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A Convenient Palladium-Catalyzed Azaindole Synthesis

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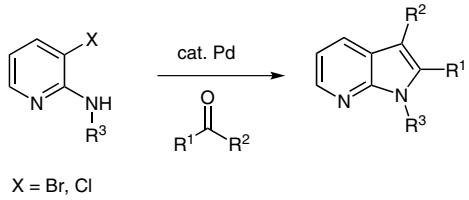

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Abstract A one-pot protocol is described which allows direct access to azaindoles from amino-halopyridines and ketones.

Key words microwave, palladium catalysis, ketone arylation, cyclization, azaindoles

The azaindole core has generated growing interest within the medicinal chemistry community[1] and thus there have been significant efforts to improve access to these compounds in recent years.[2] However, there are still limited methods available to prepare azaindoles.[3] Many of the established methods used to prepare indoles work poorly when applied to azaindoles.

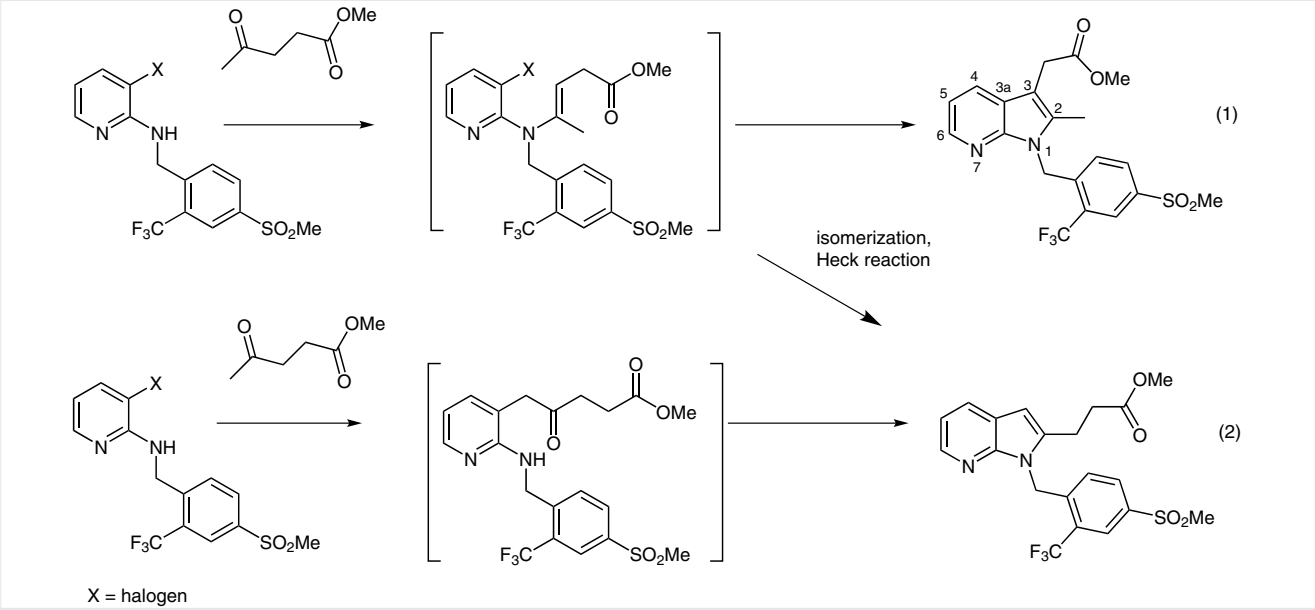
We were interested in an efficient method to access the compound described in Scheme 1 (eq. 1), which is a potential precursor to a development candidate in the Novartis pipeline. It was supposed that such a 7-azaindole derivative could be prepared by a reaction cascade involving enamine formation followed by intramolecular Heck reaction using a 2-amino-3-halopyridine and a substituted ketone as substrates (Scheme 1).[3a,b,g] With the goal of effecting the reaction type described in Scheme 1 (eq. 1), a screen of palladium-based catalyst systems and reaction conditions was carried out.[4] In general, reactivity was very low and only the starting 2-amino-3-halopyridine or the des-halo derivative were observed by LC–MS. The only experiments to provide modest conversion into 7-azaindoles were those in which the substituted ketone, in this case methyl levulinate, was used as the reaction solvent.[4] Using a catalyst described in the literature[3a] to effect such azaindole syntheses, namely bis(tri-*tert*-butylphosphine)palladium(0), mixtures of the two products described in Scheme 1 (eq. 1 and 2) were observed, with the product of eq. 2 (Scheme 1) being formed preferentially. Interestingly the use of the XPhos first-generation catalyst yielded this product as a single regioisomer, likely via the alternate order of chemical reactions – that is, ketone arylation followed by enamine formation (Scheme 1, eq. 2).[5]

Although both reaction pathways described in Scheme 1 have been described previously,[3a,e] there is only a single example that uses a nonsymmetrical alkyl ketone[3e] and, in this example, higher loadings of palladium catalyst were required (20 mol%). We therefore decided to examine whether the catalyst system identified (Scheme 1, eq. 2) could provide a general approach to azaindole synthesis using various alkyl-substituted ketones.

