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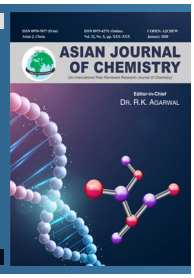

$SnCl_2$ Catalyzed Direct Synthesis of Pyrroles under Aqueous Conditions

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Synthetic substituted pyrroles are related with interesting biological activities, yet they remain inadequately explored within drug discovery. Late years have seen a growing interest in synthetic approaches that can provide access to structurally novel pyrroles so that the biological usefulness of this compound class can be more fully investigated. Herein, an efficient and versatile practical protocol for the pyrroles using stannous(II) chloride dihydrate as catalyst is described under aqueous conditions at 55 ºC in high yields. Also, this method is applicable for the preparation of diversity and oriented pyrrole derivatives.

Keywords: Stannous(II) chloride, Pyrrole, Diversity synthesis, Hexane-2,5-dione, Aqueous medium.

INTRODUCTION

The pyrrole ring framework is a pervasive auxiliary theme found in countless organically dynamic common items [1-3], strong pharmaceutical mixes [4-6] and different sorts of practical materials [7-12]. They are additionally essential structure obstructs in the amalgamation of cyclic π-conjugated oligopyrrolic frameworks, *e.g.*, porphyrins of heme, the chlorins, bacteriochlorins, chlorophyll and different porphyrinoids. Porphyrins are a gathering of natural mixes of which many happen in nature and they are sweet-smelling. The comparison to other realized porphyrins is heme, the colour in red platelets (RBC) and is a cofactor of the protein hemoglobin. They are heterocyclic macrocycles made out of four adjusted pyrrole subunits interconnected at their α-carbon particles by means of methine spans (=CH). Substituted pyrroles displaying remarkable pharmacological properties such as antibacterial [13,14], antifungal [15], anti-inflammatory [16,17], antitumor [18], antioxidant [19], estrogen receptor β-selective ligands [20] and anti-HIV activities (*e.g.*, NB-2, NB-64) [21]. Consequently, the efficient assembly of this class of molecule is of considerable importance in organic synthesis.

The utmost importance of pyrrole and its analogues in medicinal chemistry motivated total scientific field to develop a number of elegant and useful approaches towards the construction and derivatization of pyrrole ring [22,23]. As of late, conjugate addition responses have been utilized for the combination of polysubstituted pyrroles [24]. These mixes can likewise be set up from change metal intermediates [25], Aza-Wittig responses [26], reductive couplings [27], Hantzsch response [28], which gives pyrroles from response of α-chloromethyl ketones with β-ketoesters and smelling salt. Knorr reaction [29], which gives pyrroles by the response between α-aminoketones got from α-haloketones, alkali, β-ketoesters and other multistep operations [30]. Despite these new advancements, Paal-Knorr response [31], stays one of the most appealing techniques for the blend of pyrroles. Several acid catalysts have been used in the Pall-Knorr reaction including H_2SO_4, P_2O_5, CH_3COOH and many more [32].

EXPERIMENTAL

All chemicals utilized were of analytical grade and used as received from Sigma-Aldrich. All reactions under standard conditions were checked by TLC (thinlayer chromatography) on silica gel F_{254} plates. Column chromatography was performed on silica gel (200-300 meshes) and the eluting petroleum ether's distillation range was 60-90 ºC. All solvents were dried under rotary evaporator. Unless otherwise noted, ^1H & ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AX500 MHz instruments. The chemical shifts are given in parts per million

(ppm) on the delta (δ) scale. Melting points were measured on a micro melting apparatus and are uncorrected.

Synthesis of compounds 2a-j

1-(2,4-Dichlorophenyl)-1*H*-pyrrole (2a): To a mixture of 2,4-dichloro nitrobenzene (1 g, 5.20 mmol) in H_2O (10 mL) was added $SnCl_2{\cdot}2H_2O$ (3.51 g, 15.62 mmol) at room temperature and heated to 55 ºC for 30 min. After completion of the reaction (monitored by TLC), basified the reaction mixture slowly with saturated aqueous $NaHCO_3$ at 0 °C and compound was extracted with ethyl acetate (2 × 30 mL). The combined organic phase was washed with brine (1 × 15 mL), dried over anhydrous Na_2SO_4, removed solvent *in vacuo* and the crude residue was purified by column chromatography on silica gel (ethylacetate:hexane, 2:8) to afford compound **2a** (0.93 g, 85 % yield) as white crystalline powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6. 25 (t, 2H, *J* = 2.26 Hz, pyrrole protons), 6.84 (t, 2H, *J* = 2.26 Hz, -pyrrole protons), 7.29-7.39 (m, 3H, Ar-H). MS (ESI): *m/z* 213 $(M+H)^+$, 214 (M+2).

