PALLADIUM-CATALYZED CROSS-COUPLING OF PHENYLBORONIC ACID WITH HETEROCYCLIC AROMATIC HALIDES

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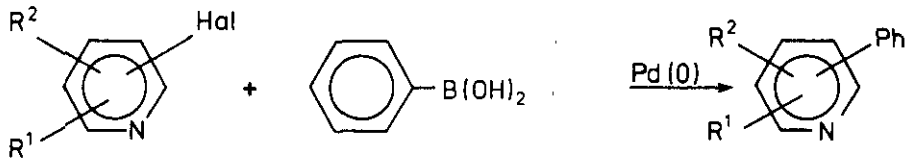
Abstract - The coupling reaction of bromo- and iodopyridines 1 with phenylboronic acid (2a) by $Pd(Ph_3P)_4$ provides a convenient route to phenylpyridines, even when electrondonating or - withdrawing substituents are present. The method is also successful for the preparation of other phenylated N-containing heterocycles 5 as phenylquinolines and -pyrimidines.

In the course of our biological studies of 2-amino-5-phenylpyridine (3g), a suspectedly carcinogenic pyrolysis product of phenylalanine,[1] we were also interested in the 3-methyl derivative and its putative N^2-oxygenated metabolites.

We synthesized 2-amino-5-phenylpyridine (3g) and several of its N^2-oxygenated derivatives[1] via a *modification of the Cadogan arylation of aromatic amines.*[2] *According to this method,* aminopyridines were diazotized with pentyl nitrite in refluxing benzene. The resulting diazonium compounds coupled with the solvent to give the desired phenylpyridines. Although this procedure was also suitable for the syntheses of the 3-methyl analogues,[3] the successful palladium-catalyzed cross-coupling of phenylboronic acid (2a) with haloarenes, developed by Miyaura et al.,[4] prompted us to investigate this procedure for the synthesis of phenylated N-containing heterocycles, especially because Miller and Dugar were able to prepare mononitrobiphenyls with this method.[5] Since 2-nitro-5-bromopyridines are more easily available, the Miyaura method allows to avoid cumbersome syntheses of 2-nitro-5-aminopyridines, which are the necessary precursors for 2-nitro-5-phenylpyridines in the Cadogan reaction.[1]

First, we examined the coupling reaction of phenylboronic acid (2a) with a number of halopyridines 1. Treatment of 1 with 2a (1.1 mol eq) in the presence of $Pd(Ph_3P)_4$ (3 mol%) and aqueous sodium carbonate (2 *mol eq) in benzene at reflux temperature gave phenylpyridines* 3 *in moderate to excellent* yields. The results are listed in Table 1.



1a-j 2a 3a-j

1,3	Hal	R^1	R^2	1,3	Hal	R^1	R^2
a	2-Br	H	H	e	5-Br	2-OH	H
b_1	3-Br	H	H	f	2-Br	3-OH	H
b_2	3-I	H	H	g	5-Br	$2-NH_2$	H
b_3	3-Cl	H	H	h	5-Br	$2-NH_2$	$3-CH_3$
c	4-Br	H	H	i	5-Br	$2-NO_2$	H
d	5-Br	$2-OCH_3$	H	j	5-Br	$2-NO_2$	$3-CH_3$

Table 1 shows that the three isomeric phenylpyridines 3a-3c can be prepared from the three corresponding bromopyridines 1a, $1b_1$ and 1c. The yield of 2-phenylpyridine (3a) was moderate (53%), possibly due to lack of electronegativity of the 2-position of the pyridine ring.

Although only one test was done, it seems likely that iodopyridines are equally good starting compounds, because the reaction with 3-iodopyridine ($1b_2$) gave 84% of 3-phenylpyridine, the same result as with 3-bromopyridine ($1b_1$) (86%). As was expected from the study of Miyaura et al., 3-chloropyridine ($1b_3$) did not react and no trace of 3-phenylpyridine (3b) could be detected.[4]

Miyaura et al. already showed, that cross-coupling with bromobenzenes, substituted with the electrondonating methoxyl group, worked well (66% from p-methoxybromobenzene).[4] Table 1 shows, that the same holds true for 2-methoxy-5-bromopyridine (1d); 65% of 2-methoxy-5-phenylpyridine (3d) was obtained.

An effort to prepare 2-hydroxy-5-phenylpyridine (3e) from 1e was not successful.[14] Possibly this is due to the fact that 2-hydroxypyridines almost entirely exist in the keto-form and it is very likely that, for the same reason, the method is not suitable for synthesizing 4-hydroxyphenylpyridines.[15]

In agreement with this explanation, the preparation of 2-phenyl-3-hydroxypyridine (3f) from 2-bromo-3-hydroxypyridine (1f), that cannot exist in the keto-form, gave 57% yield. This moderate yield

Table 1. Reaction of Phenylboronic Acid (2a) with Various Halopyridines 1.

