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Transition Metal Catalyzed Synthesis of 5-Azaindoles

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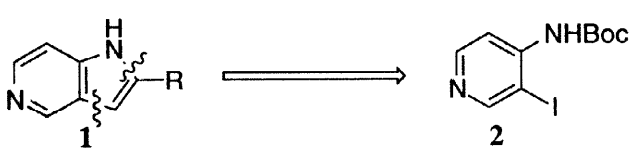
Abstract: In an effort to develop synthetic procedures for the preparation of 2-substituted 5-azaindoles, the synthesis and cyclization reactions of acetylenic aminopyridines was explored. A novel method for the synthesis of 2-substituted 5-azaindoles via a transition metal catalyzed reaction is described.

During the course of our investigation of a novel series of antagonists of platelet activating factor (PAF), it was necessary to develop an efficient, viable pathway for the synthesis of 2-substituted 5-azaindoles. The chemistry of azaindoles has been previously reviewed,[1] however, few methods for the preparation of 5-azaindoles have been described. Even less general are routes to 2-substituted 5-azaindoles, since the designs of the published routes exclude the possibility of 2-substitution. In addition, many of the known syntheses of 5-azaindoles suffer from relative inaccessibility of starting materials, poor yields and irreproducibility.[2] In this letter we wish to report a highly efficient method for the preparation of a variety of 2-substituted 5-azaindoles via the palladium catalyzed cycloaddition and/or copper(I)-catalyzed cyclization of amine alkyne substrates.

Palladium mediated cyclization reactions of alkynes are of great current interest. The general application of palladium-catalyzed reaction has provided new avenues for the preparation of condensed heteroaromatic compounds that were inaccessible through classical methods. It has been extensively utilized for the preparation of various substituted heterocycles including benzofurans[3] and indoles.[4,5] However, there are only a few examples in the literature make use of palladium chemistry for the synthesis of 3-substituted 5- and 7-azaindoles.[6] Similarly, only a few examples of Cu(I) catalyzed indoles[7] and 7-azaindole[8] formation have appeared.

Our synthetic strategy is outlined in Scheme 1, and involves palladium-catalyzed carbon-carbon bond formation as a key step, from which a variety of 2-substituted 5-azaindoles (**1**) are obtained by coupling of the appropriately ortho-functionalized pyridine **2** with terminal alkynes.

Scheme 1



1 **2**

In our initial studies, using the conditions reported by Larock et al.,[5] pyridyl iodide **2** was treated with propyne and the desired 2-methyl-5-azaindole **3e** was obtained in 65% yield (Scheme 2). During the course of the reaction, it was observed that azaindole **3e** was formed via the coupling product **4e**. Specifically, when the

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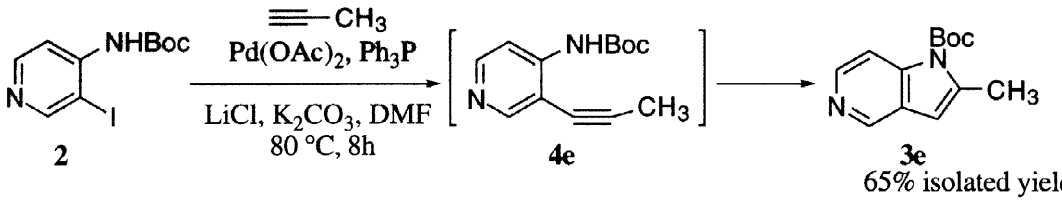
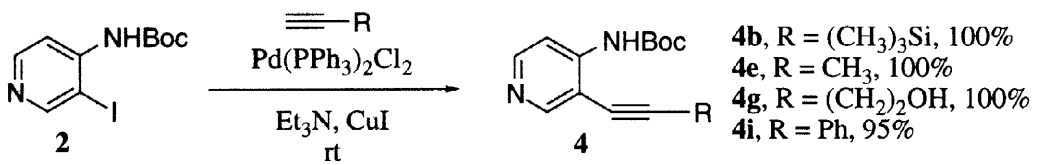
reaction was intervened at 1 hour, only **4e** was obtained; at 1.6 hour, the ratio of **3e** to **4e** was 1:11. This suggests that the pathway of forming azaindoles from terminal alkynes under Larock's conditions is different from the proposed mechanism for the formation of indoles via the annulation of internal acetylene, which involves a migratory insertion of an intermediate aryl Pd(II) compound into the triple bond.[5]