1-(2,4-Difluorophenyl)-1*H*-pyrrole (2b): White solid, m.p.: 50-52 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27 (t, 2H, *J* = 2.26 Hz, -pyrrole protons), 6.85-7.01 (m, 4H, Ar-H), 7.28 (m, 1H, Ar-H). MS (EI): *m/z* (%) = 179 (M^+, 100 %).

Methyl 5-methoxy-4-(prop-2-ynloxy)-2-(1*H*-pyrrol-1-yl)benzoate (2c): White solid, m.p.: 94-96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (t, 1H, *J* = 2.26 Hz, 1H), 3.64 (s, 3H, -OCH_3), 3.94 (s, 3H, -CO_2CH_3), 4.78 (d, 2H, *J* = 2.26 Hz, -OCH_2), 6.20 (t, 2H, *J* = 2.26 Hz, pyrrole protons), 6.68 (t, 2H, *J* = 2.26 Hz, pyrrole protons), 6.95 (s, 1H, Ar-H), 7.32 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.39, 56.44, 56.87, 75.81, 77.58, 109.21, 112.79, 113.28, 122.48, 134.98, 148.31, 149.58, 171.55. HRMS (ESI) calcd. (found) for $C_{16}H_{15}NO_4$ 286.1079 (286.1090) $[M+H]^+$. Anal. calcd. (found) % for $C_{16}H_{15}NO_4$: C, 67.36 (67.41); H, 5.30 (5.26); N, 4.91 (4.90); O, 22.43 (22.40).

Methyl 7-methoxy-2-methyl-4-(1*H*-pyrrol-1-yl)benzofuran-5-carboxylate (2d): Pale brown solid, m.p.: 127-129 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H, C2-CH_3), 3.65 (s, 3H, -OCH_3), 4.06 (s, 3H, -CO_2CH_3), 6.22 (t, 2H, *J* = 2.08 Hz, pyrrole protons), 6.29 (s, 1H, -C3-H), 6.71 (t, 2H, *J* = 2.08 Hz, pyrrole protons), 7.19 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ13.99, 52.29, 56.36, 101.78, 104.14, 107.10, 108.82, 122.48, 129.12, 143.60. HRMS (ESI) calcd. (found) for $C_{16}H_{15}NO_4$ 286.1079 (286.1068) $[M+H]^+$. Anal. calcd. (found) % for $C_{16}H_{15}NO_4$: C, 67.36 (67.40); H, 5.30 (5.28); N, 4.91 (4.90); O, 22.43 (22.42).

5-(1*H*-Pyrrol-1-yl)-2-*p*-anisole[*d*]thiazole (2e): Yellow thick liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H, -OCH_3), 6.32 (t, 2H, *J* = 2.07 Hz, pyrrole protons), 6.98 (d, 2H, *J* = 8.87 Hz, Ar-H), 7.12 (t, 2H, *J* = 2.07 Hz, -pyrrole protons), 7.38-7.43 (dd, 1H, $J_{(1,2)}$ = 2.26 Hz, $J_{(1,3)}$ = 8.68 Hz, Ar-H), 7.86 (d, 1H, *J* = 8.68 Hz, Ar-H), 7.98-8.05 (m, 3H, Ar-H). MS (ESI): *m/z* 307 $(M+H)^+$.

5-(1*H*-Pyrrol-1-yl)-2-*p*-tolylbenzo[*d*]thiazole (2f): Pale yellow solid, m.p.: 98-100 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, Ar-CH_3), 6.32 (t, 2H, *J* = 2.26 Hz, pyrrole protons), 7.12 (t, 2H, *J* = 2.26 Hz, pyrrole protons), 7.24-7.45 (m, 3H, Ar-H), 7.84-8.10 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.73, 109.76, 111.36, 110.69, 114.35, 118.34, 119.64, 122.30, 129.08, 129.81, 130.74, 139.70, 141.82, 155.06. HRMS (ESI) calcdd. (found) for $C_{18}H_{14}N_2S$ 291.0955 (291.0968) $[M+H]^+$. Anal. calcd. (found) for $C_{18}H_{14}N_2S$: C, 74.45 (74.40); H, 4.86 (4.82); N, 9.65 (9.60); S, 11.04 (11.02).

