

A Facile and Clean Direct Cyanation of Heteroaromatic Compounds Using a Recyclable Hypervalent Iodine(III) Reagent

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The facile and clean direct cyanating reaction of pyrroles and thiophenes has been achieved using a recyclable hypervalent iodine(III) reagent **1b by a simple solid-liquid separation of the products and the reagent.**

Key words cyanation; hypervalent iodine(III) reagent; recycle; heteroaromatic compound; direct method

Heteroaromatic compounds are often significant components of natural compounds and pharmaceuticals.^{1,2)} The cyanating reaction of heteroaromatic compounds is one of the important organic transformations in organic synthesis, since the cyano group is readily converted into a variety of other functional groups through carboxy groups, amines, *etc.*³⁾ Therefore, several synthetic methods, both stepwise^{4,5)} and direct^{6–9)} ones have already been developed. Among them, the latter methods seem to be convenient, especially in electron-rich heteroaromatic compounds, such as pyrroles, that are unstable in their halogenated or metallated forms. The direct introduction of the cyano functionality into these heteroaromatic compounds was usually achieved by electrophilic substitution reactions, but it is not a widely accepted method due to the necessity of using ‘unstable cyano cation equivalents.’

From this point of view, the direct cyanating reaction using a stable cyanide (CN[−]) under oxidative conditions is considered to be an alternative and attractive method.¹⁰⁾ We have recently developed a novel and direct oxidative cyanating reaction of heteroaromatic compounds induced by a hypervalent iodine(III) reagent, phenyliodine bis(trifluoroacetate) (PIFA), with BF₃·Et₂O (Chart 1) at room temperature.¹¹⁾ The present method has significant advantages; *i.e.*, availability of a low toxic, readily accessible and easy handling hypervalent iodine(III) organo-oxidant^{12–16)} and a stable trimethylsilyl cyanide (TMSCN), high selectivity and versatility of heteroaromatic compounds (*i.e.*, pyrroles, thiophenes and indoles). Therefore, it might become a powerful method to synthesize these useful heteroaromatic cyanides. However, in this reaction, a large amount of volatile and inseparable iodobenzene (PhI), the reduced form of PIFA, was co-produced after the reactions, which makes isolation of the reaction products troublesome. For these reasons, we decided to find another suitable hypervalent iodine(III) alternative for the oxidative cyanating reaction.

We now report the reaction using 1,3,5,7-tetrakis[4-bis(trifluoroacetoxy)iodo]phenyl]adamantane (**1b**, Fig. 1), a recyclable hypervalent iodine(III) reagent bearing an

adamantane core,¹⁷⁾ instead of PIFA with the combination of BF₃·Et₂O in the presence of TMSCN. The present method not only directly produces the heteroaromatic cyanides in high yields, but also facilitates the isolation of the cyanated products utilizing the insolubility of **2** in MeOH.

With a 0.5 eq of **1b** (200 mol% iodine(III) atom), BF₃·Et₂O (4 eq) and TMSCN (3 eq) in dichloromethane, we first examined the cyanating reaction of *N*-tosyl pyrrole **3a** (Table 1, Eq. 1). In accord with our expectation, the reaction smoothly proceeded under homogeneous conditions to give the 2-cyanated product **4a** in 85% yield without the formation of other regioisomers by reaction at the 3-position (entry 1). To set up the reaction, premixing of all the reagents is essential in order to generate the active iodine(III) species before adding **3a**; the iodine(III) reagent **1b**, TMSCN and BF₃·Et₂O should be pre-mixed for 30 min, otherwise **4a** would be obtained in lower yields. Similar to the previous result, **4a** was not formed by treatment of **1a** having acetoxy group.

As shown in Table 1, **1b** gave a variety of corresponding α -cyanated products **4** in good to excellent yields. It is noted that the sterically demanding pyrrole **3d** also afforded the 2-cyanated product **4d** (entry 4). The reaction proceeded in the presence of some functional groups, which are available for further transformations after the reactions (entries 5, 7, 8). However, with the pyrrole **3i**, the yield of **4i** was slightly decreased due to the undesired competitive oxidation of the electron-rich phenyl ether ring (entry 9). The polysubstituted pyrroles **3j** and **3k** gave the desired products in similar ways (entries 10, 11). Interestingly, **1b** showed sufficiently high reactivities to give the cyanated products in a yield comparable to or better than PIFA. In contrast, the conventional polymer-supported reagents,^{18,19)} poly(diacetoxyiodo)styrene (PDAIS) and poly[bis(trifluoroacetoxy)iodo]styrene (PBTIS), also provided the cyanated products, but the yields were considerably lower than those of **1b** due to the insolubility of PDAIS and PBTIS.

