,  $\alpha$ -oximation of methylene groups in ketones, facile cleavage of C=N bond to ketones, and desulfurization of thioacetals and thioketals, and other useful organic syntheses are described.

### INTRODUCTION

Both thionitrites (1) and thionitrates (2) are less stable than the corresponding oxygen analogs such as alkyl nitrites or alkyl nitrates.



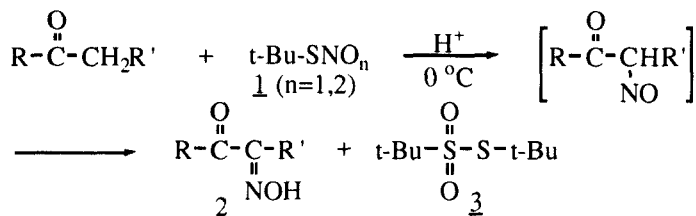
A few stable alkyl thionitrites (1) have been prepared by treating alkanethiols with either alkyl nitrites<sup>1</sup>, nitrosyl chloride<sup>2</sup>, or nitrous anhydrides<sup>3</sup>. Attempts to prepare arylthionitrites have also been made though unsuccessfully<sup>2,4</sup>. Since alkyl thionitrites of low molecular weight were characterized mainly by IR spectroscopic analysis in the gas phase due mainly to their instability, the yields and purities of these thionitrites were not reliable because of their ready decomposition. However, bulky groups' thio- $\text{NO}_n$  ( $n=1,2$ ) such as tertiarybutyl-thionitrite or -thionitrate is quite stable in aprotic solvents such as chloroform, carbon tetrachloride, tetrahydrofuran and ether, and can be expected to be better reagent for organic syntheses due to the weaker bond of sulfur - nitrogen than oxygen - nitrogen of nitrites. Spectral data of IR and UV could be successfully obtained at ca. 4 °C. Various interesting reactions of nitrosation, diazotization, nucleophilic substitution, and addition to olefines have been developed using tertiarybutyl thio-nitrites and -nitrates. In the course of studying oxidation of disulfide with  $\text{N}_2\text{O}_4$ , it was found that thiols reacted quickly with one equivalent amount of  $\text{N}_2\text{O}_4$  to give thionitrites in quantitative yields<sup>5</sup>. Dinitrogen tetroxide,  $\text{N}_2\text{O}_4$ , is known to be in an equilibrium with

$\text{NO}^+$  and  $\text{NO}_3^-$  ion.



Probably the electrophilic attack of  $\text{NO}^+$  on the sulfur atom of the thiol forms the corresponding thionitrite and nitric acid. The yields are almost quantitative, if the amount of  $\text{N}_2\text{O}_4$  was controlled to be equivalent, while the reaction temperature was kept sufficiently low i.e., below  $-10^\circ\text{C}$ , and hence remarkably higher in comparison with those in the known reaction of thiols with other alkylthionitrites, nitrosyl chloride or nitrous anhydride.

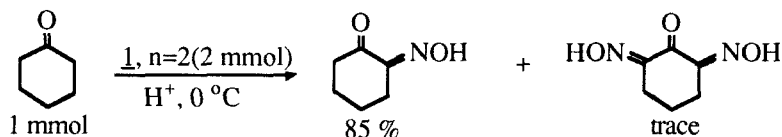
**DIRECT  $\alpha$ -OXIMATION** It was found that various ketones containing  $\alpha$ -methylene group reacted readily with t-butyl thionitrate (**1**,  $n=2$ ) at  $0^\circ\text{C}$  to afford the corresponding  $\alpha$ -oximinoketones (**2**) in excellent yields as shown below<sup>6</sup>.

