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# Rapid, Efficient, and Room Temperature Synthesis of Nitrones in Excellent Yields over MgO under Solvent-Free Conditions

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ABSTRACT: *A large variety of C-aryl and C-alkyl nitrones were synthesized within 0.5–15 min via the condensation of aldehydes with N-(methyl, phenyl, or t-butyl)hydroxylamines over MgO by hand-grinding with an agate mortar. These reactions were investigated under different conditions and over different solid supports including basic alumina, montemorillonite, MgO, and molecular sieves (pore size 3 Å). In the more interesting cases, nitrones were prepared over MgO without heating and any catalyst. In this procedure, nitrones were prepared in a very short time, excellent yields, and good purity without using harmful solvents in the workup.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:177–181, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20527

## *INTRODUCTION*

Nitrones are highly valuable intermediates in organic synthesis. They behave as electrophiles toward organometallics and as 1,3-dipoles in cycloadditions [1]. Nitrones are reactive 1,3-dipoles of the allyl class that are also usually generated in situ. Nitrones have proved to be very useful tools in the synthesis of structurally complex molecules, usually allowing a high degree of diastereocontrol. In this context, both the [3 + 2] cycloaddition of nitrones to alkenes [2,3] and the alkylation of nitrones by organometallic reagents [4] have been extensively studied and have become reliable synthetic procedures. One of the most common procedures for the synthesis of nitrones is the condensation of aldehydes and ketones with *N*-monosubstituted hydroxylamines [5,6]. However, this method is difficult for the preparation of nonconjugated cyclic nitrones and bulky alkyl group containing ketonitrones. Another method for the preparation of nitrones is the oxidation of *N*,*N*-disubstituted hydroxylamines [7] in which yellow mercuric oxide [8] is most commonly used as an oxidant. Direct oxidation of secondary amines was also reported as a useful method for the preparation of nitrones [9]. Andrade et al. reported the microwave (MW)-assisted neat procedures for the synthesis of nitrones [10]. The synthesis of nitrones in a ball mill has been reported in solvent-free conditions [11]. In continuation of our recent interest to use ionic liquids (ILs), water or solvent-less systems as a green reaction medium [12,13], we report here the preparation of a variety of nitrones without using MW and conventional heating technique in solvent-less system over MgO solid support. For comparison, the procedure was also examined in several ILs by grinding or under MW irradiation.

## *RESULTS AND DISCUSSION*

In a typical procedure, a mixture of *N*-methylhydroxylamine hydrochloride, benzaldehyde, and

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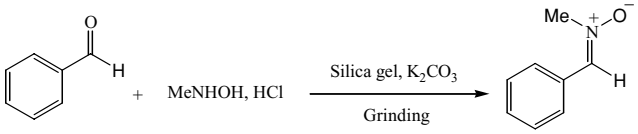



**SCHEME 1**

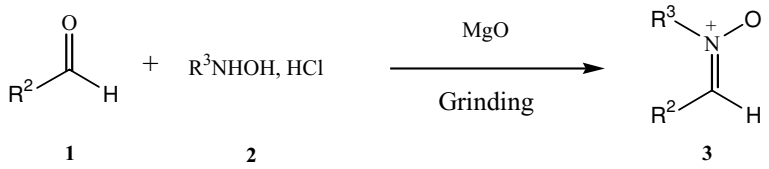
$K_2CO_3$ adsorbed on the surface of silica gel was grinded in a mortar for a certain period of time as required to complete the reaction (Scheme 1). The elution of the reaction mixture with chloroform followed by the evaporation of solvent furnished the crude product **3a**, which was purified by recrystallization. MW irradiation of the mixture, in place of grinding, leads to a messy product with the formation of a tarry material. For optimizing the conditions, we used the substrates in different ratios. It was found that the best results were obtained with 1:1 starting material ratio. Several solid supports were screened for this typical reaction for complete conversions as monitored by thin layer chromatography (TLC) to afford the desired product (Table 1). Evidently, MgO was found to be superior in terms of yield (98%) and reaction time (2.5 min) as compared with other supports (entries 1–4). In another experiment, equimolar amounts of reactants were treated in several butylmethylimidazolium (bmim)-based ILs, [bmim]X, with varying anions such as $Cl^-$, $BF_4^-$, and $PF_6^-$ at room temperature. The observation shows that the reaction in ILs was slower than the reaction by hand grinding of reactants over MgO (entries 5–7). The reactions in ILs were conducted at higher temperatures for optimizing the conditions and no significant improvements were observed in yields or reaction times. For comparison, the direct condensation of the reactants over solid supports or in ILs was carried out under MW irradiation in optimized conditions, and the pertinent results are given in Table 1. From the results obtained, as shown in Table 1, it is clear that the reaction over MgO should be the method of choice for synthesizing nitrones, since a comparatively higher yield was achieved in a shorter reaction time.

