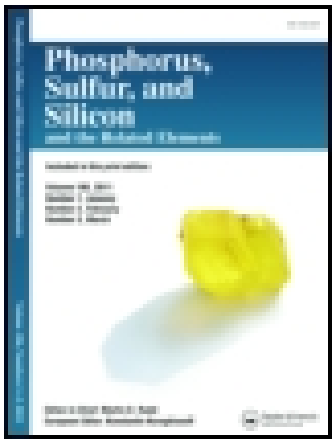

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

A FACILE AND NEW METHOD FOR THE SYNTHESIS OF α-ARYL-N-METHYLNITRONES IN SOLVENT-FREE MEDIA USING SILICA GEL-NaOH

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Published online: 16 Aug 2010.

To cite this article: M. M. Alavi Nikje , M. A. Bigdeli & H. Imanieh (2004) A FACILE AND NEW METHOD FOR THE SYNTHESIS OF α-ARYL-N-METHYLNITRONES IN SOLVENT-FREE MEDIA USING SILICA GEL-NaOH, Phosphorus, Sulfur, and Silicon and the Related Elements, 179:8, 1465-1468, DOI: 10.1080/10426500490463790

To link to this article: http://dx.doi.org/10.1080/10426500490463790

Phosphorus, Sulfur, and Silicon, 179:1465–1468, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490463790

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A FACILE AND NEW METHOD FOR THE SYNTHESIS OF α-ARYL-N-METHYLNITRONES IN SOLVENT-FREE MEDIA USING SILICA GEL-NaOH

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(Received November 25, 2003)

Substituted α-aryl-N-methylnitrones are prepared by the condensation reaction of N-methylhydroxylamine hydrochloride and benzaldehydes in solvent-free media using silica-gel–NaOH catalyst system. The yields are excellent regardless of the electron-donating or electron-accepting nature of the substituents on benzaldehyde. Similar ketones are unreactive under these conditions, rendering chemoselectivity of the method.

Keywords: α-Aryl-N-methylnitrones; chemoselectivity; silica gel-NaOH; solvent-free media

Numerous methods of preparation of α-aryl-N-methylnitrones are known.[1–6] Each method exhibits merits as well as shortcomings. One of the most important methods is the condensation of N-methylhydroxylamine hydrochloride with substituted benzaldehydes. Decomposition of N-methylhydroxylamine hydrochloride and the need to heat up or even to reflux the reaction mixture results in low yields.[1–6,10] The second factor responsible for diminished reactivity is the formation of water in the course of the reaction which, if not removed, will stop the reaction midway and hydrolyze the initially formed nitrone. In order to find a possible way around this difficulty, and motivated by recent interest in carrying out reactions in solvent-free media,[7] an emphasis on green chemistry,[8] and in the continuation of our experiments for the nitrone synthesis in dry media,[9] we decided to reexamine the procedure in dry media using silica-gel–NaOH catalyst

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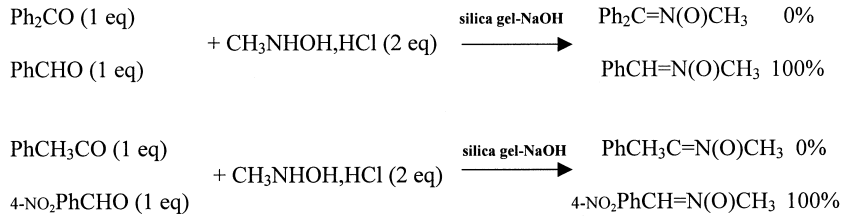
TABLE I Dry Media α-aryl-N-Methylnitrones Synthesis Using Silica-Gel–NaOH Catalyst

Nitrone	Melting point(C)	Yields(%)
α-phenyl-N-methylnitrone	82–84	92
α-(4-methylphenyl)-N-methylnitrone	119–121	87
α-(2-furyl)-N-methylnitrone	89–92	85
α-(2-nitrophenyl)-N-methylnitrone	91–94	98
α-(2-hydroxyphenyl)-N-methylnitrone	141–143	84
α-(2,4-dimethoxyphenyl)-N-methylnitrone	132–135	92
α-(4-nitrophenyl)-N-methylnitrone	216–219	96
α-(4-chlorophenyl)-N-methylnitrone	127–130	85
α-(3-nitrophenyl)-N-methylnitrone	119–122	96

system which to the best of our knowledge is the first example used in such reactions. We have found an ideal condition to carry out the reaction using silica-gel–NaOH catalyst in dry media system to synthesize α-aryl-N-methylnitrones in high yields (Table I). Benzaldehydes bearing electron-accepting as well electron-donating groups react similarly under these conditions.

We are pleased with the results not only from the point of view of reporting an improved preparative method but also from of an environmental standpoint. Our method is solvent-free, clean, and eco-friendly. Working up procedure is simple, and the purity of the products is high even before recrystallization.

An important piece of observation made was that the corresponding ketones failed to react under these conditions. 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, while the ketone did not react at all (Scheme 1).



SCHEME 1 Chemoselective aldonitrones synthesis in the presence of similar ketones.

The reaction also gave no results in dry media without the use of silica-gel–NaOH catalyst system. Therefore, this methodology could be

used selectively for the preparation of α-aryl-N-methylnitrones from compounds that contain both aldehyde- and keton-functional groups. We believe that silica gel enhances the reaction by absorbing the water produced during the reaction which needs to be removed in order for the reaction to be completed. Dry media absorbs the excess water efficiently and prevents the hydrolysis of formed nitrone. In conclusion, the reported procedure is a new, facile, and environmentally friendly method for the preparation of α-aryl-N-methylnitrones. The reaction is fast, the procedure is simple, and the yields are high.

EXPERIMENTAL

All benzaldehydes, sodium hydroxide flakes, silica gel 60, and N-methylhydroxylamine hydrochloride were purchased from Merck.The α-phenyl-N-methylnitrone is known and was characterized by comparison with the melting point, IR, and NMR spectral data of an authentic sample.[10] For other nitrones, the IR and NMR spectra were obtained and found to be consistent with the structures assigned.

Preparation of α-Phenyl-N-methylnitrone

General Procedure

A mixture of sodium hydroxide flakes (0.6 mmol), silica gel 60 (0.3 gr relative to 1.2 mmol aldehyde), and N-methylhydroxylamine hydrochloride (1.2 mmol) and benzaldehyde (1.2 mmol) was grand thoroughly for 6 min. The reaction mixture was set aside for a further 4 min at ambient temperature. To the crude product mixture $CHCl_3$ (2×10 ml) was added and filtered. The solvent was evaporated to dryness and the residue was appropriately crystallized from petroleum ether (60–80°C) to afford the α-phenyl-N-methylnitrone in 92% yield.

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