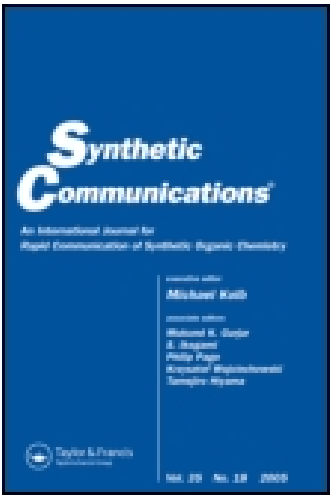

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HYPERVALENT IODINE IN SYNTHESIS. 62: A TANDEM DIMERIZATION-CYCLOCONDENSATION OF ENAMINE-ESTERS WITH [BIS(TRIFLUOROACETOXY)-IODO]BENZENE: A METHOD OF SYNTHESIS OF HIGHLY SUBSTITUTED PYRROLES

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HYPERVALENT IODINE IN SYNTHESIS. 62: A TANDEM DIMERIZATION-CYCLOCONDENSATION OF ENAMINE-ESTERS WITH [BIS(TRIFLUOROACETOXY)-IODO]BENZENE: A METHOD OF SYNTHESIS OF HIGHLY SUBSTITUTED PYRROLES

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ABSTRACT

A tandem dimerization-cyclocondensation of enamine-esters with [bis(trifluoroacetoxy)iodo]benzene(BTI) provides an effective method for synthesis of highly substituted pyrroles.

The oxidative dimerization is one of the most useful reaction for constituting symmetric molecules in organic synthesis. In recent years, a variety of hypervalent organoiodine(III) reagents[1] have become available and have been successfully used for oxidative dimerization.[2–6] Recently, we also reported[7] the oxidative dimerization of isopropylidene 5-alkylmalonates

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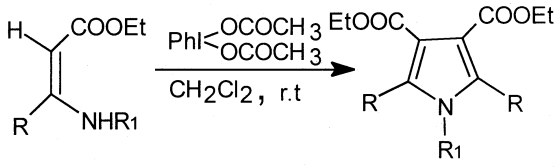
by using (diacetoxyiodo)benzene(DIB) gives 5,5′-bis(isopropylidene alkylmalonates). In continuing study of the applications of oxidative dimerization by using hypervalent organoiodine(III) reagents in organic synthesis, we examined the reaction of enamine-esters with (diacyltoxyiodo)benzene and observed the formation of highly substituted C_2-symmetric pyrrole derivatives via a tandem dimerization-cyclocondensation. Herein we wish to report our results.

At first, we took the reaction of enamine-esters **1a** with (diacetoxy iodo)benzene(DIB) as the sample into investigation (**Scheme 1**). The reaction was carried out in methylene chloride at room temperature for 8 hours. After work-up, 3,4-diethoxycarbonyl-1,2,5-trimethylpyrrole **2a** was obtained in 43% yield.

We found the significant improvement of the yield for the reaction and relatively short the reaction time were observed when [bis-(trifluoroacetoxy)iodo]benzene (BTI) was used instead of DIB, as shown in **Table 1**.



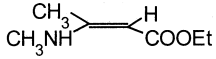
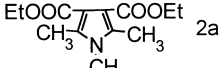
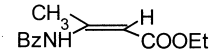
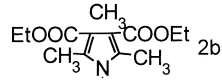
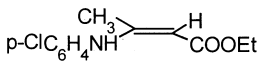
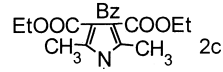
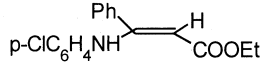
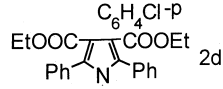
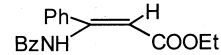
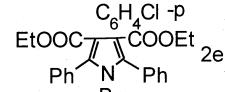
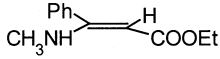
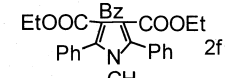
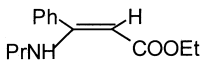
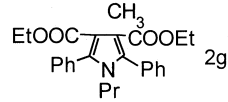
Scheme 1.