5-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-*p*-tolylbenzo[*d*]-thiazole (2g): Pale yellow solid, m.p.: 91-93 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 6H, -CH_3), 2.45 (s, 3H, Ar-CH_3), 5.84 (s, 2H, pyrrole protons), 7.18-7.31 (m, 3H, Ar-H), 7.86-8.00 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.55, 29.68, 110.67, 114.33, 118.33, 119.61, 122.24, 127.47, 129.77, 141.80. HRMS (ESI) calcd. (found) for $C_{20}H_{18}N_2S$ 319.1268 (319.1283) $[M+H]^+$. Anal. calcd. (found) % for $C_{20}H_{18}N_2S$: C, 75.44 (75.40); H, 5.70 (5.72); N, 8.80 (8.85); S, 10.07 (10.04).

2-Chloro-5-(1*H*-pyrrol-1-yl)benzoic acid (2h): White solid, m.p.: 123-125 °C (lit. [31] 125-128 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27 (t, 2H, *J* = 2.07 Hz, -pyrrole protons), 7.10 (t, 2H, *J* = 2.07 Hz, pyrrole protons), 7.46-7.57 (m, 2H, Ar-H), 7.88 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.99, 118.72, 121.70, 123.01, 128.79, 131.97, 131.78, 131.97, 138.59, 166.20. MS (ESI): *m/z* 222 $(M+H)^+$. Anal. calcd. (found) (%) for $C_{11}H_8NO_2Cl$: C, 59.61 (59.64); H, 3.64 (3.62); Cl, 16.00 (19.98), N, 6.32 (6.30).

2-Phenyl-7-(1*H*-pyrrol-1-yl)quinoxaline (2i): Pale brown solid, decomposition point 191 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (t, 2H, *J* = 2.26 Hz, pyrrole protons), 7.25 (t, 2H, *J* = 2.26 Hz, -pyrrole protons), 7.48-7.59 (m, 3H, Ar-H), 7.86-7.92 (dd, 1H, $J_{(1,2)}$ = 2.26 Hz, $J_{(1,3)}$ = 9.05 Hz, Ar-H), 8.03 (d, 1H, *J* = 3.02 Hz, Ar-H), 8.15-8.23 (m, 3H, Ar-H), 9.31 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.17, 111.85, 117.73, 119.21, 122.79, 127.59, 129.13, 130.35, 130.64, 139.66, 141.56, 142.54, 143.04. HRMS (ESI) calcd. for $C_{18}H_{13}N_3$ 272.1187 $[M+H]^+$, found 272.1188. Anal. calcd. (%) for $C_{18}H_{13}N_3$ calcd. (found): C, 79.68 (79.64); H, 4.83 (4.82); N, 15.49 (15.45).

1-(2-Fluro-4-methylphenyl)-2,5-dimethyl-1*H*-pyrrole (2j): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99 (s, 6H, -CH_3), 2.43 (s, 3H, Ar-CH_3), 5.81 (s, 2H, -pyrrole protons), 6.97-7.13 (m, 3H, Ar-H). ^{13}C NMR (MHz, $CDCl_3$): 12.41, 21.14, 105.80, 116.86, 117.12, 125.06, 129.11, 130.04, 140.42, 159.71. MS (ESI): *m/z* 204 $(M+H)^+$, 226 (M+Na).

2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)benzenamine (3a): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (s, 6H, -CH_3), 3.37-3.46 (bs, 2H, -NH_2), 5.83 (s, 2H, -pyrrole protons), 6.75 (t, 1H, *J* = 7.70 Hz, Ar-H), 7.02 (d, 1H, *J* = 6.98 Hz, Ar-H), 7.15 (t, 1H, *J* = 7.70 Hz, Ar-H). MS (EI): *m/z* (%) 186 (M^+, 100 %).

4-(1*H*-Pyrrol-1-yl)benzenamine (3c): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40-3.75 (bs, 2H, -NH_2), 6.20 (t, 2H, *J* = 2.07 Hz, -pyrrole protons), 6.65 (d, 2H, *J* = 8.49 Hz, Ar-H), 6.88 (t, 2H, *J* = 2.07 Hz, pyrrole protons), 7.13 (d, 2H, *J* = 8.49 Hz, Ar-H). MS (EI): *m/z* (%) 158 (M^+, 100 %).

