A CONVENIENT SYNTHESIS OF 3-ARYLPYRIDINES BY THE PALLADIUM CATALYZED COUPLING REACTION OF DIETHYL(3-PYRIDYL)BORANE WITH ARYL HALIDES

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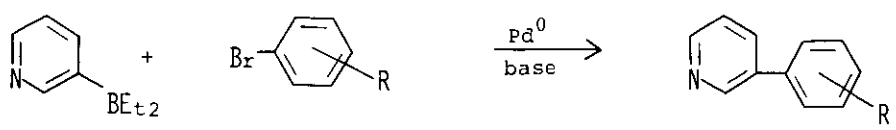
Abstract ——— The utilization of heteroarylborane to the preparation of a variety of 3-arylpyridines by the palladium catalyzed cross coupling reaction between diethyl(3-pyridyl)borane and aryl halides in the presence of bases is described.

Previous methods for the arylation of pyridine, a direct route to synthesize arylpyridines, such as Gomberg-Hey reaction or the use of organometallic compounds, suffer from limitations in potential applicabilities.[1] While, it has been well recognized that the organoborane possesses a considerable validity as synthetic intermediates and has been especially effective in carbon-carbon bond formation.[2] Recently, Suzuki et al. reported a new methodology for the preparation of arylated alkenes by the cross coupling reaction of vinylic boranes with aryl halides in the presence of palladium catalyst and bases.[3]

In the course of our studies on borylheterocycles, we have previously reported that diethyl(3-pyridyl)borane (1) is readily accessible from 3-lithiopyridine, prepared from 3-bromopyridine and BuLi *in situ*, and triethylborane in high yield.[4] We wish to report here an efficient method for the synthesis of a variety of 3-arylpyridines (3) from 1. (Chart 1)



1 2 3

Chart 1

Treatment of 1 with 2 (1.5 mol eq) in the presence of $Pd(Ph_3P)_4$ (5-10 mol%) and a base (3 mol eq) in benzene or THF under nitrogen atmosphere at reflux temperature gave 3-arylpyridines (3) in good yield. Effects of the base used to the reaction were briefly examined. When triethylamine or sodium acetate was used as a base, unsatisfactory results were obtained. Utilization of sodium ethoxide or KOH-Bu_4NBr was proved to be highly effective. The results of reactions were summarized in Table 1. Since a satisfactory result was attained by the use of the decreased amount of the catalyst, the following experiments were carried out with 5 mol % of $Pd(Ph_3P)_4$.

Table 1

Reaction of 1 with bromobenzene to 3-phenylpyridine (3; R=H)

Catalyst (mol%)	Solvent	Base [a]	Time (h)	Yield (%)
10	Benzene	NaOEt-EtOH	1	84 [b]
10	THF	Et_3N	6	— [c]
10	THF	NaOAc	5	— [c]
10	THF	NaOAc-Bu_4NBr	5	— [c]
10	THF	KOH-Bu_4NBr	1	85
5	THF	KOH-Bu_4NBr	2	80

a) 3 mol eq.
b) Picrate; mp 154-155 °C (lit.[5] 150-151 °C).
c) Unchanged 1 was recovered. The present observations are analogous to those mentioned by Suzuki et al.[3]

As a wide range of functional groups may be tolerable under these conditions, the present method seemed to provide the simplest route for the synthesis of 3-arylpyridines with various substituents on the phenyl ring. (Table 2)
A possible reaction course which is similar to that proposed by A. Suzuki[4] is shown in Chart 2.
Further applications of the above reaction to other heterocycles (e.g., substituted pyridines and quinolines) are under investigation.

Table 2 Reaction of 1 with various bromobenzene derivatives (2)

2		3	
R	Time (h)	Yield (%)	mp (°C)
2-Me	3	58	169-171 b),c)
4-Me	2	84	177-179 b),c)
2-OMe	3	50	184-185 (lit.[6] 182-182.5)
4-OMe	3	75	64 (lit.[7] 64-65)
2-NO_2	3	75	184-185 (lit.[8] 182-183)
4-NO_2	2	87	149-150 (lit.[8] 146-147)
2-$COCH_3$	2	53	180-181.5 b),c)
4-$COCH_3$	2	73	80-81 c)
2-Cl	3	15	174-176 b),c),d)
4-Cl	2	86	170-171 b),c)
2-COOMe	3	59	187-188 b),c)
4-COOMe	2	65	193-194 b),c)
2-NHCOPh	3	50	129-129.7 c)

a) All reactions were carried out in the presence of 1 (1 mol eq), 2 (1.5 mol eq), $Pd(Ph_3P)_4$ (5 mol%), Bu_4NBr (0.1 mol eq) and KOH (3 mol eq) under N_2 atmosphere in THF. b) Picrate c) All compounds gave satisfactory elemental analysis and spectral (IR, PMR and Mass) data. d) The depression of the yield presumably resulted from the lability of o-chlorobromobenzene under the basic condition.

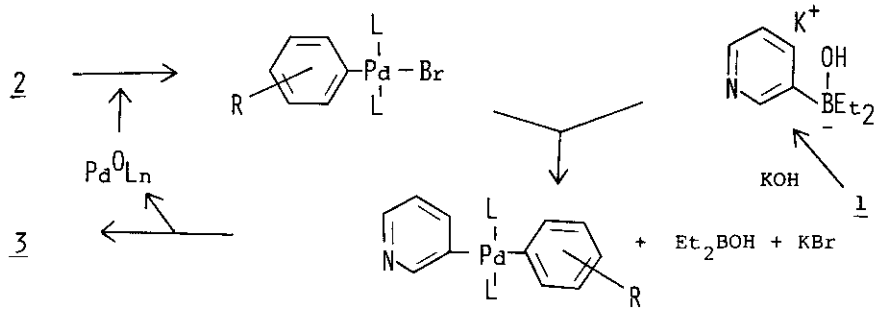


Chart 2

The following procedure is representative of the reaction described in this communication.

Preparation of 3-(p-Tolyl)pyridine ——— To a stirred mixture of p-bromotoluene (427.5 mg) and $Pd(Ph_3P)_4$ (116 mg) in THF (10 ml) under N_2 atmosphere at room temperature, Bu_4NBr (64.4 mg), powdered KOH (336 mg) and 1 (294 mg) were added. Then, the mixture was heated under reflux for 2 h. The mixture was diluted with AcOEt, washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by Flash column chromatography[10] [silica gel (E. Merck No. 9385), hexane:AcOEt=2:1] to give 287 mg (84%) of 3-(p-tolyl)pyridine.

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