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Direct Synthesis of Bipyrroles Using Phenyliodine Bis(trifluoroacetate) with Bromotrimethylsilane

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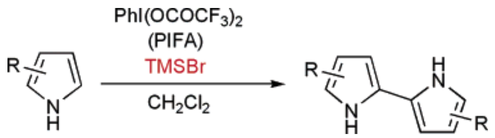
ABSTRACT



The hypervalent iodine(III) reagent, phenyliodine bis(trifluoroacetate) (PIFA), mediates the unprecedented, oxidative coupling reaction of pyrroles to give α-linked bipyrroles selectively in the presence of bromotrimethylsilane. This straightforward synthesis could provide 2,3′-bipyrrole by the choice of a *N*-substituent of pyrrole. Mechanistic consideration of the present reaction is also described.

Bipyrrole structures occur in natural products, pigments, and porphyrin mimics and are known as common components in molecular recognition and self-assembly systems.[1] Recently, some electron-rich bipyrroles have been applied as a precursor of oligo- or polypyrroles,[2] which are valuable compounds in the field of material sciences due to their beneficial physical properties such as high conductivity.[3] Under these circumstances, bipyrroles are increasing in importance in a wide range of modern science research studies. However, their practical synthetic methods are quite limited, especially for bipyrroles not having electron-withdrawing groups.[4−6] A classical stepwise approach starting from pyrrolinones and pyrroles is a promising way to synthesize the electron-rich 2,2′-bipyrroles, in which formation of dihydrobipyrroles **1** followed by the dehydrogenation of **1** produced the 2,2′-bipyrroles (Scheme 1).[7] In contrast, little attention has been paid to the oxidative coupling reaction of pyrroles for the preparation of bipyrroles, though the direct oxidative coupling reaction of pyrroles using palladium(II) salts has been reported.[8]

However, even in this case, substoichiometric amounts of palladium(II) salts are required to obtain the 2,2′-bipyrroles in good yields, and sometimes an undesired mixture of byproducts were produced. Consequently, indirect ap-

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(1) (a) Mervyn, H. *Chem. Rev.* **1996**, *5*, 19. (b) Korostova, S. E.; Mikhaleva, A. I.; Trofimov, B. A. *Russ. Chem. Rev.* **1999**, *68*, 459. (c) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17. (d) Gale, P. A.; Anzenbacher, P., Jr.; Sessler, J. L. *Coord. Chem. Rev.* **2001**, *222*, 57. (e) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substance: Synthesis, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, 2001.

(2) Müllen, K., Wegner, G., Eds. *Electronic Materials: The Oligomer Approach*; Wiley-VCH: Verlag GmbH, 1998.

(3) (a) Kanazawa, K.; Diaz, A. F.; Geiss, R. H.; Gill, W. D.; Kwak, J. F.; Logan, J. A.; Rabolt, J. F.; Street, G. B. *J. Chem. Soc., Chem. Commun.* **1979**, 854. (b) Ogasawara, M.; Funahashi, K.; Demura, T.; Hagiwara, T.; Iwata, K. *Synth. Met.* **1986**, *14*, 62. (c) Baughman, R. H. *Science* **2005**, *308*, 63.

(4) The oxidative couplings: (a) Ceacareanu, D. M.; Gerstenberger, M. R. C.; Haas, A. *J. Heterocycl. Chem.* **1985**, *22*, 281. (b) Oda, K.; Sakai, M.; Ohno, K.; Machida, M. *Heterocycles* **1999**, *40*, 277. (c)Wasserman, H. H.; Petersen, A. K.; Xia, M.; Wang, J. *Tetrahedron Lett.* **1999**, *40*, 7567.