Synthesis of pyrroles from *o*-nitro aniline (4a-d): To a mixture of 2-nitroaniline (1 g, 5.20 mmol and 2,5-hexanedione (1.1g, 5.22 mmol) in H_2O (10 mL) was added $SnCl_2{\cdot}2H_2O$ (3.51 g, 15.62 mmol) at room temperature and heated to 55 ºC for 30 min. After completion of the reaction (monitored by TLC), basified the reaction mixture slowly with saturated aqueous $NaHCO_3$ at 0 ºC and compound was extracted with ethyl acetate (2 × 30 mL). The combined organic phase was washed with brine (1 × 15 ml), dried over anhydrous Na_2SO_4, removed solvent *in vacuo* and the crude residue was purified

by column chromatography on silica gel (ethylacetate:petroleum ether, 2:8) to afford compound **4a** (0.93 g, 85% yield) as white crystalline powder.

Methyl 7-methoxy-2-methyl-4-(1*H*-pyrrol-1-yl)benzofuran-5-carboxylate (4a): Pale brown solid, m.p.: 127-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H, C2-CH_3), 3.65 (s, 3H, -OCH_3), 4.06 (s, 3H, -CO_2CH_3), 6.22 (t, 2H, *J* = 2.08 Hz, -pyrrole protons), 6.29 (s, 1H, -C3-H), 6.71 (t, 2H, *J* = 2.08 Hz, -pyrrole protons), 7.19 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.99, 52.29, 56.36, 101.78, 104.14, 107.10, 108.82, 122.48, 129.12, 143.60. HRMS (ESI) calcd. (found) for $C_{16}H_{15}NO_4$ 286.1079 (286.1068) $[M+H]^+$. Anal. calcd. (found) % for $C_{16}H_{15}NO_4$: C, 67.36 (67.40); H, 5.30 (5.28); N, 4.91 (4.90); O, 22.43 (22.42).

2-(4-Methoxyphenyl)-5-(1*H*-pyrrol-1-yl)benzo[*d*]-thiazole (4b): Yellow thick liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H, -OCH_3), 6.32 (t, 2H, *J* = 2.07 Hz, -pyrrole protons), 6.98 (d, 2H, *J* = 8.87 Hz, Ar-H), 7.12 (t, 2H, *J* = 2.07 Hz, pyrrole protons), 7.38-7.43 (dd, 1H, $J_{(1,2)}$ = 2.26 Hz, $J_{(1,3)}$ = 8.68 Hz, Ar-H), 7.86 (d, 1H, *J* = 8.68 Hz, Ar-H), 7.98-8.05 (m, 3H, Ar-H). MS (ESI): *m/z* 307 $(M+H)^+$.

5-(1*H*-Pyrrol-1-yl)-2-*p*-tolylbenzo[*d*]thiazole (4c): Pale yellow solid, m.p.: 98-100 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, Ar-CH_3), 6.32 (t, 2H, *J* = 2.26 Hz, -pyrrole protons), 7.12 (t, 2H, *J* = 2.26 Hz, -pyrrole protons), 7.24-7.45 (m, 3H, Ar-H), 7.84-8.10 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.73, 109.76, 111.36, 110.69, 114.35, 118.34, 119.64, 122.30, 129.08, 129.81, 130.74, 139.70, 141.82, 155.06. HRMS (ESI) calcd. for $C_{18}H_{14}N_2S$ 291.0955 $[M+H]^+$, found 291.0968. Anal. calcd. (found) % for $C_{18}H_{14}N_2S$: C, 74.45 (74.40); H, 4.86 (4.82); N, 9.65 (9.60); S, 11.04 (11.02).

5-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-*p*-tolylbenzo[*d*]-thiazole (4d): Pale yellow solid, m.p.: 91-93 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 6H, -CH_3), 2.45 (s, 3H, Ar-CH_3), 5.84 (s, 2H, -pyrrole protons), 7.18-7.31 (m, 3H, Ar-H), 7.86-8.00 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.55, 29.68, 110.67, 114.33, 118.33, 119.61, 122.24, 127.47, 129.77, 141.80. HRMS (ESI) calcd. for $C_{20}H_{18}N_2S$ 319.1268 $[M+H]^+$, found 319.1283 Anal. calcd. (found) % for $C_{20}H_{18}N_2S$: C, 75.44 (75.40); H, 5.70 (5.72); N, 8.80 (8.85); S, 10.07 (10.04).

