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Synthesis of N-Substituted Indole Derivatives via PIFA-Mediated Intramolecular Cyclization

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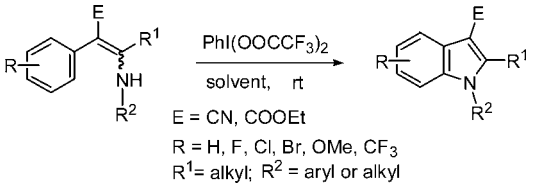
ABSTRACT



A variety of N-arylated and N-alkylated indole derivatives were synthesized by way of a phenyliodine bis(trifluoroacetate) (PIFA)-mediated intramolecular cyclization. This novel method allows for the construction of an indole skeleton by joining the N-atom on the side chain to the benzene ring at the last synthetic step. Other novel pyrrole-fused aromatic compounds can also be achieved by this method.

The construction of a substituted indole skeleton has been a topic of great interest for many years because the indole unit has found ever-expanding uses in both natural products and designed medicinal agents.[1] Accordingly, there exists a large and varied selection of methods for their synthesis.[2] A survey of the literature shows that these methods can be basically generalized into the following categories: (1) The N-atom of the indole nucleus is introduced by applying the N-functionalized arene (e.g., an aryl amine or a nitroarene, etc.) as the starting material in the early synthetic stage (**a** in Figure 1).[2,3] In the overall strategy, the functionalization of the indole's benzenoid portion greatly depends on the diversity of the N-containing benzene derivatives. (2) The N-moiety is connected to the benzene ring through transition-metal-catalyzed aryl amination reactions (**b** in Figure 1).[2,4] However, for the substrates of this class, the presence of a halogen substituent in the ortho position of the benzene ring is indispensable. (3) The N-moiety on the side chain is joined to the benzene ring without a halogen substituent in the ortho position at the last synthetic step. To the best of our knowledge, this least exploited strategy only includes the synthesis of N-unsubstituted indoles via a thermolytic rearrangement of α-arylazirines[5] and the synthesis of *N*-hydroxyindoles from 1-aryl-2-nitroalkene derivatives[6] (**c** in Figure 1).

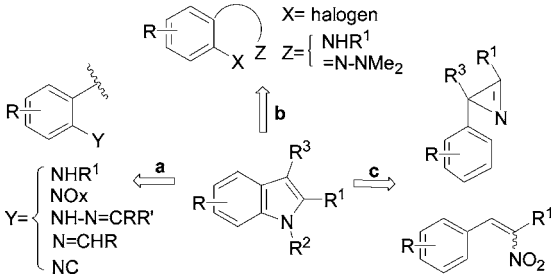


Figure 1. General strategies for the construction of the indole skeleton.

(1) For recent references of indole-containing natural products and designed medicinal agents, see: (a) Lounasmaa, M.; Tolvanen, N. *Nat. Prod. Rep.* **2000**, *17*, 175−191. (b) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2002**, *19*, 148−180. (c) Wacker, D. A.; Kasireddy, P. *Tetrahedron Lett.* **2002**, *43*, 5189−5191. (d) Smart, B. P.; Oslund, R. C.; Walsh, L. A.; Gelb, M. H. *J. Med. Chem.* **2006**, *49*, 2858−2860.

(2) For recent reviews of indole synthesis, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873−2920.

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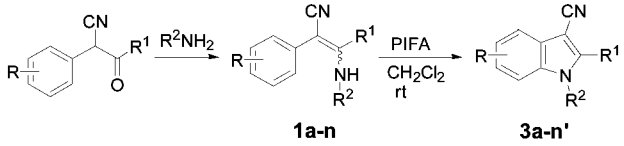
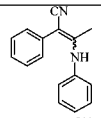
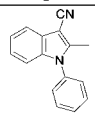
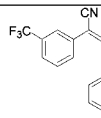
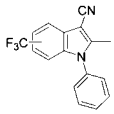
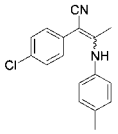
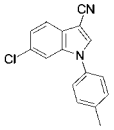
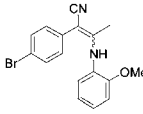
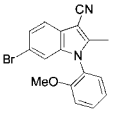
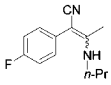
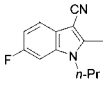
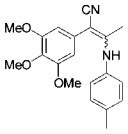
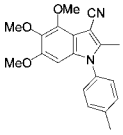
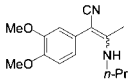
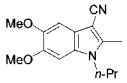
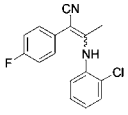
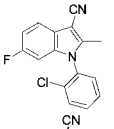
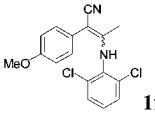
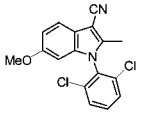
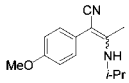
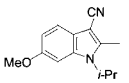
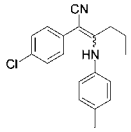
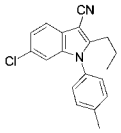
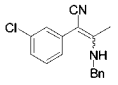
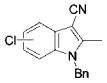
Table 1. Synthesis of N-Substituted Indole-3-carbonitrile Derivatives via Intramolecular Cyclization Mediated by PIFA*



