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Iodobenzene Dichloride/Zinc Chloride-Mediated Synthesis of *N*-Alkoxyindole-3-carbonitriles from 3-Alkoxyimino-2-arylalkylnitriles via Intramolecular Heterocyclization

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Abstract. A series of *N*-alkoxyindole-3-carbonitriles were synthesized, under mild conditions, via intramolecular heterocyclization of the readily available 3-alkoxyimino-2-arylalkylnitriles mediated by iodobenzene dichloride/zinc chloride. The mechanism of the reaction proposes the formation of a key intermediate of nitrenium cation from a chlorination and dechlorination process facilitated by the hypervalent iodine reagent and Lewis acid respectively.

Keywords: *N*-alkoxyindole; hypervalent iodine(III) reagent; intramolecular heterocyclization; one-pot; nitrenium ion

The *N*-alkoxyinodole framework bearing a characteristic *N*-alkoxy moiety is often found in natural products.[1] For instances, 9-methoxycarbazole-3-carbaldehyde, isolated from *Murraya euchrestifolia* HAYATA (Rutaceae),[1b] paniculidine B, isolated from *Murraya paniculata* (Linn.) Jack,[2] and phytoalexin, produced by wasabi (*Wasabia japonica*. syn. *Eutrema wasab*)[3] (Figure 1) all possess the *N*-alkoxyindole motif in their respective chemical structure. Furthermore, *N*-alkoxyinodole compounds can also be used as a pharmacophore in drug discoveries.[4] For examples, indole-3-carbinol, isolated from *Brassica*, has shown to have anticarcinogenic effects.[5] *N*-methoxylated indole-3-carbinol showed stronger inhibition to the colon cancer cell lines DLD-1 and HTC-115 and higher efficiency as an inducer of cytochrome P-450 1A1 in cultured cells than unsubstituted indole-3-carbinol.[5,6] Similarly, functionalization of the indole nitrogen with a methoxy moiety in melatonin led to an increase of activity to nearly five folds.[7] Moreover, *N*-alkoxyindoles are used to serve as precursors of other indole derivatives by dealkoxylation through nucleophilic substitution reactions[8] with 1-alkoxy as the leaving group[9] and hydrogenation reaction.[10]

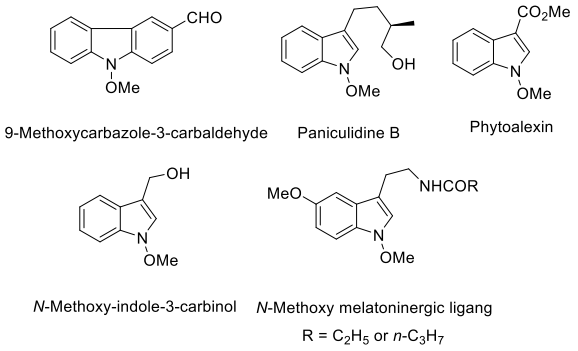
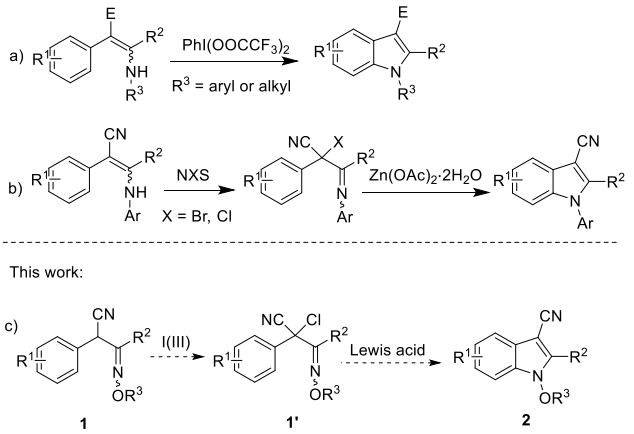


Figure 1. Representative Natural products and Pharmaceutical agents containing the *N*-alkoxyinodole framework.

