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Novel and Direct Oxidative Cyanation Reactions of Heteroaromatic Compounds Mediated by A Hypervalent Iodine(III) Reagent

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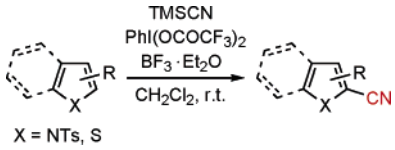
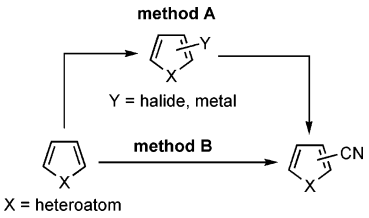
ABSTRACT



The hypervalent iodine(III) reagent phenyliodine bis(trifluoroacetate) (PIFA) mediates the selective cyanation reactions of a wide range of electron-rich heteroaromatic compounds such as pyrroles, thiophenes, and indoles under mild conditions. These reactions proceed via a cation radical intermediate, and the key for the successful transformation presumably depends on the oxidation–reduction potential of the substrates used. The synthetic utility has been demonstrated through the conversion of these biologically important pyrroles 2f and 2g.

Heteroaromatic cyanides such as pyrroles, indoles, and thiophenes are of substantial interest for a wide range of researchers from organic and pharmaceutical chemistries to material science due to their ubiquity of natural products[1] and unique physical properties in polymer form.[2] On the basis of these considerations, effective methods for the introduction of the cyanide functionality into these heteroaromatic compounds are considered to be very important, because nitriles are valuable intermediates in organic synthesis for yielding a broad spectrum of compounds.[3] To date, two representative methodologies have already been reported (Scheme 1). One of them is a stepwise approach (method A); though *prefunctionalized* substrates are needed, the transition-metal-catalyzed cyanation of aryl halides[4] and the electrophilic cyanation of metalated aryls[5] have attracted widespread interest for organic synthesis in terms of high selectivity and versatility of substrates. However, introduction of cyanide into a pyrrole ring is difficult using such methods because the starting halogenated pyrroles are very unstable.[6] Therefore, another approach such as direct introduction of unfunctionalized pyrroles is important to obtain these cyanated compounds. The direct introduction of cyanide into

Scheme 1



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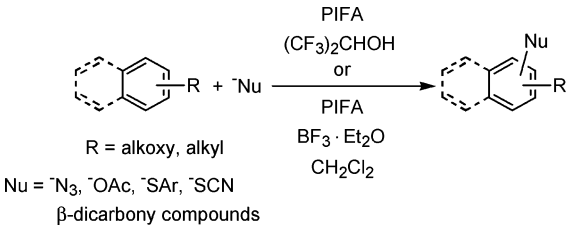
heteroaromatic compounds has also been reported using chemical agents[7] and photo- or electrochemical operations (method B).[8] The latter approach is believed to be desirable in nature by not requiring any functionality, but the utility has usually been limited to practical applications perhaps because of problems concerning the cyanation reagents. All reported cyanation procedures need the highly electrophilic cyano cation equivalent ($^{+}$CN) as cyanation sources, which are relatively unstable and difficult to prepare and handle and even in some cases possess reactivity too high to allow for selective control of the reactions. Therefore, new methodologies and reagents for enabling the direct cyanation have been strongly desired.

Recently, hypervalent iodine(III) reagents have been recongnized as useful synthetic tools due to their low toxicity, ready availability, and ease of handling.[9] As a continuation of our study on hypervalent iodine chemistry, we have previously reported the hypervalent iodine(III)-induced mild and efficient direct nucleophilic substitutions of phenyl ethers[10] and alkylarenes[10e] in the presence of various nucleophiles such as $^{-}$SCN,[10a] $^{-}$SAr,[10a,b] $^{-}$OAc, β-dicarbonyl compounds,[10d] and $^{-}N_3$[10c−e] (Scheme 2). These results

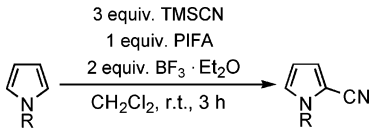
Scheme 2



encouraged us to examine the cyanide anion ($^{-}$CN) as a stable nucleophilic cyanide source for direct oxidative cyanation. We now report a phenyliodine bis(trifluoroacetate) (PIFA)-mediated reaction that allows the direct oxidative conversion of a wide range of heteroaromatic compounds into cyanides using trimethylsilyl cyanide at room temperature.