entry	substrate	product	yield (%)[a]	entry	substrate	product	yield (%)[a]
1	 **1a**	 **3a**	86	8	 **1h**	 **3h** **3h'**	5-CF_3: 41 7-CF_3: 43
2	 **1b**	 **3b**	92	9	 **1i**	 **3i**	80
3	 **1c**	 **3c**	82	10	 **1j**	 **3j**	81
4	 **1d**	 **3d**	71	11	 **1k**	 **3k**	74
5	 **1e**	 **3e**	85	12	 **1l**	 **3l**	87
6	 **1f**	 **3f**	78	13	 **1m**	 **3m**	70
7	 **1g**	 **3g**	73	14	 **1n**	 **3n** **3n'**	5-Cl: 45 7-Cl: 41

* Conditions: all reactions were carried out by adding dropwise 1.3 equiv of PIFA in CH_2Cl_2 to a solution of 1 equiv of **1** in CH_2Cl_2 over 30 min, stirred at room temperature. [a] Isolated yield after silica gel chromatography.

Herein, we report an entirely new and general synthetic technology for the construction of the N-substituted indole framework (Schemes in Tables 1 and 2), which is characterized by the following features: (1) The indole ring formation allows for the N-moiety to be annulated to the benzene ring at the last synthetic step, which enables the easy functionalization of the benzenoid portion with a variety of substituents. (2) The presence of a halogen substituent in the ortho position is not required.

To our knowledge, phenyliodine bis(trifluoroacetate) (PIFA), a readily available hypervalent iodine reagent with low toxicity, has been used widely as a selective oxidizing agent to generate a nitrenium ion intermediate, which can undergo inter- or intramolecular reaction.[7] This prompts us

(3) (a) Ragaini, F.; Rapetti, A.; Visentin, E.; Monzani, M.; Caselli, A.; Cenini, S. *J. Org. Chem.* **2006**, *71*, 3748−3753. (b) Lu, B. Z.; Zhao, W.; Wei, H.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271−3274. (c) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307−3310. (d) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689−6690. (e) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127−3128. (f) Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838−5845. (g) Yamaguchi, M.; Arisawa, M.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1998**, 1399−1400. (h) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662−5663. (i) Kulkarni, M. G.; Davawala, S. I.; Dhondge, A. P.; Gaikwad, D. D.; Borhade, A. S.; Chavhan, S. W. *Tetrahedron Lett.* **2006**, *47*, 1003−1005. (j) Penoni, A.; Volkmann, J.; Nicholas, K. M. *Org. Lett.* **2002**, *4*, 699−701. (k) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62−69.

(4) (a) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028−1030. (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263. (c) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403−406. (d) Ackermann, L. *Org. Lett.* **2005**, *7*, 439−442. (e) Brown, J. A. *Tetrahedron Lett.* **2000**, *41*, 1623−1626. (f) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4257−4260.

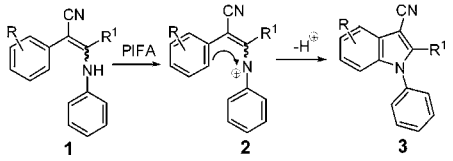
(5) (a) Tercel, M.; Gieseg, M. A.; Denny, W. A.; Wilson, W. R. *J. Org. Chem.* **1999**, *64*, 5946−5953. (b) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058−1059.

(6) (a) Foucaud, A.; Razorilalana-Rabearivony, C.; Loukakou, E.; Person, H. *J. Org. Chem.* **1983**, *48*, 3639−3644. (b) Zhang, R.; Liao, X.; Gao, Z. *Synthesis* **1990**, *9*, 801−802.

(7) (a) Romero, A. G.; Darlington, W. H.; Jacobsen, E. J.; Mickelson, J. W. *Tetrahedron Lett.* **1996**, *37*, 2361−2364. (b) Correa, A.; Herrero, M. T.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron* **2003**, *59*, 7103−7110. (c) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739−6744. (d) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 3501−3505.

to test whether a substrate such as 2-aryl-3-arylamino-2-alkenenitriles **1** (Scheme 1) could also give stable nitrenium ion **2**

Scheme 1. Proposed Scheme for the Construction of N-Arylated Indole Derivatives Mediated by PIFA



mediated by PIFA, followed by intramolecular cyclization to furnish N-arylated indole-3-carbonitrile derivatives **3**.

