Synthesis of Polysubstituted Pyrroles via $PhI(OAc)_2$-Mediated Oxidative Coupling of Enamine Esters and Ketones

Jun-Yan Wang, Su-Ping Liu, Wei Yu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, P. R. of China
E-mail: yuwei@lzu.edu.cn.

Received 1 April 2009

Abstract: Enamine esters or ketones could undergo homocoupling by the action of (diacetoxyiodo)benzene in the presence of $BF_3{\cdot}OEt_2$, giving rise to pyrrole products. This reaction could be used to synthesize symmetric polysubstituted pyrroles. Some asymmetric polysubstituted pyrroles could also be prepared using this protocol.

Key words: (diacetoxyiodo) benzene, oxidative coupling, enamine esters, pyrroles

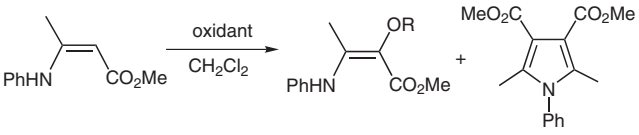
The pyrrole ring system is one of the most important heterocyclic structures which exist in naturally occurring products.[1] Many pyrrole-containing compounds exhibit important biological and pharmaceutical activities,[2] and are of great utility in material sciences.[3] Therefore, the synthetic studies on pyrroles have been of great interest to organic chemists over the years.[4] While many recent efforts have led to diverse new synthetic pathways toward pyrrole skeleton,[5] it is still much desirable to develop simple, convenient methods for the synthesis of polysubstituted pyrroles.

Hypervalent iodine reagents are now playing an increasingly important role in organic synthesis.[6] The versatility and the ready availability of hypervalent iodine compounds, combined with their environmentally benign character, render them superior oxidants for a variety of organic transformations. Recently, there has been much interest in using hypervalent iodine reagents to effect oxidative carbon–carbon coupling under metal-free conditions. For instances, Kita et al.[7] employed hypervalent iodine(III) reagents to effect a variety of oxidative aryl–aryl coupling reactions. The homocoupling of 1,3-dicarbonyl compounds could also be achieved by the action of hypervalent iodine(III) reagents.[8]

In a previous study, Spyroudis and Varvoglis et al. found that the reactions between 3-aminocrotonate and [hydroxy(tosyloxy)iodo]benzene (HTIB or Koser' reagent) gave rise to alkenyl phenyliodonium tosylate, which could undertake vinyl substitution reactions with a variety of nucleophiles. Accompanied with the major alkenyl phenyliodonium tosylate product, a small amount of dimethylpyrrole-3,4-dicarboxylate was also obtained in about 5% yield.[9] This type of transformation was previously achieved under electrochemical conditions,[10] and by using $Pb(OAc)_4$ as the oxidant.[11] However, the yields were generally low. Better results were obtained when Ce(IV) was used as the oxidant, but the substrates were limited to β-aminocinnamates.[12] We reexamined this type of reactions recently, in the hope that conditions could be found to raise the yields of pyrrole products significantly under metal-free conditions.

To achieve this goal, three different hypervalent iodine(III) reagents were tested. The results are summarized in Table 1. Firstly, Spyroudis and Varvoglis' work was repeated using HTIB as the oxidant, and the same results

Table 1 Screening of Reaction Conditions with **1a** as Substrate[a]



1a R = Ts, **2a-1**; R = Ac, **2a-2**; **3a**

Entry	Oxidant (equiv)	Additive (equiv)	Time (h)	Products (yield, %)[b]
1	PhI(OH)OTs (1)	none	3.5	**2a-1** (50), **3a** (15)
2	$PhI(OAc)_2$ (1)	none	2.5	**2a-2** (80), **3a** (8)
3	$PhI(OAc)_2$ (1)	$BF_3{\cdot}OEt_2$ (1)	2	**3a** (60)
4	$PhI(OAc)_2$ (0.6)	$BF_3{\cdot}OEt_2$ (1)	2	**3a** (70)
5	$PhI(OAc)_2$ (0.6)	$BF_3{\cdot}OEt_2$ (0.2)	2	**3a** (81)
6	PhI(OH)OTs (0.6)	$BF_3{\cdot}OEt_2$ (0.2)	2	**3a** (77)
7	PhIO (0.6)	$BF_3{\cdot}OEt_2$ (0.2)	overnight	**3a** (76)[c]
8	PhIO (0.6)	TMSOTf (0.6)	overnight	**3a** (75)[c]
9	$PhI(OAc)_2$ (1)	CSA (1)	0.5	mixture
10	$PhI(OAc)_2$ (1)	TfOH (1)	0.5	mixture
11	$PhI(OAc)_2$ (1)	$TsOH{\cdot}H_2O$ (1)	2	mixture
12	$PhI(OAc)_2$ (1)	K_2CO_3 (1)	2	**3a** (55)
13	$PhI(OAc)_2$ (1)	DBU (1)	0.5	mixture

[a] The reactions were carried out in CH_2Cl_2 at 10 °C.
[b] Isolated yield.
[c] Conditions: –78 °C to r.t.