Though *N*-alkoxyindole derivatives have received considerable attention from organic and medicinal chemists, only a few approaches have been explored to achieve the *N*-alkoxyindole skeleton compared to the existing plethora syntheses of many other types of substituted indoles. This is mainly due to the requirement of specific starting materials and/or reagents for constructing the *N*-alkoxyindole framework. The most common strategy is methylation of *N*-hydroxyindoles, via Somei's method, to produce *N*-methoxyindole derivatives.[8d,9a,11] Intramolecular cyclization is another commonly adopted approach. Selvakumar *et al* reported the cyclization of 2-(2-nitrophenyl)malonate or 2-(2-nitrophenyl)cyanoester mediated by NaCl/DMSO at high temperatures.[12] Penoni's group also reported a one-pot strategy for the preparation of *N*-methoxyindoles via base-promoted cycloaddition of nitrosoarenes with alkynes followed by methylation with Me_2SO_4.[13] In 2003, Creary and co-workers realized a DMSO facilitated

intramolecular cyclization of 2-chloro-2,2-diphenylacetaldehyde *O*-methyloxime during their research on carbocation-forming reactions.[14] Our group also realized the synthesis of *N*-alkoxyindole-3-carbonitrile through an intramolecular oxidative cyclization of 3-alkoxyimino-2-arylalkylnitriles mediated by $FeCl_3$ in which $FeCl_3$ functioned as a single electron oxidant.[15]



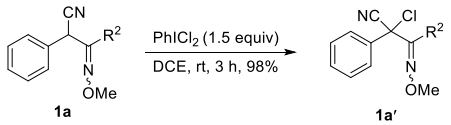
Scheme 1. Proposed Route to Access *N*-Alkoxyindoles Based on Our Previously Reported Approaches for Indole Synthesis

Hypervalent iodine(III) reagents have attracted extensive interests from synthetic chemists during the past several decades due to their easy-to-handle, non-toxic and environmental benign properties compared to other oxidative reagents involving heavy metals such as Pb(IV), Hg(II) and Ti(III).[16] Being recognized these desirable properties, hypervalent iodine(III) reagents have been widely applied in many oxidative reactions leading to the formation of *N*-containing heterocycles.[17] In 2006, we utilized phenyliodine bis(trifluoroacetate) (PIFA) as an oxidant to realize an intramolecular cyclization protocol for the synthesis of *N*-substituted indole derivatives from *N*-aryl or *N*-alkyl enamine substrates (Scheme 1a).[18] However, shortly afterwards we realized the protocol did not work for 3-alkoxyimino-2-arylalkylnitriles, an *N*-alkoxyimine substrate, to afford the desired *N*-alkoxyindole products.[15]

In 2011, we reported an alternative approach for the formation of *N*-arylindoles from *N*-aryl enamine substrate, the process of which involved NBS or NCS-mediated halogenation followed by a $Zn(OAc)_2{\cdot}2H_2O$-mediated dehalogenation and subsequent C-N bond formation (Scheme 1b).[19] Inspired by this work, we launched an investigation of whether 3-alkoxyimino-2-arylalkylnitriles could undergo a similar halogenation-dehalogenation process to give the *N*-alkoxyindole product. However, the reaction failed as neither NBS or NCS was able to convert 3-alkoxyimino-2-arylalkylnitrile to its halogenated product.

Here in this communication, we report the formation of *N*-alkoxyindole products via a chlorination-dechlorination process facilitated by a combination of a hypervalent iodine reagent, iodobenzene dichloride ($PhICl_2$), and Lewis acid, zinc chloride ($ZnCl_2$), and followed by intramolecular hetrocyclization reaction (Scheme 1c).

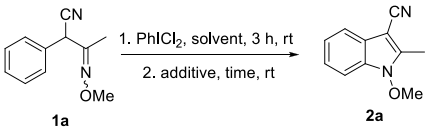
3-(Methoxyimino)-2-phenylbutanenitrile **1a**, which can be easily prepared from the commercially available *β*-ketonitrile in two steps according to the known procedures,[20,21] was selected as the model substrate to test the feasibility of the proposed transformation. When substrate **1a** was treated with 1.5 equiv of $PhICl_2$ in 1,2-dichloroethane (DCE) at room temperature, a chlorinated imine product **1a′** was obtained in nearly quantitative yield (Scheme 2).



