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Copper-Catalyzed Direct Synthesis of 3-Arylindoles

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

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A direct method for the preparation of various 3-arylindoles from their corresponding nitrosoarenes has been developed. Various substituted nitrosoarenes and alkynes were employed to obtain substituted indoles by using a Cu^{II}–Cu^{0} catalytic system. This is a two-step method that involves annulation of the nitrosoarene and alkyne followed by deoxygenation to give 3-arylindoles.

Introduction

Over the past few decades the area of heterocyclic synthesis has especially benefited from novel copper-facilitated transformations, as these operations are generally tolerant to a wide range of functionalities and are therefore applicable to the synthesis of complex molecules. The high stability and low cost of copper catalysts make them a better alternative to other expensive metal catalysts. Copper has a high affinity for polar functional groups such as amines and alcohols. The redox chemistry of copper has been well established and utilized for various organic transformations.[1]

Numerous methods have been reported for the synthesis of various nitrogen heterocycles using copper catalysts. Indoles are the most significant heterocycles among all the known nitrogen heterocycles, because the indole moiety is one of the most frequently encountered subunits in pharmacologically active compounds.[2] Various 2- and 3-arylindoles display significant antimicrobial activity against the Gram-positive microorganism *Bacillus cereus*.[3] Substituted indole INF55 is a promising lead in helping a wide range of antibiotics stay in bacterial cells.[4] Some aryl-substituted indoles have been implicated in the inhibition of bacterial histidine kinases.[5a] Some of the pharmaceutically important compounds containing a 3-arylindole skeleton are shown in Figure 1.[5b]

Fulvastatin (**i**) is a member of the statin drug family and is used for many treatments, and it is also found to exhibit antiviral activity against hepatitis C.[5c] Substituted 3-(4-fluorophenyl)-1*H*-indoles **ii** were found to act as serotonin HT_2 antagonists.[5d] Another example of an active compound of this class is 4-fluoro-3-phenylindole (**iii**), which is an inhibitor of brassinin glucosyltransferase, a phytoalexin detoxifying enzyme from the fungus *Sclerotinia sclerotiorum*.[3,5e]

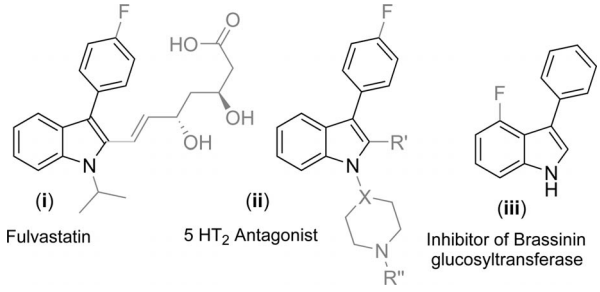

Figure 1. Some pharmaceutically active compounds containing the 3-arylindole skeleton.

The synthesis and functionalization of indoles has been the object of research for over 100 years, and a variety of well-established classical methods are now available.[6] Traditional synthetic methods for 3-arylated indoles involve the metal-catalyzed C-3 arylation or coupling reactions using Pd catalysis.[7] However, methods for the regioselective synthesis of 3-arylated indoles are limited. Consequently, there is a continued demand for the development of general, flexible, and especially regioselective synthetic methods for this structural moiety. Recently, a few such regioselective methods starting from nitroarenes, aryl hydroxylamines, and nitrosoarenes have been reported by Nicholas et al.,[8] Ragaini et al.,[5b,9] and by us[10] using various metal (Ru, Fe, Pd, and Au) catalysts.

Results and Discussion

In connection with our ongoing research on Cu^{I}-catalyzed carbon–heteroatom bond formation to access organonitrogen compounds[11] and heterocycles,[12] we have extended our methods to access valuable 3-arylindoles. By taking cues from our previous report on Cu-catalyzed allylic aminations with nitrosoarenes (Scheme 1) in which formation of *N*-allylhydroxylamine followed by deoxygenation

[a] Department of Chemistry, University of Louisiana at Lafayette, Lafayette, Louisiana 70504, USA
Fax: +1-337-482-5677
E-mail: rss1805@louisiana.edu

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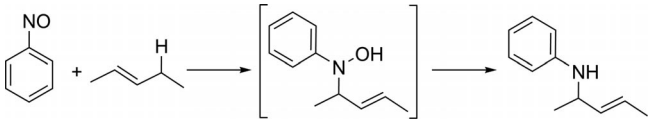
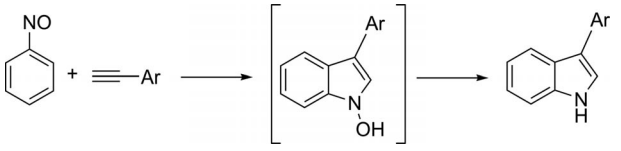
occurs to give *N*-allylamine,[13] we envisaged that the formation of *N*-hydroxyindole followed by deoxygenation could lead to 3-arylindoles (Scheme 2).



