JOC*Note*

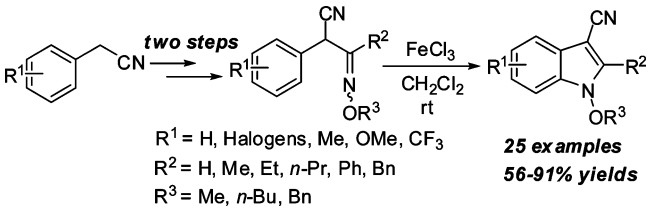
Formation of *N*-Alkoxyindole Framework: Intramolecular Heterocyclization of 3-Alkoxyimino-2-arylalkylnitriles Mediated by Ferric Chloride

Yunfei Du,[†] Junbiao Chang,*[,†,‡] John Reiner,[†] and Kang Zhao*[,†]

The School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China, and Department of Chemistry, Zhengzhou University, Zhengzhou 450001, China

combinology@yahoo.com

Received November 15, 2007



A variety of functionalized *N*-alkoxyindole-3-carbonitrile derivatives are achieved under remarkably mild conditions by applying a $FeCl_3$-mediated intramolecular heterocyclization of 3-alkoxyimino-2-arylalkylnitriles. This novel synthesis allows the *N*-moiety on the side chain to be annulated to the benzene ring as the final synthetic step, which enables the functionalization of the benzenoid portion of the indole at an early stage of the synthesis.

The *N*-alkoxyinodoles have attracted considerable attention since a number of alkaloids possessing the *N*-methoxyindole skeleton have been isolated and reported in the literature.[1] Furthermore, the biological activity of some indole-based pharmaceutical agents can be considerably improved after replacing the indole N−H with an *N*-methoxy moiety.[2] While the potential importance of the *N*-alkoxyindole skeleton is evident, a survey of the literature indicated that the methods developed for the synthesis of the *N*-alkoxyindole nucleus can be generalized into the following types: (1) methylation of *N*-hydroxyindoles with dimethyl sulfate or diazomethane (path a in Figure 1);[1c,3] (2) dehydration of 2-hydroxyindoline derivatives catalyzed by aqueous HCl (path b in Figure 1);[4] (3) cyclization of the requisite *o-nitro* functionalized substrate mediated by NaCl/DMSO at high temperature (path c in Figure 1);[5] (4) alkylative cycloaddition of *nitroso*arenes with alkynes in the presence of K_2CO_3/Me_2SO_4 (path d in Figure 1);[6] and (5) intramolecular cyclization of an *a*-aryl ketone oxime derivative via a nitrenium ion intermediate (path e in Figure 1).[7]

An intramolecular cyclization strategy in which a pendant nitrogen moiety is annulated to a benzene ring provides a unique access to multiply substituted indoles since such a method would avoid using the use of "privileged" *N*-functionalized arenes as starting materials and the introduction of the nitrogen atom could be postponed to a later synthetic step.[8] Herein, we report such an intramolecular cyclization method for the construction of *N*-alkoxyindoles by direct C−H amination of an aromatic ring with a side chain *N*-moiety thus enabling access to an assortment of benzo-functionalized indoles.

In a previous study,[8g] we reported a PIFA-mediate oxidative cyclization for the conversion of compound **2′** to compound **3′**. Since this cyclization protocol easily produced indoles with either an *N*-alkyl or *N*-aryl group, we were interested in extending the reaction to access natural products with the *N*-alkoxyindole skeleton. The oxime ether substrate **2**, prepared from β-ketonitriles **1**, under identical cyclization conditions could also produce the desired *N*-alkoxyindole **3**;[9] however, the yield (9−35%) was fairly unsatisfactory (entries 1−6, Table

[†] Tianjin University.
[‡] Zhengzhou University.