Consequently, we extended the grinding method over MgO to other aldehydes in the presence of *N*-methyl-, *N*-phenyl-, and *N-tert*-butylhydroxylamine hydrochlorides (**2a**, **2b**, and **2c**, respectively) to obtain the corresponding nitrones (Scheme 2). The procedure is simple and straightforward consisting of the cogrinding of the two components in a mortar. After the appropriate time, the reaction mixture is dissolved in $CHCl_3$ and analyzed by TLC. The products were purified by recrystallization from suitable solvent and characterized by $^1$H NMR, $^{13}$C NMR, infrared (IR), and elemental analyses and mass spectrometry. Melting points (entries 1, 3–6, and 10–15) of all the products were compared with those reported in the literature. Aromatic aldehydes, containing electron-withdrawing groups (entries 5 and 10) as well as electron-donating groups (entries 2, 6, 7, 9, 11–13, and 15), reacted smoothly to afford the corresponding products in excellent yields. In general, the aromatic aldehydes react faster than the aliphatic aldehydes (entries 16 and 17). In all the cases, the reactions were completed within 2.5–15 min of the reaction time. In the majority of the entries, the nitrones were formed fast, with final yields ranging from good to excellent (Table 2). We conducted these reactions on a 20-mmol scale and found them they underwent a smooth transformation to the nitrone derivatives in good yields. Thus, the present procedure is amenable for scaling up.

**TABLE 1** Effect of Different Solid Supports and Ionic Liquids on Synthesis of *N*-Methyl-*C*-phenylnitrone[a]

| | | | *Grinding* | | *Microwave*[d] |
|---|---|---|---|---|---|
| *Entry* | *Solid Support/Base* | *Ionic Liquid*[b] | *Time (min)* | *Yield*[c] *(%)* | *Yield (%)* |
| 1 | MgO | – | 2.5 | 98 | 45 |
| 2 | Alumina/$K_2CO_3$ | – | 8 | 72 | 55 |
| 3 | Molecular sieves (pore size 3 Å)/$K_2CO_3$ | – | 10 | 61 | 50 |
| 4 | Silica gel/$K_2CO_3$ | – | 12 | 50 | 45 |
| 5 | – | [bmim]Cl | 65 | 25 | 60 |
| 6 | – | [bmim]$PF_6$ | 60 | 30 | 70 |
| 7 | – | [bmim]$BF_4$ | 60 | 32 | 65 |

Abbreviation: bmim, butylmethylimidazolium.
[a]Reactants used: 0.5 mmole of benzaldehyde, 0. 5 mmole of methylhydroxylamine hydrochloride, and 0.5 mmole of base.
[b]Reactants were mixed in 2 mL of ionic liquid.
[c]Isolated yields after recrystallization.
[d]Comparative experiment under microwave activation 10 min at 80°C (optimized conditions).




1 2 3

**2a:** $R^3$=Me, **2b:** $R^3$=Phenyl, **2c:** $R^3$=t-Butyl

**3a:** $R^2$ = Phenyl, $R^3$ = Me
**3b:** $R^2$ = 2-Methoxyphenyl, $R^3$ = Me
**3c:** $R^2$ = 2-Pyridyl, $R^3$ = Me
**3d:** $R^2$ = 2-Furyl, $R^3$ = Me
**3e:** $R^2$ = 4-Cyanophenyl, $R^3$ = Me
**3f:** 4-Methylphenyl, $R^3$ = Me
**3g:** $R^2$ = 2-Hydroxyphenyl, $R^3$ = Ph
**3h:** $R^2$ = 5-Bromo-2-hydroxyphenyl, $R^3$ = Ph
**3i:** $R^2$ = 2,3-Dihydroxyphenyl, $R^3$ = Ph
**3j:** $R^2$ = 4-Nitrophenyl, $R^3$ = Ph
**3k:** $R^2$ = 4-Methoxyphenyl, $R^3$ = Ph
**3l:** $R^2$ = 3-Ethoxy-2-hydroxyphenyl, $R^3$ = t-Butyl
**3m:** $R^2$ = 2-Hydroxy-4-methoxyphenyl, $R^3$ = t-Butyl
**3n:** $R^2$ = 5-Bromo-2-hydroxyphenyl, $R^3$ = t-Butyl
**3o:** $R^2$ = 2-Hydroxy-5-methoxyphenyl, $R^3$ = t-Butyl