Scheme 2



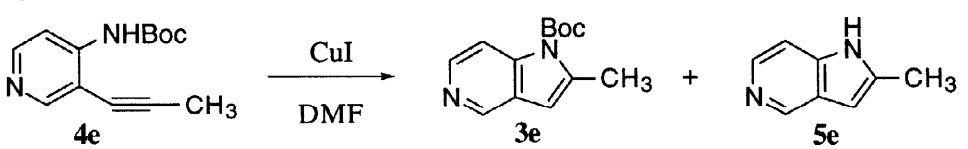
Having identified **4e** as an intermediate, we then investigated the possibility of preparation of azaindole **3e** through a two step pathways, namely, conventional coupling reaction to prepare **4e** followed by a separate cyclization step to form **3e**. As shown in Scheme 3, *o*-aminoacetylenic pyridines **4e** were obtained in high yield utilizing the Castro-Stevens coupling conditions of terminal acetylenes with pyridyl halides.[9] Although Pd(II) and

Scheme 3



Hg(II) have all been reported to catalyze intramolecular cyclization of amines with alkynes to synthesize 2-substituted indoles,[10,11] in our hands, similar reaction conditions mostly led to recovered starting material. Copper(I) has been shown to promote the formation of indoles[7] and 7-azaindole[8] from the corresponding *o*-aminoacetylene in refluxing DMF. Aminoalkyne **4e** was therefore heated in DMF in the presence of catalytic amount of CuI at 120 °C for 10 hour, and two products **3e** and **5e** were obtained in 9% and 49% respectively (Scheme 4). At a somewhat lower temperature (80 °C), only **3e** was obtained in 84% yield. A one pot coupling and cyclization reaction was also investigated (80 °C, 16 h), and it was discovered that the desired azaindole **3e** could be obtained, although longer reaction times were required, and the reaction yields (75-90%) and results varied from time to time. The two-step reaction was preferred.

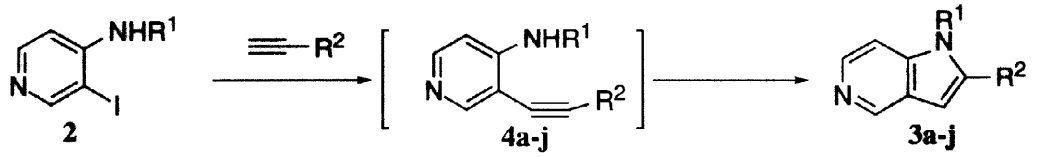
Scheme 4

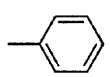
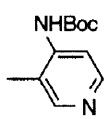


	3e	5e
120 °C	9%	49%
80°C	84%	0%

The application of this methodology to the synthesis of a variety of 2-substituted 5-azaindoles is summarized in Table I. The cyclization of the *o*-aminoacetylenes to 2-substituted 5-azaindoles proceeded smoothly in the presence of catalytic amounts of CuI (0.02 equivalent), the cyclization reached completion in 2-6 hours in DMF with moderate heating. The Cu(I)-catalyzed cyclization is quite general for a variety of substituted acetylenes, *i.e.*,

Table I. Synthesis of 5-Azaindoles via Palladium- and/or Copper-Catalyzed Cyclization.



entry	substrates	R^1	R^2	temperature (°C)	time (h)	procedure	% yield[a]
1	4a	Boc	H	80	6	A	30 and 10% dimer
2	2	Boc	$(CH_3)_3Si$	80	8	B	-[b]
3	4b	Boc	$(CH_3)_3Si$	80	10	A	90[12,b]
4	4c	Boc	$^tBu(CH_3)_2Si$	100	8	A	-[b]
5	4d	H	CH_3	80	24	A	-[b]
6	4e	Boc	CH_3	80	2	A	84
7	2	Boc	CH_3	80	8	B	65
8	4f	Ac	CH_3	120	10	A	-[b]
9	2f	Ac	CH_3	110	3.5	B	48[c]
10	4g	Boc	$(CH_2)_2OH$	80	2	A	38
11	4h	Boc	$(CH_2)_2OTHP$	80	2	A	68
12	2	Boc	$(CH_2)_2OTHP$	80	8	B	44
13	4i	Boc		80	6	A	67
14	4j	Boc		80	2	A	95

Procedure A: The mixture of alkynylpyridine (0.5 mmol) and CuI (0.01 mmol) was heated in 10 mL of DMF. Procedure B: Reactions were run by stirring 5 mol % $Pd(OAc)_2$, pyridyl iodide (0.5 mmol), alkyne (0.6-0.75 mmol), LiCl (0.5 mmol), K_2CO_3 (2.5 mmol), and 5 mol % PPh_3 in 10 mL DMF. *a*) All yields are isolated yields. *b*) Trace or no product was obtained; starting material or desilyation product was recovered. *c*) The product is 2-methyl-5-azaindole.

