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Direct Cyanation of Heteroaromatic Compounds Mediated by Hypervalent Iodine(III) Reagents: In Situ Generation of PhI(III)−CN Species and Their Cyano Transfer

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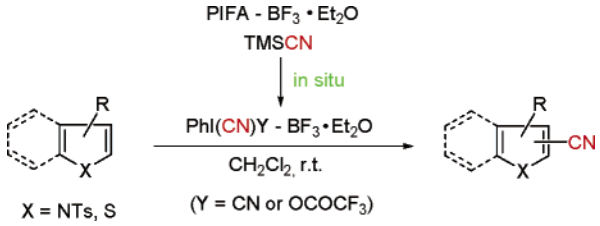

Hypervalent iodine(III) reagents mediate the direct cyanating reaction of a wide range of electron-rich heteroaromatic compounds such as pyrroles **1**, thiophenes **3**, and indoles **5** under mild conditions (ambient temperature), without the need for any prefunctionalization. Commercially available trimethylsilylcyanide is usable as a stable and effective cyanide source, and the reaction proceeds in a homogeneous system. The *N*-substituent of pyrroles is crucial to avoid the undesired oxidative bipyrrole coupling process, and thus a cyano group was introduced selectively at the 2-position of *N*-tosylpyrroles **1** in good yields using the combination of phenyliodine bis(trifluoroacetate) (PIFA), TMSCN, and BF_3•Et_2O at room temperature. In the reaction mechanism, cation radical intermediates of heteroaromatic compounds are involved as a result of single electron oxidation, and the key to successful transformations seems to depend on the oxidation potential of the substrates used. Thus, the reaction was also successfully extended to other heteroaromatic compounds having oxidation potentials similar to that of *N*-tosylpyrroles such as thiophenes **3** and indoles **5**. However, regioisomeric mixtures of the products derived from the reaction at the 2- and 3-positions were obtained in the case of *N*-tosylindole **5a**. Further investigation performed in our laboratory provided insights into the real active iodine(III) species during the reaction; the reaction is induced by an active hypervalent iodine(III) species having a cyano ligand in situ generated by ligand exchange reaction at the iodine(III) center between trifluoroacetoxy group in PIFA and TMSCN, and effective cyanide introduction into heteroaromatic compounds is achieved by means of the high cyano transfer ability of the hypervalent iodine(III)−cyano intermediates. In fact, the reaction of *N*-tosylpyrrole **1a** with a hypervalent iodine(III)−cyano compound (e.g., (dicyano)iodobenzene **8**), in the absence of TMSCN, took place to afford the 2-cyanated product **2a** in good yield, and an effective preparation of the intermediates is of importance for successful transformation. 1,3,5,7-Tetrakis[4-{bis(trifluoroacetoxy)-iodo}phenyl]adamantane **12**, a recyclable hypervalent iodine(III) reagent, was also comparable in the cyanating reactions as a valuable alternative to PIFA, affording a high yield of the heteroaromatic cyanide by facilitating isolation of the cyanated products with a simple workup. Accordingly, after preparing the active hypervalent iodine(III)−CN species by premixing of a recyclable reagent **12**, TMSCN, and BF_3•Et_2O for 30 min in dichloromethane, reaction of a variety of pyrroles **1** and thiophenes **3** provided the desired cyanated products **2** and **4** in high yields. The iodine compound **13**, recovered by filtration after replacement of the reaction solvent to MeOH, could be reused without any loss of activity (the oxidant **12** can be obtained nearly quantitatively by reoxidation of **13** using *m*-CPBA).

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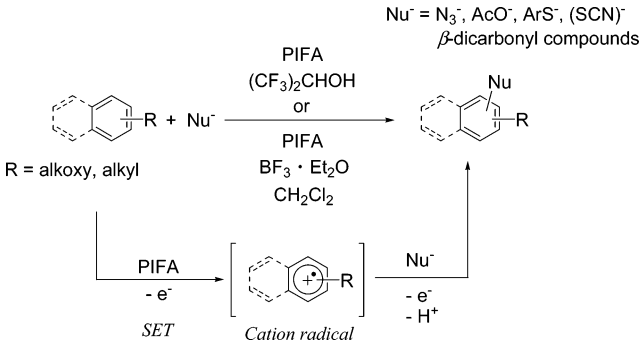
Introduction

Heteroaromatic compounds constitute general motifs in natural compounds and pharmaceuticals and are of substantial interest in a wide range of research studies from organic and pharmaceutical chemistries to material sciences due to their unique physical properties.[1,2] Along with these considerations, heteroaromatic cyanides are one of the important classes of compounds to build up complex molecules, because the cyano group is readily converted to a variety of other functional groups through the carboxylic acids and the amines, and so forth.[3] Therefore, it is important to develop efficient methods to introduce the cyano group into heteroaromatic compounds, and several synthetic methods have been reported thus far.[4−10]

The reported cyanating reactions of heteroaromatic compounds are generally classified into two representative methodologies; namely, a stepwise approach or a direct method. Despite the need for prefunctionalized substrates, the former approach involving a transition-metal-catalyzed cyanation of heteroaromatic halides[4] and electrophilic cyanation of metalated heteroaromatics using cyano electrophiles[5] has attracted widespread interest for organic synthesis in terms of the high selectivity and versatility of substrates. However, introduction of a cyano functionality into a pyrrole ring, an electron-rich heteroaromatic ring, is difficult when using such an approach, because the requisite functionalized pyrroles are relatively unstable.[11] Therefore, the latter method enabling direct introduction of a cyano group into pyrroles is important and desirable especially for an electron-rich heteroaromatic ring, but it is not a widely accepted method due to problems concerning the preparation of unstable *cyano cation equivalents* ($^{+}$CN) and the difficulty of the reaction control.[6−9] In this view, a direct cyanating reaction using stable *cyanide ion* ($^{-}$CN) under oxidative conditions[10] would become an alternative attractive method for the synthesis of these compounds because facile and effective methods had not yet appeared.