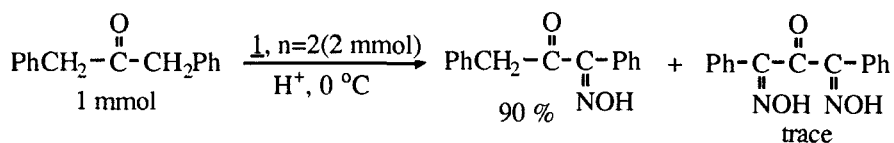


The  $\alpha$ -oximinoketones have been known to be an important intermediate for the synthesis of amino acids. Although alkyl nitrite, nitrous acid, or sodium nitrite in acetic acid are used for the synthesis of  $\alpha$ -oximinoketones, the yields are varied and selectivity for mono oximation on methylene carbon is low when the ketones have two methylene groups at both  $\alpha$ -positions.

t-Butyl thionitrate appears to be better reagent for the C-nitrosation of ketones due to the more facile cleavage of sulfur-nitrogen bond than that of oxygen-nitrogen bond of nitrites and also to the better leaving group of the sulfinyl group than alkoxy group ( $\text{RO}^-$ ) in the nitrosating step. Indeed, t-butylthionitrate reacted with propiophenone to give the higher yield of the oxime than those obtained using nitrites.

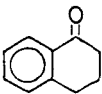
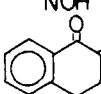
Moreover, t-butyl thionitrate resulted in a selectivity towards the mono oximation on the  $\alpha$ -carbon of the ketones which have two methylene groups at its both  $\alpha$ -positions as shown below.





The selectivity is probably due to a steric effect by the bulky t-butyl group and the mild reaction conditions. In contrast to the above high selectivity, when methyl nitrite (2 mmol) was used with cyclohexanone (1 mmol) or dibenzyl ketone (1 mmol), 2,6-dioximinocyclohexanone (61 %) or 1,3-dioximinodibenzyl ketone (68 %) was obtained respectively. The results obtained are shown in Table I.

TABLE I. Synthesis of  $\alpha$ -Oximinoketones with t-BuSNO<sub>n</sub> in THF

Run	Substrates	$\underline{1}$	$\frac{\underline{1}}{\text{Substrate}}$	Reaction Time(h)	Product (% yield) <sup>a</sup>
1	$\text{Ph}-\overset{\text{O}}{\text{C}}-\text{CH}_2\text{CH}_3$	n=2	1.2	0.3	$\text{Ph}-\overset{\text{O}}{\text{C}}-\underset{\text{NOH}}{\text{C}}-\text{CH}_3$ (97)
2	"	n=1	1.2	3	" (30)
3	$\text{PhCH}_2-\overset{\text{O}}{\text{C}}-\text{CH}_3$	n=2	1.2	0.6	$\text{PhCH}_2-\overset{\text{O}}{\text{C}}-\underset{\text{NOH}}{\text{C}}-\text{CH}_3$ (93)
4	"	n=1	1.5	4	" (50)
5	$\text{Ph}-\overset{\text{O}}{\text{C}}-\text{CH}_2-\text{Ph}$	n=2	1.4	0.4	$\text{Ph}-\overset{\text{O}}{\text{C}}-\underset{\text{NOH}}{\text{C}}-\text{Ph}$ (96)
6	$\text{Ph}-\overset{\text{O}}{\text{C}}-\text{CH}_2\text{CH}_2\text{Ph}$	n=2	1.2	1	$\text{Ph}-\overset{\text{O}}{\text{C}}-\underset{\text{NOH}}{\text{C}}-\text{CH}_2\text{CH}_2\text{Ph}$ (78)
7		n=2	1.5	1	 (83)
8	$\text{Ph}-\overset{\text{O}}{\text{C}}-\text{CH}_2-\overset{\text{O}}{\text{C}}-\text{Ph}$	n=2	1.4	4.5	$\text{Ph}-\overset{\text{O}}{\text{C}}-\underset{\text{NOH}}{\text{C}}-\overset{\text{O}}{\text{C}}-\text{Ph}$ (50)
9	"	n=1	1.5	6.3	" (0) <sup>b</sup>

a: Isolated yields. b: Most of starting material was recovered

When *t*-butyl thionitrite (1, *n*=1) which is less stable than *t*-butyl thionitrate (1, *n*=2) was used as the nitrosating reagent, the yields of oxime are low (Run 2,4 and 9) due to its unstability.

