ORGANIC LETTERS

2009
Vol. 11, No. 11
2417−2420

PIDA-Mediated Oxidative C−C Bond Formation: Novel Synthesis of Indoles from *N*-Aryl Enamines

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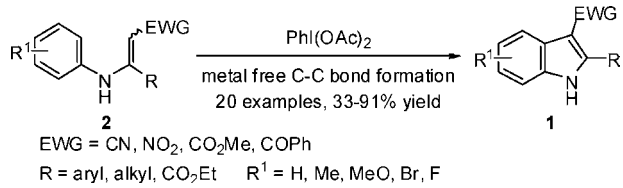
Received March 18, 2009

ABSTRACT



A variety of functionalized indoles were synthesized from *N*-aryl enamines via PIDA-mediated oxidative carbon−carbon bond formation. The features of the present reaction include facilitative preparation of substrates 2, good functional group tolerance, and mild reaction conditions without transition metals.

Carbon−carbon bond construction[1] is the essence of organic synthesis and the foundation for the formation of complicated structures. In recent decades, there has been great progress on C−C bond formation because of the development of transition metal-catalyzed processes, such as the Suzuki,[2a−c] Stille,[2d,e] Heck,[2f] and olefin metathesis reactions,[2g−i] which have been widely used in the synthesis of natural products and pharmacologically active compounds. However, there are still some problems with these metal-catalyzed reactions, such as carefully controlled reaction conditions (e.g., exclusion of air, moisture, and impurities), cost of transition-metal catalysts or ligands, and heavy metal residue in drug development. Additionally, in view of the increased attention to environmental problems, transition-metal-free methods are preferable for the construction of C−C bonds. In this paper, we report a new transition-metal-free synthetic technology for direct oxidative C−C bond formation mediated by polyvalent iodine reagents.

Owing to the facilitation of preparation and low toxicity compared with classic transition-metal oxidants, polyvalent iodine reagents have been extensively used in modern organic synthesis,[3] of which iodine(III) derivatives (e.g., PIFA, phenyliodine(III) bis(trifluoroacetate) and PIDA, phenyliodine(III) diacetate) have become extremely powerful tools for oxidizing the nitrogen atom[4,5] for new C−N or N−N bond formation. Nevertheless, the utilization of hypervalent iodine reagents to construct C−C bonds is seldom reported, especially without transition metals. Based on our successful application of PIFA in constructing the indole framework via C−N bond formation,[5] herein we

(1) For recent reviews on C−C bond formation, see: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365. (b) Fagnoni, M.; Dondi, D.; Ravelli, D.; Albini, A. *Chem. Rev.* **2007**, *107*, 2725–2756. (c) Li, C. *Chem. Rev.* **2005**, *105*, 3095–3165. (d) Dilman, A. D.; Ioffe, S. L. *Chem. Rev.* **2003**, *103*, 733–772. (e) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196. (f) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1769. (g) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067–2096. (h) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137–202.

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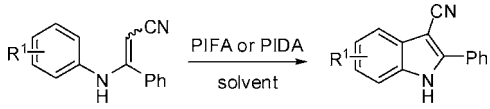
(3) For recent reviews on polyvalent iodine reagents: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. (b) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997–3008.

10.1021/ol900576a CCC: $40.75
Published on Web 05/06/2009

developed a novel C−C bond formation strategy for indole synthesis via the PIDA-mediated oxidization of the *N*-aryl enamine **2**.

3-Phenyl-3-phenylaminoacrylonitrile derivatives **2** were readily prepared as a mixture of cis and trans isomers, via the acetic acid-catalyzed condensation[6] of 3-oxo-3-arylpropionitriles[7] and corresponding anilines. Screening of a series of solvents, including CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$, MeCN, THF, EtOAc, 1,4-dioxane, EtOH, DMF, and DMSO, showed that alkyl chlorides are desired for the conversion of **2** to **1**. Further optimization results are summarized in Table 1. Oxidation of substrates **2a**−**c**

Table 1. Reaction Conditions Optimization for Indole Synthesis from 3-Phenyl-3-phenylaminoacrylonitrile Derivatives **2**[a]



2
2a R^1 = H
2b R^1 = 4-Me
2c R^1 = 5-Br

1
1a R^1 = H
1b R^1 = 5-Me
1c R^1 = 5-Br

entry	oxidant (equiv)	*T* (°C)	time (h)	product **1**	yield[b] (%)
1[c]	PIFA (1.3)	−78 to rt		**1a**	40
2[c]	PIFA (1.3)	−78 to rt		**1b**	54
3[c]	PIFA (1.3)	−78 to rt		**1c**	55
4[d]	PIDA (1.1)	60	5	**1b**	72
5[d]	PIDA (1.3)	60	2	**1b**	84
6[d]	PIDA (1.5)	60	2	**1b**	61
7[d]	PIDA (1.3)	80	2	**1b**	76