First, the reaction of a range of 2-amino-3-halopyridine derivatives **1** with acetone was investigated (Table 1). Pleasingly, the reaction worked equally well with both bromide (**1a**) and chloride (**1b**) derivatives (Table 1, entries 1 and 2). Furthermore, unsubstituted 2-amino-3-bromopyridine (**1c**) could be successfully converted into the target 7-azaindole (Table 1, entry 3), although a longer reaction time was required. A *tert*-butyldiphenylsilyl protecting group (Table 1, entry 4) did not survive the reaction conditions, and only the 2-amino-3-bromopyridine (**1c**) and product **2b** could be observed by LC–MS. The same was true in the case of the *tert*-butoxycarbonyl protecting group (Table 1, entry 5).

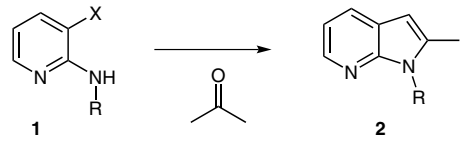
The reaction conditions were then applied to a range of different ketones (Table 2) using 2-aminobenzyl-3-bromopyridine **1a** as the test substrate.

In the case of 2-methyl levulinate the 7-azaindole synthesis proceeded smoothly to provide product **3a** in acceptable yield (Table 2, entry 1). For the unsymmetrical ketones 2-pentanone and 4-methylpentan-2-one (Table 2, entries 2 and 3) the products **3b** and **3c** were prepared in good yield; in these cases the excess ketone could be successfully removed in vacuo. In the case of a more sterically hindered ketone, 3,3-dimethylbutan-2-one (Table 2, entry 4), a mod-



Scheme 1 (1) Targeted 7-azaindole synthesis with methyl levulinate. (2) Observed 7-azaindole synthesis with methyl levulinate. *Reagents and conditions*: $MgSO_4$, methyl levulinate, K_3PO_4 (3 equiv), Xphos first-generation catalyst (4 mol%), AcOH (1 equiv), 140 °C, 18 h.

Table 1 Synthesis of 7-Azaindole Products **2**[a]



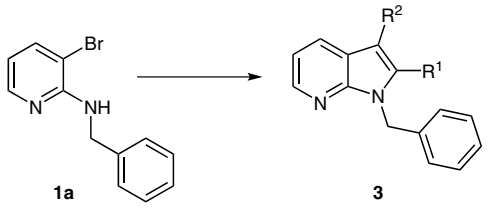
Entry	2-Amino-3-halo-pyridine derivative	Reaction time (h)	7-Azaindole product	Isolated yield (%)[b]
1	**1a** R = Bn, X = Br	6	**2a** R = Bn	80
2	**1b** R = Bn, X = Cl	6	**2a** R = Bn	79
3	**1c** R = H, X = Br	48	**2b** R = H	59
4	**1d** R = TBDPS, X = Br	48	**2c** R = TBDPS	–
5	**1e** R = Boc, X = Br	48	**2d** R = Boc	–

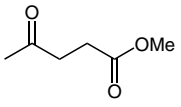
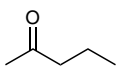
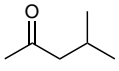
[a] Reaction conditions: 2-amino-3-halopyridine derivative (1.9 mmol), $MgSO_4$ (1715 mg), acetone (7.5 mL), AcOH (1.9 mmol), K_3PO_4 (3.8 mmol), chloro(2-dicyclohexylphosphino-2′,4′6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (0.076 mmol), 140 °C.
[b] Single regioisomer.

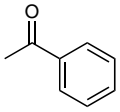
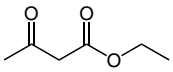
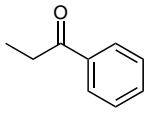
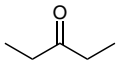
erate yield of the product **3d** could also be obtained although the reaction required longer to reach completion (16 h). Acetophenone (Table 2, entry 5) also provided the expected product **3e** in acceptable yield.