Substrate 1	Product[a] 3	Reaction Time (hrs)	Yield[b] (%)	mp (°C)
a	a	5	53	oil[c]
b_1	b	1.5	86	oil[d]
b_2	b	4.5	84	oil[d]
b_3	b	9	0	
c	c	4	86	79-80 (Lit.[6] 77-78)
d	d	1	65	oil[e]
e	e	9	0	
f	f	1	57	194[f] (Lit.[7] 205)
g	g	3	79	134-135 (Lit.[1] 134-135)
h	h	3	88	113-114[8]
i	i	5	76	115-116 (Lit.[1] 115-116)
j	j	4	61	78-79[9]

a) All compounds gave satisfactory spectral (^{1}H-nmr and mass) data. Spectral data of compounds, not described earlier, have been given in notes.

b) Isolated yield based on the halopyridine.

c) Picrate; mp 177-178 °C (lit.[10] 175 °C)

d) Picrate; mp 163-163.5 °C (lit.[11] 162-163 °C)

e) Picrate; mp 165-167 °C (lit.[12] 170-171 °C)

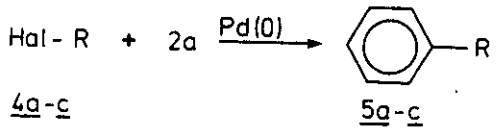
f) Picrate; mp 195-196 °C (lit.[13] 201-201.5 °C)

again is due to the use of a 2-bromopyridine as starting material as explained above and not to the presence of the hydroxy-group.[16]

In contrast to the unsuccessful preparation of 2-hydroxy-5-phenylpyridine (5e), the phenylation of the amines 1g and 1h gave the 2-amino-5-phenylpyridines 3g and 3h in respectively 79 and 88% yields. This may be explained by the fact that the 2-aminopyridines are believed to exist mainly in the amino-form rather than as the tautomeric imines.[15]

The yield of the nitrophenylpyridines 3i and 3j (76 and 61%) was lower than that obtained by Miller and Dugar for a series of nitrobiphenyls (88-89%),[5] but a great improvement compared to the synthesis via 2-nitro-5-pyridinamines according to Cadogan.[1]

Secondly, we examined cross-coupling of phenylboronic acid (2a) with 4-iodopyrazole (4a), 3-bromoquinoline (4b) and 5-bromopyrimidine (4c) to see, whether this method was also applicable to other



4a-c 5a-c

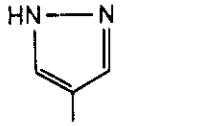
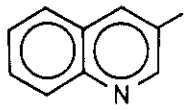
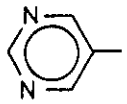
4,5	Hal	R
a	4-I	
b	3-Br	
c	5-Br	

Table 2. Reaction of Phenylboronic Acid (2a) with Various N-Containing Heterocyclic Halides 4.

Product[a] 5	Reaction Time (hrs)	Yield[b] (%)	mp (°C)
a	22	0	
b	3	93	51.5-52.5 (Lit.[17] 52)
c	1	87	34-36[c] (Lit.[18] 23-27)

a) All compounds gave satisfactory spectral (^{1}H-nmr and mass) data.

b) Isolated yield based on the halide.

c) Picrate; mp 131-133 °C (lit.[18] 120 °C)

aromatic N-heterocycles. The results, obtained under the same reaction conditions, are listed in Table 2. The quinoline 4b and pyrimidine 4c gave excellent yields (resp. 93 and 87%), but 4-iodopyrazole (4a) was inert under the conditions used. Obviously the aromatic character of the pyrazole ring is insufficient for an effective coupling reaction.

A wide variety of arylboronic acids can be prepared by substitution reactions of the parent phenyl-

boronic acid, such as nitration, oxidation and halogenation.[19] We intend to use these properties to introduce several substituents in the phenyl ring of phenylpyridines and this will be subject of further study.

As compared with known procedures to phenylate pyridines the present method is experimentally simpler and gives better yields. Moreover, the easiness with which substituents can be introduced into the pyridine ring and possibly also into the phenyl ring, makes the method a very valuable tool in the synthesis of a large variety of phenylpyridines or other N-containing aromatic heterocycles.

GENERAL PROCEDURE

To a mixture of 0.3 mmol of $Pd(PPh_3)_4$, 20 ml of benzene, 10 mmol of the N-heterocyclic halide, and an aqueous solution of Na_2CO_3 (10 ml of a 2M solution) 11 mmol of phenylboronic acid (dissolved in a minimum amount of ethanol) was added. This reaction mixture was refluxed under vigorous stirring for the appropiate length of time (see Table 1 and 2). After the reaction had been completed, as judged from TLC, the mixture was extracted with ethyl acetate. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel.[20]

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8. ^{1}H-Nmr (acetone-d_6) δ 2.12 (s, 3 H, Me), δ 4.74 (bs, 2 H, NH_2), δ 7.2-7.6 (m, 6 H, C_6H_5+4-H), δ 9.35 (d, 1 H, J = 2.3 Hz, 6-H); ms m/z (relative intensity) 184 (M^+ 100), 183 (10), 156 (16).

9. ^{1}H-Nmr ($CDCl_3$) δ 2.37 (s, 3 H, Me), δ 7.4-7.6 (m, 5 H, C_6H_5), δ 7.82 (d, 1 H, J = 2.1 Hz, 4-H) δ 8.51 (d, 1 H, J = 2.1 Hz, 6-H); ms m/z (relative intensity) 214 (M^+ 36), 184 (3), 168 (100), 153 (17), 141 (31).

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14. Compound 1e was synthesized by diazotizing 1g and converting the diazonium salt into 1e by boiling it in aqueous hydrochloric acid. Using unpurified 1e for the coupling reaction we were able to isolate 2-chloro-5-phenylpyridine from the reaction mixture. This was caused by contamination of the crude 1e with 2-chloro-5-bromopyridine. From this event it can be concluded that chlorophenylpyridines can be selectively prepared in the reaction with bromochloropyridines.

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16. We synthesized 4-hydroxybiphenyl from 4-bromophenol and phenylboronic acid under the same reaction conditions in 97% yield.

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