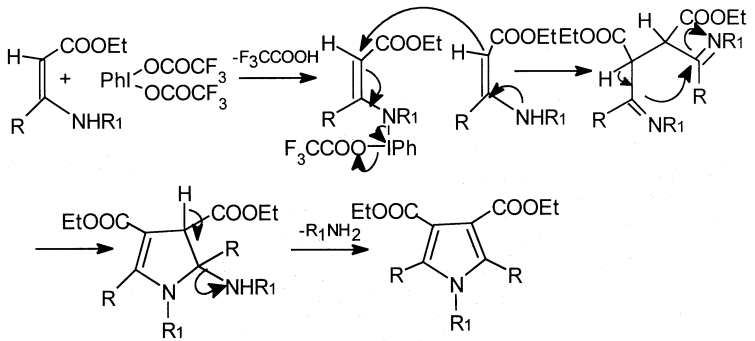
In order to examine the scope of this reaction, a number of enamine-esters were examined. All the enamine-esters in **Table 1** were smoothly converted to corresponding pyrrole derivatives by treatment with DIB or BTI. The products were characterized by Mp., ^{1}H NMR, IR and MS-spectra.

A plausible mechanism of the reaction is analogous to the oxidation of β-aminocinnamates with lead tetraacetate(LTA)[8] and is shown in **Scheme 2**.

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.[9] The literature methods of preparing highly substituted C_2-symmetric pyrroles include the oxidation of enamines with LTA,[8,10,11,12] or the anodic dimerization of enamines,[13] or the 1,3-dipolar cycloaddition of azalactones to alkynes,[14,15] or the reaction of 2,5-disubstituted pyrroles with dimethyl acetylenedicarboxylate[16] or the Knorr reaction of α-aminoketones with a ketone having a reactive methylene group alpha to the carbonyl group, and the Hantzsch reaction of

Table 1. Synthesis of 1,2,3,4,5-Pentasubstituted Pyrroles 2a~g

Enamine-Esters	Reaction Time DIB(hrs)	BTI(hrs)	Products	Yield,% DIB	BTI	Lit[8]
 1a	6.5	2	 2a	43	87	41
 1b	3	0.5	 2b	37	63	34
 1c	5	1	 2c	31	56	20
 1d	6	1.5	 2d	26	48	11
 1e	4.5	0.5	 2e	46	55	12
 1f	7	2	 2f	48	54	14
 1g	6	3.5	 2g	43	61	18



Scheme 2.

α-holoketones with enamines.[17] However, these methods have some disadvantages such as using toxic reagents, uncommon starting material, harsh reaction conditions and poor yields. Present reaction represent an effective method for the synthesis of highly substituted C_2-symmetric pyrroles.

In conclusion, A tandem dimerization-cyclocondensation of enamine-esters with BTI provides an effective method for synthesis of highly substituted pyrroles. Further study for the reaction of other enamines with BTI is under way and will be reported in due course.

EXPERIMENTAL

Uncorrected melting points were determined with a micro melting point apparatus. ^{1}H NMR spectra were measured on a AVANCE DMX500 spectrometer using TMS as an internal standard. IR spectra were recorded with a Perkin Elmer 683 spectrometer. Mass spectra were obtained by electron impact at 70 eV (HP5989B). Preparation of substituted pyrroles **2a**∼**2g**; General procedure:

To a solution of **1a** (0.143 g, 1 mmol) in CH_2Cl_2 (20 ml) was added BTI (0.430 g, 1 mmol). The mixture was stirred for 2 hours at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel plate by using a mixture of cyclohexane-ethyl acetate (4:1) as eluent to afford 3,4-diethoxycarbonyl-1,2,5-trimethyl-pyrrole **2a** as a pale yellow solid, 0.11 g, yield: 87%. Mp. 71∼73°C (lit.[8] 71∼72°C); IR(KBr): 1715 cm^{-1}(vs), 1550 cm^{-1}(s), 1446 cm^{-1}(s), 1420 cm^{-1}(s); ^{1}H NMR($CDCl_3$): δ 4.24∼4.30 (4H, q, J = 7 Hz), 3.39 (3H, s), 2.35 (6H, s), 1.25∼1.34 (6H, t, J = 7 Hz); Ms: 253 (M^+, 8.92), 208 (13.65), 180 (14.64), 146 (10.93), 104 (29.27), 43 (100).