SCHEME 1. Direct Oxidative Introduction of Nucleophiles into Phenyl Ethers and Alkylarenes via Cation Radical Intermediates



Hypervalent iodine(III) reagents have mild oxidation abilities, similar to the highly toxic heavy metal oxidizers such as Pb(IV), Tl(III), and Hg(II), and have been recognized recently as a useful synthetic tool due to their low toxicity, ready availability, and easy handling.[12] Over the past decade, we have focused on a new, efficient, and mild oxidative transformation of electron-rich aromatic compounds using hypervalent iodine(III) reagents and have developed phenyliodine(III) bis(trifluoroacetate) (PIFA)-induced direct oxidative nucleophilic substitutions of phenyl ethers and alkylarenes by a variety of nucleophiles such as $^{-}$N$_3$,[13a,e] $^{-}$OAc and β-dicarbonyl compounds,[13b] $^{-}$SAr,[13d,e] and $^{-}$SCN[13e] under mild conditions (Scheme 1). The oxidative transformation could be rationalized by the formation of cation radical intermediates, which are generated by single electron transfer (SET) of phenyl ethers to PIFA.[13d] Subsequent intermolecular attack of nucleophiles followed by a further one-electron oxidation and deprotonation completes the oxidative aromatic substitution to give the observed products. Encouraged by these results, we have now examined the possibility of direct oxidative substitution of heteroaromatic compounds by cyanide ion ($^{-}$CN) as a stable nucleophilic cyanide source. Fortunately, our attempts have been realized successfully and have given rise to the direct oxidative introduction of cyanide into a wide

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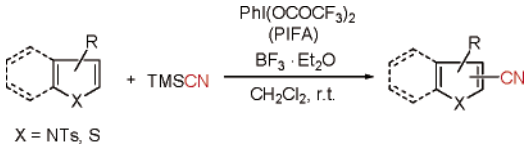
SCHEME 2. Direct Oxidative Cyanation of Various Heteroaromatic Compounds Induced by PIFA



range of heteroaromatic compounds such as pyrroles **1**, thiophenes **3**, and indoles **5** (Scheme 2).[14]

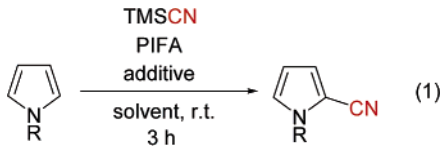
Herein, we wish to report in full detail the novel oxidative cyanating reaction of heteroaromatic compounds by the combination of PIFA, TMSCN, and BF_3·Et_2O at room temperature. The further investigation described herein revealed that the reaction would be mediated by hypervalent iodine(III) species having cyano ligands,[15,16] in situ generated from PIFA, TMSCN, and BF_3·Et_2O, and involves the cyano transfer from the active PhI(III)−CN species to heteroaromatic compounds. A facile and clean cyanating reaction has also been demonstrated using a recyclable hypervalent iodine(III) reagent as a useful alternative to PIFA.

Results and Discussion

Direct Cyanating Reaction of Pyrroles Using PIFA. Consulting our previous results on oxidative nucleophilic substitution reactions of phenyl ethers and alkylarenes, we first examined cyanation of 1*H*-pyrrole by PIFA in $(CF_3)_2CHOH$ or the combination of PIFA and BF_3·Et_2O in dichloromethane at ambient temperature using TMSCN as a soluble cyanide source, which gave only disappointing results; only trace amounts of cyanation products were detected by TLC and GC with unidentified byproducts (Table 1, entries 1 and 2). We then conducted the reaction at lower temperature (−78 °C). Similarly to the preliminary results, no introduction of cyanide into 1*H*-pyrrole was observed in this case, but instead mainly oxidative coupling products were obtained.[17] These results are clearly attributed to the excessive nucleophilicity of the pyrrole ring itself, and so we attempted to survey suitable *N*-substituents of pyrroles that can modulate nucleophilicity of the pyrrole ring.

Accordingly, we tried the reactions of pyrroles with electron-withdrawing groups at their *N*-position. After a number of unsuccessful attempts of the reactions at −78 °C, we finally found that the cyanating reaction would proceed at room temperature by choosing a tosyl group (Ts) as a suitable *N*-protecting group. Thus, *N*-tosylpyrrole **1a** was selectively converted to 2-cyano-*N*-tosylpyrrole **2a** in 59% yield with some extent of unreacted starting **1a** by the combination of PIFA and BF_3·Et_2O in CH_2Cl_2 at room temperature (entry 4). The

TABLE 1. Optimization of Reaction Conditions: Effect of *N*-Substituents in Direct Oxidative Cyanation of Pyrrole (Eq 1)



entry[a]	R	additive	solvent	yield of cyanated product (%)[b]
1	H	none	$(CF_3)_2CHOH$	trace
2	H	BF_3·Et_2O	CH_2Cl_2	trace
3	Boc[e]	BF_3·Et_2O	CH_2Cl_2	complex
4	Ts (**1a**)	BF_3·Et_2O	CH_2Cl_2	59
5	TIPS[e]	BF_3·Et_2O	CH_2Cl_2	55
6	Me	BF_3·Et_2O	CH_2Cl_2	20
7	Ts (**1a**)	none	$(CF_3)_2CHOH$	no reaction
8	Ts (**1a**)	TMSOTf	CH_2Cl_2	34
9[c]	Ts (**1a**)	BF_3·Et_2O	CH_2Cl_2	35
10[d]	Ts (**1a**)	BF_3·Et_2O	CH_2Cl_2	83