**DETHIOACETALIZATION OF THIOACETALS** Thioacetals and thioketals were readily cleaved to carbonyl compounds in excellent yields by treating with *t*-butyl thionitrite at ca. 0 °C in acetonitrile under mild conditions. The conversion of thioketals to the ketones appears to be initiated *via* nitrosation on two sulfur atoms of thioketals, followed by intramolecular transfer of nitroso oxygen.

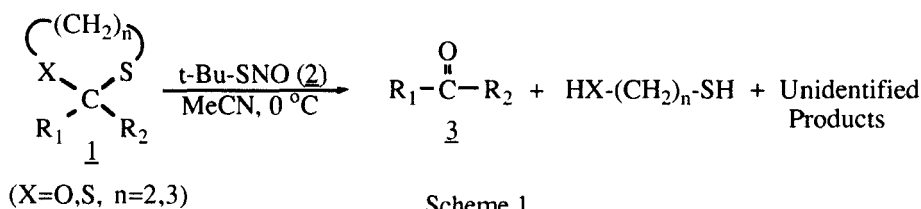
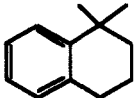
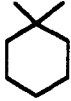


TABLE II. Oxidation of Thioacetals and Thioketals.

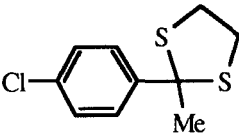
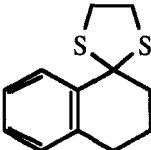
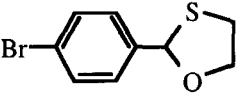
Run	R <sub>1</sub>	R <sub>2</sub>	X	n	<u>2</u> (eq.)	Time (h)	Yields (%) <sup>a</sup>
1	Ph	H	S	3	4	0.05	98
2	<i>p</i> -Cl-Ph	Me	S	2	2	1.5	90
3	Ph	Ph	S	2	3	3	95
4			S	2	3	0.3	90
5			S	2	3	0.6	85
6	Me	Et	S	2	3	1	73
7	<i>o</i> -Cl-Ph	H	O	2	1.2	0.6	95
8	<i>p</i> -NO <sub>2</sub> -Ph	Me	O	2	1.2	0.6	98
9	<i>o</i> -Br-Ph	H	O	2	1.2	0.3	93

a : Isolated yields

Various thioacetals or thioketals readily reacted with *t*-butyl thionitrite under mild conditions in acetonitrile without using aqueous media to afford the corresponding parent carbonyl compounds in excellent yields together with dithio or 2-mercaptoethanol and other unidentified products (Scheme 1)<sup>7</sup>. The results obtained are summarized in Table II.

The amount of **2** for the dethioacetalization was controlled depending on the number of sulfur atoms of the substrates. In the case of 1,3-dithian or 1,3-dithiolan, more than two equivalents of **2** was used the maximum yield of the carbonyl compound was achieved. While, 1,3-oxathiolan containing one sulfur atom reacted with one equivalent of **2** to give the carbonyl compounds in quantitative yields. Most of known methods for the dethioacetalization have been considered to proceed through hydrolytic cleavage in aqueous media<sup>8,9</sup>. However our new procedures to cleave 1,3-dithian, 1,3-dithiolan, and 1,3-oxathiolan have been performed in organic solvent such as anhydrous acetonitrile. Here a question is arised where the oxygen of carbonyl group comes. In order to see whether the oxygen of carbonyl group is originated from water or from *t*-butyl thionitrite, 1,3-dithiolan and 1,3-oxathiolan have been treated with **2** in the presence of <sup>18</sup>O-labelled water (<sup>18</sup>O content = 97 atom%). The results obtained are summarized in Table III.