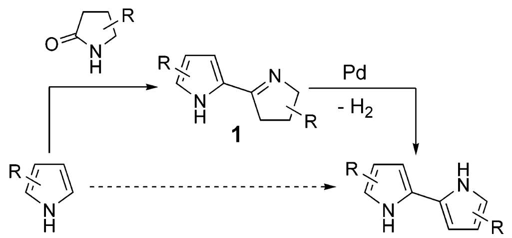
(5) Ullman-type couplings: (a) Vogel, E.; Balci, M.; Kakumanu, P.; Kogh, P.; Lex, J.; Ermer, O. *Angew. Chem. Int. Ed.* **1987**, *26*, 928. (b) Sessler, J. L.; Cyr, M. J.; Lynch, V.; McGhee, E.; Ibers, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 2810. (c) Shevchuk, S. V.; Davis, J. M.; Sessler, J. L. *Tetrahedron Lett.* **2001**, *42*, 2447. (d) Skowronek, P.; Lightner, D. A. *Monatsh. Chem.* **2003**, *134*, 889. For recent reports, see: (e) D'Alesssion, R.; Rossi, A. *Synlett* **1996**, 513. (f) Shevchuk, V. S.; Davis, J. M.; Sessler, J. L. *Tetrahedron Lett.* **2001**, *42*, 2447. (g) Merz, A.; Anikin, S.; Lieser, B.; Heinze, J.; John, H. *Chem.−Eur. J.* **2003**, *9*, 449. (h) Fürstner, A.; Radkowski, K.; Peters, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 2777.

(6) Using donor−acceptor cyclopropanes: Yu, M.; Pantos, G. D.; Sessler, J. L.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 1057.

(7) Rapoport, H.; Castagnoli, N., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 2178. (b) Bordner, J.; Rapoport, H. *J. Org. Chem.* **1965**, *30*, 3824. (c) Brown, D.; Griffiths, D.; Rider, M. E.; Smith, R. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 455.

10.1021/ol060333m CCC: $33.50

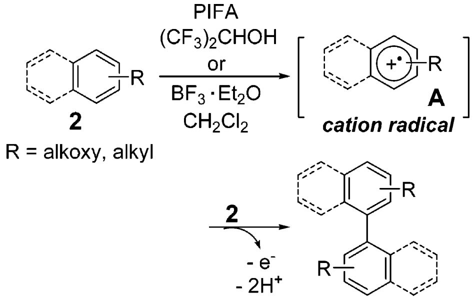
Scheme 1



proaches involving decarboxylation steps were required in many cases.[5,6] Therefore, development of new methods for the synthesis of various types of bipyrroles remains an important issue.

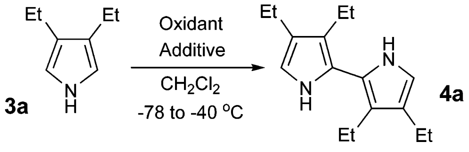
Hypervalent iodine(III) reagents, such as phenyliodine diacetate (PIDA) and phenyliodine bis(trifluoroacetate) (PIFA), hydroxy(tosyloxy)iodobenzene (HTIB), and iodosobenzene, have been widely recognized as safe and useful oxidants having reactivities similar to those of the highly toxic heavy metal oxidizers.[9] We have previously developed the PIFA-induced mild and efficient direct oxidative coupling reaction of phenyl ethers and alkylarenes in $(CF_3)_2CHOH$ or using $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (Scheme 2).[10] The reaction would proceed via the cation radical intermediates **A**,[11] and the carbon−carbon bond formation could oxidatively occur by the reaction of **A** with neutral molecules of substrates to give the corresponding biaryl products. Recently, we discovered that the Lewis acids play an important role not only in the activation of the hypervalent iodine(III) reagents but also in determining the course of the reaction.[10c] During our investigation on the hypervalent iodine(III) chemistry, we have found that bipyrroles could be formed in the reaction of pyrroles depending on the Lewis acids used. Herein, we report a novel straightforward synthetic method using PIFA with bromotrimethylsilane (TMSBr), which provides the facile and selective construction of 2,2′-bipyrroles and even 2,3′-bipyrrole.

Scheme 2



The influences of Lewis acids on the oxidative coupling reaction of 3,4-diethylpyrrole **3a** leading to 2,2′-bipyrrole **4a**,[5c] are summarized in Table 1. $BF_3{\cdot}Et_2O$, the most common Lewis acid for the oxidative coupling reaction of phenyl ethers and alkylarenes, did not give a good result; although almost all of **3a** was consumed, insoluble oligomeric products were mainly obtained in this case (entry 1). After an extensive number of unfavorable results using the boron-based Lewis acids, we found that **4a** was produced when using silicon-based Lewis acids (entries 2−5). Of all the Lewis acids treated, TMSBr gave the best result, and thus **4a** was obtained in 75% yield (69% yield based on consumed **3a**) at −40 °C (entry 4). Using the pentavalent iodine reagent, other heavy metal and organic oxidants (entries 6−9), and Brønsted acids, such as CF_3CO_2H and HNO_3, instead of TMSBr, we did not obtain **4a**, but oligomeric products were formed.

