ORGANIC LETTERS

1999
Vol. 1, No. 4
553−556

Synthesis of Isoquinolines and Pyridines by the Palladium- and Copper-Catalyzed Coupling and Cyclization of Terminal Acetylenes

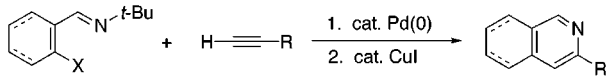
Kevin R. Roesch and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

larock@iastate.edu

Received May 3, 1999

ABSTRACT



X = iodide, bromide

R = alkyl, aryl, alkenyl

3-Substituted isoquinolines have been synthesized by the coupling of aryl- and alkenyl-substituted terminal acetylenes with the *tert*-butylimine of *o*-iodobenzaldehyde in the presence of a palladium catalyst. Alkyl-substituted acetylenes fail to undergo this annulation process. However, the intermediate iminoalkynes containing aryl, alkenyl, and alkyl substituents produced from these palladium-catalyzed reactions undergo copper-catalyzed cyclization in excellent yields and short reaction times. Isoquinolines and pyridines have thus been prepared in a one-pot synthesis via coupling of aryl-, alkenyl-, and alkyl-substituted terminal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes or 3-halo-2-alkenals in the presence of a palladium catalyst and subsequent copper-catalyzed cyclization of the resulting iminoalkynes. The total synthesis of the isoquinoline natural product decumbenine B has been accomplished in seven steps and 20% overall yield by employing this palladium-catalyzed coupling/cyclization methodology.

The palladium-catalyzed annulation of alkynes has recently proven to be a powerful method for the construction of a variety of carbo- and heterocycles. For example, the annulation of internal alkynes has been employed by us for the synthesis of indoles,[1] benzofurans,[2] benzopyrans,[2] isocoumarins,[2] indenones,[3] isoquinolines,[4] α-pyrones,[5] and polycyclic aromatic hydrocarbons.[6] In addition, the transition metal-catalyzed cyclization of alkynes which possess a nucleophile in proximity to the triple bond by in situ coupling/cyclization reactions,[7] and reactions promoted by σ-vinyl-, σ-aryl-, and σ-alkynylpalladium complexes,[8] have also been shown to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles.

During the course of our investigation of the iminoannulation of internal alkynes, we observed an interesting isoquinoline synthesis when trimethylsilyl-substituted alkynes were employed.[4] To our surprise, 3-phenylisoquinoline (**2**),

(1) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D., *J. Org. Chem.* **1998**, *63*, 7652.

(2) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.

(3) Larock, R. C.; Doty, M. J.; Cacchi, S. J. *J. Org. Chem.* **1993**, *58*, 4579.

(4) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.

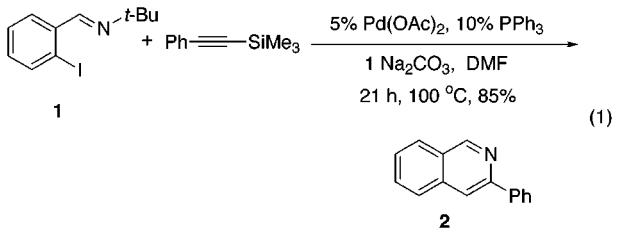
(5) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.

(6) (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

(7) For recent leading references, see: (a) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101 and references therein. (b) Chaudhuri, G.; Chowdhury, C.; Kundu, N. G. *Synlett* **1998**, 1273. (c) Montiero, N.; Balme, G. *Synlett* **1998**, 746. (d) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863. (e) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327 and references therein. (f) Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435. (g) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363. (h) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280 and references therein. (i) Chowdhury, C.; Kundu, N. G. *J. Chem. Soc., Chem. Commun.* **1996**, 1067. (j) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86. (k) Candiani, I.; DeBernardinis, S.; Cabri, W.; Marchi, M.; Bedeschi, A.; Penco, S. *Synlett* **1993**, 269. (l) Zhang, H.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4449. (m) Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311. (n) Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307.

10.1021/ol990067v CCC: $18.00
Published on Web 07/20/1999

and not the expected disubstituted heterocycle 4-phenyl-3-(trimethylsilyl)isoquinoline, was isolated in 85% yield from the palladium-catalyzed reaction of *N*-(2-iodobenzylidene)-*tert*-butylamine (**1**) and 1-phenyl-2-(trimethylsilyl)acetylene (eq 1). Herein, we report that monosubstituted isoquinolines



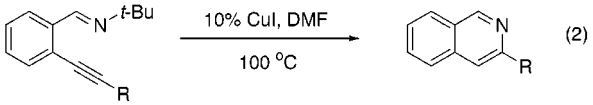
(1)

and pyridines can be synthesized in good to excellent yields by the coupling of terminal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst and subsequent copper-catalyzed cyclization of the intermediate iminoalkynes.

