An Efficient Synthesis of 3-Heteroarylpyridines via Diethyl-(3-pyridyl)-borane

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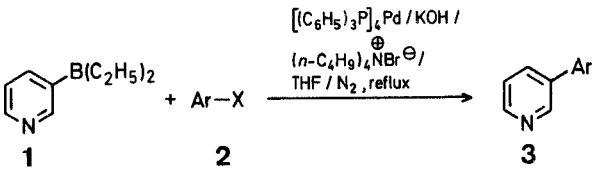
As a result of pharmaceutical interest and their occurrence as tobacco alkaloids, numerous routes have been reported for the synthesis of heteroaryl derivatives of pyridines[1]. However, for the direct introduction of heteroaryl groups in the β-position of pyridines, a number of difficulties has been encountered when using classical methods. The main problems

are the lack of regioselectivity and low yields (Gomberg-Bachmann reaction), the restricted applicability to active halides and the concomitant formation of homo-coupling products (Ullmann reaction), or the tedious procedure and limited scope of the reactants (Grignard reaction).

Recently it has been demonstrated that the heteroarylation of pyridines by palladium- or nickel-catalyzed cross-coupling reaction of bromopyridines with heteroarylzinc chlorides has a number of advantages over the classical methods[2]. As reported by Suzuki et al.[3], alkenylboranes and organic halides yield cross-coupling products when reacted in the presence of a palladium catalyst and an appropriate base.

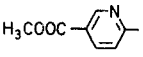
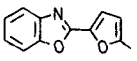
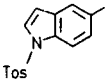
We now report the synthesis of 3-heteroarylpyridines **3** by palladium-catalyzed cross-coupling of diethyl-(3-pyridyl)-borane (**1**) with heteroaryl halides **2** in the presence of a base. Compound **1** is readily obtained from the reaction of 3-lithiopyridine with triethylborane followed by iodination[4].



The reaction is carried out by refluxing a mixture of **1** and **2** in the presence of potassium hydroxide, tetra-*n*-butylammonium bromide, and a catalytic amount of tetrakis [triphenylphosphine]palladium in tetrahydrofuran under nitrogen. Both 2-chloro- and 2-bromopyridine exhibit sufficient reactivity and other halopyridines with various functional groups can also be used.

The reaction offers an efficient method for the regioselective synthesis of a wide range of bipyridines, some of which are minor constituents of tobacco and tobacco smoke. Furthermore, the palladium-catalyzed cross-coupling reaction of **1**

Table. 3-Heteroarylpyridines **3a–m** prepared

Aryl Ar	Halide X	Product[a]	Yield[b] [%]	m.p. [°C] (solvent) or b.p. [°C]/torr	Molecular Formula[c] or Lit. Data	m.p. [°C] of Picrate
	Cl	**3a**	82	106°/1	b.p. 295–296°/760[5]	163–165°
	Br	**3a**	85		m.p. 165–168°[d,6]	
	Br	**3b**	83	166°/1	b.p. 165–175°/1[7] m.p. 199.5–201°[d,7]	202–203°
	Br	**3c**	77	126°/1	$C_{11}H_{10}N_2O$ (186.2) [$C_{17}H_{13}N_3O_8$ (387.3)][e]	201–203°
	Br	**3d**	63	136–137° (acetone/hexane)	$C_{12}H_{10}N_2O_2$ (214.2)	–
	2 Cl	**3e**	37	76–78° (acetone/hexane)	$C_{15}H_{11}N_3$ (233.3)	
	Br	**3f**	82	175°/15	b.p. 160°/9[6] m.p. 231–232°[d,8]	229–230°
	Br	**3g**	77	128–129° (C_2H_5OAc/hexane)	$C_{14}H_{10}N_2$ (206.2)	–
	Cl	**3h**	70	55–57° (PE)	m.p. 58°[9] [$C_{20}H_{13}N_5O_7$ (435.4)][e]	187–190°
	Cl	**3i**	47	150–152° (acetone/hexane)	$C_9H_7N_3$ (157.2)	–
	Br	**3j**	75	95°/1	121–122°/4[10]	–
	Br	**3k**	62	125–126.5° [acetone/(i-C_3H_7)$_2$O]	$C_{16}H_{10}N_2O_2$ (262.3)	–
	Br	**3l**[f]	39	syrup	$C_{22}H_{20}N_2O_2S$ (376.5)	231–234°
	Br	**3m**	47	145–147° (acetone/hexane)	$C_{20}H_{16}N_2O_2S$ (348.5)	–

[a] I.R., ^{1}H-N.M.R., and mass spectra are in accord with the structures.
[b] Yield of isolated product.
[c] Elemental compositions confirmed by microanalyses (C ± 0.21, H ± 0.09, N ± 0.18) for **3c, d, g, h, k** or high resolution mass spectrometry (m/e ± 0.0013 for M^+) for **3b, e, i, j, l, m.**
[d] Lit. m.p. of picrate.
[e] Molecular formula of picrate.
[f] R = 2,4,6-trimethylbenzenesulfonyl (mesitylenesulfonyl).

proceeds with other heteroaryl halides such as 3-bromothiophene, 2-bromofuran, 3-bromoquinoline, bromoindoles, etc. (Table). The method is a useful alternative to the classical methods and has the advantages of ready accessibility of the reagents, absence of side reactions, good yields, and experimental simplicity. The scope of the reaction and its extension to other heterocyclic systems are under investigation.

2,3′-Bipyridine (3a); Typical Procedure:

A mixture of diethyl-(3-pyridyl)-borane (**1**; 1.17 g, 8.0 mmol), 2-bromopyridine (1.88 g, 12.0 mmol), powdered potassium hydroxide (1,8 g, 32 mmol), tetra-*n*-butylammonium bromide (1.28 g, 4 mmol), and tetrakis[triphenylphosphine]palladium (462 mg, 0.4 mmol) in tetrahydrofuran (30 ml) is refluxed under nitrogen for 8 h. The mixture is then diluted with ethyl acetate (100 ml), washed with brine (40 ml), and dried with anhydrous magnesium sulfate. After removal of the solvent the residue is chromatographed on silica gel with ethyl acetate as eluent to give **3a**; yield: 1.07 g (85%).

Further purification is achieved by distillation; b.p. 106°C/1 torr (Ref.[5], b.p. 295–296°C/760 torr).

The picrate of **3a** is obtained by addition of an ethanol solution of picric acid to an ethanol solution of **3a** and subsequent recrystallization from ethanol; m.p. 163–165°C (Ref.[6], m.p. 165–168°C).

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