Table 1. Survey of Oxidants for the Oxidative Coupling Reaction of **3a**



entry[a]	oxidant	additive	yield of **4a** (%)[b]
1	PIFA	$BF_3{\cdot}OEt_2$	n.d.
2	//	TMSOTf	17
3	//	TMSCl	22
4	//	TMSBr	75 (69)[c]
5	$(PhIO)_n$	//	31
6	DMP[d]	//	trace
7	$Tl(OCOCF_3)_3$	//	n.d.[e]
8	CAN[f]	//	n.d.
9	DDQ[g]	//	n.d.

[a] Reaction conditions: 3 equiv of **3a**, 1 equiv of oxidant, 2 equiv of additive. [b] Isolated yields based on oxidant. [c] Isolated yields based on consumed **3a**. [d] DMP = Dess−Martin periodinane. [e] n.d. = not detected. [f] CAN = ceric ammonium nitrate. [g] DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

The present reaction proceeded with a wide range of electron-rich pyrroles having various substitutions (Table 2).[12] It should be noted that *N*-nonprotected pyrroles were usable, and the reaction was rapid enough to finish in 1 h. Although there was concern of forming the regioisomers of bipyrroles

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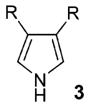
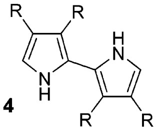
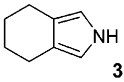
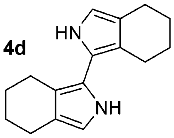
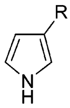
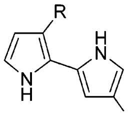
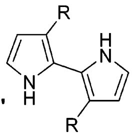
(8) (a) Itahara, T. *J. Chem. Soc., Chem. Commun.* **1980**, 49. (b) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5272. (c) Boger, D. L.; Patel, M. *Tetrahedron Lett.* **1987**, *28*, 2499. Oxidative homocoupling of 2-substituted thiophenes: (d) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074.

(9) For recent reviews, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Kita, Y.; Takada, T.; Tohma, H. *Pure. Appl. Chem.* **1996**, *68*, 627. (c) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997. (d) Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267. (e) Ochiai, M. In *Chemistry in Hypervalent Compounds*; Akiba, K., Ed.; Wiley-VCH: New York, 1999; Chapter 12. (f) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (g) *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Springer-Verlag: Berlin, Heidelberg, 2003. (h) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (i) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656.

(10) (a) Tohma, H.; Morioka, H.; Takizawa, S.; Arisawa, M.; Kita, Y.; *Tetrahedron* **2001**, *57*, 345. (b) Tohma, H.; Iwata, M.; Maegawa, T.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 9241. (c) Dohi, T.; Morimoto, K.; Kiyono, Y.; Maruyama, A.; Tohma, H.; Kita, Y. *Chem. Commun.* **2005**, 2930 and references therein.

(11) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684.

Table 2. PIFA-Induced Selective Synthesis of α-Linked Bipyrroles **4** from 1-*H* Pyrroles **3**

entry[a]	substrate	product	yield (%)[b]
	 **3**	**4** 	
1	R = Et (**3a**)	**4a**	75 (69)[c]
2	= H (**3b**)	**4b**	78
3	= *i*Bu (**3c**)	**4c**	60
4	 **3d**	**4d** 	61
	 **3**	 **4'**  **4"**	
5	R = Me (**3e**)	**4’e + 4’’e**	58 (**4’e**) 12 (**4’’e**)
6	= Hep (**3f**)	**4’f + 4’’f**	60 (**4’f**) 9 (**4’’f**)
7	= $(CH_2)_3CO_2Me$ (**3g**)	**4’g + 4’’g**	82 (**4’g**) 13 (**4’g**)
8	= Ph (**3h**)	**4’h + 4’’h**	70 (**4’h**) 13 (**4’’h**)
9	= 4-$MeOC_6H_4$ (**3i**)	**4’i + 4’’i**	52 (**4’i**) < 1 (**4’’i**)
10	= 4-BrC_6H_4 (**3j**)	**4’j + 4’’j**	68 (**4’j**) 8 (**4’’j**)

[a] Reaction conditions: 3 equiv of **3**, 1 equiv of PIFA, 2 equiv of TMSBr. [b] Isolated yields based on PIFA. [c] Isolated yield based on consumed **3a**.

in the case of pyrrole **3b** itself, 2,2′-bipyrrole **4b**[6a] was obtained in 78% yield in high selectivity (entry 2). Similar results were obtained with sterically hindered **3c** and 4,5,6,7-tetrahydro-2*H*-isoindole **3d** (entries 3 and 4).

