JOC Note
pubs.acs.org/joc

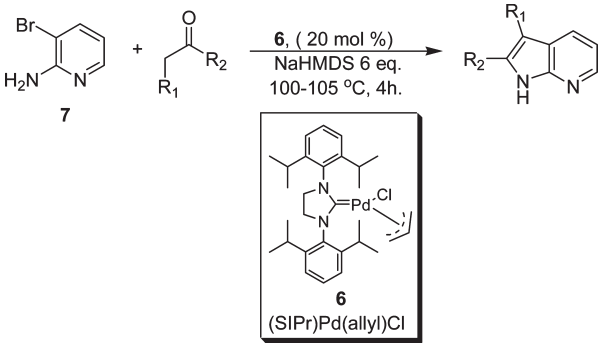
One-Pot Synthesis of Azaindoles via Palladium-Catalyzed α-Heteroarylation of Ketone Enolates

Steven H. Spergel,* Danielle R. Okoro,† and William Pitts

Bristol-Myers Squibb, Princeton, New Jersey 08543-4000, and †Hunter College, New York, New York 10065

steven.spergel@bms.com

Received April 1, 2010



A convenient, one-pot method for the construction of a variety of azaindoles using simple ketones and haloaminopyridines is described.

Azaindoles represent one of the most important heterocyclic scaffolds in medicine, and as a result, several methodologies have been invented for their construction.[1] However, these methods were not amenable to late-stage diversification while executing our medicinal chemistry SAR plan. As part of our effort to identify inhibitors of IκB Kinaseβ, IKK-2, we sought to prepare derivatives of tricycle **1** with diversity at the 7-position (2-azaindole position, Scheme 1).[2] Our original SAR diversification plan was based on direct arylation chemistry utilizing **1** (R = H) as a key intermediate; however, we were unsuccessful.[3] After some experimentation, the synthetic pathway which was adopted relied upon a 5-*endo-dig* cyclization from an appropriately substituted acetylene precursor. Despite the initial success of this route for 2-phenyl-substituted 7-azaindoles, SAR generation was slowed due to the stepwise nature of the coupling−cyclization protocol, which failed to translate into an efficient one-pot process.[4] Reaction of acetylene **3** (or its TMS-protected version) with aryl bromides was not practical since complex mixtures were obtained, with **1** (R = H) being the major product observed under all conditions.[5] In this paper, we report a simple one-step method for the construction of a variety of azaindoles using simple ketones and haloaminopyridines.

The difficulty encountered in the Sonagashira approach (Scheme 1) led us to explore the reaction of ketones with common intermediate **2** (Scheme 2). The palladium-catalyzed enamine−Heck indole synthesis,[6,8] extended by Nazaré[7a] and others to the preparation of azaindoles, was only productive, in this instance, with ethyl pyruvate.[8] We also investigated the Pd-catalyzed tandem coupling of *gem*-dichloroolefins[7b] described by Lautens. This method affords good yields in the case of simple azaindoles but was unsuccessful in our complex system. Since these methods were not able to generate the diversity to sustain our discovery program, the palladium-catalyzed α-arylation of enolates was explored. Such an approach would provide the azaindole **5** through a Reissert-type intermediate. To our knowledge, this methodology had been applied to indoles[11] but has not been extended to the preparation of azaindoles.

Buchwald and Hartwig have pioneered the palladium-catalyzed α-arylation of enolates.[12] We conducted scouting reactions with **2** (I and Br) and a substituted acetophenone under Buchwald conditions[13] ($Pd_2(dba)_3$, xantphos, with K_3PO_4, Cs_2CO_3, NaOtBu, or $NaN(SiMe_3)_2$, in THF at 70 °C) but did not detect any desired product **5**.[14] After exploration of

(1) (a) Popowycz, F.; Routier, S.; Joseph, B.; Merour, J.-Y. *Tetrahedron* **2007**, *63*, 1031. (b) Song, J. J.; Reeves, J., T.; Gallou, F.; Tan, Z.; Yee, N., K.; Senanayake, C., H. *Chem. Soc. Rev.* **2007**, *36*, 1120 (further review). (c) Popowycz, F.; Merour, J.-Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 8689.

