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7-Azaindoles via carbolithiation of vinyl pyridines

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Abstract—The sequential reactions of a pyridine vinylation and alkene carbolithiation constitutes a new route to substituted 7-azaindoles. The methodology involves a reaction sequence of controlled carbolithiation of the vinyl double bond, subsequent trapping of the formal di-anion intermediate with a suitable electrophile, followed by an in situ ring closure and dehydration. The reaction sequence allows for aryl, heteroaryl, alkyl and keto substituents to be included at different positions around the heterocycle.

1. Introduction

The intermolecular carbolithiation of alkenes and alkynes has recently emerged as a profitable approach to target-directed synthesis.[1] The synthetic potential of carbolithiation lies in the fact that both a new carbon–carbon and carbon–lithium bond are generated in tandem. This allows for further in situ transformations to be carried out at the newly created carbon–lithium centre, which can be incorporated into novel synthetic designs. This methodology has been applied to the formation of carbocycles[2] and we have recently developed unique methods for the formation of indoles,[3] quinolines[4] and stereoselective alkene synthesis.[5] As an expansion of this work we have now addressed the 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine), as interest in it as a functional heterocyclic scaffold continues to intensify (Fig. 1).[6] 7-Azaindoles can be considered as a one nitrogen analogue of the indole ring system with the substitution of C-7 by a basic nitrogen atom often modifying the pharmacological properties of known indole pharmacophores. This has given rise to the synthesis of an increasing number of such derivatives with the potential to address a spectrum of applications.[7] For example, 7-azaserotonin and 7-azatryptophan are known to impart unique medicinal and biophysical properties when compared to their indole counterparts, tryptophan and serotonin.[8] Additionally, numerous potential pharmaceutical uses such as protein kinase inhibitors, H_1 antagonists and PPAR agonists are being currently being investigated.[9]

Figure 1. 7-Azaindole.

To date, synthetic routes to the 7-azaindole scaffold have primarily focused on modified indole syntheses such as the Fischer,[10] Madelung,[11] or transition metal catalysed cross-coupling/heteroannulation of 2-amino-3-halo-pyridines with alkynes[12] or ketones.[13] Additional approaches have utilised 2-aminobenzyl carbanion intermediates[14] and the regioselective opening of 2-chloro-3-oxiran-2-ylpyridines with amines, followed by nucleophilic aromatic substitution and in situ dehydration.[15]

2. Results and discussion

The synthetic starting point was the commercially available 2-aminopyridines **1a–d**, which were *N*-protected with pivaloyl chloride, using standard procedures, to provide compounds **2a–d** (Scheme 1).[16] Subsequent directed pyridine lithiation at C-3 with *n*-BuLi and in situ reaction with dibromoethane generated the 3-bromo-pyridin-2-ylamines **3a–d** with yields in the range of 81–25%.[17] The low yield of **3b** was due to the competitive formation of the 4-methyl brominated product. The route to *N*-methyl substituted analogue, 3-bromo-5-methyl-pyridin-2-yl-methylamine, **3e** was carried out according to literature procedures (Scheme 1, inset).[18]

The vinylation of **3a–e** was achieved via Suzuki–Miyaura cross-coupling with 0.5 molar ratio of 2,4,6-trivinylcyclotriboroxane–pyridine complex **4** (Table 1). In each case all the starting substrate was consumed and the desired 3-vinyl-pyridin-2-ylamine products **5a–e** were isolated in good to

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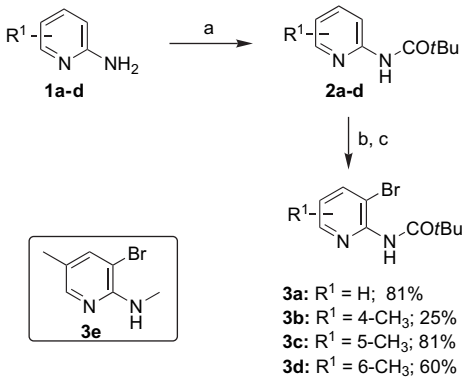
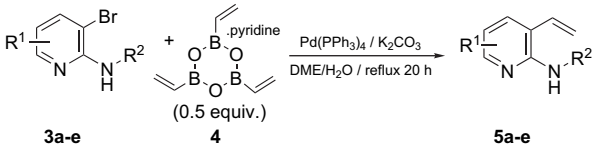


Scheme 1. Reagents and conditions: (a) *t*-BuCOCl, TEA, CH_2Cl_2, 0 °C, 1 h; (b) *n*-BuLi, THF, −30 to 0 °C, 5 h; (c) $Br(CH_2)_2Br$, −78 °C to rt, 1 h.

excellent yields. This versatile vinylation reagent has previously proven an effective substitute for vinyl boronic acid in coupling reactions with arylhalide substrates.[19] This provided a range of starting substrates functionalized on the pyridine ring at C-4, 5 and 6 and on the 2-amino group with pivaloyl (CO*t*-Bu) and alkyl (Me) groups to examine our carbolithiation methods.

