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A practical synthesis of substituted 2,6-diaminopyridines via microwave-assisted copper-catalyzed amination of halopyridines

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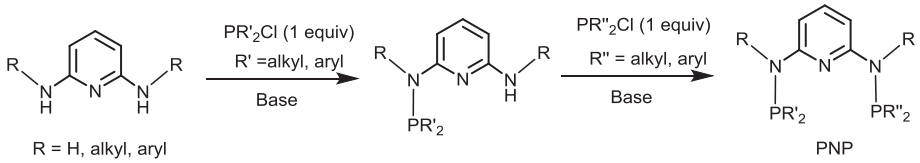
ABSTRACT

A microwave assisted copper-catalyzed amination protocol is reported utilizing a series of 2,6-dihalo- and 2-amino-6-halo pyridine precursors. Using this procedure, selective substitution of one or two halogens by aryl or alkylamines was achieved within 2–6 h with temperatures between 80 and 225 °C affording 2,6-diaminopyridines in good to excellent isolated yields. The reaction allows easy variation between educts and different *N*-substitutions. The target compounds are valuable precursors for the synthesis of bis-phosphorylated 2,6-diaminopyridines which are used as PNP pincer ligands in transition metal complexes.

1. Introduction

The 2,6-diaminopyridine molecule is a useful scaffold for the design of tridentate ligands in coordination and organometallic chemistry, agrochemicals, dyes, and pharmacologically potent building blocks.[1–6] The most frequently applied methods are nucleophilic substitutions often catalyzed by copper, copper salts or proline[7–9] and Buchwald–Hartwig aminations.[10–14] Recently, Kempe et al. developed an Ir-catalyzed protocol for both symmetrically and non-symmetrically *N*,*N*′-dialkylated 2,6-diamino pyridines from 2,6-diaminopyridine and alcohols.[15] All methods basically yield the 2,6-diaminopyridines and it depends on the specific target which one performs better.

In recent years we have been focusing on the chemistry of transition metal complexes bearing PNP pincer ligands based on the 2,6-diaminopyridine scaffold.[16] In these PNP ligands the central pyridine ring contains -NRPR′$_2$ (R′=H, alkyl, R=alkyl, aryl) substituents in the two ortho positions. This methodology was first developed for the synthesis of *N*,*N*′-bis(diphenylphosphino)-2,6-diaminopyridine (PNP-Ph).[17] In these ligands the aromatic pyridine ring and the phosphine moieties are connected via NH, *N*-alkyl, or *N*-aryl linkers (Scheme 1). Accordingly, the development of a simple general method for the selective formation of N,N′-disubstituted 2,6-diamino pyridines is of great importance for the design of new PNP ligands. It has to be noted that most substituted 2,6-diaminopyridines are commercially not available.



Scheme 1.

Here we describe a simple microwave assisted copper catalyzed amination protocol utilizing various 2,6-dihalo- and 2-amino-6-halo pyridine precursors **I**–**VII** as shown in Scheme 2. This simple

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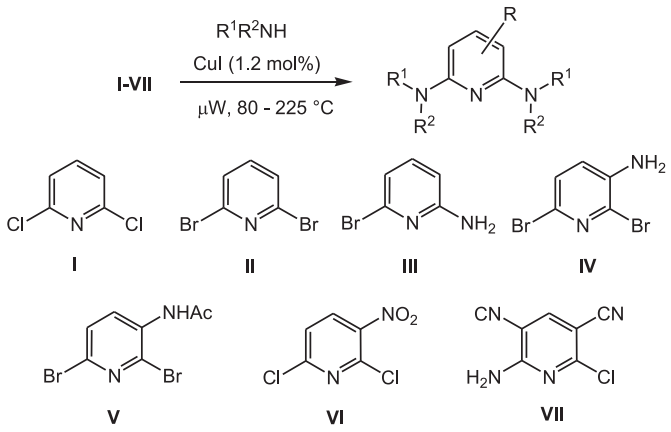

Scheme 2.

procedure permits the selective substitution of one or two halogens by primary and secondary aryl and alkylamines in a relatively short time to afford a series of 2-amino- and/or 2,6-diaminopyridines in high isolated yields. This methodology constitutes a practical alternative to other methods.

2. Results and discussion

Treatment of compounds **I**–**VII** (4.2 mmol) with various primary and secondary amines in the presence of catalytic amounts of CuI (1.2 mol %) and traces of water (100 μL) afforded selectively mono or disubstituted aminopyridines depending on the reaction conditions (Table 1). The addition of small amounts of water was necessary in order to achieve the required temperature under microwave conditions. None of these reactions required any additional organic solvents.

