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Smiles Rearrangement as a Tool for the Preparation of Dihydrodipyridopyrazines

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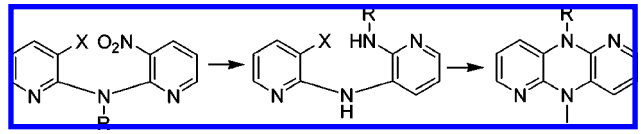
ABSTRACT



A novel methodology for the synthesis of isomer A of dihydrodipyridopyrazines was developed. The key transformation features a Smiles rearrangement of nitro substituted *N,N′*-dipyridinylamines, potential precursors of isomer B obtained by the alkylation of compounds prepared by a Pd-catalyzed reaction and subsequent cyclization.

As part of our research program directed toward the design and synthesis of dihydrodipyridopyrazines (DHDPP), a new family of planar nitrogen heterocycles with potential antitumoral activity,[1] we focused on methods for obtaining selectively the two isomers of these compounds (isomer **A** and isomer **B**, Figure 1).

In our previous studies, the synthesis of DHDPP was achieved by an arynic cyclization of 2-*N*-alkylamino-3-halopyridines in the presence of the complex base $NaNH_2$−*t*BuONa, leading to a mixture of the two isomers **A** and **B** with a total yield of the reaction not exceeding 50%.[2]

Very recently,[3] we developed a sequence substitution−reduction−cyclization−substitution by starting from the adequate nitro-substituted *N,N′*-dipyridinylamines obtained through Pd-catalyzed reactions that allowed selective access to unsymmetrical 5,10-dialkyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazines and 5,10-dialkyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazines in good yields. The synthesis of dihydrodipyridopyrazinic isomer **B** was achieved by cyclization in the *ortho* position of the pyridinic nitrogens.

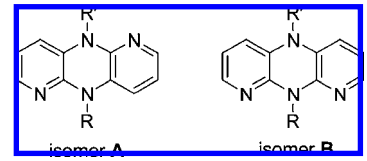


Figure 1. Structures of dihydrodipyridopyrazinic isomers.

As a continuation of our interest in the synthesis development of the isomer **B** of DHDPP, we envisioned the cyclization in the *meta* position of the pyridinic nitrogens (Scheme 1).

Surprisingly, molecules with the structure of the isomer **A** of DHDPP were obtained by using our proposed synthetic route depicted in Scheme 1, based on the reduction of the

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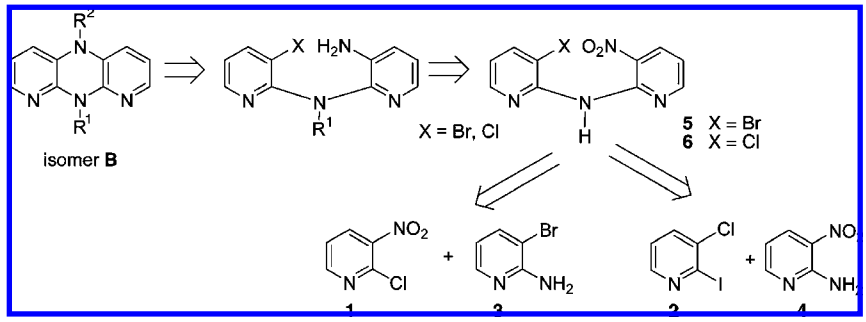
Scheme 1. Retrosynthetic Analysis of the Dihydrodipyridopyrazinic Isomer **B**



adequate 3-nitro-3′-halo-*N*,*N*′-dipyridinylamines (**5** and **6**) obtained by Pd-catalyzed reactions, followed by cyclization of the resulted amines.

We report herein this alternative synthetic method for isomer **A**, which involves an unexpected *N*−*N* type Smiles rearrangement on the pyridine ring during the reduction reaction of the potential precursors of isomer **B**.

In view of the high efficency of the Pd−Xantphos catalyst system[4] in our earlier work on the univocal synthesis of DHDPP,[3] we chose the same reaction conditions to perform the synthesis of the nitro-substituted *N*,*N*′-dipyridinylamines possessing the required structures. We first examined the reaction of 2-chloro-3-nitropyridine **1** with 2-amino-3-bromopyridine **3** using 10 mol % of $Pd(OAc)_2$ as the palladium source, 20 mol % of Xantphos as the ligand, 1.5 equiv of K_2CO_3 as the base, and 1,4-dioxane as the solvent which led to the coupling product **5**, in 83% yield. The coupling reaction between 3-chloro-2-iodopyridine **2** and 2-amino-3-nitropyridine **4** using 15 mol % of $Pd(OAc)_2$ with the same ratio Xantphos/$Pd(OAc)_2$ = 2/1 gave the desired product **6**, another potential precursor of isomer **B**, with a very good yield (91% yield).

For the compound **5** it was possible to isolate single crystals permitting its study by X-ray crystallography (Figure 2).

