SHORT PAPER

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Hypervalent iodine in synthesis 72: a tandem dimerisation-cyclocondensation of enaminones with [bis(trifluoroacetoxy)iodo]benzene: an effective method for the synthesis of highly substituted pyrroles†

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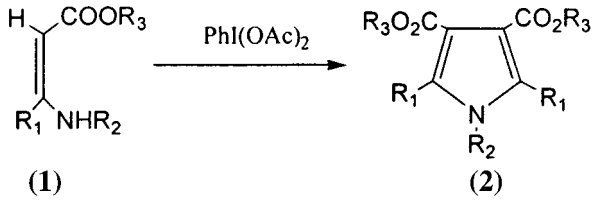
A tandem dimerisation–cyclocondensation of enaminones with [bis(trifluoroacetoxy)iodo]benzene(BTI) provides an effective method for the synthesis of highly substituted pyrroles. It has some advantages over existing methodologies such as accessible starting material, nontoxic reagents, mild reaction conditions.

Keywords: hypervalent iodine, dimerisations–cycloconolenation, pyrroles

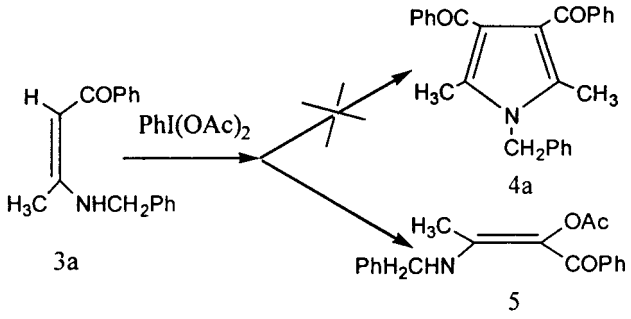
Highly substituted pyrrole derivatives have attracted much interest in the past few years, since they are the main structural element of many alkaloids and pharmacologically active compounds.[1a] The literature methods of preparing highly substituted C_2-symmetric pyrroles include the oxidation of enamines with LTA,[1] the anodic dimerization of enamines,[2] the 1,3-dipolar cycloaddition of azalactones to alkynes,[3,4] the reaction of 2,5-disubstituted pyrroles with dimethyl acetylenedicarboxylate,[5] the Knorr reaction of α-aminoketones with a ketone having a reactive methylene group alpha to the carbonyl group, and the Hantzsch reaction of α–haloketones with enamines.[6] However, these methods have some disadvantages such as using toxic reagents, inaccessible starting material, harsh reaction conditions and poor yields.

Oxidative dimerisation is one of the most useful reaction for preparing symmetrical molecules in organic synthesis. In recent years, a variety of hypervalent organoiodine(III) reagents have become available and have been successfully used for oxidative dimerisation.[7–12] Recently, we have reported a simple and convenient method for the synthesis of highly substituted pyrroles (**2**) by the dimerisation-cyclocondensation of enamine-esters (**1**) with (diacetoxy)iodobenzene (DIB)[13] (Scheme 1).



Scheme 1

In order to extend the synthetic utility of our methodology, we investigated the reaction of enaminones with DIB, expecting formation of the substituted pyrroles bearing acyl groups. We found when 3-benzylamino-1-phenylbut-2-en-1-one (**3a**) was treated with DIB, a yellow compound was obtained in 87% yield instead of the expected N-benzyl-2,5-dimethyl-3,4-dibenzoyl pyrrole (**4a**). The microanalytical data IR, ^{1}H NMR, MS spectra of this compound all were in agreement with those of 2-acetoxyl-3-benzylamino-1-phenylbut-2-en-1-one (**5**) (Scheme 2).



Scheme 2

In order to achieve the synthesis of **4a**, we used [bis(trifluoroacetoxy)iodo]benzene (BTI) which is a stronger oxidising agent and has a weaker nucleophilic group, CF_3COO^-, instead of DIB. As expecting, stirring the **3a** and BTI in methylene chloride at room temperature gave **4a** (63%). In order to examine the generality of this reaction, a number of enaminones were examined. The results are summarised in Table 1. The products (Compounds **4**) were characterised by m.p., microanalyses, IR, ^{1}H NMR and MS spectra.

A plausible mechanism of the reaction is analogous to the oxidation of β–aminocinnamates with DIB[13] and is shown in Scheme 3.

In conclusion, a tandem dimerisation–cyclocondensation of enaminones with BTI provides an effective method for the synthesis of highly substituted pyrroles. It has some advantages over existing methodologies such as accessible starting material, nontoxic reagents, mild reaction conditions.

Experimental

Melting points were measured on a X_4-Data microscope melting point apparatus and are uncorrected. Microanalyses were obtained using Carlo-Erba 1110. IR spectra were recorded with a VECTOR 22 (Bruker) spectrometer. ^{1}H NMR spectra were obtained at 400 Hz (AVANCE DMX400) or 60 Hz for solutions in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained by electron impact at 70 ev (HP5989B).