Scheme 1. Cu-catalyzed allylic amination from nitrosoarenes and olefins.

As shown in Scheme 2, we propose the synthesis of 3-arylindoles through ring annulation starting from the corresponding arylacetylenes and nitrosoarenes followed by deoxygenation using our copper-catalyzed protocol developed for allylic amination, which involves the use of catalytic amounts of $CuCl_2{\cdot}2H_2O$ (0.2 equiv.) and Cu powder (0.6 equiv.) to produce a Cu^I species in situ.[14]



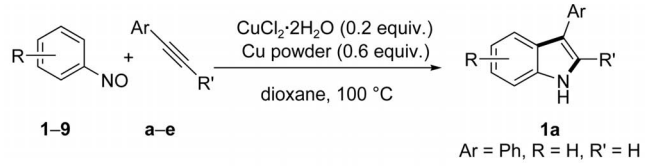
Scheme 2. Formation of 3-arylindole by annulation and deoxygenation.

We tested the initial reaction of nitrosobenzene (1 mmol) with phenylacetylene (5 mmol) using $CuCl_2{\cdot}2H_2O$ (0.2 mmol) and Cu powder (0.6 mmol) in dioxane at 100 °C. Nitrosobenzene was added slowly over a period of 4 h by using a syringe pump and the reaction was then continued. The reaction was complete in 6 h, and we observed the formation of 3-phenylindole, which was isolated in 62% yield. In addition to 3-phenylindole, azoxybenzene and aniline were formed as side products, which were identified by GC–MS analysis.

When the solvents were surveyed at the same temperature, the reaction was found to proceed more efficiently in 1,4-dioxane than in other solvents like THF, MeCN, DME, and toluene. Lowering the temperature led to longer reaction times. With the established optimized conditions, we next set out to determine the scope and practicality of the method through the synthesis of substituted indoles. Nitrosoarenes **2**–**9** prepared from the corresponding anilines by using a catalytic hydrogen peroxide oxidation method[15] were converted smoothly into their corresponding 3-arylindoles **2a**–**9c** in shorter reaction times. As shown in Table 1, a variety of substituents are well tolerated. *para*-Substituted nitrosoarenes containing electron-withdrawing groups work more efficiently than nitrosoarenes containing electron-donating substituents. This observation is similar to our previous report on an Au-catalyzed approach.[10]

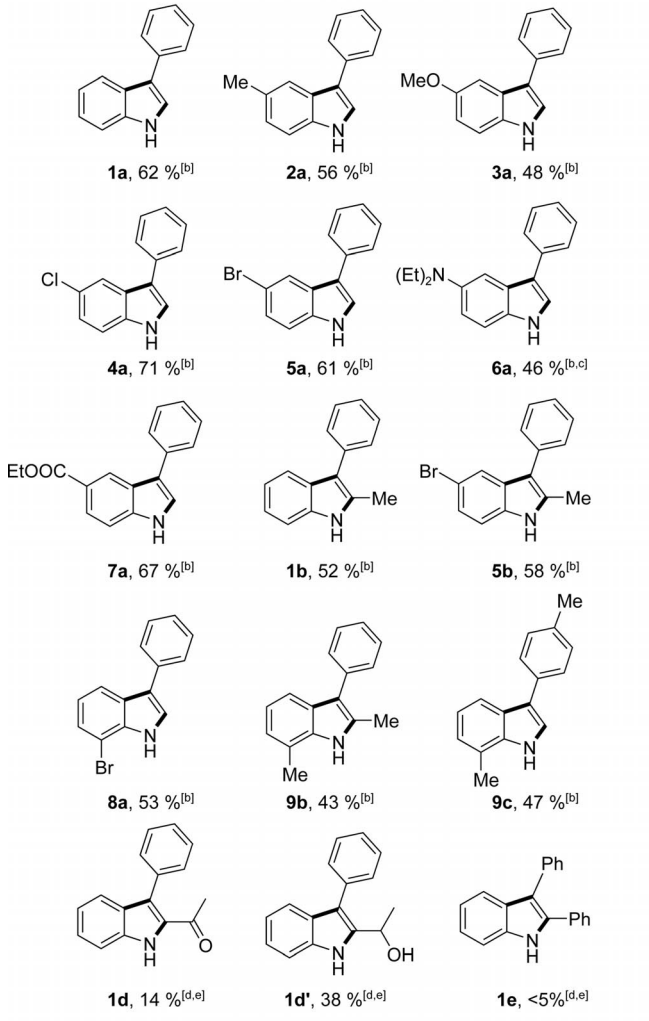
A range of alkynes such as phenylacetylene (**a**), 1-phenylpropyne (**b**), 4-ethynyltoluene (**c**), 4-phenyl-3-butyn-2-ol (**d**), and diphenylacetylene (**e**) were tested with nitrosoarenes **1**, **5**, **8**, and **9**. Terminal alkynes **a** and **c** were found to react well, and the corresponding 3-arylindoles were isolated in good yields up to 71%. reactions involving nonterminal alkynes **b**, **d**, and **e** either were less efficient or no reaction was observed. Alkyne **b** provided corresponding indoles **1b**, **5b**, and **9b** in moderate yields with nitrosobenzenes **1**, **5**, and **9**, respectively, whereas alkyne **d** yielded products **1d** and **1d′**. Formation of **1d** is due to the oxidation of the secondary alcohol present in alkyne **d** to the corresponding ketone. Unfortunately, the reaction of nitrosobenzene with diphenylacetylene (**e**) gave less than 5% yield, and the product was confirmed by GC–MS analysis.

