Nitrosation of Active Methyl and Methylene Groups on *N*-Heteroaromatics

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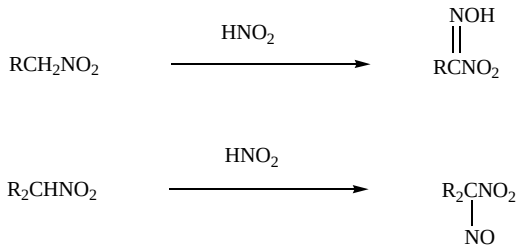
Abstract: The preparation of oxime by nitrosation of active methyl and methylene groups of *N*-heteroaromatics is presented. The reaction of *N*-heteroaromatics with alkyl nitrite in the presence of a base in liq. NH_3 or THF and the difference of reactivity based on *E*-*Z* geometrical isomers of oxime are discussed experimentally and theoretically.

Keywords: Nitrosation, active methyl and methylene groups, *N*-heteroaromatics, alkyl nitrite, liquid ammonia, oxime, geometrical isomer.

INTRODUCTION

Nitrosation reactions are now standard procedures both in the laboratory and in industry to bring about useful products and important intermediates in organic synthesis. Some nitrosations which are industrially important include the formation of azo dyes by diazotization of aromatic and heterocyclic amines, the formation of hydroxylamine by nitrosation of bisulphate ions, the production of ε-caprolactam and hence nylon 6 by the nitrosation of cyclohexane derivatives, the use of nitroso compounds in rubber production as well as the use of alkyl nitrites and metal nitrosyl complexes as vasodilators in medicine. It is well documented that the nitrosation reaction of aliphatic carbon atoms like active methyl, methylene and methine groups result in the formation of nitroso or oximino derivatives (Scheme **1**) [1].



Scheme 1.

Oxime is usually obtained by the reaction of a carbonyl compound with hydroxylamine, and this oximation requires more reaction steps to prepare a carbonyl compound than nitrosation. For example, 9-acridinaldehyde oxime is obtained by the reaction of hydroxylamine with 9-acridinaldehyde which is conveniently prepared by pyridinium chlorochromate oxidation of 9-methylacridine [2]. Oxime function is often involved in various types of medicines, for example, in antibiotics like cefdinir and cefuroxime axetil, and pralidoxime iodide (PAM) as an antidote for organophosphate compound poisoning.

Recent reviews also deal with only aliphatic and alicyclic *C*-nitrosation along with *N*-nitrosation, which is sometimes found in alkylating agents like nimustine or ranimustine for cancer, *S*-nitrosation or *O*-nitrosation [3, 4]. With a few exceptions, the replacement of hydrogen on an aliphatic carbon atom requires the presence of electron-withdrawing groups, such as acyl, aroyl, carbonyl, carboxyl, carbalkoxyl, nitro, cyano, imino or aryl groups adjacent to the carbon to be nitrosated. However, up to present, almost no previous works besides our studies on oxime formation by the nitrosation of active methyl or methylene groups of *N*- heteroaromatics, which form the basic frameworks of medicines, have appeared in literature. We have already once finished the study of oxime synthesis by nitrosation till the beginning of 1990. However, the recent strong demands of development of new vasodilators by nitrosation encouraged us to summarize our previous works on nitrosation first and embark upon new medicine synthesis by *N*-nitrosation. Thus, this review deals with nitrosation of active methyl and methylene groups of *N*-heteroaromatics in particular, including pyridine, quinoline and pyrimidine derivatives, to exemplify useful methods for oxime formation and show the difference of reactivity based on *E*-*Z* geometrical isomers of oxime.

(1) Nitrosation in Liquid NH_3 (liq. NH_3)

In 1963, Goto *et al*. for the first time, carried out the nitrosation of active methyl group of picolines and their *N*-oxides with amyl nitrite in the presence of metal amide in liq. NH_3 to obtain the corresponding aldoximes, acid amide and nitrile as shown in Table **1** [5, 6].

The configurations (*E* or *Z* forms) of the aldoximes in Table **1** are later unambiguously assigned using $\delta_{OH} - \delta_{CH=N}$ values in ^1H – NMR spectra [7, 8]. Based upon these results, it may be given as a conclusion that the methyl group of picoline *N*-oxide is much more reactive than that of picoline, and that the 4-substituted methyl group is more reactive than the 2-isomer and the methyl group at the 3-position of the pyridine ring, which is almost unreactive toward amyl nitrite under these conditions. Furthermore, it is very interesting that the reaction of 4-methylpyridine 1-oxide (**6**) with isoamyl nitrite ($C_5H_{11}ONO$) in the presence of $NaNH_2$ in liq. NH_3 gave only 4-pyridinecarboxamide 1-oxide (**14**) (41% yield) at room temperature and at -33 °C a thermodynamically unstable aldoxime, (*Z*)-4-pyridinecarbaldehyde 1-oxide oxime (**10*Z***) in good yield. On the other hand, in the case of the reaction of 2-methylpyridine 1-oxide (**4**) under the same conditions, a thermodynamically stable aldoxime, (*E*)-2-pyridinecarbaldehyde 1-oxide oxime (**9*E***) was obtained both at room temperature and at -33 °C. In 1941, Vermillion and Hauser reported that, in the presence of KNH_2 in liq. NH_3 at room temperature, (*Z*)-*p*-anisaldehyde oxime changes *via* nitrile and amidine into the corresponding amide, while under similar conditions, (*E*)-*p*-anisaldehyde oxime is mostly recovered, being partly decomposed (Scheme **2**) [9].