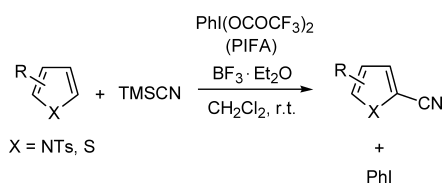


Chart 1

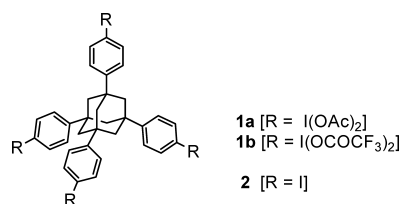
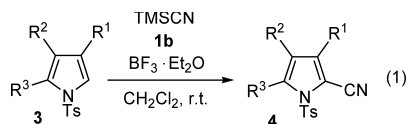


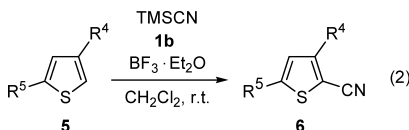
Fig. 1. Recyclable Hypervalent Iodine(III) Reagents Based on an Adamantane Structure

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Table 1. Direct Oxidative Cyanating Reaction of Pyrroles Using a Recyclable Hypervalent Iodine(III) Reagent **1b** (Eq. 1)

Entry ^{a)}	Substrate 3			Time (h)	Yield of 4 (%) ^{b)}
	R ¹	R ²	R ³		
1	H	H	H (3a)	6	85 (4a)
2	Me	H	H (3b)	6	71 (4b)
3	Hep	H	H (3c)	6	72 (4c)
4	<i>t</i> -Bu	H	H (3d)	6	98 (4d)
5	(CH ₃) ₃ CO ₂ Me	H	H (3e)	6	85 (4e)
6	C ₆ H ₅	H	H (3f)	6	92 (4f)
7	2-BrC ₆ H ₄	H	H (3g)	6	95 (4g)
8	4-BrC ₆ H ₄	H	H (3h)	6	90 (4h)
9	4-MeOC ₆ H ₄	H	H (3i)	4	45 (4i)
10	Et	Et	H (3j)	6	75 (4j)
11	Me	H	Me (3k)	6	70 (4k)

a) The molar ratio of **3**, **1b**, BF₃·Et₂O and TMSCN is 1:2×1/4:4:3. b) Isolated yields after purification.

Table 2. Direct Oxidative Cyanating Reaction of Thiophenes Using **1b** (Eq. 2)

Entry ^{a)}	Substrate 5		Time (h)	Yield of 6 (%) ^{b)}
	R ⁴	R ⁵		
1	Me	H (5a)	15	79 (6a)
2	Hex	H (5b)	15	68 (6b)
3	<i>c</i> -Hex	H (5c)	15	75 (6c)
4	OMe	H (5d)	4	77 (6d)
5	C ₆ H ₅	H (5e)	7	75 (6e)
6	H	Me (5f)	6	64 (6f)

a) The molar ratio of **5**, **1b**, BF₃·Et₂O and TMSCN is 1:2×1/4:4:3. b) Isolated yields after purification.

Thiophenes **5** have similar oxidation potentials as *N*-tosyl pyrroles,^{20,21} and thus are applicable for the cyanating reaction (Table 2). The 2-cyano thiophenes **6** were obtained from a wide range of thiophenes **5** having different oxidation potentials (entries 1—5), and 2-methylthiophene **5f** also reacted at the α -position of the sulfur atom to give the 2-cyano-5-methylthiophene **6f** (entry 6).