SYNLETT 2009, No. 15, pp 2529–2533
Advanced online publication: 27.08.2009
DOI: 10.1055/s-0029-1217743; Art ID: W05009ST

were obtained. When methyl 3-phenylaminocrotonate (**1a**) was used as the substrate, the pyrrole product **3a** was obtained in higher yield, but still the major product was the 2-tosylate-substituted product **2a-1** (entry 1). Using (diacetoxyiodo)benzene (DIB) instead of HTIB led to the similar reaction consequences (entry 2). As the reactions involving hypervalent iodine(III) reagents are often influenced by acids, we envisioned that the composition of the products might be changed by the addition of acids. Indeed, we found that when $BF_3{\cdot}OEt_2$ or TMSOTf was used together with hypervalent iodine(III) reagents, **3a** became the major product (entries 3–6). Beside HTIB and DIB, PhIO was also an effective oxidant to promote the formation of **3a** in the presence of Lewis acids (entries 7 and 8). The best results were obtained when 0.6 equivalents of hypervalent iodine(III) reagents and 0.2 equivalents of $BF_3{\cdot}OEt_2$ were used (entries 5–7). The use of Brønsted acids such as TsOH, TfOH, and CSA, however, led to the formation of complex mixture (entries 9–11). It is interesting to note that the yield of **3a** could also be raised significantly by the addition of K_2CO_3 (entry 12), while the organic base 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) failed to deliver the same result (entry 13).

Following the screening of the reaction conditions, various substituted enamine esters and ketones were treated with the optimized conditions next. As shown in Table 2, good to excellent yields were observed for enamine esters except for **1m** and **1n**, while the reactions of enamine ketones gave rise to 2-acetoxy-substituted enamine ketones as the minor products beside pyrroles (entries 11 and 12). In the cases of **1m** and **1n**, however, mixtures were formed, among which indoles were obtained in the yields of 20% and 10%, respectively (entries 13 and 14). In general, the yields of pyrroles formed from enamine esters and ketones under our reaction conditions are much higher than those using $Pb(OAc)_4$ as oxidant or under electrochemical conditions,[10,11] demonstrating the superior activity of hypervalent iodine reagents for this type of transformations.

Table 2 $PhI(OAc)_2$-Mediated Synthesis of Pyrroles from Enamine Esters and Ketones[a]

