ACS Catalysis

LETTER

pubs.acs.org/acscatalysis

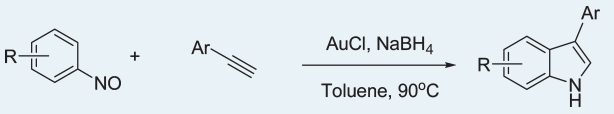
Gold-Catalyzed Synthesis of 3-Arylindoles via Annulation of Nitrosoarenes and Alkynes

Siva Murru, August A. Gallo, and Radhey S. Srivastava*

Department of Chemistry, University of Louisiana at Lafayette, Lafayette, Louisiana 70504, United States

Supporting Information

ABSTRACT: We have successfully developed a Au-catalyzed annulation method to produce substituted 3-arylindoles from the reaction of nitrosoarenes with arylsubstituted acetylenes under reductive conditions using sodium borohydride. Terminal alkynes reacted better than non-terminal ones with various substituted nitrosoarenes to afford regioselective 3-substituted indoles. This method is simple and straightforward and can be applied successfully to the synthesis of highly substituted indoles.



KEYWORDS: annulation, 3-arylindole, alkynes, nitrosoarenes, gold catalysis

The indole moiety can be found in numerous biologically active natural products, alkaloids and pharmaceuticals.[1] The indole alkaloids are structurally similar to endogenous amines and neurotransmitters, which led us to postulate possible neurological activity. A number of indole-based drugs that are currently on the market belong to the triptan family, and they are used mainly in the treatment of migraine headaches.[2] The bis and tris indoles are a class of marine natural products that are found to be active in the development of new drug leads.[3] Hence, there is an increasing demand for the development of general, efficient, and especially regioselective synthetic methods to access this heterocyclic moiety. One such direct strategy is the Fischer indole[4] and related synthesis, which employs aryl hydrazines and ketones.[5] To increase the efficiency, selectivity, and substrate scope, transition metal-catalyzed cyclization of o-substituted aryl acetylene precursors has proven to be a versatile method for the synthesis of highly substituted indoles.[6] Moreover, cyclization reactions of *o*-alkynylanilines have been reported.[7] A similar strategy was applied to access indole fragments via reductive cyclization of (2-nitroaryl) alkynes using stoichiometric reagents and catalysts.[8] Pd-catalyzed reductive amination of nitroalkenes for the synthesis of 3-phenylindoles is reported.[9] Although these methods are useful to access valuable indole heterocycles, most of them suffer due to the reduced availability of suitably substituted precursors.

To overcome this limitation, continuous efforts were made toward accessing these indoles directly from commercially available and simple aromatics. Nicholas et al. have reported the synthesis of indoles and *N*-methoxy indoles via reductive annulation/cycloaddition of aryl nitro-/nitrosoarenes/aryl hydroxylamines with alkynes.[10] This same group has also reported the mechanistic pathways of indole formation using kinetics and DFT calculations.[10d] A recent report on the one-pot synthesis of meridianins and meridianin analogues also utilized the chemistry of annulation of alkynes and nitrosoarenes.[11] A similar reaction was also reported by Ragaini et al. using Pd-catalyzed reductive annulation of nitroarenes.[12] However, these methods require high CO pressure and high temperature for the reduction of either precursor nitroarenes or in situ generated hydroxy indoles. Therefore, a need to develop an alternative and direct method to access the valuable 3-substituted indoles is necessitated.

