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2,6-Diamination of Substituted Pyridines *via* Heterogeneous Chichibabin Reaction

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Abstract

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A series of ring substituted pyridines was selected for the sodium amide initiated heterogeneous Chihibabin amination to obtain 2,6-diaminopyridine derivatives which are important synthons for the preparation of PNP pincer ligands. The substrates were treated with an excess of sodium amide in neat mineral oil as solvent under an argon atmosphere. The reaction required temperatures of up to 215°C under vigorous stirring with an overall reaction time of 3-5 h. In the case of methyl, *tert*-butyl, phenyl, pyridinyl, and hydroxyl substituted pyridines the desired products were obtained in good to excellent yields (63-96%). Thus, the Chichibabin reaction provides an inexpensive and economic alternative to methodologies starting from halo pyridines or pyridine N-oxides provided that the substituents are inert under the harsh reaction conditions.

Keywords: Amination, 2,6-diaminopyridines, heterocycles, Chichibabin reaction

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1. Introduction

Ring-substituted 2,6-diaminopyridines are an important class of heterocycles which are useful building blocks for macrocycles, polymers, agrochemicals, dyes, and pharmacologically potent molecules.^{1,2,3,4,5,6} Furthermore 2,6-diaminopyridines are valuable scaffolds for the design of tridentate ligands in coordination and organometallic chemistry. We are particularly interested in using ring-substituted 2,6-diaminopyridines as building blocks for new tridentate PNP ligands, so called pincer ligands, which are typically obtained according to Scheme 1.⁷



Scheme 1 Synthesis of PNP pincer ligands based on the 2,6-diaminopyridine scaffold

Since 2,6-diaminopyridine is the only commercially available and convenient precursor, we sought a new efficient general synthetic route to obtain ring substituted 2,6-diaminoyridines. For this purpose, we selected the sodium amide initiated amination of pyridine, known as the Chichibabin reaction.⁸ A DFT calculated mechanism of the Chichibabin reaction was recently reported.⁹ This method is very useful for the preparation of 2-aminopyridine and parent 2,6-diaminopyridine by the reaction of pyridine with sodium amide under heterogeneous conditions, but was hardly applied to ring-substituted pyridines. A rare example of a 2,6-diamination under Chichibabin reaction growther albeit in only 22% yield.¹⁰ It has to be emphasized that the Chichibabin reaction provides an inexpensive and economic alternative to methodologies starting from halo pyridines *via* nucleophilic substitutions catalysed by copper, copper salts or proline,^{11,12,13,14} and Buchwald-Hartwig aminations,^{15,16,17,18,19} or pyridine N-oxides.²⁰ Moreover, this reaction allows the synthesis of unsymmetrically alkylated diaminopyridines which are otherwise difficult to prepare.²¹

2,6-Diamino-4-methylpyridin

2. Results and discussion

A series of substituted pyridines were treated with an excess (3-6-equivs) of sodium amide in mineral oil (white oil, liquid paraffin) as solvent under an argon atmosphere. It has to be noted that Bojarska-Dahlig reported the use of Vaseline as solvent,²² while Banerjee recently significantly improved and optimized the heterogeneous Chichibabin reaction by using mineral oil as reaction medium.²³ Running the reactions in neat N,N-dimethylaniline improved the solubility of the reactants and increased the reaction rates, but due the toxicity of this solvent as well as its high polarity, workup to obtain pure products turned out to be difficult and was thus not further used. Additives (10%) such as *n*-dodecylamine, and *n*-tributylamine showed no appreciable effects as reaction rates and yields are

concerned. Moreover, it is important to mention that with the solvents N,N-dimethylaniline, decalin, or tetralin the required high temperatures are not obtained resulting in lower yields.^{9,24} Accordingly, neat mineral oil was used as reaction medium throughout where reaction temperatures of 215°C were easily reached. An overview of all substrates tested is given in Scheme 2. However, only in the case of methyl, *tert*-butyl, phenyl, pyridinyl, and hydroxyl substituted pyridines the desired products were obtained (Table 1). The reaction mixture was typically heated stepwise from 120 up to 215°C under vigorous stirring with an overall reaction time of 3-5 h. Higher temperatures and/or longer



