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Synthesis of Polysubstituted Pyrroles in Aqueous Medium Directly From Nitro Compounds[1]

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Abstract—A novel approach for the synthesis of polysubstituted pyrroles has been followed through multicomponent reaction of nitro compounds, phenacyl bromide or its derivatives and dialkyl acetylene dicarboxylates using indium in dilute aqueous HCl at room temperature. The products are formed in high yields (75–87%) in 10–16 h.

Keywords: polysubstituted pyrrole, three component reaction, In/HCl, nitro compounds

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INTRODUCTION

Pyrroles are valuable and important heterocyclic compounds. They were found in different natural bioactive molecules [1], including drugs like atrovastin calcium, and pharmaceutical agents [2]. They are also versatile synthetic intermediates in organic synthesis [3]. Some of the pyrrole derivatives are widely applied in material science [4]. A number of procedures have been developed for the synthesis of pyrrole-containing new heterocyclic molecules because of their biological activity and synthetic utility. One of the simplest syntheses is the Paal-Knorr synthesis which involves condensation of 1,4-dicarbonyl compounds with primary amines in the presence of acids/metal catalysts [5]. Later, high atom economy multicomponent protocols have been developed for the synthesis of pyrroles [6]. However, many of the developed methods suffer from various drawbacks such as harsh reaction conditions, tedious experimental procedure, unsatisfactory yields and long reaction time [7]. Herein, we describe an efficient new multicomponent reaction for the synthesis of the polysubstituted pyrroles starting from nitro compounds in aqueous medium.

Polysubstituted pyrroles were directly obtained by the multicomponent reaction of nitro compounds, phenacyl bromide or its derivatives and dialkyl acetylenedicarboxylates by using indium metal powder in dilute aqueous HCl at room temperature (Scheme 1).

[1] The text was submitted by the authors in English.

RESULTS AND DISCUSSION

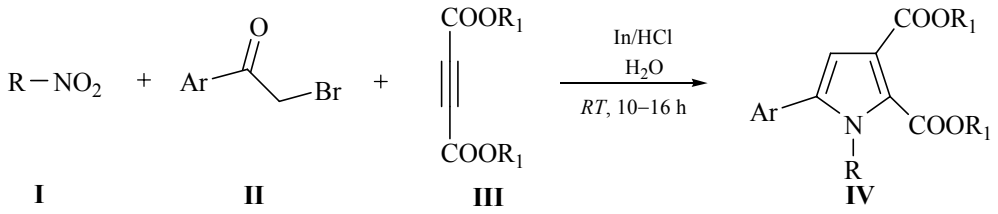
Initially, the reaction of nitro compounds, phenacyl bromide, and dialkyl acetylene dicarboxylate was conducted using different metals such as Fe, Zn, Sn, and In in aqueous HCl at room temperature (Table 1). Considering the reaction time and the yield of the prepared pyrrole, indium was found to be most effective. Subsequently, it was applied to prepare a series of pyrroles from phenacyl bromide or its derivatives, dialkyl acetylene dicarboxylates and different nitro compounds (Table 2). The reaction was complete within 10–16 h and the products were formed in good yields (75–87%). The derivatives of phenacyl bromide containing electron withdrawing groups also afforded the products smoothly. Dimethyl as well as diethyl acetylene dicarboxylate were applied to prepare

Table 1. Synthesis of polysubstituted pyrroles using different metals[a]