Synthesis of pyrroles from *o*-nitro aniline: The synthesis began with the esterification of commercially available vanillic acid with CH_3OH in the presence of conc. H_2SO_4 to afford compound **5**. Ester **5** was nitrated with a mixture of fuming HNO_3 and $SnCl_4$ at -20 ºC (dry ice/CCl_4) in CH_2Cl_2. The resulted nitro compound **6** was subjected to Claisen rearrangement by treating with propargyl bromide in the presence of K_2CO_3 under microwave irradiation for 7 min in a sealed tube to afford cyclized product **6** in good yield. Resulted benzofuran was treated with 2,5-dimethoxy tetrahydrofuran in the presence of $SnCl_2{\cdot}2H_2O$ in H_2O at 55 ºC for 60 min to afford target compound **5a** in 85 % yield. The ^{1}H NMR of this compound showed three singlets at δ 2.46, 3.65, and 4.06 corresponding to -CH_3, -OCH_3, and -CO_2CH_3, respectively. The protons of pyrrole ring appeared at δ 6.22 and 6.71 as triplets with coupling constant value (*J*) of 2.08 Hz and the proton of furan ring appeared at δ 6.29 ppm as singlet. In ESI-MS spectra, (M+H) peak appeared at 268.

Methyl 7-methoxy-2-methyl-4-(1*H*-pyrrol-1-yl)benzofuran-5-carboxylate (5b): Pale brown solid, m.p.: 127-129 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H, C2-CH_3), 3.65 (s, 3H, -OCH_3), 4.06 (s, 3H, -CO_2CH_3), 6.22 (t, 2H, *J* = 2.08 Hz, pyrrole protons), 6.29 (s, 1H, -C3-H), 6.71 (t, 2H, *J* = 2.08 Hz, pyrrole protons), 7.19 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.99, 52.29, 56.36, 101.78, 104.14, 107.10, 108.82, 122.48, 129.12, 143.60. HRMS (ESI) calcd. (found) for $C_{16}H_{15}NO_4$ 286.1079 (286.1068) $[M+H]^+$. Anal. calcd. (found) % for $C_{16}H_{15}NO_4$: C, 67.36 (67.40); H, 5.30 (5.28); N, 4.91 (4.90); O, 22.43 (22.42).

2-(4-Methoxyphenyl)-5-(1*H*-pyrrol-1-yl)benzo[*d*]-thiazole (5c): Yellow thick liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H, -OCH_3), 6.32 (t, 2H, *J* = 2.07 Hz, pyrrole protons), 6.98 (d, 2H, *J* = 8.87 Hz, Ar-H), 7.12 (t, 2H, *J* = 2.07 Hz, pyrrole protons), 7.38-7.43 (dd, 1H, $J_{(1,2)}$ = 2.26 Hz, $J_{(1,3)}$ = 8.68 Hz, Ar-H), 7.86 (d, 1H, *J* = 8.68 Hz, Ar-H), 7.98-8.05 (m, 3H, Ar-H). MS (ESI): *m/z* 307 $(M+H)^+$.

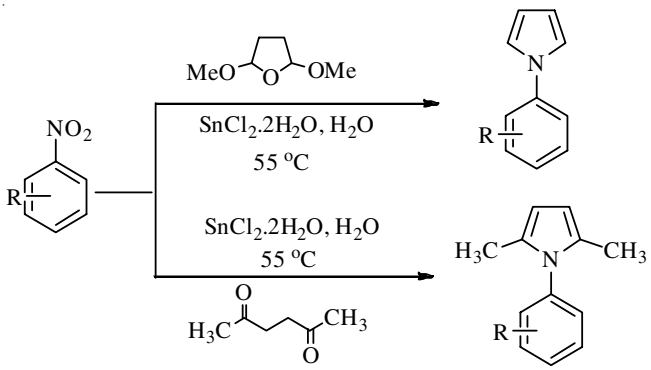
5-(1*H*-Pyrrol-1-yl)-2-*p*-tolylbenzo[*d*]thiazole (5d): Pale yellow solid, m.p.: 98-100 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, Ar-CH_3), 6.32 (t, 2H, *J* = 2.26 Hz, pyrrole protons), 7.12 (t, 2H, *J* = 2.26 Hz, pyrrole protons), 7.24-7.45 (m, 3H, Ar-H), 7.84-8.10 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.73, 109.76, 111.36, 110.69, 114.35, 118.34, 119.64, 122.30, 129.08, 129.81, 130.74, 139.70, 141.82, 155.06. HRMS (ESI) calcd. (found) for $C_{18}H_{14}N_2S$: 291.0955 (291.0968) $[M+H]^+$. Anal. calcd. (found): for $C_{18}H_{14}N_2S$: C, 74.45 (74.40); H, 4.86 (4.82); N, 9.65 (9.60); S, 11.04 (11.02).

