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Synthesis of 3-Iodoindoles by Electrophilic Cyclization of *N*,*N*-Dialkyl-2-(1-alkynyl)anilines

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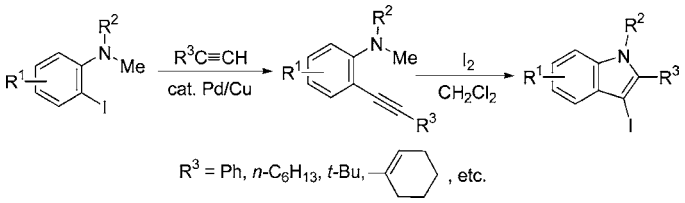
ABSTRACT



A wide variety of *N*-alkyl-3-iodoindoles are readily prepared under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of *N*,*N*-dialkyl-*o*-iodoanilines and terminal alkynes, followed by electrophilic cyclization by I_2. Alkyl-, aryl-, and vinylic-substituted alkynes all undergo iodocyclization in excellent yields.

The indole nucleus is prevalent in a wide variety of biologically active natural and unnatural compounds.[1] The synthesis and functionalization of indoles have been the major objectives of research for over one hundred years. Among the most recent synthetic targets have been pharmacologically active ergot alkaloids,[2] the antitumor agents ellipticine[3] and mitomycin C,[4] and more complex "dimeric" indole alkaloids, such as vincristine and vinblastine.[5] A number of synthetic approaches to this class of compounds have been introduced in recent years.[6]

Many synthetic methods, including palladium-catalyzed intermolecular annulation[6a,b] and transition metal catalyzed intramolecular cyclization,[6c−e] have been successfully employed in the synthesis of indoles. However, some of these approaches are either incompatible with functionality[6f] or sometimes restricted by a lack of regioselectivity.[6a] Recent success in the synthesis of benzo[*b*]furans,[7] furopyridines,[8] isoquinolines,[9] and benzo[*b*]thiophenes[10] by the electrophilic

(1) (a) McKay, M. J.; Carroll, A. R.; Quinn, R. J.; Hooper, J. N. A. *J. Nat. Prod.* **2002**, *65*, 595. (b) Verpoorte, R. *Alkaloids* **1998**, 397−433. (c) Sundberg, R. J. *Prog. Heterocycl. Chem.* **1989**, *1*, 111. (d) Saxon, J. E. *Nat. Prod. Rep.* **1986**, *3*, 357. Saxon, J. E. *Nat. Prod. Rep.* **1987**, *4*, 591. Saxon, J. E. *Nat. Prod. Rep.* **1989**, *6*, 1. (e) Sundberg, R. J. Indoles. In *Best Synthetic Methods*; Academic Press: San Diego, 1996. (f) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.

(2) (a) Manske, R. H. F. *The Alkaloids*; J. Wiley: New York, 1959−1979; Vols. 1−17. (b) Hesse, M. *Indolalkaloids in Tabellin*; Springer: Berlin, Germany, 1964. (c) Glasby, J. S. *Encyclopedia of Alkaloids*; Plenum Press: New York, 1975.

(3) Horwell, D. C. *Tetrahedron* **1980**, *36*, 3123.

(4) (a) Mangeney, P.; Andreanmialisoa, R.; Langlois, Y. *J. Am. Chem. Soc.* **1979**, *101*, 2243. (b) Iyengar, B. S.; Remers, W. A.; Catino, J. J. *J. Med. Chem.* **1989**, *32*, 1866.

(5) (a) Oikawa, Y.; Yonemitsu. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1479. (b) Tokuyama, H.; Fukuyama, T. *Kagaku Kogyo* **2001**, *52*, 416. (c) Xiong, W. N.; Yang, C. G.; Jiang, B. *Bioorg. Med. Chem.* **2001**, *9*, 1773.

(6) (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. (c) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (d) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, *5*, 620. (e) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. *Eur. J. Org. Chem.* **1999**, *64*, 1137. (f) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2488. (g) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (h) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662. (i) Pete, B.; Toke, L. *Tetrahedron Lett.* **2001**, *42*, 3373. (j) Kamijo, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3230. (k) Kamijo, S.; Yamamoto, Y. *J. Am. Soc. Chem.* **2002**, *124*, 11940. (l) Yasuhara, A.; Takeda, Y.; Suzuki, N.; Sakamoto, T. *Chem. Pharm. Bull.* **2002**, *50*, 235. (m) Rossiter, S. *Tetrahedron Lett.* **2002**, *43*, 4671. (n) Zhou, T.; Chen, Z. C. *Synth. Commun.* **2002**, *32*, 903. (o) Hegedus, L. S. *Angew. Chem.* **1988**, *100*, 1147. (p) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Oxford, UK, 2000; pp 73−187.

