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Convenient synthesis of selected *meta*- and *ortho*-substituted pentaarylpyridines *via* the Suzuki-Miyaura cross-coupling reaction

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ABSTRACT

The first synthesis of sterically demanding, stable at room temperature atropisomeric derivatives of penta-(*ortho*-substituted phenyl)pyridines is described. The Suzuki-Miyaura cross-coupling reaction of pentabromopyridine and selected *meta*- and *ortho*-tolylboronic acids afforded a series of pentaarylpyridine derivatives. The structures of two room temperature stable atropisomeric derivatives of penta-(*o*-tolyl)pyridines were confirmed by single-crystal X-ray analysis. Racemic atropisomers were examined by ^{1}H NMR spectroscopy with a chiral solvating agent in order to visualize the presence of individual enantiomers.

Introduction

Atropisomers are interesting stereoisomers possessing axial chirality resulting from restricted rotation around single bonds, and are found in many classes of compounds.[1–5] In particular, oligoaryl-substituted pyridines have gained attention due to their role as chiral ligands, building blocks in supramolecular chemistry, or new materials with important electrochemical or photochemical properties.[6–8]

Recently, Langer and co-workers reported a pentafold Suzuki-Miyaura reaction of pentachloropyridine with *para*-substituted phenylboronic acids to give a series of pentaaryl substituted pyridines.[9] Also, the site-selective arylation of commercially available 2,3,5,6-tetrachloropyridine or 3,5-dibromo-2,6-dichloropyridine with substituted boronic acids was described.[10,11] Karadeniz and co-workers presented a facile and efficient synthetic route towards a series of substituted triarylpyridines of pharmacological interest.[12] In 2014, a fully regiocontrolled polyarylation of pyridine was reported by Doebelin and co-workers,[13] involving five sequential, fully regiocontrolled Suzuki-Miyaura cross-coupling reactions. Another regiocontrolled polyarylation of pyridine was presented in 2015.[14] In this case, the thermal [4+2]cycloaddition of tetraarylthiophene *S*-oxide and 2-cyanopyridine was used to furnish various pentaarylpyridines.

Finally, we have been interested in the phenomenon of atropisomerism occurring in *ortho*-substituted tri- and diarylpyridine derivatives.[15–17]

Results and discussion

Expecting that decoration of the pyridine core with five sterically demanding substituents would give rise to molecules of unique static and dynamic stereochemical properties, we considered the Suzuki-Miyaura cross-coupling reaction for this purpose. Initially, we started with commercially available pentachloropyridine which was subjected to several trial reactions with selected *ortho*-substituted phenylboronic acids under various conditions. Despite much effort, we obtained only inseparable mixtures of partially arylated products contaminated with various de-chlorinated derivatives, which might be attributed to the insufficient reactivity of the C-Cl bonds. We therefore considered the use of pentabromopyridine which was expected to be much more reactive. Unfortunately, this compound is not commercially available and its synthesis requires the use of 80% oleum which is also not readily accessible.[18] Fortunately, after some experimentation, we developed a procedure for the convenient preparation of pentabromopyridine **3**. Bromination of 4-hydroxypyridine **1** with dry bromine in 65% oleum produced 2,3,5,6-tetrabromopyridin-4-ol **2** in

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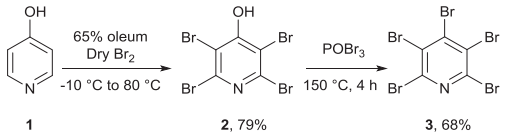
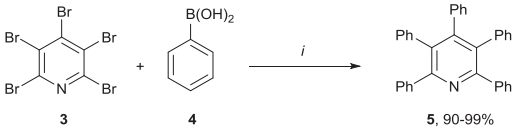
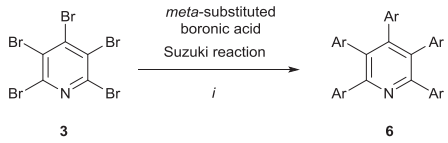


Scheme 1. Synthesis of 2,3,4,5,6-pentabromopyridine **3**.



Scheme 2. Synthesis of compound **5**. (*i*) **3** (1.0 eq.), **4** (10 eq.), $Pd(OAc)_2$ (5.0 mol%), SPhOS (5.0 mol%), K_3PO_4 (9.0 eq.), toluene (10 mL), 90 °C, 1 h (see ESI for optimization details).



Entry	Compound	Ar	Yield (%)[a]
1	**6a**	3-(Me)C_6H_4	88
2	**6b**	3-(CF_3)C_6H_4	83
3	**6c**	3-(Cl)C_6H_4	80
4	**6d**	3-(MeO)C_6H_4	89

[a] Isolated yield

Scheme 3. Synthesis of **6a-d**. (*i*) **3** (1.0 eq.), *meta*-substituted boronic acid (15 eq.), $Pd(OAc)_2$ (5.0 mol%), SPhOS (5.0 mol%), K_3PO_4 (9.0 eq.), toluene (10 mL), 90 °C, 2 h.

79% yield, which in a subsequent reaction with $POBr_3$ gave the desired product **3** in 68% yield (Scheme 1).