[a] Reactions were performed using 3 equiv of TMSCN, 1 equiv of PIFA, and 2 equiv of additive otherwise noted. [b] Isolated yield of the pure cyanated compounds. [c] Iodosobenzene was used instead of PIFA. [d] Two equivalents of PIFA and 4 equiv of BF_3·Et_2O were used. [e] Boc = *t*-butoxycarbonyl, TIPS = tri(isopropyl)silyl.

corresponding 2-cyanated products were also obtained with other *N*-substituents (entries 5 and 6), but the methyl group caused a more remarkable polymerization than the Ts and TIPS groups. Here, it should be noted that premixing of all reagents is essential in the order of PIFA, TMSCN, and BF_3·Et_2O; they were mixed for 30 min before adding **1a** for performing successful transformations. Otherwise, **2a** was obtained in poorer yields. In contrast, no reaction was observed in $(CF_3)_2CHOH$, a most effective solvent in the oxidative nucleophilic substitution of phenyl ethers.[13] Other Lewis acids and iodine(III) compounds such as phenyliodine diacetate (PIDA) and [hydroxyl(tosyloxy)-iodo]benzene (HTIB) did not produce any cyanation products except for iodosobenzene with BF_3·Et_2O (entry 9).[18] Using an excess of PIFA and BF_3·Et_2O improved the yield of cyanated product **2a** without any detectable side products derived from over-oxidations of **2a**.[19] Thus, *N*-tosylpyrrole **1a** was added to the stirred solution including 2 equiv of PIFA, 4 equiv of BF_3·Et_2O, and 3 equiv of TMSCN in dichloromethane. After reacting for 3 h, all starting **1a** was consumed and **2a** was obtained in 83% yield (entry 10).

To confirm the scope of the reaction, we attempted to apply the reaction to a variety of pyrroles using the optimized condition. As a result, the present reaction is applicable to a wide range of substituted pyrroles, and these results are summarized in Table 2. The cyanating reaction of pyrroles, having aliphatic substituents at their 3-position, smoothly proceeded and afforded the corresponding 2-cyanated products (entries 2−5). The structure of the cyanation product **2b** was determined from the ^1H NMR measurement (coupling constant, J_{H4-H5} = 3.0 Hz) or by converting the cyanation product to the

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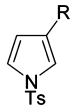
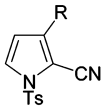
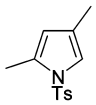
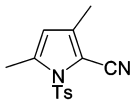
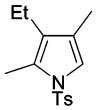
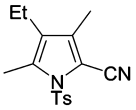
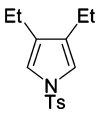
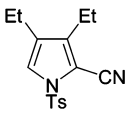
(18) Among the cyanide sources, trimethylsilyl cyanide gave the best yield compared with other compounds such as diethyl cyanophosphonate, tributyltin cyanide, and a combination of potassium cyanide and 18-crown-6.

(19) It was reported that the oxidation potentials of *N*-tosylpyrrole **1a** and 2-cyano-*N*-tosylpyrrole **2a** are 1.96 and 2.56 {E_p^{ox} (V vs SCE)}, respectively: Tajima, T.; Nakajima, A.; Fuchigami, T. *J. Org. Chem.* **2006**, *71*, 1436.

TABLE 2. PIFA-Mediated Direct Oxidative Cyanating Reaction of Pyrroles 1

Entry[a]	Substrate (**1**)	Cyanated product (**2**)	Yield (%)[b]
1	 R = H (**1a**)	 (**2a**)	83
2	= Me (**1b**)	(**2b**)	70
3	= Hep (**1c**)	(**2c**)	71
4	= *t*-Bu (**1d**)	(**2d**)	94
5	= $(CH_2)_3CO_2Et$ (**1e**)	(**2e**)	86
6	= 4-BrC_6H_4 (**1f**)	(**2f**)	90
7	= 2-BrC_6H_4 (**1g**)	(**2g**)	97
8	=4-$MeOC_6H_4$ (**1h**)	(**2h**)	45
9	 (**1i**)	 (**2i**)	43
10	 (**1j**)	 (**2j**)	58
11	 (**1k**)	 (**2k**)	73

[a] Reactions were performed using 3 equiv of TMSCN, 2 equiv of PIFA, and 4 equiv of $BF_3{\cdot}Et_2O$ for 3 h at room temperature. [b] Isolated yield of the pure cyanated compounds.