In the case of the 3-substituted pyrroles, useful head to tail dimers **4′**[13] were obtained in preference to head to head dimers **4″** (entries 5−10).[10c] The regiochemistry of the products was determined by measurement of their ^{1}H NMR or by comparing them to authentic samples.[13c] Some functional groups (ester, ether, halogen, etc.) are tolerable under the reaction conditions, but electron-deficient pyrroles, such as 1-tosylpyrrole, did not react at all.

The reaction was applicable to the indole **5**,[14] though the addition product **7**[15] was formed (29% yield based on PIFA) together with the desired bisindole **6** (74% yield based on PIFA) (Figure 1).

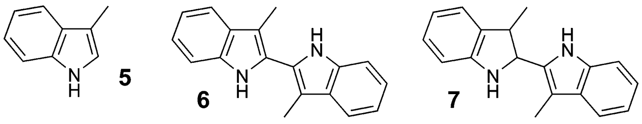
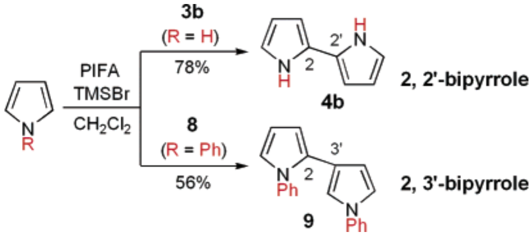


Figure 1. Oxidative coupling reaction of 3-methylindole **5**.

Next, we tried to apply the present reaction to the synthesis of other types of bipyrroles because no facile methods have appeared. We found that it was made possible by choosing the phenyl group as the suitable *N*-substituent of pyrrole. Thus, the 2,3′-bipyrrole **9**[16] was obtained in 56% yield using *N*-phenyl pyrrole **8** under the reaction conditions (Scheme 3).[17]

Scheme 3



A possible reaction mechanism of the present oxidative coupling reaction of the pyrroles and indole is illustrated in

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(12) **Typical Experimental Procedure:** To a stirred solution of 1*H*-pyrrole **3a** (111 mg, 0.9 mmol) in CH_2Cl_2 (15 mL) were quickly added PIFA (0.3 mmol) and TMSBr (0.6 mmol) at −78 °C. The reaction mixture was then stirred for 1 h, while the reaction temperature was maintained below −40 °C. After the reaction completion, saturated aqueous $NaHCO_3$ (ca. 20 mL) was added to the mixture and then stirred for an additional 10 min at ambient temperature. 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 (neutral)/*n*-hexane-AcOEt) to give the pure 2,2′-bipyrrole **4a** (56 mg, 75%) as a colorless oil. The less polar fractions gave unreacted **3a** as a pure form (31 mg).

(13) For utility of the head to tail dimers of heteroaromatic compounds, see: (a) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. (b) McCullough, R. D. *Adv. Mater.* **1998**, *10*, 93. (c) Benincori, T.; Brenna, E.; Sannicolò, F.; Zotti, G.; Zecchin, S.; Schiavon, G.; Gatti, C.; Frigerio, G. *Chem. Mater.* **2000**, *12*, 1480. (d) Gatti, C.; Frigerio, G.; Benincori, T.; Brenna, E.; Sannicolò, F.; Zotti, G.; Zecchin, S.; Schiavon, F. *Chem. Mater.* **2000**, *12*, 1490.

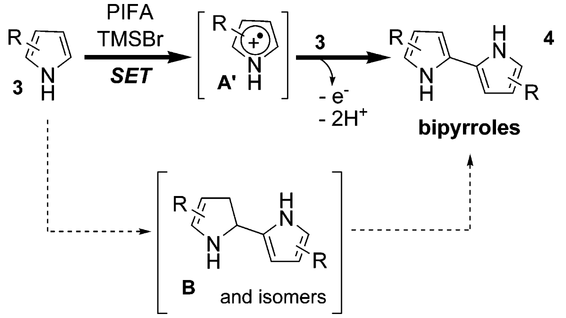
(14) The intramolecular oxidative coupling reaction of the *N*-free bisindolylmaleimide hardly occurs using PIFA with $BF_3{\cdot}Et_2O$: Faul, M. M.; Sullivan, K. A. *Tetrahedron Lett.* **2001**, *42*, 3271.