(2) Kempson, J.; Guo, J.; Das, J.; Moquin, R. V.; Spergel, S. H.; Watterson, S. H.; Langevine, C. M.; Dyckman, A., J.; Burke, J., R.; Taylor, T.; McIntyre, K.; Barrish, J. C.; Pitts, W. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2646–2649.

(3) (a) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. Attempts at the direct arylation of the H-compound were conducted in 2005, prior to the retraction of this paper in: *J. Am. Chem. Soc.* **2006**, *128*, 8364. We did not explore direct C-2 arylation of N-substituted azaindoles for which there is precedence. For example, see: (b) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (c) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357.

(4) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Park, S. S.; Choi, H.-K.; Yum, E. K.; Ha, D.-C. *Tetrahedron. Lett.* **1998**, *48*, 221. (c) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2488.

(5) This result was consistent with previous literature reports; see: Kumar, V.; Dority, J. A.; Bacon, E. R.; Singh, B.; Lesher, G. Y. *J. Org. Chem.* **1992**, *57*, 6995.

(6) Chen, C.-Y.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676.

(7) (a) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526. (b) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152.

(8) This reaction proceeded in approximately 30% yield for ethyl pyruvate. We subjected a mixture of **2** (I or Br) and a substituted acetophenone to the Nazare conditions; however, none of the desired product formed. No improvements were seen when microwave conditions were employed.[9] Control experiments with **2** and a substituted acetophenone in the presence of dehydrating reagents such as *p*-TsOH,[10] magnesium sulfate, or 4A molecular sieves at elevated temperature failed to demonstrate the formation of the anticipated enamine, although removal of the Boc protecting group was evident under forcing conditions.

(9) Lachance, N.; April, M.; Joly, M.-A. *Synthesis* **2005**, *15*, 2571.

(10) Blanche, Y.; Sinibaldi-Troin, M.-E.; Hichour, M.; Benezech, V.; Chavignon, O.; Gramain, J.-C.; Teulade, J.-C.; Chapat, J.-P. *Tetrahedron* **1999**, *55*, 1959.

(11) After this research was conducted, a thorough search of the literature identified that this methodology had been applied to indoles. See: Cho, C. S.; Kim, J. H.; Kim, T.-J.; Shim, S. C. *J. Chem. Res.* **2004**, *9*, 630.

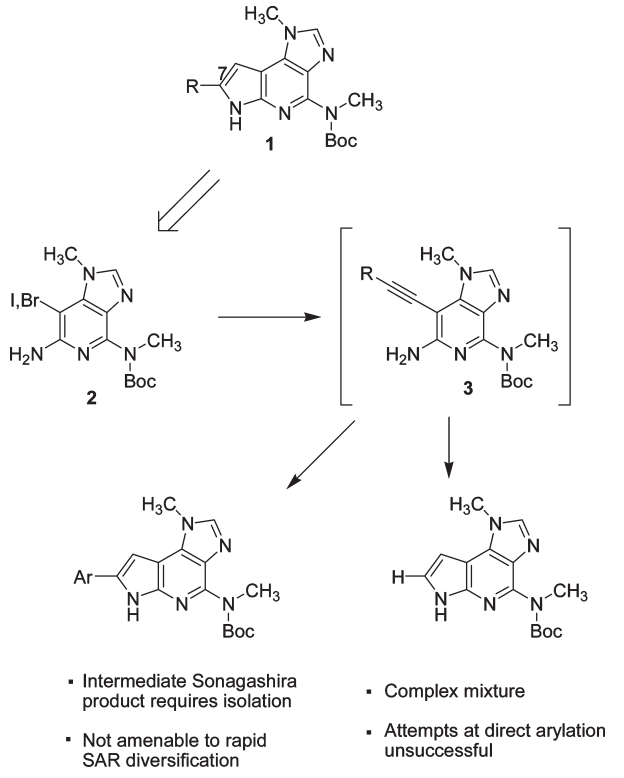
(12) For reviews, see: (a) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953. (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