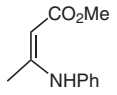
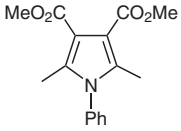
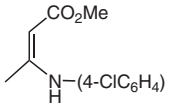
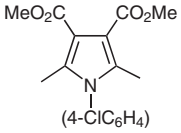
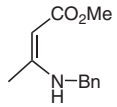
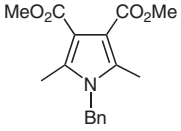
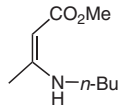
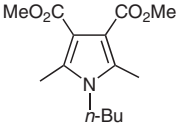
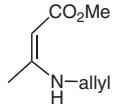
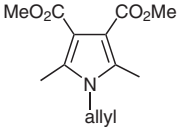
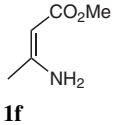
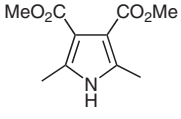
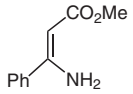
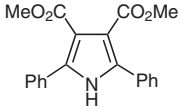
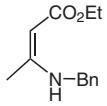
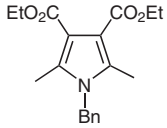
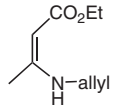
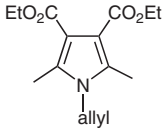
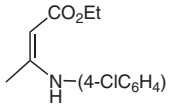
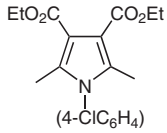
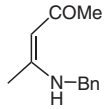
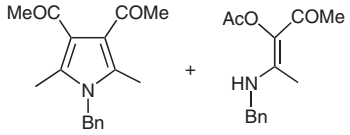
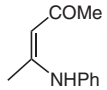
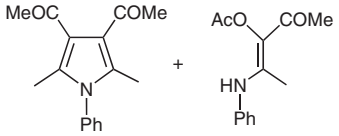
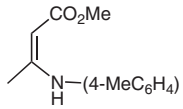
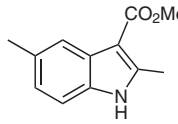
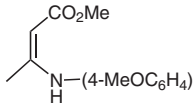
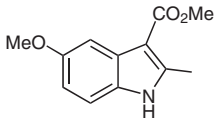
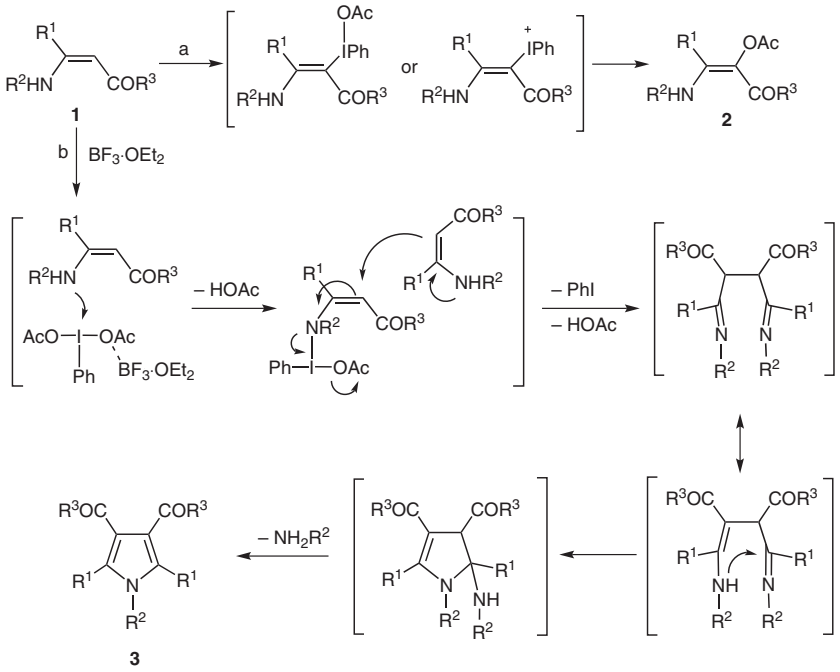
Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1a**	2	 **3a**	81
2	 **1b**	2.5	 **3b**	68
3	 **1c**	1.5	 **3c**	89
4	 **1d**	1.5	 **3d**	95
5	 **1e**	1.5	 **3e**	88
6	 **1f**	2	 **3f**	71

Table 2 $PhI(OAc)_2$-Mediated Synthesis of Pyrroles from Enamine Esters and Ketones[a] (continued)

Entry	Substrate	Time (h)	Product	Yield (%)[b]
7	 **1g**	3.5	 **3g**	44
8	 **1h**	1.5	 **3h**	89
9	 **1i**	1.8	 **3i**	92
10	 **1j**	2	 **3j**	70
11	 **1k**	3.5	 **3k** + **2k**	60 (**3k**) 18 (**2k**)
12	 **1l**	4.5	 **3l** + **2l**	51 (**3l**) 20 (**2l**)
13	 **1m**	0.5	 **4m** + mixture	20 (**4m**)
14	 **1n**	0.5	 **4n** + mixture	10 (**4n**)

[a] To a solution of $BF_3{\cdot}OEt_2$ (0.04 mmol) and **1** (0.2 mmol) in 0.5–1.0 mL CH_2Cl_2 was added DIB (0.12 mmol), and the reaction mixture was stirred at 0–10 °C. After the reaction finished as monitored by TLC, the solvent was evaporated under reduced pressure, and the residual was treated with flash chromatography to give the pure products.
[b] Isolated yields.

Our results indicated that Lewis acids played a critical role in determining the reaction consequences. It has been proposed that the pyrrole products might result from the activation of amino groups in enamine esters by hypervalent iodine reagents, while the 2-substituted products be generated via iodonium salts **5** (Figure 1).[9] We speculate that the reason why Lewis acids such as $BF_3{\cdot}OEt_2$ could promote the formation of pyrroles in these reactions might be because they would facilitate the attack on hypervalent iodine reagents by amino groups (path b, Scheme 1), and thus make the formation of pyrroles more favorable. This mechanism was partly supported by the experiments that pyrrole products **3a** could not be formed from **1a** and **2a-2**, and the reaction between **1a** and iodonium salt **5a**, though could take place, proceeded much slower and gave rise to mixture of **2a-1** and **3a**.



