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# 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 Kröhnke 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*,[1] *Botrytis cinerea*,[2] *Erysiphe graminis*,[3] *Venturia inaequalis*,[3] *Leptosphaeria nodorum*,[4,5] and *Puccinia recondita*.[6] 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.[7] 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.[8] 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.

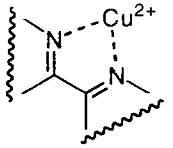


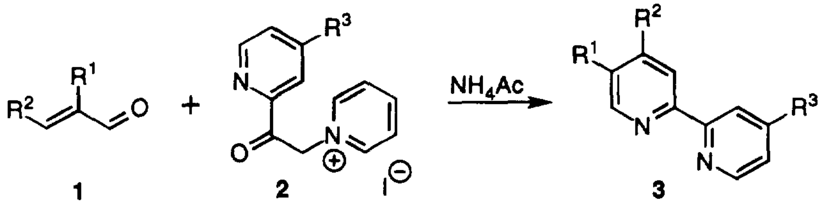
Figure 1

2,2'-Bipyridine derivatives also possess two nitrogen atoms with a relative γ disposition and they readily form complexes with transition metals including copper.[9] We had prepared some unsymmetrically substituted 2,2'-bipyridine derivatives as part of a separate project,[10] 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.

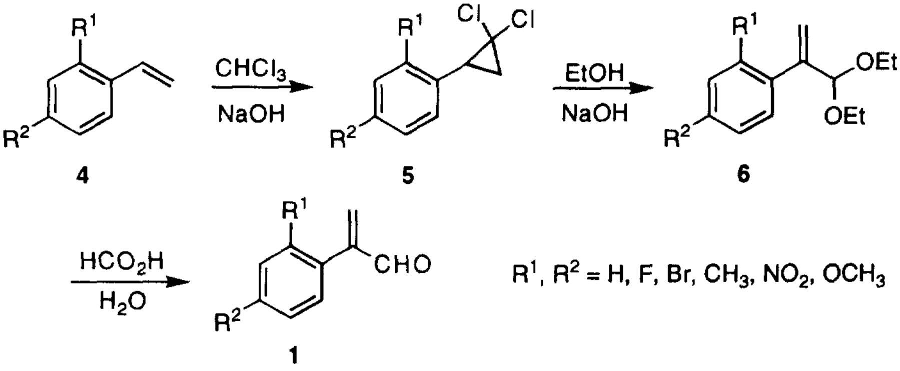
## Synthesis

Metal-mediated coupling reactions are highly efficient for preparing 2,2'-bipyridine and its symmetrically substituted derivatives,[11] however, this method falls short of being a general procedure since it is practical only for symmetrical oligopyridines. Condensation procedures such as the Kröhnke reaction[12] can be used to prepare unsymmetrically substituted 2,2'-bipyridines. α,β-Unsaturated aldehydes and ketones

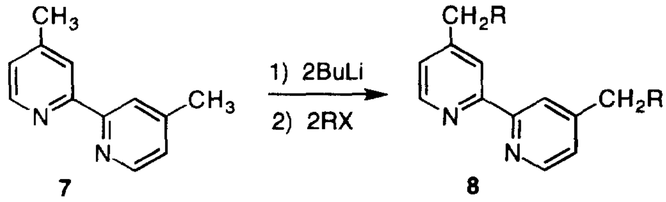
**1** are reacted with pyridacylpyridinium salts **2** to give the bipyridine products **3**.[13] This reaction gives highly variable yields depending on the substitution pattern, and furthermore can produce mixtures of isomers.[14]



The pyridacylpyridinium salt **2** ($R^3$ = H) is readily prepared by treating commercially available 2-acetylpyridine with iodine in pyridine.[12] For the substituted pyridacylpyridinium salt **2** ($R^3 = CH_3$) the starting material, 2-acetyl-4-methylpyridine, was prepared from 2-cyano-4-methylpyridine according to the method of Case and Kasper.[15] Some of the α,β-unsaturated aldehydes **1** required for the Kröhnke procedure were commercially available (eg. cinnamaldehyde derivatives, **1**; $R^1$ = H, $R^2$ = substituted phenyl). In other cases (**1**; $R^1$ = substituted phenyl, $R^2$ = H) a three step procedure starting from the appropriate styrene derivative **4** was employed.[16] 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.[12] 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,[17] or an aldehyde,[18] to give the substituted products **8** (entries 1–4, Table 1).[19]



## 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**.

| Entry | Compound 3 | | | Percent Disease Control at 200 ppm$^{\#}$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | CB | GDM | RB | RSB | TLB | WFR | WS | WLR | WPM |
| 1 | H | i-Pr | i-Pr | 0 | NT | 67 | 73 | 0 | 12 | NT | NT | 38 |
| 2 | H | Bu | Bu | 0 | NT | 85 | 93 | 0 | 44 | NT | 33 | **21**$^{*}$ |
| 3 | H | $C_5H_{11}$ | $C_5H_{11}$ | 0 | NT | 27 | 93 | 0 | 0 | NT | 90 | **92** |
| 4 | H | $C_{12}H_{25}$ | $C_{12}H_{25}$ | 0 | NT | 0 | 0 | 0 | 0 | NT | NT | 0 |
| 5 | Me | H | H | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 24 |
| 6 | $CH_2OPh$ | H | H | 0 | NT | 0 | 0 | 0 | 0 | 0 | 0 | 11 |
| 7 | Ph | H | H | 45 | 96 | 87$^{*}$ | 0 | 23 | 0 | 100 | **60**$^{*}$ | **100**$^{*}$ |
| 8 | p-FPh | H | H | 0 | NT | 32 | 100 | 24 | **27** | **32**$^{*}$ | 64 | **55**$^{*}$ |
| 9 | p-ClPh | H | H | 0 | **50** | 97 | 100 | 0 | 81 | 98 | 65 | 99$^{*}$ |
| 10 | p-BrPh | H | H | 0 | NT | 0 | 0 | 0 | 0 | **58** | 20 | **19**$^{*}$ |
| 11 | p-MePh | H | H | 59 | NT | 32 | 0 | 0 | 0 | 95$^{*}$ | 84$^{*}$ | 99$^{*}$ |
| 12 | p-OMePh | H | H | 0 | **65** | 97 | 19 | 0 | 75 | 40 | 93 | 92 |
| 13 | p-$NO_2$Ph | H | H | 0 | 60 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14 | Ph | H | Me | **28** | NT | 32 | 0 | 0 | 69 | **96**$^{*}$ | 93 | **47** |
| 15 | H | Ph | H | 0 | 96 | 74 | 0 | 0 | 0 | **94**$^{*}$ | **11**$^{*}$ | 95$^{*}$ |
| 16 | H | o-$NO_2$Ph | H | 41 | NT | 32 | 0 | 24 | 0 | **76**$^{*}$ | 67 | 0 |
| 17 | H | o-OMePh | H | 0 | NT | 32 | 0 | 24 | 0 | **27** | 85 | 93$^{*}$ |
| 18 | H | Ph | Me | 30 | NT | 53 | 81 | 0 | 66 | **19**$^{*}$ | 99 | 99 |
| 19 | H | o-OMePh | Me | 0 | NT | 53 | 81 | 0 | 86 | **12**$^{*}$ | **19** | **30**$^{*}$ |

$^{\#}$ 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 (*Phtyopthora 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**, $R^1$ = 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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[13] Typical procedure: A mixture of methacrolein (1.4 g, 20 mmol), N-(2-pyridacyl)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 ($MgSO_4$), 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%.

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[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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