(1) (a) Konda, Y.; Onda, M.; Hirano, A.; Omura, S. *Chem. Pharm. Bull.* **1980**, *28*, 2987. (b) Ito, C.; Wu, T.-S.; Furukawa, H. *Chem. Pharm. Bull.* **1988**, *36*, 2377. (c) Kawasaki, T.; Kodama, A.; Nishida, T.; Shimizu, K.; Somei, M. *Heterocycles* **1991**, *32*, 221. (d) Somei, M. *Heterocycles* **1999**, *50*, 1157. (e) Soledade, M.; Pedras, C.; Sorenson, J. L. *Phytochemistry* **1998**, *49*, 1959. (f) Selvakumar, N.; Khera, M. K.; Reddy, B. Y.; Srinivas, D.; Azhagan, A. M.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 7071. (g) Boger, D. L.; Keim, H.; Oberhauser, B.; Schreiner, E. P.; Foster, C. A. *J. Am. Chem. Soc.* **1999**, *121*, 6197. (h) Somei, M. *Adv. Heterocycl. Chem.* **2002**, *82*, 101. (i) Kinoshita, T.; Tatara, S.; Ho, F.-C.; Sankawa, U. *Phytochemistry* **1989**, *28*, 147. (j) Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1983**, *31*, 3198. (k) Sung, Y.-I.; Koike, K.; Nikaido, T.; Ohmoto, T.; Sankawa, U. *Chem. Pharm. Bull.* **1984**, *32*, 1872. (l) Kinoshita, T.; Tatara, S.; Sankawa, U. *Chem. Pharm. Bull.* **1985**, *33*, 1770. (m) Agerbirk, N.; Petersen, B. L.; Olsen, C. E.; Halkier, B. A.; Nielsen, J. K. *J. Agric. Food Chem.* **2001**, *49*, 1502. (n) Kutschy, P.; Dzurilla, M.; Takasugi, M.; Török, M.; Achbergerová, H. R.; Rária, M. *Tetrahedron* **1998**, *54*, 3549. (o) Acheson, R. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, CA, 1990; Vol. 51, pp 105−175.

(2) (a) Neave, A. S.; Sarup, S. M.; Seidelin, M.; Duss, F.; Vang, O. *Toxicol. Sci.* **2005**, *83*, 126. (b) Stephensen, P. U.; Bonnesen, C.; Schaldach, C.; Andersen, O.; Bjeldanes, L. F.; Vang, O. *Nutr. Cancer* **2000**, *36*, 112. (c) Tsotinis, A.; Eleutheriades, A.; Hough, K.; Sugden, D. *Chem. Commun.* **2003**, 382.

(3) (a) Dean, F. M.; Patampongse, C.; Podimuang, V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 583. (b) Masanori, S.; Kensuke, K.; Keiko, T.; Toshihiko, M.; Yumiko, K.; Yoshikazu, F. *Heterocycles* **1995**, *40*, 119.

(4) (a) Somei, M.; Yamada, F.; Kurauchi, T.; Nagahama, Y.; Hasegawa, M.; Yamada, K.; Teranishi, S.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **2001**, *49*, 87. (b) Somei, M.; Sato, H.; Kaneko, C. *Heterocycles* **1983**, *20*, 1797.

(5) (a) Selvakumar, N.; Reddy, Y.; Azhagan, A. M.; Khera, M. K.; Babu, J. M.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 7065. (b) Selvakumar, N.; Khera, M. K.; Reddy, Y.; Srinivas, D.; Azhagan, M.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 7071. (c) Selvakumar, N.; Rajulu, G. G. *J. Org. Chem.* **2004**, *69*, 4429.

(6) Penoni, A.; Palmisano, G.; Broggini, G.; Kadowaki, A.; Nicholas, K. M. *J. Org. Chem.* **2006**, *71*, 823.

(7) Creary, X.; Wang, Y.-X.; Jiang, Z. *J. Am. Chem. Soc.* **1995**, *117*, 3044.

