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Carbolithiation of vinyl pyridines as a route to 7-azaindoles

Bertrand Cottineau and Donal F. O'Shea*

Centre for Synthesis and Chemical Biology, Conway Institute, Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

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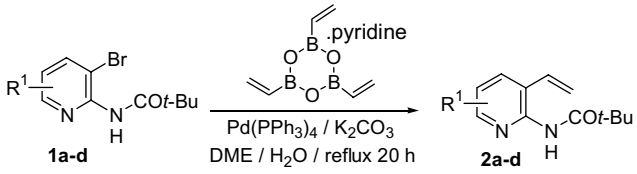
Abstract—An effective synthesis of the 7-azaindole ring system has been developed from substituted 2-amino-3-vinyl pyridines. The methodology involves a novel cascade reaction sequence of controlled carbolithiation of the vinyl double bond, subsequent trapping of the intermediate organolithium with a suitable electrophile, followed by ring closure and dehydration.

7-Azaindoles (1*H*-pyrrolo[2,3-*b*]pyridines) are the most widely studied one nitrogen analogue of the indole ring system.[1] The substitution of indole C-7 by an sp^2 hybridised nitrogen provides a construct containing a hydrogen bond donor and acceptor in a rigid three-atom arrangement. The introduction of the basic nitrogen atom can modify the medicinal properties of known indole pharmacophores, which has led to the synthesis of an increasing number of such analogues.[2] In recent years a wide range of potential pharmaceutical[3] and agrochemical[4] applications for this class of heterocycle have been investigated.

To date, synthetic routes to the 7-azaindole scaffold have primarily focused on modified indole syntheses such as the Fischer,[5] Madelung[6] routes, or transition metal catalysed cross-coupling/heteroannulation of 2-amino-3-halo-pyridines with alkynes[7] or ketones.[8] Our goal was to devise a new route based on a vinyl carbolithiation of 2-amino-3-vinyl pyridines as the key synthetic step which offers the potential advantage of directly introducing further molecular diversity onto the ring system. The use of carbolithiation methodology has seen increasing use as a powerful method for complex ring synthesis.[9] We have previously demonstrated a successful carbolithiation approach for the generation of diversely functionalised indoles from *ortho*-amino styrenes.[10]

The synthesis of our required starting materials, the substituted 3-vinyl-pyridin-2-ylamines **2a–d** was readily achieved in high yields by the Suzuki-Miyaura cross coupling of **1a–d** with the 2,4,6-trivinylcyclotriboroxane-pyridine complex, which has been previously shown to be an effective surrogate for vinyl boronic acid in coupling reactions (Scheme 1, Table 1).[11,12] This provided starting substrates **2** functionalised on the pyridine ring at either C-4, -5 or -6 and on the 2-amino group with a pivaloyl (CO*t*-Bu) group as a representative sample to test the synthetic protocol.

To the best of our knowledge, no carbolithiation reaction has been previously described on vinyl-pyridine derivatives so, as a precursor to our azaindole study, the reaction of **2** with a range of organolithiums, followed by aqueous quenching of the intermediate



Scheme 1. Vinylation of **1a–d**.

Table 1. Vinylation of **1a–d**

Entry	Substrate	R^1	Product	Yield (%)
1	**1a**	H	**2a**	85
2	**1b**	4-Me	**2b**	80
3	**1c**	5-Me	**2c**	83
4	**1d**	6-Me	**2d**	75

Keywords: 7-Azaindole; Carbolithiation; Cascade reaction.
* Corresponding author. Tel.: +353 1 7162425; e-mail: donal.f.oshea@ucd.ie

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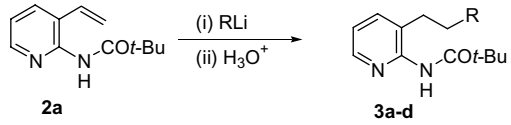
lithiated species was carried out. We used **2a** as a model substrate with reactions carried out in THF at −78 °C (Scheme 2). Our results showed that carbolithiation is highly effective with primary, secondary and tertiary alkyllithiums with no additives being required (Table 2, entries 1–3).[13] Under these conditions no addition of alkyllithium onto the pyridine ring was observed. This reaction was also attempted with phenyllithium but no addition to the vinyl double bond was observed (entry 4).