Methyl 7-methoxy-2-methyl-4-nitrobenzofuran-5-carboxylate (7): In a sealed tube, propargyl bromide (2.00 g, 16.83 mmol) was added to a solution of compound **5** (3.47 g, 15.30 mmol) in *N,N*-diethylaniline (10 mL) followed by K_2CO_3 (5.27 g, 38.26 mmol) and the reaction mixture was irradiated to microwave for 7 min. After completion of the reaction (monitored by TLC), the reaction mixture was directly poured on silica gel column (60-120 mesh) and eluted with ethyl acetate:pet ether (3:7) to afford compound **7** (2.83 g, 70 % yield) as pale yellow powder. m.p.: 120-122 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (s, 3H, C2-CH_3), 3.92 (s, 3H, -OCH_3), 4.11 (s, 3H, -CO_2-CH_3), 6.86 (s, 1H, C3-H), 6.95 (s, 1H, C6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.07, 53.23, 56.81, 103.39, 105.67, 126.59, 127.00, 143.93, 147.90, 160.62, 167.10. MS (ESI): *m/z* 288 $(M+Na)^+$. Anal. calcd. calcd. (found) % for $C_{12}H_{11}NO_6$: C, 54.34 (54.32); H, 4.18 (4.16); N, 5.28 (5.26); O, 27.25 (27.23).

RESULTS AND DISCUSSION

As part of our ongoing drug discovery program, which aims to develop new selective and environmentally benign methodologies for the synthesis of heterocycles, herein, we report an efficient one-step procedure for the conversion of nitro compounds to their corresponding *N*-functionalized pyrroles that would be highly amenable to a parallel approach **(Scheme-I)**. To the best of our knowledge, however, generality and applicability of $SnCl_2$ in the synthesis of *N*-functionalized pyrroles in aqueous medium is not known.

Two reagents that have been utilized widely for the reduction of nitro gathering were $Na_2S_2O_4$ and Fe/acid. To begin with, we endeavored the one-pot strategy utilizing 2,4-dichloro-

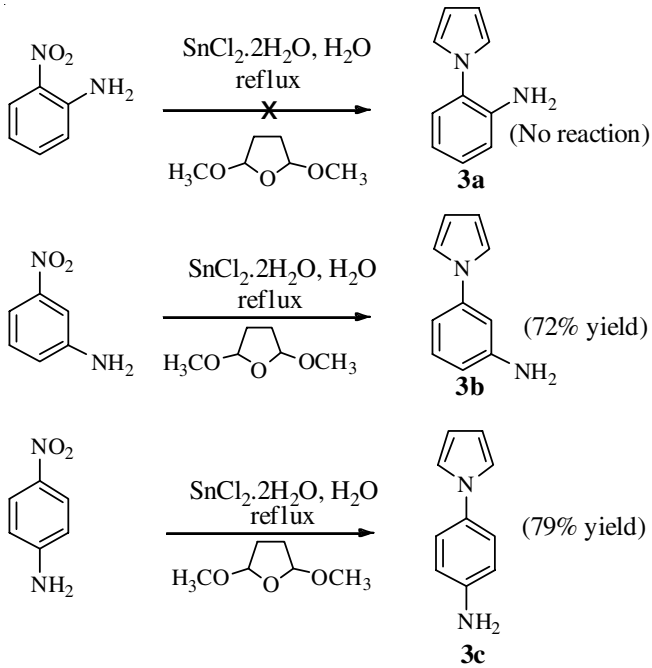


Scheme-I: Synthesis of pyrrole from nitrobenzene

nitrobenzene, 2,5-dimethoxytetrahydrofuran and $Na_2S_2O_4$ in refluxing acidic corrosive and got a low yield of the ideal item (25 % and 20 %, 2,5-dimethoxytetrahydrofuran and γ-diketone individually, Table-1). Moreover, it was found that a response under these conditions was fanciful and irreproducible. The utilization of $Na_2S_2O_4$ and *p*-TsOH in toluene did not yield any of an ideal items (entry 2). Moreover, utilization of Fe and HCl or Fe and *p*-TsOH in EtOH and toluene separately, did not yield any item (entries 2 and 4). The nitro gathering experienced decrease easily under these response conditions yet neglected to cyclize.