(8) (a) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403. (b) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501. (c) Foucaud, A.; Razorilalan-Rabearivony, C.; Loukakou, E.; Person, H. *J. Org. Chem.* **1983**, *48*, 3639. (d) Tercel, M.; Gieseg, M. A.; Denny, W. A.; Wilson, W. R. *J. Org. Chem.* **1999**, *64*, 5946. (e) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058. (f) Brown, J. A. *Tetrahedron Lett.* **2000**, *41*, 1623. (g) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919.

(9) For our previous work describing this, see: Zhao, K.; Chang, J.; Guo, H.; Du, Y. *Faming Zhuanli Shenqing Gongkai Shuomingshu*, CN 1 629 140, 22 Jun 2005; *Chem. Abstr.* **2006**, *144*, 128851.

10.1021/jo7024477 CCC: $40.75
Published on Web 02/13/2008

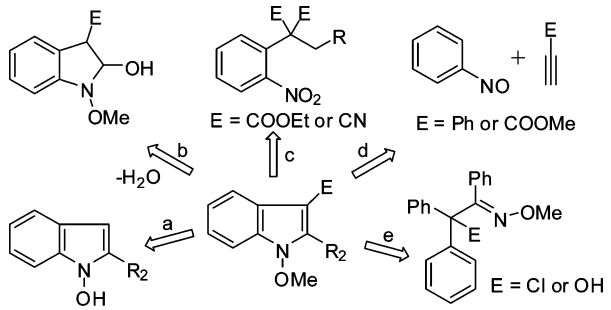


FIGURE 1. Existing strategies for construction of the *N*-methoxyindole skeleton.

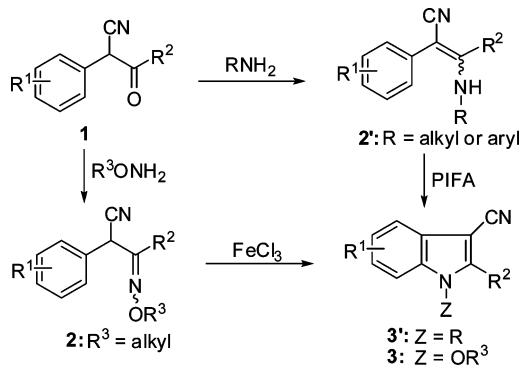
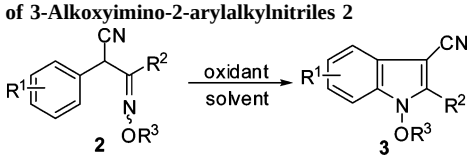


FIGURE 2. Synthesis of *N*-substituted indoles by joining the pendent *N*-moiety to the benzene ring.

1), although substrate **2** in each case was totally consumed.[10] A subtle change in the electronic configuration of the oxime ether **2** as compared to the enamine **2′** is apparently the cause for the observed difference in reactivity. Thus new oxidative cyclization conditions were investigated (entries 7−14, Table 1) which led to the discovery that the single electron oxidant $FeCl_3$ could conveniently convert **2a** into **3a**. A study to optimize reaction parameters by using **2a** as substrate (entries 15−20, Table 1) indicated that CH_2Cl_2 was a desirable solvent for the reaction, and at least 2 equiv of $FeCl_3$ was needed for the complete consumption of **2a**. As the reaction proceeded, the formation of gaseous HCl was observed. Furthermore, it was found that the isomeric oximes, cis isomer **2b-1** and trans isomer **2b-2**, afforded the same cyclized product **3b** in yields of 79% and 82%, respectively. For all subsequent studies, a mixture of the two oxime isomers[11] was used directly without separation. The results listed in Table 2 demonstrated that both electron-withdrawing and electron-donating aromatic substituents could be tolerated. Entries 9 and 10 (Table 2) showed that when R^3 was a bulkier *n*-butyl or benzyl group, the reaction was not significantly altered. However, when R^2 was a bulkier phenyl or benzyl group (entries 2 and 12−15, Table 2), the reaction time was obviously longer and the yields were reduced (56−64%). When R^2 was hydrogen (entry 11, Table 2), the 2-unsubstituted *N*-alkoxyindole **3j** was obtained in acceptable yield. The reaction was also compatible with multiple substituents on the benzene ring (entries 17 and 21, Table 2).