(7) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432.

(8) Arcadi, A.; Cacchi, S.; Giuseppe, S. D.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409.

(9) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.

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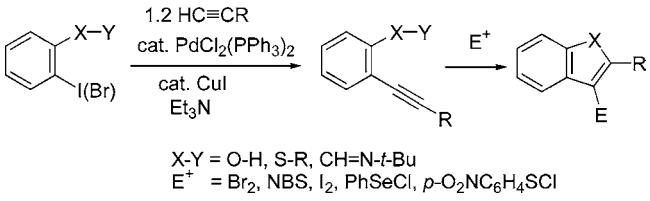
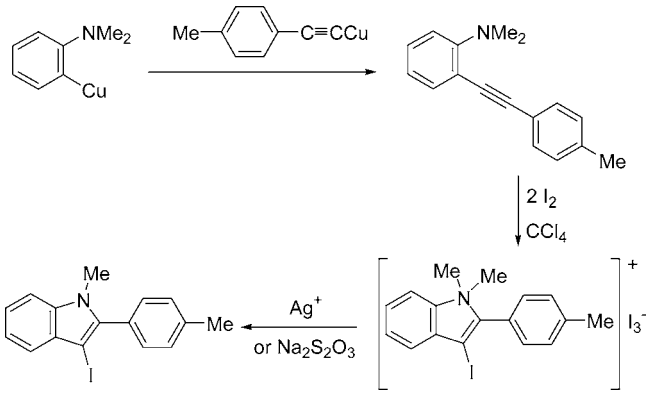
cyclization of appropriately functionalized aromatic acetylenes,[11] readily prepared by Sonogashira coupling of the corresponding aryl halides and terminal alkynes[12] (Scheme 1), encouraged us to examine the possibility of preparing indoles by a similar strategy.

Scheme 1



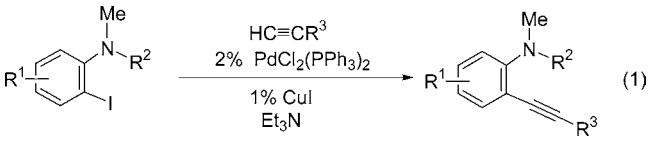
Although Hoedt reported an approach to the synthesis of 1-methyl-2-*p*-tolylindole and its 3-iodo derivative by a related process involving iodocyclization (Scheme 2),[13] the unusual

Scheme 2



preparation of the arylalkyne starting material, the separation of the indolium triiodide salt, and the stepwise addition of sodium thiosulfate or a silver salt are not particularly attractive synthetically. Furthermore, the yield of the above cyclization was only 66% or less. Finally, the scope of the cyclization step has not been examined.

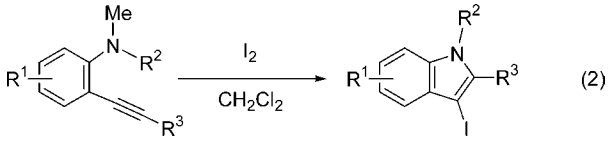
We wish to report a much more efficient approach to 3-iodoindoles involving the palladium/copper-catalyzed coupling of *N*,*N*-dialkyl-*o*-iodoanilines and terminal alkynes, followed by electrophilic cyclization. The aryl-alkynes required for our approach to indoles are readily prepared by the Sonogashira coupling[12] of *N*,*N*-dialkyl-*o*-iodoanilines and terminal alkynes (eq 1). The yields of this process range from



(1)

70% to 94% and this procedure readily accommodates considerable functionality.

Since Hoedt had previously established that *N*,*N*-dimethyl-2-(*p*-tolylethynyl)aniline undergoes facile iodocyclization in CCl_4,[13] we first examined the reaction of our alkynes with I_2 in CH_2Cl_2. We were extremely pleased to see that our *N*,*N*-dialkyl-2-(1-alkynyl)anilines react in less than 2 h at room temperature to afford the 3-iodoindole directly and only a trace of the indolium triiodide salt was observed (eq 2).



(2)

Adding aqueous $Na_2S_2O_3$ solution spontaneously decomposed the triiodide salt and afforded almost quantitative yields of the corresponding 3-iodoindoles (see Table 1). Virtually no differences in the rates of reaction or the overall yields have been observed using alkynes bearing an aryl, a hindered alkyl, a straight chain alkyl, or a vinylic group (Table 1, entries 1−4). Even the alkyne **3** bearing a bulky *tert*-butyl group affords a high yield of the desired indole (entry 2). This iodocyclization process also readily accommodates a wide variety of functional groups, including nitriles, halides, nitro groups, ethers, and esters, either on the alkyne moiety (entries 5 and 6) or the aromatic ring (entries 7−10).