Having determined that vinyl carbolithiation could be effectively achieved with **2**, we proceeded to react the generated intermediate lithiated species with DMF as the electrophile in order to develop our route for the synthesis of 7-azaindoles (Scheme 3). The expected reaction sequence would involve NH deprotonation of **2** followed by carbolithiation of the vinyl double bond thereby generating a new lithiated intermediate, which upon reaction with the electrophile would generate an aldehyde precursor. Acidification would then result in ring closure by intramolecular reaction of the reacted electrophile and amino substituent, dehydration and *N*-pivaloyl deprotection to yield the product.

The reaction of **2a** with *t*-BuLi, subsequent treatment with DMF followed by acidification with hydrochloric acid did generate the desired azaindole **4a** in 40% yield (Table 3, entry 1). Unexpectedly, as a by-product of the pivaloyl-deprotected **3a** was also isolated in significant quantities. A possible explanation for this could be ineffective deprotonation of the amide prior to vinyl carbolithiation. This was overcome by a modification of the reaction procedure in which NH deprotonation

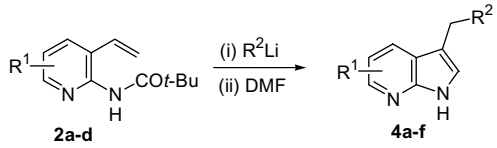


Scheme 2. Carbolithiation of **2a**.

Table 2. Carbolithiation of **2a**[a]

Entry	Substrate	R	Product	Yield (%)
1	**2a**	*t*-Bu	**3a**	85
2	**2a**	*s*-Bu	**3b**	88
3	**2a**	*n*-Bu	**3c**	70
4	**2a**	Ph	—	0[b]

[a] Conditions: (i) RLi (4 equiv), −78 °C, 1 h, THF; (ii) H_2O.
[b] Starting material recovered.



Scheme 3. Synthesis of 3-, 3,4-, 3,5- and 3,6-disubstituted-7-azaindoles.

Table 3. Synthesis of 3-, 3,4-, 3,5- and 3,6-disubstituted-7-azaindoles[a]

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

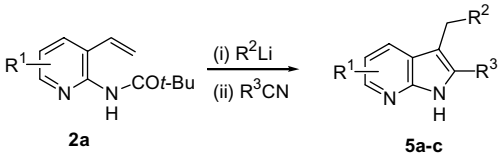
[a] Conditions: (i) PhLi (1.5 equiv) −30 °C, 1 h, THF; (ii) R^2Li (2 equiv), −78 °C, 1 h; (iii) DMF, −78 °C, 10 min; (iv) 3 M HCl, reflux, 12 h.
[b] Conditions: (i) R^2Li (2 equiv), −78 °C, 1 h; (ii) DMF, −78 °C, 10 min; (iii) 3 M HCl, reflux, 12 h.

of **2** was first carried out with phenyllithium prior to treatment with an alkyllithium. This improved the isolated yield of the 7-azaindole **4a** to 69% (entry 2).[14]

The sequence was extended to the reactions of **2a–d** with either *tert*-, *sec*- or *n*-butyllithium and DMF. This led to the generation of the 7-azaindoles **4b–f** in good yields (entries 3–7).

In order to facilitate the introduction of diversity at C-2 of the azaindole scaffold, we exploited substituted nitriles as electrophiles (Scheme 4). Thus treatment of generated organolithium intermediates with either benzo-, thiophene-2-carbo-, or 2,2-dimethylpropionitrile yielded the desired products after acidification (Table 4).[15,16] The 7-azaindoles **5a–c** were isolated in moderate to good yields and the procedure allowed introduction of various substituents on C-2 such as aryl, heteroaryl and sterically bulky alkyl groups.