Taking into account this report by Vermillion and Hauser, the fact that only **14** was obtained in the nitrosation of **6** with $C_5H_{11}ONO$ in the presence of $NaNH_2$ in liq. NH_3 at room temperature strongly indicates that **14** was formed *via* an originally thermodynamically unstable *Z*-isomer. This estimation was confirmed through the following experimental and theoretical studies (*vide infra*). The corresponding *E* and *Z* isomers of aldoxime, which were obtained by nitrosation of **4** and **6**, were treated under the same conditions as those of the nitrosation to give the results shown in Table **2** [10].

These experimental results described above obviously indicate that in the nitrosation of **6** at room temperature the thermodynamically unstable *Z*-isomer **10*Z*** could be first formed, and then *via* nitrile and amidine, it could be converted into amide eventually. At -33 °C only **10*Z*** is formed, which is isomerized by post-treatment,

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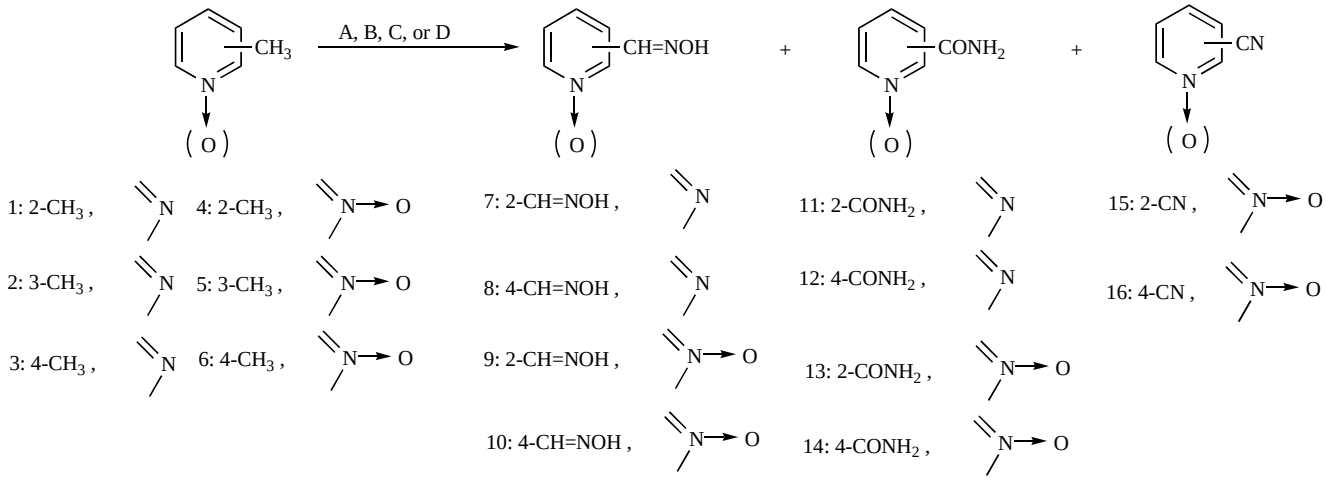
Table 1. Reaction of Methylpyridines and Their 1-Oxides under Conditions A - D



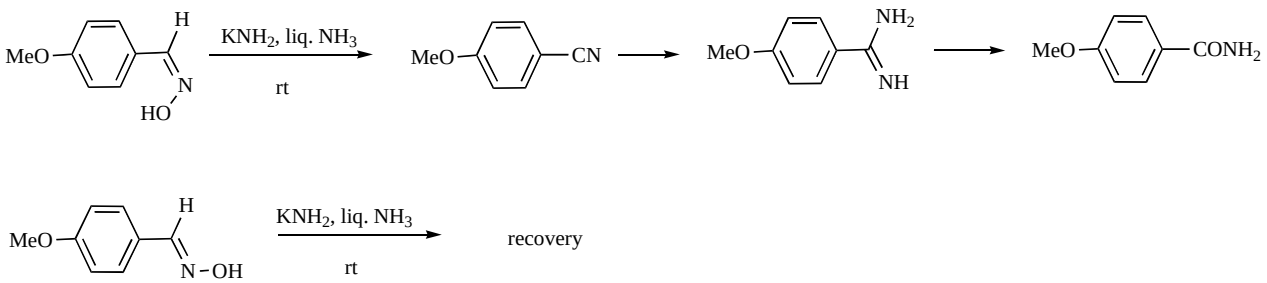
Reactant	Conditions [a]	Product (%)		
		aldoxime	amide	nitrile
1	**A**		2(**11**) [b]	
	B	23(**7**)		
2	**A**			
	B			
3	**A**		18(**12**)	
	B	66(**8**)	5(**12**)	
4	**A**	51(**9*E***) [c]	6(**13**)	
	B	57(**9*E***)	17(**13**)	
	C	46(**9*E***)	8(**13**)	
	D	23(**9**)	5(**13**)	
5	**A**			
	B			
6	**A**		41(**14**)	
	B	71(**10*Z***)	10(**14**)	2(**16**)
	C	50(**10*Z***)	5(**14**)	

a) **A**: $C_5H_{11}ONO$, $NaNH_2$, liq. NH_3, rt **B**: $C_5H_{11}ONO$, KNH_2, liq. NH_3, -33 °C