We have investigated the electronic effect of various substituents on the aniline moiety in this electrophilic cyclization. This reaction does not require the presence of a strong electron-donating functional group, such as a methoxy group, to enhance the nucleophilicity of the nitrogen in the dialkylamino group. Simple unsubstituted anilines (entries 1−6) and even anilines bearing strong electron-withdrawing groups, like nitro or ester groups (entries 7, 8, and 10), give excellent yields of the desired indole products, even though the nitro and ester electron-withdrawing functional groups no doubt significantly lower the nucleophilicity of the dialkylamino group.

The use of two different alkyl groups on the nitrogen of the aniline affords interesting selectivity. Compound **19** with a methyl and an *n*-butyl group on the nitrogen undergoes electrophilic cyclization smoothly and the total conversion

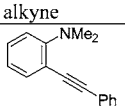
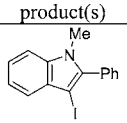
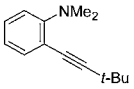
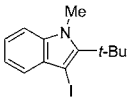
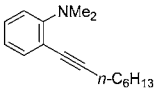
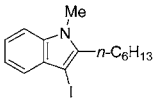
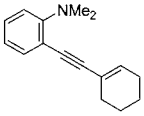
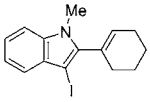
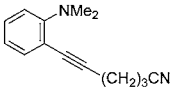
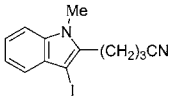
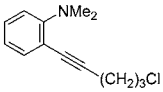
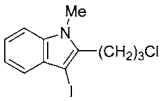
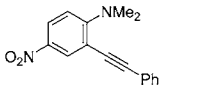
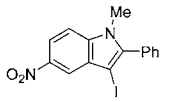
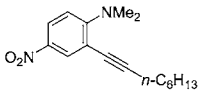
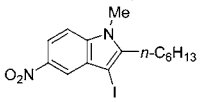
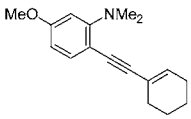
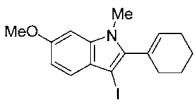
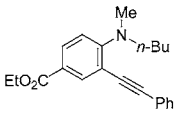
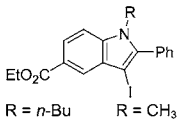
(10) (a) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (b) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *5*, 651.

(11) For other examples of iodine-promoted cyclization of alkynes to give heterocycles, see: (a) Knight, D. W.; Redfern, A. L.; Gilmore, J. J. *Chem. Soc., Perkin Trans. 1* **2002**, 622. (b) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 2859. (c) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857. (d) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, *40*, 7193. (e) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798. (f) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Chem. Commun.* **1998**, 2207. (g) Redfern, A. L.; Gilmore, J. *Synlett* **1998**, 731. (h) Ren, X.-F.; Konaklieva, M. I.; Shi, H.; Dicy, H.; Lim, D. V.; Gonzales, J.; Turos, E. *J. Org. Chem.* **1998**, *63*, 8898. (i) Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 1007. (j) El-Taeb, G. M. M.; Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 5945.

(12) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 5, pp 203−229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(13) Hoedt, W. M. R.; Koten, G. V.; Noltes, J. G. *Synth. Commun.* **1977**, *7*, 61.

Table 1. Synthesis of *N*-Alkyl-3-iodoindoles (eq 2)[a]

entry	alkyne		time (h)	product(s)		isolated yield (%)
1		**1**	2		**2**	100
2		**3**	2		**4**	96
3		**5**	2		**6**	94
4		**7**	2		**8**	85
5		**9**	4		**10**	86
6		**11**	4		**12**	73
7		**13**	0.5		**14**	100
8		**15**	0.5		**16**	95
9		**17**	2		**18**	100
10		**19**	0.5	 R = *n*-Bu **20** R = CH_3 **21**		98 (72:28)