Run no.	Metal[a]	Time, h	Yield, %[b]
1	Zn	24	59
2	Sn	24	61
3	Fe	24	65
4	In	10	87

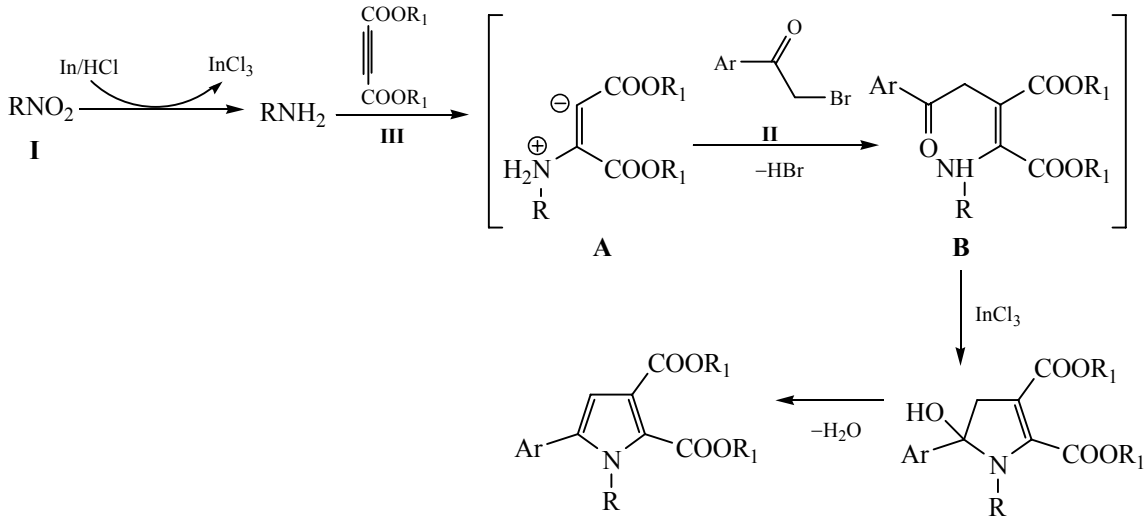
[a] Reaction conditions: nitrobenzene (1 mmol), 1 N aqueous HCl (1 mL), metal (2 mmol), dimethyl acetylene dicarboxylate (1 mmol), phenacyl bromide (1.1 mmol), and 5 mL of water at room temperature. [b] Yields of isolated pure compound after column chromatography.

Scheme 1.



I: R = Aryl, Alkyl, **II**: Ar = Phenyl, **III, IV**: R^1 = Me, Et.

Scheme 2.



the pyrrole derivatives. The structure of the products was established by IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

The present synthesis of polysubstituted pyrroles consists of three steps in one pot. Initially, the nitro compounds **I** on treatment with In/HCl are reduced to amines, which then react with dialkyl acetylene dicarboxylate **III** to form zwitter-ion **A** [8] and the reaction of the latter with phenacyl bromide **II** to produce intermediate **B**. Cyclisation of **B** followed by aromatization afforded the polysubstituted pyrroles **IV** (Scheme 2).

EXPERIMENTAL

TLC: Precoated silica-gel plates (60 F_{254}, 0.2-mm layer, E. Merck). Column chromatography: Silica gel, 60–120 mesh. mp: Fischer-Johns apparatus; uncorrected. IR Spectra: Thermo Nicolet Nexus 670 FT-IR spectrophotometer; in KBr. ^{1}H and ^{13}C NMR spectra: Bruker Avance 300 and Innova 75 MHz instrument, in $CDCl_3$; δ, ppm; internal standard – Me_4Si, *J*,n Hz. ESI-MS: Finnigan MAT 1020 mass spectrometer.

General procedure. To a mixture of nitro compound **I** (1.0 mmol) were added indium metal powder (325 mesh, 2 mmol), 1 N aqueous HCl (1 mL), dialkyl acetylene dicarboxylate (1.0 mmol). After 5 min, phenacyl bromide or its derivative (1.1 mmol) was added. The reaction mixture was stirred at room temperature for 10–16 h and monitored by TLC. After completion, the reaction mixture was washed with saturated $NaHCO_3$ solution (3 × 5 mL) and water (3 × 5 mL) and extracted with EtOAc (3 × 5 mL). The extract was concentrated and the residue was subjected to column chromatography (silica gel, hexane/EtOAc) to obtain pure product.

The IR, ^{1}H and ^{13}C NMR and mass spectra and analytical data of the products are given below.

Dimethyl 1,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (IVa). IR spectrum, ν, cm^{-1}: 1727, 1498, 1447, 1255. ^{1}H NMR spectrum: δ, ppm: 7.52–7.21 m (10H), 6.98 s

Table 2. Synthesis of polysubstituted pyrroles using indium metal in aqueous HCl at room temperature