In general, the reactions of amines with 2,6-dichoropyridine (**I**) led to the exclusive formation of mono substituted products **1**–**3** in good to excellent isolated yields. It has to be noted, that even at higher temperatures the formation of disubstituted products was not observed. In the case of piperazine, both amine sites reacted with **I** and no mono substituted piperazine derivative was formed (entry 3). With 2,6-dibromopyridine (**II**), on the other hand, depending on the reaction temperature both mono and the desired disubstituted products were obtained in high yields (entries 4, 5, 7–19) and showed a good substrate scope. Alkyl, aryl and benzylamines reacted readily to form compounds **4**–**15**. The use of chiral amines *R*- and *S*-1-phenylethane amine, allowed the preparation of chiral 2,6-diaminpyridnes (entries 11 and 12). By lowering the temperature also mono substituted aminopyridines could be obtained. This has been exemplarily shown for isopropylamine. Compound **6** could be obtained selectively (entry 6) which is an interesting building block for mixed diaminopyridines. In the case of anilines (entries 14 and 15) the reaction required a small amount of $Pd(PPh_3)_4$ as co-catalyst (0.2 mol %) and the yields were rather low. In this particular case, other established methods achieve much high yields.[18–20] Surprisingly, under the standard reaction conditions allyl amine and *N*,*N*-methylbenzylamine reacted only to yield the mono substituted compounds **16** and **17**. With benzylamine no identifiable products could be isolated. At higher reaction temperatures decomposition to intractable materials took place. The formation of compounds **18** and **19** demonstrates that also with secondary amines and **II** directly 2,6-diaminopyridines can be obtained. Precursors **III** and **17** were utilized as entries into mixed 2,6-diaminopyridines (entries 20–24). Finally we tested mono and dichloro and bromopyridines bearing both activating and deactivating groups (**IV**–**VII**) as synthetic entry into mixed 2,6-diaminopyridines (entries 25–30). Deactivating groups from **VI** and **VII** led to faster and better conversion under milder conditions. Moreover, the amination in the case of chlorides was faster and proceeded at much lower temperatures as compared to the bromide precursors (entries 27–30). Also the amination of **VI** and **VII** with aqueous ammonia to yield **27** and **28** worked very well with 93 and 97% isolated yields (entries 27 and 28). Compounds **25**–**30** are particularly interesting since the functional groups may allow cleavage or conversion into other functionalities. It has to be mentioned that all functionalized systems were less air sensitive than the diamines lacking additional substituents in the pyridine ring.

3. Conclusion

A microwave assisted copper-catalyzed amination protocol is reported utilizing a series of 2,6-dihalo- and 2-amino-6-halo pyridine precursors. With the exception of NH_3, methyl- and ethylamine, where aqueous solutions were used, the reaction is basically solvent free and only traces of water were added to achieve the required temperatures under microwave conditions. This protocol generally afforded the corresponding products in good yields with easy purification steps. Using this procedure, selective substitution of one or two halogens by aryl- or alkylamines was achieved within 2–6 h at temperatures between 80 and 225 °C affording 2,6-diaminopyridines in good to excellent isolated yields. The target compounds are valuable precursors for the synthesis of bis-phosphorylated 2,6-diaminopyridines which are used as PNP pincer ligands in transition metal complexes.

4. Experimental section

4.1. General notes

Unless otherwise noted, chemicals were purchased from commercial suppliers and were used without further purification. Precursors **III**, **IV**, **V** and **VII** where synthesized according to the literature.[21–23] Microwave reactions were performed on a CEM Explorer PLS microwave unit. Column chromatography was performed on silica gel 60 from Merck. For thin layer chromatography (TLC) aluminum backed silica gel was used. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. All samples were analyzed by LC-IT-TOF-MS in the positive ion detection mode with the recording of MS and MS/MS spectra. Room temperature ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on Bruker DXP 200 and AVANCE-250 spectrometers and were referenced internally to residual protio-solvent, and solvent resonances, respectively, and are reported relative to tetramethylsilane (δ=0 ppm).

4.2. Typical experimental procedure for the synthesis of *N*-alkyl and *N*-aryl 2,6-diamino pyridines

Compounds **I**–**VII** (4.22 mmol), catalytic amounts of CuI (10 mg, 0.052 mmol) and water (100 μL) were treated with 6 equiv of the respective amine and sealed in a 5 mL microwave vial. $Pd(PPh_3)_4$ (10 mg, 0.008 mmol) was added in the case of anilines. After the reaction was completed (see Table 1), 2 equiv of solid K_2CO_3 were added. The resulting product was obtained after filtration and washing with water as an analytically pure crystalline solid. Otherwise all volatiles were then evaporated and purified by flash column chromatography (**A**) or bulb-to-bulb distillation (**B**). In the case of methylamine and ethylamine the corresponding aqueous solution was used without extra water addition.