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A New Chemo-Selective Method For N-Nitrosation of Secondary Amines

[1]Vyankat Shiwaram Sharma Bhaskarrao Anipindiwar, [2] Dr. Sachin Bhat

[1]Research Scholar, Department of Chemistry, SRK University, Bhopal (India)

[2]Professor, Department of Chemistry, SRK University, Bhopal (India)

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KEYWORDS

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ABSTRACT:

Nitrosation is an important industrial unit process that produces commercially valuable intermediates. The purpose of the N-Nitrosation reaction is to introduce one or more nitroso groups into the reacting molecules. This paper summarizes some of the most recent developments in the field of secondary amine N-nitrosation as reported in the literature. We discovered that p-toluenesulfonic acid is a low-cost, commercially available reagent that may be employed in a variety of organic syntheses and transformations. We decided to do this study because of the utility of p-toluenesulfonic acid and the lack of studies on its use for N-nitrosation of secondary amines. As a result, we've opted to use p-toluenesulfonic acid-sodium nitrite as a new nitrosating agent for secondary amine N-nitrosation. We describe p-toulenesulfonic acid (p-TSA) as a proton source for secondary amine N-nitrosation under mild and diverse circumstances in this paper.

1.1 INTRODUCTION

The chemistry of amine N-nitrosation is a well-known and important process in chemical synthesis.[1] Nitrosation is an important industrial unit process that produces commercially valuable intermediates. The purpose of the N-Nitrosation reaction is to introduce one or more nitroso groups into the reacting molecules. N-Nitrosamines have attracted a lot of attention in recent years, owing to their potent mutagenic and carcinogenic effects.[2] Nitrosation of amines is of special interest since the resulting N-nitrosamines are physiologically active, exhibiting actions such as vasodilation, platelet aggregation, inflammation, and neural plasticity.[3] Pesticides, lubricants, and antioxidants are all made from nitroso compounds.[4] The N-nitrosamino group is employed as a synthetic intermediate with a NO activating group in the production of different G-amino compounds. [5] They can also be used as synthetic intermediates to create a variety of N-N bonded functions. Because of a partial double bond character between two nearby nitrogens, impeded rotation around the N-N bond leads in numerous interesting stereochemical properties in this family of compounds.[6,7] For mechanistic organic and biological chemists, nitrosation of primary, secondary, or tertiary amines has long been a particularly busy and rewarding topic of research. Combining the synthetic and mechanistic components of nitrosation or trans-nitrosation has also been attempted.[8] Nitrosation of amines is important for industry since nitrosated chemicals are used in medications and colours.

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1.2 REVIEW OF LITERATURE

This papersummarizes some of the most recent developments in the field of secondary amine N-nitrosation as reported in the literature. N-nitrosation of secondary amines with sodium nitrite and solid acid reagents such as oxalic acid dihydrate,[9] inorganic acidic salts,[10] hydrolysable chloride salts,[11] alumina-methanesulfonic acid (AMA),[12] molybdatophosphoric acid (MPA),[13] citric acid,[14] silica sulfuric acid,[15] Nafion-H,[16] tungstate sulfuric acid (TS In most of the approaches, a heterogeneous reaction state was found. Despite the fact that there are several methods for nitrosation, newer methods continue to draw attention due to their experimental simplicity and effectiveness. The following are some of the most recent and elegant approaches.

Demir *et al.* (1992)[19]employed trichloro nitromethane 3 in combination with sodium nitrite ($NaNO_2$) in the presence of wet SiO_2 to generate HNO_2 in situ for the N-nitrosation of secondary amines 1 and obtained good yields of N-nitroso compounds 2. This was a system that was entirely diverse.

Zolfigol *et al*. (2001)[20] ·novel [NO Crown'H $(NO_3)_2$] compound 4 as a nitrosonium ion (NO) source was described by Zolfigol and colleagues. Under moderate and homogenous circumstances, this may be used with sodium nitrite in the presence of dry SiO_2 to convert a range of secondary amines 1 to the equivalent N-nitroso compounds 2, yielding quantifiable yields . The 18-Crown-6 is recyclable and reusable.