$SnCl_2{\cdot}2H_2O$ can work as a chemo specific lessening specialist just as mellow Lewis corrosive and was an appealing reagent for doing this reductive cyclization. Utilizing $SnCl_2{\cdot}2H_2O$ in refluxing H_2O, great yields of an ideal item (82 % normal more than 2 runs) was achieved. The response was likewise analyzed in various solvents, for example, benzene (30 %), THF (60 %), CH_3CN (40 %), EtOH (65 %) and dissolvable free conditions (10 %) for correlation. Low yields of item were framed in natural solvents even after 5 h. The response was additionally advanced by differing the time and the quantity of reciprocals of $SnCl_2{\cdot}2H_2O$ is required for this change. At last, 3.0 equiv of $SnCl_2{\cdot}2H_2O$ was found to be optimum amount for ideal yields; extreme measure of reagent did not expand the yield astoundingly. The response was operationally basic and all reagents were blended in H_2O and refluxed until the response finished, preceding fluid workup and confinement by segment chromatography. Having set up the ideal conditions for response, an assortment of substituted nitro benzenes was analyzed to investigate the extension and impediments of the response (Table-1).

In this part of the cases analyzed, a response continued easily in water, commonly bearing a solitary item in quantitative yield (78-88 %). The response obliges a scope of practical information, including electron-giving just as electron-pulling back substituents on the nitrobenzene. Likewise, under these response conditions, stearically upset nitro benzenes (Table-2) gave the comparing items in quantitative yields. Besides, electron-lacking nitro benzenes gave the related *N*-functionalized pyrroles in exceptional returns. Furthermore, the conventional methods could be effectively connected to an enormous scale process. Likewise, the yields obtained with *m*-nitroaniline and *p*-nitroaniline were somewhat lower than those obtained with electron donating substrates when subjected to the established reaction conditions, whereas *o*-nitroaniline found to be unaffected even after longer reaction time, further signify the chemoselectivity of $SnCl_2{\cdot}2H_2O$ (**Scheme-II**).



Scheme-II: Preparation of substituted pyrrole-chemoselectivity

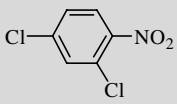
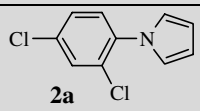
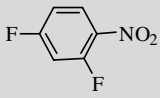
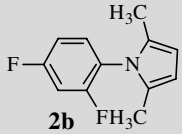
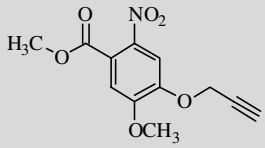
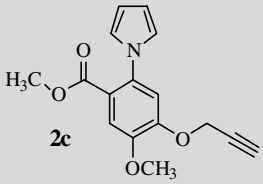
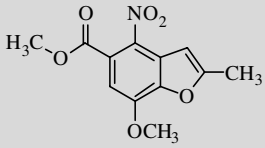
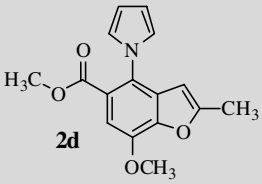
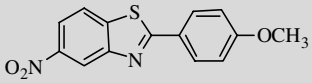
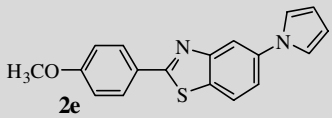
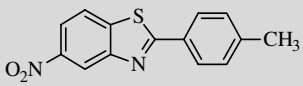
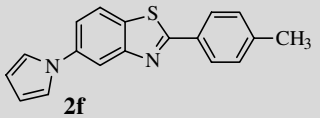
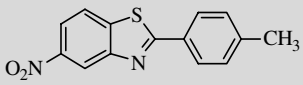
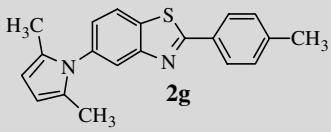
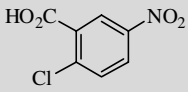
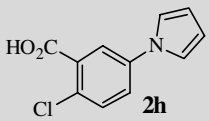
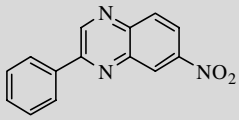
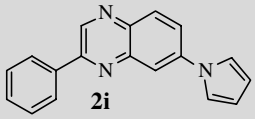
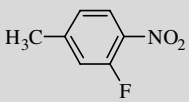
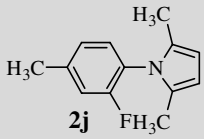
In the same way, a reaction of *o*-nitroaniline with 2,5-hexanedione under the identical reaction conditions was observed, interestingly, corresponding pyrrole compound **4a** was isolated in good yield. This might be due to the higher reactivity of 2,5-hexanedione over 2,5-dimethoxytetrahydrofuran. Initially, 2-nitroaniline was reacted with 2,5-hexanedione in the presence of $SnCl_2{\cdot}2H_2O$ in H_2O under reflux for 30 min, two products (**4a** and **4b**) were isolated. Next, same reaction was continued for 60 min under identical conditions surprisingly, product **4a** formed exclusively as a single product without any formation of **4b** (**Scheme-III**).