Scheme 1

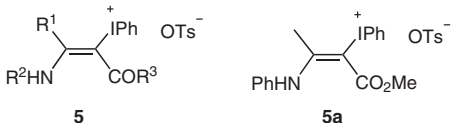


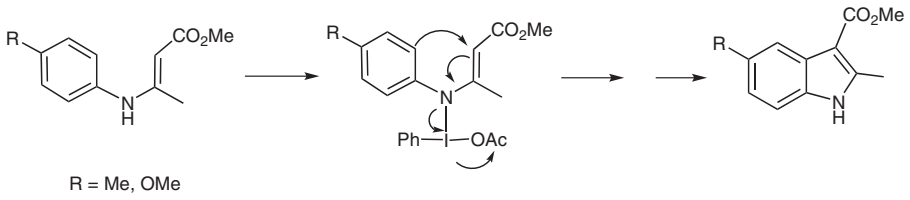
Figure 1

When electron-rich aryl groups were attached to the amino group, as in the case of **1m** and **1n**, indole products were formed probably as the result of intramolecular aryl attack (Scheme 2). Similar oxidative cyclization of *N*-aryl enamines leading to the formation of indoles were recently achieved with $Pd(OAc)_2$ as catalyst.[13] Very recently, Zhao et al. reported that DIB could effect the formation of indoles from *N*-aryl enamines in good yields in DCE. It is noteworthy that while their reaction conditions and substrates were similar to ours, the results they obtained were different.[14]

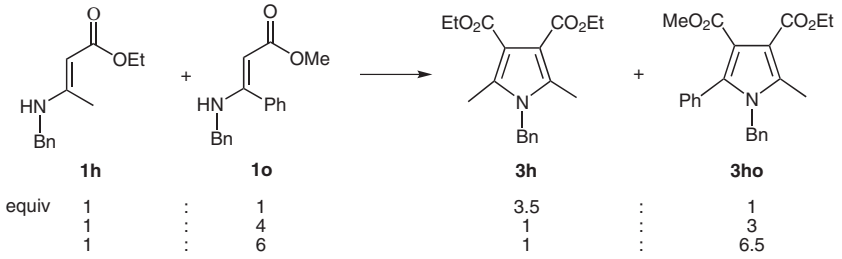
With the successful synthesis of symmetric pyrroles, attempts were made to prepare asymmetric polysubstituted pyrroles next. After some exploration of reaction conditions, we found that 3-phenyl substituted enamine esters were much less reactive than their 3-methyl-substituted counterparts. Therefore, we hoped that by using excessive amount of 3-phenyl substituted enamine esters, cross-coupling might take place between 3-phenyl and 3-alkyl enamine esters. Just as expected, when **1h** (1 equiv) and **1o** (1 equiv) were mixed and treated with DIB and $BF_3{\cdot}OEt_2$, homocoupling product **3h** was obtained as the major product, along with the cross-coupling product **3ho**. Use of four equivalents of **1o** led to the formation of **3ho** as the major product. The optimistic conditions were found when six equivalents of **1o** were used, with **3ho** and **3h** formed in the ratio of 6:1 (Scheme 3). The unreacted **1o** could be recovered after reaction. Various asymmetrically substituted pyrroles could be accessed in good yields under the reaction conditions,[15] as shown in Figure 2. It should be pointed out that when the reactions were performed, the amino group on both the 3-phenyl and 3-alkyl enamine esters should be equally substituted (as in the case of **1h** and **1o**). Otherwise mixed products, which were different at the amino group, would be formed.

In summary, the oxidative coupling of enamine esters and ketones under the conditions of $PhI(OAc)_2$ and $BF_3{\cdot}OEt_2$ led to the formation of pyrroles. The presence of $BF_3{\cdot}OEt_2$ was critical to guarantee a good yield for the pyrrole product. This protocol provides a convenient and mild method for the synthesis of polysubstituted pyrroles.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.



Scheme 2



Scheme 3 *Reagents and conditions*: $PhI(OAc)_2$ (1.1 equiv), $BF_3{\cdot}OEt_2$ (0.2 equiv).