C: $C_5H_{11}ONO$, $NaNH_2$, liq. NH_3, -33 °C **D**: $C_5H_{11}ONO$, NaOH, liq. NH_3, rt

b) The number in parenthesis indicates the compound number.

c) *E* and *Z* in parenthesis show *E*-form and *Z*-form of oxime

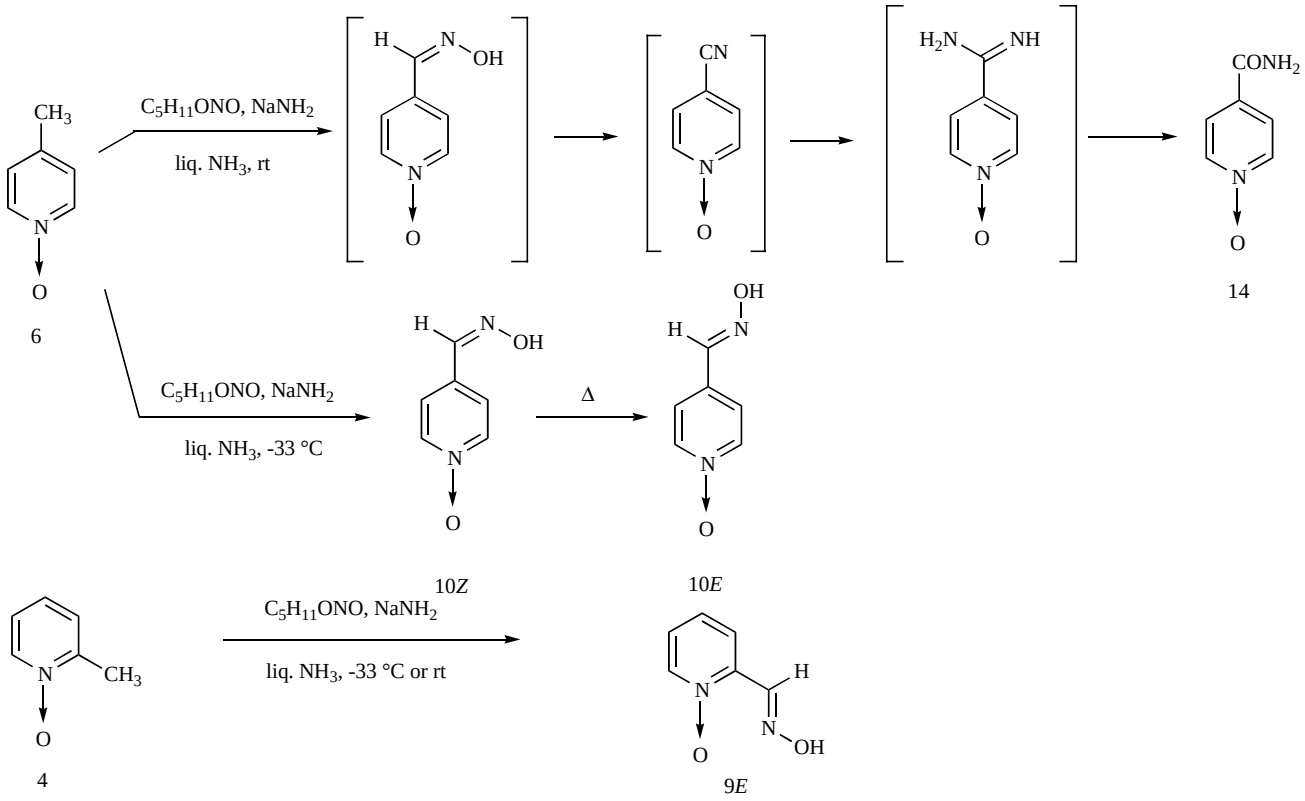


Scheme 2.

Table 2. Reaction of Pyridinecarbaldehyde 1-Oxide Oximes with $NaNH_2$ in the Presence of $C_5H_{11}ONO$ and $C_5H_{11}OH$ in liq. NH_3

Reactant	Temperature	Product (%)				Recovery (%)	Isomer (%) [a]			
		amide		nitrile						
		13	14	15	16		9*E*	9*Z*	10*E*	10*Z*
9*E*	rt [d]	5.5				90				
9*E*	-33 °C					quant. [b]				
9*Z*	rt	40+5 [c]		14			12			
9*Z*	-33 °C	18					47			
10*E*	rt		3		3	90				
10*E*	-33 °C					quant.				
10*Z*	rt		22		20	4			7	
10*Z*	-33 °C		4		4	84				

a) isomerized aldoxime b) quantitative recovery c) deoxygenated amide d) room temperature



Scheme 3.

such as heating. On the other hand, in the nitrosation of **4**, both at room temperature and at -33 °C, only the thermodynamically stable *E*-isomer 9***E*** was formed (Scheme **3**).

Successively, nitrosation of quinaldine, lepidine and their *N*-oxides with amyl nitrite in the presence of metal amide (KNH_2 and $NaNH_2$) in NH_3 at -33 °C was investigated to give the corresponding oxime as a main product along with nitrile and amide [11]. The nitrosation of the present starting materials never proceeded in the presence of EtONa (or EtOK) - $C_5H_{11}ONO$ in EtOH.