1-benzyl-3,4-diethoxycarbonyl-2,5-dimethylpyrrole (2b): Mp. 61∼63°C (lit.[8] 61.5∼63°C); IR(KBr): 1750 cm^{-1}(vs), 1530 cm^{-1}(m), 1440∼1470 cm^{-1}(s), 1390 cm^{-1}(s); ^{1}H NMR($CDCl_3$): δ 6.91∼7.36 (5H, m), 5.03 (2H, s), 4.21∼4.34 (4H, q, J = 7 Hz), 2.32 (6H, s), 1.36(6H, t, J =7 Hz).

1-(p-chlorophenyl)-3,4-diethoxycarbonyl-2,5-dimethylpyrrole (2c): Mp. 98∼100°C (lit.[8] 98∼99.5°C); IR(KBr): 1740 cm^{-1}(vs), 1565 cm^{-1}(s), 1445 cm^{-1}(s), 1400 cm^{-1}(w); ^{1}H NMR($CDCl_3$): δ 7.31∼7.34 (2H, m), 7.02∼7.04 (2H, m), 4.22∼4.23 (4H, q, J = 7 Hz), 2.10 (6H, s), 1.30∼1.34(6H, t, J = 7 Hz).

1-(p-chlorophenyl)-3,4-diethoxycarbonyl-2,5-diphenylpyrrole (2d): Mp. 174∼176°C (lit.[8] 175∼177°C); IR(KBr): 1740 cm^{-1}(vs), 1560 cm^{-1}(s), 1440 cm^{-1}(s), 1395 cm^{-1}(w); ^{1}H NMR(CCl_4, 60 MHz): δ 7.13 (10H, s), 6.90∼7.05 (2H, m), 6.65∼6.85 (2H, m), 4.02∼4.18 (4H, q, J = 7 Hz), 1.05∼1.20 (6H, t, J = 7 Hz).

1-benzyl-3,4-diethoxycarbonyl-2,5-diphenylpyrrole (2e): Mp. 120∼122°C (lit.[8] 120∼121.5°C); IR(KBr): 1745 cm^{-1}(vs), 1550 cm^{-1}(m), 1450 cm^{-1}(s), 1415 cm^{-1}(s); ^{1}H NMR(CCl_4, 60 MHz): δ 6.60∼7.75 (15H, m), 4.87(2H, s), 4.02∼4.20 (4H, q, J = 7 Hz), 1.00∼1.10 (6H, t, J = 7 Hz).

3,4-diethoxycarbonyl-2,5-diphenyl-1-methylpyrrole(2f): Mp. 125∼127°C (lit.[8] 125∼126.5°C); IR(KBr): 1760 cm^{-1}(vs), 1560 cm^{-1}(s), 1500 cm^{-1}(w), 1425 cm^{-1}(s); ^{1}H NMR(CCl_4, 60 MHz): δ 7.23∼7.76(10H, m), 4.10∼4.38(4H, q, J = 7 Hz), 3.36(3H, s), 1.00∼1.30(6H, t, J = 7 Hz).

3,4-diethoxycarbonyl-2,5-diphenyl-1-propylpyrrole (2g): Mp. 89∼91°C (lit.[8] 91.5∼93°C); IR(KBr): 1765 cm^{-1}(vs), 1550 cm^{-1}(s), 1450∼1470 cm^{-1}(s), 1390 cm^{-1}(s); ^{1}H NMR(CCl_4, 60 MHz): δ 7.16∼7.75 (10H, m), 3.95∼4.20 (4H, q, J = 7 Hz), 3.62∼3.74 (2H, t, J = 6 Hz), 2.20∼2.32 (2H, m), 1.05∼1.25 (6H, t, J = 7 Hz), 0.40∼0.55 (3H, t, J = 6 Hz).

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