**SCHEME 2**

**TABLE 2** Synthesis of Nitrones by Hand-Grinding over MgO under Solvent-Free Conditions

| *Entry* | *$R^2$* | *$R^3$* | *Time (min)* | *Product* | *Melting Point (°C) Found (Lit. [Ref.] Reported, °C)* | *Yield (%)[a]* |
|---|---|---|---|---|---|---|
| 1 | Phenyl | Methyl | 2.5 | **3a** | 83–85 ([10] 83–84) | 98 |
| 2 | 2-Methoxyphenyl | Methyl | 3 | **3b** | 84–84.5[b] | 95 |
| 3 | 3-Pyridyl | Methyl | 4.5 | **3c** | 74–76 ([10] 75–79) | 89 |
| 4 | 2-Furyl | Methyl | 5 | **3d** | 88–90 ([10] 90) | 92 |
| 5 | 4-Cyanophenyl | Methyl | 3 | **3e** | 183–185 ([14] 187) | 90 |
| 6 | 4-Methylphenyl | Methyl | 5.5 | **3f** | 117–120([11] 118–120) | 91 |
| 7 | 2-Hydroxyphenyl | Phenyl | 4.5 | **3g** | 129–131[b] | 91 |
| 8 | 5-Bromo-2-hydroxyphenyl | Phenyl | 5 | **3h** | 173–176[b] | 89 |
| 9 | 2,3-Dihydroxyphenyl | Phenyl | 5.5 | **3i** | 159–161[b] | 94 |
| 10 | 4-Nitrophenyl | Phenyl | 4.5 | **3j** | 181–183 ([10] 183–184) | 93 |
| 11 | 4-Methoxyphenyl | Phenyl | 3.5 | **3k** | 113–116 ([10]115–116) | 90 |
| 12 | 3-Ethoxy-2-hydroxyphenyl | *t*-Butyl | 6 | **3l** | 90–92 ([15] 91.9) | 87 |
| 13 | 2-Hydroxy-4-methoxyphenyl | *t*-Butyl | 5.5 | **3m** | 13–116 ([15] 115.2–116) | 86 |
| 14 | 5-Bromo-2-hydroxyphenyl | *t*-Butyl | 6 | **3n** | 115–118 ([15] 118.7) | 89 |
| 15 | 2-hydroxy-5-methoxyphenyl | *t*-Butyl | 6 | **3o** | 69–71 ([14] 70.4–70.6) | 87 |
| 16 | $CH_3(CH_2)_2$- | Methyl | 15 | **3p** | Yellow oil | 71 |
| 17 | $CH_3(CH_2)_5$- | Methyl | 12 | **3q** | Yellow oil | 69 |

[a]Isolated yields after recrystallization.
[b]Spectroscopic data are shown in the experimental section.

## *CONCLUSION*

In conclusion, the present procedure provides a fast and efficient method for the synthesis of nitrones on the surface of MgO under solvent-free conditions. The notable advantages of this procedure are (a) very fast reaction time; (b) mild reaction conditions; (c) general applicability; (d) excellent yields; and (e) green synthesis avoiding toxic solvents. Thus, it provides a more practical alternative to the existing methods.

## *EXPERIMENTAL*

### *General Information*

All reagents were purchased from the Merck company and used without further purification. $^1$H NMR spectra were obtained in $CDCl_3$ solution on a Bruker Avance AC-400 MHz (or 300 MHz) spectrometer and $^{13}$C NMR spectra at 100 MHz (or 75 MHz) on the aforementioned instrument. Mass spectra, using electron ionization (EI)-mass spectrometry (MS), were recorded on a Shimadzu GCMS-QP-2000A mass spectrometer. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer and are reported in percentage atomic abundance. All melting points are uncorrected and measured in an open glass capillaries on a Stuart melting point apparatus.