Two examples were tested containing an ethyl rather than a methyl ketone (Table 2, entries 7 and 8). In both cases these reactions did provide some of the desired product (**3g** 26% and **3h** 28% yield); however, a major byproduct in these cases was the dehalogenated starting material **1a**. Presumably the first step in the process (α-arylation of the ketone) is slower for an ethyl ketone compared to a methyl ketone and therefore the dehalogenation pathway becomes competitive.[6]

Table 2 Synthesis of 7-Azaindole Products **3**[a]



Entry	Ketone substrate	7-Azaindole product	Reaction time (h)	Isolated yield (%)
1		**3a** $R^1 = CH_2CH_2CO_2Me$, R^2 = H	2	73
2		**3b** R^1 = *n*-Pr, R^2 = H	6	83
3		**3c** R^1 = *i*-Bu, R^2 = H	6	83
4		**3d** R^1 = *t*-Bu, R^2 = H	16	65

Entry	Ketone substrate	7-Azaindole product	Reaction time (h)	Isolated yield (%)
5		**3e** R^1 = Ph, R^2 = H	16	73
6		**3f** R^1 = CH_2CO_2Me, R^2 = H	6	59
7		**3g** R^1 = Ph, R^2 = Me	48	26
8		**3h** R^1 = Me, R^2 = Me	16	28

[a] Reaction conditions according to general procedure A:[7] 2-amino-3-halopyridine derivative (1.9 mmol), $MgSO_4$ (1715 mg), ketone (7.5 mL), AcOH (1.9 mmol), K_3PO_4 (3.8 mmol), chloro(2-dicyclohexylphosphino-2′,4′6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (0.076 mmol), 140 °C.

Finally, attention was turned towards the synthesis of other azaindole regioisomers from the corresponding amino-bromopyridines **4**. As described previously in Table 1, the 2-amino-3-bromopyridine provided the target product **2b** in modest yield (59%). However, in the case of 2-bromo-3-aminopyridine **4a** only dimerization of this starting material could be detected (LC–MS), presumably due to the propensity of the 2-bromo substituent to undergo substitution. Pleasingly, the other regioisomers tested (Table 3, entries 3 and 4) did lead to the expected products **5b** and **5c** albeit in lower yields than for the 7-azaindole derivative **2b**.

In summary, the procedure described herein allows for rapid and convenient access to a variety of 2-substituted 7-azaindole derivatives in good yield from methyl ketones and 2-amino-3-halopyridines. Two examples of 2,3-substituted 7-azaindoles could also be prepared using this methodology, albeit in lower yield. Other regioisomeric bromoaminopyridines were tested under the standard reaction conditions, providing both 5- and 6-azaindole derivatives.

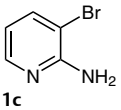
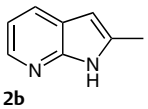
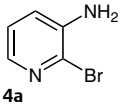
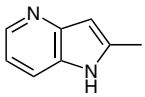
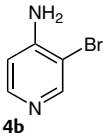
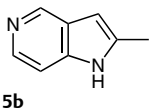
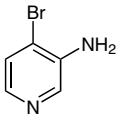
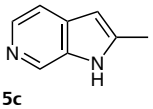
Acknowledgment

We would like to acknowledge Dr Fabrice Gallou for helpful discussions in the preparation of this manuscript.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379492.

Table 3 Synthesis of Other Azaindole Regioisomers[a]

Entry	Substrate	Target product	Isolated yield (%)
1	 **1c**	 **2b**	59
2	 **4a**	 **5a**	0
3	 **4b**	 **5b**	28
4	 **4c**	 **5c**	26

[a] Reaction conditions (entries 2–4): Compound **2b** was prepared using general procedure A,7 compounds **4a–c** were subjected to the conditions described in general procedure B:7 amino-3-halo pyridine derivative (1.5 mmol), $MgSO_4$ (1354 mg), acetone (5.9 mL), AcOH (1.5 mmol), K_3PO_4 (3.0 mmol), and chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (0.06 mmol), 140 °C, 48 h.