Optimization of the reaction conditions using phenylboronic acid (10 eq.) showed that the use of $Pd(OAc)_2$ with SPhOS as the catalyst in the presence of K_3PO_4 led to a quantitative yield (ESI, Table 1, Entry 9). We also found that the use of a phosphine ligand was not necessary (ESI, Table 1, Entries 10–11). The ligand-free systems based on $Pd(OAc)_2$ (10 mol%) or $PdCl_2(CH_3CN)_2$ (10 mol %) in the presence of K_3PO_4 in toluene, produced compound **5** in good yields (>90%).

The reaction of **3** with various *meta*-substituted phenylboronic acids under the optimized conditions; K_3PO_4 (9.0 eq.) as the base, toluene as solvent and $Pd(OAc)_2$/SPhOS (5.0 mol% for both components) as the catalyst, afforded the corresponding pentaarylpyridines **6a-d** in 80–89% yield. However, in this process 15 eq. of the *meta*-substituted phenylboronic acids were required and the reaction time was increased to 2 h. Changing the base to *t*-BuOK (6 eq.) resulted in reaction completion within 60 min. The products of incomplete arylation of **3** were not observed. Compounds **6a**–**6c**, to the best of our knowledge, have not been reported. The literature method for the preparation of compound **6d**[6] gave the product in a significantly lower yield (Scheme 3).

The promising results of coupling **3** with *meta*-substituted boronic acids encouraged us to attempt the reaction with *ortho*-substituted boronic acids, leading to sterically demanding penta-(*ortho*-substituted phenyl)pyridines (see Schemes 2 and 4).

The treatment of **3** with *o*-tolylboronic acid **7** under the same conditions as for *meta*-substituted boronic acids, gave a mixture of two pentaarylpyridine derivatives in 55% total yield and an approximately 2:1 (**9** and **10**, respectively) ratio. Both compounds had the same mass spectra and very similar NMR spectra. Due to the presence of restricted rotation around the $C_{pyridine}$-C_{aryl} single bonds caused by steric interaction of the *ortho*-substituents, they represent room temperature stable atropisomers. These were separated by column chromatography and subjected to single crystal X-ray crystallography. Compound **8** was also observed in the reaction mixture which was presumably an intermediate product of coupling **3** with *o*-tolylboronic acid **7**. The structure of **8** was also confirmed by single crystal X-ray analysis (Fig. 1).

In the majority of cases, *in situ* generated palladium complexes using the Buchwald ligand SPhOS[19] and $Pd(OAc)_2$ as a palladium source were used. The use of other combinations of palladium source and ligand did not give improved results. Using $Pd(OAc)_2$ in the presence of K_3PO_4 in toluene, we obtained, after 30 min, the desired products in moderate yield and a 3:2:1 (**8**:**9**:**10**, respectively) ratio. Extending the reaction time from 30 min to 24 h led to an improved coupling reaction (Table 1, Entry 5). Increasing the amount of boronic acid from 15 eq. to 20 or 30 eq. did not give a better outcome (Entries 2–3). When the solvent was changed to xylene with a higher temperature (Entry 7), the yield increased

Table 1
Optimization for the synthesis of **8**–**10**.

Entry	**7** (eq.)	Solvent	Temp. (°C)	Catalyst[a]	Time (h)	Base (eq.)	Yield (%)[b]			Total yield[d] (%)
							8	**9**	**10**	
1	15	Toluene	90	$Pd(OAc)_2$; SPhOS	0.5	K_3PO_4 (9)	22	16	8	46
2	15	Toluene	90	$Pd(OAc)_2$; SPhOS	1	K_3PO_4 (9)	35	14	6	55
3	20	Toluene	90	$Pd(OAc)_2$; SPhOS	1	K_3PO_4 (9)	35	14	9	58
4	30	Toluene	90	$Pd(OAc)_2$; SPhOS	1	K_3PO_4 (9)	33	16	11	60
5	20	Toluene	90	$Pd(OAc)_2$; SPhOS	24	K_3PO_4 (9)	23	33	25	81
6	15	Xylene	140	$Pd(OAc)_2$; SPhOS	1	K_3PO_4 (9)	39	18	16	73
7	15	Xylene	140	$Pd(OAc)_2$; SPhOS	24	K_3PO_4 (9)	25	34	32	91
8	15	Toluene	90	$Pd(OAc)_2$; SPhOS	0.5	*t*-BuOK (6)	23	17	8	48
9	15	THF	60	$Pd(OAc)_2$; SPhOS	24	K_3PO_4 (9)	66	–	–	66
10	15	$PhNO_2$	170	$Pd(OAc)_2$; SPhOS	10 min[c]	K_3PO_4 (9)	58	–	–	58
11	15	Toluene	90	$Pd(OAc)_2$[e]	2	K_3PO_4 (9)	–	–	–	–
12	15	Toluene	90	$Pd(OAc)_2$[e]	2	*t*-BuOK (6)	–	–	–	–
13	15	Toluene	90	$PdCl_2(CH_3CN)_2$[e]	2	K_3PO_4 (9)	–	–	–	–
14	15	Toluene	90	$PdCl_2(CH_3CN)_2$[e]	2	*t*-BuOK (6)	–	–	–	–

[a] 5.0 mol% for both components.
[b] Isolated yield.
[c] Longer heating caused catalyst decomposition.
[d] Total yield of isolated products **8**–**10**.
[e] 10 mol%.