Table 1. Preparation of 3-aryl-substituted indoles from nitrosoarenes and alkynes.[a]



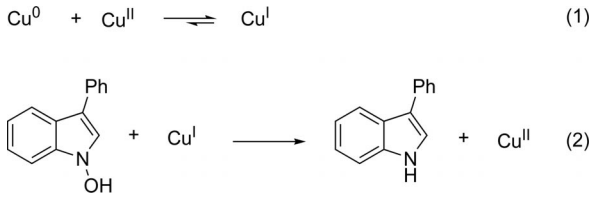
1–9 **a–e** **1a**

Ar = Ph, R = H, R' = H



[a] Reaction conditions: **1** (1 mmol), **a** (5 mmol), $CuCl_2{\cdot}2H_2O$ (0.2 mmol), Cu powder (0.6 equiv.), dioxane (8 mL), 100 °C, 5 h. [b] Isolated yield. [c] Reaction continued up to 20 h. [d] Compounds **1d** and **1d′** were isolated as a mixture. Compound **1e** could not be isolated. [e] GC yield.

Based on our previous reports on allylic amination and indole formation,[10,11g] this catalytic process must be involved in the formation of *N*-hydroxyindole, which will be deoxygenated further to give 3-arylindole, and this same finding was confirmed by a controlled experiment starting from *N*-hydroxyindole. The in situ generated Cu^{I} species (Scheme 3, Equation 1) from Cu^{II} and Cu^{0} is responsible for deoxygenation of *N*-hydroxyindole (Scheme 3, Equation 2), which in turn is converted into Cu^{II} and the cyclic process continues.



Scheme 3. Deoxygenation of *N*-hydroxyindole by in situ generated Cu^{I} species and its regeneration from the corresponding Cu^{0} and Cu^{II} salts.

In this catalytic process, Cu^{I} might be the real catalytic species generated from the redox couple of Cu^{0} powder and Cu^{II} salt. Similar deoxygenation by Cu^{I} from *N*-allylhydroxylamine was observed and proved by Lau et al.[16]

Conclusions

In conclusion, we have developed a direct Cu-catalyzed protocol for the synthesis of 3-arylindoles. The nitrosoarenes afforded the corresponding indoles through annulation followed by deoxygenation in good to moderate yields. Thus, with the appropriate choice of substrates, differently substituted indoles can be obtained.

Experimental Section

A Schlenk flask was charged with $CuCl_2 \cdot 2H_2O$ (0.2 equiv.), Cu powder (0.6 equiv.), dioxane (5 mL), and phenylacetylene (**a**; 5 equiv.). The flask was placed in a preheated oil bath at 100 °C, and then a solution of nitrosobenzene **1** (1 mmol) in dioxane (5 mL) was added slowly with the help of a syringe pump over a period of 4 h under a positive pressure of nitrogen. The reaction mixture was cooled and filtered through Celite using diethyl ether. The solvent was reduced under vacuum, and further purification of the crude product was achieved by column chromatography (hexane/ethyl acetate).

Supporting Information (see footnote on the first page of this article): ^{1}H NMR spectroscopic data and copies of the spectra.

Acknowledgments

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[1] a) N. Krause, *Modern Organocopper Chemistry*, Wiley-VCH, Weinheim, **2002**; b) D. S. Surry, D. R. Spring, *Chem. Soc. Rev.* **2006**, *35*, 218; c) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; d) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; e) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337; f) S. R. Chemler, P. Fuller, *Chem. Soc. Rev.* **2007**, *36*, 1153.