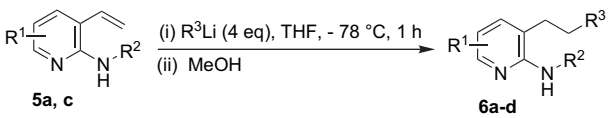
Table 1. Cross-coupling of **3a–e** with a vinyl boronic acid equivalent



Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**3a**	H	CO*t*-Bu	**5a**	85
2	**3b**	4-Me	CO*t*-Bu	**5b**	60
3	**3c**	5-Me	CO*t*-Bu	**5c**	83
4	**3d**	6-Me	CO*t*-Bu	**5d**	75
5	**3e**	5-Me	Me	**5e**	86

To the best of our knowledge, no carbolithiation reaction has previously been described on vinyl-pyridine derivatives. As such, the reaction of **5** with a range of organolithiums, followed by protonation, thereby generating the substituted pyridines **6** was carried out as a precursor study (Table 2). We used **5a** and **5c** as model substrates, with reactions carried out in THF at −78 °C. Our results showed that carbolithiation is highly effective with primary, secondary and

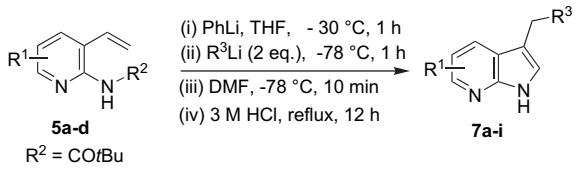
Table 2. Carbolithiation of substituted 3-vinyl-pyridin-2-ylamines



Entry	Substrate	R^1	R^2	R^3	Product	Yield[a] (%)
1	**5a**	H	CO*t*-Bu	*t*-Bu	**6a**	85
2	**5a**	H	CO*t*-Bu	*s*-Bu	**6b**	88
3	**5a**	H	CO*t*-Bu	*n*-Bu	**6c**	70
4	**5c**	5-Me	CO*t*-Bu	*t*-Bu	**6d**	79
5	**5a**	H	CO*t*-Bu	Ph	—	0[b]

[a] Isolated purified yield.
[b] Starting material recovered.

Table 3. Synthesis of 3,4-, 3,5- and 3,6- substituted 7-azaindoles



Entry	Substrate	R^1	R^3	7-Azaindole	Yield[a] (%)
1	**5a**	H	*t*-Bu	**7a**	40[b]
2	**5a**	H	*t*-Bu	**7a**	69
3	**5a**	H	*s*-Bu	**7b**	78
4	**5a**	H	*n*-Bu	**7c**	63
5	**5b**	4-Me	*t*-Bu	**7d**	75
6	**5c**	5-Me	*t*-Bu	**7e**	65
7	**5c**	5-Me	*s*-Bu	**7f**	81
8	**5c**	5-Me	*n*-Bu	**7g**	75
9	**5d**	6-Me	*t*-Bu	**7h**	82
10	**5d**	6-Me	*s*-Bu	**7i**	80

[a] Isolated purified yield.
[b] Conditions: (i) *t*-BuLi (2 equiv), −78 °C, 1 h; (ii) DMF, −78 °C, 10 min; (iii) 3 M HCl, reflux, 12 h.

tertiary alkyllithiums with the alkyl addition products **6a–d** isolated in good yields (Table 2, entries 1–4). Despite the known propensity of the pyridine heterocycle to undergo addition reactions with alkyllithiums, under these conditions no addition of alkyllithium to the pyridine ring was observed.[20] The reaction was also attempted with phenyllithium, but no addition to the vinyl double bond was observed and only starting material was isolated upon reaction work-up (entry 5).

Having identified conditions under which vinyl carbolithiation could be achieved, we proceeded to react the generated intermediate lithiated species with DMF, substituted nitriles or acetic anhydride as electrophile in order to develop our route to 7-azaindoles. The carbolithiation of **5a** with *t*-BuLi and subsequent treatment with DMF was followed by mild acidification. The extracted crude product was heated under reflux with 3 M hydrochloric acid to generate the desired azaindole **7a** in a moderate 40% yield (Table 3, entry 1). Unexpectedly, a byproduct of the pivaloyl-deprotected **6a** was also isolated in significant quantities. A

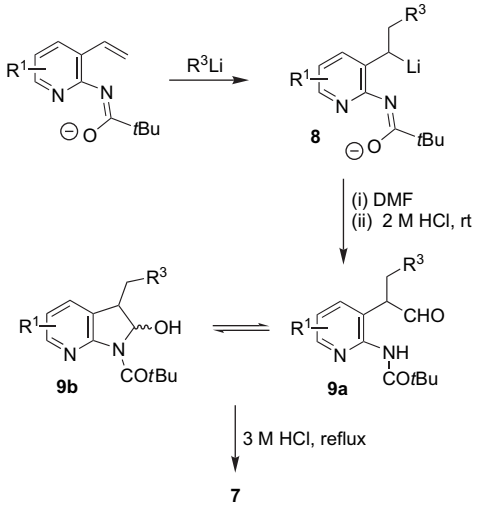


Figure 2. Reaction sequence.