The surprising results obtained from silyl acetylenes (eq 1) encouraged us to examine the mechanism of this interesting transformation and to define the scope and limitations of this new isoquinoline synthesis. On the basis of the regiochemical outcome of much of our other alkyne annulation chemistry in which the palladium adds to the more hindered end of the alkyne,[1−6] the expected products from the reaction with trimethylsilyl-substituted alkynes were either the 3,4-disubstituted products retaining the silyl group or the corresponding 4-substituted isoquinoline arising from desilylation of the 3,4-disubstituted isoquinoline. Since the major product isolated from the reaction of **1** and 1-phenyl-2-(trimethylsilyl)acetylene possessed a phenyl substituent in the 3-position of the isoquinoline, it seemed plausible that desilylation and subsequent in situ coupling and cyclization was taking place to give the observed products. This was confirmed by the observation that 2-(2-phenylethynyl)-benzaldehyde could be isolated, after hydrolysis of the imine during workup, if the reaction was not allowed to proceed to completion.

It was therefore anticipated that terminal acetylenes would undergo this annulation. Indeed, phenylacetylene was subsequently observed to participate in the palladium-catalyzed reaction with **1** to afford an 85% yield of **2** when employing 1 equiv of **1**, 1.1 equiv of phenylacetylene, 5 mol % of $PdCl_2(PhCN)_2$, and 1 equiv of Na_2CO_3 in DMF at 100 °C for 14 h. By employing these same reaction conditions, 3-(cyclohex-1-enyl)isoquinoline (**3**) was synthesized from **1** and 1-ethynylcyclohexene in 78% yield after a 78 h reaction time. Unfortunately, the attempted annulation of **1** and other terminal acetylenes bearing simple alkyl groups, namely cyclohexyl acetylene and 1-hexyne, afforded none of the desired isoquinolines.

In an attempt to increase the generality of this annulation process, we subsequently investigated the palladium-catalyzed cyclization of the presumed intermediate iminoalkynes **3a** and **3c**. Iminoalkyne **3a** could be cyclized to isoquinoline **2** in 88% yield by employing 5 mol % of $PdCl_2(PhCN)_2$ and 1 equiv of Na_2CO_3 in DMF at 100 °C for 14 h. However, **3c** could not be cyclized using these reaction conditions. Interestingly, by employing 10 mol % of CuI, instead of $PdCl_2(PhCN)_2$, as the catalyst for the cyclization, 3-phenylisoquinoline could be obtained in quantitative yield from the cyclization of **3a** (eq 2). In addition, iminoalkynes containing alkenyl, and most importantly alkyl substituents, also cyclized to the desired monosubstituted isoquinolines in excellent yields in short reaction times (eq 2).



(2)

R = Ph (**3a**, 3 h, 91%), cyclohex-1-enyl (**3b**, 4 h, 81%), cyclohexyl (**3c**, 4 h, 93%)

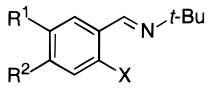
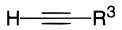
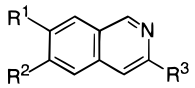
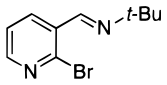
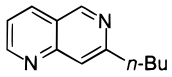
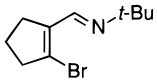
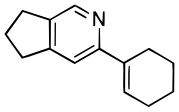
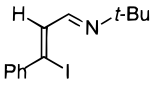
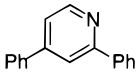
On the basis of this work, it was felt that a reasonable mechanism for this terminal alkyne annulation process involves coupling of the aryl halide and terminal acetylene to produce the intermediate iminoalkyne, followed by cyclization to the isoquinoline. The reaction conditions employed for any one-pot synthesis must therefore be compatible with both steps in the catalytic cycle. Since both palladium and/or copper have been shown by us to effect both of these individual steps, we felt it should be possible to efficiently synthesize the desired monosubstituted isoquinolines in a single process.

We subsequently observed that the following reaction conditions readily effect this isoquinoline synthesis. The imine (0.5 mmol), the terminal acetylene (0.6 mmol), 2 mol % of $PdCl_2(PPh_3)_2$, and 1 mol % of CuI in 2 mL of Et_3N were heated at 55 °C until the coupling was judged complete by thin-layer chromatography. The solvent and the precipitates were subsequently removed (since they apparently interfere in the subsequent cyclization), and DMF (5 mL) and 10 mol % of CuI were added to the residue. The resulting mixture was then heated at 100 °C until the cyclization was judged complete by thin-layer chromatography. By employing this reaction sequence, a variety of isoquinolines have been synthesized in good to excellent yields (Table 1).

