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New stable atropisomers derived from 2,4,6-collidine and related compounds

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ABSTRACT

The Suzuki–Miyaura cross-coupling reaction of 3,5-dibromo-2,4,6-collidine and bromo derivatives of 2,6- and 2,4-lutidine with several *ortho*-substituted boronic acids produced a library of arylated pyridines. The reaction conditions were carefully optimized to allow high yield of the desired products. In several cases the presence of stable atropisomers were detected, even at elevated temperature during GC–MS analysis. Some of the diastereomers were isolated and characterized by spectroscopic methods and X-ray crystallography. Racemic forms of selected samples were tested by ^{1}H NMR spectroscopy in the presence of chiral solvating agents in order to visualize the presence of individual enantiomers.

1. Introduction

Atropisomerism is a kind of stereochemical phenomenon that arises from restricted rotation around certain single bonds, which behave as axes of chirality. The term atropisomer is derived from the Greek *atropos*, meaning 'not turning'. The name was coined by Kuhn in 1933 and it was first experimentally visualized by resolution of enantiomers of 6,6′-dinitro-2,2′-diphenic acid by Christie in 1922.[1] In biaryls the atropisomerism is generated by the presence of sterically demanding substituents placed at the *ortho*-position of the aryl moiety, thus causing restricted rotation around the pivotal bond. The steric hindrance introduced by substituents along with a geometry of the planar framework of the molecule and other intramolecular forces (hydrogen bonding, π-stacking, ionic interactions) define configurational or conformational stability of atropisomers. On the contrary to interconvertible rotamers, stable atropisomers are, by definition, fully resolvable at room temperature when their rotation barrier exceeds 23.3 kcal mol^{-1}, which corresponds to at least 1000 s of their half-life.[2] The phenomenon of atropisomerism has broad implications to organic chemistry because several atropisomeric ligands have found widespread applications in metal catalysis[3] and also in bioorganic chemistry and pharmacology.[4]

During our study on atropisomerism in aryl-pyridine derivatives we found that the Suzuki reaction of tribromo-2,6-lutidine with 2-methoxyphenylboronic acid gave 3,4,5-tri-(2-methoxyphenyl)-2,6-lutidine in the form of a mixture of three, stable at room temperature, atropisomers. Each of them was isolated and fully characterized, including their stereochemistry determination.[5]

In this report we describe further extension of the research on other derivatives of 3,5-diaryl substituted 2,4-, 2,6-lutidines and 2,4,6-collidines. We expected that the introduction of phenyl rings with bulky *ortho* substituents at positions 3 and 5 of the pyridine core would inhibit their rotation around $C_{3,5pyridine}$–C_{phenyl} bond thus generating stable and separable atropisomers. We expected that aromatic bulky substituents such as 2-trifluoromethylphenyl and 2-chlorophenyl would be feasible since their attachment to the pyridine core might be conveniently performed by the Suzuki–Miyaura cross-coupling reaction of the corresponding halogenated collidine **1**, 2-, 4-alkoxy and 2-, 4-diamino lutidines **5**–**8** and **9**–**10**, respectively (Scheme 1). We also expected that proper functionalization at positions 2 and 4 of the pyridine ring would open a possibility for further transformation of the corresponding biaryls into other polyarylated heterocycles.

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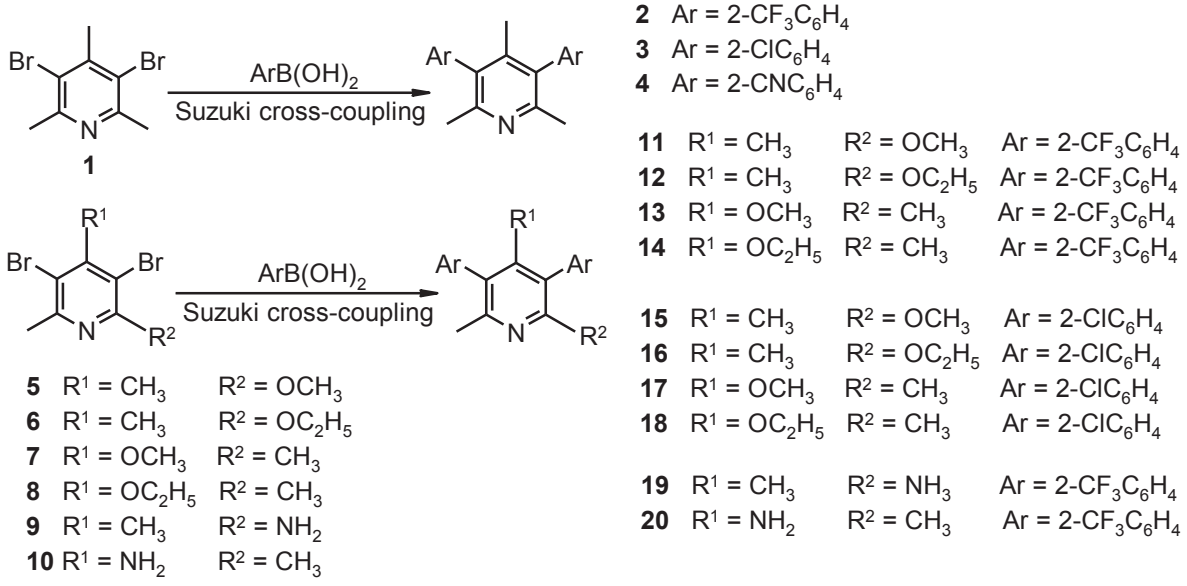


Scheme 1. Synthesis of 3,5-diarylpyridines **2**–**3** and **11**–**20**; reagents and conditions: **1**, **5**–**10** (1.0 equiv), $ArB(OH)_2$ (4.5 equiv), K_3PO_4 (4.0 equiv), $Pd(OAc)_2$ (5% mol), *S*-Phos (10% mol), toluene, 90 °C, 4 h; for compound **4** (1.0 equiv), $ArB(OH)_2$ (10 equiv), K_3PO_4 (4.0 equiv), $Pd(OAc)_2$ (5% mol), *S*-Phos (10% mol), toluene, 90 °C, 72 h.

