FACILE DENITROSATION OF CYCLIC N-NITROSAMINES WITH HYDRAZOIC ACID

S. Ponnuswamy, A. Akila, and D. Kiruthiga Devi
PG and Research Department of Chemistry, Government Arts College (Autonomous), Coimbatore, Tamil Nadu, India

GRAPHICAL ABSTRACT

Abstract A simple and facile method for the denitrosation of cyclic N-nitrosamines using HN₃ (concentrated H₂SO₄ + NaN₃) is reported. In this method, limited usage of this reagent does not affect the carbonyl group.

Keywords Denitrosation; 1,4-diazepan-5-one; hydrazoic acid; piperidin-4-one; Schmidt rearrangement

INTRODUCTION

Gaseous HCl and other reagents such as TiCl₂-NaBH₄, NiCl₂-NaBH₄, and chlorosulfonyl isocyanate have been used earlier as denitrosating agents.[1] The use of metallating agents such as lithium diisopropylamide (LDA), followed by alkylation and denitrosation, would lead to α-alkylated amines.[2] The denitrosation can also be carried out by treatment with lithium aluminium hydride (LAH) followed by Raney nickel.[3] However, all these processes involve either strong acidic conditions or conditions in which some functional groups would be reduced. A better method involving BF₃ with furan / thiophene / tetrahydrofuran (THF) in the presence of NaHCO₃ was also reported.[4a] Furthermore, the denitrosation of N-nitrosoamines has also been successfully accomplished using an HBr/CH₃COOH system[4b,c] and others,[4d,e] as well as enzymatically.[4f]
The reagents reported herein, namely concentrated H$_2$SO$_4$ + NaN$_3$ and CH$_2$Cl$_2$ (DCM) as solvent, are mild and inexpensive and do not involve tedious reaction conditions, workup procedure, or 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-diazepean-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-diazepean-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-diazepean-5-one (2), we isolated the 3,3-dimethyl-2,7-diphenyl-1,4-diazepean-5-one (1) as an exclusive product. Furthermore,
we tested the same experimental condition with several \(N\)-nitroso-2,6-diaryl-piperidin-4-ones using excess reagent and in all the cases, denitrosation followed by the Schmidt rearrangement to 1,4-diazepan-5-one was observed (representative examples are given in Scheme 2). However, a controlled reaction involving a catalytic amount of the reagent (0.4 mmol + 2.5 mmol 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.

To check the denitrosation reaction in the absence of a carbonyl group, we employed several \(N\)-nitroso-2,6-diaryl-piperidines, 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 and 32–36,\(^{[5]}\) and the denitrosated product has been isolated as an exclusive product (Scheme 3). In both cases, only a catalytic amount of the reagent was used. The identity of the product in all these cases is confirmed by the presence of the carbonyl group.

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**Scheme 3.** Denitrosation of \(N\)-nitroso-3,3-dimethyl-2,6-diphenyl-piperidines and \(N\)-nitroso-2,7-diphenyl-1,4-diazepan-5-ones.
reactions was checked with the reported melting point and infrared (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 NaN₃ or concentrated H₂SO₄ alone. Hence HN₃ is the reagent involved in denitrosation. In the absence of a carbonyl group, HN₃ 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 faster in the presence of a carbonyl group; that is, denitrosation is faster in 2–8 and 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 on a Bucker FT-IR z-model spectrometer using KBr pellets. The ¹H and ¹³C NMR spectra were recorded in a CDCl₃ solution using tetramethylsilane (TMS) as the internal standard on 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 and 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 concentrated H₂SO₄ (5 ml) and CH₂Cl₂ (DCM) (10 ml) in a round-bottomed flask equipped with a magnetic stirrer. Then, NaN₃ (0.4 mmol) was added in small portions with vigorous stirring. After the addition was over, the reaction mixture was stirred for 2 h. Then the solution was poured into crushed ice and neutralized with ammonia solution. A similar procedure was followed for nitroso piperidines and nitroso diazepines. For the conversion of 3–8 to 1 and 9–13, for 5 mmol of 3–8, 6 mmol of HN₃ was added. The yield of the product varies between 50 and 90%. Analytical data for denitrosated compounds are presented in the 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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