In a continuation of our ongoing program in developing methods for metal-catalyzed nitrogenation reactions[13] and synthesis of various *N*-heterocycles,[14] we were interested in developing a direct method to access 3-arylindoles from aryl acetylenes and nitrosoarenes using a Au catalyst (Scheme 1). Inter- and intramolecular annulation chemistry by Nicholas using Ru catalysts,[10a,10b] Ragaini using Pd-catalysts,[12a] and Tokunaga using Au-catalysts[8g] have been reported. Even though some of the methods of preparation of 3-phenylindoles are effective, however, most methods require multistep preparation of precursor substrates, and harsh reaction conditions and result in low yields and long reaction times. Among the nitrogen precursors used for the annulation reaction, nitrosoarenes are preferred over the other, because nitroarenes require severe reaction conditions and limited availability of arylhydroxylamines. Herein, we report Au-catalyzed intermolecular reductive annulation of nitrosoarenes (**1**−**9**) and alkynes (**a**−**c**) to produce 3-aryl indoles. (Table 1, entries **1**−**12**).

Initially we performed the annulation reaction with nitrosobenzene (**1**) and phenylacetylene (**a**) using *p*-dioxane as solvent and Au(I)Cl as catalyst. The observed yield of 3-phenylindole (**1a**) was 84% (GC/MS analysis), but only a 10% isolated yield of **1a** was obtained, and the remaining product was found to be corresponding *N*-hydroxyindole. This observation is consistent with the previous findings by the Nicholas group.[10] When the amount of AuCl catalyst was increased, we observed that the yield of 3-phenylindole also increased, which indicates the catalyst was consumed well before the reaction was over.

Received: September 29, 2010
Revised: November 1, 2010
Published: December 13, 2010

Scheme 1. Formation of 3-Phenylindole via annulation of Nitrosobenzene and Alkyne

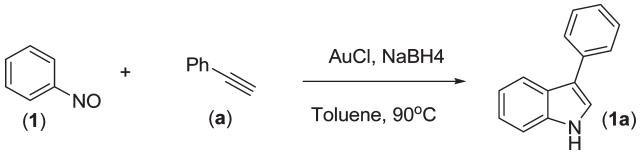


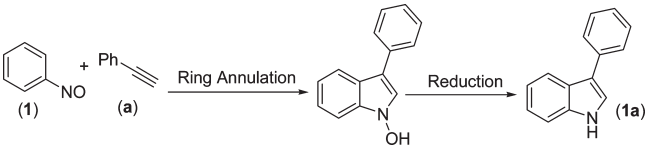
Table 1. Synthesis of 3-Phenylindoles from Nitrosoarenes and Arylacetylenes[a]

No.	Nitrosoarene	Acetylene	Product	% Yield [b]
1.	(1)	(a)	(1a)	67
2.	(2)	(a)	(2a)	59
3.	(3)	(a)	(3a)	48
4.	(4)	(a)	(4a)	63
5.	(5)	(a)	(5a)	54
6	(6)	(a)	(6a)	42 [c]
7	(7)	(a)	(7a)	47
8.	(8)	(b)	(8b)	36
9.	(1)	(b)	(1b)	45
10.	(5)	(b)	(5b)	48
11.	(8)	(c)	(8c)	39
12.	(9)	(a)	(9a)	58

[a] Reaction conditions: nitrosoarene (1 mmol), alkyne (5 mmol), AuCl (10 mol %), $NaBH_4$ (1.5 equiv), toluene (10 mL); temp, 90 °C; 6 h. [b] Isolated. [c] Reaction continued up to 14 h.

This may be due to the oxidation of Au(I) to Au(III), which in turn becomes inactive for the reduction of the remaining *N*-hydroxyindole. Speculating this may be the cause, we added 1 equiv of a reducing agent (sodium borohydride) to help to regenerate the active catalytic system. Our assumption was correct because the isolated yield of 3-phenylindole (**1a**) increased to 67%. To confirm further, we have carried out an experiment with sodium borohydride in the absence of Au catalyst. Unfortunately, no indole formation was observed, and the only product formed was azoxybenzene, which confirms the requirement of the Au catalyst. Further optimization of the present reaction conditions revealed that the optimum temperature is 90 °C, and the best solvent is toluene among various polar and nonpolar solvents tested (*p*-dioxane, acetonitrile, ethanol, tetrahydrofuran, etc.). Under the same conditions, the optimized catalytic amount of AuCl is found to be 10 mol % and TON is ∼7−8.

