ORGANIC LETTERS

2006
Vol. 8, No. 15
3307−3310

Efficient Access to Azaindoles and Indoles

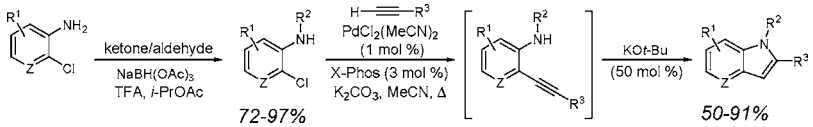
Mark McLaughlin,* Michael Palucki, and Ian W. Davies

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

mark_mclaughlin@merck.com

Received May 19, 2006

ABSTRACT



An expedient, catalytic method for the synthesis of diverse azaindoles and indoles, starting from readily available and inexpensive starting materials, is described. Conditions were developed for effective reductive alkylation of electron-deficient *o*-chloroarylamines, substrates previously viewed as poor partners in this reaction. The derived *N*-alkylated *o*-chloroarylamines were elaborated to *N*-alkylazaindoles and *N*-alkylindoles via a novel one-pot process comprising copper-free Sonogashira alkynylation and a base-mediated indolization reaction.

Indole and azindole heterocycles are prevalent substructures in naturally occurring and synthetic molecules displaying biological activity.[1] Consequently, the development of efficient ways to prepare these compounds continues to be an active area of research.[2] Aside from the vast array of more traditional methods, there exists a variety of organometallic techniques for indole synthesis.[3] In particular, the cyclization of *o*-alkynylanilines, normally prepared from *o*-haloanilines via the Sonogashira reaction,[4] has been widely documented.[5] Although this method has proven valuable, examination of the literature reveals considerable scope for refinement of the existing procedures. Significantly, the *o*-haloaniline starting materials most often used for the initial Sonogashira step are iodo or bromo species.[6] Therefore, an indolization process capable of utilizing less expensive *o*-chloroanilines would be useful.

A recent report described the synthesis of indoles starting from 1,2-dihaloarenes via sequential Sonogashira and amination reactions, allowing access to indoles bearing nitrogen substituents.[7] However, potentially significant drawbacks of this method are the fairly harsh reaction conditions (>100 °C) and the use of relatively high loadings of transition-metal catalysts (10 mol % of Cu and 5 mol % of Pd). Given that 1-bromo-2-iodobenzenes and 1-chloro-2-iodobenzenes are normally prepared via Sandmeyer iodination of the corresponding *o*-haloanilines, an alternative approach to *N*-substituted indoles starting from *o*-haloanilines appeared potentially more direct. Thus, a sequence based around reductive alkylation of *o*-haloanilines followed by Sonogashira coupling/indole construction was envisaged (Figure 1). In view of the ready availability and inexpense of 3-amino-2-chloropyridine and 2-chloroanilines, the development of efficient methods for their transformation into substituted azaindoles/indoles was investigated.

(1) For leading references on the biological activity associated with the indole substructure, see: (a) Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005**, *70*, 2555−2567. (b) Van Zandt, M. C.; Jones, M. L.; Gunn, D. E.; Geraci, L. S.; Jones, J. H.; Sawicki, D. R.; Sredy, J.; Jacot, J. L.; DiCioccio, A. T.; Petrova, T.; Mitschler, A.; Podjarny, A. D. *J. Med. Chem.* **2005**, *48*, 3141−3152.

(2) For a recent review, see: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075.

(3) For a review of the Pd-catalyzed synthesis of heterocycles, see: Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2309.

(4) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470.

(5) Originally, the Cu-promoted Castro reaction: (a) Castro, C. E.; Stevens, R. D. *J. Org. Chem.* **1963**, *28*, 2163. (b) Stevens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313−3315. For early work on the Pd-catalyzed version, see: Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 2225−2249.

(6) For example, see: (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037−1040. (b) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539−541. For recent examples where *o*-chloroanilines were used in alternative indolization processes, see: (c) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526−4528. (d) Shen, M.; Li, G.; Lu, B. L.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129−4132. (e) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Commun.* **2004**, 2824−2825.

(7) Ackermann, L. *Org. Lett.* **2005**, *7*, 439−442.

10.1021/ol061232r CCC: $33.50
Published on Web 06/22/2006

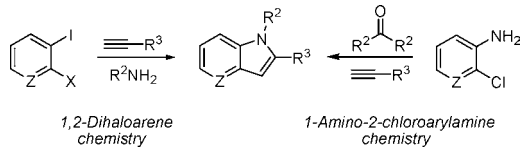
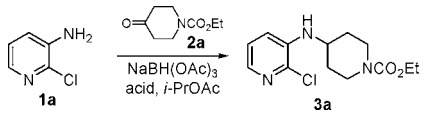


Figure 1. Alternative routes to substituted indoles.