TABLE 1. Conditions Screened for the Intramolecular Cyclization Reaction of 3-Alkoxyimino-2-arylalkylnitriles 2



entry[a]	oxidant (equiv)	2	solvent	temp (°C)	time (h)	yield (%)[b]
1	PIFA (1.3)	**2a**	CH_2Cl_2	rt	24	10[c]
2	PIFA (1.3)	**2c**	CH_2Cl_2	rt	24	15[c]
3	PIFA (1.3)	**2f**	CH_2Cl_2	rt	24	13[c]
4	PIFA (1.3)	**2o**	CH_2Cl_2	rt	24	9[c]
5	PIFA (1.3)	**2t**	CH_2Cl_2	rt	24	35[c]
6	PIFA (1.3)	**2a**	toluene	105	12	12[c]
7	I_2 (5)	**2a**	CH_2Cl_2	rt	6	0
8	MnO_2 (3)	**2a**	CH_2Cl_2	rt	6	0
9	DDQ (3)	**2a**	CH_2Cl_2	rt	6	0
10	CAN (3)	**2a**	MeOH	rt	6	0
11	$Cu(Oac)_2 \cdot H_2O$ (4)	**2a**	AcOH	110	6	0
12	$Mn(OAc)_3 \cdot 2H_2O$ (3)	**2a**	AcOH	110	6	0
13	$FeCl_3 \cdot 6H_2O$ (3)	**2a**	CH_2Cl_2	rt	6	0
14	$FeCl_3$ (1.5)	**2a**	CH_2Cl_2	rt	3	50[d]
15	$FeCl_3$ (2.0)	**2a**	CH_2Cl_2	rt	2	77
16	$FeCl_3$ (2.2)	**2a**	CH_2Cl_2	rt	<1	82
17	$FeCl_3$ (2.2)	**2a**	MeOH	rt	12	0
18	$FeCl_3$ (2.2)	**2a**	EtOAc	rt	12	trace
19	$FeCl_3$ (2.2)	**2a**	MeCN	rt	12	trace
20	$FeCl_3$ (2.2)	**2a**	THF	rt	12	trace

[a] All reactions were run in commercial grade solvents without inert atmosphere protection. [b] Isolated yields after silica gel chromatography. [c] Contains several unidentified byproducts. [d] 20% of **2a** recovered.

Meta-Substituted aromatic reactants have the possibility of producing two regioisomeric products. With the *m*-chloro- or *m*-trifluoromethylbenzenes (entries 18 and 19, Table 2), similar quantities of the regioisomeric indoles were observed; however, for the substrates **2s**, **2t**, and **2v**, the single regioisomeric products **3s**, **3t**, and **3v** were found, respectively.

An important extension of this heterocyclization methodology is to use alternative types of aromatic rings to generate different classes of pyrrole-fused heterocycles such as the hitherto unknown **3u**−**w** from the substrates **2u**−**w**. It is noteworthy that in the ^{13}C NMR spectra, the *N*-methoxy group signal in **3r** is split into a quartet, apparently the result of through space coupling[12] with the fluorines of the trifluoromethyl group at the 7 position, while this coupling is not observed in **3r′**.