known unprotected 2-cyano 1*H*-pyrrole.[20] Although trace amounts of 5-cyanated products were detected by ^1H NMR (less than 3%), high regioselectivities were observed in each case. Thus, 3-methylpyrrole **1b** gave **2b** in 71% isolated yield after column chromatography (entry 2). More sterically demanding pyrroles with higher alkyl groups **1c** and **1d** were also applicable to the reaction, and notably, a *t*-butyl group did not affect the regioselectivity and yield (entries 3 and 4). The 3-aryl pyrroles also gave 2-cyanated pyrroles selectively as a single isomer (entries 6−8). The reaction worked in the presence of some functional groups, which are convenient for further transformations toward more complex molecules (entries 5−7).[21] Apparently, **2f** and **2g** are hardly accessible not only by a stepwise approach such as the palladium-catalyzed cyanation of an aryl halide but also by the selective introduction of a bromide into aryl rings after cyanation. In pyrrole **1h**, the yield was slightly decreased because of the competitive undesired oxidation attributed to the electron-rich phenyl ether ring, though the cyanated product **2h** was obtained as a sole isolable cyanated product (entry 8). Polyalkylated pyrroles **1i**−**k** gave the desired products as the less substituted pyrroles, but the yields were decreased probably due to the considerable acid-catalyzed oligomerization of **1i**−**k**. (entries 9−11). In all cases, the products did not lead to further oxidation and polycyanated products were not observed. The tosyl groups in the products **2** were easily removable by the standard procedures such as NaOH in MeOH or EtOH.[22]

Direct Oxidative Cyanation of Other Heteroaromatic Compounds. Next, we planned to extend the present cyanating reaction to other heteroaromatic compounds having oxidation

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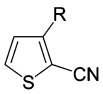
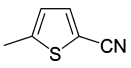
TABLE 3. PIFA-Mediated Direct Oxidative Cyanation of 3- or 2-Substituted Thiophenes 3

Entry[a]	Substrate (**3**)	Cyanated product (**4**)	Yield (%)[b]
1	 R = Me (**3a**)	 (**4a**)	79
2	= Hex (**3b**)	(**4b**)	65
3	= *c*-Hex (**3c**)	(**4c**)	59
4	= OMe (**3d**)	(**4d**)	42
5	= C_6H_5 (**3e**)	(**4e**)	68
6	= CN (**3f**)	-	-[c]
7	= CO_2Me (**3g**)	-	-[c]
8	 (**3h**)	 (**4h**)	62[d]

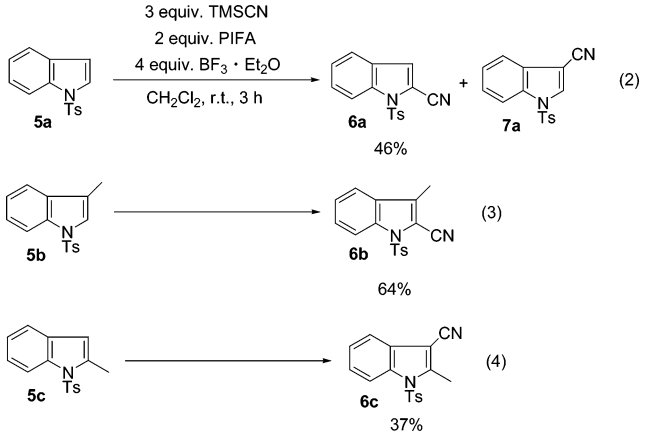
[a] All reactions were performed using 3 equiv of TMSCN, 2 equiv of PIFA, and 4 equiv of BF_3·Et_2O for 3 h at room temperature. [b] Isolated yield of the pure products after purification. [c] No reaction. [d] Yield was determined by GC.

potentials similar to that of *N*-tosylpyrroles **1**. In the wake of our recent success in alkylthiophene oxidations using PIFA,[17b,c] we next examined the reaction for thiophenes **3**. Consequently, it became clear that 2-cyanated thiophenes **4** were obtained in acceptable yields from a wide range of thiophenes **3** having different oxidation potentials (Table 3).[23] Similar to pyrroles, 1° and 2° alkyl thiophenes **3a**−**c** selectively gave 2-cyanation products in good to moderate yields (entries 1−3). These reactions are quite sensitive relative to the electronic character of thiophenes, but a donating group is acceptable in this reaction (entry 4). Thiophenes **3e** were also converted to 2-cyano biaryl derivative **4e** in a similar manner (entry 5). Meanwhile, thiophenes **3f** and **3g** having electron-withdrawing groups did not react at all under the present reaction conditions (entries 6 and 7). 2-Methylthiophene **3h** also reacted at the position adjacent to the sulfur atom to give 2-cyano-5-methylthiophene **4h** selectively (entry 8).

This cyanation protocol is also extendable to indoles **5**, despite being slightly problematic in yields and regioselectivities (Scheme 3). Thus, for indole **5a**, **6a** was produced, but a small amount of the regioisomeric isomer **7a** derived from the reaction at the β-position was also detected (eq 2), though introduction of cyanide into the β-position of the nitrogen atom was not observed at all in the cases of pyrroles **1**. 3-Methylindole **5b** sufficiently gave 2-cyanated product **6b** (eq 3); otherwise, **5c** reacted at the 3-position to give the corresponding cyanation product **6c** in turn (eq 4), as anticipated by the result of eq 2.