Iranpoor *et al.* (2005)[21]used dinitrogen tetroxide (N2O4) impregnated activated charcoal to N-nitrosate secondary amines 1 in high yields, yielding the corresponding N-nitroso derivatives 2. N-nitrosation of tertiary amine has also been reported.

Montazerozohori *et al.* (2006)[22]announced the discovery of a novel solid acid reagent, i.e. Under heterogeneous conditions, wet molybdate sulfuric acid (MSA) 5 as an H^+ source, which can be utilised in combination with sodium nitrite to convert a range of secondary amines 1 to their corresponding N-nitroso compounds 2, yielded good yields (Scheme 4). The reagent (MSA) can be easily filtered out and reused without losing its action.

Zarchi *et al.* (2007)[23]found that crosslinked poly (4-vinylpyridinium) chloride [P_4-H]Cl 7 and quaternized crosslinked poly(N-methyl-4-vinylpyridinium)-nitrite [P4-Me]NO2 9 are both effective nitrosating agents. These catalysts were used to N-nitrosate secondary amines 6 with sodium nitrite in ethanol under mild conditions at room temperature (Scheme 5). This approach has a number of distinct advantages, including chemoselectivity, the avoidance of C-nitrosation side products, and a straightforward work-up technique. The polymeric reagent could be regenerated and used again in a subsequent process. This approach worked with a wide range of secondary amines with different functions

Bamoniri et al. (2007)[24] described the use of trichloromelamine 10 in combination with sodium nitrite in the presence of wet silica gel as an effective nitrosating agent for the transformation of secondary amines 1 into matching N-nitrosamines 2 in good to outstanding yields under mild circumstances (Scheme 6). In the absence of wet silica gel, nitrosation did not occur.

The combination of $PPh_3/Br_2/n\text{-}Bu_4NNO_2$ as a new reagent system for the effective production of N-nitrosamines 2 from the corresponding secondary amines 1 was described by Iranpoor et al. (2008)[25]

Wu *et al.* (2008)[26] reported that using nitric oxide with traces of oxygen as a nitrosating agent for the N-nitrosation of chemical 11 resulted in high yields of extremely diastereoselective product 12. The ability of this reaction to nitrosate a wide range of amine compounds, including heterocyclic amines, in a short amount of time demonstrates its general efficiency.

Shen *et al.* (2009)[27] found that regioselective N-nitrosation of dihydropyrimidinones 13 with nitric oxide (NO) resulted in high quantities of the

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JCHR (2023) 13(5), 1-9 | ISSN:2251-6727

corresponding N-(3)-nitrosamides 14. A nucleophilic assault was most likely responsible for the reaction. Aprotic and polar solvents like acetonitrile and tetrahydrofuran substantially encouraged the reaction, but protic solvents with high dielectric constants like methanol and water strongly opposed it.

Chaskar *et al.* (2009)[28,] in good to exceptional yields, Chaskar et al. described bismuth (III) chloride ($BiCl_3$) and sodium nitrite as a benign and efficient nitrosating reagent for the N-nitrosation of secondary amines 1 and tetrazoles 15 under ambient conditions to the corresponding N-nitrosamines 2 and N-nitroso tetrazoles 16.

Although numerous reagents for the N-nitrosation of secondary amines are known in the literature, they all have limitations such as substrate generality, severe reaction conditions, stoichiometric amounts of catalyst, harmful gas use, and so on. This opens the door to the creation of milder N-nitrosation conditions for secondary amines. The well-known critical step in the nitrosation reaction is the production of nitrosonium ion (NO^+). We discovered that p-toluenesulfonic acid is a low-cost, commercially available reagent that may be employed in a variety of organic syntheses and transformations. We decided to do this study because of the utility of p-toluenesulfonic acid and the lack of studies on its use for N-nitrosation of secondary amines. As a result, we've opted to use p-toluenesulfonic acid-sodium nitrite as a new nitrosating agent for secondary amine N-nitrosation. We'd like to show you how to N-nitrosate secondary amines in a straightforward and chemo-selective way. We describe p-toulenesulfonic acid (p-TSA) as a proton source for secondary amine N-nitrosation under mild and diverse circumstances in this paper.