Generation of the required substrates **1** is readily achieved in 68−81% yields by reaction of the ketonitriles with substituted anilines in acetic acid.[8] The ketonitriles are obtained by reaction of various substituted benzyl cyanides with carboxylic ester in a basic medium provided by NaH in THF[9] (see Supporting Information).

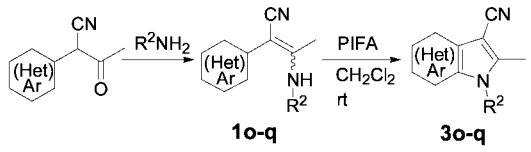
We first utilized 2-phenyl-3-phenylamino-but-2-enenitrile **1a** (Table 1, entry 1), a mixture of trans and cis isomers, to examine the possibility of the proposed transformation. Treating **1a** with PIFA in CH_2Cl_2 nearly instantly furnished the desired cyclized product **3a** in 86% yield. Other solvents such as CH_3CN, THF, EtOH, and EtOAc were also studied. The results indicated that CH_3CN and EtOAc were the desirable solvents for this reaction, whereas THF and EtOH gave poor results. Parallel experiments using 1, 1.1, 1.3, and 1.5 equiv of PIFA showed that 1.3 equiv of PIFA was enough for the total conversion of **1a** (see Supporting Information).

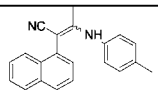
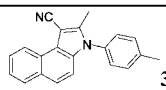
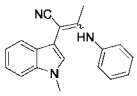
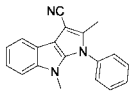
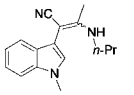
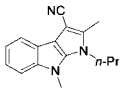
Having established the optimal conditions, we then sought to probe the scope of the reaction and found that both electron-rich and electron-poor substrates could be successfully employed (Table 1, entries 2−8). All of the reactions were very fast and completed in just 30 min, over which the dropwise adding of PIFA in CH_2Cl_2 was finished. Comparative experiments by adding PIFA in one pot to a solution of the substrates in CH_2Cl_2 indicated that in all cases the reaction was finished within 5 min. Good to high yields (71−92%) were obtained for these reactions. The lower yield of **3d**, shown in Table 1, is likely due to the formation of some unidentified byproducts. It is worth noting that for the substrate with a CF_3 group in the meta position of the benzene ring (Table 1, entry 8) the intramolecular cyclization furnished a mixture of 5-substituted and 7-substituted regioisomers, in a yield of 41% and 43%, respectively. Contrary to our expections, the strong electron-withdrawing group CF_3 did not affect the reaction time and yield.

The scope and utility of this method is further studied by changing arylamines into alkylamines. The required substrates (Table 1, **1i**−**n**) are readily obtained in 67−90% yields by reaction of ketonitriles with alkylamines in the presence of acetic acid in ethyl alcohol. To our pleasant surprise, the substrates of this class also smoothly afford the desired cyclized products (Table 1, **3i**−**n′**) within 30 min and in good yields (70−87%). Similarly, for the substrate with a chloro group in the meta position (Table 1, **1n**), the cyclization also furnished the 5-substituted and 7-substituted regioisomers, in a yield of 41% and 45%, respectively (Table 1, entry 14).

Encouraged by the above results, we initiated studies toward using other aromatic rings and found that the compounds **3o**−**q** shown in Table 2 were successfully

Table 2. Synthesis of Novel Pyrrole-Fused Heterocyclic Compounds via Intramolecular Cyclization Meidated by PIFA*



entry	substrate	product	yield(%)[a]
1	 1o	 3o	78
2	 1p	 3p	66
3	 1q	 3q	64

* Conditions: see Table 1. [a] Isolated yield after silica gel chromatography.

achieved in 64−78% yields within 30 min by this method. The requisite substrates **1o**−**q**[10] were prepared by a method similar to that described above (see Supporting Information).

In light of the above results, we replaced the cyano group with a carboxylic ester and came to investigate the reactions of the substrates **1r**,**s**, which were prepared by a similar method and should possess *Z*-geometries due to the existence of a hydrogen bond between the NH group and the carbonyl group of the ester.[11] To our delight, substrates **1r**,**s** also furnished the desired cyclized product under the same reaction conditions, in a yield of 75% and 68%, respectively (see Scheme 2).

All the structures of the products are determined by detailed study of the spectroscopic data. Furthermore, product **3d** is unambiguously confirmed through X-ray crystallographic analysis (see Supporting Information).