Reductive alkylation of electron-deficient arylamines is known to be difficult[8] and there are no reports of this reaction using 3-amino-2-chloropyridine as the amine partner. Indeed, our initial efforts to conduct this reaction between 3-amino-2-chloropyridine **1a** and ethyl 4-piperidone carboxylate **2a** using $NaBH(OAc)_3$ (STAB) were thwarted by insufficient imine/iminium concentration and competing direct reduction of the carbonyl (Table 1, entry 1). Even with 300 mol % of the ketone, the conversion of the amine remained below 50%.

Table 1. Optimization of the Reductive Alkylation Process[a]



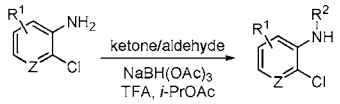
entry	acid (mol %)	ketone (mol %)	STAB (mol %)	amine conv (%)	assay yield[b] (%)
1	AcOH (0)	100	120	36	15
2	AcOH (50)	100	120	34	15
3	AcOH (100)	100	120	39	19
4	AcOH (200)	100	120	46	20
5	AcOH (300)	100	120	52	22
6	AcOH (1000)	100	120	55	34
7	AcOH (solvent)	100	120	60	54
8	AcOH (solvent)	150	170	99	97
9	TFA (100)	120	150	97	94
10	TFA (200)	120	150	100	99
11	TFA (200)	110	120	99	98
12	$MeSO_3H$ (200)	110	120	6	3

[a] Reaction conditions: All reactions conducted at rt using amine **1a** as the limiting reagent. [b] Conversion and assay yields were determined by LC versus purified standards.

The standard literature recommendation[8] for poorly nucleophilic amines is to add 100−150 mol % of AcOH, along with a concomitant increase in the amounts of carbonyl component and STAB. In the present case, poor yields were still obtained with added AcOH, although a trend toward increasing yield with increasing quantities of acid was clear (Table 1, entries 2−6).

With this observation in mind, AcOH was used as solvent for this reaction and a high assay yield was obtained, with 150 mol % of ketone and 170 mol % of STAB necessary for total consumption of the amine (Table 1, entry 8).[9] At this point, the use of alternative stronger acids was studied. The use of 100 mol % of TFA resulted in a yield comparable to that obtained with AcOH as the solvent (Table 1, entry 9). Further development led to optimal conditions (Table 1, entry 11).[10,11] The reaction did not function well in the presence of 200 mol % of $MeSO_3H$ (Table 1, entry 12). Gratifyingly, the developed conditions gave good results across a range of aldehyde and ketone substrates (Table 2).[12]

Table 2. Reductive Amination Reactions[a]



entry	arylamine	carbonyl	product	yield (%)[b]
1	**1a**	**2b**	**3b**	97
2	**1a**	**2c**	**3c**	90
3	**1a**	**2d**	**3d**	94
4	**1a**	**2e**	**3e**	89
5	**1a**	**2f**	**3f**	88[c]
6	**1a**	**2g**	**3g**	91
7	**1b**	**2b**	**3h**	94
8	**1c**	**2d**	**3i**	85
9	**1d**	**2b**	**3j**	84
10	**1e**	**2d**	**3k**	84
11	**1f**	**2d**	**3l**	72

[a] Reaction conditions: amine (100 mol %), carbonyl (110 mol %), TFA (200 mol %), and STAB (120 mol %) in *i*-PrOAc at rt. [b] Yields refer to isolated material. [c] 130 mol % of ketone used.

The ability to use aldehydes under these acid-promoted conditions is notable since competing carbonyl reduction was reported to be a significant issue with these more reactive substrates.[8] Application of the same conditions to 2-chloroaniline reductive alkylations also led to high yields (Table 2). In certain instances, the reductively alkylated products could be directly crystallized in high purity following

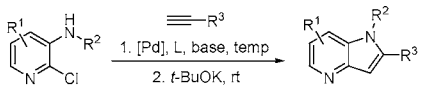
(8) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862.

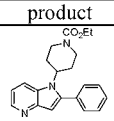
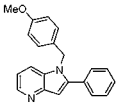
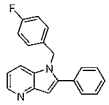
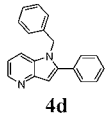
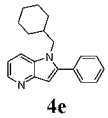
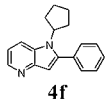
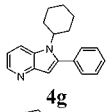
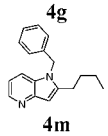
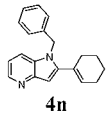
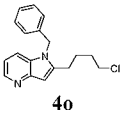
aqueous workup. When the products were oils, chromatography was necessary to obtain analytically pure material. In general, however, the crude products from these reductive alkylations were sufficiently pure for direct use in the subsequent indolization chemistry.