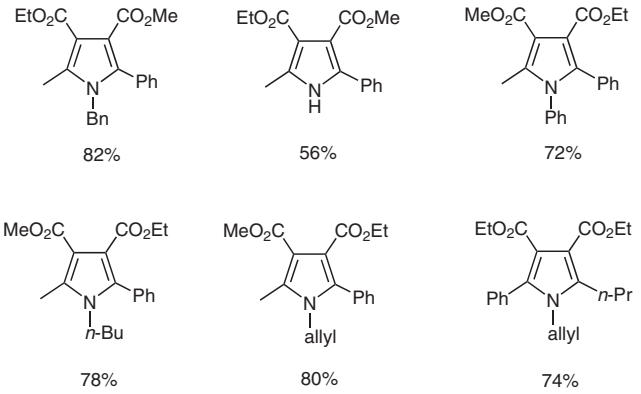


Figure 2 Isolated yields based on 3-methyl or 3-propyl enamine esters which were totally converted (see ref. 15 for experimental details)

Acknowledgment

We thank the National Natural Science Foundation of China (No. 20772053) for financial support.

References and Notes

(1) Fürstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582.
(2) (a) Huffman, J. W. *Curr. Med. Chem.* **1999**, *6*, 705. (b) Agarwal, S.; Cämmerer, S.; Filali, S.; Fröhner, W.; Knöll, J.; Krahl, M. P.; Reddy, K. R.; Knölker, H. J. *Curr. Org. Chem.* **2005**, *9*, 1601.
(3) Domingo, V. M.; Aleman, C.; Brillas, E.; Julia, L. *J. Org. Chem.* **2001**, *66*, 4058.
(4) (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491. (b) Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238.
(5) For some recent examples of pyrrole synthesis, see: (a) Su, S.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (b) St. Cyr, D. J.; Martin, N.; Arndtsen, B. A. *Org. Lett.* **2007**, *9*, 449. (c) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (d) Peng, L.; Zhang, X.; Ma, J.; Zhong, Z.; Wang, J. *Org. Lett.* **2007**, *9*, 1445. (e) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (f) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313. (g) Attanasi, O. A.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Spinelli, D. *Org. Lett.* **2008**, *10*, 1983. (h) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629. (i) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019. (j) Liu, X.; Huang, L.; Zheng, F.; Zhan, Z. *Adv. Synth. Catal.* **2008**, *350*, 2778. (k) Queiroz, M. J. R. P.; Begouin, A.; Pereira, G.; Ferreira, P. M. T. *Tetrahedron* **2008**, *64*, 10714. (l) Alcaide, B.; Almendros, P.; Carrascosa, R.; Redondo, M. C. *Chem. Eur. J.* **2008**, *14*, 637. (m) Tan, B.; Shi, Z.; Chua, P. J.; Li, Y.; Zhong, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 758. (n) Lygin, A. V.; Larionov, O. V.; Korotkov, V. S.; de Meijere, A. *Chem. Eur. J.* **2009**, *15*, 227. (o) Tejedor, D.; Lõpez-Tosco, S.; González-Platas, J.; Garcia-Tellado, F. *Chem. Eur. J.* **2009**, *15*, 838. (p) Kim, Y.; Kim, J.; Park, S. B. *Org. Lett.* **2009**, *11*, 17.
(6) (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (c) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656. (d) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2853.
(7) (a) Tohma, H.; Iwata, M.; Maegawa, T.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 9241. (b) Dohi, T.; Motimoto, K.; Kiyono, Y.; Maruyama, A.; Tohma, H.; Kita, Y. *Chem. Commun.* **2005**, 2930. (c) Dohi, T.; Motimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007. (d) Dohi, T.; Ito, M.; Motimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 1301. (e) Kita, Y.; Norimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668.
(8) Yan, J.; Zhong, L. R.; Chen, Z. C. *J. Org. Chem.* **1991**, *56*, 49.
(9) Papoutsis, I.; Spyroudis, S.; Varvoglis, A. *Tetrahedron* **1998**, *54*, 1005.
(10) Koch, D.; Schafer, H. *Angew. Chem.* **1973**, *85*, 264.
(11) (a) Carr, R. M.; Norman, R. O. C.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 156. (b) Sukari, M. A.; Vernon, J. M. *Tetrahedron* **1983**, *39*, 793.
(12) Tsai, A.; Chuang, C.-P. *Tetrahedron* **2006**, *62*, 2235.
(13) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 7230.
(14) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417.
(15) **Procedures for the Preparation of Asymmetric Pyrroles** $BF_3{\cdot}OEt_2$ (0.04 mmol) was added to a solution of 3-alkyl-enamine esters (0.2 mmol) and 3-phenyl-enamine esters (1.2 mmol) in 1 mL CH_2Cl_2, followed by DIB (0.22 mmol), and the mixture was stirred at 0–10 °C. After the reaction finished as indicated by TLC, the mixture was concentrated under reduced pressure, and the residue was treated with flash column chromatography to give the product.