Mechanistic Consideration. The reaction mechanism of the cyanating reaction of heteroaromatic compounds with PIFA is considered to be similar to that of the previous oxidative substitution reactions of phenyl ethers and alkylarenes by oxygen, nitrogen, sulfur, and carbon nucleophiles, including a cation radical intermediate involving SET by the action of PIFA. However, as noted above, premixing of all reagents is essential

SCHEME 3. Cyanating Reaction of Indole Derivatives 5 with PIFA



before adding substrates for the successful transformations in the present case; this might imply the formation of alternative iodine(III) species before starting the cyanating reaction, and the real oxidant is not just PIFA. To clarify the precise reaction mechanism for the direct oxidative cyanating reaction, we have challenged the isolation and spectroscopic detection of the real hypervalent iodine(III) species by ^1H and ^{13}C NMR, but all these efforts failed due to their instability. Next, assuming ligand exchange at the iodine(III) center between the trifluoroacetoxy group in PIFA and the cyanide in TMSCN, we focused on hypervalent iodine(III) compounds having cyano ligands. These compounds have previously been reported by Stang and Zhdankin,[15,16] and therefore, we synthesized (dicyanoiodo)-benzene **8** according to the literature method[15a] and performed the cyanating reaction of **1a** using **8** with BF_3·Et_2O under similar reaction condition, but without TMSCN, to confirm the involvement of such hypervalent iodine(III)−CN species in the direct oxidative cyanating reaction (Scheme 4). Although the solid **8** itself is not reactive, it gradually started the reaction after activation by BF_3·Et_2O and cyanated product **2a** was produced in an acceptable yield, according to our expectation.[24]

(22) (a) Anderson, H. J.; Loader, C. E.; Xu, R. X.; Le, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, *63*, 896 (b) Masaguer, C. F.; Ravina, E.; Rueyo, J. *Heterocycles* **1992**, *34*, 1303.

(23) In our measurements, the representative oxidation potentials of thiophenes **3** are as follows: 1.64 for **3a**, 1.68 for **3b**, 1.70 for **3c**, 1.55 for **3d**, and 1.35 for **3e** {E_p^{ox} (V vs SCE)}.

SCHEME 4. Cyanating Reaction Using a Hypervalent Iodine(III) Compound 8 Having Cyano Ligands

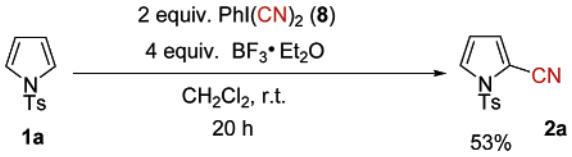


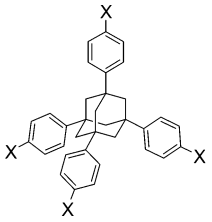
TABLE 4. Effect of the Aryliodine(III) Structures in Direct Oxidative Cyanation of *N*-Tosyl-3,5-dimethylpyrrole 1i

entry	$ArI(OCOCF_3)_2$[a]	time (h)	yield of **2i** (%)[b]
1	Ar = C_6H_5 (PIFA)	3	43
2	= 4-Me (**9**)	3	54
3	= 4-Cl (**10**)	3	50
4	= C_6F_5 (**11**)	24	6

[a] Two equivalents of $ArI(OCOCF_3)_2$ were used. [b] Isolated yields of the pure cyanated compound **2i** after silica gel column chromatography.

From the results, it is clear that one of the important steps is an effective generation of real iodine(III)−cyano active intermediate. With this perspective, we decided to examine several aryliodine bis(trifluoroacetate) compounds modulating the stability and reactivity in our cyanating reaction. Table 4 shows the results in *N*-tosyl-3,5-dimethylpyrrole **1i** using PIFA and other aryliodine(III) bis(trifluoroacetate) compounds **9**−**11** bearing some functional groups. Because the iodine atoms of hypervalent iodine(III) compounds have a certain degree of Lewis acidity, it is thought that selection of electron-rich aryl moieties contribute to make the iodine(III) more stable, whereas electron-deficient aryl moieties enhance their reactivity; in other words, decrease their stability. As a result, a direct oxidative cyanating reaction of **1i** using PIFA and aryliodine bis(trifluoroacetate) compounds **9**−**11** showed clear distinctions according to their oxidant structures; 4-methyl- and 4-chloro-substituted **9** and **10** afforded the cyanated product **2i** in yields higher than PIFA, while a strong oxidation reagent **11**[25] having an electron-withdrawing group did not work like the former two compounds in our system (low conversion of **1i**, only 6% yield of **2i**), apparently suggesting that both effective generation and stability of the iodine(III)−cyano intermediates are highly important.

A plausible reaction mechanism of the cyanating reaction is depicted in Scheme 5. First, PIFA reacts with TMSCN with or without the assistance of BF_3·Et_2O to generate hypervalent iodine(III) species having cyano ligands by ligand exchange reaction at the iodine(III) center between trifluoroacetoxy group in PIFA and TMSCN. The activated iodine(III)−CN by BF_3·Et_2O induces SET oxidation of heteroaromatic compounds to produce their cation radicals **A** via a CT complex under reaction conditions analogous to those of our previously developed PIFA-induced reactions,[13] typical heavy metal oxidations,[26] and



12 [X = $I(OCOCF_3)_2$]

13 [X = I]

FIGURE 1. Low-molecular recyclable hypervalent iodine(III) bis(trifluoroacetate) **12** having an adamantane structure.

electrolytic oxidations[10,27] yielding aromatic or heteroaromatic cation radicals. The cation radical formation was sufficiently supported by direct measurement of electron spin resonance spectroscopy (see Supporting Information, Chart 1) and effective inhibition of their reaction by a radical scavenger, galvinoxyl. The observed regioselectivity of the introduction of the cyano group into the 3-substituted heteroaromatic compounds is also consistent with the result of the calculated spin density of the intermediates.[10b,28] During the reaction, room temperature is required not only to prepare active iodine(III)−cyano species but also to generate the cation radicals **A** by SET, and therefore, the premier PhI(III)−CN compounds have weaker SET oxidation ability compared to that of PIFA. The regioselective cyano transfer toward **A** followed by oxidation and deprotonation gave the observed cyanation products along with an iodobenzene coproduct. From the present reaction mechanism, it is obvious that effective generation of the real iodine(III)−cyano active intermediate, the ability of one-electron oxidation, and successive cyano transfer determine the efficiency of the transformation. The precise reason for hypervalent iodine(III) reagents as effective oxidants in the cyanating reaction over heavy metal oxidizers (and/or electrolytic oxidations) is yet unclear, but mild and effective generation of cation radical intermediates **A** as well as rapid transfer of cyanide from the iodine(III) atom into **A** seem to be important.