(13) Fox, J. M.; Huang, X.; Chieffi, A. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

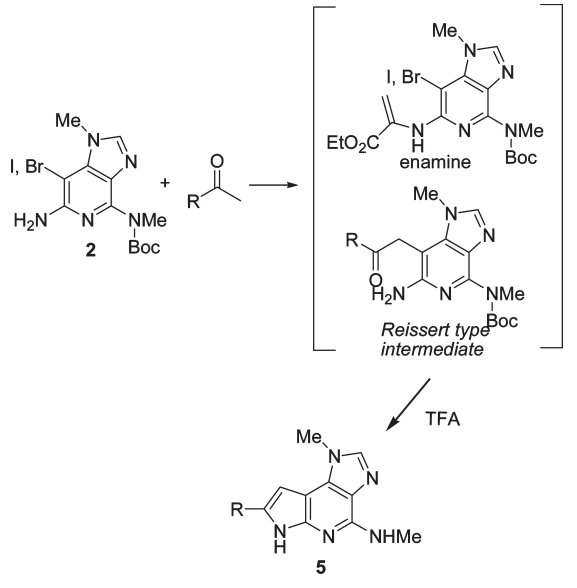
(14) We cannot disclose the exact structure of **5**; however, the aryl ring contains no functionality which might interfere with the reaction.

Published on Web 07/01/2010 DOI: 10.1021/jo100623d

SCHEME 1. Initial Disconnections Explored



SCHEME 2. Ketone Routes Explored

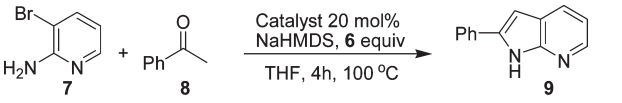


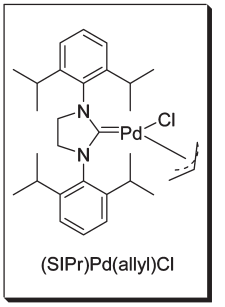
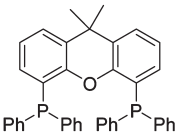
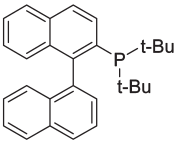
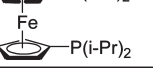
several alternative catalyst systems, we found the N-heterocyclic carbene catalyst, (SIPr)Pd(allyl)Cl, **6**, described by Nolan[15] when used under standard conditions (NaOtBu, THF at 70 °C) resulted in partial conversion to **5** by LCMS analysis.

In an effort to drive the reaction to completion, the temperature was increased from 70 to 100 °C (sealed vessel).

(15) (a) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053 (commercially available from Strem Chemical Co. catalog no. 46-0039). (b) For a review of N-heterocyclic carbene catalysis, see: Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440.

TABLE 1. Catalyst Scan



Entry	Catalyst	Conversion
1	 (SIPr)Pd(allyl)Cl **6**	74%[a]
2[c]		<10%[b]
3[d]		<10%[b]
4[c]	$P(t\text{-Bu})_3$	60%[a]
5[c]		70%[a]

[a]isolated yield. [b]Determined by NMR integration. [c]$Pd(dba)_2$. [d]$Pd(OAc)_2$.

These conditions produced a more complete reaction (43% isolated yield); however, a significant amount of ketone self-condensation product was evident.

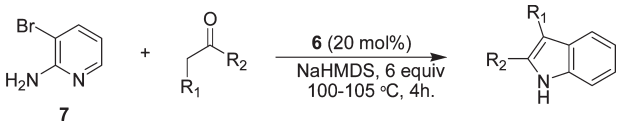
Substitution of sodium or lithium (in the case of aryl iodides) hexamethylsilylamide for sodium *tert*-butoxide and extending the reaction time to 4 h resulted in essentially complete conversion of starting material, and following workup and TFA deprotection, analogues **5** were isolated in moderate yields.