### *Preparation of Nitrones in ILs: General Procedure*

The selected aldehyde (0.2 mmol), monosubsituted hydroxylamine (**2a–2c**) (0.2 mmol), and IL (2 ml)

were stirred at room temperature for appropriate time (Table 2). The completion of reaction was monitored by TLC, with EtOAc/petroleum as the eluent. After the completion of the reaction, the mixture was extracted with ether. The extracts were concentrated on a rotary evaporator and the crude mixture was purified by recrystallization with EtOH/EtOAc to afford the corresponding nitrones.

### *Preparation of Nitrones over Solid Supports: General Procedure*

The selected aldehyde (0.2 mmol), the monosubsituted hydroxylamine (**2a–2c**) (0.2 mmol), and the solid support (2 g) were cogrinded in a mortar at room temperature for appropriate time (Table 2). The completion of reaction was monitored by TLC, with EtOAc/petroleum as the eluent. After the completion of the reaction, the mixture was extracted with $CHCl_3$. The extracts were concentrated on a rotary evaporator and the crude mixture was purified by recrystallization with EtOH/EtOAc to afford the corresponding nitrones (Table 2).

### *Selected Spectroscopic Data*

*C-(2-Methoxyphenyl)-N-methyl-nitrone (***3b***).* IR $\nu_{max}/cm^{-1}$: 1578 (C=N), 1138 (N—O), and 1025 (C—O). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.55 (s, 1H, nitronyl H), 7.39 (dt, $J = 1.58$ Hz and $J = 8.40$ Hz, 1H), 7.10 (dd, $J = 1.45$ Hz and $J = 80$ Hz, 1H), 6.96 (d, $J = 8.25$ Hz, 1H), 6.85 (t, $J = 8.00$ Hz, 1H), 3.77 (3H, s, $OCH_3$); $\delta_C^{13}C$ NMR ($CDCl_3$, 100 MHz) 158.59, 140.92, 133.09, 130.93, 119.18, 117.99, 115.54, 69.05, 51.06; EI-MS $[MH]^+$ *m/z* 166; Anal. calcd. (%) for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found (%): C, 64.98; H, 6.69; N, 8.42.

*C-(2-Hydroxyphenyl)-N-phenyl-nitrone (***3g***).* IR $\nu_{max}/cm^{-1}$: 3500–3150 (OH), 1586 (C=N), 1159 (N—O), and 1033 (C—O). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 12.40 (s, 1H, OH), 7.92 (s, 1H, nitronyl H), 7.60–7.39 (m, 6H, ArH), 7.23 (t, $J = 9.2$ Hz, 1H), 7.04 (d, $J = 11.15$ Hz, 1H), 6.95 (t, $J = 9.8$ Hz, 1H); $\delta_C$ $^{13}C$ NMR ($CDCl_3$, 100 MHz) 134.72, 134.69, 129.21, 128.20, 126.26, 125.39, 125.32, 121.16, 118.99, 118.95, 117.98; EI-MS $[MH]^+$ *m/z* 214; Anal. calcd. (%) for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found (%): C, 72.98; H, 5.13; N, 6.48.

*C-(5-Bromo-2-hydroxyphenyl)-N-phenyl-nitrone (***3h***).* IR $\nu_{max}/cm^{-1}$: 3500–3100 (OH), 1581 (C=N), 1160 (N—O), and 1030 (C—O). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 12.35 (s, 1H, OH), 8.21 (s, 1H, nitronyl H), 7.82–7.76 (m, 2H, ArH), 7.53 (t, $J = 3.3$ Hz, 3H), 7.12 (dd, $J = 1.58$ Hz and $J = 7.59$ Hz, 1H), 6.83 (d, $J = 7.59$ Hz, 1H), 6.75 (d, $J = 1.58$ Hz, 1H); $\delta_C$ $^{13}C$ NMR ($CDCl_3$, 75 MHz) 147.54, 147.42, 145.81, 141.30, 130.63, 129.41, 123.23, 121.84, 119.85, 117.73, 115.99; EI-MS $[MH]^+$ *m/z* 291; Anal. calcd. (%) for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79. Found (%): C, 53.35; H, 3.42; N, 4.68.