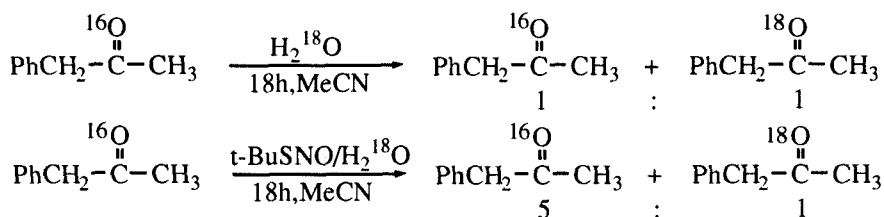
TABLE III. <sup>18</sup>O - Isotope experiment in Desulfurization Reactions.

Run	Substrate	H <sub>2</sub> <sup>18</sup> O(eq.) <sup>c</sup>	Time(h)	Yield(%) <sup>a</sup>	C=O <sup>16</sup> :C=O <sup>18</sup>
1		1	24	8	3 : 1 <sup>b</sup>
2		3	48	10	1 : 3
3		1.8	1	87	22 : 1

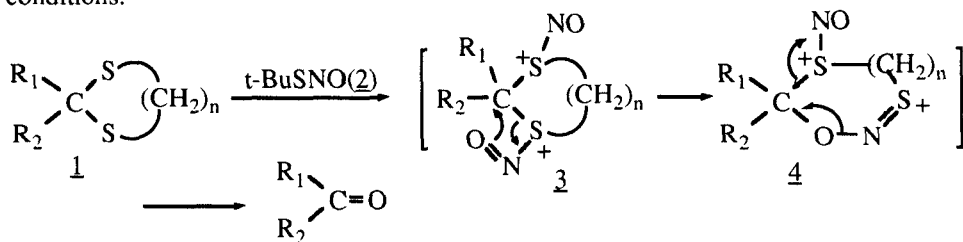
a : Isolated yields. b : Determined by mass spectroscopy. c : 97.2 atom% <sup>18</sup>O

The incorporation of <sup>18</sup>O into the carbonyl group from H<sub>2</sub><sup>18</sup>O can be explained by

the experiments that oxygen exchange occurs under the reaction condition and that an equilibrium between the carbonyl products and  $\text{H}_2^{18}\text{O}$  exists. When phenylacetone was treated with 2 equivalents of  $\text{H}_2^{18}\text{O}$  in acetonitrile in the presence of 2 ( 1 equivalent amount) and in the absence of 2 at 0 °C for 18h,  $^{18}\text{O}$  incorporations into phenylacetone were confirmed respectively as shown below.



These results seem to indicate clearly that the conversion of thioketals to the ketones involves an intramolecular cleavage of the ring intermediate (4) : namely the oxygen of carbonyl group is originated from the nitroso group of 2 as illustrated in the mechanistic path (Scheme 2) like in the case of desulfurization of thioamides derivatives<sup>10</sup>. Although the detailed mechanism of this reaction is not clear, 2 is considered to be an excellent reagent for the dethioacetalization under mild and neutral conditions.

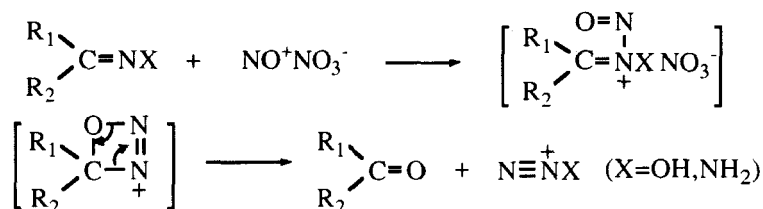



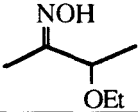
Scheme 2

### FACILE CONVERSION OF OXIMES AND HYDRAZONES INTO KETONES

Treatment of various oximes and hydrazones with dinitrogen tetroxide ( $\text{N}_2\text{O}_4$ ) at low temperature in acetonitrile gave the corresponding ketones respectively in excellent yields<sup>11</sup>. The reaction appears to be initiated by nitrosation on nitrogen atom to form a four membered ring intermediate by following substantial ring cleavage as shown below. Our new carbonyl generation method using dinitrogen tetroxide can be carried out in aprotic solvents such as tetrahydrofuran, chloroform, carbon tetrachloride, and acetonitrile under mild conditions and at the wide range of the reaction temperature from 0 °C to -40 °C. The reaction time is shorter than 30 minutes and the product yields are

higher than those from the known methods. Thus this method is widely available particularly for the substrates which are soluble in aprotic organic solvents.

