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Three-component direct synthesis of substituted pyrroles from easily accessible chemical moieties using hypervalent iodine reagent

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ABSTRACT

A novel and simple three-component system has been developed to synthesize substituted pyrroles from corresponding amines and nitrostyrenes using (diacetoxyiodo)benzene at reflux temperature in ethanol. The good to excellent yields were obtained with different types of functional groups.

Pyrroles are an important class of heterocyclic compounds found in many natural products and pharmaceuticals.[1] Pyrrole and its derivatives play a major role in drug discovery exhibiting various biological activities such as antibacterial,[2] fungicidal,[3] anti-tuberculosis,[2] antidiabetic,[4] anti-inflammatory,[5] antiviral,[6] and anticancer[7]. Some examples of therapeutically active pyrroles are shown in Figure 1.

Although several useful strategies[8] are known for the construction of the pyrrole moiety, the most-often used protocols are Pall–Knorr (the cyclocondensation of primary amines with 1,4-diketones),[9] Knorr (condensation of α-aminoketone and active methylene group of ketones),[10] and Hantzsch[11] reactions (reaction of α-haloketones and β-enaminones). Many of these reactions have various drawbacks such as harsh reaction conditions, availability of the starting materials, regiospecificity, prolonged reaction time, functional group compatibility, and multistep synthetic operations. New efficient protocols such as multi-component reactions (MCR) have surmounted many of these limitations.[12] Advantages of MCRs over classical stepwise methods are high atom-economy, no need of isolation, and purification of intermediates thereby minimizing cost, labor, time, and waste. Previously multi-component reactions (MCR) are reported for the synthesis of pyrroles, which were four-component coupling reaction of 1,3-dicarbonyl compounds, amines, aldehydes, and nitroalkanes in the presence of $FeCl_3$ and $NiCl_2{\cdot}6H_2O$ as well as five-component reaction by using $PdCl_2(PPh_3)_2$.[13] All these methods give lower yield as well as required longer reaction time. It also involved the use of a metal, the removal of which often requires cumbersome work-up and purifications. Thus, simple and efficient protocols for synthesis of substituted pyrroles from readily available chemical moieties using stable, non-toxic, easy to handle, and inexpensive reagents are highly desirable. Hypervalent iodine (III) reagents are useful alternatives to traditional metal reagents due to their mild reactivity, safety, low toxicity, and easy handling etc.[14] Our lab is working on versatile methodologies using different hypervalent iodine reagents.[15] We now wish to report a novel three-component direct synthesis of substituted pyrroles from easily available chemical moieties using (diacetoxyiodo)benzene (DIB).

Aniline and nitrostyrene were chosen as the model substrates for optimization studies and treated with acetylacetone in the presence of (diacetoxyiodo)benzene in refluxing ethanol. The reaction afforded desired 1-(2-methyl-1,4-diphenyl-1*H*-pyrrol-3-yl)ethanone in 4 h (Scheme 1). No significant increase in the yield was observed when more than 1 equiv of DIB was used. Different combinations of aniline, nitrostyrene, and acetyl acetone were examined and finally optimal yield was observed with 2, 1, and 1.2 equiv, respectively. The effect of the temperature on the model reaction was studied and it was observed that the reflux temperature produced the best results. A variety of solvents such as methanol, ethanol, dichloromethane, THF, and toluene were tested. Ethanol was the most suitable solvent for the reaction.

Further, the scope of the reaction was investigated with a variety of amines and nitrostyrenes under the optimized condition.[16] The results are shown in Table 1. The method was versatile as anilines and benzylamines and even cyclohexylamine afforded good yields. It is particularly noteworthy that benzylamines (entries