[a] Optimal reaction conditions: **2** (1 equiv), PIDA (1.3 equiv), $ClCH_2CH_2Cl$, 60 °C. [b] Isolated yields after silica gel chromatography. [c] The reactions were run in CH_2Cl_2. [d] The reactions were run in $ClCH_2CH_2Cl$.

by PIFA in CH_2Cl_2 afforded the desired indoles in moderate yields at −78 °C (Table 1, entries 1−3), but decreased yields at elevated temperature (not shown). Use of PIDA in 1,2-dichloroethane improved the yield of **1b** greatly (84%) at 60 °C (Table 1, entry 5). The conversion was very slow at 40 °C (not shown) and resulted in a slightly decreased yield (76%) at 80 °C (Table 1, entry 7). Parallel experiments (Table 1, entries 4−6), using 1.1, 1.3, and 1.5 equiv of PIDA indicated that 1.3 equiv of PIDA was optimal for the total conversion of **2b** to **1b** and more oxidant led to a lower yield.

A variety of 3-aryl-3-arylaminoacrylonitriles **2** were subjected to the above optimal reaction conditions (Table 1, entry 5) to probe the reaction scope and generality (Table 2, entries 1−13). Substrates with both electron-donating (Table 2, entries 2, 4−7, and 9−13) and electron-withdrawing (Table 2, entries 3 and 8) substituents were directly converted to desired indoles in 33−91% yields. The presence of methoxy group in substrates (Table 2, entries 4, 6, and 12) decreased the yields of corresponding indoles, with unidentified byproduct. In the case of 3,4-disubstituted and meta-substituted substrates (Table 2, entries 5 and 8), two regioisomeric indole products were formed. At the same time, a good regioselectivity was observed during the formation of **1f** (Table 2, entry 6), which could be due to the steric hindrance caused by the methoxy group. The steric block effect of the ortho-substituted methyl group on the other benzene ring could be responsible for the lower yield of **1m** (Table 2, entry 13).

Good functional group tolerance of this methodology also allows for the replacement of the *cyano* group in substrates by other electron-withdrawing groups, such as *nitro* and carboxylic ester groups (Table 2, entries 14 and 15). Substrates **2n** and **2o**, generated only as the *Z*-isomers[8] via the condensation of anilines with 2-nitro-1-phenylethanone[9] and 3-oxo-3-phenylpropionic acid methyl ester,[10] respectively, also furnished the indoles in decent yields.

In light of the encouraging results, we initiated further studies by replacing the aromatic R group in the substrates with an alkyl group (Table 3, entries 1−4). The required substrates were obtained through the condensation of 3-oxo-3-alkylpropionitriles[4,11] and 4-methylaniline. The desired indoles were successfully achieved under the optimal reaction conditions. The substrate **2t**, containing benzoyl and carboxylic ester groups (Table 3, entry 5), was also oxidized to corresponding indole **1t**, using 1.8 equiv of PIDA at refluxing temperature. The structure of **1t** was further confirmed by X-ray crystallography (Figure 1).

An intramolecular S_N2'-type cyclization mechanism for PIDA-mediated oxidation of substrate **2a** to indole **1a** is shown as follows (Scheme 1): The intermediate **3a** is formed from the reaction of substrate **2a** with PIDA by losing one molecule of acetic acid. Due to the presence of EWG at the β position, the enamine formation, which can be confirmed by NMR, might promote the facile production of **3a**. Then the N−I bond in **3a** cleaves, with comcomitant electrocyclic ring closure and the subsequent

(4) For selected examples, for C−N bond formation: (a) Tellitu, I.; Serna, S.; Herrero, M. T.; Moreno, I.; Domnguez, E.; SanMartin, R. *J. Org. Chem.* **2007**, *72*, 1526–1529. (b) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. *Org. Lett.* **2007**, *9*, 5345–5348. (c) Fan, R.; Wen, F.; Qin, L.; Pu, D.; Wang, B. *Tetrahedron Lett.* **2007**, *48*, 7444–7447. (d) Correa, A.; Tellitu, I.; Domnguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316–8319. (e) Aggarwal, R.; Sumran, G.; Saini, A.; Singh, S. P. *Tetrahedron Lett.* **2006**, *47*, 4969–4971. For N−N bond formation: (f) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 3501–3505. (g) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *Tetrahedron* **2006**, *62*, 11100–11105.

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(8) The assignment of the *Z*-isomer could be due to the existence of a hydrogen bond between NH group and the carbonyl group of the ester (or nitro group). For the references, see ref 5. Casarrubios, L.; Pérez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358–8359.

