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# The synthesis of substituted pyridylpyrimidine fungicides using palladium-catalysed cross-coupling reactions

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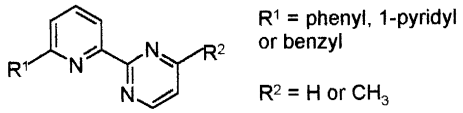
**Abstract**

Various substituted phenyl, pyridyl and benzyl zinc chlorides have been generated from the corresponding lithium or magnesium organometallic reagents. These have been cross-coupled with 2-(6-bromo-2-pyridyl)pyrimidines in the presence of tetra*kis*(triphenylphosphine)palladium(0) to produce a series of substituted pyridylpyrimidine fungicides in 32–99% yields. 

*Keywords:* coupling reactions; palladium catalysts; pyridines, pyrimidines; fungicides.

As part of a research programme designed to identify new agrochemical fungicides with novel modes of action, we have been involved in the synthesis of pyridylpyrimidines (**1**) (Fig. 1).[1] These compounds are broad spectrum fungicides, acting by cycling copper through cell membranes, where it accumulates internally to toxic levels.[2]




**(1)**

Fig. 1.

These pyridylpyrimidines (**1**) are generally prepared by a pyrimidine ring synthesis[1a,3] involving the condensation of a substituted picolinamidine with a β-dicarbonyl compound or a suitably protected form such as the formylacetone dimethylacetal.[3] This route also requires the initial synthesis of the substituted picolinamidine[4] from a 2-cyanopyridine.[5] The route is not very convenient for preparing a range of compounds (**1**) in which the $R^1$ group is varied widely.

An alternative approach involving the palladium-catalysed cross-coupling reaction of an organometallic derivative of $R^1$ with a bromopyridylpyrimidine (**2**) is much more attractive and versatile. In this

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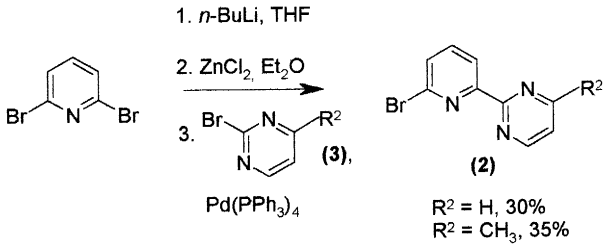
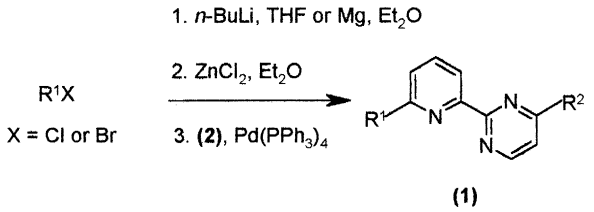
case, the $R^1$ group being varied is introduced in the last step of the sequence. The key intermediates (**2**) ($R^2$=H or $CH_3$) are available in multi-gram quantities by a palladium-catalysed cross-coupling reaction of the organozinc species derived from 2,6-dibromopyridine with a 2-bromopyrimidine (**3**) (Scheme 1). Lithiation of 2,6-dibromopyridine at −60°C with *t*-butyllithium (*t*-BuLi) is reported to give 2-bromo-6-lithiopyrimidine selectively.[6] Bromination of the corresponding 2-chloropyrimidines with phosphorus tribromide[7] generates the 2-bromopyrimidines in 80% yield. The 2-chloropyrimidines are prepared in 70% yield by chlorination (using phosphorus oxychloride) of the available 2-hydroxypyrimidines.




Scheme 1.

Several cross-coupling reactions of this type are known to be induced by organozinc reagents[8] generally prepared from lithio derivatives using an excess of zinc chloride[9] or zinc bromide. In this procedure, the organometallic derivatives of $R^1$ are prepared by reaction of substituted bromobenzenes and bromopyridines with *n*-butyllithium (*n*-BuLi) or by the treatment of substituted benzyl chlorides with magnesium to form the corresponding Grignard reagents (Scheme 2). These organometallic derivatives (1.5–2.0 equivalents) are transmetallated using 3.0 equivalents of anhydrous zinc chloride. The resulting organozinc reagents are coupled with the bromopyridines (**2**) (1.0 equivalents) in the presence of a catalytic amount of tetra*kis*(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, under refluxing conditions, to afford the required pyridylpyrimidines (**1**) in moderate to very high yields (32–99%) (Table 1).



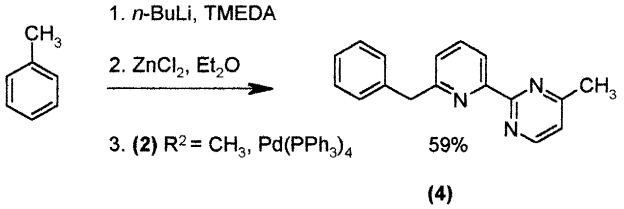

Scheme 2.