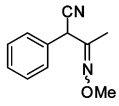
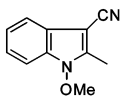
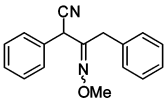
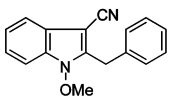
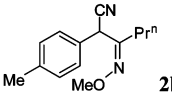
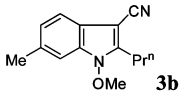
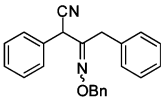
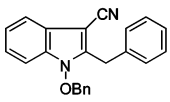
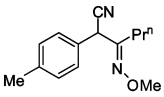
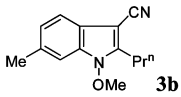
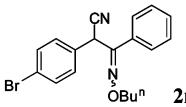
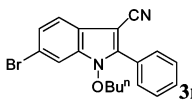
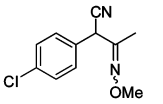
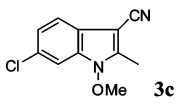
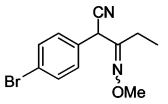
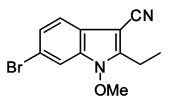
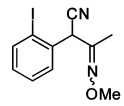
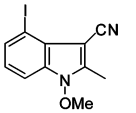
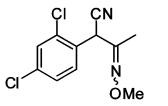
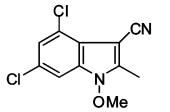
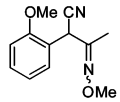
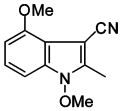
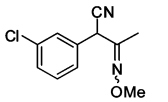
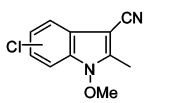
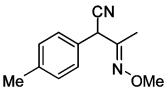
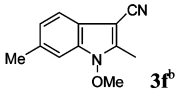
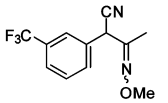
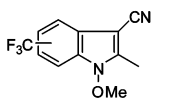
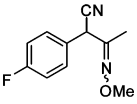
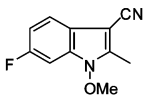
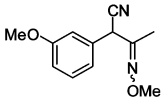
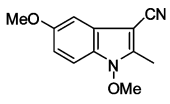
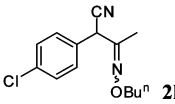
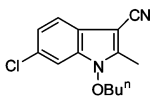
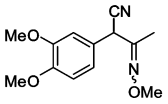
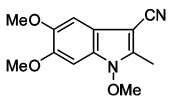
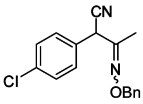
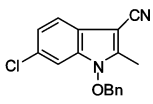
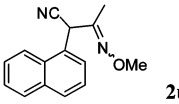
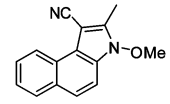
In our investigation of the scope and generality of this heterocyclization method, we found that seemingly closely related substrates (**4**−**8** in Figure 3), when applied to the same reaction conditions, yielded none of the expected cyclized product, which indicates that a benzylic *cyano* group plays a crucial role in the course of the reaction. Interestingly, the result that substrates **7** and **8** were unable to cyclize could be predicted by the fact that only a single desired product **3m** was obtained for substrate **2m** (entry 14, Table 1), which implies that formation of an intermediate with a double bond conjugated with the benzene ring that will be cyclized by the pendent

(10) In all cases, no successful results were achieved by varying experimental parameters: (a) use of various solvents, (b) adding TFA or $BF_3 \cdot Et_2O$ as catalyst, and (c) carrying out the reactions at temperatures ranging between −78 and 150 °C.

(11) For the assignment of the cis and trans geometries, see: (a) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 6922. (b) Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cuningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284. (c) Johnson, J. E.; Ghafouripour, A.; Haug, Y. K.; Cordes, A. W.; Pennington, W. T. *J. Org. Chem.* **1985**, *50*, 993. (d) Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*, 252.

(12) For the evidence of C−F space-coupling, see: (a) Jaime-Figueroa, S.; Kurz, L. J.; Liu, Y.; Cruz, R. *Spectrochim. Acta, Part A* **2000**, *56*, 1167. (b) Gribble, G. W.; Olson, E. R. *J. Org. Chem.* **1993**, *58*, 1631.