Scheme 2. Two-Step Formation of 3-Phenylindole via Annulation and Reduction Process



Under the optimized conditions, phenylacetylene (**a**) was reacted with various substituted nitrosoarenes (**1**−**9**). All the para-substituted nitrosoarenes (Table 1, entries **2**−**6** and **9**) reacted well to give the corresponding 3-phenylindoles in moderate to good yields, whereas ortho-substituted nitrosoarenes (Table 1, entries **7** and **8**) led to lower yields. This may be due to either steric hindrance or availability of only one ortho position for cyclization. Interestingly, all the nitrosoarenes (**1**−**9**) containing electron-poor and -rich substituents provided the corresponding 3-phenyl indoles regioselectively in fair yields. Slightly higher conversions were observed in the case of electron-poor nitrosoarenes. To our delight, the nitrosoarene-containing ester group at the para position (**9**) also gave good yield without any reduction in the ester group (Table 1, entry **12**).

No side reactions were observed while using the bromo- and chloro-substituted nitrosoarenes (Table 1, entries **4**, **5**, **7**, and **10**). The 5-bromo- and chloroindoles can be used for further functionalization as valuable substituted indole scaffolds.[15] Interestingly, the *N*,*N*-diethylamino nitrosobenzene (**6**), commonly found to be an inactive nitrogen fragment donor in metal-catalyzed allylic aminations, reacted with phenylacetylene to yield the corresponding indole (**6a**, 42%), though in low yield. The common side product in these reactions is azoxybenzene in smaller amounts (∼5−10%).

We then further explored the scope of indole formation reaction of nitrosobenzene (**1**), *p*-bromonitrosobenzene (**5**) and *o*-nitrosotoluene with other substituted phenyl acetylenes (**b**, **c**), and the results are summarized in Table 1. The phenylpropyne (**b**) with various nitrosoarenes underwent annulation to afford the desired products (**1b**, **5b**, and **8b**) in good to moderate yields. But the reaction of 4-ethynyltoluene with *o*-tolylnitrosobenzene (**c**) gave the corresponding 3-phenylindole (**8c**) in only 39% yield.

Consistent with the observation of other research groups, we believe that two steps are involved in the formation of 3-phenylindoles. The first step is an uncatalyzed annulation of nitrosobenzene and alkyne to give *N*-hydroxy-3-phenylindole, followed by the AuCl/$NaBH_4$ catalyzed reduction to give 3-arylindoles, as shown in Scheme 2.

dx.doi.org/10.1021/cs100024n |*ACS Catal.* 2011, 1, 29–31

In summary, we have successfully developed a Au-catalyzed, one-pot synthesis of substituted 3-arylindoles in moderate to good yields. The addition of a reducing agent is essential for the complete reduction of the hydroxyindole so as to generate an active catalytic system. This annulation method is simple and straightforward, and it can be applied successfully for various arylacetylenes and nitrosoarenes. Further studies on the activity of the catalyst and mechanism are underway.

EXPERIMENTAL SECTION

Procedure for the 3-Phenylindole (1a) Formation. A Schlenk flask was charged with AuCl (10 mol %), toluene (5 mL), phenylacetylene (**a**) (5 mmol), and sodium borohydride (1.2 mmol). The flask was placed in a preheated oil bath at 90 °C, and then a solution of nitrosobenzene **1** (1 mmol) in toluene (5 mL) was added slowly with the help of a syringe pump over a period of 6 h under a positive pressure of nitrogen. The reaction mixture was cooled and filtered over Celite using diethyl ether. The solvent was reduced under vacuum, and further purification of the crude product was achieved by column chromatography using hexane and ethyl acetate as eluents.

ASSOCIATED CONTENT

Supporting Information. General procedure for the preparation of nitrosoarenes, ^{1}H and ^{13}C NMR spectroscopic data and spectra for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: rss1805@louisiana.edu.