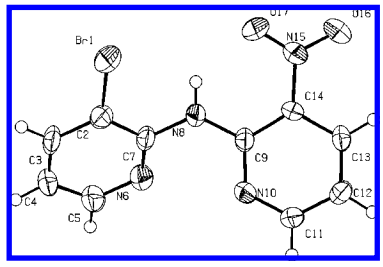
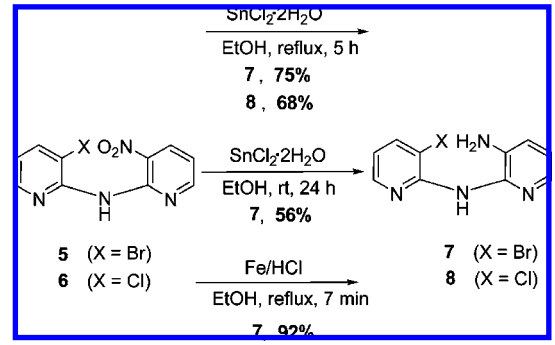


Figure 2. X-ray structure of compound **5**.

Using the compounds **5** and **6** as starting material, we examined the possibility to obtain the isomer **B** of dihydrodipyridopyrazines.

The reduction of the nitro group of the compounds **5** and **6** was carried out using either tin chloride dihydrate in ethanol[5] (at reflux or at room temperature) or iron and hydrochloric acid 37% in refluxing ethanol[6] (Scheme 2).

Scheme 2



In all cases, the NMR analysis carried out within various solvents did not allow us to conclude on the structure of the obtained products (spectrum peaks poorly resolved proton, carbons absent in the spectrum of ^{13}C NMR). Only the treatment of chloroform solutions of **7** and **8** with some drops of trifluoroacetic acid (TFA) made the analysis possible. We can note that the compound **7** was obtained with an excellent yield of 92% using Fe/HCl in refluxing ethanol for only 7 min.

Finally, the structure of **7** was established by X-ray diffraction, clearly identifying the substitution positions on the pyridine rings (Figure 3).

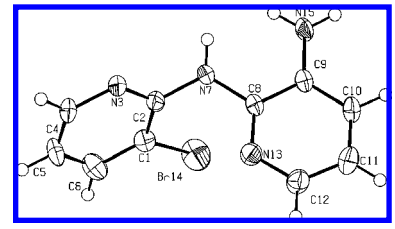


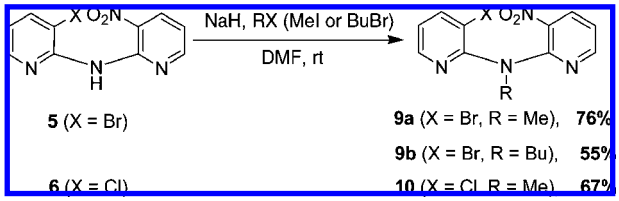
Figure 3. X-ray structure of compound **7**.

The intramolecular cyclization of **7** was unsuccessful by using various methods of Pd-catalyzed cyclization as those

used by Tietze ($Pd_2(dba)_3$, *o*-(di-*tert*-butylphosphino) biphenyl, and *t*BuONa in toluene)[7] and Nolan (Pd-carbene, *t*BuONa in toluene)[8] or using the $Pd(OAc)_2$−Xantphos catalyst system.[4] All these attempts resulted only in the recovery of the starting products.

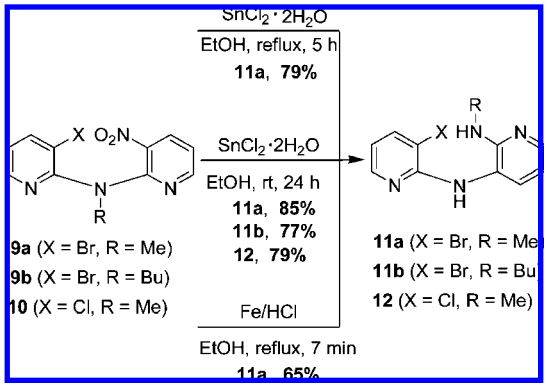
In the continuation of our study, we decided to fix an alkyl group on the nitro-substituted *N*,*N*′-dipyridinylamines **5** and **6**, before the reduction step. The alkylated compounds **9a**, **9b**, and **10** were obtained in acceptable yields by treating **5** and **6** with the corresponding alkyl halides in the presence of sodium hydride in dimethylformamide (Scheme 3).

Scheme 3



The reduction of the nitro group of alkylated compounds **9a**, **9b**, and **10** was performed using the methods previously described. Reductions by $SnCl_2 \cdot 2H_2O$ or by Fe/HCl led to the same product (Scheme 4).

Scheme 4



The ^1H NMR spectrum intrigued us by the fact that two hydrogens of the amine function (the presence of the NH being highlighted by exchange with heavy water) present two separate signals. On the other hand, the ^{13}C NMR and mass spectra correspond to the awaited product. Thus, the reaction sequence for the formation of **11a**, **11b**, and **12** is considered to involve the reduction of the nitro group followed by the Smiles rearrangement.