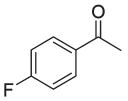
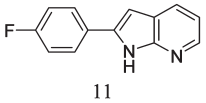
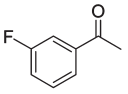
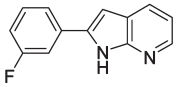
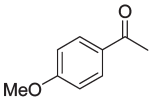
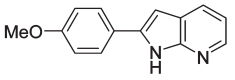
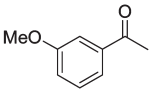
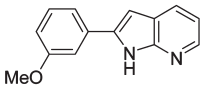
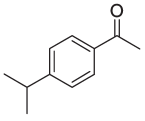
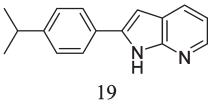
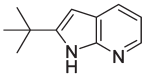
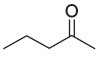
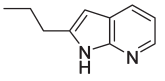
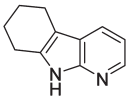
We returned to examine several catalyst systems (under optimized conditions, as for **5**) in a model system (Table 1). Consistent with the results we had obtained previously, use of (SIPr)Pd(allyl)Cl, **6** (entry 1), proceeded to completion, and 2-phenylazaindole (**9**) was isolated in 74% yield. Lowering the catalyst loading to 10 mol % resulted in incomplete reaction at 4 h (43% conversion); thus, a 20 mol % catalyst loading was used to screen the other catalyst systems. Use of xantphos or *rac*-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl, which have recently been shown to be effective in the reaction of orthobromophenols and ketones to produce benzofurans,[16] did not proceed to any appreciable extent (entries 2 and 3).

Use of $P(tBu)_3$ (entry 4), which has been shown to be effective for α-arylation in a number of systems,[17] and bis-(diisopropyl)phosphinoferrocene (entry 5), which was the

(16) Eidamshaus, C.; Burch, J. D. *Org. Lett.* **2008**, *10*, 4211.
(17) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1549.

TABLE 2. Ketone Substrate Scope



Entry	Ketone	Azaindole	Yield
1	 10	 11	94%
2	 12	 13	58%
3	 14	 15	87%
4	 16	 17	48%
5	 18	 19	81%
6	 20	 21	87%
7	 22	 23	60%[a]
8	 24	 25	51%

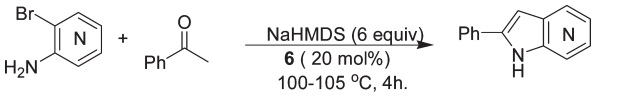
[a] > 95% single isomer by NMR.

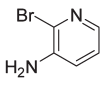
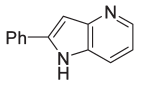
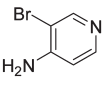
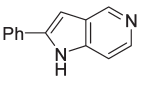
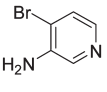
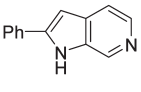
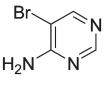
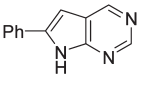
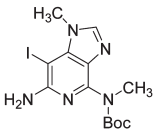
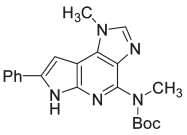
most effective catalyst reported for indole formation,[11] produced **9** in yields approaching that of (SIPr)Pd(allyl)Cl, **6**.