These experimental results indicate that the present nitrosation is very practical as a synthetic method of the corresponding oximes of quinaldine and lepidine. In the nitrosation of lepidine 1-oxide resinification is mainly produced because of the high reactivity, but the formation of quinoline-4-carboxaldehyde oxime was identified in spite of the small amount. These results suggest that the order of reactivity is picoline < picoline *N*-oxide < methylquinoline < methylquinoline *N*-oxide and the methyl group at the γ– position is more active than methyl group at the α– position in pyridine and quinoline derivatives [11]. In the case of pyrimidine derivatives, an alkyl group at the 4-position was exclusively attacked by RONO [12-14].

Nitrosation reactions of ethylpyridine, phenethylpyridine, and benzylpyridine, and their *N*-oxides were also examined to give the corresponding ketoximes at moderate to good yields [15]. The preparations of oxime by nitrosation of active methyl and methylene groups of *N*-heteroaromatics are summarized under a variety of

nitrosation conditions (Conditions A – K) in Table **3**. In particular, the use of potassium *t*-butoxide (*t*-BuOK) as a base in liq. NH_3 (Conditions H and H') outstandingly improved the nitrosation to give the corresponding oximes in high yields (Entries 1, 2, 4, 5, 6, 45 and 46). Treatment of methylpyridines and their 1-oxides with *t*-butyl nitrite in the presence of *t*-BuOK in liq.NH_3 gave the corresponding aldoximes in good yields except for in the case of 3-methylpyridine (Entry 3). In the nitrosation of 3-methylpyridine at room temperature, the corresponding oxime and amide were obtained in the yields of 18 % and 20 %, respectively [16].

It was found from these reactions that *N*-oxygenation markedly increases the reactivity of the methylene group and 4-substituted substrate is usually more reactive than 2-substituted substrate, sometimes indicating lower yields by resinification owing to the high reactivity.

Beckmann rearrangement of the thus obtained oximes was investigated to assign the geometry of those oximes [18, 19].

(2) Nitrosation in Solvent Other than Liq. NH_3

Oxime formation by nitrosation in solvents other than liq. NH_3 was investigated in THF (Conditions I, J, and K) to give satisfactory results. For example, nitrosation of 1-ethylisoquinoline and the *N*-oxide with alkyl nitrite was studied under Condition I (*t*-BuONO, *t*-BuOK, 0 °C in THF) and Condition J (*t*-BuONO, *t*-BuOK – *n*-BuLi, 0 °C in THF), respectively, to give the corresponding oximes in good yields (Entries 45 and 46). Consequently, these two systems were found to be generally effective for nitrosation of not only isoquinolines, but also pyridine and quinoline derivatives [8]. Moreover, it is of interest to note that the nitrosation of lepidine 1-oxide under Condition A resulted in resinification because of the high reactivity of this substrate [11], but the nitrosation under Condition J gave only the *E*-isomer of the corresponding oxime in good yield (Entry 34) [8].

Nitrosation would be performed under both basic and acidic reaction conditions and give the different products according to the reaction conditions which are sometimes important in medicinal chemistry as follows. However, acid catalyzed nitrosation procedures are often avoided due to the possibility of Beckmann rearrangement of the resultant oximes [22]. The oximes of compounds type XC(=NOH)Y, where X, Y = $COCH_3$, CN, COOR, CONHR, and X + Y = $C_6H_4(CO)_2$ were prepared by nitrosation of an activated methylene group with sodium nitrite ($NaNO_2$) in an acid medium, and ^{13}C and ^{15}N NMR spectra of those oximes were measured to give the information on *E* - *Z* isomerism at the C=NOH bond [23]. A one-step synthesis of haloglyoximes from amidoximes with active methylene was accomplished by nitrosation with $NaNO_2$ in conc. HCl or HBr [24]. Nitrosation of phenolic compounds under both acidic ($NaNO_2$ – $EtCO_2H$ – H_2O) and basic (*i*-$AmNO_2$ - K_2CO_3 - DMF) conditions gave the corresponding *ortho*-nitrosoproducts and *p*-quinone monooximes, respectively, and the others showed antiviral activities [25]. A series of 1,2,3,4-tetrahydroquinoline-2,3,4-trione 3-oximes (QTOs) was synthesized by nitrosation of 2,4-quinolinediols in the presence of $NaNO_2$ – NaOH – H_2SO_4 and indicated potent inhibition of the *N*-methyl-D-aspartate (NMDA) receptors as the result of the structure-activity relationship study [26]. Nitrosation of (1R)-(+)-camphor with *i*-$AmNO_2$ in the presence of *t*-BuOK in THF led to *anti*-(1R)-(+)-camphorquinone 3-oxime in high yields and excellent stereoselectivity was observed leading to preferential formation of the *anti*-isomer [22]. Various olefins, such as styrenes and α,β-unsaturated carbonyl compounds were directly converted to the corresponding oximes in good or moderate yields by reduction-nitrosation with *t*-BuONO and triethylsilane in the presence of cobalt(II) porphyrin as a catalyst [27]. Nitrosation and coupling reactions on the active methylene group of the 3-substituted-5-(substituted benzyl)-6-oxo-1,6-dihydro-1,2,4-triazines gave oximes and arylhydrazones of the 3-substituted-5-(substituted benzoyl)-6-oxo-1,6-dihydro-1,2,4-triazines, which were cyclized to the 3,5-disubstituted isoxazolo[4,5-e]1,2,4-triazines and 3-methyl-5,7-diaryl pyrazolo[4,3-e] 1,2,4-triazines [28]. Treatment of α-methylene ketones with $NaNO_2$ and aqueous HCl in THF provides the corresponding (*Z*)-1,2-dione monoximes and 1,2-diketones as a function of nature and stoichiometry of the nitrosating reagent [29]. A one-pot process involving hydrolysis of corresponding ester of aβ-alkyl-, β-aryl- or β-hetaryl-β-oxo acid, nitrosation at the activated methylene group, and treatment of the resulting intermediate with hydroxylamine in the presence of urea, afforded 3-alkyl-4-amino, 3-amino-4-aryl- and 3-amino-4-hetarylfurazans [30,31].