1.3 RESULTS AND DISCUSSION

We discovered that p-toluenesulfonic acid-mediated N-nitrosation of secondary amines 1 with $NaNO_2$ could be achieved in our work for the synthesis of N-nitrosamines 2. Thus, we submitted morpholine 1a to p-toluenesulfonic acid-mediated N-nitrosation with $NaNO_2$ under mild conditions at room temperature, yielding 97 percent N-nitrosomorpholine 2a.

With varied equivalents of p-TSA ranging from 0.5 to 2, we investigated a variety of solvents, including CH_2Ch_2 CH_3CN, CH_3OH, $CHCl_3$ diethyl ether, and others, and determined that CH_2Cl_2 at ambient temperature is the best solvent system for N-nitrosation.

Table 1. N-Nitrosation of morpholine 1a using various solvents

Entry	Solvent	Yield(%)
1	CH3CN	92
2	CH3OH	88
3	CHCl3	91
4	CH2Cl2	97
5	Diethylether	85
6	THF	51
7	Acetone	70

Various cyclic secondary amines were N-nitrosated to broaden the scope of the process. We discovered that N-nitrosation of substituted cyclic secondary amines proceeded smoothly, yielding large yields of N-nitrosamines with good selectivity, as reported in the results and reaction conditions. **Table 1.2**.

Journal of Chemical Health Risks

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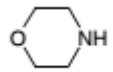
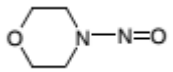
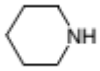
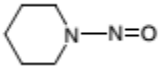
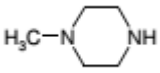
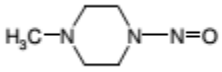
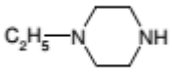
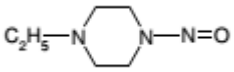
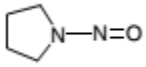
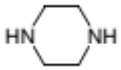
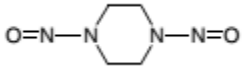
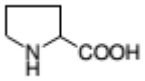
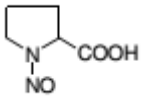
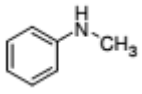
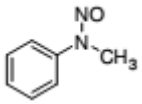
JCHR (2023) 13(5), 1-9 | ISSN:2251-6727

Table 1.2. N-Nitrosation of cyclic secondary amines

Entry	Substrate (1a-h)	Product(2a-h)	Time(mins)	Yield(%)
1.	 1a	 2a	**5**	**97**
2.	 1b	 2b	**3**	**92**
3.	 1c	 2c	**20**	**95**
4.	 1d	 2d	**15**	**85**
5.	 1e	 2e	**5**	**97**
6.	 1f	 2f	**5**	**95[C]**
7.	 1g	 2g	**720**	**90**
8.	 1h	 2h	**4**	**91**

C-nitrosation was not detected at all in the activated aromatic ring of N-methyl aniline Ih, which is surprising. This is because p-toluenesulfonic acid is a better proton source for activating the nitrogen sites of secondary amines by forming nitrosonium ion (NO^+) with sodium nitrite and therefore deactivating

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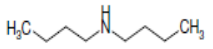
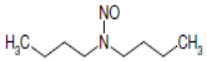
JCHR (2023) 13(5), 1-9 | ISSN:2251-6727

the aromatic ring for nucleophilic nitrosation. We only found selective dinitrosation product 2f in the case of piperazine 1f. As shown in Table 1, cyclic secondary amines (piperidine, N-substituted piperazine, pyrrolidine, and L-proline) were N-nitrosated in high yields to yield the corresponding N-nitrosamines 2a-h.