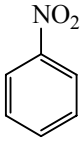
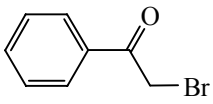
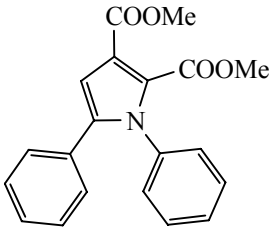
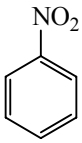
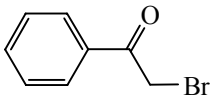
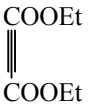
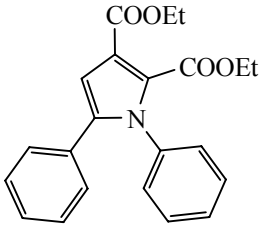
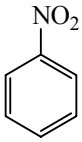
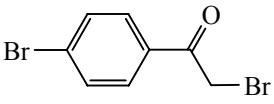
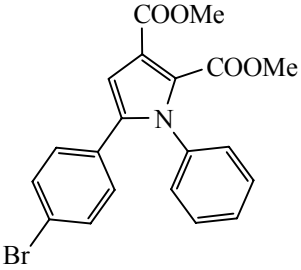
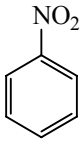
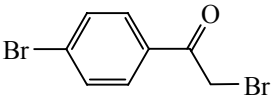
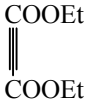
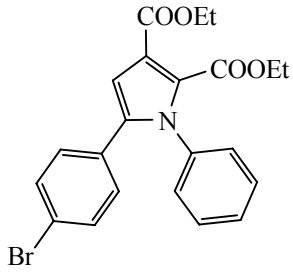
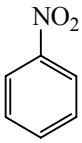
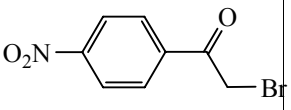
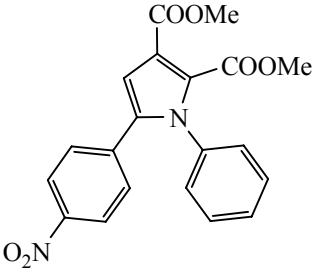
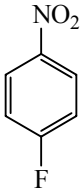
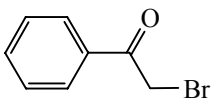
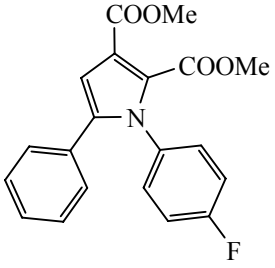
Comp. no.	Nitro compounds	Phenacyl bromide	Dialkyl acetylene dicarboxylate	Polysubstituted pyrrole	Time, h	Isolated yield, %
IVa					10	87
IVb					10	86
IVc					13	85
IVd					13	84
IVe					16	75
IVf					12	81

Table 2. (Contd.)

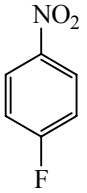
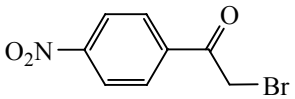
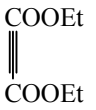
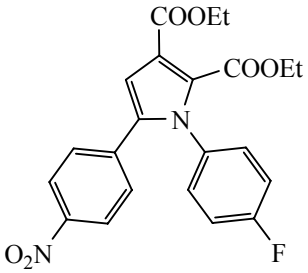
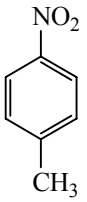
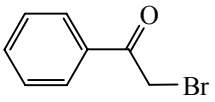
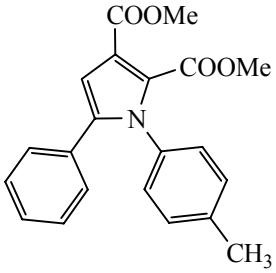
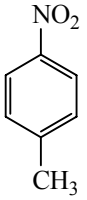
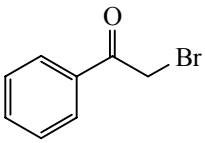
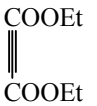
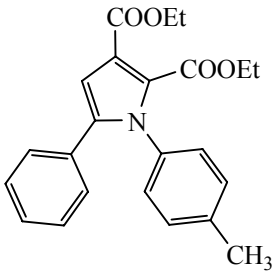
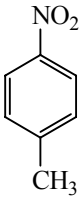
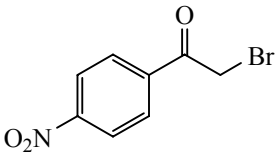
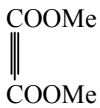
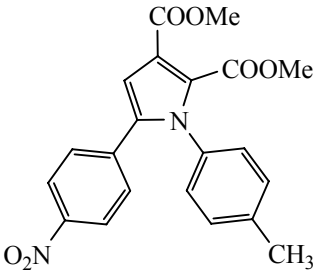
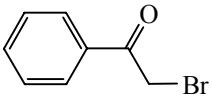
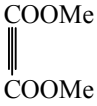
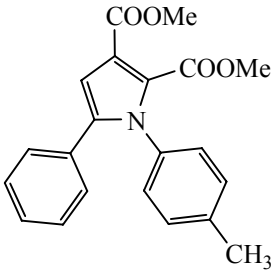
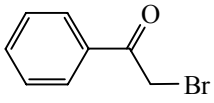
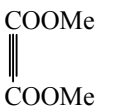
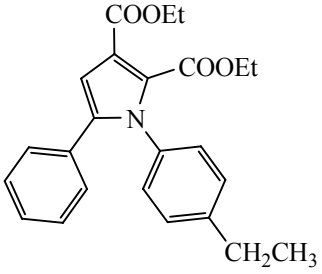
Comp. no.	Nitro compounds	Phenacyl bromide	Dialkyl acetylene dicarboxylate	Polysubstituted pyrrole	Time, h	Isolated yield, %
IVg					12	75
IVh					12	82
IVi					12	82
IVj					16	80
IVk	$H_3C–NO_2$				10	85