2. Results and discussion

The starting material—halogenated collidine **1** and lutidines **7**–**10**, were prepared according to the procedures described in the literature.[6–11] The novel alkoxybromopyridines **5** and **6** were synthesized in two steps starting from 4,6-dimethylpyrid-2-one with subsequent alkylation of intermediary 3,5-dibromo-4,6-dimethylpyrid-2-one[12] (Scheme 2).

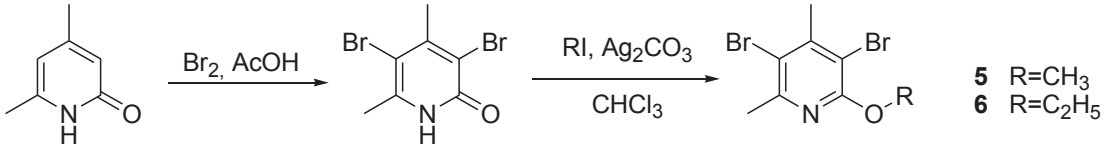
Our previous studies have shown that halogenated heterocycles such as **1**, **5** and **6** are good partners in Suzuki cross-coupling reactions with a wide array of arylboronic acids.[12–14] The screening tests confirmed that readily available catalytic system consisted of palladium species $Pd(OAc)_2$, $Pd_2(dba)_3$ and ligands, e.g., *o*-tolyl, $P(Cyc)_3$ showed moderate or high reactivity when used with relatively high catalyst loading (3–5%).[14] Although the conversion of substrates was almost complete, the desired diarylated products were always accompanied by side-products, such as monoaryldesbromo and monoarylbromopyridines. The best results were obtained using a catalyst based on $Pd(dppf)Cl_2{\times}CH_2Cl_2$ and $Pd(OAc)_2$ with Buchwald ligands (*S*-Phos, *X*-Phos).

Our initial attempts were focused on the optimization of the cross-coupling reaction between collidine **1** and 2-(trifluoromethyl)phenylboronic acid to obtain full conversion of the substrate and improve the yield of diarylpyridine **2** without generation of side-products **21** and **22** (Scheme 3). We assumed that optimized conditions would be suitable for further preparation of pyridines **3**, **4**, **11**–**20**. The results of trial reactions were collected in Table 1.

The reference material for our preliminary study, 3-bromo-5-(2-trifluoromethyl)phenyl-2,4,6-trimethylpyridine **22** and 3-(2-trifluoromethyl)phenyl-2,4,6-trimethylpyridine **21**, were obtained by treatment of pyridine **1** with 1.6 equiv of 2-(trifluoromethyl) phenylboronic acid in the presence of $Pd(OAc)_2$/*S*-Phos and K_3PO_4 in toluene at 75 °C for 2 h. Bromo derivative **22** was isolated in 37% yield and subsequently was debrominated into **21** in ethanol under hydrogen in the presence of Pd/C (Scheme 4).

The cross-coupling reaction between **1** and 2-(trifluoromethyl) phenyl boronic acid was first performed with readily available catalysts $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $Pd(OAc)_2/P(Cyc)_3$ in the presence of CsF, K_2CO_3, K_3PO_4 as bases in toluene, DMF, or acetonitrile as solvents. Unfortunately, in any case neither traces of the desired product **2** nor pyridines **21** and **22** were detected in the reaction mixtures.

The GC–MS analysis revealed the presence of a self condensation product of boronic reagent—2,2′-bis-(trifluoromethyl)biphenyl and the product of debromination of the substrate **1**. The Suzuki coupling in the presence of $Pd(dppf)Cl_2{\times}CH_2Cl_2$ as catalyst with K_2CO_3 in dioxane was also tested with various boronic acids. Only a little amount of debrominated and monoarylated products were observed. Unfortunately, no improvement was achieved when 5% mol of $Pd(dppf)Cl_2{\times}CH_2Cl_2$ was applied along with several bases (KF, K_2CO_3, K_3PO_4, CsF, Cs_2CO_3), varying the temperature of the reaction (80–110 °C), and solvents (dioxane, toluene, DMF, acetonitrile). Occasionally, the formation of traces of **20** and **21** (2–4%) were detected. More promising results were obtained when we used Buchwald[15] ligand *X*-Phos together with $Pd(OAc)_2$ as palladium source (Table 1, entry 1). However, the main products were still pyridines **20** and **21** with significant amount of 2,2′-bis-(trifluoromethyl)biphenyl. We thus continued the screening of various bases, solvents and other Buchwald ligand (*S*-Phos).[16] As shown in Table 1, CsF was more effective than K_3PO_4 used with *X*-Phos (entry 2). The reaction completely failed when toluene was replaced by



Scheme 2. Synthesis of 2-alkoxypyridines **5** and **6**.