TABLE 2. Synthesis of *N*-Alkoxyindoles 3 via Intramolecular Heterocyclization of 3-Alkoxyimino-2-arylalkylnitriles 2 Mediated by $FeCl_3$[c]

entry	substrate **2**	product **3**	time (min)	yield (%)[a]	entry	substrate **2**	product **3**	time (min)	yield (%)[a]
1	 **2a**	 **3a**	40	82	13	 **2l**	 **3l**	60	64
2	 **2b-1**	 **3b**	90	79	14	 **2m**	 **3m**	60	60
3	 **2b-2**	 **3b**	90	82	15	 **2n**	 **3n**	120	56
4	 **2c**	 **3c**	40	91	16	 **2o**	 **3o**	50	75
5	 **2d**	 **3d**	40	82	17	 **2p**	 **3p**	25	86
6	 **2e**	 **3e**	15	68	18	 **2q**	 **3q** / **3q′**	30	7-Cl: 42 / 5-Cl: 37
7	 **2f**	 **3f**[b]	20	83	19	 **2r**	 **3r** / **3r′**	20	7-CF_3: 40 / 5-CF_3: 38
8	 **2g**	 **3g**	30	87	20	 **2s**	 **3s**	10	70
9	 **2h**	 **3h**	25	79	21	 **2t**	 **3t**	10	74
10	 **2i**	 **3i**	40	62	22	 **2u**	 **3u**	40	72
11	**2j**	**3j**	20	60	23	**2v**	**3v**	40	75
12	**2k**	**3k**	80	57	24	**2w**	**3w**	25	65

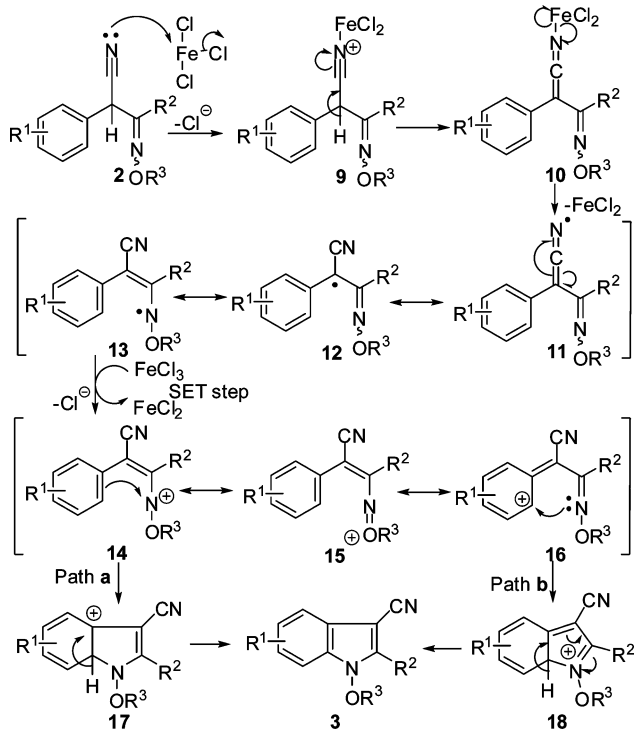
[a] Isolated yields after silica gel chromatography. [b] The structure of **3f** was further confirmed by X-ray crystal analysis. See the Supporting Information for details. [c] Conditions: all reactions were carried out with 1 equiv of **2**, 2.2 equiv of ferric chloride in CH_2Cl_2 at rt.

FIGURE 3. Other models that failed to cyclize via $FeCl_3$.

N-moiety is required. Besides, it was very surprising to find that the most similar substrate **5**, differing from substrate **2t** by replacement of the nitrile with an ester, also failed to provide any detectable cyclized product under the same reaction conditions. A possible explanation for this might be that in the presence of an ester group, $FeCl_3$ would act as a Lewis acid, rather than a single electron oxidant. However, this method still has a significant implication for the synthesis of a large number of *N*-alkoxyindole derivatives since the *cyano* group is a versatile functionality.