(3) Theoretical Approach for the Elucidation of the Reaction Mechanism of Nitrosation of Active Methyl and Methylene Groups on *N*-heteroaromatics

The reactivity of active methyl and methylene groups of nitrogen-containing heteroaromatics like pyridine, pyrimidine, quinoline, and quinazoline derivatives with alkyl nitrite in the presence of an amide ion is discussed in terms of the charge transfer ability (CTA) values according to CNDO/2 as well as PPP calculations. The experimental results for nitrosation can be quite reasonably interpreted and account for the difference of reactivity of methyl heterocycle of pyridines, pyrimidines, quinolines, and quinazolines in terms of CTA values in the deprotonation step. These results suggest that the CT process plays an important role in such intermolecular hydrogen bonding-type activated complexes. Intermolecular perturbation energies and binding energies of these methylheteroaromatics are also discussed (Fig. **1**) [20].

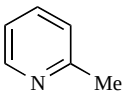
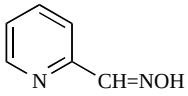
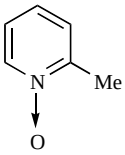
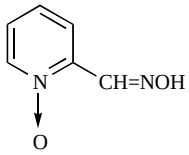
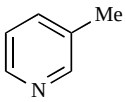
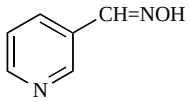
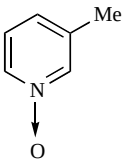
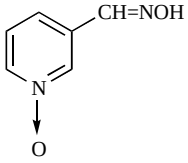
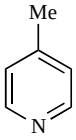
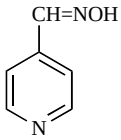
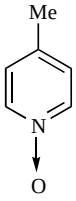
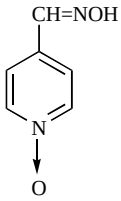
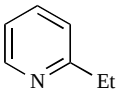
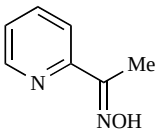
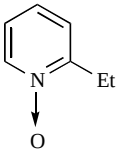
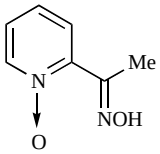
Moreover, CTA values in the deprotonation step of the nitrosation and the deuterium exchange reaction interpreted a difference of the reactivity of active methyl groups of various pyridines, pyrimidines and their *N*-oxides and oxo derivatives. In particular, the experimental values for the *N*-oxides could be well interpreted in terms of CTA values only when the calculations were performed in the conformation in which a 1:1 complex of sodium ion with the *N*-oxides was formed (Fig. **2**) [32].

The difference of the reactivity for the nitrosation using *t*-BuONO and *t*-BuOK in THF (Condition I) between 1-ethylisoquinoline and 1-ethylisoquinoline 2-oxide, which indicated the opposite tendency compared with the usual case, was reasonably explained in view of Frontier electron density of a hydrogen atom, the net charge of a hydrogen atom and the energetic terms of the Klopman-Salem equation by semi-empirical molecular orbital calculations (MNDO method) (Scheme **4**) [8].

4-Ethylquinoline 1-oxide reacted with isopropyl nitrite and sodium amide in liq.NH_3 to give 2-amino-4-ethyl-quinoline 1-oxide as the main product. Similar amination also occurred with lepidine 1-oxide and quinoline 1-oxide, but only the corresponding oximes were formed from reactions of 4-ethylquinoline and lepidine under the same conditions. Isopropyl nitrite was shown to be most potent as an oxidant compared with other oxidants used in such amination. The difference was explained in terms of $\Delta\Delta H_f$ and LUMO energies calculated by the semi-empirical molecular orbital calculation (MNDO method) (Scheme **5**) [21].

In the case of the nitrosation of 4-methylpyridine 1-oxide (**6**) with isoamyl nitrite ($C_5H_{11}ONO$) in the presence of $NaNH_2$ in liq.NH_3 at room temperature, only 4-pyridinecarboxamide 1-oxide (**14**) was obtained, while at -33 °C a thermodynamically unstable aldoxime, (*Z*)-4-pyridinecarbaldehyde 1-oxide oxime (**10*Z***), which was easily transformed into *E*-form by heating, was obtained. On the other hand, the nitrosation of 2-methylpyridine 1-oxide (**4**) gave only a thermodynamically stable aldoxime, (*E*)-2- pyridinecarbaldehyde 1-oxide oxime (**9*E***), both at room temperature and at -33 °C, as already mentioned in detail above.