ACKNOWLEDGMENT

We are grateful for financial support from the Louisiana Board of Regents.

REFERENCES

(1) (a) Aygun, A.; Pindur, U. *Curr. Med. Chem.* **2003,** *10,* 1113. (b) Gul, W.; Hamann, M. T. *Life Sci.* **2005,** *78,* 442. (c) Leboho, T. C.; Michael, J. P.; van Otterlo, W. A. L.; van Vuuren, S. F.; de Koning, C. B. *Bioorg. Med. Chem. Lett.* **2009,** *19,* 4948. (d) Medvedev, A. E.; Ivanov, A. S.; Kamyshanskaya, N. S.; Kirkel, A. Z.; Moskvitina, T. A.; Gorkin, V. Z.; Li, N. Y.; Marshakov, V. Yu. *Biochem. Mol. Biol. Int.* **1995,** *36,* 113.

(2) (a) Sheftell, F. D.; Bigal, M. E.; Tepper, S. J.; Rapaport, A. M. *Expert Rev. Neurother.* **2004,** *4,* 199. (b) Balbisi, E. A. *Int. J. Clin. Pract.* **2004,** *58,* 695. (c) Markus, F.; Mikko, D. K. *Expert Opin. Pharmacother.* **2007,** *8,* 3029. (d) Kochanowska-Karamyan, A. J.; Hamman, M. T. *Chem. Rev.* **2010,** *110,* 4489.

(3) Gupta, L.; Talwar, A.; Chauhan, M. S. *Curr. Med. Chem.* **2007,** *14,* 1789.

(4) (a) Fischer, E.; Jourdan, F. *Ber.* **1883,** *16,* 2241. (b) Fischer, E.; Hess, O. *Ber.* **1884,** *17,* 559. (c) Robinson, B. *Chem. Rev.* **1963,** *63,* 373. (d) Robinson, B. *Chem. Rev.* **1969,** *69,* 227.

(5) Banerjee, S.; Barnea, E.; Odom, A. L. *Organometallics* **2008,** *27,* 1005.

(6) (a) Batail, N.; Bendjeriou, A.; Lomberget, T.; Barret, R.; Dufaud, V.; Djakovitch, L. *Adv. Synth. Catal.* **2009,** *351,* 2055. (b) Xu, Z.; Hu, W.; Zhang, F.; Li, Q.; Lu, Z.; Zhang, L.; Jia, Y. *Synthesis* **2008,** *24,* 3981. (c) Ackermann, L.; Sandmann, R.; Villar, A.; Kaspar, L. T. *Tetrahedron* **2007,** *64,* 769.

(7) (a) Larock, R. C. *J. Organomet. Chem.* **1999,** *576,* 111. (b) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997,** *62,* 2676. (c) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004,** *43,* 4526. (d) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Commun.* **2004,** 2824. (e) Kruger, K.; Tillack, A.; Beller, M. *Adv. Synth. Cat.* **2008,** *350,* 2153.

(8) (a) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002,** *43,* 7699. (b) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004,** *69,* 1126. (c) Tarshits, D. L.; Tarasov, S. Y.; Buyanov, V. N. *Russ. Chem. Bull. Int. Ed.* **2005,** *54,* 2586. (d) Park, J. G.; Sill, P. C.; Makiyi, E. F.; Garcia-Sosa, A. T; Millard, C. B.; Schmidt, J. J.; Pang, Y.-P. *Bioorg. Med. Chem.* **2006,** *14,* 395. (e) Naffziger, M. R.; Ashburn, B. O.; Perkins, J. R.; Carter, R. G. *J. Org. Chem.* **2007,** *72,* 9857. (f) Kim, J. S.; Han, J. H.; Lee, J. J.; Jun, Y. M.; Lee, B. M.; Kim, B. H. *Tetrahedron Lett.* **2008,** *49,* 3733. (g) Yamane, Y.; Liu, X.; Hamasaki, A.; Ishida, T.; Haruta, M.; Yokoyama, T.; Tokunaga, M. *Org. Lett.* **2009,** *11,* 5162.