the alkyne can bear alkyl, aryl and heterocyclic groups. Yields are relatively low when a free hydroxyl group is present, however, they improve when the hydroxyl group is protected (entry 11). The alkyl carboxyl group seems to be the best accepted activating group on nitrogen for the cyclization reaction. When the nitrogen is unsubstituted or bears a tosyl or acetyl group, only the unreacted *o*-aminoacetylenes are recovered. Under Larock's conditions, cyclization product deacetylated 5-azaindole (entry 9) was obtained in moderate yield.

As seen in entry 2-4, silyl groups do not tolerate the cyclization reaction conditions, the only product was desilated *o*-aminoacetylene. Prolonged reaction times or elevated temperatures afforded desilated cyclized product, but in low yield.[12] This may due to the formation of alkynylcopper in DMF.[13]

In summary, two types of 2-substituted 5-azaindole syntheses were investigated. Both reactions involve 4-amino-3-iodopyridines as common intermediates, proceed under mild reaction conditions and offer fair to good yields of 2-substituted 5-azaindoles. The techniques described here provide enabling alternatives to more traditional methods for the construction of 2-substituted 5-azaindoles.

References and Notes

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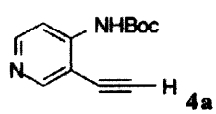
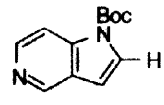
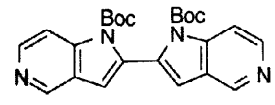
12. Desilylation product **4a** was formed first, then was converted to azaindole **3a** and dimer **5**.



4a



3a



5

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14. Data for representative compounds (phys. state, ^{1}HNMR and ^{13}C NMR [300 Mhz] ($CDCl_3$); MS [DCI-NH_3]): **3a**: solid, mp 140-142 °C, ^{1}HNMR 1.69 (9H, s), 6.65 (1H, dd, J_1 = 0.6 Hz, J_2 = 3.8 Hz), 7.62 (1H, d, J = 3.8 Hz), 8.00 (1H, bs), 8.49 (1H, bs), 8.92 (1H, bs); MS 236 $(M+NH_4)^+$, 219 $(M+H)^+$, 163, 119. **3e**: solid, mp 87-90 °C; ^{1}HNMR 1.70 (9H, s), 2.62 (3H, d, J = 1.0 Hz), 6.40 (1H, t, J = 1.0 Hz), 7.94 (1H, d, J = 5.7 Hz), 8.39 (1H, d, J = 5.8 Hz), 8.76 (1H, s); ^{13}CNMR 16.9, 28.2, 84.9, 105.9, 110.4, 131.9, 139.2, 142.0, 143.0; MS 233$(M+H)^+$, 133. **3h**: oil; ^{1}HNMR 1.48-1.84 (6H, m), 1.70 (9H, s), 3.35 (2H, dt, J_1 = 15.4 Hz, J_2 = 1.0 Hz), 3.50 (1H, m), 3.77 (1H, dt, J_1 = 9.9 Hz, J_2 = 6.4 Hz), 3.83 (1H, m), 4.09 (1H, dt, J_1 = 9.4 Hz, J_2 = 6.8 Hz), 4.64 (1H, dd, J_1 = 3.0 Hz, J_2 = 4.3 Hz), 6.53 (1H, t, J = 1.0 Hz), 7.91 (1H, d, J = 5.8 Hz), 8.39 (1H, J = 5.8 Hz), 8.78 (1H, s); MS 347$(M+H)^+$, 247. **3i**: solid, mp 130-132 °C, 1.32 (9H, s), 6.62 (1H, s), 7.42 (5H, m), 8.06 (1H, d, J = 5.4 Hz), 8.49 (1H, d, J = 5.4 Hz), 8.89 (1H, s); MS 295, 195. **3j**: solid, mp 183-185 °C(decomposed); ^{1}HNMR 1.30 (9H, s), 1.48 (9H, s), 6.63 (1H, bs), 6.75 (1H, d, J = 0.9 Hz), 8.17 (1H, d, J = 6 Hz), 8.19 (1H, d, J = 5.7 Hz), 8.37 (1H, s), 8.53 (1H, J = 6 Hz), 8.56 (1H, J = 5.7 Hz), 8.95 (1H, s); MS 411$(M+H)^+$, 291, 233.