Scheme 2. $PhICl_2$-Mediated Chlorination of 3-Methoxyimino-2-phenylbutanenitrile

After the formation of **1a′**, additive $BF_3{\cdot}Et_2O$ was added into the reaction mixture to investigate whether the reaction could deliver the desired *N*-methoxyindole product with satisfactory results such as in a one-pot fashion. We were very pleased to find that the second step went to completion 24 h later,

Table 1. Conditions Optimization for the $PhICl_2$/Lewis Acid-mediated One-pot Synthesis of 3-(Methoxyimino)-2-phenylbutanenitrile **1a**[a]



Entry[a]	Additive (equiv)	Solvent	Time/h[b]	Yield[c](%)
1	$BF_3{\bullet}Et_2O$ (2.0)	DCE	24	20
2	$AlCl_3$ (1.0)	DCE	12	73
3	$Zn(OAc)_2{\bullet}2H_2O$ (1.0)	DCE	12	0
4	$CoCl_2{\bullet}6H_2O$ (1.0)	DCE	12	0
5	$ZnBr_2$ (1.0)	DCE	3.5	73
6	$ZnCl_2$ (1.0)	DCE	5	91
7	$ZnCl_2$ (2.0)	DCE	4	81
8	$ZnCl_2$ (0.5)	DCE	6	93
9	$ZnCl_2$ (0.5)	THF	12	<5%
10	$ZnCl_2$ (0.5)	DMF	12	<5%
11	$ZnCl_2$ (0.5)	CH_3CN	12	<5%
12	$ZnCl_2$ (0.5)	toluene	12	<5%

[a]Reaction conditions: **1a** (2.0 mmol), $PhICl_2$ (3.0 mmol), additive in solvent (20 mL). [b]Time for the second step. [c]Isolated yield.

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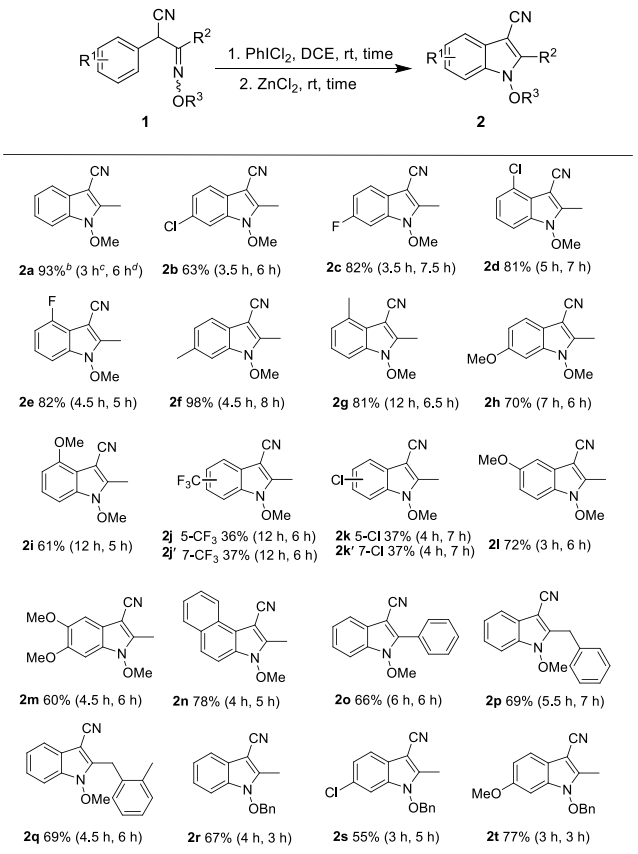
and the desired *N*-methoxy-indole-3-carbonitrile **2a** was obtained in 20% (Table 1, entry 1). This preliminary result, albeit low in yield, encouraged us to carry out further screenings of variables to identify the optimal conditions for this one-pot dechlorination-and-hetreocyclization process. Screening of various Lewis acids showed that $ZnCl_2$ was the most effective for this transformation, which agreed with the previous reactions[19] (Table 1, entries 2-6). The use of two-fold dosage of $ZnCl_2$ resulted into a lower yield (Table 1, entry 7), although the reaction time was shortened. Reducing the amount of $ZnCl_2$ to 0.5 equiv increased the yield up to 93% (Table 1, entry 8). Finally, other solvents including THF, DMF, CH_3CN and toluene were tested, but none of them gave a better yield compared to DCE (Table 1, entries 9-12).