Scheme 2 Overview of ring-substituted pyridines tested in the heterogeneous Chichibabin reaction

reaction times did not result in higher yields rather than partial decomposition of the products. A color change from orange to brown to black was observed in all reactions. The evolution of hydrogen gas indicated the beginning of the reaction at about 120°C due to the formation 2-aminopyridines. At about 180°C the second amination step was initiated which, after 3h additional heating at 215 °C, led to formation of the 2,6-diaminopyridines (**1-9**) and 6-aminopyridine-2(1H)-one (**10**) (Table 1). It has to be noted that **1** was also obtained with 4-methylpyridine-2-amine (Table 1, entry 2). All these compounds were obtained in good to excellent isolated yields. 4-Hydroxy-pyridine-2,6-diamine (**9**) was first isolated from the reaction mixture as its nitrate salt **8** (Table 1, entry 9) which is sparingly water soluble. Isolation of free **9** was carried out by treating the nitrate salt with potassium hydroxide and was obtained in 96% isolated yield. Arienzo²⁵ and Kilburn²⁶ described an alternative procedure to obtain **9** *via* a Hofmann or Curtius rearrangement using chelidamic acid as precursor. Bojarska-Dahlig and Banerjee also used the Chichibabin reaction for the synthesis of **9** utilizing a slightly different procedure.^{2,5} Compound **10** was prepared recently *via* deamination of 2,6-diaminopyridine in concentrated hydrochloric acid with 83 % isolated yield.²⁷ This emphasizes the advantage of the

Chichibabin reaction reported here in comparison to alternative procedures for the synthesis of **9** and **10**.

For the Chichibabin reaction, the optimal pK_a range of pyridines is believed to be in the range of 5-8 and it was postulated that outside this range no reaction takes place. However, also 2-hydroxypyridine/2-pyridinone and 4-hydroxypyridine/4-pyridinone with pK_a values of 11.7/1.3 and 11.1/3.1, respectively, reacted readily with sodium amide to yield **8** and **10** (Table 1, entries 9 and 10). All compounds were fully characterized by their melting points, HRMS, ¹H and ¹³C{¹H} NMR spectroscopy (see supporting information).

Finally, under the standard reaction conditions all other substrates used (Scheme 2) did not afford the desired 2,6-diaminopyridines. For instance, pyridines featuring -COOH, -CONH₂ and -CON(CH₃)₂ substituents in the 3- and 4-position were decarboxylated yielding parent 2,6-diaminopyridine. For comparison, McGill and co-workers reported the conversion of nicotinic acid to 6-amino-nicotinic acid at lower temperature (122°-145° C) and 360 psi albeit in low yields (26 %).²⁸ Likewise, all other 3- and -4-substituted pyridines did not react at all or underwent elimination and polymerization reactions yielding intractable material which could not be characterized. Moreover, while pyridines with methyl and *tert*-butyl substituents (Table 1, entries 1-5) reacted cleanly to afford 2,6-diaminopyridines, 4-ethylpyridine and 4-benzylpyridine formed 4-vinylpyridine and intractable polymeric materials, respectively. Accordingly, for these type of 2,6-diamonopyridines different methodologies have to be used.²⁹

3. Conclusion

A series of substituted pyridines was selected for the sodium amide initiated heterogeneous Chihibabin amination to obtain 2,6-diaminopyridine derivatives. The substrates were treated with an excess of sodium amide in neat mineral oil as solvent under an argon atmosphere. The reaction required temperatures of up to 215°C under vigorous stirring with an overall reaction time of 3-5 h. In the case of methyl, *tert*-butyl, phenyl, pyridinyl, and hydroxyl substituted pyridines the desired products were obtained in good to excellent yields. All other 3- and -4-substituted pyridines featuring, for instance COOH, -CONH₂ and -CON(CH₃)₂, -NH₂, -NMe₂, -SH, benzyl, and ethyl substituents, underwent uncontrolled elimination and polymerization reactions to yield intractable materials. The Chichibabin reaction provides an inexpensive and atom economic alternative to methodologies starting from halo pyridines or pyridine N-oxides provided that the substituents are inert under the harsh reaction conditions.

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Supplementary data



Table 1. Synthesis of 2,6-diaminopyridines and 6-aminopyridine-2(1H)-one

TOC

2,6-Diamination of Substituted Pyridines *via* Heterogeneous Chichibabin Reaction

A series of methyl, *tert*-butyl, phenyl, pyridinyl, and hydroxyl substituted 2,6-diaminopyridines is prepared *via* the heterogeneous Chichibabin amination in neat mineral oil at temperatures up to 215°C with an overall reaction time of 3-5 h.



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