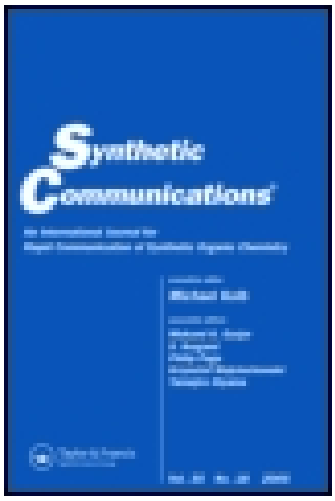

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Facile Denitrosation of Cyclic N-Nitrosamines with Hydrazoic Acid

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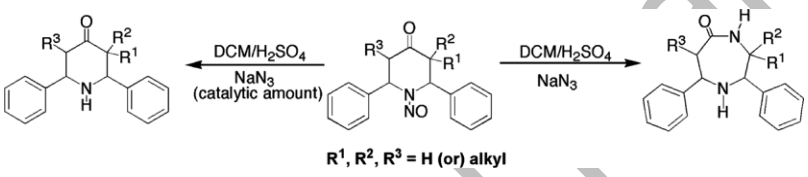
Abstract

A simple and facile method for the denitrosation of cyclic *N*-nitrosamines using HN_3 (Conc.H_2SO_4 + NaN_3) is reported. In this method limited usage of this reagent does not affect the carbonyl group.



KEYWORDS: Denitrosation, Hydrazoic acid, Schimdt rearrangement, Piperidin-4-one, 1,4-diazepan-5-one

INTRODUCTION

Gaseous HCl and other reagents such as $TiCl_2$-$NaBH_4$, $NiCl_2$-$NaBH_4$ and chlorosulphonyl isocyanate were used earlier, as denitrosating agents.[1] The use of metallating agents such as LDA followed by alkylation and denitrosation would lead to α-alkylated amines.[2] The denitrosation can also be carried out by treatment with LAH followed by Raney Ni.[3] However, all these processes involve either strong acidic conditions or conditions in which some functional groups would be reduced.

Comparatively a better method involving BF_3 with furan/thiophene/THF in presence of $NaHCO_3$ was also reported.[4a] Furthermore, the denitrosation of *N*-nitrosoamines have also been successfully accomplished using HBr/CH_3COOH system[4b,c] and others[4d,e] as well as enzymatically.[4f]

The reagents reported herein, namely Conc.H_2SO_4 + NaN_3 and CH_2Cl_2 (DCM) as solvent are mild, cheaper and do not involve tedious reaction conditions, workup procedure and purification of the product.

RESULTS AND DISCUSSION

As part of our ongoing research on the synthesis of substituted *N*-nitroso-1,4-diazepan-5-ones, we attempted the synthesis of *N*-nitroso-3,3-dimethyl-2, 7-diphenyl-1,4-diazepan-5-one (**2**) by employing the nitrosation of 3, 3-dimethyl-2, 7-diphenyl-1,4-diazepan-5-one (**1**, **Scheme-1**). However, we encountered a difficulty in this usual route.[5] Hence an attempt has been made to synthesize *N*-nitroso-3,3-dimethyl-2,7-diphenyl-1,4-diazepan-5-one (**2**) from *N*-nitroso-3,3-dimethyl-2,6-diphenylpiperidin-4-one (**7**) using the Schmidt rearrangement (**Scheme-2**). Interestingly, it resulted in denitrosation and rearrangement. Instead of the expected *N*-nitroso-3,3-dimethyl-2,7-diphenyl-1,4-diazepan-5-one (**2**), we isolated the 3,3-dimethyl-2,7-diphenyl-1,4-diazepan-5-one (**1**) as an exclusive product. Furthermore, we tested the same experimental condition with several *N*-nitroso-2,6-diarylpiperidin-4-ones using excess reagent and in all the cases, denitrosation followed by the Schmidt rearangement to 1,4-diazepan-5-one was observed (Representative examples are given in **Scheme-2**). However, a controlled reaction involving the catalytic amount of the reagent (0.4m.mol + 2.5 m.mol compound) results in only denitrosation and the

corresponding piperidin-4-ones **14-19** were isolated as an exclusive product in all the cases studied (**Scheme-2**). Hence, in this method, limited use of the reagent has not affected the carbonyl group.

In order to check the denitrosation reaction in the absence of a carbonyl group, we employed several *N*-nitroso-2,6-diarylpiperidines **20-25**[6] (**Scheme-3**). In all these cases the denitrosated product was isolated as an exclusive product. Representative examples are given in **Scheme- 3.** Furthermore, the denitrosation has also been tested with *N*-nitroso-2,7-diphenyl-1,4-diazepan-5-ones **2, 32-36**[5] and the denitrosated product has been isolated as an exclusive product (**Scheme-3**). In both the cases only a catalytic amount of the reagent was used. The identity of the product in all these reactions has checked with the reported melting point, IR and NMR spectra (Tables S1-S3, Figures S1-S23, available online in the Supplemental Material).