Having secured access to a range of *N*-substituted intermediates, attention was focused on the planned indole synthesis. For the Sonogashira coupling step, the goal was to realize economical and mild reaction conditions. Based on observations[13] made during the course of a concurrent study of Pd-catalyzed reactions using related 2-chloropyridine compounds, a novel protocol for Sonogashira coupling of these derivatives was developed. It was found that 2 mol % of $Pd(OAc)_2$ and 4 mol % of dppb with K_2CO_3 as the base in MeCN at 80 °C was an effective, copper-free catalyst system for Sonogashira coupling of 3-amino-2-chloropyridines with various alkynes. To our knowledge, this is the first report of this simple and inexpensive catalyst system for this transformation. Attempts to extend these conditions to the chloroaniline substrates led to incomplete conversion, which prompted utilization of alternative conditions. In this regard, it was found that a slight modification of Buchwald's excellent copper-free conditions[14] was successful across all substrates in this report. For the 2-chloropyridine series, successful coupling was achieved at 60 °C using K_2CO_3 as the base, MeCN as the solvent, and only a small excess of the alkyne component (105 mol %).[15] Significantly, under these conditions, alkyne decomposition was negligible, obviating the need for slow addition of this reaction partner.[16] In accord with previous observations,[14] the more electron-rich chloroaniline series required more elevated temperatures (80 °C) to achieve full conversion.

Knochel has reported[17] the cyclization of *o*-alkynylanilines using superstoichiometric quantities (130−210 mol %) of KH or *t*-BuOK in NMP; however, no examples of the cyclization of *N*-substituted substrates were included. In the present work, the prepared substrates bearing additional *N*-substitution were studied, and modified conditions were developed. It was not critical to use NMP as solvent and the reaction proceeded equally well in THF or MeCN. The absence of an indolic NH proton in the products raised the possibility of using catalytic amounts of base. Indeed, while truly catalytic quantities of base were insufficient, sub-

Table 3. Azaindole Synthesis[a]



entry	substrate	alkyne	product	yield (%)[b]
1	**3a**		 **4a**	88
2	**3b**		 **4b**	90
3	**3c**		 **4c**	89
4	**3d**		 **4d**	87
5	**3e**		 **4e**	86
6	**3f**		 **4f**	83
7	**3g**		 **4g**	88
8	**3d**		 **4m**	91
9	**3d**		 **4n**	90
10	**3d**		 **4o**	86

[a] Reaction conditions: substrate (100 mol %), alkyne (110 mol %), $Pd(OAc)_2$ (2 mol %), dppb (4 mol %), K_2CO_3 (300 mol %), MeCN (10 mL/g), 80 °C, 16 h, then 1 M *t*-BuOK in THF (50 mol %), rt. [b] Yields refer to isolated material using the $Pd(OAc)_2$/dppb system. Alternatively, substrate (100 mol %), alkyne (105 mol %), $PdCl_2(MeCN)_2$ (1 mol %), X-Phos (3 mol %), K_2CO_3 (300 mol %), MeCN (10 mL/g), 60 °C, 16 h, then 1 M *t*-BuOK in THF (50 mol %), rt afforded similar yields.

(9) ^{1}H NMR (AcOH-d_4) analysis of a mixture of amine **1a** and ketone **2a** indicated <5% equilibrium imine/iminium concentration.

(10) ^{1}H NMR study of the TFA system again indicated <5% equilibrium imine/iminium concentration.

(11) The direct use of $NaBH_4$ was investigated for the conversion of **1a** to **2a**, although competing carbonyl reduction was anticipated to be a serious issue. Nevertheless, complete conversion of the amine partner was achieved with a 130−140 mol % charge of the carbonyl partner and slow addition (∼5 h) of the reductant, affording a 95% assay yield of **2a**. Depending upon the application, this procedure could prove more economical since $NaBH_4$ is substantially cheaper than commercial STAB. However, the operational simplicity and decreased quantities of alcohol byproduct associated with the STAB-mediated process made this the preferred method.

(12) Certain carbonyl substrates such as aromatic/unsaturated ketones and sterically hindered ketones are known[8] to perform poorly in reductive alkylation reactions. Under the conditions developed here, the following carbonyl compounds exhibited poor reactivity (<10% conversion): acetophenone, α-tetralone, pinacolone, and methyl isobutyl ketone.

(13) See the accompanying paper: McLaughlin, M.; Paluki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311−3314.

