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



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## 2-Bromo-6-iodo-3-methoxypyridine 5b yielded monoarylated 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<sup>1</sup> and Promothiocin A<sup>2</sup> 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<sup>3</sup> 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.<sup>4</sup> In view of the current general interest in arylated pyridine derivatives, <sup>5-7</sup> 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



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.<sup>8</sup> 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.<sup>9,10</sup>

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

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Pd(PPh<sub>3</sub>)<sub>4</sub> 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<sup>8</sup> 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)



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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	Pyridine	Arylated product	Ar <sup>1</sup>	Ar <sup>2</sup>	Mp/°C	Yield (%) <sup>a</sup>
	5b	6b	Ph	_	110	70
	5c	6c	Ph	_	84-86	62
:	5b	7b	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	_	199-200	96
:	5b	8b	4-MeC <sub>6</sub> H <sub>4</sub>	_	109-110	75
:	5b	9b	2-Thienyl	_	100-102	57
	6b	10b	Ph	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	90–94	60
	7b	11b	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	122-124	44
	7b	12b	$3-NO_2C_6H_4$	4-MeC <sub>6</sub> H <sub>4</sub>	124-126	43
	8b	13b	4-MeC <sub>6</sub> H <sub>4</sub>	$3-NO_2C_6H_4$	102-106	87
	9b	14b	2-Thienyl	Ph	116-120	67
<sup>a</sup> Yields refer to isolated compounds. All compounds have been fully characterised.						

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

## Acknowledgements

Experimental

Compounds **1b** and **1d** were prepared by a literature procedure.<sup>11</sup> 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<sub>2</sub>CO<sub>3</sub> solution (5 mL), Pd(PPh<sub>3</sub>)<sub>4</sub> (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<sub>2</sub>Cl<sub>2</sub> (15 mL) and water (5 mL) were added to the residue. The organic layer was separated, washed with water (3 × 5 mL), dried (MgSO<sub>4</sub>), 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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