Note

1,3-Dipolar cycloadditions: Part VIII —
Microwave irradiation assisted synthesis of
N-methyl-C-aryl nitrones

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N-Methyl-C-arylnitrones have been synthesized in very high
yields within a few minutes from N-methyl-hydroxyamine hydrochloride and aryl aldehydes in presence of sodium hydrogen carbonate in methylene chloride using the microwave irradiation technique.

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Nitrones are important 1,3-dipolar species, which undergo cycloadditions to double and triple bonds to yield reduced isoxazole derivatives. The latter serve as valuable synthetic templates for synthesizing various 1,3-difunctionalised compounds as well as heterocyclic compounds. Our continuing interest in nitrones cycloadditions led us to develop methods based on the use of microwave irradiation techniques for very rapid high-yielding synthetic procedures for C,N-disubstituted nitrones. The previously reported, and now commonly utilised procedure, for the synthesis of N-methyl-C-arylnitrones consists of refluxing a mixture of N-methylhydroxyamine hydrochloride and the appropriate aldehyde in the presence of a mild base for several hours in refluxing dichloromethane. It was found that the reflux times of the order of 6-12 hr were necessary to obtain good yields.

Recently, many research groups have shown the wide applicability of microwave irradiation techniques in enhancing reaction rates of chemical reactions; moreover these are attended with the formation of cleaner products and operational simplicity.

We report herein an improved synthetic procedure for N-methyl-C-arylnitrones utilising microwave irradiation techniques. Reaction times could be drastically curtailed to a few minutes and yields significantly improved to nearly quantitative in most cases by utilising this procedure.

\[
\begin{align*}
\text{Ar} &- \text{CHO} + \text{Me}-\text{NOH.HCl} & \text{NaHCO}_3 & \rightarrow \text{MW irradiation} \\
\text{Ar} &- \text{CH} = \text{N} &\text{Me} - \text{O} & + \text{NaCl} + \text{2H}_2\text{O} + \text{CO}_2
\end{align*}
\]

Results and Discussion

The appropriate aromatic aldehyde was taken with a small excess (1:1.3-1.4 molar ratio) of N-methylhydroxyamine hydrochloride in anhydrous dichloromethane, excess sodium hydrogen carbonate was added, and the mixture subjected to microwave irradiation for a period usually varying from 2 to 6 min. The reaction mixtures were analyzed by 300 MHz $^1$H NMR spectroscopy of aliquots taken after intervals of 2 or 3 min. At the end of the reaction period the reaction mixture was diluted with chloroform, filtered and evaporated to dryness in a rotary evaporator. The residue was subjected to $^1$H NMR analysis. The nitrone was then crystallized. Alternatively, the reaction mixture, after filtration, could be directly added to the dipolarophile or a solution of the dipolarophile in an appropriate solvent.

The $^1$H NMR analysis showed that for most of the aromatic aldehydes the conversion to nitrones was essentially complete within 2 to 6 min from the commencement of the reaction. The results are collected in Table I. However, the reaction rate diminished when an ortho-substituent or a strongly electron-donating para-substituent such as methoxyl, was present. The reaction rate also slowed down on dilution of the reaction mixture with chlorobenzene.

We believe that this procedure developed by us for the synthesis of N-methyl-C-arylnitrones is the method of choice in view of the excellent yields obtained, short reaction times and the cleanness and ease of operation.

Experimental Section

A BPL-Sanyo model domestic microwave oven BMO-700T was used at a power setting of about 1200 Watts, Bruker AM-300L NMR spectrometer for analyzing the samples in CDCl$_3$ solution and Perkin-Elmer FT-IR for recording IR spectra. Spectroscopic and analytical results were in conformity with expectations for the synthesized nitrones.
Table I — Microwave-assisted synthesis of N-methyl-C-aryl nitrones

<table>
<thead>
<tr>
<th>SL No.</th>
<th>Substituted Benzaldehydes Ph-R; R=</th>
<th>Reaction time min</th>
<th>Isolated yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>p-NO₂</td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>m-NO₂</td>
<td>6</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>p-Cl</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>m-Cl</td>
<td>6</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>p-Br</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>m-Br</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>o-OMe</td>
<td>15</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>p-OMe</td>
<td>15</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>Cinnamaldehyde</td>
<td>2</td>
<td>95</td>
</tr>
</tbody>
</table>

Note: Percentage conversions as determined by 300 MHz $^1$H NMR measurements were as follows: 1, 2, 3, 4, 6, 7 > 99% after 6 min; 5-96% at 6 min; 10-100% after 2 min; 8-83.5% after 6 min, 94% after 15 min; 9-43% after 3 min, 57% after 15 min.

General procedure. In a typical experiment N-methylhydroxylamine hydrochloride (1.82 g, 2.2 mmole), aromatic aldehyde (1.6 mmole) and sodium hydrogen carbonate (480 mg, 5.7 mmole) were taken in anhydrous dichloromethane (5-6 mL) in a 25 mL Erlenmeyer flask and subjected to microwave irradiation for periods usually varying from 2 to 6 min; on occasion this was extended to 30 min. A cooling device resembling a cold finger filled with ice was fitted on the top of the flask. At the end of the reaction period the reaction mixture was diluted with chloroform to 15-20 mL, filtered and evaporated to dryness in a rotary evaporator. The residue was analyzed by 300 MHz $^1$H NMR. The nitrone was then crystallized from ethanol, methanol or petrol-benzene. The nitrones were characterised from their $^1$H NMR, $^{13}$C NMR and FT-IR spectra, and comparison with authentic samples available in our laboratory.

In a typical experiment with p-chlorobenzaldehyde the reaction was monitored by observing the 300 MHz $^1$H NMR intensities of the following proton signals—p-chlorobenzaldehyde: δ 9.98 (s, CHO), 7.99 and 7.82 (d each, 8.4Hz, H-2,6 and H-3,5); C-p-chlorophenyl-N-methyl-nitrone: δ 7.36 (s, CH), 8.17 (d, 8.7 Hz, H-2,6), δ 7.38 (d, 8.7 Hz, H-3,5). Relative intensities showed conversion of 93% after 2 min and 99.5% after 6 min.

In conclusion our procedure marks a significant improvement over the existing one in terms of the rapidity of the reaction and the yields obtained. We believe our procedure represents the method of choice for the facile preparation of N-methyl-C-aryl-nitrones.

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References