Preparation of pyrroles **4a–4f***: General procedure:* To a solid of BTI (0.516 g, 1.2 mmol) was added a solution of 3a (0.502 g, 2 mmol) in CH_2Cl_2 (20 ml), the mixture was stirred for 3 hours at room temperature. The solution was then concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using a mixture of cyclohexane–ethyl acetate (4:1) as the eluent to give 0.248g (63%) of *N-benzyl-2,5-dimethyl-3,4-dibenzoyl pyrrole (***4a***)* as a pale yellow powder. m.p. 171–174°C; IR(KBr): 1690 cm^{-1}(s), 1545 cm^{-1}(s), 1455 cm^{-1}(s), 1375 cm^{-1}(s); ^{1}H NMR: δ6.90–7.85(m,15H), 4.45(s,2H), 2.05(s,6H); MS: 393(M^+,1.94),

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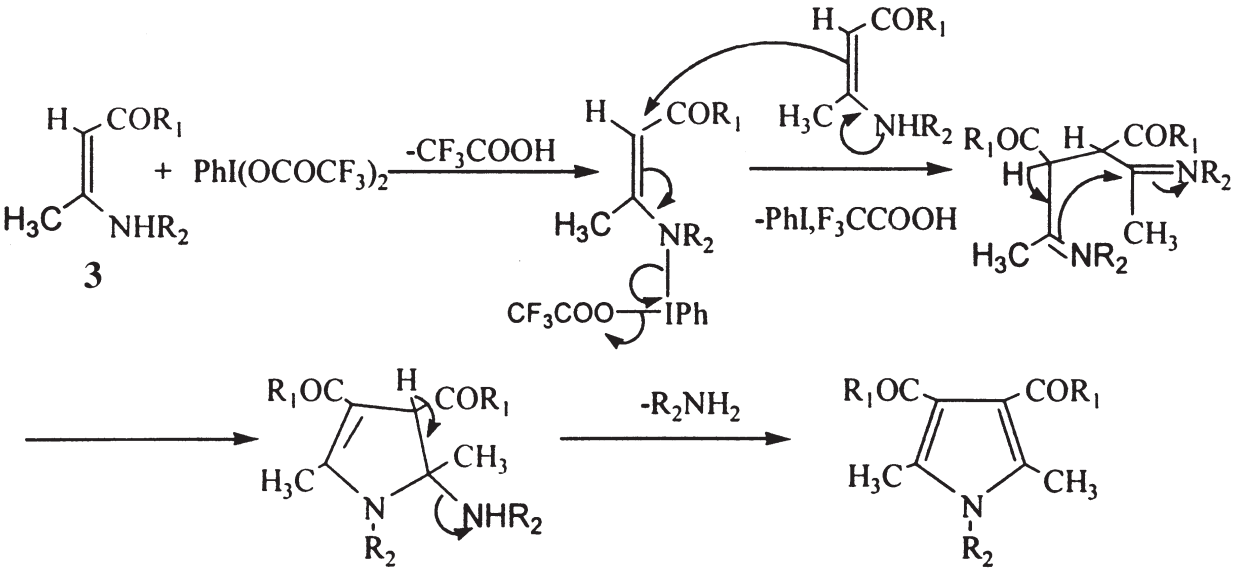
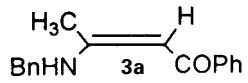
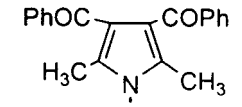
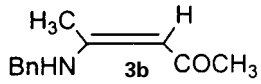
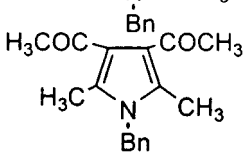
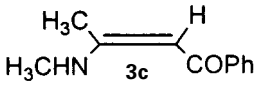
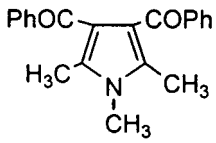
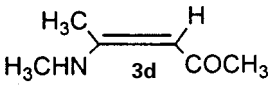
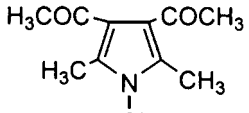
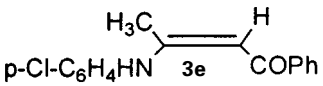
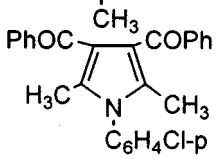
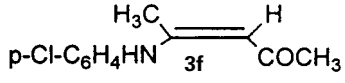
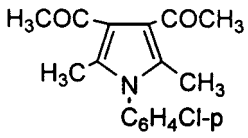
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 3

Table 1 Synthesis of carbonylpyrrole derivatives (**4a–4f**)

Enamine-Ketones	Reaction time/h	Products		Yield/%
	3.0		(**4a**)	63
	3.5		(**4b**)	42
	1.5		(**4c**)	32
	2.0		(**4d**)	37
	4.5		(**4e**)	43
	5.0		(**4f**)	34

203(91.63), 161(100), 145(24.44), 132(11.09), 105(4.77), 91(8.55), 77(5.01); Anal. Calcd for $C_{27}H_{23}NO_2$: C,82.42; H,5.89; N,3.56. Found: C,82.78; H,5.52; N,3.18.