The N-nitrosation reaction of alkyl amines was also of interest. Thus, sodium nitrite was used to carry out p-toluenesulfonic acid-mediated N-nitrosation of secondary amines 1, yielding N-nitrosamines 2 in good quantities. (**Scheme 12**).

Table 3 shows that secondary alkyl amines generated N-nitrosation in 93-95 percent of cases. However, after a very short period, dicyclohexylamine 1k and dibutylamine Il yielded N-nitrosodicyclohexylamine 2k and N-nitrosodibutylamine 21 95 percent yields, respectively.

Table 1.3. N-Nitrosation of alkyl amines

Entry	Substrate (15a-d)	Product (16a-d)	Time (mins)	Yield (%)
1	Et_2NH	$Et_2N—N=O$	20	93
	1i	**2i**		
2	$(iso\text{-}Pr)_2NH$	$(iso\text{-}Pr)_2N—N=O$	90	95
	1j	**2j**		
3	$(c\text{-}C_6H_{11})_2NH$	$(c\text{-}C_6H_{11})_2N—N=O$	2	95
	1k	**2k**		
4			4	95
	1l	**2l**		

Mechanism

The p-TSA combines with sodium nitrite to create sodium salt and nitrous acid in the first stage. When p-toluenesulfonic acid combines with nitrous acid and eliminates water, the nitrosonium electrophile is generated. In the presence of water, the generated nitrosonium ion interacts with secondary amines 1 to produce N-nitrosamines 2.

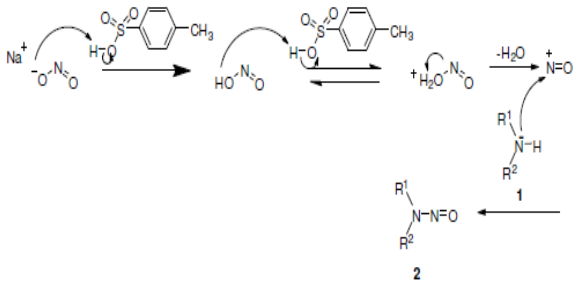


Figure 1.1 Mechanism for p-TSA mediated N-nitrosation of secondary amine

We wanted to see how chemoselective this approach was, so we ran a competitive reaction using N-methyl aniline 1h and anisole 17. After 1 hour, only secondary amine nitrosation was seen, whereas anisole remained unaffected in the reaction mixture. N-nitroso-N-methyl aniline 2h is the lone result of the nitrosation process of N-methyl aniline lh, demonstrating the method's chemoselectivity. As a result, unlike some other approaches, the nitrosonium ion (NO+) attacks just the nitrogen sites of secondary amines, even when an aromatic moiety is physically attached to a nitrogen atom in this system.

Dinitrosation of piperazine 1f was easily accomplished using a 1:1.1 molar ratio of the reagent and a variety of conditions, whereas mononitrosation was unsuccessful despite varying the molar ratios of the reactant and reagent and a variety of conditions.

The N-nitrosation of L-proline 1g furnished N-nitroso-L-proline 2g in good yield and the chiral centre remained intact. This reaction was very slow as compared to others.

1.4 EXPERIMENTAL PROCEDURE

Procedure for N-nitrosation of secondary amines:

At room temperature, p-toluenesulfonic acid (6.0 mmol) was gently added to a stirred suspension of sodium nitrite (6.0 mmol), secondary amine (5.7 mmol) in dichloromethane (10 mL). The reaction mixture was thoroughly agitated for the required amount of time, and TLC (SiO_2 pet ether/EtOAc)

Journal of Chemical Health Risks

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JCHR (2023) 13(5), 1-9 | ISSN:2251-6727

was used to monitor the reaction's completion. The insoluble material was removed by filtration and rinsed with CH_2Cl_2 after the reaction was completed.

