Monatshefte für Chemie 132, 1547–1549 (2001)

Monatshefte für Chemie
Chemical Monthly

An Efficient and Rapid Chemoselective Synthesis of α-Aryl-N-methylnitrones in Dry Media

Mohammad A. Bigdeli* and **Mir M. A. Nikje**

Faculty of Chemistry, Teacher Training University, Tehran, Iran

Summary. A simple, efficient, and eco-friendly procedure was developed for the condensation of N-methylhydroxylamine hydrochloride with benzaldehydes bearing electron-donating or electron-withdrawing substituents in the presence of powdered molecular sieves (3 Å) in a solventless system. α-Aryl-N-methylnitrones are obtained in excellent yields (80–100%); similar aromatic ketones do not react under these conditions, rendering the method chemoselective.

Keywords. α-Aryl-N-methylnitrones; Dry media; Chemoselective synthesis; Molecular sieve; Condensation.

Introduction

There are several methods of preparation of α-aryl-N-methylnitrones [1–6], all of them having merits and drawbacks. One disadvantage common to all is that they are conducted in organic solvents. An efficient, mild, and eco-friendly procedure would therefore be of interest. A literature survey showed no reports on syntheses of α-aryl-N-methylnitrones in solventless systems.

Heterogeneous organic reactions have proven useful both in the laboratory and in industry. In these reactions, the reagents are supported on porous solids. The advantages of such procedures over conventional solution phase reactions result from good dispersion of active reagent sites, associated selectivity, and easier work-up. The recyclability of some of the solid supports renders the processes truly eco-friendly. In view of the current thrust on solid state synthesis [7] and the emphasis on green chemistry [8], there is a merit in developing a solventless method for the preparation of α-aryl-N-methylnitrones using inexpensive, commercially available starting materials and non-polluting catalysts.

Condensation of N-methylhydroxylamine hydrochloride with benzaldehydes is the most common method employed for the synthesis of α-aryl-N-methylnitrones. Usually, it is executed in ethanol and requires warming or even reflux in most cases [1, 6–9]. In this communication we report on the use of molecular sieve (3 Å) as a catalyst for the synthesis of nitrones in a solventless medium.

---

* Corresponding author. E-mail: mbig@saba.tmu.ac.ir

Results and Discussion

The ability of molecular sieve (3 Å) to facilitate the reaction of various benzaldehydes with N-methylhydroxylamine hydrochloride in dry media was demonstrated, and the resulting data are summarized in Table 1. Aromatic aldehydes with electron-donating or electron-withdrawing substituents were converted to the corresponding nitrones in high yields in less than 15 minutes.

In order to evaluate the influence of molecular sieve (3 Å), the reaction of benzaldehyde and N-methylhydroxylamine hydrochloride without molecular sieve was also tested. However, the aldehydes remained unchanged after 30 min of grinding thoroughly in a mortar.

Another important observation is the exclusive reaction of aldehydes with N-methylhydroxylamine hydrochloride, irrespective of the presence of ketones. When one equivalent of an aldehyde in the presence of one equivalent of a similar ketone was treated with two equivalents of N-methylhydroxylamine hydrochloride, only the aldehyde was selectively converted to the corresponding nitrone, whereas the ketone did not react at all (Scheme 1).

$$\begin{array}{l} \text{Ph}_2\text{CO (1 equiv.)} \\ \text{PhCHO (1 equiv.)} \end{array} + \text{CH}_3\text{NHOH}\cdot\text{HCl (2 equiv.)} \longrightarrow \begin{array}{lr} \text{Ph}_2\text{C}{=}\text{N(O)CH}_3 & 0\% \\ \text{PhCH}{=}\text{N(O)CH}_3 & 100\% \end{array}$$

$$\begin{array}{l} \text{PhCH}_3\text{CO (1 equiv.)} \\ \text{4-NO}_2\text{PhCHO (1 equiv.)} \end{array} + \text{CH}_3\text{NHOH}\cdot\text{HCl (2 equiv.)} \longrightarrow \begin{array}{lr} \text{PhCH}_3\text{C}{=}\text{N(O)CH}_3 & 0\% \\ \text{4-NO}_2\text{PhCH}{=}\text{N(O)CH}_3 & 100\% \end{array}$$

Scheme 1

Therefore, this methodology can be used selectively for the preparation of α-aryl-N-methylnitrones of compounds containing both aldehyde and ketone functionalities.