Facile and Clean Cyanating Reaction Using a Recyclable Hypervalent Iodine(III) Reagent 12. Although the present cyanating reaction is applicable to various types of electron-rich heteroaromatic compounds and therefore might become a powerful method for synthesizing these useful heteroaromatic cyanides, excess PIFA was required for the successful transformation, and the products were usually contaminated with a large amount of coproduct iodoarenes after the reactions. The limitation causes a difficulty concerning isolation of the reaction products and stands in the way of practical applications. In an effort to improve the system, we employed 1,3,5,7-tetrakis[4-{bis(trifluoroacetoxy)iodo}phenyl]adamantane (**12**, Figure 1), a recyclable hypervalent iodine(III) reagent having reactivity similar to that of PIFA,[29] instead of PIFA in the cyanating reaction (Table 5).

Using **12** (0.5 equiv, 200 mol % iodine atom), BF_3·Et_2O (4 equiv), and TMSCN (3 equiv), we performed the cyanating reaction of *N*-tosylpyrrole **1a**. As expected, 2-cyanated product **2a** was obtained in 85% yield with the same regioselectivity

(24) In contrast, a cyanoaryliodonium salt, $PhI^+(CN)$ ^-OTf, did not afford cyanated product **2a** in the presence of BF_3·Et_2O (only 3% isolated yield) when using **1a**. This result implies that our oxidative cyanating reaction involves tricoordinate neutral cyanoaryliodine(III) species.

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(26) (a) Juliá, L.; Davies, A. G.; Rueda, D. R.; Calleja, F. J. B. *Chem. Ind.* **1989**, 78. (b) Tormo, J.; Moreno, F. J.; Ruiz, J.; Fajarí, L.; Juliá, L. *J. Org. Chem.* **1997**, *62*, 878. (c) Yoshino, K.; Nakajima, S.; Sugimoto, R. *Jpn. J. Appl. Phys.* **1987**, *26*, L1038. (d) Souto, R.; Maior, M.; Hinkelmann, K.; Eckert, H.; Wudl, F. *Macromolecules* **1990**, *23*, 1268.

(27) (a) Avila, D. V.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1111. (b) Shichiri, T.; Toriumi, M.; Tanaka, K.; Yamabe, T.; Yamauchi, J.; Deguchi, Y. *Synth. Met.* **1989**, *33*, 389. (c) Andrieux, C. P.; Audebert, P.; Hapiot, P.; Saveant, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 2439. (d) Davies, A. G.; Julia, L.; Yazdi, S. N. *J. Chem. Soc., Perkin Trans. 2* **1989**, 239.

(28) Ando, S.; Ueda, M. *Synth. Met.* **2002**, *129*, 207.

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SCHEME 5. Plausible Mechanism of Oxidative Cyanation Induced by a Hypervalent Iodine(III) Reagent

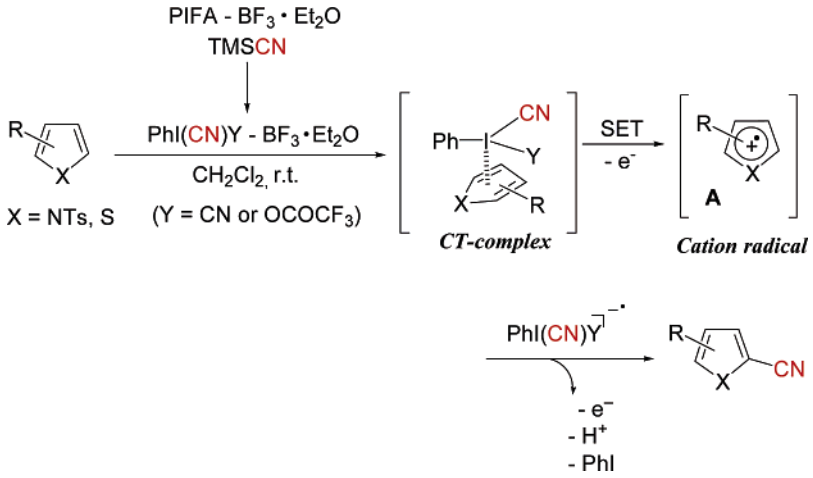

TABLE 5. Direct Oxidative Cyanation of Pyrroles 1 and Thiophenes 3 Using a Recyclable Hypervalent Iodine(III) Reagent 12

entry[a]	substrate	time (h)	yield (%)[b]	entry[a]	substrate	time (h)	yield (%)[b]
1	**1a**	6	85	9	**1i**	6	70
2	**1b**	6	71	10	**1j**	6	75
3	**1c**	6	72	11	**3a**	15	79
4	**1d**	6	98	12	**3b**	15	68
5	**1e**	6	85	13	**3c**	15	75
6	**1f**	6	90	14	**3d**	4	77
7	**1g**	6	95	15	**3e**	7	75
8	**1h**	4	45	16	**3h**	6	64

[a] **12** [0.5 equiv, 200 mol % of I(III)], TMSCN (3 equiv), and BF_3•Et_2O (4 equiv) were used. [b] Isolated yield of the pure cyanated compounds after silica gel column chromatography.