Characterization data:

N-Nitrosomorpholine (2a):

Molecular formula : $C_4H_8N_2O_2$

N-Nitrosopiperidine (2b):

Molecular formula : $C_5H_{10}N_2O$

***N*-Nitroso-N-methylpiperazine (2c):**

Molecular formula : $C_5H_{11}N_3O$

***N*-Nitroso-N-ethylpiperazine (2d):**

Molecular formula : $C_6H_{13}N_3O$

***N*-Nitrosopyrrolidine (2e):**

Molecular formula : $C_4H_8N_2O$

***N,N*-DiNitrosopiperazine (2f):**

Molecular formula : $C_4H_8N_4O_2$

***N*-Nitroso-L-proline (2g):**

Molecular formula : $C_5H_8N_2O_3$

***N*-MethyI-N-nitrosoaniline (2h):**

Molecular formula : $C_7H_8N_2O$

***N*-Nitrosodiethylamine (2i):**

Molecular formula : $C_4H_{10}N_2O$

***N*-Nitrosodiisopropylamine (2j):**

Molecular formula : $C_6H_{14}N_2O$

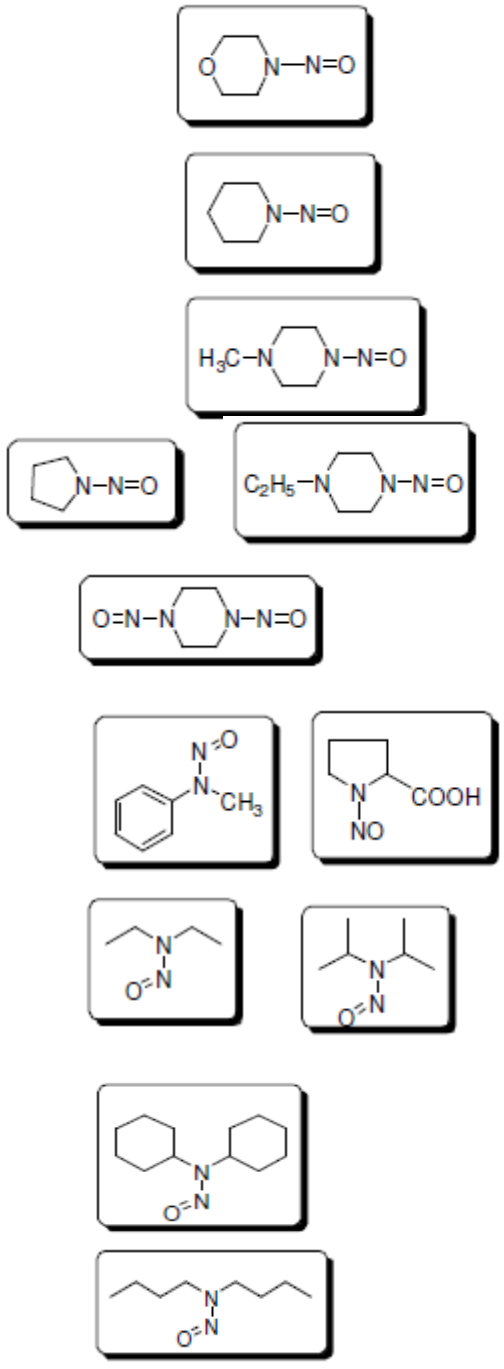
***N*-Nitrosodicyclohexylamine (2k):**

Molecular formula : $C_{12}H_{22}N_2$

***N*-Nitrosodibutylamine (21):**

Molecular formula : $C_8H_{18}N_2O$

To obtain N-nitrosamines, the filtrate was dried over Na_2SO_4 and concentrated under reduced pressure.



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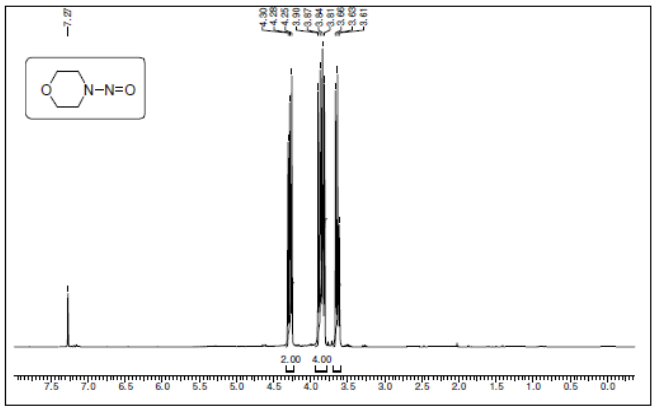
JCHR (2023) 13(5), 1-9 | ISSN:2251-6727