The described organolithium addition–cyclisation methodology provides a new entry into the 7-azaindole ring system which is capable of facilitating the introduction of aryl, heteroaryl and alkyl substituents around the heterocycle scaffold. The use of organolithiation as the key synthetic step for the assembly of other cascade reaction sequences is currently under investigation.



Scheme 4. Synthesis of 2,3-disubstituted-7-azaindoles.

Table 4. Synthesis of 2,3-disubstituted-7-azaindoles[a]

Entry	Substrate	R^1	R^2	R^3	7-Azaindole	Yield (%)[a]
1	**2a**	H	*t*-Bu	Ph	**5a**	70
2	**2a**	H	*t*-Bu	*t*-Bu	**5b**	58
3	**2a**	H	*t*-Bu	C_4H_3S	**5c**	38

[a] Conditions: (i) PhLi (1.5 equiv), −30 °C, Et_2O, 1 h; (ii) R^2Li (2 equiv), −78 °C 1 h; (iii) R^3CN, 0 °C, 1 h; (iv) 12 M HCl, reflux, 12 h.

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12. Representative procedure for the synthesis of **2a–d**: A stirred solution of **1** (3.87 mmol) in DME (10 mL) under nitrogen was treated with palladium(0) tetrakistriphenylphosphine (0.19 mmol, 5 mol %). The reaction mixture was stirred at room temperature for 20 min and 2,4,6-trivinylcyclotriboroxane (1.94 mmol), potassium carbonate (3.87 mmol) and water (2.3 mL) were added. The reaction mixture was heated under reflux for 20 h, then after cooling to room temperature, water (20 mL) was added and the solution was extracted with diethyl ether (2×20 mL). The organic layers were combined, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to yield product **2**. Analysis for **2a**: white solid, (85%), mp 87–88 °C. IR (KBr plate): 3169, 2967, 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 9H), 5.22 (d, $J = 11.0$ Hz, 1H), 5.38 (d, $J = 17.6$ Hz, 1H), 6.59 (dd, $J = 11.0$, 17.6 Hz, 1H), 7.18 (dd, $J = 4.8$, 7.7 Hz, 1H), 7.69 (bs, 1H), 7.90 (dd, $J = 1.6$, 7.7 Hz, 1H), 8.32 (dd, $J = 1.6$, 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 27.6, 39.9, 116.5, 121.9, 128.0, 132.2, 135.0, 147.5, 148.1, 177.2. ES^+-MS: *m/z* 205 (75) $(M+H)^+$. HRMS: found $(M+H)^+$ 205.1351. $C_{12}H_{17}N_2O$ requires 205.1341. Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71; found: C, 70.35; H, 8.21; N, 13.61%.
13. Representative procedure for the synthesis of **3a–c**: A stirred solution of **2** (0.24 mmol) in dry THF (5 mL) at −78 °C under nitrogen was treated dropwise with the organolithium (0.98 mmol) over 10 min. The reaction mixture was stirred at −78 °C for a further 1 h following which it was treated with water (1 mL). The mixture was allowed warm to room temperature, extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography to yield the product. Analysis for **3a**: white solid, (85%), mp 102–103 °C. IR (KBr plate): 3220, 3161, 1678, 1594 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (s, 9H), 1.40 (s, 9H), 1.45–1.48 (m, 2H), 2.56–2.62 (m, 2H), 7.18 (dd, $J = 7.6$, 4.7 Hz, 1H), 7.63 (dd, $J = 7.6$, 1.5 Hz, 1H), 8.04 (bs, 1H), 8.30 (dd, $J = 4.7$, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.1, 27.9, 29.5, 39.7, 44.3, 122.2, 134.4, 138.9, 146.0, 148.1, 177.8. ES^+-MS: *m/z* 263 (100) $(M+H)^+$. HRMS: found $(M+H)^+$ 263.2123. $C_{16}H_{27}N_2O$ requires 263.2123. Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68; found: C, 72.88; H, 9.65; N, 10.81%.
14. Representative procedure for the synthesis of **4a–f**: A stirred solution of **2** (0.23 mmol) in dry THF (5 mL) at −78 °C under nitrogen was treated dropwise with phenyllithium (0.34 mmol) over 10 min. The reaction was warmed to −30 °C, stirred at this temperature for 1 h and recooled to −78 °C. Alkyllithium (0.46 mmol) was added over 5 min and the reaction stirred at −78 °C for a further 1 h. DMF (2.3 mmol) was added and the reaction stirred for 20 min at −78 °C. Aqueous HCl (2 M, 3 mL) was added and the reaction mixture warmed to room temperature and then added carefully, over 10 min, to a saturated potassium carbonate solution (20 mL). The solution was extracted diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was treated with aqueous HCl (3 M, 10 mL) and the solution heated under reflux for 12 h. The reaction mixture was cooled to room temperature, slowly added to a saturated potassium carbonate solution (20 mL) and extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under