This is a new reagent and the method is also a synthetically useful one. Denitrosation does not occur with either NaN_3 (or) Con. H_2SO_4 alone. Hence HN_3 is the reagent involved in denitrosation. In the absence of a carbonyl group, HN_3 behaves as a denitrosating agent. However, in the presence of a carbonyl group, by controlling the usage of the reagent, we can carry out either chemoselective denitrosation alone or both denitrosation and Schmidt rearrangement. Furthermore, the rate of the reaction is found to be faster in presence of a carbonyl group *ie*. denitrosation is fast in **3-8** and **2, 32-36** when compared to **20-25**.

EXPERIMENTAL

Thin-layer chromatography (TLC) was carried out to monitor the course of the reaction. All the reported melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded in BRUCKER FT-IR α-model spectrometer using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution using TMS as the internal standard in Bruker AMX 400 and 100 MHz NMR spectrometers, respectively. Unless otherwise stated, all the reagents and solvents used were of high grade and purchased from Aldrich and Merck. All the solvents were distilled prior to use.

All the parent *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-ones **3-8,** *N*-nitroso-*r*-2,*c*-6-diphenylpiperidines **20-25** and *N*-nitroso-2,7-diphenyl-1,4-diazepan-5-ones **2, 32-36** were prepared by following the literature methods.[5-9]

PROCEDURE FOR DENITROSATION

In a typical reaction dry**,** powdered *N*-nitroso-*r*-2,*c*-6-diphenylpiperidin-4-one (5 mmol) was added, in portions, to cold Con. H_2SO_4 (5 ml) and CH_2Cl_2 (DCM) (10 ml) in a round bottomed flask equipped with a magnetic stirrer. Then, NaN_3 (0.4 mmol) was added in small portions with vigorous stirring. After the addition was over, the reaction mixture was stirred for 2 hours. Then the solution was poured into crushed ice and neutralised with ammonia solution. Similar procedure was followed for nitroso piperidines and nitroso diazepines. For the conversion of **3-8** to **1**, **9-13**, for 5 mmol of **3-8**, 6 mmol of HN_3 was added. The yield of the product varies between 50 and 90%. Analytical data

for denitrosated compounds are presented in supplementary data (**Table-S1**). The compounds **26-31** and **37-41** have been synthesized similarly.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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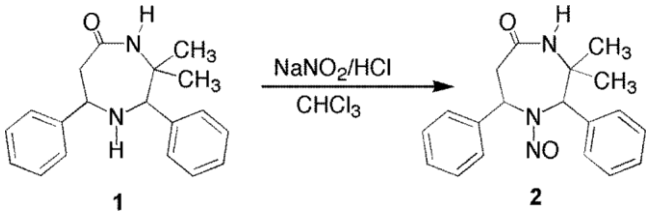
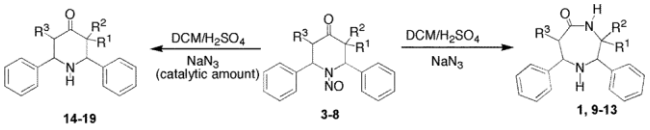
Scheme 1. Nitrosation of 3,3-dimethyl-2,7-diphenyl-1,4-diazepan-5-one



1 2

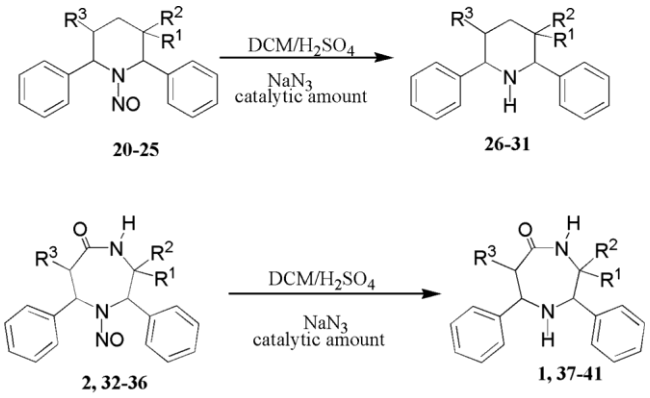
Scheme 2. Denitrosation of *N*-nitroso-3,3-dimethyl-2,6-diphenyl-piperidin-4-one



14-19 3-8 1, 9-13

		R^1	R^2	R^3	
14	**3**	H	H	H	**9**
15	**4**	CH_3	H	H	**10**
16	**5**	Et	H	H	**11**
17	**6**	*i*-Pr	H	H	**12**
18	**7**	CH_3	CH_3	H	**1**
19	**8**	CH_3	H	CH_3	**13**

Scheme 3. Denitrosation of *N*-nitroso-3,3-dimethyl-2,6-diphenyl-piperidines & *N*-nitroso-2,7-diphenyl-1,4-diazepan-5-ones



		R^1	R^2	R^3		
20	**32**	H	H	H	**26**	**37**
21	**33**	CH_3	H	H	**27**	**38**
22	**34**	Et	H	H	**28**	**39**
23	**35**	*i*-Pr	H	H	**29**	**40**
24	**2**	CH_3	CH_3	H	**30**	**1**
25	**36**	CH_3	H	CH_3	**31**	**41**