Solid support synthesis of fungicidal pyrazoles using microwaves

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A series of 3-aryl-4-[N-ethyl-7-methyl-4-oxo-naphthyridin-3-yl carboxyl]-3-pyrazolin-5-ones have been synthesized by the reaction of corresponding hydrazones using acidic alumina under microwave irradiation (MWI). The reaction rate increases with improved yields. The synthesized compounds are screened for their antifungal activity against A. niger and A. flavus.

Pyrazoles and their derivatives have been investigated extensively by the organic chemists due to their close association with the biological activities. 1, 3, 8-Naphthyridine derivatives are also pharmacologically important. 4, 5. Reaction on solid support without using solvent usually with open vessel in domestic microwave oven are currently in use for synthetic chemist to create ecofriendly atmosphere.

Keeping in view the utility of MWI and our interest in synthesizing the pharmacologically important pyrazoles, we report herein the synthesis of pyrazole derivatives containing quinolone moiety in dry media using MWI with a view to developing a rapid, safe and economical method devoid of solvent usage.

Results and Discussion

Polysubstituted pyrazoles were synthesized under MWI using acidic alumina. Hydrazones 5a-f were prepared from nalidixic acid hydrazide 3 and aryl aldehydes 4 by refluxing in ethanol, which were cyclized on acidic alumina to give corresponding pyrazoles (cf. Scheme I). They were characterized on the basis of their IR and 1H NMR data (Table I). The shifting of signal from δ 8.2 to 10.2 of -NH group and disappearance of singlet at δ 6.2 due to -COCH3CO- group in 1H NMR spectra confirmed the formation of pyrazoles.
their antifungal activity against fungi. Cyclocondensation of hydrazones required to obtain condensed pyrazoles. With constant heating at reaction was completed in 2-3 min when carried out under MWI using solid support (Table I) which makes it rapid, clean, efficient and cheap technology, while the same heating in classical approach.

<table>
<thead>
<tr>
<th>Compd</th>
<th>mp °C</th>
<th>Conventional heating</th>
<th>Microwave heating</th>
</tr>
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<tbody>
<tr>
<td>5a</td>
<td>125-27</td>
<td>52/12</td>
<td>75/2</td>
</tr>
<tr>
<td>5b</td>
<td>153-56</td>
<td>60/14</td>
<td>78/2</td>
</tr>
<tr>
<td>5c</td>
<td>160-62</td>
<td>53/15</td>
<td>73/2</td>
</tr>
<tr>
<td>5d</td>
<td>176-78</td>
<td>70/20</td>
<td>86/1.5</td>
</tr>
<tr>
<td>5e</td>
<td>135-38</td>
<td>65/18</td>
<td>75/1.5</td>
</tr>
<tr>
<td>5f</td>
<td></td>
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<tr>
<td>6a</td>
<td>170-72</td>
<td>53/12</td>
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<td>183-85</td>
<td>59/12</td>
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<tr>
<td>6c</td>
<td>163-65</td>
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<tr>
<td>6f</td>
<td>132-34</td>
<td>65/14</td>
<td>79/1.5</td>
</tr>
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</table>

Table I—Physical and spectral data of compounds 5a-f, 6a-f

The significance of our approach using solid support under microwave is that in classical approach, cyclocondensation of hydrazones required 15-20 hr with constant heating at 100-200°C while the same reaction was completed in 2-3 min when carried out under MWI using solid support (Table I) which makes it rapid, clean, efficient and cheap technology to obtain condensed pyrazoles.

**Antifungal activity**

All the synthesized pyrazoles were screened for their antifungal activity against fungi, A. niger and A. flavus by the paper disc diffusion method. The zone of inhibition was measured in millimeters. The antifungal activity of the test compound was compared with that of salicylic acid as standard using DMF as solvent.

The results of antifungal screening showed that all the pyrazoles displayed weaker activity with respect to salicylic acid.

**Experimental Section**

Melting points were recorded on an electrothermal apparatus and are uncorrected. IR (KBr) spectra were...
recorded on a Perkin-Elmer spectrophotometer (model 559) and $^1$H NMR spectra on a Hitachi R-600 FT NMR spectrometer operating at 90 MHz using TMS as internal standard (chemical shifts in $\delta$, ppm). The purities of the compounds were checked on silica gel coated Al plates (Merck). A Padmini Essentia microwave oven, Model Brownie, at 2450 MHz was used for MWI.

Ethyl (N-ethyl)-7-methyl-4-oxo-naphthyridine-3-carboxyacetate 2 and N-ethyl-7-methyl-4-oxo-naphthyridine-3-carboxy acetic acid hydrazide 3 were prepared according to literature method $^4$.

**General procedure for the synthesis of $\alpha$-(N-ethyl-7-methyl-4-oxo-naphthyridine-3-carboxy) acetyl arylaldehyde hydrazone derivatives 5a-f.** Hydrazide 3 (0.01 mole) and arylaldehyde 4a-f (0.01 mole) were taken in ethanol (15 mL) in 250 mL Erlenmeyer flask. The reaction mixture was irradiated inside a microwave oven for 1-2 min, reaction mixture was cooled and solid separated was filtered off, washed with cold ethanol and recrystallized from ethanol to yield compounds 5a-f.

**General procedure for the synthesis of 3-aryl-4-(N-ethyl-7-methyl-4-oxo-naphthyridin-3-yl carboxy)-3-pyrazolin-5-ones 6a-f.** Acidic alumina (20 g) was added to the solution of compound 5a-f (0.01 mole) dissolved in dichloromethane (10 mL) at room temperature. The reaction mixture was thoroughly mixed and adsorbed material was dried in air and placed in an alumina bath $^5$ inside the microwave oven for 3-4 min. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled and the product was extracted with dichloromethane (3 x 10 mL). Removal of the solvent under reduced pressure afforded the compounds 6a-f which were purified by recrystallization with ethanol.

**References**