SYNTHESIS AND FUNGICIDAL ACTIVITY OF 2,2'-BIPYRIDINE DERIVATIVES

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Abstract. A series of substituted 2,2'-bipyridine derivatives was prepared using the Krönke reaction and alkylation of 4,4'-dimethyl-2,2'-bipyridine. These compounds were screened for fungicidal activity against 9 plant diseases. 5-Phenyl-2,2'-bipyridine exhibited strong preventative and curative fungicidal activity against wheat powdery mildew (Erisyphe graminis) and wheat leaf rust (Puccinia recondita).

Derivatives of 2-(2-pyridyl)pyrimidine have been extensively patented as broad spectrum agrichemical fungicides active against, for example, Piricularia oryzae, Botrytis cinerea, Erysiphe graminis, Venturia inaequalis, Leptosphaeria nodorum, and Puccinia recondita. Other linked heterocycles having two nitrogen atoms with a relative γ disposition, such as 3-(2-pyridyl)isoquinolines, also exhibit anti-fungal activity against a variety of phytopathogens. The mode of action of 2-(2-pyridyl)pyrimidines has been investigated and the fungicidal effect was clearly linked to the bio-availability of copper. It is believed that toxic levels of intercellular copper arise via the cycling of copper-ligand complexes (Figure 1) through the cell membrane. No fungicidal activity was observed in copper-free media, and EDTA (by itself without effect on fungal growth) antagonised the effect of the fungicide.

2,2'-Bipyridine derivatives also possess two nitrogen atoms with a relative γ disposition and they readily form complexes with transition metals including copper. We had prepared some unsymmetrically substituted 2,2'-bipyridine derivatives as part of a separate project, and consequently we examined their fungicidal activity. The initial positive results prompted us to prepare additional derivatives and herein we describe the synthesis and fungicidal activity of a variety of substituted 2,2'-bipyridine derivatives.

Synthesis

Metal-mediated coupling reactions are highly efficient for preparing 2,2'-bipyridine and its symmetrically substituted derivatives, however, this method falls short of being a general procedure since it is practical only for symmetrical oligopyridines. Condensation procedures such as the Krönke reaction can be used to prepare unsymmetrically substituted 2,2'-bipyridines. α,β-Unsaturated aldehydes and ketones
are reacted with pyridacylpyridinium salts 2 to give the bipyridine products 3. This reaction gives highly variable yields depending on the substitution pattern, and furthermore can produce mixtures of isomers.

The pyridacylpyridinium salt 2 (R³ = H) is readily prepared by treating commercially available 2-acetylpyridine with iodine in pyridine. For the substituted pyridacylpyridinium salt 2 (R³ = CH₃) the starting material, 2-acetyl-4-methylpyridine, was prepared from 2-cyano-4-methylpyridine according to the method of Case and Kasper. Some of the α,β-unsaturated aldehydes 1 required for the Kröhnke procedure were commercially available (e.g. cinnamaldehyde derivatives, 1; R¹ = H, R² = substituted phenyl). In other cases (1; R¹ = substituted phenyl, R² = H) a three step procedure starting from the appropriate styrene derivative 4 was employed. The styrene derivative 4 was treated with chloroform and sodium hydroxide to give the 1,1-dichloro-2-phenylcyclopropane derivative 5 which was then heated at reflux with ethanol in the presence of sodium hydroxide to give the substituted atropaldehyde diethyl acetal 6. The acetal was treated with formic acid and water at 0°C to give the atropaldehyde derivative 1. These α,β-unsaturated aldehydes 1 underwent condensation with pyridacylpyridinium salts 2 under the standard Kröhnke conditions. Several compounds (entries 5–19, Table 1) were prepared in this way.

4,4'-Disubstituted 2,2'-bipyridines can also be prepared by lithiation of commercially available 4,4'-dimethyl-2,2'-bipyridine 7 at low temperature followed by quenching with an appropriate electrophile such as an alkyl halide, or an aldehyde, to give the substituted products 8 (entries 1–4, Table 1).
Biological Results and Discussion.

Nineteen 2,2'-bipyridine derivatives were tested under greenhouse conditions for activity against nine plant diseases. The biological data are presented in Table 1. In general, the alkyl substituted 2,2'-bipyridines (Entries 1–6) exhibited moderate or poor fungicidal activity. Where activity was present it was against *Erisyphe graminis*.