Table 3. Preparation of Oximes by Nitrosation of Active Methyl and Methylene Groups of *N*-Heteroaromatics under Conditions A - K

Entry	Reactant	Reaction Conditions[a)]	Oxime	Yield (%)[b)]
1		B, E, H I, J, K		23 [5], 75*E* [6], 75 [16] 9 [8], 20*E* [8] + 16*Z* [8], 70 [16]
2		A, B, C D, H, I		51 [5], 57*E* [5], [16], 46 [5] 23 [5], 66*Z* [16], 57 [8]
3		E, H, H'		1.5 [6], 9*E* [16], 18*E* [16]
4		H		71 [16]
5		B, E H, J		66 [5], 30*Z* [6] 80 [16], 41*Z* [8]
6		B, C, H		71*Z* [5, 16], 50 [5], 81*E* [16]
7		B		26 [15]
8		B		77*E* [15] + 2*Z* [15]

a) **E**: *n*-BuONO, $NaNH_2$, liq. NH_3, -33 °C
F: EtONO, KNH_2, liq. NH_3, -33 °C
G: EtONO, $NaNH_2$, liq. NH_3, -33 °C
H: *t*-BuONO, *t*-BuOK, liq. NH_3, -33 °C
H': *t*-BuONO, *t*-BuOK, liq. NH_3, rt
I : *t*-BuONO, *t*-BuOK, THF, -78 °C → rt
J : *t*-BuONO, *t*-BuOK, *n*-BuLi, THF, -78 °C → rt
K: *t*-BuONO, LTMP-TMEDA, THF, -78 °C

b) *E* and *Z* show *E*-form and *Z*-form of oxime

Table 3. contd….

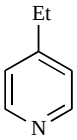
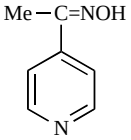
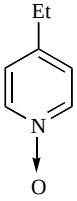
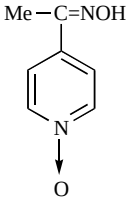
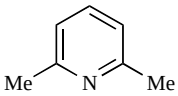
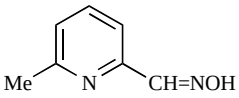
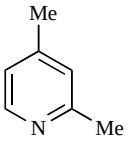
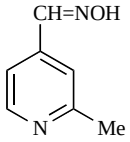
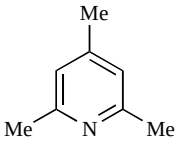
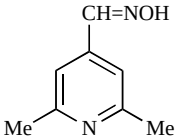
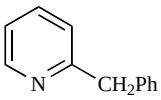
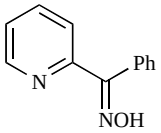
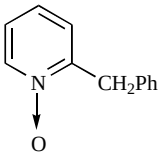
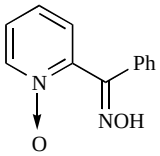
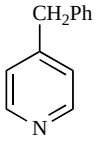
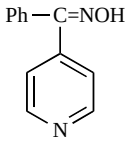
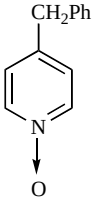
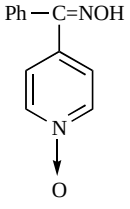
Entry	Reactant	Reaction Conditions	Oxime	Yield (%)
9		B, E		35 [15], 44 [6]
10		B		57 [15]
11		E		50*Z* [6]
12		E, F		84*Z* [6], 37 [12]
13		F		40 [12]
14		B		73 [15]
15		B		86 [15]
16		B		93 [15]
17		B		94 [15]

Table 3. contd….

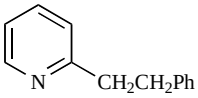
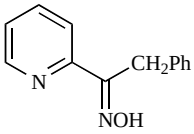
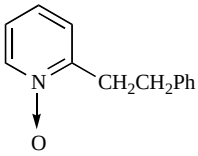
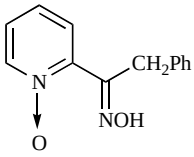
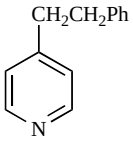
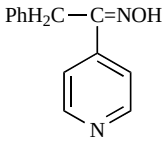
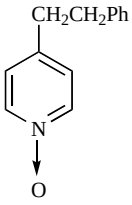
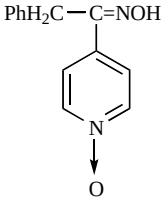
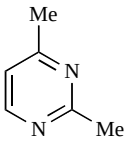
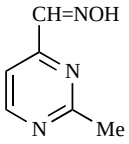
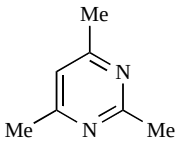
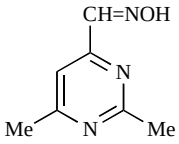
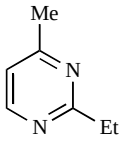
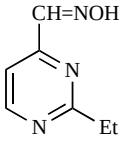
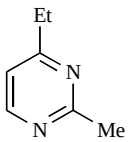
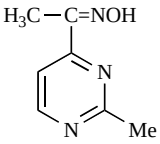
Entry	Reactant	Reaction Conditions	Oxime	Yield (%)
18		B		29 [15]
19		B		54 [15]
20		B		45 [15]
21		B		32 [15]
22		G		79 [12]
23		G		87 [12]
24		F or G		53 [20]
25		F or G		70 [20]

Table 3. contd….