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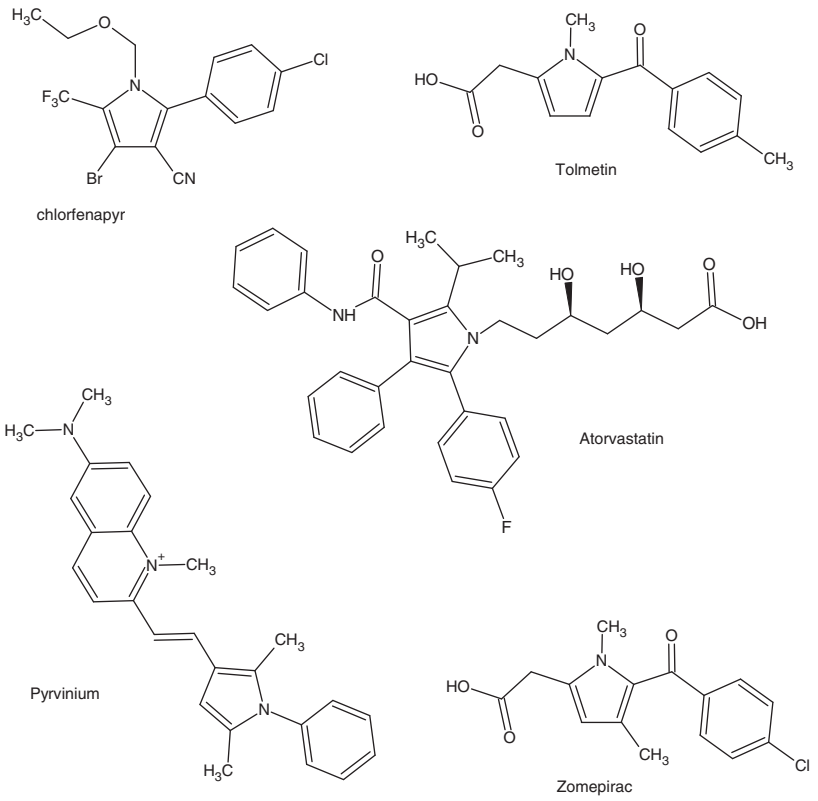
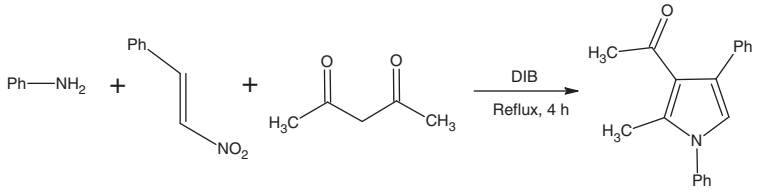
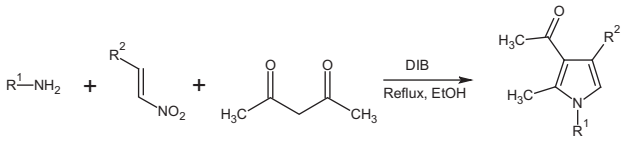


Figure 1. Therapeutically active pyrroles.



Scheme 1. Synthesis of pyrrole from aniline and nitrostyrene using DIB at reflux temperature.

Table 1
Substrate scope[a,b]



Entry	R^1	R^2	Time (h)	% Yield[c]
1	Ph	Ph	4	74
2	Ph	*o*-BrC_6H_4	4	72
3	$PhCH_2$	Ph	3	85
4	$PhCH_2$	*p*-FC_6H_4	3	82
5	$PhCH_2$	*p*-$NO_2C_6H_4$	3	78
6	*p*-$OMeC_6H_4$	Ph	4	78
7	*p*-$OMeC_6H_4$	*p*-ClC_6H_4	4	75
8	*p*-$OMeC_6H_4$	*p*-$OMeC_6H_4$	4	74
9	*p*-ClC_6H_4	*p*-MeC_6H_4	4	70
10	*p*-BrC_6H_4	*p*-ClC_6H_4	4	70
11	*p*-MeC_6H_4	*p*-$OMeC_6H_4$	4	74
12	Cyclohexyl	*p*-ClC_6H_4	4	76

[a] All reactions of amines (2 equiv) and nitrostyrenes (1 equiv) with acetylacetone (1.2 equiv) were performed at reflux temperature using DIB (1 equiv) in ethanol.
[b] All reported products were identified by comparison of their melting point, IR, NMR spectra, and MS with literature data.
[c] Isolated yields after column chromatography.