(14) (a) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173−6177. (b) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993−5996.

(15) In the current work, the more economical K_2CO_3 was found to perform equally as well as the recommended Cs_2CO_3.

(16) In the original Buchwald study, unproductive consumption of arylalkynes was observed in reactions conducted at more elevated temperatures (90 °C), necessitating a slow addition protocol.

(17) (a) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571−1587. (b) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488−2490. The authors of these reports indicate that excess base was necessary due to formation of unreactive potassium salts of the product indoles.

stoichiometric amounts (50 mol %) of 1 M *t*-BuOK in THF solution were found to effectively promote the indolization process.

Having demonstrated that both the Sonogashira and base-mediated cyclization reactions were clean and high yielding, a one-pot process appeared feasible. For the majority of substrates, direct treatment of the Sonogashira reaction mixture with 50 mol % of *t*-BuOK resulted in rapid and clean cyclization to the indole at rt. Isolation of the products in good yield was normally accomplished following aqueous workup and chromatography. Tables 3 and 4 summarize the results of application of these protocols to the series of *N*-substituted arylamines prepared via the reductive alkylation chemistry. All substrates performed well in the Sonogashira coupling using one or other of the described procedures. However, a definite electronic effect was observed for the base-promoted indolization of the alkynylated intermediates. It was found that all pyridine-based substrates and other electron-deficient alkynylated arylamines performed satisfactorily in the indolization, regardless of the substituent on the incipient indole nitrogen atom.

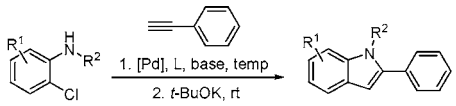
In contrast, more electron-rich intermediates were either sluggish or unreactive under the standard conditions. As shown in Table 3, alkynes other than phenylacetylene also afforded good yields.

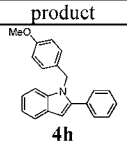
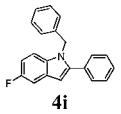
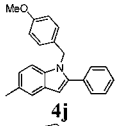
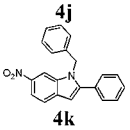
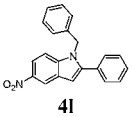
In summary, an expedient method for the synthesis of azaindoles and indoles is described. An effective procedure was developed for the reductive alkylation of amine substrates normally viewed as poor partners in this process. Under these conditions, there is no requirement for a large excess of either the carbonyl coupling partner or the reducing agent. Additionally, the direct use of simple $NaBH_4$ for these reductive alkylations is relatively uncommon and leads to a particularly economical process.

The derived *N*-substituted *o*-chloroarylamines can be converted into azaindoles or indoles via one-pot processes comprised of a novel combination of Sonogashira coupling and base-promoted indolization. These procedures are notable for the following reasons: (a) the use of cheaply available *o*-chloroarylamines rather than the more commonly documented *o*-bromo- or *o*-iodoarylamines, (b) the novel use of the economical $Pd(OAc)_2$/dppb combination as a copper-free Sonogashira coupling catalyst system for 2-chloropyridines, and (c) the relative mildness and high efficiency of the overall processes, which leads to good yields of the products.

Taken as a whole, the described chemistry outlines a method by which a range of highly functionalized azaindole or indole cores can be rapidly accessed in high yield in two steps starting from inexpensive materials with minimal purification. The ubiquity of the indoles in natural products combined with the pharmaceutical relevance of this heterocyclic substructure should render this approach broadly useful.

Table 4. Indole Synthesis[a]



entry	substrate	product	yield (%)[b]
1	**3h**	 **4h**	50[c]
2	**3i**	 **4i**	84[d]
3	**3j**	 **4j**	0[e]
4	**3k**	 **4k**	78
5	**3l**	 **4l**	72

[a] Reaction conditions: substrate (100 mol %), alkyne (110 mol %), $PdCl_2(MeCN)_2$ (1 mol %), X-Phos (3 mol %), K_2CO_3 (300 mol %), MeCN (10 mL/g), 80 °C, 16 h, then 1 M *t*-BuOK in THF (50 mol %), rt. [b] Yields refer to isolated material unless otherwise noted. [c] Complete Sonogashira coupling, incomplete indolization after 200 mol % of *t*-BuOK and 50 °C, NMR yield quoted. [d] 100 mol % of *t*-BuOK required for complete indolization. [e] Complete Sonogashira coupling; indolization failed even with excess base and heat.

Acknowledgment. We thank Robert A. Reamer and Tom J. Novak (Department of Process Research, Merck and Co., Inc.) for assistance with NMR data and mass spectrometry data acquisition, respectively.

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

OL061232R