(9) Hsieh, T. H. H.; Dong, V. M. *Tetrahedron* **2009,** *65,* 3062.

(10) (a) Penoni, A.; Nicholas, K. M. *Chem. Commun.* **2002,** 484. (b) Penoni, A.; Volkmann, J.; Nicholas, K. M. *Org. Lett.* **2002,** *4,* 699. (c) Penoni, A.; Palmisano, G.; Broggini, G.; Kadowaki, A.; Nicholas, K. M. *J. Org. Chem.* **2006,** *71,* 823. (d) Penoni, A.; Palmisano, G.; Zhao, Y.-L.; Houk, K. N.; Volkman, J.; Nicholas, K. M. *J. Am. Chem. Soc.* **2009,** *131,* 653. (e) Lamar, A. A.; Nicholas, K. M. *Tetrahedron* **2009,** *65,* 3829.

(11) Tibiletti, F.; Simonetti, M.; Nicholas, K. M.; Palmisano, G.; Parravicini, M.; Imbesi, F.; Tollari, S.; Penoni, A. *Tetrahedron* **2010,** *66,* 1280.

(12) (a) Ragaini, F.; Rapetti, A.; Visentin, E.; Monzani, M.; Caselli, A.; Cenini, S. *J. Org. Chem.* **2006,** *71,* 3748. (b) Ragaini, F.; Ventriglia, F.; Hagar, M.; Fantauzzi, S.; Cenini, S. *Eur. J. Org. Chem.* **2009,** *13,* 2185.

(13) (a) Srivastava, R. S.; Nicholas, K. M. *Tetrahedron Lett.* **1994,** *35,* 8739. (b) Srivastava, R. S.; Nicholas, K. M. *J. Org. Chem.* **1994,** *59,* 5365. (c) Srivastava, R. S.; Khan, M. A.; Nicholas, K. M. *J. Am. Chem. Soc.* **1996,** *118,* 3311. (d) Srivastava, R. S.; Nicholas, K. M. *Chem. Commun.* **1996,** 2335. (e) Srivastava, R. S.; Nicholas, K. M. *J. Am. Chem. Soc.* **1997,** *119,* 3302. (f) Srivastava, R. S.; Nicholas, K. M. *Chem. Commun.* **1998,** 2705. (g) Hogan, G. A.; Gallo, A. A.; Nicholas, K. M.; Srivastava, R. S. *Tetrahedron Lett.* **2002,** *43,* 9505. (h) Srivastava, R. S.; Khan, M. A.; Nicholas, K. M. *J. Am. Chem. Soc.* **2005,** *127,* 7278. (i) Srivastava, R. S.; Tarver, N. R.; Nicholas, K. M. *J. Am. Chem. Soc.* **2007,** *129,* 15250.

(14) (a) Murru, S.; Patel, B. K.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2009,** *74,* 2217. (b) Murru, S.; Yella, R.; Patel, B. K. *Eur. J. Org. Chem.* **2009,** 5406. (c) Murru, S.; Patel, B. K.; Ghosh, H.; Sahoo, S. K. *Org. Lett.* **2009,** *11,* 4254. (d) Murru, S.; Singh, C. B.; Kavala, V.; Patel, B. K. *Tetrahedron* **2008,** *64,* 1931.

(15) (a) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005,** *7,* 3965. (b) Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006,** *8,* 5613. (c) Itoh, T.; Mase, T. *Org. Lett.* **2004,** *6,* 4587. (d) McBride, C. M.; Renhowe, P. A.; Gesner, T. G.; Jansen, J. M.; Lin, J.; Ma, S.; Zhou, Y.; Shafer, C. M. *Bioorg. Med. Chem. Lett.* **2006,** *16,* 3789.