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

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Received July 19, 2006; accepted September 2, 2006; published online September 5, 2006

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 $BF_3 \cdot Et_2O$ (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 $BF_3 \cdot Et_2O$ 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.

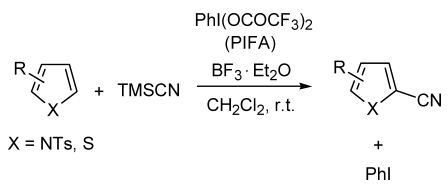

Chart 1

With a 0.5 eq of **1b** (200 mol% iodine(III) atom), $BF_3 \cdot Et_2O$ (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 $BF_3 \cdot Et_2O$ 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.

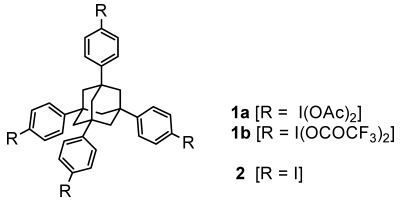

Fig. 1. Recyclable Hypervalent Iodine(III) Reagents Based on an Adamantane Structure

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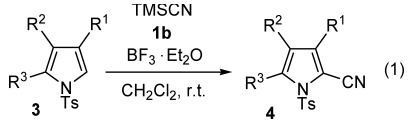
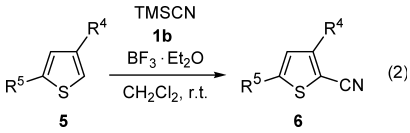
Table 1. Direct Oxidative Cyanating Reaction of Pyrroles Using a Recyclable Hypervalent Iodine(III) Reagent **1b** (Eq. 1)



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	*t*-Bu	H	H (**3d**)	6	98 (**4d**)
5	$(CH_2)_3CO_2Me$	H	H (**3e**)	6	85 (**4e**)
6	C_6H_5	H	H (**3f**)	6	92 (**4f**)
7	2-BrC_6H_4	H	H (**3g**)	6	95 (**4g**)
8	4-BrC_6H_4	H	H (**3h**)	6	90 (**4h**)
9	4-$MeOC_6H_4$	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**, $BF_3 \cdot Et_2O$ 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	*c*-Hex	H (**5c**)	15	75 (**6c**)
4	OMe	H (**5d**)	4	77 (**6d**)
5	C_6H_5	H (**5e**)	7	75 (**6e**)
6	H	Me (**5f**)	6	64 (**6f**)

a) The molar ratio of **5**, **1b**, $BF_3 \cdot Et_2O$ 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 $NaHCO_3$ aq. and solid $Na_2S_2O_3 \cdot 5H_2O$. 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 quantitatively 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 ^{1}H- and ^{13}C-NMR spectra were recorded by a JEOL JMN-300 spectrometer operating at 300 MHz in $CDCl_3$ 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 F_{254} 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 CH_2Cl_2 (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 CH_2Cl_2 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 $CHCl_3$ (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 $CHCl_3$ under reduced pressure, hexane–Et_2O (10 : 1) was added. The precipitate was filtered and washed with hexane–Et_2O (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 CF_3CO_2H–CH_2Cl_2–hexane). ^{1}H-NMR ($CDCl_3/CF_3CO_2H$=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, CH_2). ^{19}F-NMR (200 MHz, $CDCl_3/CF_3CO_2H$=10/1, hexafluorobenzene (−162.9 ppm)) δ: −74.51 (24F, s, $OCOCF_3$). *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 Direct Oxidative Cyanating Reaction Using 1b To a stirred solution of **1b** (462 mg, 0.25 mmol) and $BF_3 \cdot Et_2O$ (0.25 ml, 2 mmol) in CH_2Cl_2 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 $NaHCO_3$ aq. and solid $Na_2S_2O_3 \cdot 5H_2O$ 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 ^{1}H-NMR analysis and TLC). The filtrate including **4a** was evaporated and subjected to column chromatography (SiO_2, 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. *Rf*=0.51 (hexane/EtOAc=4/1). ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s, CH_3), 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). ^{13}C-NMR ($CDCl_3$) 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. *Rf*=0.41 (hexane/EtOAc=2/1). ^{1}H-NMR ($CDCl_3$) δ: 1.81 (2H, quint, J=7.5 Hz, CH_2), 2.22 (2H, t, J=7.5 Hz,

$\underline{CH_2}CO_2Me$), 2.37 (3H, s, CH_3), 2.50 (2H, t, J=7.5 Hz, $\underline{CH_2}(CH_2)_2CO_2CH_3$), 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 $[M+H]^+$ (Calcd for $C_{17}H_{18}N_2O_4S$: 347.1065).

2-Cyano-3-(4-methoxyphenyl)-*N*-tosylpyrrole (**4i**): Colorless crystals. mp 85—88 °C. *Rf*=0.41 (hexane/EtOAc=2/1). ^{1}H-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 $[M+Na]^+$ (Calcd for $C_{18}H_{14}N_2O_2BrSNa$: 375.0779).

Acknowledgements This work was supported by a Grant-in-Aid for Scientific Research (A) and for Encouragement of Young Scientists, and by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education Culture, Sports, Science, and Technology, Japan. T. D. also thanks the Industrial Technology Research Grant Program from the New Energy and Industrial Technology Development Organization (NEDO) of Japan.

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