[2] a) H.-P. Husson in *The Alkaloids*, *Chemistry and Pharmocology* (Ed.: A. Brossi), Academic Press, Amsterdam, **1986**, vol. 26, ch. 1, pp 1–46; b) M. Lounasmaa, P. Hanhihen in *The Alkaloids*, *Chemistry and Biology* (Ed.: G. A. Cordell), Academic Press, Amsterdam, **2000**, vol. 55, ch. 1, pp 1–88; c) M. Álvarez, J. A. Joule in *The Alkaloids*, *Chemistry and Biology* (Ed.: G. A. Cordell), Academic Press, Amsterdam, **2001**, vol. 57, ch. 3, pp 235–272; d) R. J. Sundberg, S. Q. Smith in *The Alkaloids*, *Chemistry and Biology* (Ed.: G. A. Cordell), Academic Press, Amsterdam, **2002**, vol. 59, ch. 2, pp 281–376.

[3] T. C. Leboho, J. P. Michael, W. A. L. van Otterlo, S. F. van Vuuren, C. B. de Koning, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4948.

[4] a) S. Samosorn, J. B. Bremner, A. Ball, K. Lewis, *Bioorg. Med. Chem.* **2006**, *14*, 857; b) J. L. Ambrus, M. J. Kelso, J. B. Bremner, A. R. Ball, G. Casadei, K. Lewis, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4294.

[5] a) R. J. Deschenes, H. Lin, A. D. Ault, J. S. Fassler, *Antimicrob. Agents Chemother.* **1999**, *43*, 1700; b) F. Ragaini, F. Ventriglia, M. Hagar, S. Fantauzzi, S. Cenini, *Eur. J. Org. Chem.* **2009**, *13*, 2185; c) T. Bader, J. Fazili, M. Madhoun, C. Aston, D. Hughes, S. Rizvi, K. Seres, M. Hasan, *Am. J. Gastroenterol.* **2008**, *103*, 1383; d) K. Andersen, J. Perregaard, J. Arn, J. B. Nielsen, M. Begtrup, *J. Med. Chem.* **1992**, *35*, 4823; e) M. S. C. Pedras, M. Hossain, *Bioorg. Med. Chem.* **2007**, *15*, 5981.

[6] a) R. J. Sundberg in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, vol. 4, p. 313; b) T. L. Gilchrist, *Heterocyclic Chemistry*, Addison-Wesley Longman Limited, Singapore, **1997**; c) J. A. Joule, K. Mills, G. F. Smith, *Heterocyclic Chemistry*, Stanley Thornes Ltd., Cheltenham, **1995**.

[7] a) S. Kirchberg, R. Frohlich, A. Studer, *Angew. Chem.* **2009**, *121*, 4299; *Angew. Chem. Int. Ed.* **2009**, *48*, 4235; b) N. Batail, A. Bendjeriou, T. Lomberget, R. Barret, V. Dufaud, L. Diakovitch, *Adv. Synth. Catal.* **2009**, *351*, 2055; c) F. Bellina, F. Benelli, R. Rossi, *J. Org. Chem.* **2008**, *73*, 5529.

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

[9] F. Ragaini, A. Rapetti, E. Visentin, M. Monzani, A. Caselli, S. Cenini, *J. Org. Chem.* **2006**, *71*, 3748.

[10] S. Murru, A. A. Gallo, R. S. Srivastava, *ACS Catal.* **2011**, *1*, 29.

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

[12] a) S. Murru, B. K. Patel, J. Le Bras, J. Muzart, *J. Org. Chem.* **2009**, *74*, 2217; b) S. Murru, R. Yella, B. K. Patel, *Eur. J. Org. Chem.* **2009**, 5406; c) S. Murru, B. K. Patel, H. Ghosh, S. K.

Sahoo, *Org. Lett.* **2009**, *11*, 4254; d) S. Murru, C. B. Singh, V. Kavala, B. K. Patel, *Tetrahedron* **2008**, *64*, 1931.
[13] R. S. Srivastava, *Tetrahedron Lett.* **2003**, *44*, 3271.
[14] F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann, *Advanced Inorganic Chemistry*, 6th ed., Wiley, New York, **1999**, p. 855.
[15] D. Zhao, M. Johansson, J.-E. Bäckvall, *Eur. J. Org. Chem.* **2007**, 4431.
[16] C.-M. Ho, T.-C. Lau, *New J. Chem.* **2000**, *24*, 859.

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