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Synthesis of 3-Amino-4-phenylpyridines: a Novel Strategy for the Preparation of CD Ring Models of Streptonigrin

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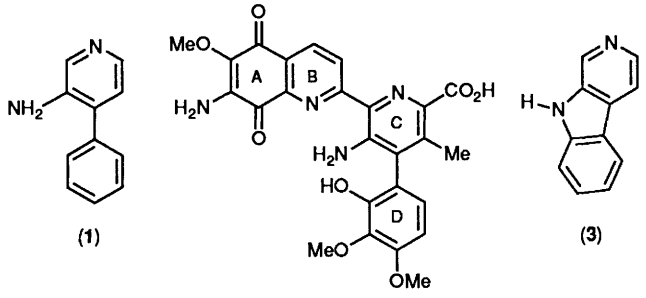
An efficient synthesis of 3-amino-4-phenylpyridine derivatives is reported. 3-Pivaloylaminopyridines were lithiated by butyl-lithium before reaction with iodine as electrophile to afford 4-iodo-3-pivaloylaminopyridines. Cross-coupling of the latter with suitable phenylboronic acids gives CD ring models of streptonigrin.

The 3-amino-4-phenylpyridine unit (**1**) occurs in alkaloids of biological interest, such as compounds of the streptonigrin series (**2**)[1] and is an interesting starting material for the synthesis of the β-carbolines (**3**).[2] Three total syntheses of



(1) (2) (3)

Scheme 1.

streptonigrin have been already described.[3–5] In each of them the required 4-phenylpyridine moiety has been elaborated by construction of the pyridine ring starting from substituted benzenes. Nonregiospecific reactions[4,5] as well as complex multistep functionalization of polycyclic structures only allowed poor overall yields. Thus the research of a convergent pathway to the streptonigrin skeleton was an interesting challenge for us and we decided to study a general methodology based on the coupling of the three main units of the structure: the quinoline, pyridine, and phenyl blocks.

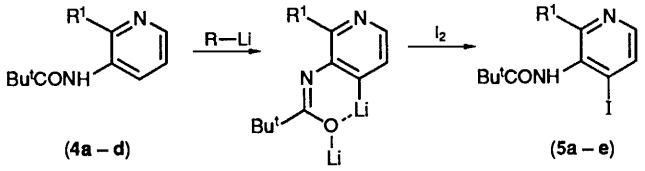
As the first part of this work we report here on a new synthesis of 3-amino-4-phenylpyridine derivatives (**1**) in two steps starting from 3-pivaloylaminopyridines (**4**) using the general palladium-catalyzed cross-coupling strategy in connection with the lithiation reaction.[6]

In previous papers we described a convenient method of functionalization of 3-pivaloylaminopyridines at the C-4 position by metallation.[7,8] This methodology has been used to introduce an iodo group at the C-4 position: lithiation of 3-pivaloylaminopyridines (method a: BuLi 2.5 equiv., Et_2O, −10 °C) followed by iodation (−70 °C to −10 °C) afforded the 4-iodopyridines (**5**) in moderate to good yields (55–75%) (Table 1). It should be pointed out that 2-butyl-4-iodo-3-pivaloylaminopyridine (**5**) (R^1 = Bu) is obtained in 25% yield under the previous conditions starting from the corresponding 2-chloro-3-pivaloylaminopyridine (**4**; R^1 = Cl). Nucleophilic substitution of chlorine occurs at the required lithiation temperature. This

Table 1. Synthesis of 4-iodo-3-pivaloylaminopyridines by lithiation of 3-pivaloylaminopyridines using iodine as electrophile.

Compound	R^1	Method	Yield (%)
(**5a**)	H	a	75
(**5b**)	OMe	a	71
(**5c**)	NHCOBu^t	a	55
(**5d**)	Bu	a	25
(**5e**)	Cl	b	18

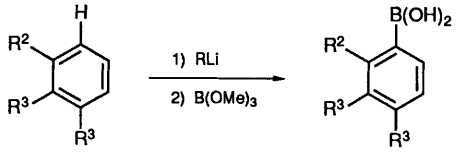
reaction could be avoided if t-butyl-lithium was used at lower temperature (method b: Bu^{t}Li 1.9 equiv., Et_2O, −50 °C). The chloro derivative (**5**; R^1 = Cl) was then selectively obtained but in low yield (18%).



(**4a–d**) (**5a–e**)

Scheme 2.

4-Iodopyridines (**5**) were submitted to a cross-coupling reaction with various phenylboronic acids (**6**).[9] [These compounds were most often prepared by directed metallation followed by boronation with $B(OMe)_3$].[10] Cross-coupling reactions were carried out following the Susuki's[11] procedure [(**5**) 1 equiv., (**6**) 1.2 equiv., $Pd(PPh_3)_4$ (3%), 2M aq. Na_2CO_3, toluene, 12 h, reflux], which led to the expected 4-phenyl-3-pivaloylaminopyridines (**7**) in good yields (68–95%) (Table 2).[12]



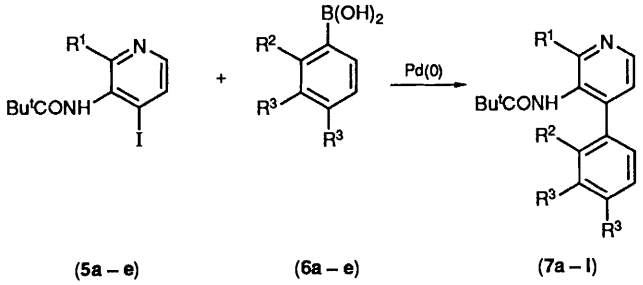
(**6a–e**)

Scheme 3.

The 2-substituted 4-phenyl-3-pivaloylaminopyridines (**7**) have been obtained in two steps from the corresponding 3-pivaloylaminopyridines in good overall yields. The C-2 substituent on the pyridine ring is of great interest in view of

Table 2. Cross-coupling reactions of 4-iodo-3-pivaloylaminopyridines with phenylboronic acids catalysed by Pd^0.

Compd. (5)	R^1	Compd. (6)	R^2, R^3	(7)	Yield (%)
(5a)	H	**(6a)**	H, H	**(7a)**	95
	H	**(6b)**	OMe, H	**(7b)**	80
	H	**(6c)**	$CONPr^i_2$, H	**(7c)**	85
	H	**(6d)**	$OCONEt_2$, H	**(7d)**	87
	H	**(6e)**	$OCONEt_2$, OMe	**(7e)**	80
(5b)	$NHCOBu^t$	**(6a)**	H, H	**(7f)**	74
	$NHCOBu^t$	**(6e)**	$OCONEt_2$, OMe	**(7g)**	72
(5c)	OMe	**(6a)**	H, H	**(7h)**	95
	OMe	**(6b)**	H, OMe	**(7i)**	68
	OMe	**(6c)**	$CONPr^i_2$, H	**(7j)**	93
	OMe	**(6d)**	$OCONEt_2$, OMe	**(7k)**	88
(5d)	Cl	**(6a)**	H, H	**(7l)**	70



(5a – e) (6a – e) (7a – l)

Scheme 4.

grafting other substrates at this position for the elaboration of more complex triaryl compounds.

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