A variety of terminal acetylenes have been employed in this palladium/copper-catalyzed process. For example, the reaction of imine **1** with aryl-, alkenyl-, and alkyl-substituted acetylenes affords the desired isoquinolines in good to excellent yields (Table 1, entries 1−4). Both electron-rich aryl bromides (entry 5) and electron-poor heteroaryl bromides (entry 6) have proven successful. Furthermore, pyridines can be synthesized by employing vinylic imines. Pyrindine **10** and pyridine **12** have been synthesized in moderate yields from vinylic imines **9** and **11**, respectively (entries 7 and 8).

(8) For recent leading references, see: (a) Monteiro, N.; Arnold, A.; Balme, G. *Synlett* **1998**, 1111. (b) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741. (c) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327 and references therein. (d) Arcadi, A.; Anacardio, R.; D'Anniballe, G.; Gentile, M. *Synlett* **1997**, 1315. (e) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280 and references therein. (f) Balme, G.; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403. (g) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (h) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976. (i) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915.

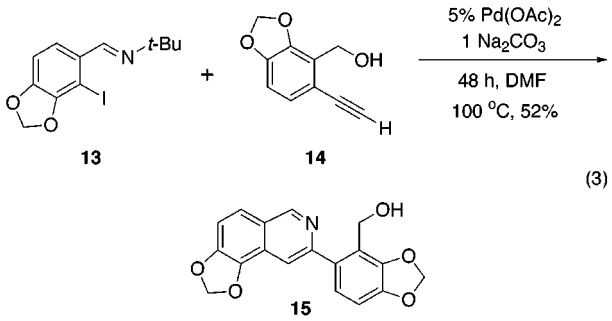
Table 1. Synthesis of Isoquinolines, Naphthyridines, and Pyridines[a]

entry	imine	alkyne	coupling time (h)	cyclization time (h)	product	% yield
						
	R¹ **R²** **X**	**R³**				
1	H H I	Ph	2	1	**2**	91
2		cyclohex-1-enyl	1	5	**3**	81
3		cyclohexyl	1	2	**4**	88
4		$CH(OEt)_2$	1	2	**5**	84
5	OCH_2O Br	cyclohexyl	2	12	**6**	76
6	 **7**	*n*-Bu	2	15	 **8**	72
7	 **9**	cyclohex-1-enyl	1	60	 **10**	55
8	 **11**	Ph	1	36	 **12**	57

[a] A representative procedure for the annulation of terminal acetylenes: 0.5 mmol of the imine, 0.6 mmol of the terminal acetylene, 2 mol % of $PdCl_2(PPh_3)_2$, and 1 mol % of CuI in 2 mL of Et_3N were heated at 55 °C to effect the coupling step. The solvent and precipitates were removed, and the residue was heated at 100 °C in the presence of 10 mol % of CuI in 5 mL of DMF to effect cyclization to the nitrogen heterocycle.

Unfortunately, this pyridine synthesis appears to be limited to aryl- and alkenyl-substituted acetylenes, since the reaction of imine **9** and *N*-(2-bromocyclohex-1-enylmethylene)-*tert*-butylamine with various *alkyl*-substituted acetylenes afforded only low yields of the desired pyridines (~10%). We have also encountered difficulties with this procedure when alcohol functionality is present in the alkyne.

To demonstrate the versatility of this annulation methodology, we have applied this coupling/cyclization process to the synthesis of the naturally occurring isoquinoline alkaloid decumbenine B (**15**). Decumbenine B was recently isolated in small amounts from the plant tubers of *Corydalis decumbens*, which have been used in Chinese folk herbal medicine for the treatment of paralytic stroke and rheumatic arthritis.[9] The only previous synthesis of this alkaloid required 18 steps and afforded only a very low overall yield.[10] Employing the palladium-catalyzed coupling/cyclization of imine **13** and alkyne **14**, since the alkyne contains alcohol functionality, decumbenine B was synthesized in seven steps and 20% overall yield (eq 3). This efficient synthesis demonstrates the synthetic utility of this approach and its ability to accommodate important functionality.



(3)

In conclusion, efficient palladium- and copper-catalyzed syntheses of isoquinolines and pyridines have been developed. A wide variety of functionalized terminal acetylenes participate in this palladium-catalyzed coupling and copper-catalyzed cyclization process to afford the desired nitrogen heterocycles in moderate to excellent yields. Further studies into the scope and limitations of this annulation process are underway.

(9) Zhang, J.; Zhu, D.; Hong, S. *Phytochemistry* **1995**, *39*, 435.
(10) Xu, X.; Qin, G.; Xu, R.; Zhu, X. *Tetrahedron* **1998**, *54*, 14179.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for donation of the palladium salts, and Merck and Co., Inc., for an Academic Development Award in Chemistry.

Supporting Information Available: General experimental procedures, ^{1}H and ^{13}C spectra for compounds **4**, **5**, **6**, **8**, and **10**, and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990067V