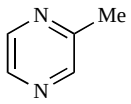
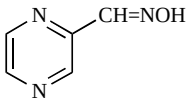
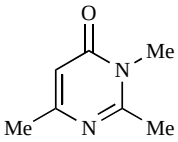
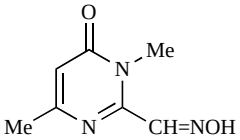
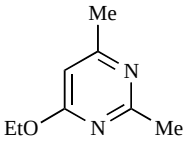
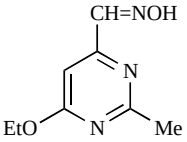
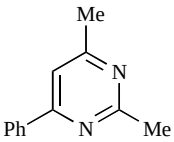
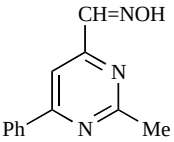
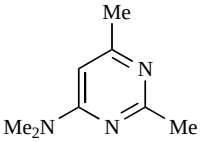
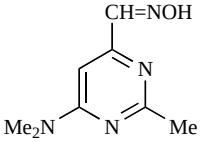
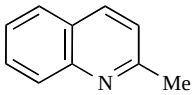
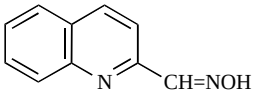
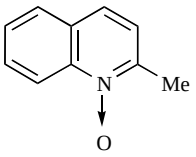
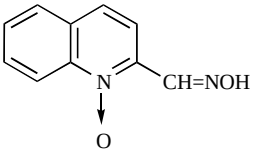
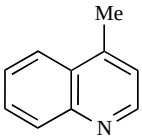
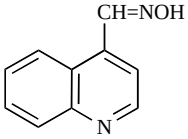
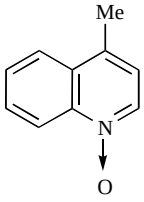
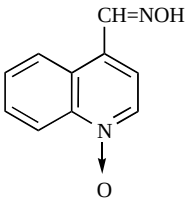
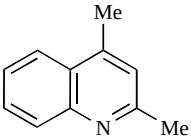
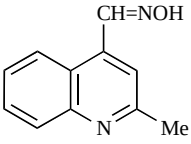
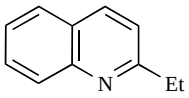
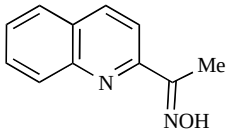
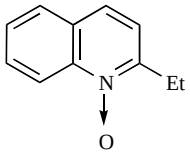
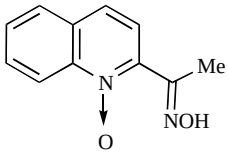
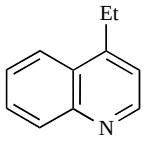
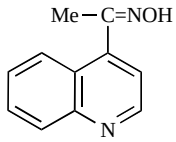
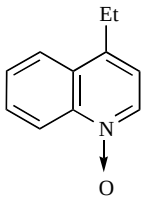
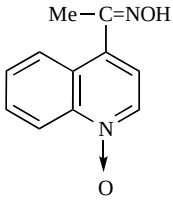
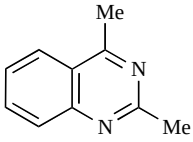
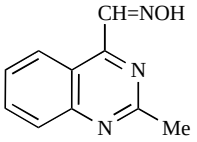
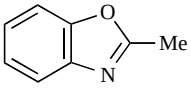
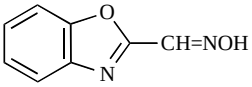
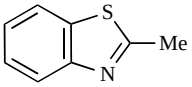
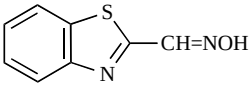
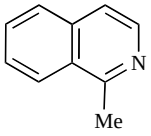
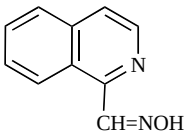
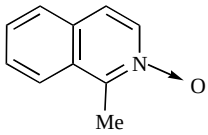
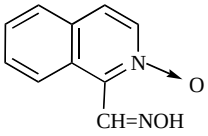
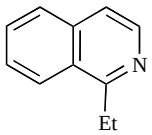
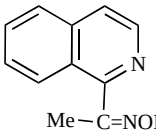
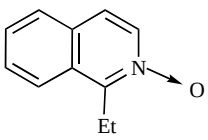
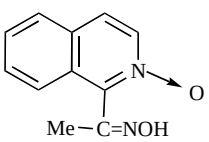
Entry	Reactant	Reaction Conditions	Oxime	Yield (%)
26		E		39*Z* [6]
27		F		74 [14]
28		F		64 [14]
29		F		78 [14]
30		F		64 [14]
31		C, E		56 [11], 28 [6]
32		B, C		51 [11], 27 [11]
33		C, I		67 [11], 92 [8]
34		I, J		32 [8], 60*E* [8]
35		F		59 [12]

Table 3. contd….

Entry	Reactant	Reaction Conditions	Oxime	Yield (%)
36		C		12*E* [17]
37		C		56*E* [17]
38		C		43*E* [21]
39		C		12*E* [21]
40		F		71 [12]
41		E		55*E* [6]
42		E		39 [6]
43		C		31*E* [8] + 18*Z* [8]
44		C		85*E* [8]
45		H, I		78*E* [8] + 16*Z* [8] 45*E* [8] + 12*Z* [8]
46		H, J		37*E* [8] + 37*Z* [8] 74 [8]

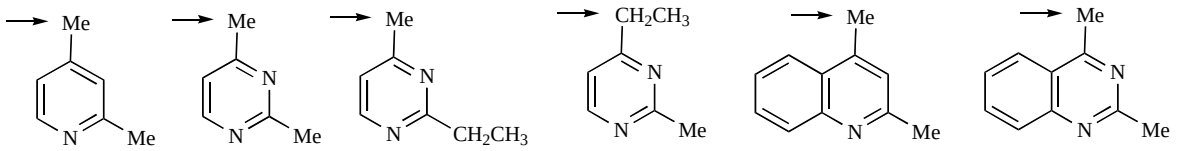


Fig. (1). Methyl or methylene groups indicated by arrows are exclusively attacked by alkyl nitrite.