Table 1. Structures and Fungicidal Activity of 2,2'-bipyridines 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound 3</th>
<th>Percent Disease Control at 200 ppm#</th>
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<tr>
<td></td>
<td>R1 R2 R3</td>
<td>CB GDM RB RSB TLB WFR WS WLR WPM</td>
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<tr>
<td>1</td>
<td>H i-Pr i-Pr</td>
<td>0 NT 67 73 0 12 NT NT 38</td>
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<tr>
<td>2</td>
<td>H Bu Bu</td>
<td>0 NT 85 93 0 44 NT NT 33 21*</td>
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<tr>
<td>3</td>
<td>H C5H11 C5H11</td>
<td>0 NT 27 93 0 0 NT 90 92</td>
</tr>
<tr>
<td>4</td>
<td>H C12H25 C12H25</td>
<td>0 NT 0 0 0 0 NT NT 0</td>
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<tr>
<td>5</td>
<td>Me H H</td>
<td>0 0 0 0 0 0 0 0 24</td>
</tr>
<tr>
<td>6</td>
<td>CH2OPh H H</td>
<td>0 NT 0 0 0 0 0 0 11</td>
</tr>
<tr>
<td>7</td>
<td>Ph H H</td>
<td>45 96 87* 0 23 0 100 60* 100*</td>
</tr>
<tr>
<td>8</td>
<td>p-FPh H H</td>
<td>0 NT 32 100 24 27 32* 64 55*</td>
</tr>
<tr>
<td>9</td>
<td>p-ClPh H H</td>
<td>0 50 97 100 0 81 98 65 99*</td>
</tr>
<tr>
<td>10</td>
<td>p-BrPh H H</td>
<td>0 NT 0 0 0 0 58 20 19*</td>
</tr>
<tr>
<td>11</td>
<td>p-MePh H H</td>
<td>59 NT 32 0 0 0 95* 84* 99*</td>
</tr>
<tr>
<td>12</td>
<td>p-OMePh H H</td>
<td>0 65 97 19 0 75 40 93 92</td>
</tr>
<tr>
<td>13</td>
<td>p-NO2Ph H H</td>
<td>0 60 0 0 0 0 0 0 0</td>
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<tr>
<td>14</td>
<td>Ph H Me</td>
<td>28 NT 32 0 0 0 69 96* 93 47</td>
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<td>15</td>
<td>H Ph H</td>
<td>0 96 74 0 0 0 94* 11* 95*</td>
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<td>16</td>
<td>H o-NO2Ph H</td>
<td>41 NT 32 0 24 0 76* 67 0</td>
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<td>17</td>
<td>H o-OMePh H</td>
<td>0 NT 32 0 24 0 27 85 93*</td>
</tr>
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<td>18</td>
<td>H Ph Me</td>
<td>30 NT 53 81 0 66 19* 99 99</td>
</tr>
<tr>
<td>19</td>
<td>H o-OMePh Me</td>
<td>0 NT 53 81 0 86 12* 19 30*</td>
</tr>
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</table>

# Values in bold represent percentage control at 40 ppm, with 100% control at 200 ppm.
* Compound shows curative activity.
NT - Not Tested

CB - Cucumber Botrytis (*Botrytis cinerea*)
GDM - Grape Downy Mildew (*Plasmopara viticola*)
RB - Rice Blast (*Pyricularia oryzae*)
RSB - Rice Sheath Blight (*Rhizoctonia solani*)
TLB - Tomato Late Blight (*Phytophthora infestans*)
WFR - Wheat Foot Rot (*Pseudocercosporella herpotrichoides*)
WS - Wheat Septoria (*Septoria nodorum*)
WLR - Wheat Leaf Rust (*Puccinia recondita*)
WPM - Wheat Powdery Mildew (*Erisyphe graminis*)

The 5-aryl substituted 2,2'-bipyridines (Entries 7–14) and 4-aryl substituted 2,2'-bipyridines (Entries 15–19) generally gave good control of *Septoria nodorum*, *Puccinia recondita* and *Erisyphe graminis*, with scattered activity against the other pathogens. A striking exception to this trend was 5-(p-nitrophenyl)-2,2'-bipyridine (Entry 13) which only gave moderate control of *Plasmopara viticola*. This is probably due to the virtual insolubility of this compound in most organic solvents. The most active of this series was 5-phenyl-2,2'-bipyridine (3, R1 = Ph) which gave 100% control of *Erisyphe graminis* at 40 ppm (Entry 7) and 71%
control at 10 ppm. This compound also had curative activity against *Pyricularia oryzae*, *Puccinia recondita* and *Erisyphe graminis*. Mammalian toxicity studies for these compounds are currently in progress.

**Acknowledgment.**

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**References and Notes.**


13. Typical procedure: A mixture of methacrolein (1.4 g, 20 mmol), N-(2-pyridaclyl)pyridinium iodide (6.3 g, 20 mmol), and ammonium acetate (8.5 g, 0.1 mol) in methanol (100 ml) was heated at reflux under nitrogen for 1 h. The methanol was evaporated and the residue added to water and extracted with heptane (3 x 50 ml). The combined extracts were dried (MgSO₄), and evaporated to give 5-methyl-2,2'-bipyridine (1.57 g, 46%) as a clear oil. Yields for these reactions varied between 25-80%.


19. Typical procedure: A solution of 4,4'-dimethyl-2,2'-bipyridine (1.84 g, 10 mmol) in freshly distilled THF (40 ml) was cooled to -78 °C under nitrogen and treated with a solution of butyllithium (11 mmol) in THF. The stirred mixture was then treated with 1-bromohexadecane (3.5 g, 11 mmol) in THF (10ml). The solution was allowed to warm to room temperature, poured into water and extracted with diethyl ether (3 x 40 ml) to give 4-heptadecyl-4'-methyl-2,2'-bipyridine (2.7 g, 66%). Yields for these reactions varied between 45-75%.

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