References and Notes

(1) For examples of azaindoles exhibiting biological activity, see: (a) Prudhomme, M. *Eur. J. Med. Chem.* **2003**, *38*, 123. (b) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080. (c) Blaazer, A. R.; Lange, J. H. M.; van der Neut, M. A. W.; Mulder, A.; den Boon, F. S.; Werkman, T. R.; Kruse, C. G.; Wadman, W. J. *Eur. J. Med. Chem.* **2011**, *46*, 5086. (d) Sandham, D. A.; Arnold, N.; Aschauer, H.; Bala, K.; Barker, L.; Brown, L.; Brown, Z.; Budd, D.; Cox, B.; Docx, C.; Dubois, G.; Duggan, N.; England, K.; Everett, B.; Furegati, M.; Hall, E.; Kalthoff, F.; King, A.; Leblanc, C. J.; Manini, J.; Meingassner, J.; Profit, R.; Schmidt, A.; Simmons, J.; Sohal, B.; Stringer, R.; Thomas, M.; Turner, K. L.; Walker, C.; Watson, S. J.; Westwick, J.; Willis, J.; Williams, G.; Wilson, C. *Bioorg. Med. Chem.* **2013**, *21*, 6582. (e) Lee, H. Y.; Pan, S. L.; Su, M. C.; Liu, Y. M.; Kuo, C. C.; Chang, Y. T.; Wu, J. S.; Nien, C. Y.; Mehndiratta, S.; Chang, C. Y.; Wu, S. Y.; Lai, M. J.; Chang, J. Y.; Liou, J. P. *J. Med. Chem.* **2013**, *56*, 8008. (f) Cheve, G.; Dayde-Cazals, B.; Fauvel, B.; Bories, C.; Yasri, A. WO 2014102377 A1 20140703, **2014**. (g) Dodd, R.; Cariou, K.; Gourdain, S.; Delabar, J. M.; Janel, N.; Rodrigues, L. F.; Dairou, J.; Denhez, C. WO 2014096093, A1 20140626, **2014**.

(2) For selected reviews on the synthesis of azaindoles, see: (a) Popowycz, F.; Routier, S.; Mérour, J.-Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 1031. (b) Song, J. J.; Reeves, T. J.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120. (c) Mérour, J.-Y.; Routier, S.; Suzenet, F.; Joseph, B. *Tetrahedron* **2013**, *69*, 4767.

(3) For selected examples of azaindole synthesis, see: (a) Nazaré, M.; Schneider, C.; Lindenscmidt, A.; Will, D. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 4526. (b) Lachance, N.; April, M.; Jolzy, M. A. *Synlett* **2005**, 2571. (c) Fang, Y. Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152. (d) de Mattos, M. C.; Alatorre-Santamaria, S.; Gotor-Fernandez, V.; Gotor, V. *Synthesis* **2007**, 2149. (e) Spergel, S. H.; Okoro, D. R.; Pitts, W. *J. Org. Chem.* **2010**, *75*, 5316. (f) Whelligan, D. K.; Thomson, D. W.; Taylor, D.; Hoelder, S. *J. Org. Chem.* **2010**, *75*, 11. (g) Majumdar, K. C.; Ganai, S.; Chattopadhyay, B.; Ray, K. *Synlett* **2011**, 2369. (h) Knapp, J. M.; Zhu, J. S.; Tantillo, D. J.; Kurth, M. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 10588. (i) Frischmuth, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 10084. (j) Leboho, T. C.; van Vuuren, S. F.; Michael, J. P.; de Koning, C. B. *Org. Biomol. Chem.* **2014**, *12*, 307.

(4) See Supporting Information for details of the initial screening experiments performed.

(5) When the 7-azaindole synthesis described in Scheme 1 was tested with acetone as solvent instead of methyl levulinate, the mass of the α-arylacetone could be detected by LC–MS (8%) along with 89% of the cyclized 7-azaindole product. Attempts to isolate this material via silica gel chromatography led to cyclization to the 7-azaindole.

(6) In the following paper on α-arylation of ketones there is a preference for arylation at the less hindered site, see: Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

(7) **General Procedure A**

To a microwave vial equipped with a magnetic stirrer was added 2-amino-3-halo pyridine derivative (1.9 mmol, 1 equiv), $MgSO_4$ (1715 mg), ketone (7.5 mL), and AcOH (0.109 mL, 1.9 mmol, 1 equiv). The reaction was purged with argon under stirring for 10 min at 22 °C. Then K_3PO_4 (807 mg, 3.8 mmol, 2 equiv) and chloro(2-dicyclohexylphosphino-2′,4′6′-triisopropyl-1,1′biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (56 mg, 0.076 mmol, 0.04 equiv) were added. The vial was closed, purged with argon under stirring for 10 min at 22 °C, and heated to 140 °C. Upon completion, the reaction mixture was filtered through silica that was subsequently rinsed with EtOAc. Concentration in vacuo provided the crude product which was purified as described in the Supporting Information or below.