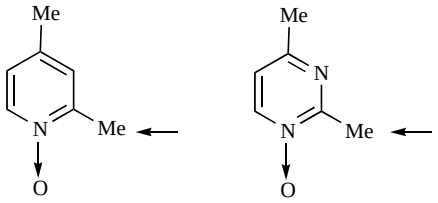
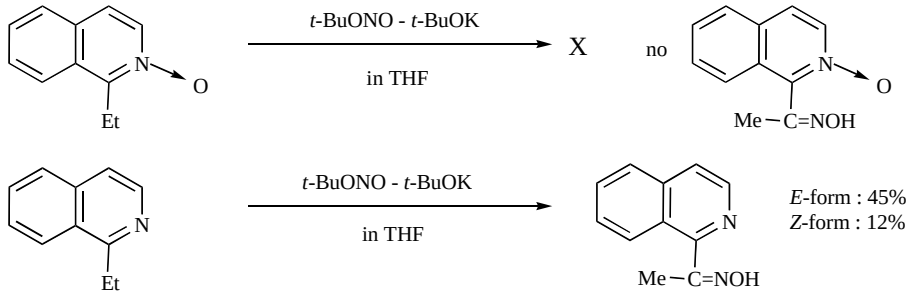
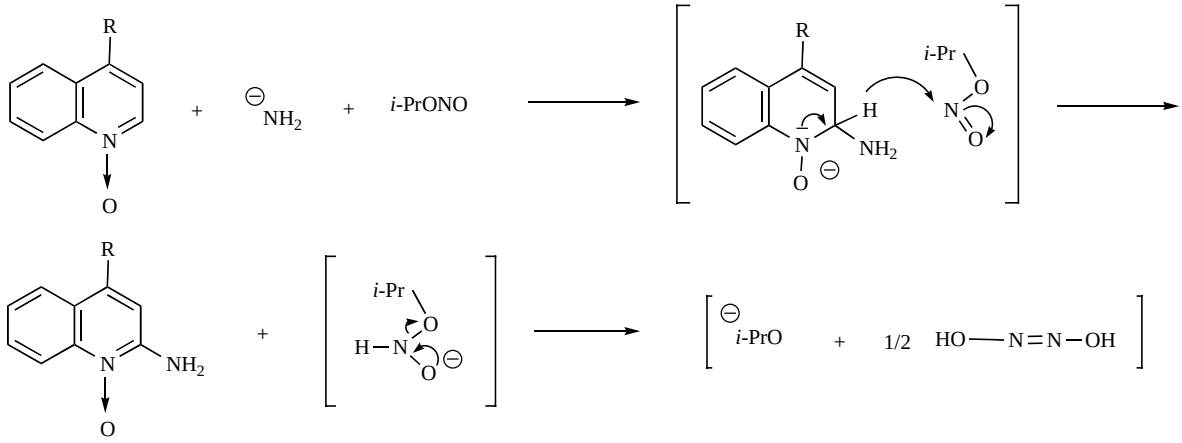


Fig. (2). Methyl groups indicated by arrows are exclusively attacked by electrophilic reagents.

The reaction mechanism of this nitrosation was also theoretically investigated by use of a semiempirical molecular orbital study (PM3 method) with methyl nitrite (CH_3ONO) as a simpler model instead of $C_5H_{11}ONO$ and the differences of reactivities between **4** and **6** for the present nitrosation were reasonably explained in terms of steric and energic factors which indicate the enthalpies of formation (ΔH) of the complex of 1-oxido-4(or 2)-pyridomethide anions and CH_3ONO with amide anions (supermolecule) (Fig. **3**) [10].



Scheme 4.



Scheme 5.

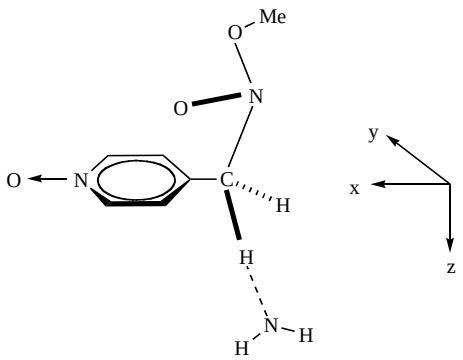


Fig. (3). Coordinate system assumed for hydrogen abstraction by NH_2^- from the complex of 1-oxido-4-pyridomethide anion and CH_3ONO.

The reaction conditions of proton abstraction in the presence of base like metal amide in liq. NH_3 would be utilized not only for nitrosation, but also for acylation [13, 33].

CONCLUSION

Nitrosation of active methyl and methylene groups on *N*-heteroaromatics like pyridine, pyrimidine, quinoline, isoquinoline, or benzimidazole derivatives, which are important as the backbone of medicines, proceeds smoothly in the presence of alkyl nitrite and base in liq. NH_3 or THF to provide the corresponding oxime in moderate to good yields. The chemoselectivity for nitrosation as well as the difference of reactivity based on E or Z forms of oxime are successfully explained experimentally and theoretically using the molecular orbital method. The present nitrosation reaction

would be applicable to not only oxime formation, but also *C*-nitrosation along with *N*-nitrosation, *S*-nitrosation and *O*-nitrosation to produce new medicines, such as new vasodilators or alkylating agents for cancer. Such investigations by our group are under way.

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