3–5) reacted very smoothly and in excellent yields (78–85%). The substitutions on nitrostyrenes had no effect on yields of the corresponding products and the electron-donating as well as the electron-withdrawing groups produced good yields.

In conclusion, a novel, facile, and highly efficient three-component method has been discovered to synthesize substituted pyrroles from easily available chemical moieties using (diacetoxyiodo) benzene under metal-free conditions. The conditions are general and applicable to variety of amine and nitrostyrene derivatives, and excellent yields are obtained with different types of functional groups.

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16. *General procedure for the synthesis of 1-(2-methyl-1,4-diphenyl-1H-pyrrol-3-yl)ethanone* (Table 1, entry 1): The mixture of aniline (0.186 g, 2 mmol), nitrostyrene (0.149 g, 1 mmol), and acetylacetone (0.120 g, 1.2 mmol) in ethanol (10 mL) was stirred vigorously at rt for 10 min. DIB (0.322 g, 1 mmol) was added slowly, then the mixture was refluxed for 4 h. After the completion of the reaction (monitored by TLC) the solvent was evaporated under the vacuum. The resulted residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was separated and washed successively with 10% sodium bicarbonate (2 × 10 mL), water (2 × 15 mL), and finally dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give crude product. The pure product (74%) was obtained as white solid after silica gel column chromatography (2% EtOAc–Hexane).
mp 104–106 °C (lit.[13b] mp 105 °C); IR (neat): 3059, 3029, 1651, 1503, 1402, 1223 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.42 (s, 3H), 6.67 (s, 1H), 7.31–7.43 (m, 7H), 7.45–7.50 (m, 3H). HRMS: *m*/*z* calcd for $C_{19}H_{18}NO$ (M+1): 276.1388; found 276.1390.
1-(1-Benzyl-2-methyl-4-phenyl-1H-pyrrol-3-yl)ethanone (Table 1, entry 3): Brown solid; mp 50–53 °C (lit.[13d] mp 54 °C); IR (neat): 3582, 3020, 2932, 1890, 1647, 1559, 1456, 1355, 1215, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.40 (s, 3H), 5.03 (s, 2H), 6.55 (s, 1H), 7.10 (d, *J* = 7.0 Hz, 2H), 7.28–7.60 (m, 8H); HRMS: *m*/*z* calcd for $C_{20}H_{19}NO$ (M+1): 290.1467; found 290.1470.
1-[1-(4-methoxyphenyl)-2-methyl-4-phenyl-1H-pyrrol-3-yl]ethanone (Table 1, entry 6): Yellowish solid; mp 89–91 °C (lit.[13b] mp 90 °C); IR (neat): 3010, 2933, 1645, 1512, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.08 (s, 3H), 2.37 (s, 3H), 3.86 (s, 3H), 6.62 (s, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 8.9 Hz, 2H), 7.30–7.35 (m, 1H), 7.36–7.38 (m, 4H). HRMS: *m*/*z* calcd for $C_{20}H_{20}NO_2$ (M+1): 306.1494; found 306.1495.
1-[4-(4-Chlorophenyl)-1-cyclohexyl-2-methyl-1H-pyrrol-3-yl]-ethanone (Table 1, entry 12): White solid; mp 99–101 °C (lit.[13b] mp 100 °C); IR (neat) 2930, 2855, 1646, 1506, 1415 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.26 (m, 2H), 1.39–1.48 (m, 2H), 1.57–1.65 (m, 2H), 1.78 (d, *J* = 13 Hz, 2H), 1.92 (d, *J* = 13 Hz, 2H), 2.00 (s, 3H), 2.46 (s, 3H), 3.91 (t, *J* = 3.7 Hz, 1H), 6.56 (s, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H); HRMS: *m*/*z* calcd for $C_{19}H_{23}ClNO$ (M+1): 316.1468; found 316.1466.