Table 2. $PhICl_2/ZnCl_2$-Mediated Synthesis of *N*-Methoxyindole-3-carbonitriles from 3-Methoxyimino-2-arylalkylnitriles[a]

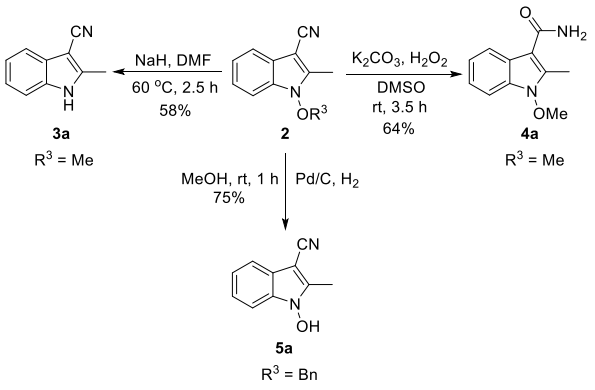


[a]Reaction conditions: **1** (2.0 mmol), $PhICl_2$ (3.0 mmol), $ZnCl_2$ (1.0 mmol) in DCE (20 mL). [b]Isolated yield. [c]Time for the first step. [d]Time for the second step.

Under the optimized conditions,[22] studies of feasibility and scope of this one-pot reaction were carried out. Results summarized in Table 2 show that a range of substituents of R^1 electron-withdrawing (fluoro, trifluoromethyl, and chloro) and electron-donating (methoxy and methyl) groups, **2a-m** were all formed in acceptable yields between 60-98%. For chlorine substituted substrates, *ortho*-substituted seemed to be more favored than *para*-substituted (**2d** vs. **2b** in 83% vs. 63%, respectively), while those with R^1 being fluorine, both *o*- and *p*-substituted gave the same satisfactory yield of 82% (Table 2, **2c** & **2e**). In contrast, for substrates bearing electron-donating methyl or methoxy group, the *para*-substituted gave higher yields than relatively to the *ortho* counterpart (Table 2, 98% vs. 81% for **2f** and **2g**, respectively; and 70% vs. 61% for **2h** and **2i**, respectively). As expected, for substrates bearing substituents at the *meta* position, separable regioisomeric products were obtained in a nearly equal amount (**2j**/**2j′** and **2k**/**2k′**). Interestingly, for the substrate bearing a methoxy group at *meta* position, only 5-methoxy indole **2l** was formed regioselectively in a 72% yield. A lower yield of the desired product was obtained for dimethoxy substituted imine **1m** due to formation of additional byproducts. It is worthy to note that this method is also applicable to substrate bearing a naphthalenyl ring, which enables the synthesis of the desired indole compound **2n**.

Concerning R^2, substrates carrying bulkier (than methyl) groups such as phenyl or benzyl all afforded the desired products **2o-q** in similar moderate yields between 66-69%.

The methoxy group in the substrate could also be replaced with other alkoxy groups. For example, when substrate **1r-t** was subjected to the standard conditions, the desired *N*-benzyloxyindole products **2r-t** could be obtained in acceptable to satisfactory yields.

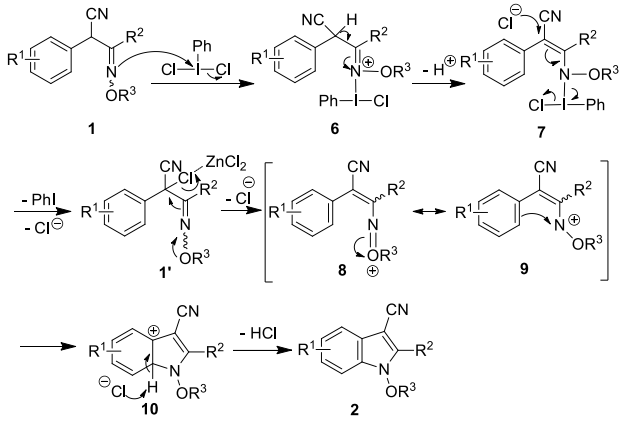


Scheme 3. Derivatization of *N*-Alkoxyindole **2**.