A wide variety of benzaldehydes with both electron-donating and electron-withdrawing substituents were treated likewise to give the corresponding nitrones in high to excellent yields (Table 1). To the best of our knowledge this is the first example of molecular sieve (3 Å) catalysis of this reaction.

Table 1. Solventless synthesis of α-aryl-N-methylnitrones using molecular sieve (3 Å)

$$\underset{\mathbf{1}}{\text{ArCH}{=}\text{O}} \xrightarrow[\text{Molecular sieve (3 Å)}]{\text{CH}_3\text{NHOH}\cdot\text{HCl}} \underset{\mathbf{2}}{\text{ArCH}{=}\text{N(O)CH}_3}$$

	Ar	Melting point/°C	Yield/%
2a	Phenyl	82–84	98
2b	4-Methylphenyl	119–121	92
2c	2-Furyl	89–91	80
2d	2-Nitrophenyl	91–94	100
2e	2-Hydroxyphenyl	141–143	88
2f	2,4-Dimethoxyphenyl	132–135	90
2g	4-Nitrophenyl	216–219	100
2h	4-Chlorophenyl	127–129	84
2i	3-Nitrophenyl	119–122	98

Experimental

All benzaldehydes, molecular sieve (3 Å), and N-methylhydroxylamine hydrochloride were purchased from Merck. Compound **2a** [9] is known and was characterized by comparision of melting point and spectroscopic data with those of an authentic sample. For compounds **2b–i**, the IR and NMR spectra are similar to that of compound **2a**.

Preparation of α-phenyl-N-methylnitrones; general procedure

A mixture of N-methylhydroxylamine hydrochloride (1.2 mmol), finely powdered molecular sieve (3 Å) (0.3 g), and benzaldehyde (1.2 mmol) were grinded thoroughly for 10 min. The reaction mixture was set aside for further 5 min at ambient temperature. To the crude product mixture, $2\times10\,cm^3$ $CHCl_3$ were added, and solid parts were filtered off. The solvent was evaporated to dryness, and the residue was crystallized from petroleum ether (60–80°C) to afford the α-phenyl-N-methylnitrones.

Acknowledgements

We acknowledge the support of the Teacher Training University for a fellowship and financial assistance.

References

[1] a) Abou-Gharbia M, Joullie MM (1977) Synthesis 318; b) Abou-Gharbia M, Joullie MM (1979) Org Prep Proced Int **11**: 95
[2] Bimanand AZ, Coates RM (1984) J Org Chem **49**: 3127
[3] Patai S, Rappoport Z (1989) Nitrones, Nitronates and Nitroxides. Wiley, New York, and references cited therein
[4] Shindo H, Umezawa B (1962) Chem Pharm Bull **10**: 492; Chem Abstr (1962) **57**: 14, 598
[5] Exner O (1955) Collection Czech Chem Commun **20**: 202; Chem Abstr (1955) **49**: 11, 603
[6] Hamer J, Macaluso A (1964) Chem Rev **29**: 473 and references cited therein
[7] Balog M, Laszlo P (1993) Organic Chemistry Using Clays. Springer, Berlin and references cited therein
[8] a) Tanaka K, Toda F (2000) Chem Rev **100**: 1025 and references cited therein; b) Varma RS (1999) Green Chemistry **1**(1): 43 and references cited therein
[9] Koyano K, Suzuki H (1968) Tetrahedron Lett **15**: 1859

Received March 26, 2001. Accepted (revised) May 7, 2001