We first examined the cyanation of pyrrole **1a** by PIFA in $(CF_3)_2CHOH$ or a combination of PIFA and $BF_3{\cdot}Et_2O$ in dichloromethane at ambient temperature, which did not give any cyanation product under such conditions but instead afforded mainly oxidative biaryl coupling products (Table 1, entry 1).[11] This result shows the high nucleophicity of the pyrrole ring itself. After a number of unsuccessful attempts, we finally found that the protecting group of the pyrrole nitrogen atom plays a crucial role (entries 2−4). Thus, *N*-tosyl pyrrole **1d** was selectively converted to 2-cyano-*N*-tosyl pyrrole **2d** in 83% yield by the combination of PIFA and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature (entry 5). The regiochemistry of the cyanation products was determined from the ^{1}H NMR measurement or by leading the cyanation products to the known compounds which have been reported before. Trimethylsilyl cyanide produced the best result as a cyanide source among those examined,[12] probably due to its good solubility in organic solvents. Other

Table 1. Direct Cyanation of *N*-Protected Pyrroles



entry	R	yield of **2** (%)[a]
1	H (**1a**)	trace
2	Boc (**1b**)	trace
3	Me (**1c**)	20 (**2c**)
4	Ts (**1d**)	59 (**2d**)
5[b]	(**1d**)	83

[a] Isolated yields. [b] Performed with 2 equiv of PIFA and 4 equiv of $BF_3{\cdot}Et_2O$.

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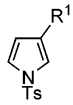
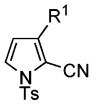
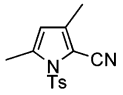
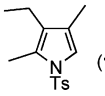
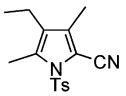
iodine(III) compounds such as phenyliodine diacetate (PIDA) and [hydroxy(tosyloxy)iodobenzene] (HTIB), gave poor results.

The present reaction is applicable for a wide range of substituted pyrroles as well as thiophenes having various types of aliphatic, aromatic, and ether substituents. These results are summarized in Table 2.[13] Although it has been

Table 2. PIFA-Mediated Direct Oxidative Cyanation of Pyrroles and Thiophenes

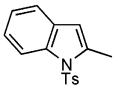
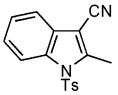
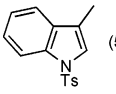
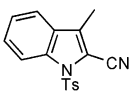
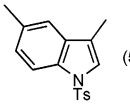
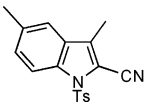
entry	substrate		product [a]		yield (%) [b]
1		R^1 = H (**1d**)		(**2d**)	83
2		Hep (**1e**)		(**2e**)	72
3		4-BrC_6H_4 (**1f**)		(**2f**)	91
4		2-BrC_6H_4 (**1g**)		(**2g**)	97
5	 (**1h**)			(**2h**)	43
6	 (**1i**)			(**2i**)	58
7		R^2 = Me (**3a**)		(**4a**)	79
8		Hex (**3b**)		(**4b**)	65
9		c-Hex (**3c**)		(**4c**)	59
10		OMe (**3d**)		(**4d**)	42
11		Ph (**3e**)		(**4e**)	68

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, and IR. [b] Isolated yields after purification by chromatography on silica gel.

widely recognized that the synthesis of 2-substituted 3-aryl pyrroles is quite difficult and only a few methods have been reported and they give low yields and lack of generality,[14a] 3-(4-bromophenyl)pyrrole **1f** and **1g** gave 2-cyanation products **2f** and **2g**, respectively, in excellent yields (entries 3 and 4). On the other hand, disubstituted pyrroles **1h** gave somewhat poor results due to the competitive formation of bipyrroles (entry 5). Trisubstituted pyrrole **1i** is applicable (entry 6). Similar to pyrroles, alkyl thiophenes **3a**−**c** selectively gave 2-cyanation products in good to moderate yields (entries 7−9). These reactions are quite sensitive to the electronic character of the thiophene (entry 10). The thiophenes **3e** are also converted to useful 2-cyano derivatives having 3-aryl groups in the same manner (entry 11).

Despite some slightly problematic yields, this cyanation protocol is available for indoles **5** (Table 3). 2-Methyl indole **5a** reacted at the 3-position to give the corresponding cyanation product **6a** (entry 1), and 3-methyl indole **5b** and **5c** reacted at the 2-position in turn (entries 2 and 3).