The obtained *N*-alkoxy-indole-3-carbonitriles **2** could be converted to other indole derivatives via known methods. For examples, the methoxy group in compound **2a** could be straightforwardly removed upon treatment with NaH in DMF at 60 °C[10,23] to provide NH-free 2-methyl-1*H*-indole-3-carbonitrile **3a** in 58% yield. In addition, the cyano group in *N*-methoxyindole **2a** could be conveniently converted to *N*-methoxyindole 3-carboxamide **4a** in the presence of K_2CO_3/H_2O_2 in DMSO with a modest yield of 64%, according to a known method.[24] Furthermore, the benzyl group in **2r** could be removed by hydrogenation over Pd/C to afford the N-OH-free *N*-hydroxyindole product **5a**, which is also a crucial

skeleton found in natural products or employed as a key intermediate in natural products syntheses[1e] (Scheme 3).

In the mechanistic studies, we ran the reaction in the present of radical scavenger TEMPO. The negative result ruled out a radical path of the reaction. A plausible mechanistic sequence is proposed in Scheme 4. First, nucleophilic attack of the iodine center of $PhICl_2$ by the nitrogen atom in substrate **1** affords the ammonium salt intermediate **6**, which can be converted to enamine **7**[25] by the loss of a proton. Then the nucleophilic addition of chloride anion to the carbon double bond in **7** followed by the reductive elimination of phenyl iodine in **7** gives α-chloro imine intermediate **1′**.[25c] Assisted by $ZnCl_2$, dechlorination occurs to convert imine **1′** to the enamine/oxonium **8**, with a resonance structure of the highly reactive species nitrenium ion intermediate **9**.[19,26] Then electrophilic cyclization occurs in **9**, followed by deprotonation/aromatization to give the target product *N*-alkoxyindole **2**.



Scheme 4. Proposed Mechanistic Pathway

In summary, we have developed an efficient $PhICl_2/ZnCl_2$-mediated synthesis of *N*-alkoxyindole-3-carbonitriles from 3-alkoxyimino-2-arylbutanenitriles via intramolecular heterocyclization. The main feature of the current method is one-pot, and the main role of the hypervalent iodine reagent is chlorinating the substrate which facilitates the formation of the cyclization through forming the key nitrenium ion intermediate. The widespread existence of the biologically and pharmacologically significant *N*-alkoxyindole compounds will render this protocol a valuable synthetic tool in organic chemistry.

Experimental Section

General One-pot Procedure for the Preparation of *N*-Alkoxyindole-3-carbonitriles 2.

To a solution of the prepared 3-alkoxyimino-2-aryl-alkylnitrilles **1** (2.0 mmol, 1.0 equiv) in DCE (20 mL) was added $PhICl_2$ (3.0 mmol, 1.5 equiv) at room temperature. After consumption of the **1**, $ZnCl_2$ (1.0 mmol, 0.5 equiv) was added in a portion-wise manner. The resulting mixture was maintained at room temperature and the reaction was monitored by TLC. Upon completion, the residue was mixed with water (20 mL) and extracted with DCM (3 x 20 mL). The organic phase was washed with brine (1 x 20 mL), dried over anhydrous Na_2SO_4 and solvent was removed by rotary evaporation. The product was isolated by flash column chromatography on silica gel (EtOAc/PE) to afford the desired compound **2**.

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[22] We also studied the reaction by adding $ZnCl_2$ together with $PhICl_2$ at the same time. The reaction provided the final product **2a** in 75% with longer time (12 h).

[23] Some other Lewis acids were also tested but gave relatively low yields: 1) $LiAlH_4$ (0.3 equiv), THF, 40 ^oC, 1 h, 54%; 2) BBr_3 (3 equiv), DCM, 25 ^oC, 24 h, 49%.

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COMMUNICATION

Iodobenzene Dichloride/Zinc Chloride-Mediated Synthesis of *N*-Alkoxyindole-3-carbonitriles from 3-Alkoxyimino-2-arylalkylnitriles via Intramolecular Heterocyclization

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