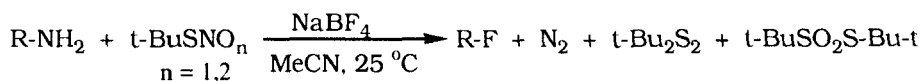
TABLE IV. Deoxygenation of Oximes with N<sub>2</sub>O<sub>4</sub>

Run	R <sub>1</sub>	R <sub>2</sub>	Temp (°C)	Time(min)	Solvent	N <sub>2</sub> O <sub>4</sub> (e.q.)	Yield(%) <sup>a</sup>
1	Me	Me	-40	10	THF	2 <sup>b</sup>	95 <sup>c</sup>
2	Me	Me	0	10	THF	3	90
3	Me	Et	-40	10	THF	3	85 <sup>c</sup>
4		NOH	-30	15	THF	3	92 <sup>c</sup>
5	Ph	Me	-35	10	THF	3	80
					MeCN	3	78
6	p-Cl-Ph	Me	-30	15	THF	3	75
					MeCN	3	70
7	Ph	Et	-40	10	THF	3	78
8	Ph	Ph	-35	10	THF	3	65
9	p-Tol	H	-40	10	MeCN	3	90
10	(Ph) <sub>2</sub> CH	Me	-40	10	MeCN	3	81
11		OE <sub>t</sub>	-40	10	MeCN	3	95 <sup>c</sup>

a: Isolated yields. b: When acetone oxime was reacted with 3 equivalent N<sub>2</sub>O<sub>4</sub>, diacetylfuroxan was produced in 90% yield. c: The yields were determined by GC (column SE-30, 3% on carbowax 20, 60 / 80 mesh, flow rate ; 30 ml / min, He)



**FLUORINATION OF AMINES** In the course of studies on the synthetic applications of thionitrite and thionitrate based on these precedents which described a nonaqueous substitutive diazotization, it was found that these diazotizing reagents could be used for the heterocyclic amine systems. Recently we have communicated a new and direct conversion of amino-heterocycles to fluoro-heterocycles using *t*-butyl thionitrite or *t*-butyl thionitrate as the nitrosating agents with sodium tetrafluoroborate.<sup>12</sup> We now supply more complete details for the synthesis of fluoro-heterocycles and extend the work to demonstrate the general utility of nonaqueous deamination reactions in the synthesis of chloro- and bromo-heterocycles.



R = heterocycle, nucleoside, nucleic acid base

Various amino-heterocycles and amino-nucleosides reacted readily with *t*-butyl thionitrite or *t*-butyl thionitrate in the presence of sodium tetrafluoroborate in neutral and aprotic media to afford the corresponding fluoro-heterocycles and fluoro-nucleosides, respectively, in good yields.

TABLE V. Fluorination of Amines with *t*-BuSNO and NaBF<sub>4</sub>

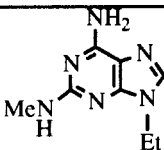
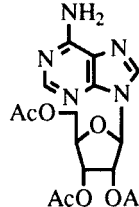
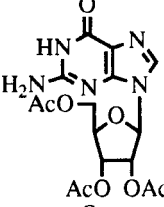
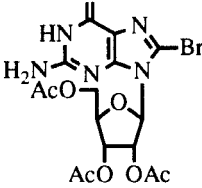
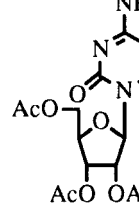
R-NH <sub>2</sub> + t-BuSNO + NaBF <sub>4</sub> $\xrightarrow{\text{MeCN}}$ R-F				
Run	Amine <sup>a</sup>	Temp (°C)	Time (h)	Yield <sup>b</sup> (%)
1		25	5	99
2		25	20	62
3		25	48	30