(Table 5, entry 1). With a variety of pyrroles **1** and thiophenes **3**, **12** gave excellent results (~98% yields) compatible with PIFA as shown in Table 5. Interestingly, the reagent gave better yields than PIFA in several cases, which is probably due to the electronic effect of the adamantyl group.

In all these transformations, **12** could be separated easily from the reaction mixtures as tetraiodide **13**, a reduced form of **12**, by a simple solid−liquid separation (i.e., filtration). Thus, after completion of the reactions, saturated $NaHCO_3$ aqueous and solid sodium thiosulfate were sequentially added to the reaction mixtures to reduce the excess **12** to tetraiodide **13**. The organic layer was then separated and evaporated under reduced pressure. To the resulting oily mixture, MeOH was added. As **13** is hardly soluble in MeOH, it was simultaneously precipitated as a white powder. The solution was filtered, and the solid **13** was washed several times with MeOH. In this way, **13** could be recovered nearly quantitatively (checked by ^{1}H NMR analysis and TLC), and it could be reoxidized to **12** in high yield by treatment with *m*-chloroperbenzoic acid (*m*-CPBA) in acetic acid/dichloromethane, followed by the treatment of trifluoroacetic acid.[29] Evaporation of the combined MeOH filtrate afforded crude cyanated products with a small amount of impurities, which were subjected to further purification (e.g., short column chromatography on silica gel) when required. As mentioned above, the present method is quite simple, clean, and versatile and consequently is a facile and convenient method to introduce a cyano group into heteroaromatic compounds.

Conclusions

We have described a direct oxidative cyanation of electron-rich pyrroles, thiophenes, and indoles using a combination of hypervalent iodine(III) reagents with TMSCN at room temperature. Our novel cyanation protocol has the following characteristic features: (i) direct and selective cyanation of unfunctionalized heteroaromatic compounds under mild conditions, (ii) use of the stable organocyanide source, (iii) applicability of various types of heteroaromatic compounds, and (iv) aryl halide function that is maintained, which is beneficial for further transformations of the cyanation products. From a mechanistic point of view, the cyanating reaction is induced by active hypervalent iodine(III) species having cyano ligands in situ generated from PIFA and TMSCN, and the effective cyanide introduction into heteroaromatic compounds might occur with the aid of rapid transfer of the cyano ligands in the hypervalent iodine(III)−CN species into a cation radical intermediate of heteroaromatic compounds. An extensive survey on hypervalent iodine(III) compounds has led to successful utilization of a recyclable hypervalent iodine(III) reagent, 1,3,5,7-tetrakis[4-{bis(trifluoroacetoxy)iodo}phenyl]adamantane **12**. Utilization of this reagent confidently leads to the practicability of the cyanating reaction due to the ease of separation of the cyanated products and recovery of the oxidation reagent. From these advantages, our novel procedure described herein will provide a new efficient alternative method to introduce cyano functionality into electron-rich heteroaromatic compounds.

Experimental Section

General Procedure for PIFA-Mediated Cyanating Reaction of Heteroaromatic Compounds. In a flame-dried two-necked round-bottomed flask, under nitrogen, to a stirred solution of PIFA (2 mmol) and BF_3•Et_2O (4 mmol) in CH_2Cl_2 (1 mL), we added trimethylsilyl cyanide (3 mmol) at room temperature. After being stirred for 30 minutes, *N*-tosylpyrrole **1a** (1 mmol) was added in one portion and stirred for an additional 3 h under the same conditions while the reaction progress was evaluated by GC or TLC. After the reaction was completed, saturated $NaHCO_3$ aqueous (ca. 10 mL) and sodium thiosulfate aqueous (ca. 5 mL) were successively 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 Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (SiO_2/*n*-hexane/AcOEt) to give pure **2a** (83%).

***N*-Tosylpyrrole-2-carbonitrile (2a):**[30] Colorless crystals, mp 114−115 °C, R_f = 0.51 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (3H, s), 6.32 (1H, t, J = 3.4 Hz), 6.95 (1H, dd, J = 3.4, 1.6 Hz), 7.37 (2H, d, J = 8.7 Hz), 7.47 (1H, dd, J = 3.4, 1.6 Hz), 7.93 (2H, d, J = 8.7 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.7, 103.7, 111.6, 112.3, 126.6, 126.6, 127.9, 130.4, 134.1, 146.5; IR (KBr, cm^{-1}): υ 2225.

3-Methyl-1-(toluene-4-sulfonyl)pyrrole-2-carbonitrile (2b).[31] This product was obtained following the general procedure mentioned above. Colorless crystals, mp 114−117 °C; R_f = 0.41 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$): 2.11 (3H, s), 2.37 (3H, s), 6.11 (1H, d, J = 3.0 Hz), 7.29 (3H, m), 7.83 (2H, d, J = 8.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): 12.1, 21.7, 102.1, 111.7, 114.2, 126.2, 127.8, 130.3, 134.3, 139.1, 146.2; IR (KBr, cm^{-1}): ν 2222; HRFABMS Calcd for $C_{13}H_{12}N_2O_2S$ $(M + H)^+$, 261.0683. Found, 261.0690.