Table 2. (Contd.)

Comp. no.	Nitro compounds	Phenacyl bromide	Dialkyl acetylene dicarboxylate	Polysubstituted pyrrole	Time, h	Isolated yield, %
IVl	$H_3CH_2C–NO_2$				10	83

(1H), 3.81 s (3H); 3.69 s (3H). ^{13}C NMR spectrum: δ, ppm: 167.1, 160.8, 139.6, 133.3, 128.8, 128.2, 127.9, 127.0, 126.1, 126.0 125.1, 123.2, 122.4, 117.1, 52.4, 52.0. ESI-MS: *m/z* 336 $[M + H]^+$; Calculated, %: C 71.64; H 5.08; N 4.18. $C_{20}H_{17}NO_4$. Found, %: C 71.58; H 5.12; N 4.22.

Diethyl 1,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (IVb). IR spectrum, ν, cm^{-1}: 1720, 1598, 1502, 1413, 1240. ^{1}H NMR spectrum, δ, ppm: 7.49–7.20 m (10H), 6.93 s (1H), 4.28 q (2H, *J* = 7.0 Hz), 4.16 q (2H, *J* = 7.0 Hz), 1.24 t (3H, *J* = 7.0 Hz), 1.12 t (3H, *J* = 7.0 Hz). ^{13}C NMR spectrum, δ, ppm: 166.4, 160.1, 146.5, 140.0, 133.1, 128.8, 128.2, 127.9, 127.1, 126.4, 125.9, 124.4, 123.2, 122.2, 61.5, 61.0, 14.0, 13.9. ESI-MS: *m/z* 364 $[M + H]^+$; Calculated, %: $C_{22}H_{21}NO_4$: C 72.73; H 5.79; N 3.86%. Found, %: C 72.85; H 5.72; N 3.82%.

Dimethyl 5-(4-bromophenyl)-1-phenyl-1*H*-pyrrole-2,3-dicarboxylate (IVc). IR spectrum, ν, cm^{-1}: 1716, 1450, 1412. ^{1}H NMR spectrum, δ, ppm: 7.52–7.41 m (5H), 7.38–7.21 m (4H), 6.92 s (1H), 3.81 s (3H), 3.69 s (3H). ^{13}C NMR spectrum, δ, ppm: 166.6, 160.4, 140.0, 139.2, 132.2, 131.1, 130.8, 129.0, 128.5, 126.0, 125.2, 124.2, 123.5, 120.2, 52.2, 52.0. ESI-MS: *m/z* 414, 416 $[M + H]^+$; Calculated, %: C 57.97; H 3.86. $C_{20}H_{16}BrNO_4$. Found, %: C 57.91; H 3.82; N 3.41.

Diethyl 5-(4-bromophenyl)-1-phenyl-1*H*-pyrrole-2,3-dicarboxylate (IVd). IR spectrum, ν, cm^{-1}: 1716, 1452, 1403. ^{1}H NMR spectrum, δ, ppm: 7.52–7.38 m (6H), 7.40–7.25 m (3H), 6.91 s (1H), 4.25 q (2H, *J* = 7.0 Hz), 4.12 q (2H, *J* = 7.0 Hz), 1.22 t (3H, *J* = 7.0 Hz), 1.11 t (3H, *J* = 7.0 Hz). ^{13}C NMR spectrum, δ, ppm: 166.1, 160.2, 141.3, 139.2, 132.1, 131.8, 129.2, 129.0, 128.2, 126.1, 125.6, 124.6, 123.4, 121.0, 61.2, 61.0, 13.9, 13.2. ESI-MS: *m/z* 444, 442 $[M + H]^+$; Calculated, %: C 60.00; H 4.55; N 3.18. $C_{22}H_{20}BrNO_4$. Found, %: C 60.21; H 4.62; N 3.12.