1.5 SPECTRAL DATA

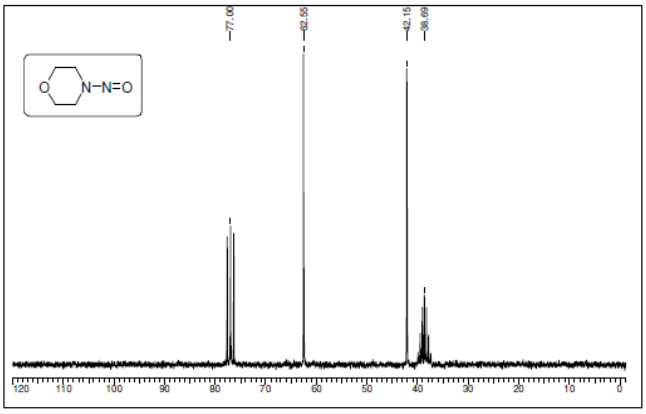
Table 4: ^{1}H and ^{13}C NMR spectrum of some selected compounds are given below:

Sr.No.	Spectra
1	^{1}HNMRand^{13}CNMRspectraof**2a**
2	^{1}HNMRand^{13}CNMRspectraof**2e**
3	^{1}HNMRand^{13}CNMRspectraof**2j**
4	^{1}HNMRand ^{13}CNMRspectraof**2k**

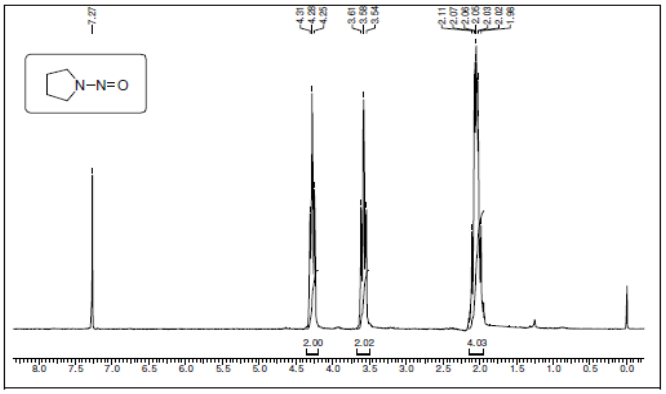
1. ^{1}H NMR spectra of *N*-Nitrosomorpholine (2a):



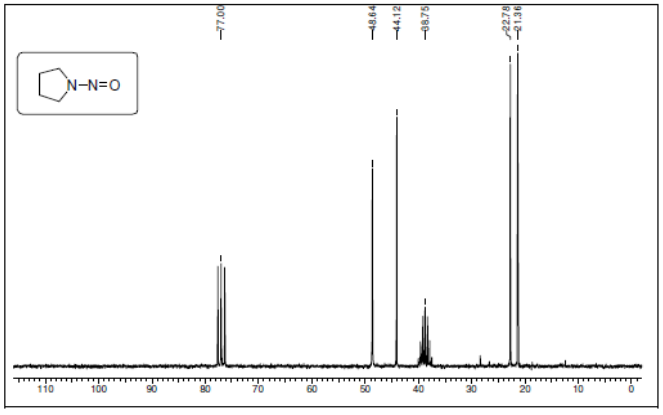
1. ^{13}C NMR spectra of N-Nitrosomorpholine (2a):



2. ^{1}H NMR spectra of N-Nitrosopyrrolidine (2e):



2. ^{13}C NMR spectra of N-Nitrosopyrrolidine (2e):