a) Molar ratio ; Amine : *t*-BuSNO : NaBF<sub>4</sub> = 1 : 2 : 2

b) Isolated yields after chromatographic purification

Heterocyclic amines including protected nucleosides reacted with *t*-butyl thionitrite (*t*-BuSNO) in the presence of sodium tetrafluoroborate to give the corresponding fluorinated products. The results obtained are listed in Table V.

TABLE VI. Fluorination of Amines with *t*-BuSNO<sub>2</sub> and NaBF<sub>4</sub>

$\text{R-NH}_2 + \text{t-BuSNO}_2 + \text{NaBF}_4 \xrightarrow{\text{MeCN}} \text{R-F}$				
Run	Amine <sup>a</sup>	Temp (°C)	Time (h)	Yield <sup>b</sup> (%)
1		25	2	50
2		25	20	26
3		25	20	48
4		25	10	56
5		25	3	72

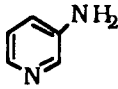
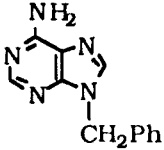
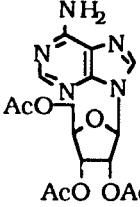
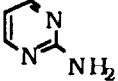
a) Molar ratio ; Amine : *t*-BuSNO<sub>2</sub> : NaBF<sub>4</sub> = 1 : 2 : 2

b) Isolated yields after the chromatography

In a similar manner, when *t*-butyl thionitrate ( $t\text{-BuSNO}_2$ ) was used instead of *t*-butyl thionitrite as a diazotizing reagent in the presence of sodium tetrafluoroborate, the reasonable yields of fluorine compounds were obtained. The results obtained are shown in Table VI.

Although *t*-butyl thionitrite is also an effective deaminating reagent, it is not thermally stable as compared to *t*-butyl thionitrate, and hence *t*-butyl thionitrate is more efficient than *t*-butyl thionitrite. Thus *t*-butyl thionitrate appears to be more effective deamination reagent for the direct fluorination in the presence of sodium tetrafluoroborate. Aminopyridine, 9-substituted purine nucleosides, and 2-amino-5-nitrothiazole were reacted with *t*-butyl thionitrite or *t*-butyl thionitrate in the presence of anhydrous cupric halides ( $\text{CuX}_2$ ,  $\text{X} = \text{Cl}, \text{Br}$ ) in acetonitrile at room temperature to effect a direct conversion of amino-group to chlorine or bromine. These direct halogenation reactions of heterocyclic primary amines in the presence of cupric chloride ( $\text{CuCl}_2$ ) afforded better yields than those in case using cupric bromide ( $\text{CuBr}_2$ ). The results obtained are shown in Table VII and VIII.

TABLE VII. Halogenation of Amines with *t*-BuSNO and  $\text{CuCl}_2$

$\text{R-NH}_2 + t\text{-BuSNO} + \text{CuCl}_2 \xrightarrow{\text{MeCN}}$		R-Cl		
Run	Amine <sup>a</sup>	Temp (°C)	Time (h)	Yield <sup>b</sup> (%)
1		25	6	82
2		25	24	35 <sup>c</sup>
3		25	24	42
4		25	4	trace

a) Molar ratio : Amine :  $t\text{-BuSNO}$  :  $\text{CuCl}_2 = 1 : 2 : 2$

b) Isolated yields after chromatographic purification

c) Dry MeCN - THF (3 ml : 3 ml) was used.

While, alkyl thionitrates of oxygen analogous of alkyl nitrates have been examined for the deaminative halogenation even in heating with cupric halides, but failed to obtain deaminative products. Thus, t-butylthionitrate was found to be an effective deamination reagent.