(15) We have observed the slow formation of the addition product **7** in the absence of PIFA. For the related studies on the Lewis acid-catalyzed reaction, see: (a) Smith, G. F.; Walters, A. E. *J. Chem. Soc.* **1961**, 940. (b) Hinman, R. L.; Shull, E. R. *J. Org. Chem.* **1961**, *26*, 2339.

(16) Farnier, M.; Soth, S.; Fournari, P. *Can. J. Chem.* **1976**, *54*, 1083.

(17) A certain degree of the 2,2′-bipyrrole formed, but it decomposed under the reaction conditions.

Scheme 4



Scheme 4. As presumed from our previous reports,[11] electrolytic[3] or some chemical oxidations[18] yielding pyrrole cation radicals, i.e., cation radical **A′**, appear to be generated from the pyrroles **3** through a one-electron oxidation by the action of PIFA−TMSBr. **A** then reacts with **3** to give the bipyrroles **4** after the further one-electron oxidation followed by deprotonation. Although an alternative stepwise mechanism involving **B**[19] is conceivable, the former explanation is more reasonable based on the following experimental result; thus, the isolated dihydroindole **7**, which was slowly formed during the oxidative coupling reaction condition of **5**, did not produce bisindole **6** in the presence of PIFA and TMSBr. Our persistent attempts to detect the dihydropyrroles **B** also suggested the absence of **B** during the reaction, and effective inhibition of the reaction by the radical scavenger, galvinoxyl, supports the former cation radical pathway.

Because pyrroles cause acid-catalyzed oligomerization or polymerization by treatment with strong acids even at low temperature, TMSBr acts as a suitable Lewis acid not only to activate PIFA but also to suppress the oligomerization process of the pyrroles during the coupling reaction. However, the precise intermediate of the coupling reaction is yet unclear, and we consider the following two alternative reaction intermediates generated in situ: (a) a bromonium ion in the form of a hypobromite or the bromate(I) complex by PIFA-induced oxidation of the bromide ion[20] and (b) activated I(III) species containing an I−Br bond.[21,22] Extensive studies on the mechanism and real intermediate of the coupling reaction will be done and described elsewhere.

In conclusion, we have developed the hypervalent iodine(III)-induced effective oxidative coupling reactions of electron-rich pyrroles and indoles using TMSBr as an appropriate Lewis acid. This is the first straightforward synthesis of a variety of bipyrroles in good yields, and therefore, it might accelerate further applications of these compounds in the research fields already mentioned. Applications of these useful bipyrrole compounds are also underway in our laboratory.

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Supporting Information Available: Experimental details 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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(18) (a) Ricciardi, G.; Lelj, F. *Polyhedron* **1992**, *11*, 2089. (b) Van der Schoor, R. C. G. M.; Van de Leur, R. H. M.; De Wit, J. H. W. *Synth. Met.* **1999**, *99*, 17. (c) Ayad, M. M. *J. Mater. Sci. Lett.* **2003**, *22*, 1577 and references therein.

(19) Bender, C. O.; Bonnett, R. *J. Chem. Soc. C* **1968**, 252.

(20) (a) Monenschein, H.; Sourkouni-Argirusi, G.; Schubothe, K. M.; O'Hare, T.; Kirschning, A. *Org. Lett.* **1999**, *1*, 2101. (b) Sourkouni-Argirusi, G.; Kirschning, A. *Org. Lett.* **2000**, *2*, 3781.

(21) (a) Tohma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 1306. (b) Tohma, H.; Maegawa, T.; Takizawa, S.; Kita, Y. *Adv. Synth. Catal.* **2002**, *344*, 328.

(22) (a) Amey, R. L.; Martin, J. C. *J. Org. Chem.* **1979**, *44*, 1779. (b) Macdonald, T. L.; Navasimhan, N. *J. Org. Chem.* **1985**, *50*, 5000. (c) Karada, N. N.; Shirodkar, S. G.; Dhoot, B. M.; Waghmare, P. B. *J. Chem. Res.* **2005**, 274.