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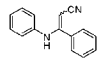
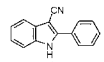
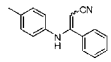
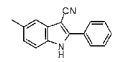
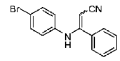
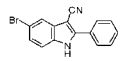
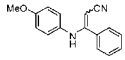
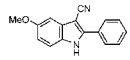
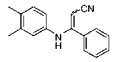
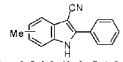
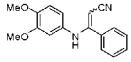
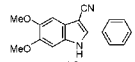
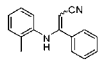
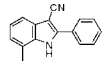
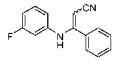
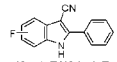
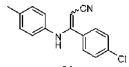
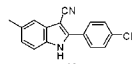
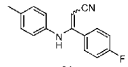
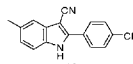
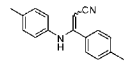
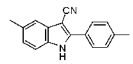
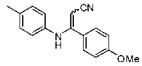
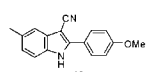
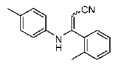
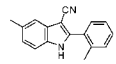
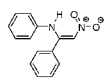
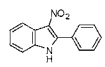
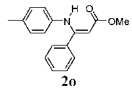
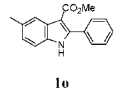
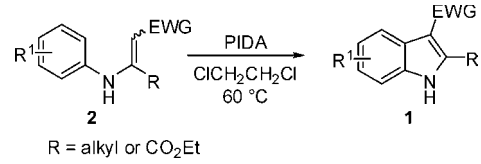
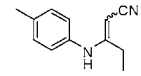
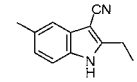
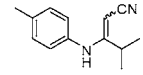
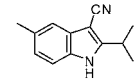
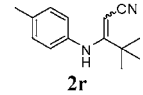
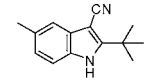
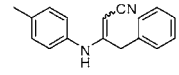
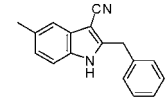
Table 2. Scope of PIDA-Mediated Indole Synthesis[a]

entry	substrate 2	product 1	yield (%)[b]
1	 2a	 1a	83
2	 2b	 1b	84
3	 2c	 1c	78
4	 2d	 1d	51
5	 2e	 1e: 4,5-Me/1e': 5,6-Me	80 (1/ 1.4[c])
6	 2f	 1f	33
7	 2g	 1g	88
8	 2h	 1h: 4-F/1h': 6-F	38 (1h) 48 (1h')
9	 2i	 1i	83
10	 2j	 1j	90
11	 2k	 1k	91
12	 2l	 1l	64
13	 2m	 1m	38
14[d]	 2n	 1n	62
15	 2o	 1o	71

[a] Optimal reaction conditions: **2** (1 equiv), PIDA (1.3 equiv), $ClCH_2CH_2Cl$, 60 °C. [b] Isolated yields after silica gel chromatography. [c] The ratio of the regioisomers was determined by ^1H NMR. [d] The reaction was carried out using 1.8 equiv of PIDA in $ClCH_2CH_2Cl$ at refluxing temperature.

Table 3. Further Variation of Substrates **2**[a]



entry	substrate 2	product 1	yield (%)[b]
1	 2p	 1p	41
2	 2q	 1q	76
3	 2r	 1r	83
4	 2s	 1s	74
5[c]	2t	1t	51

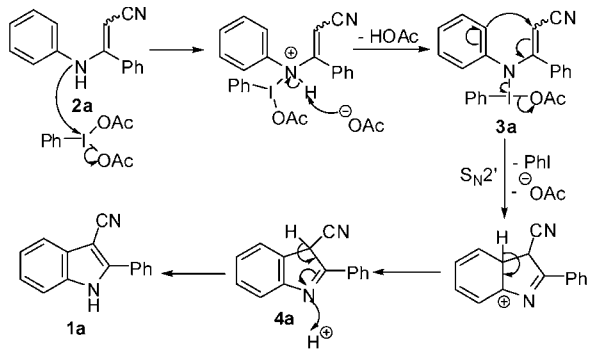
[a] Optimal reaction conditions: **2** (1 equiv), PIDA (1.3 equiv), $ClCH_2CH_2Cl$, 60 °C. [b] Isolated yields after silica gel chromatography. [c] The reaction was carried out using 1.8 equiv of PIDA in $ClCH_2CH_2Cl$ at refluxing temperature.

proton elimination to afford **4a**. Finally, the tautomerization of **4a** forms the indole structure **1a**.

In summary, we have established an efficient, direct oxidative and transition metal-free C−C bond formation method to construct the indole framework. In this methodology, prefunctionalization of the reaction center is not required, which makes the preparation of substrates from

Figure 1. X-ray crystal structure of **1t**.

Scheme 1. Intramolecular S_N2'-type Cyclization Mechanism for the PIDA-Mediated Construction of Indole **1a**



available starting materials more facilitative. Good functional group tolerance allows structurally diverse substituted indoles to form from corresponding substrates under mild reaction conditions. Use of PIDA without transition metals makes the reactions friendlier to the environment. Now our group is studying further application of this C−C bond formation method in other heterocyclic compounds synthesis.

Acknowledgment. We acknowledge the National Natural Science Foudation of China (No. 20802048) for financial support. We also thank Dr. Xiaodong Xu of Institute for Hepatitis and Virus Research for critical reading of the manuscript and Miss Xiling Zhao, University of California, San Diego, for revising our English text.

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.

OL900576A