General Procedure B

To a hydrogenation vial flushed with argon was added 2-amino-3-halo pyridine derivative (1.5 mmol, 1 equiv), $MgSO_4$ (1354 mg), acetone (5.9 mL), AcOH (0.086 mL, 1.5 mmol, 1 equiv), K_3PO_4 (637 mg, 3.0 mmol, 2 equiv), and chloro(2-dicyclohexylphosphino-2′,4′6′triisopropyl-1,1′biphenyl)[2-(2-aminoethyl)-phenyl]palladium(II) (44 mg, 0.06 mmol, 0.04 equiv). The vial was inserted into the hydrogenation apparatus, purged with nitrogen twice, and heated at 140 °C for 48 h. The reaction mixture was filtered through silica washing with acetone followed by 20% MeOH in acetone. Concentration in vacuo provided the crude product that was purified as described in the Supporting Information or below. Selected examples of azaindoles prepared:

Methyl 3-(1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)propanoate (3a)

Prepared following general procedure A, starting from *N*-benzyl-3-bromopyridin-2-amine (**1a**) and methyl levulinate. The reaction required 2 h heating at 140 °C. Purification by flash chromatography (20% *tert*-butyl methyl ether in heptanes, R_f = 0.18) followed by trituration with 2-methyl pentane gave the product as a white powder (406 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (obs. t, *J* = 7.6 Hz, 2 H), 3.00 (obs. t, *J* = 7.6 Hz, 2 H), 3.68 (s, 3 H), 5.59 (s, 2 H), 6.27 (s, 1 H), 7.02–7.09 (m, 3 H), 7.19–7.29 (m, 3 H), 7.85 (dd, *J* = 7.8, 1.5 Hz, 1 H), 8.29 (dd, *J* = 4.6, 1.6 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 22.2, 32.2, 44.8, 51.8, 97.3, 116.0, 120.3, 126.4, 127.3, 127.6, 128.7, 137.9, 140.0, 142.2, 148.6, 172.7. LC–MS: *m/z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_2^+$: 295.1; found: 295.1.

1-Benzyl-2-isobutyl-1*H*-pyrrolo[2,3-*b*]pyridine (3c)

Prepared following general procedure A, starting from *N*-benzyl-3-bromopyridin-2-amine (**1a**) and 4-methylpentan-2-one. The reaction required 6 h heating at 140 °C under microwave irradiation. Purification by flash chromatography (5% EtOAc in heptanes, R_f = 0.14) gave the product as an off-white solid (418 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.8 Hz, 6 H), 1.94 (obs. septet, *J* = 6.8 Hz, 1 H), 2.53 (dd, *J* = 6.8, 0.8 Hz, 2 H), 5.57 (s, 2 H), 6.28 (obs. s, 1 H), 6.98–7.03 (m, 2 H), 7.06 (dd, *J* = 7.7, 4.6 Hz, 1 H), 7.18–7.28 (m, 3 H), 7.85 (dd, *J* = 7.7, 1.6 Hz, 1 H), 8.26 (dd, *J* = 4.8, 1.5 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 22.6, 27.8, 36.2, 44.8, 98.5, 115.9, 120.5, 126.3, 127.1, 127.2, 128.6, 138.3, 141.1, 141.7, 148.5. LC–MS: *m/z* [M + H]$^+$ calcd for $C_{18}H_{21}N_2^+$: 265.2; found: 265.2.

1-Benzyl-3-methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (3g)

Prepared following general procedure A, starting from *N*-benzyl-3-bromopyridin-2-amine (**1a**) and propiophenone. The reaction required 48 h heating at 140 °C. Purification by reverse-phase flash chromatography (50% MeCN in H_2O to 100% MeCN; R_f = 0.26, MeCN–H_2O = 8:2) gave the product as an orange oil (150 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 3 H), 5.44 (s, 2 H), 6.84–6.88 (m, 2 H), 7.08–7.15 (m, 4 H), 7.24–7.27 (m, 2 H), 7.36–7.41 (m, 3 H), 7.89 (dd, *J* = 7.8, 1.5 Hz, 1 H), 8.35 (dd, *J* = 4.8, 1.5 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 9.1, 45.8, 107.5, 115.6, 121.2, 126.6, 126.7, 126.8, 128.2, 128.2, 128.3, 130.5, 131.5, 137.7, 138.7, 143.0, 148.4. LC–MS: *m/z* [M + H]$^+$ calcd for $C_{21}H_{19}N_2^+$: 299.2; found: 299.2.