In all these transformations, **1b** could be easily separated from the reaction mixtures as the tetraiodide **2**, a reduced form of **1b**, by a simple solid-liquid separation, *i.e.*, filtration. Thus, after the reactions were completed, the remaining **1b** was reduced to **2** by the sequential treatment of saturated NaHCO₃ aq. and solid Na₂S₂O₃·5H₂O. The organic layer was then separated and evaporated under reduced pressure. To the resulting oily mixture, MeOH was added to precipitate **2**. Since **2** is only slightly soluble in MeOH, it was simultaneously precipitated as a fine powder. The solution was then filtered to remove **2** and the solid residue was washed several times with MeOH. In this way, **2** could be nearly quantita-

tively recovered and the recycling of **1** was achieved without any loss of activity by reoxidation of the recovered **2** using *m*-chloroperbenzoic acid (*m*CPBA) in acetic acid/dichloromethane.¹⁷⁾ From the combined MeOH filtrate, the crude cyanated product **4** was obtained along with a small amount of impurities, which were subjected to further purification, *e.g.*, short column chromatography on silica gel, if required. As already described, the present protocol is quite simple, clean and versatile, and consequently, is a facile and convenient method for the introduction of the cyano group into electron-rich heteroaromatic compounds.

Experimental

General The ¹H- and ¹³C-NMR spectra were recorded by a JEOL JMN-300 spectrometer operating at 300 MHz in CDCl₃ at 25 °C with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad singlet, m=multiplet), coupling constant (Hz) and interpretation. The infrared spectra (IR) were obtained using a Hitachi 270-50 spectrometer; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium) or w (weak). The mass spectra were obtained using a Shimadzu GCMS-QP 5000 instrument with ionization voltages of 70 eV. The high resolution mass spectra were performed by the Elemental Analysis Section of Osaka University. Column chromatography and TLC were carried out on Merck Silica gel 60 (230—400 mesh) and Merck Silica gel F₂₅₄ plates (0.25 mm), respectively. The spots and bands were detected by UV irradiation (254, 365 nm).

Preparation of **1b** To a stirred solution of 1,3,5,7-tetrakis(4-iodophenyl)adamantane **2** (1.42 g, 1.5 mmol) in CH₂Cl₂ (150 ml)—AcOH (150 ml) was added *m*CPBA (69% purity, 3.12 g, 18 mmol) at room temperature. The mixture was stirred for 12 h under the same reaction conditions, while the cloudy solution became clear. The resultant mixture was filtered, and CH₂Cl₂ was removed from the filtrate using a rotary evaporator. Hexane was added to the residue to precipitate 1,3,5,7-tetrakis[4-(diacetoxyiodo)phenyl]adamantane **1a**. After filtration, the crude product was washed several times with hexane, and then dried *in vacuo* to give **1a** (2.09 g, 97%).

1a (1.01 g, 0.71 mmol) was dissolved in CHCl₃ (15 ml), then trifluoroacetic acid (15 ml) was slowly added to the solution at room temperature. The mixture was stirred for 1.5 h under the same reaction conditions. After removal of the CHCl₃ under reduced pressure, hexane—Et₂O (10:1) was added. The precipitate was filtered and washed with hexane—Et₂O (10:1) several times, and dried *in vacuo* to give **1b** (1.17 g, 89%) as a solid.

1b: A slightly yellow crystals. mp (decomp.) 196—203 °C (from CF₃CO₂H—CH₂Cl₂—hexane). ¹H-NMR (CDCl₃/CF₃CO₂H=10/1) δ : 8.24 (8H, d, *J*=8.7 Hz, ArH), 7.73 (8H, d, *J*=8.7 Hz, ArH), 2.30 (12H, s, CH₃). ¹⁹F-NMR (200 MHz, CDCl₃/CF₃CO₂H=10/1, hexafluorobenzene (−162.9 ppm)) δ : −74.51 (24F, s, OCOF₃). Anal. Calcd for C₅₀H₂₈F₂₄O₁₆: C, 32.49; H, 1.53. Found: C, 32.82; H, 1.86.