vacuum. The residue was purified by silica gel column chromatography to yield the product **4**. Analysis for **4a**: white solid, (69%), mp 151–152 °C. IR (KBr plate): 3143, 3089, 2947, 2896, 2864, 1581 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 9H), 2.61 (s, 2H), 7.06 (dd, $J = 4.8$, 7.9 Hz, 1H), 7.12 (s, 1H), 7.91 (d, $J = 7.9$ Hz, 1H), 8.29 (d, $J = 4.8$ Hz, 1H), 10.80 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 32.2, 39.4, 112.4, 115.2, 121.7, 124.0, 128.1, 141.9, 148.7. ES^+-MS: *m/z* 189 (100) $(M+H)^+$. HRMS: found $(M+H)^+$ 189.1384. $C_{12}H_{17}N_2$ requires 189.1392. Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88; found: C, 76.23; H, 8.64; N, 14.73%.

15. Improved results were obtained when using diethyl ether as solvent instead of THF.
16. Representative procedure for the synthesis of **5a–c**: A stirred solution of **2** (0.39 mmol) in dry diethyl ether (8 mL) at −78 °C under nitrogen was treated dropwise with phenyllithium (0.58 mmol) over 10 min. The reaction was warmed to −30 °C, stirred at this temperature for 1 h and recooled to −78 °C. Alkyllithium (0.78 mmol) was added over 10 min and the reaction stirred at −78 °C for a further 1 h. Nitrile (19.5 mmol) was added and the reaction stirred for 1 h at 0 °C. Aqueous HCl (2 M, 3 mL) was added and the reaction mixture warmed to room temperature and added to a saturated potassium carbonate solution (20 mL). The solution was extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was passed through a short bed of silica eluting with diethyl ether/pentane (7:3) and the organic solvent removed under vacuum. The residue was treated with 12 M HCl (10 mL) and the solution heated under reflux for 12 h. The reaction mixture was cooled to room temperature, carefully added over 10 min to a saturated potassium carbonate solution (30 mL) and extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography using ether/cyclohexane (6:4) as eluent to yield the product **5a–c**. Analytical data for **5a**: white solid, (70%), mp 175–176 °C. IR (KBr plate): 3134, 3081, 3035, 2955, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.76 (s, 9H), 2.91 (s, 2H), 7.06 (dd, $J = 4.8$, 7.9 Hz, 1H), 7.38–7.43 (m, 1H), 7.49–7.54 (m, 2H), 7.73 (d, $J = 7.0$ Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 1H), 8.03 (d, $J = 4.8$, 1H), 12.7 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.0, 34.2, 37.4, 109.0, 115.1, 123.5, 128.4, 128.7, 129.1, 134.6, 134.6, 137.2, 141.6, 148.8. ES^+-MS: *m/z* 265 (100) $(M+H)^+$. HRMS: found $(M+H)^+$ 265.1701. $C_{18}H_{21}N_2$ requires 265.1705. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60; found: C, 81.35; H, 7.65; N, 10.47%.