Dimethyl 5-(4-nitrophenyl)-1-phenyl-1*H*-pyrrole-2,3-dicarboxylate (IVe). IR spectrum, ν, cm^{-1}: 1712, 1600, 1511, 1443. ^{1}H NMR spectrum, δ, ppm: 8.22 d (2H, *J* = 8.0 Hz), 7.58 d (2H, *J* = 8.0 Hz); 7.51–7.41 s (3H); 7.39–7.32 m (2H); 7.02 s (1H); 3.82 s (3H); 3.71 s (3H). ^{13}C NMR spectrum, δ, ppm: 166.2, 160.1, 146.5, 139.9, 138.2, 129.6, 129.0, 128.2, 126.1, 126.0, 125.2, 123.8, 122.0, 120.5, 52.1, 52.0; ESI-MS: *m/z* 381 $[M + H]^+$. Calculated, %: C 63.17, H 4.21, N 7.37. $C_{20}H_{16}N_2O_6$. Found, %: C 63.23, H 4.26, N 7.31.

Dimethyl 1-(4-fluorophenyl)-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (IVf). IR spectrum, ν, cm^{-1}: 1714, 1451, 1415. ^{1}H NMR spectrum, δ, ppm: 7.50–7.29 m (7H), 7.12 t (2H, *J* = 7.0 Hz), 6.98 s (1H), 3.83 s (3H), 3.71 s (3H). ^{13}C NMR spectrum, δ, ppm: 166.0 d (*J* = 280 Hz), 161.1, 160.1, 146.9, 141.0, 138.3, 132.5, 129.2, 129.0, 127.8, 127.2, 126.7, 125.5, 121.2, 115.2, 115.0 d (*J* = 30 Hz), 52.2, 51.7. ESI-MS: *m/z* 354 $[M + H]^+$; Calculated, %: C 67.99; H 4.53; N 3.97. $C_{22}H_{16}FNO_4$. Found, %: C 67.89; H 4.56; N 3.91.

Diethyl 1-(4-fluorophenyl)-5-(4-nitrophenyl)-1*H*-pyrrole-2,3-dicarboxylate (IVg). IR spectrum, ν, cm^{-1}: 1721, 1600, 1515. ^{1}H NMR spectrum, δ, ppm: 8.22 d (2H, *J* = 8.0 Hz), 7.59 d (2H, *J* = 8.0 Hz), 7.35 t (2H, *J* = 8.0 Hz), 7.12 t (2H, *J* = 8.0 Hz), 7.00 s (1H), 4.30 q (2H, *J* = 7.0 Hz), 4.15 q (2H, *J* = 7.0 Hz), 1.20 t (3H, *J* = 7.0 Hz), 0.88 t (3H, *J* = 7.0 Hz); ^{13}C NMR spectrum, δ, ppm: 168.1 d (*J* = 280 Hz), 164.9, 161.4, 147.0, 140.1, 135.8, 130.9, 129.1, 129.0, 128.9, 125.1, 123.5, 122.2, 121.1, 115.6, 115.0 d (*J* = 30 Hz), 61.2, 60.8, 13.0, 12.9. ESI-MS: *m/z* 449 $[M + Na]^+$; Calculated, %: C 72.21; H 5.44; N 4.01. $C_{21}H_{19}NO_4$. Found, %: C 72.28; H 5.40; N 4.07.

Dimethyl 5-phenyl-1-*p*-tolyl-1*H*-pyrrole-2,3-dicarboxylate (IVh). IR spectrum, ν, cm^{-1}: 1720, 1659, 1451, 1415. ^1H NMR spectrum, δ, ppm: 7.43–7.31 m (3H), 7.30–7.20 m (4H), 7.19–7.02 m (2H), 6.95 s (1H), 3.81 s (3H), 3.70 s (3H), 2.41 s (3H); ^{13}C NMR spectrum, δ, ppm: 167.1, 161.1, 142.1, 138.7, 136.3, 133.3, 131.2, 129.2, 128.6, 128.4, 128.2, 128.0, 127.2, 125.6, 51.8, 51.2, 22.0. ESI-MS: *m/z* 350 $[M + H]^+$; Calculated, %: C 72.21, H 5.44; N 4.01. $C_{21}H_{19}NO_4$. Found, %: C 72.28; H 5.40; N 4.07.