Cyanating Reaction of 1a Using (Dicyanoiodo)benzene (8). To a stirred solution of **8** (2 mmol) and $BF_3{\cdot}Et_2O$ (4 mmol) in CH_2Cl_2 (1 mL), we added *N*-tosylpyrrole **1a** (1 mmol) under nitrogen atmosphere. The solution was then stirred for 20 h at room temperature. TLC analysis of the reaction indicated that formation of cyanated product **2a** was a major product with a small amount remaining as **1a**. The cyanated product **2a** was separated and purified according to the general experimental procedure using PIFA mentioned above.

Preparation of 1,3,5,7-Tetrakis[4-bis(trifluoroacetoxyiodo)-phenyl]adamantane (12). To a stirred solution of 1,3,5,7-tetrakis-(4-iodophenyl)adamantane **13** (1.42 g, 1.5 mmol) in CH_2Cl_2 (150 mL)/AcOH (150 mL) was added *m*-CPBA (3.12 g, 12.4 mmol, 69% purity) at room temperature. The mixture was stirred for 12 h under the same reaction conditions, as the clear solution became clouded. The resultant mixture was filtered, and CH_2Cl_2 was removed from the filtrate using a rotary evaporator. Hexane was added to the AcOH solution when white solid was immediately precipitated. After filtration, the crude product was washed with hexanes several times and was dried in vacuo to give 1,3,5,7-tetrakis[4-(diacetoxyiodo)phenyl]adamantane (2.09 g, 97%).

Then, 1,3,5,7-tetrakis[4-(diacetoxyiodo)phenyl]adamantane (1.01 g, 0.71 mmol) was dissolved in $CHCl_3$ (15 mL). To the solution, trifluoroacetic acid (15 mL) was slowly added at room temperature. The mixture was stirred for an additional 1.5 h under the same reaction conditions. After removal of the solvent under reduced pressure, hexane/Et_2O (=10:1) was added to precipitate **12**. The precipitate was filtered and washed with hexane/Et_2O (=10:1) several times and dried in vacuo to give **12** (1.17 g, 89%) as a slightly yellow solid.

12: A slightly yellow solid; mp 196−203 °C dec (from CF_3CO_2H/CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$/CF_3CO_2H = 10/1) δ 2.30 (12H, s), 7.73 (8H, d, J = 8.7 Hz), 8.24 (8H, d, J = 8.7 Hz); ^{19}F NMR (200 MHz, $CDCl_3$/CF_3CO_2H = 10/1, hexafluorobenzene (−162.9 ppm)) δ −74.5 (s); Anal. Calcd for $C_{50}H_{28}F_{24}I_4O_{16}$: C, 32.49; H, 1.53. Found: C, 32.82; H, 1.86.

Typical Procedure for Cyanating Reaction Using Recyclable Hypervalent Iodine(III) Reagent 12. To a mixture of **12** (462 mg, 0.25 mmol) and TMSCN (0.20 mL, 1.5 mmol) in CH_2Cl_2 (1 mL) was slowly added $BF_3{\cdot}Et_2O$ (0.25 mL, 2 mmol) at room temperature. The mixture was then stirred for 30 min, while the solution changed gradually to become homogeneous and yellow in color. *N*-Tosyl-3,5-dimethylpyrrole **1i** (124 mg, 0.5 mmol) was then added to the solution in one portion and stirred for an additional 6 h. Saturated $NaHCO_3$ aqueous and solid sodium thiosulfate (ca. 1 g) were successively added to the reaction mixture. After being stirred for 5 min, the organic layer was separated, dried with Na_2SO_4, and evaporated to remove the solvent. MeOH (10 mL) was added to the residue to precipitate tetraiodide **13**, and then it was filtered. The solid was washed with MeOH several times to recover tetraiodide **13** nearly quantitatively (checked by ^{1}H NMR analysis and TLC, quant.). The filtrate including **2i** was evaporated and subjected to short column chromatography (SiO_2, hexane/AcOEt) to give 3,5-dimethyl-*N*-tosylpyrrole-2-carbonitrile **2i** (124 mg, 70%) as a white powder.

3,5-Dimethyl-*N*-tosylpyrrole-2-carbonitrile (2i):[32] Colorless crystals; mp 148−151 °C, R_f = 0.38 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (3H, s), 2.37 (3H, s), 2.38 (3H, s), 5.80 (1H, s), 7.28 (2H, d, J = 8.4 Hz), 7.80 (2H, d, J = 8.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 11.9, 15.0, 21.7, 112.6, 115.0, 127.0, 130.0, 130.8, 135.0, 137.2, 137.5, 145.5; IR (KBr, cm^{-1}): υ 2214; HRFABMS Calcd for $C_{14}H_{15}O_2N_2S$ $(M + H)^+$, 275.0884. Found, 275.0871.

3,4-Diethyl-1-(toluene-4-sulfonyl)pyrrole-2-carbonitrile (2k).[33] This product was obtained following the general procedure mentioned above. Colorless crystals, mp 120−122 °C; R_f = 0.41 (hexane/EtOAc = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11−1.25 (6H, m), 2.33−2.61 (7H, m), 7.16 (1H, s), 7.35 (2H, d, J = 8.1 Hz), 7.90 (2H, d, J = 8.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.5, 14.2, 18.1, 18.7, 21.8, 101.2, 111.9, 122.9, 127.6, 129.2, 130.1, 134.5, 144.1, 145.8; IR (KBr, cm^{-1}): ν 2220; Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.55; H, 5.99; N, 9.26.

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Supporting Information Available: General experimental procedure and detailed spectroscopic data for all new materials, reagents, and products including ^{1}H and ^{13}C NMR spectra charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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