Potential mechanistic sequences are proposed in Scheme 1. (1) The coordination of $FeCl_3$ with the *cyano* group, followed by an abstraction of the benzylic proton from **9** and the

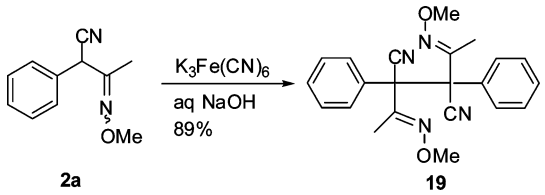
SCHEME 1. Proposed Mechanistic Pathways



subsequent removal of $FeCl_2$ from **10** would give the stable nitrogen-based radical **11**, with resonance structures carbon based radical **12** and the *N*-radical **13**. (2) Mediated by ferric chloride, a second SET (single electron transfer) process would occur to convert *N*-radical **13** to the nitrenium ion **14**. (3) The electrophilic attack on the nitrenium ion by the benzene ring[13] with the subsequent loss of a proton would afford **3** (path a, Scheme 1). Alternatively, from the resonance structure **16**, the nitrogen lone pair could nucleophilicly attack the ring carbocation to give **18**. Finally, rearomatizaiton of **18** by loss of a proton would give the titled compounds **3** (path b, Scheme 1). The above proposed mechanism accounts well for the experimental facts such as the formation of gaseous HCl and the need for 2 equiv of $FeCl_3$ for a complete reaction.

Although no intermolecular coupled products of carbon-based radical **12** were detected in any of the reactions with $FeCl_3$, we found that substrate **2a**, after treatment with $K_3Fe(CN)_6$, conveniently furnished the homodimer **19** in high yield without any formation of **3a** (Scheme 2). This result suggests that the radical species initially generated with $FeCl_3$ must be rapidly converted to the nitrenium ion **14** while $K_3Fe(CN)_6$, being a less potent oxidant (compared with $FeCl_3$), could not fulfill the transformation of **13** into **14** and gave the intermediate radical **12** long enough lifetime for dimerization to occur.

SCHEME 2. An Oxidative Coupling Reaction of 2a Mediated by $K_3Fe(CN)_6$



In summary, we have discovered a conceptually different route for the preparation of the *N*-alkoxyindole skeleton. Compared with existing methods, the key features of this new method include a tolerance to various functional groups, ready availability of the starting materials, and remarkably mild reaction conditions. Complementary to the recently described cyclodehydration of *a*-aryl ketone oximes to indoles,[8f] this method generates the indole from its alkyl oxime ether **2** but without cleavage of the N−O bond. The widespread occurrence of *N*-alkoxyindole derivatives in natural products and pharmaceuticals might render this method broadly useful.

Experimental Section

General Procedure for the Synthesis of *N*-Alkoxyindole-3-carbonitriles 3. To a solution of 3-alkoxyimino-2-aryalkylnitrles **2** (4 mmol) in CH_2Cl_2 (30 mL) was added in one portion the $FeCl_3$ (10 mmol) powder with stirring at room temperature. TLC was used to monitor the reaction process until the total consumption of **2**. To the solution was then added H_2O (20 mL), and stirring was continued for an additional 5 min. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the organic layer was dried with anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by silica gel chromatography, using a mixture of petroleum ether and EtOAc as eluent, to give the pure products **3**; the reaction time and yields are reported in Table 2. (See the Supporting Information for details.)

Acknowledgment. We thank the Tianjin Municipal Science and Technology Commission (043186011) and the Basic Research Project (No. 2003AA223151) of the MOST for financial support. J.C. thanks the National Natural Science Foundation of China (No. 20672030).

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds and X-ray structural data for **3f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO7024477

(13) For selective nitrenium ion's such intramolecular cyclization reactions, see: (a) Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728. (b) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2255. (c) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394. (d) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739. (e) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *Tetrahedron* **1987**, *43*, 2577. (f) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053. (g) Correa, A.; Herrero, M. T.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartín, R. *Tetrahedron* **2003**, *59*, 7103. (h) Correa, A.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartín, R. *J. Org. Chem.* **2005**, *70*, 2256. (i) Correa, A.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartín, R. *J. Org. Chem.* **2006**, *71*, 3501. (j) Correa, A.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartín R. *Org. Lett.* **2006**, *8*, 4811 and references cited therein.