N-benzyl-2,5-dimethyl-3,4-diacetylpyrrole (**4b**)*:* m.p. 230°C(dec.); IR(KBr): 1715 cm^{-1}(vs), 1570 cm^{-1}(s), 1450 cm^{-1}(s), 1380 cm^{-1}(s); ^{1}H NMR: δ7.05–7.75(m,5H), 4.38(s,2H), 2.24(s,6H), 2.03(s,6H); MS: 269(M^+,36.50), 239(35.68), 225(85.51), 152(53.25), 91(4.43), 43(100); Anal. Calcd for $C_{17}H_{19}NO_2$: C,75.81; H,7.11; N,5.20. Found: C,75.53; H,6.86; N,5.58.

1,2,5-trimethyl-3,4-dibenzoylpyrrole (**4c**)*:* m.p. 170–172°C; IR(KBr): 1716 cm^{-1}(s), 1676 cm^{-1}(s), 1623 cm^{-1}(s), 1555 cm^{-1}(s), 1448 cm^{-1}(s), 1352 cm^{-1}(s); ^{1}H NMR: δ7.33–7.53(m,10H), 3.49(s,3H), 2.63(s,6H); MS: 317(M^+,0.60), 162(15.79), 105(100), 77(47.31); Anal. Calcd for $C_{21}H_{19}NO_2$: C,79.47; H,6.03; N,4.41. Found: C,79.82; H,5.74; N,4.15.

1,2,5-trimethyl-3,4-diacetylpyrrole (**4d**)*:* m.p. 138–140°C (lit.[14]140–142^{0}C); ^{1}H NMR: δ3.45(s,3H), 2.28(s,6H), 2.12(s,6H).

N-(p-chlorophenyl)-2,5-dimethyl-3,4-dibenzoyl pyrrole (**4e**)*:* m.p. 211–213°C; IR(KBr): 1710 cm^{-1}(vs), 1540 cm^{-1}(s), 1510 cm^{-1}(s), 1410 cm^{-1}(s), 1390 cm^{-1}(s), 825 cm^{-1}(s); ^{1}H NMR: δ7.10–8.20 (m,14H), 2.16(s,6H); MS: 415(M^+,0.45), 413(M^+,1.33), 338(4.83), 336(14.39), 154(56.22), 152(100), 129(16.42), 127(37.05), 113(16.77), 111(43.20); Anal. Calcd for $C_{26}H_{20}ClNO_2$: C,75.44; H,4.87; N,3.38. Found: C,75.77; H,5.27; N,3.02.

*N-(p-chlorophenyl)-2,5-dimethyl-3,4-diacetyl pyrrole (***4f***):* m.p. 180°C(dec.); IR(KBr): 1725 cm^{-1}(vs), 1710 cm^{-1}(vs), 1550 cm^{-1}(s), 1480 cm^{-1}(s), 1350 cm^{-1}(s); ^1H NMR: δ7.33–7.62(m,2H), 7.02–7.20(m,2H), 2.60(s,6H), 2.15(s,6H); MS: 291(M^+,0.38), 289(M^+,1.10), 276(3.67), 274(10.88), 154(30.01), 152(88.29), 129(8.31), 127(24.33), 113(10.76), 111(30.84), 43(100); Anal. Calcd for $C_{16}H_{16}ClNO_2$: C,66.31; H,5.57; N,4.83. Found: C,65.98; H,5.93; N,5.17.

*2-acetoxyl-3-benzylamino-1-phenylbut-2-en-1-one (***5***):* m.p. 106–108°C; IR(KBr): 3300–3200 cm^{-1}, 1755 cm^{-1}, 1705 cm^{-1}, 1300 cm^{-1}, 1145 cm^{-1}; ^1H NMR: δ7.10–8.90(m,10H), 4.50 (d,2H,*J*=5Hz), 2.21(s,3H), 1.80(s,3H); MS: 309(M^+,14.15), 266(0.92), 176(30.23), 134(73.64), 105(16.11), 91(100), 77(15.48), 43(13.98); Anal. Calcd for $C_{19}H_{19}NO_3$: C,73.77; H,6.19; N,4.53. Found: C,74.03; H,5.87; N,4.22.

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