Journal of Chemical Health Risks

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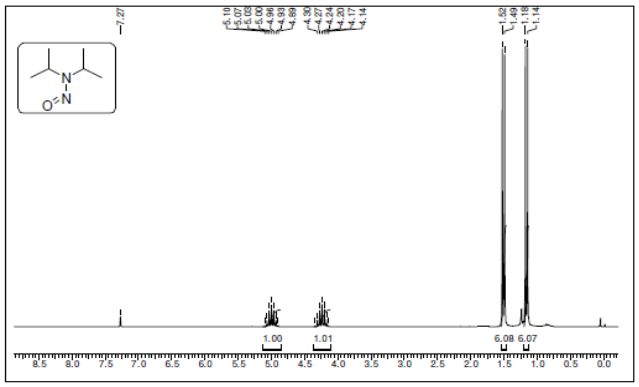
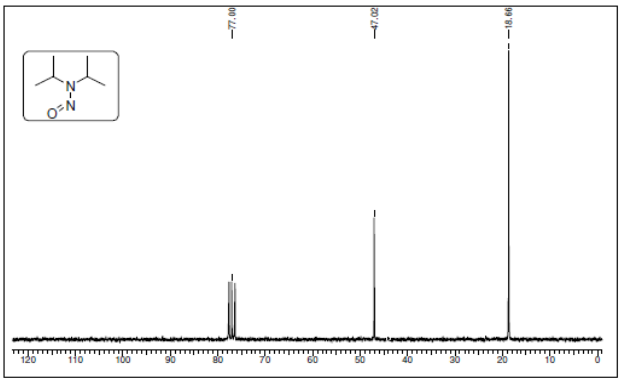
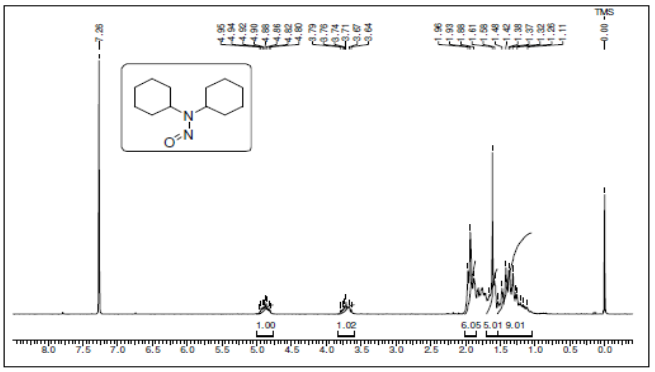
3. ^{1}H NMR spectra of N-Nitrosodiisopropylamine (2j):



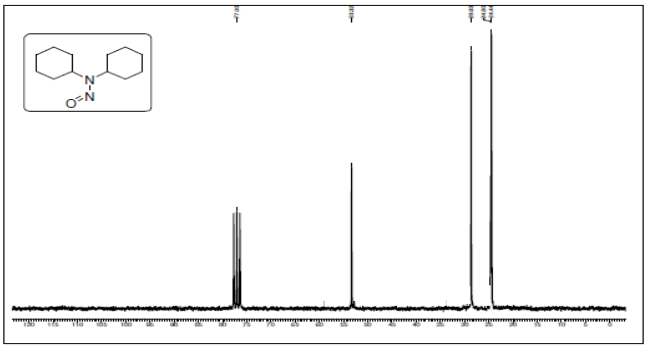
4. ^{13}C NMR spectra of N-Nitrosodiisopropylamine (2j):



5. ^{1}H NMR spectra of N-Nitrosodicyclohexylamine (2k):



6. ^{13}C NMR spectra of N-Nitrosodicyclohexylamine (2k):



SUMMARY

We have devised a simple and efficient process for N-nitrosation of secondary amines using p-toluenesulfonic acid, which is affordable, commercially available, and readily available. P-toluenesulfonic acid (p-TSA) is a superior proton source in terms of handling and availability when compared to other proton sources. The technique is straightforward to use, with a quick set-up, high yield, good chemo and regio selectivity, and no C-nitrosation side products. Our approach tolerates a wide range of functional groups and works well with aliphatic and cyclic secondary amines.

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