COMMUNICATION

Arylated pyridines: Suzuki reactions of *O*-substituted 2,6-dihalogenated-3-hydroxypyridines

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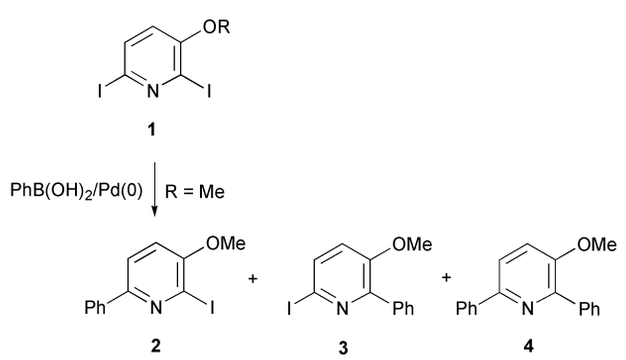
2-Bromo-6-iodo-3-methoxypyridine 5b yielded mono-arylated derivatives 6b–9b and teraryls 10b–14b in selective Suzuki reactions.

Aryl-substituted pyridine derivatives have recently attracted considerable synthetic attention in natural product chemistry, materials chemistry and other areas. The macrocycles Nosiheptide[1] and Promothiocin A[2] are both tri-arylated pyridine derivatives bearing three pendant thiazole substituents and these compounds are representative examples from the natural product arena whereas poly(thienopyridines) and related compounds[3] are well known examples from the materials chemistry field. Bryce and co-workers have recently reported the synthesis of a range of 2-aryl-3-hydroxypyridine derivatives from furan precursors.[4] In view of the current general interest in arylated pyridine derivatives,[5–7] we have been interested in exploring methods for preparing these types of heterocycle from commercially available and inexpensive 3-hydroxypyridine.

Our preliminary investigations focused on the *O*-substituted 2,6-diiodo compounds **1b–f** (Scheme 1) which were prepared



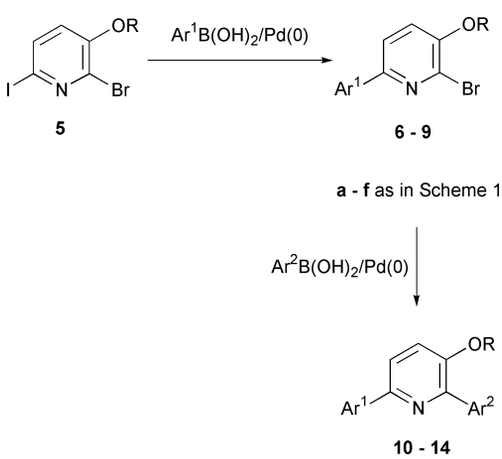
a, R = H; **b**, R = Me; **c**, R = CH_2Ph; **d**, R = COMe; **e**, R = COPh; **f**, R = $CONEt_2$

Scheme 1

from 2,6-diiodo-3-hydroxypyridine **1a** using standard procedures for protecting phenolic groups. Compound **1a** was readily prepared from 3-hydroxypyridine following a literature procedure.[8] We anticipated that the two iodo-substituents might be replaced sequentially by two aryl groups and that the protected 3-hydroxy group might also be replaced at a later stage (*e.g.* as its trifluoromethanesulfonate) by an additional group since trifluoromethanesulfonates and other groups are well known substrates for the Suzuki and other cross-coupling reactions.[9,10]