TABLE VIII. Halogenation of Amines with t-BuSNO<sub>2</sub> and CuX<sub>2</sub> (X = Cl, Br)

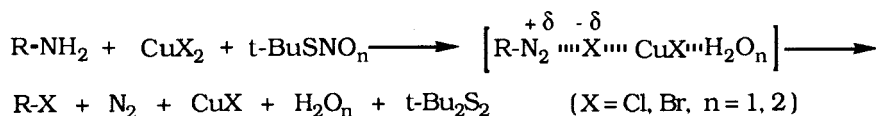
R-NH <sub>2</sub> + t-BuSNO <sub>2</sub> + CuX <sub>2</sub> $\xrightarrow{\text{MeCN}}$ R-X					
Run	Amine <sup>a</sup>	CuX <sub>2</sub>	Temp (°C)	Time (h)	Yield <sup>b</sup> (%)
1		CuCl <sub>2</sub>	25	6	95
2		CuBr <sub>2</sub>	25	6	80
3		CuCl <sub>2</sub>	25	4.5	88
4		CuBr <sub>2</sub>	25	4.5	77
5		CuCl <sub>2</sub>	25	24	69 <sup>c</sup>
6		CuBr <sub>2</sub>	25	24	32 <sup>c</sup>
7		CuCl <sub>2</sub>	25	24	82
8		CuBr <sub>2</sub>	25	24	62

a) Molar ratio ; Amine : t-BuSNO : CuX<sub>2</sub> = 1 : 2 : 2

b) Isolated yields after chromatographic purification

c) Dry MeCN - THF (3 ml : 3 ml) was used.

These halogenations probably involve an initial formation of an intermediate diazonium salt like the case of deamination of arylamines with alkyl nitrates<sup>13,14</sup>, thionitrates or thionitrates<sup>15</sup>. The plausible reaction mechanism is shown as follows.



## REFERENCES

1. H. Lecher and W. Siefhen, **Ber.**, **59**, 1314 (1926).
2. H. S. Tasker and H. O. Jones, **J. Chem. Soc.**, **95**, 1910 (1909).
3. R. J. Philipe and H. Moor, **Spectrochimica Acta.**, **17**, 1004 (1961) : R. J. Philipe **J. Mol. Spectroscopy**, **6**, 492 (1961).
4. H. Reinboldt, **Ber.**, **59**, 1311 (1926).
5. Y. H. Kim, D. Fukushima and S. Oae, **J. Chem. Soc. Chem. Commun.**, 470 (1977). *ibid*, **Tetrahedron Lett.**, 1211 (1978).
6. Y. H. Kim, Y. J. Park, and K. Kim, **Tetrahedron Lett.**, **30**, 2833 (1989).
7. Y. H. Kim and Y. J. Park, **Heteroatom Chem.**, **1**, 237 (1990).
8. G. A. Olah, Y. D. Vankar, M. Arvanaghi and G. K. A.Parkash, **Synthesis**, 720 (1979).
9. G. Stark and K. zhao, **Tetrahedron Lett.**, **30**, 287 (1989).
10. Y. H. Kim and H. J. Kim, **Tetrahedron Lett.**, **28**, 1669 (1989).
11. S. B. Shim, K. Kim and Y. H. Kim, **Tetrahedron Lett.**, **28**, 645 (1987).
12. Y. H. Kim, C. H. Lee and K. Y. Chang, **Tetrahedron Lett.**, **31**, 3019 (1990).
13. M. P. Doyle and W. J. Bryher, **J. Org. Chem.**, **44**, 1572 (1979).
14. M. P. Doyle, B. Siegfried and J. J. Hammond, **J. Am. Chem. Soc.**, **98**, 1627 (1976).
15. S.Oae, K. Shinhama and Y. H. Kim, **Bull. Chem. Soc. Jpn.**, **53**, 1065 (1980).