Typical Procedure for Direct Oxidative Cyanating Reaction Using **1b** To a stirred solution of **1b** (462 mg, 0.25 mmol) and BF₃·Et₂O (0.25 ml, 2 mmol) in CH₂Cl₂ was slowly added TMSCN (0.20 ml, 1.5 mmol) at room temperature. The mixture was stirred for 30 min, while the yellow color of the solution gradually changed to white. *N*-Tosylpyrrole **3a** (111 mg, 0.5 mmol) was then added to the solution in one portion and stirred for an additional 6 h. Saturated NaHCO₃ aq. and solid Na₂S₂O₃·5H₂O were successively added to the reaction mixture. After being stirred for 5 min, the organic layer was separated and evaporated. MeOH (10 ml) was added to the reaction mixture, and it was filtered. The solid residue was washed several times with MeOH, and the residue was recovered as tetraiodide **2** (confirmed by ¹H-NMR analysis and TLC). The filtrate including **4a** was evaporated and subjected to column chromatography (SiO₂, hexane/AcOEt) to give 2-cyano-*N*-tosylpyrrole **4a** (105 mg, 85 %) as a white powder.

2-Cyano-*N*-tosylpyrrole (**4a**)²²⁾: Colorless crystals. mp 114—115 °C. *R*_f=0.51 (hexane/EtOAc=4/1). ¹H-NMR (CDCl₃) δ : 2.44 (3H, s, CH₃), 6.32 (1H, t, *J*=3.4 Hz, pyrrole), 6.95 (1H, dd, *J*=3.4, 1.6 Hz, pyrrole), 7.37 (2H, d, *J*=8.7 Hz, Ts), 7.47 (1H, dd, *J*=3.4, 1.6 Hz, pyrrole), 7.93 (2H, d, *J*=8.7 Hz, Ts). ¹³C-NMR (CDCl₃) δ : 21.69, 103.74, 111.63, 112.30, 126.56, 126.57, 127.85, 130.36, 134.12, 146.52. IR (KBr) cm^{−1}: 2225 (CN, s).

4-(2-Cyano-*N*-tosylpyrrole-3-yl)butyric Acid Methyl Ester (**4e**): Colorless crystals. mp 110—112 °C. *R*_f=0.41 (hexane/EtOAc=2/1). ¹H-NMR (CDCl₃) δ : 1.81 (2H, quint, *J*=7.5 Hz, CH₂), 2.22 (2H, t, *J*=7.5 Hz,

$\text{CH}_2\text{CO}_2\text{Me}$), 2.37 (3H, s, CH_3), 2.50 (2H, t, $J=7.5$ Hz, $\text{CH}_2(\text{CH}_2)_2\text{CO}_2\text{CH}_3$), 3.58 (3H, s, CO_2CH_3), 6.16 (1H, d, $J=3.0$ Hz, pyrrole 4-H), 7.28—7.33 (3H, m), 7.83 (2H, d, $J=8.1$ Hz, Ts). ^{13}C -NMR (CDCl_3) δ : 21.72, 24.65, 25.79, 33.00, 51.62, 101.69, 111.46, 112.91, 126.46, 127.76, 130.33, 134.14, 142.49, 146.33, 173.27. IR (KBr) cm^{-1} : 2220 (CN, m). HR-FAB-MS: m/z 347.1043 $[\text{M}+\text{H}]^+$ (Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4\text{S}$: 347.1065).

2-Cyano-3-(4-methoxyphenyl)-*N*-tosylpyrrole (**4i**): Colorless crystals. mp 85—88 °C. $R_f=0.41$ (hexane/EtOAc=2/1). ^1H -NMR (CDCl_3) δ : 2.37 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 6.45 (1H, d, $J=3.3$ Hz, pyrrole 4-H), 6.86 (2H, d, $J=8.4$ Hz), 7.30 (2H, d, $J=8.4$ Hz), 7.43 (1H, d, $J=3.0$ Hz, pyrrole 5-H), 7.50 (2H, d, $J=8.4$ Hz), 7.89 (2H, d, $J=8.4$ Hz). ^{13}C -NMR (CDCl_3) δ : 21.75, 55.32, 98.56, 111.66, 112.96, 114.36, 123.16, 126.75, 127.98, 128.48, 130.36, 134.15, 141.11, 146.41, 160.20. IR (KBr) cm^{-1} : 2216 (CN, s). HR-FAB-MS: m/z 375.0793 $[\text{M}+\text{Na}]^+$ (Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2\text{BrSNa}$: 375.0779).

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