*C-(2,3-Dihydroxyphenyl)-N-phenyl-nitrone (***3i***).* IR $\nu_{max}/cm^{-1}$: 3450–3000 (OH), 1569 (C=N), 1151 (N—O), and 1035 (C—O). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 12.40 (s, 1H, OH), 8.00 (s, 1H, nitronyl H), 7.77–7.75 (m, 2H, ArH), 7.52–7.47 (m, 5H, ArH and OH), 7.30 (d, $J = 2.3$ Hz, 1H), 6.90 (d, $J = 8.88$ Hz, 1H); $\delta_C$ $^{13}C$ NMR ($CDCl_3$, 100 MHz) 159.04, 145.92, 139.56, 137.07, 134.38, 130.82, 129.46, 122.29, 121.79, 118.70, 110.70; electrospray ionization-MS $[MH]^+$ *m/z* 230; Anal. calcd. (%) for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found (%): C, 68.05; H, 4.83; N, 6.09.

## *REFERENCES*


[1] (a) Merino, P.; Padwa, A. (Eds.). Science of synthesis; Thieme: Stuttgart, 2004; Vol. 27, pp. 511–580; (b) Bortolini, O.; D'Agostino, M.; De Nino, A; Maiuolo, L.; Nardi, M.; Sindona, G. Tetrahedron 2008, 64, 8087–8081.

[2] Confalone, P. N.; Huie, E. M. Org React 1988, 36, 1.

[3] Torsell, K. B. G. In Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis; Feuer, H. (Ed.); VCH Publishers: New York, 1988, 75–93.

[4] Bloch, R. Chem Rev 1998, 98, 1407.

[5] (a) Tice, C. M.; Ganem, B. J Org Chem 1983, 48, 5048–5050; (b) Bigdeli, M. A.; Nikje, M. M. A. Monatsh Chem 2001, 132, 1547–1549; (c) Alavi Nikje, M. M.; Bigdeli, M. A.; Imanieh, H. Phosphorus Sulfur Silicon Relat Elem 2004, 179, 1465–1468.

[6] (a) Chan, K. S.; Yeung, W.-K.; Chan, R.-J.; Wang, T.-C.; Mak, W. J Org Chem 1995, 60, 1741–1747; (b) Sandler, S. R.; Karo, W. In Organic Functional Group Preparations, 2nd ed.; Academic Press: San Diego, 1989; Vol. 3, pp. 351–376.

[7] (a) Fenselau, A. H.; Hamamura, E. H.; Moffatt, J. G. J Org Chem 1970, 35, 3546; (b) Smith, P. A. S.; Gloyer, S. E. J Org Chem 1975, 40, 2508; (c) Nojima, M.; Takeuchi, K.; Fukui, E.; Tokura, N. J Chem Soc [Perkin Trans. 1] 1976, 2202.

[8] Ali, S. A.; Hashmi, S. M. A.; Siddiqui, M. N.; Wazeer, M. I. M. Tetrahedron 1996, 52, 14917.

[9] (a) Mitsui, H.; Zenki, S.; Shiota, T.; Murahashi, S-I. J Chem Soc, Chem Commun 1984, 874; (b) Murahashi, S-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. J Org Chem 1990, 55, 1736; (c) Murahashi, S-I.; Shiota, T.; Imada, Y. Org Synth 1991, 70, 265; (d)Yamazaki, S. Bull Chem Soc Jpn 1997, 70, 877.

[10] Andrade, M. M.; Barros, M. T.; Pinto R. C. Tetrahedron 2008, 64, 10521–10530.

[11] Colacino, E.; Nun, P.; Colacino, F. M.; Martinez, J.; Lamaty, F. Tetrahedron 2008, 64, 5569–5576.
[12] (a) Valizadeh, H.; Shockravi, A. Tetrahedron Lett 2005, 46, 3501–3503; (b) Valizadeh, H.; Vaghefi, S. Synth Commun (in press).
[13] (a) Valizadeh, H.; Amiri, M.; Gholipur, H. J Heterocycl Chem 2009, 46, 108–110; (b) Valizadeh, H.; Mamaghani, M.; Badrian, A. Synth Commun 2005, 35, 785–790.
[14] Yijima, C.; Tsujimoto, T.; Suoa, K.; Yamauchi, M. Bull Chem Soc Jpn 1986, 59, 2165–2170.
[15] Waterbury, D. L.; Carney, J. M.; Wilcox, A. L. US Patent, 6 197 826, 2001.