Diethyl 5-phenyl-1-*p*-tolyl-1*H*-pyrrole-2,3-dicarboxylate (IVi). IR spectrum, ν, cm^{-1}: 1720, 1601, 1519, 1460. ^1H NMR spectrum, δ, ppm: 7.42 d (2H, J = 8.0 Hz), 7.33 t (2H, J = 8.0 Hz), 7.30–7.21 m (5H), 6.94 s (1H), 4.30 q (2H, J = 7.0 Hz), 4.15 t (2H, J = 7.0 Hz), 2.41 s (3H), 1.31 t (3H, J = 7.0 Hz), 1.18 t (3H, J = 8.0 Hz). ^{13}C NMR spectrum, δ, ppm: 166.7, 160.1, 138.9, 137.1, 133.8, 131.1, 129.8, 128.5, 127.8, 127.0, 126.1, 126.0, 124.6, 121.4, 61.2, 61.0, 21.0, 13.6, 13.5. ESI-MS: *m/z* 378 $[M + H]^+$; Calculated, %: C 73.21; H 6.10; N 3.71. $C_{23}H_{23}NO_4$. Found, %: C 73.29; H 6.15; N 3.78.

Dimethyl 5-(4-nitrophenyl)-1-*p*-tolyl-1*H*-pyrrole-2,3-dicarboxylate (IVj). IR spectrum, ν, cm^{-1}: 1731, 1556, 1492. ^1H NMR spectrum, δ, ppm: 8.21 d (2H, J = 8.0 Hz), 7.58 d (2H, J = 8.0 Hz), 7.39–7.03 m (4H), 7.01 s (1H), 3.82 s (3H), 3.60 s (3H), 2.41 s (3H). ^{13}C NMR spectrum, δ, ppm: 166.1, 160.2, 146.4, 140.0, 139.0, 136.4, 130.1, 129.9, 128.3, 128.1, 127.1, 125.1, 123.2, 123.1, 52.1, 52.0, 22.2. ESI-MS: *m/z* 395 $[M + H]^+$. Calculated, %: C 63.96, H 4.57, N 7.11. $C_{21}H_{18}N_2O_6$. Found, %: C 63.87; H 4.57; N 7.54.

Dimethyl 1-methyl-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (IVk). IR spectrum, ν, cm^{-1}: 1710, 1596, 1447. ^1H NMR spectrum, δ, ppm: 7.36–7.15 m (5H), 6.81 s (1H), 3.90 s (3H), 3.78 s (3H), 3.72 s (3H). ^{13}C NMR spectrum, δ, ppm: 167.1, 160.4, 133.9, 133.2, 128.5, 126.9, 126.5, 125.8, 123.2, 121.1, 51.6, 51.0, 29.1. ESI-MS: *m/z* 274 $[M + H]^+$. Calculated, %: C 65.93; H 5.50; N 5.13 %. $C_{15}H_{15}NO_4$. Found, %: C 65.86; H 5.54; N 5.07 %.

Diethyl 1-ethyl-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (IVl). IR spectrum, ν, cm^{-1}: 1721, 1607, 1462. ^1H NMR spectrum, δ, ppm: 7.41–7.12 m (5H), 6.87 s (1H), 4.40–4.11 m (6H), 1.42 t (3H, J = 7.0 Hz), 1.31 t (3H, J = 7.0 Hz), 1.22 t (3H, J = 7.0 Hz). ^{13}C NMR spectrum, δ, ppm: 167.2, 159.8, 133.5, 128.0, 127.2, 126.4, 123.9, 123.2, 122.0, 120.1, 61.0, 60.3, 44.5, 17.0, 13.7 (2Me). ESI-MS: *m/z* 316 $[M + H]^+$; Calculated, %: C 68.57; H 6.67; N 4.44. $C_{18}H_{21}NO_4$. Found, %: C 68.69; H 6.61; N 4.40.

CONCLUSIONS

We have developed a novel efficient method for the one pot synthesis of polysubstituted pyrroles involving the reaction of nitro compounds, phenacyl bromide and dialkyl acetylene dicarboxylate with indium metal in dilute aqueous HCl at room temperature. The direct application of nitro compounds, reaction in water, mild experimental conditions, smooth conversion, and impressive yields are the advantages of the present method.

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