We initially postulated that **1** would give stable aryl nitrenium ion intermediate **2** in the presence of PIFA, which would act as an electrophile to attack the benzene ring and

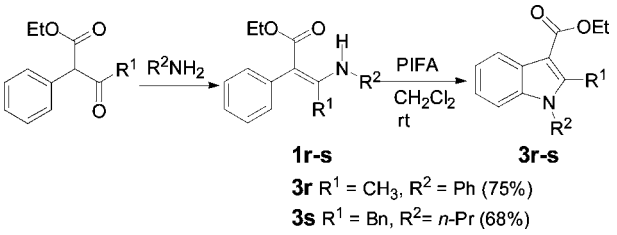
(8) (a) Walther, R. V. *J. Prakt. Chem.* **1911**, *83*, 171−182. (b) Heller, K. *J. Prakt. Chem.* **1929**, *121*, 193−203. (c) Hauser, C. R.; Murray, J. G. *J. Am. Chem. Soc.* **1955**, *77*, 2851−2852. (d) Ryabukhin, Y. *J. Heterocycl. Chem.* **1999**, *36*, 97−104.

(9) Chen, C.; Wilcoxen, K. M.; Huang, C. Q.; McCarthy, J. R.; Chen, T.; Grigoriadis, D. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3669−3673.

(10) For the preparation of the required (1-methyl-1*H*-indol-3-yl)-acetonitrile, see: Snyder, H. R.; Eliel, E. L. *J. Am. Chem. Soc.* **1948**, *70*, 1703−1705.

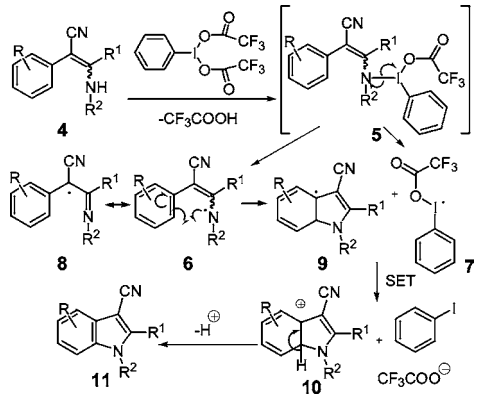
(11) For the assignment of this *Z*-geometry, see: Casarrubios, L.; Pérez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358−8359.

Scheme 2. Synthesis of the N-Substituted Indole-3-carboxylic Acid Ester via Intramolecular Cyclization Mediated by PIFA



give the desired product. However, it seemed this mechanism could not explain well the following experimental facts: (1) The reaction related to the electron-withdrawing group on the benzene ring did not affect the rate or yield of the final products. (2) 2-Aryl-3-alkylamino-2-alkenenitrile derivatives (Table 1, **1i**−**n**), which were not likely to generate stable nitrenium ion intermediates, could also furnish the desired products (Table 1, **3i**−**n′**) in good yields within a short period of time. On the basis of these, we propose a plausible radical cyclization pathway, shown in Scheme 3. It is assumed that

Scheme 3. Another Possible Mechanism



intermediate **5** would be formed from the reaction of the substrates **4** and PIFA by losing one molecule of CF_3COOH. Then, the N−I bond in **5** would homolytically cleave to give radicals **6** and **7** (N-radical **6** may tautomerize to give benzylic radical **8**). Next, the intramolecular addition of an N-radical to the benzene ring would give **9**, which generates carbocation **10** in the presence of radical **7**, via a possible SET pathway. Last, abstraction of a proton from **10** would regenerate the aromatic system to afford **11**. This proposed mechanism is likely supported by the previous literature which described radical cyclization reactions[12] and the SET pathway for oxidation reaction of the hypervalent iodine reagent, respectively.[13]

In summary, we have demonstrated a novel synthesis of N-arylated and N-alkylated indole derivatives which allows for the efficient connection of the N-moiety to the functionalized benzene ring at the last synthetic step. Furthermore, this methodology can be extended to the construction of other novel pyrrole-fused aromatic compounds. The features of the present method include the availability of the starting materials, the mild reaction conditions, and the simplicity of the workup. The widespread use of the indole skeleton in natural products combined with its pharmaceutical importance should render this method broadly useful. Ongoing studies are in progress to elucidate the scope and limitation of the method by replacing the cyano or ester group with other substituents.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds and X-ray structural data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Artis, D. R.; Cho, I. S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456−2466. (b) Martinez, E.; Newcomb, M. *J. Org. Chem.* **2006**, *71*, 557−561.

(13) Thottumkara, A. P.; Vinod, T. K. *Tetrahedron Lett.* **2002**, *43*, 569−572.