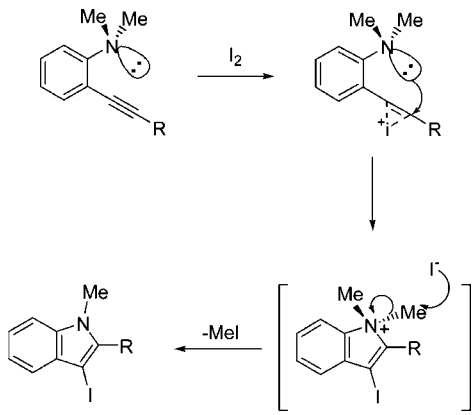
[a] All reactions were run with 0.25 mmol of the alkyne, 2 equiv of I_2 in 5 mL of CH_2Cl_2 at 25 °C, followed by addition of 5 mL of saturated aqueous $Na_2S_2O_3$ to remove the excess I_2.

is almost quantitative (entry 10). Due to the different steric effects of a methyl group and an *n*-butyl group in an S_N2 reaction, the less hindered methyl group is more easily removed by attack of the iodide formed during electrophilic cyclization than is the *n*-butyl group. The ratio of *N*-*n*-butylindole **20** to *N*-methylindole **21** is 72 to 28.

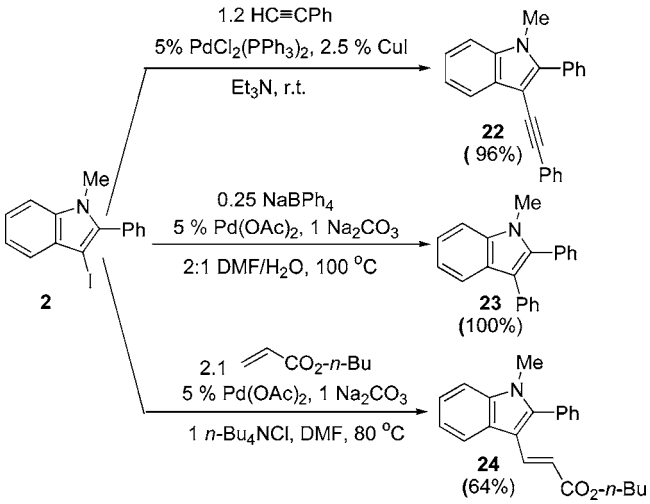
Mechanistically, we believe that these cyclizations proceed by anti attack of the electrophile and the nitrogen of the *N*,*N*-dialkylamino group on the alkyne to produce an iodoindolium salt, which undergoes facile methyl group removal via S_N2 displacement by the iodide present in the reaction mixture (Scheme 3). The saturated aqueous $Na_2S_2O_3$ solution has been used simply to remove the unreacted I_2 and to generate more iodide nucleophile for the S_N2 displacement.

The success of this reaction is presumably due to several factors. First, the two alkyl groups enhance the nucleophi-

Scheme 3



Scheme 4



licity of the nitrogen. Second, the interaction between the two alkyl groups and the internal triple bond favors an orientation of the nitrogen with its lone pair of electrons pointing toward the triple bond. Third, the highly nucleophilic iodide ion formed during the cyclization facilitates removal of the methyl or other alkyl group. Fourth, the use of CH_2Cl_2 as the solvent increases the solubility of the resulting indolium salts, facilitating dealkylation by iodide.

We believe that this approach to 3-iodoindoles should prove very useful for the synthesis of additional more highly substituted indoles, particularly when one considers that there are many ways to transform the resulting iodide functional group into other substituents. For example, the *N*-methyl-3-iodo-2-phenylindole produced by this strategy can be further functionalized by applying palladium-catalyzed coupling reactions, such as Sonogashira[12] and Suzuki[14] cross-coupling processes and the Heck reaction[15] (Scheme 4). One should be able to prepare many other 2,3-disubstituted indoles using these iodoindole substrates and known palladium methodology.

During our study of this iodocyclization approach to the synthesis of *N*-alkyl-3-iodoindoles, similar approaches have been developed independently by Barluenga using carbamates or sulfonamides derived from *o*-(1-alkynyl)anilines[16] and by Knight using *N*-tosyl-2-(1-alkynyl)anilines.[17] However, Barluenga's approach utilizes a very expensive iodonium salt IPy_2BF_4, plus the very strong, toxic acid HBF_4; requires careful temperature control; and provides quite variable yields. Knight's method employs I_2 under relatively mild reaction conditions, but the addition of 3 equiv of K_2CO_3 might affect certain base-sensitive functional groups in the starting materials. The present procedure is run under neutral reaction conditions, is more efficient and convenient, and produces *N*-alkylindoles.

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Supporting Information Available: General experimental procedures and characterization data for all starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (c) Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 49. (d) Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457.

(15) (a) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (b) Brase, S.; De Meijere, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 99. (c) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: San Diego, 1985; pp 276−287.

(16) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 2406.

(17) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, *539*.