Since the yield using (SIPr)Pd(allyl)Cl, **6**, appeared to be slightly better, we chose it to conduct a substrate scan. Acetophenones (entries 1−5), alkyl ketones (entries 6 and 7), and cyclohexanone (entry 8) afforded azaindoles in yields ranging from good to excellent (Table 2). Examination of the crude NMR of **23** showed the 2-propylazaindole as the predominant isomer (> 20:1 by ^{1}HNMR). This ability to employ unsymmetrical ketones represents an improvement over the enamine−Heck methodology, although we did not extend this observation further. The formation of a predominant regioisomer has also been observed in the related indole and benzofuran syntheses.[11,16]

With these results in hand, we turned our attention to the preparation of other fused azaheterocycles (Table 3). We found that the method appears to be general for other electron-deficient heterocyclic systems, although the yields

TABLE 3. Heterocycle Substrate Scope



Entry	Heterocycle	Product	Yield[a]
1	 26	 27	27%
2	 28	 29	41%
3	 30	 31	14%
4	 32	 33	62%
5	 2	 34	56%

[a] No optimization was attempted.

ranged from low (entries 1−3) to moderate (entries 4 and 5). Other than the enamine−Heck route,[9] there are few methods reported to provide access to all of the azaindole regioisomers.[18]

We have demonstrated the application of N-heterocyclic carbene palladium catalysts to the construction of azaindoles and related heterocycles via ketone α-arylation chemistry. We have demonstrated the utility of this method as an alternative to the stepwise approach, relying upon a 5-*endo-dig* cyclization of acetylenes as part of our medicinal chemistry effort. The recent report of the synthesis of azaindole **15**, from 2-aminopicoline in three steps (one protection step) in 57% overall yield,[19] underscores the need for alternative methodologies to provide rapid and convenient access to azaindoles. Our one-pot approach does not require the use of an amine protecting group, can be applied to nonsymmetrical ketones with excellent regioselectivity, and allows for late-stage diversification, making it a useful addition to current methodologies.

Experimental Section

General Procedure. Sodium bis(trimethylsilyl)amide, 1.0 M in THF (1.5 mL, 1.5 mmol), was added to a solution of allyl(1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)palladium(IV) chloride (**6**) (28.7 mg, 0.05 mmol) and ketone (1.0 mmol) in THF (1 mL) at rt. After the mixture was stirred for 5 min at rt, *o*-bromoaminoheterocycle (0.25 mmol) was added as a solution in

(18) For a successful multistep strategy to provide all 2-aryl-substituted azaindole isomers, see: Kuzmich, D.; Mulrooney, C. *Synthesis* **2003**, *11*, 1671.

(19) Parcerisa, J.; Romero, M.; Pujol, M. D. *Tetrahedron* **2008**, *64*, 500.

THF (0.2 mL), and the reaction was heated to 100−105 °C in a pressure tube for 4 h. After being cooled to rt, the reaction mixture was partitioned between EtOAc (30 mL) and saturated NH_4Cl solution (30 mL). The organic layer was washed with saturated NH_4Cl solution (30 mL), and the combined aqueous layers were back-extracted with EtOAc (15 mL). After drying ($MgSO_4$) and filtration, the combined organic layer was concentrated to afford a residue that was chromatographed on a silica gel, eluting with an EtOAc/Hex gradient. Concentration of the pure fractions afforded the product.

Characterization data for 9: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, J = 1.5 Hz, 1 H), 7.10 (dd, J = 7.8, 4.8 Hz, 1 H), 7.40 (t, J = 7.4 Hz, 1 H), 7.52 (t, J = 7.6 Hz, 2 H), 7.88 (d, J = 7.1 Hz, 2 H), 7.96 (dd, J = 7.8, 1.3 Hz,1 H), 8.30 (dd, J = 4.8, 1.3 Hz, 1 H), 12.31 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 97.40, 116.13, 122.42, 125.97 (2 C), 128.24, 128.77, 129.08 (2 C), 132.51, 139.66, 142.12, 150.06; HRMS calcd for $C_{13}H_{11}N_2$ $[M + H]^+$ 195.09168, found 195.09173.

Acknowledgment. We would like to thank Bethanne Warrack and Sarah Traeger from Discovery Analytical Sciences for their analytical support and Dr. James Kempson and Dr. Scott Watterson for helpful suggestions regarding the preparation of this paper.

Supporting Information Available: Experimental procedures and full characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.