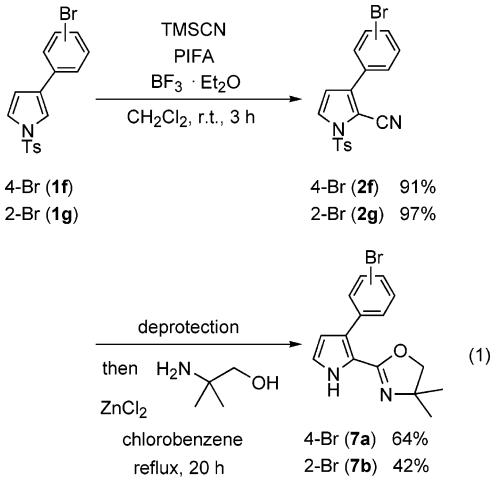
Table 3. PIFA-Mediated Direct Oxidative Cyanation of Indole Derivatives

entry	substrate	product [a]	yield (%) [b]
1	 (**5a**)	 (**6a**)	37
2	 (**5b**)	 (**6b**)	64
3	 (**5c**)	 (**6c**)	62

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, and IR. [b] Isolated yields after purification by chromatography on silica gel.

To demonstrate the synthetic utility of this novel direct oxidative cyanation reaction, we conducted transformations of the cyanation products **2f** and **2g** because these 3-aryl pyrroles are physiologically very important (Scheme 3).[14] Thus, deprotection of the tosyloxy group of **2f** and **2g** followed by treatment with 2-amino-2-methyl-1-propanol gave the 2-dihydrooxazole compounds **7a** and **7b**, respectively (eq 1). Apparently, these products are hardly accessible not only by a stepwise approach such as the palladium-catalyzed cyanation of aryl halides but also by the selective

Scheme 3



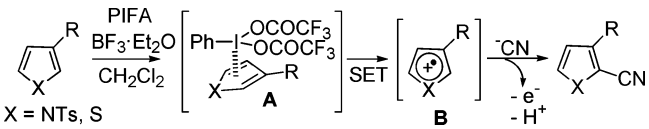
(12) Among the cyanide sources, trimethylsilyl cyanide gave the best yield compared with other reagents such as diethyl cyanophosphonate, tributyltin cyanide, and a combination of potassium cyanide and 18-crown-6.

(13) **Typical Experimental Procedure.** To a stirred solution of PIFA (2 mmol) and BF_3·AcOEt (4 mmol) in CH_2Cl_2 (1 mL) was added trimethylsilyl cyanide (3 mmol) at room temperature. After stirring for 30 min, *N*-tosyl pyrrole **1d** (1 mmol) was added in one portion, and the mixture was stirred for additional 3 h under the same condition while checking the reaction progress by GC or TLC. After the reaction was complete, saturated aqueous sodium thiosulfate (ca. 5 mL) was added to the mixture. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extract was dried with $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (SiO_2/*n*-hexanes−Et_2O) to give pure **2d** (83%).

introduction of a bromide into aryl rings after cyanation. It is thought that aryl bromide functions in compounds **7a** and **7b** are advantageous for construction of more complex molecules via C−C, C−N, and C−O bond formations.

A plausible mechanism of the present reaction is depicted in Scheme 4. Cation radical **B** is initially formed from the

Scheme 4



heteroaromatic compounds with PIFA−BF_3·Et_2O via CT-complex **A** under the reaction conditions analogous to those of our previously developed PIFA-induced reactions[10,11] or typical heavy metal oxidations,[15] yielding aromatic cation radicals. The cation radical **B** then reacts with the cyanide anion by an one-electron oxidation followed by deprotonation to give the observed cyanation product. The formation of **B** was supported by the effective inhibition of the reaction in the presence of the radical scavenger, galvinoxyl. The precise reason PIFA is an effective oxidizer in this cyanation reaction is still unclear, but the mild and effective generation of cation radical **B** induced by PIFA−BF_3·Et_2O might be important.

In summary, we have developed the direct oxidative cyanation of heteroaromatic compounds using a hypervalent iodine(III) reagent. Our novel cyanation protocol has the following characteristic features: (i) direct cyanation of unfunctionalized heteroaromatic compounds under mild conditions, (ii) a stable organocyanide source is usable, (iii) various types of heteroaromatic compounds are applicable, and (iv) the aryl halide function is maintained, which is beneficial for further transformations of the cyanation products. From these points of view, our novel cyanation procedure described herein will provide a new alternative method. Application of this cyanation reaction will be presented in the near furture.

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Supporting Information Available: Experimental details for preparation and detailed spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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