The Suzuki reactions of compounds **1b–f** with one mol equivalent of phenylboronic acid were investigated with the expectation that cross-coupling would occur regioselectively at the least sterically crowded 6-position leaving the 2-iodo group free for a subsequent coupling reaction. However, in the $Pd(PPh_3)_4$ catalysed Suzuki reactions of compounds **1d** and **1e** with phenylboronic acid in a mixture of boiling dimethoxyethane and 2 M sodium carbonate solution, loss of the *O*-substituent was observed. Mono-phenylation reactions of **1b**,**c** and **f** were also disappointing and a complex mixture of products was always obtained (by proton NMR spectroscopy). For example, the mixture obtained from the Suzuki reaction of compound **1b** with one mol equivalent of phenylboronic acid showed four methoxy signals attributed to unreacted starting material **1b**, diphenylated product **4** and presumably both regioisomers **2** and **3** of mono-phenylated material. An authentic sample of the diphenylated compound **4** (73% yield, mp 76–78 °C) was readily prepared from compound **1b** using an excess of phenylboronic acid.

We next turned our attention to the chemoselective mono-arylation reactions of *O*-substituted 2-bromo-3-hydroxy-6-iodopyridine derivatives **5b** and **5c**. These compounds were prepared by iodination of 2-bromo-3-hydroxypyridine[8] giving compound **5a** followed by either *O*-methylation yielding compound **5b** (mp 99–100 °C) or *O*-benzylation yielding compound **5c** (mp 81–82 °C). In the mono-arylation reactions of compounds **5b** and **5c** with a series of boronic acids (Scheme 2)



Scheme 2

excellent chemoselectivity was observed and the arylated products **6b–9b** and **6c** indicated in Table 1 were isolated in moderate to good yields (57–96%). The mono-arylated compounds **6b–9b** were then subjected to a second Suzuki reaction (Scheme 2) giving the 2,6-diarylated products **10b–14b** in moderate–good yields (43–87%) as depicted in Table 1. With the exception of the electron-deficient 3-nitrophenyl group, the yields for the introduction of the second aryl group were generally not as good as for the first arylation reaction. This is presumably a consequence of the less reactive bromine atom and greater steric hindrance at the 2-position.

In summary, compound **5b** has been shown to undergo

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Table 1

	Pyridine	Arylated product	Ar^1	Ar^2	Mp/°C	Yield (%)[a]
	5b	**6b**	Ph	–	110	70
	5c	**6c**	Ph	–	84–86	62
	5b	**7b**	3-$NO_2C_6H_4$	–	199–200	96
	5b	**8b**	4-MeC_6H_4	–	109–110	75
	5b	**9b**	2-Thienyl	–	100–102	57
	6b	**10b**	Ph	3-$NO_2C_6H_4$	90–94	60
	7b	**11b**	3-$NO_2C_6H_4$	Ph	122–124	44
	7b	**12b**	3-$NO_2C_6H_4$	4-MeC_6H_4	124–126	43
	8b	**13b**	4-MeC_6H_4	3-$NO_2C_6H_4$	102–106	87
	9b	**14b**	2-Thienyl	Ph	116–120	67

[a] Yields refer to isolated compounds. All compounds have been fully characterised.

selective Suzuki reactions giving access to a variety of arylated pyridines.

Experimental

Compounds **1b** and **1d** were prepared by a literature procedure.[11] The preparation of compound **6b** from 2-bromo-6-iodo-3-methoxypyridine **5b** is representative. Other Suzuki reactions were performed under similar conditions.

A mixture of compound **5b** (0.5 g, 1.59 mmol), phenylboronic acid (0.15 g, 1.59 mmol), 2 M aqueous Na_2CO_3 solution (5 mL), $Pd(PPh_3)_4$ (0.08 g) in dimethoxyethane (15 mL) was heated at reflux with stirring (24 h) under an atmosphere of nitrogen. After cooling to room temperature the reaction mixture was evaporated and CH_2Cl_2 (15 mL) and water (5 mL) were added to the residue. The organic layer was separated, washed with water (3 × 5 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by column chromatography over silica gel (eluent; ethyl acetate–petroleum ether bp 40–60 °C 3 : 7) giving the product **6b** as a cream coloured solid (0.29 g, 70%). Compounds **7b** and **10b** crystallised from the cooled (room temperature) reaction mixture and were collected by filtration.

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