The Smiles rearrangement[9,10] represents a class of intramolecular nucleophilic aromatic substitutions resulting in the migration of an aromatic ring from one heteroatom to another. It is known that the Smiles rearrangement necessitates an electron-deficient center to proceed at a reasonable rate (e.g., nitro, sulfonyl, or halogen). Although this type of rearrangement is commonly catalyzed by a base, there are several precedents for acid-catalyzed rearrangements in systems containing azaheterocycles.[11]

Thus, this sequence appears to be another example of Smiles rearrangement with a halogen as the activating group,[12] which must exert its effect through a predominantly inductive mechanism.

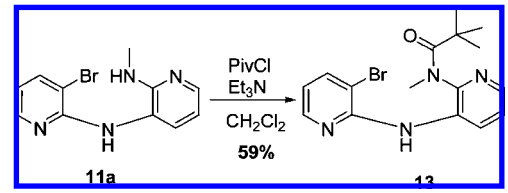
Previous reports regarding the mechanism of the acid-catalyzed Smiles rearrangement proposed that the proton activates the migration of the aromatic ring (the pyridine ring in this case).[11a] Additionally, the Smiles rearrangement shown here occurred in the 2-position of the pyridine ring system, a position which is activated toward nucleophilic attack.

Compounds **11a**, **11b**, and **12** appeared to us, as the first examples of the acid-catalyzed *N*−*N* type Smiles rearrangement of halogenated *N*,*N*′-dipyridinylamines.

It is interesting to note that the products **11a**, **11b**, and **12** were isolated with good yields (65−85%), the best result (85%) being recorded during the reduction of **9a** with tin chloride at room temperature. Variation in the length of the alkyl group of the nitro-substituted *N*,*N*′-dipyridinylamines contributes to the lowering of the reaction yield.

The structure of **11a** was also confirmed by its conversion into **13**. The acylation reaction of the product **11a** with pivaloyl chloride enabled us to isolate the compound **13** substituted on the methylated nitrogen. The yield of product **13** was 59%, with recovery of approximately 21% of the starting substrate (Scheme 5).

Scheme 5



The ORTEP representation of the compound **13** clearly indicates that the pivaloyl group is on the nitrogen substituted by methyl, indirectly establishing the structure of the Smiles rearrangement product **11a** (Figure 4).

Synthesis of Isomers A of DHDPP. The Pd-catalyzed cyclization of the Smiles rearranged compounds **11a** and **11b**, achieved in the presence of the $Pd(OAc)_2$−Xantphos catalyst system, provided access to the monosubstituted derivatives **14a** and **14b**. The crude products were then engaged in the alkylation reaction with methyl iodide, the

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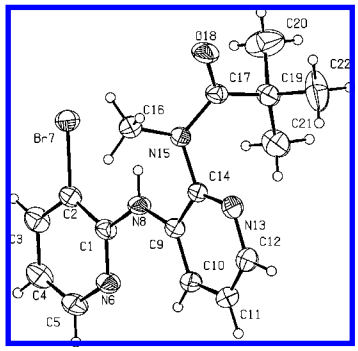
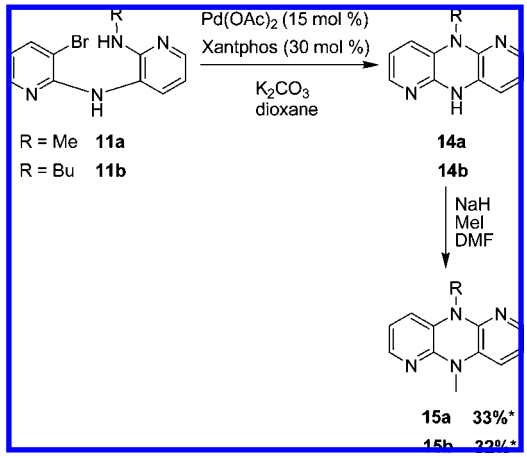


Figure 4. X-ray structure of compound **13**.

sequence leading to the awaited dihydrodipyridopyrazinic isomers **A** (**15a** and **15b**) with a 32−33% yield, calculated over two steps (Scheme 6).

Scheme 6



* Yields calculated over two steps.

The spectroscopic and physical data of products **15a** and **15b** were identical to those recorded for the compound previously isolated by the sequence of Pd-catalyzed coupling−alkylation−reduction−cyclization−alkylation reactions (isomer **A** of DHDPP).

In contrast to the successful cyclization of **11a** and **11b**, the treatment of the chloride substituted compound **12** with palladium acetate and Xantphos under the conditions previously used did not lead to the desired product, only 65% of the starting product being recovered.

In summary, we have demonstrated the occurrence of an acid-catalyzed *N*−*N* type Smiles rearrangement in the formation of dihydrodipyridopyrazinic isomer **A** starting from the 3-nitro-3′-halo-*N*,*N*′-dipyridinylamines, potential precursors of the isomer **B**.

This new method complements existing strategies for the synthesis of dihydrodipyridopyrazines, even if it is limited in terms of low total yield.

Exploration of this new strategy in the synthesis of other interesting molecules is currently underway.

Supporting Information Available: Experimental procedures, characterization data, NMR spectra for all new compounds, X-ray crystal structure coordinates, and files for compounds **5**, **7**, and **13** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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