Table 1

| Entry | Conditions | $R^1$ | $R^2$ | X | Yield % |
|---|---|---|---|---|---|
| 1 | *n*-BuLi, THF | 2-Cl-phenyl | $CH_3$ | Br | 71 |
| 2 | *n*-BuLi, THF | 3-Cl-phenyl | $CH_3$ | Br | 94 |
| 3 | *n*-BuLi, THF | 4-Cl-phenyl | $CH_3$ | Br | 99 |
| 4 | *n*-BuLi, THF | 4-$CH_3$-pyrid-2-yl | $CH_3$ | Br | 74 |
| 5 | *n*-BuLi, THF | 6-$CH_3$-pyrid-2-yl | $CH_3$ | Br | 32 |
| 6 | Mg, $Et_2O$ | benzyl | H | Cl | 79 |
| 7 | Mg, $Et_2O$ | 2-Cl-benzyl | H | Cl | 60 |
| 8 | Mg, $Et_2O$ | 4-$CH_3$-benzyl | H | Cl | 41 |
| 9 | Mg, $Et_2O$ | 4-F-benzyl | $CH_3$ | Cl | 47 |
| 10 | Mg, $Et_2O$ | 3-Cl-benzyl | $CH_3$ | Cl | 58 |

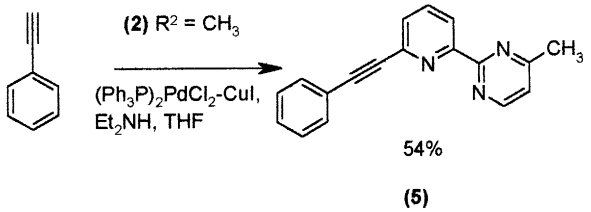
This one-pot synthesis involving sequential metallation, transmetallation and cross-coupling reactions provides an extremely effective and versatile route to pyridylpyrimidines (**1**). A related protocol[10] was being employed, around the same time this research programme was being carried out, to make the 2,2′-bipyridyl sub-unit of the caerulomycin antibiotics.

Benzyllithium, prepared by the direct lithiation of toluene with *n*-BuLi in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA),[11] can also be used successfully in these reactions as an alternative to benzylmagnesium chloride (Table 1, Entry 6). The subsequent transmetallation and cross-coupling reactions gave 2-(6-benzylpyrid-2-yl)-4-methylpyrimidine (**4**) (Scheme 3) in 59% yield after purification.




Scheme 3.

In a further extension of this methodology, the bromopyridylpyrimidine (**2**) ($R^2$=$CH_3$) can also be cross-coupled with phenylacetylene and bis(triphenylphosphine)palladium chloride–cuprous chloride ($(Ph_3P)_2PdCl_2$–CuCl) in diethylamine[12] to give the disubstituted acetylene (**5**) (Scheme 4) in 54% yield.[13]




Scheme 4.

The experimental details of this cross-coupling procedure are illustrated by the preparation of 2-(6-*m*-chlorobenzylpyrid-2-yl)-4-methylpyrimidine) (Table 1, Entry 10).

Anhydrous zinc chloride (24 ml, 24 mmol of a 1.0 M solution in diethyl ether) was added dropwise to a stirred solution of *m*-chlorobenzylmagnesium chloride (8 mmol) in anhydrous diethyl ether (40 ml) at 20°C under a nitrogen atmosphere. To this mixture was added 2-(6-bromopyrid-2-yl)-4-methylpyrimidine (1.0 g, 4 mmol) and tetra*kis*(triphenylphosphine)palladium(0) (100 mg, 0.087 mmol) in dry THF (25 ml). The mixture was refluxed for 2 hours, cooled to room temperature and poured into 10% ethylenediaminetetraacetic acid disodium salt solution (150 ml) at pH 8. The aqueous layer was extracted with ethyl acetate and the combined organic solutions dried and concentrated in vacuo to give a bright orange oil. This was purified by HPLC[1] (silica gel eluted with 2% MeOH in EtOAc) to give (**1**) (Table 1, Entry 10) as an orange gum (58%).

$^1$H NMR (270 MHz, $CDCl_3$); $\delta$=2.66 (s, 3H), 4.37 (s, 2H), 7.09 (d, *J*=7.1 Hz, 1H), 7.15–7.30 (m, 4H), 7.18 (d, *J*=5.0 Hz, 1H), 7.75 (t, *J*=7.1 Hz, 1H), 8.34 (d, *J*=7.1 Hz, 1H), 8.81 (d, *J*=5.0 Hz, 1H) ppm. $M^+$-294 and 296.

[1] Substantial losses of material were noted during chromatography as the compounds were presumably bound to trace metals on silica gel. This could be overcome by eluting a pyridylpyrimidine down the column and removing the metal chelate with 20% MeOH in $CH_2Cl_2$. The same column could then be used for subsequent chromatography after this conditioning.

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