TABLE-1
PREPARATION OF SUBSTITUTED PYRROLES FROM NITRO BENZENE UNDER DIFFERENT REACTION CONDITIONS

Entry	Acid	Reducing agent	Solvent	Time (h)	Temp. (°C)	Yield (%)[a]
1	AcOH	$Na_2S_2O_4$	AcOH	2	55	25[b], 20[c]
2	TsOH	$Na_2S_2O_4$	Toluene	2	55	0
3	HCl	Fe	EtOH	2	55	0
4	TsOH	Fe	Toluene	2	55	0
5	$SnCl_2$	$SnCl_2$	EtOH	2	55	65
6	$SnCl_2$	$SnCl_2$	MeOH	2	55	70
7	$SnCl_2$	$SnCl_2$	H_2O	2	55	85[b], 81[c]

[a]Isolated yields. [b]2,5-dimethoxytetrahydrofuran was used. [c]γ-diketone was used.

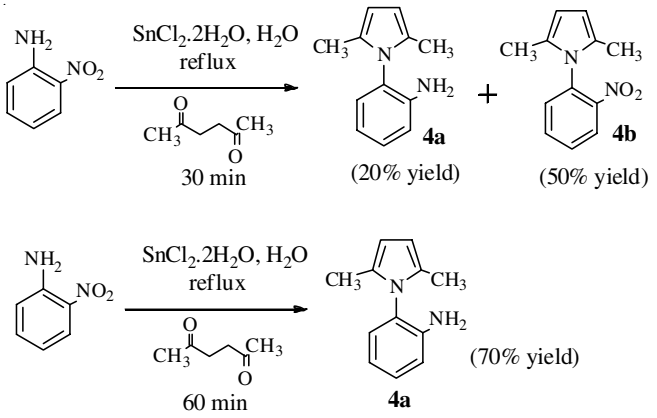
TABLE-2
SYNTHESIS OF *N*-FUNCTIONALIZED PYRROLES IN AQUEOUS MEDIUM

Entry	Substrate	Product[a]	Yield (%)[b]
1		 **2a**	85
2		 **2b**	83
3		 **2c**	88
4		 **2d**	85
5		 **2e**	84
6		 **2f**	81
7		 **2g**	80
8		 **2h**	82
9		 **2i**	78
10		 **2j**	86

[a]All products were characterized by IR, ^{1}H NMR and mass spectrometry. [b]Isolated yield after purification.

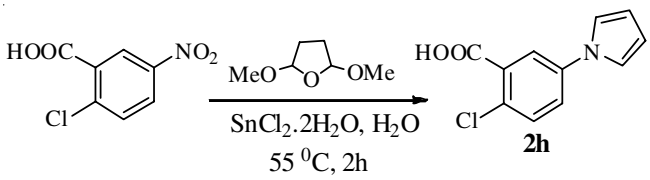
The reason for the formation of single product *i.e.*, **4a** in the second condition is might be due to expected mechanism (**Scheme-IV**). Herein, a first step is the addition of an amine to one of the carbonyl groups yielding hemiaminal A, which can eliminate water to form imine B. Next, ring closure of imine B produces C, which can convert to D immediately. Finally, a loss of water from D resulted in the formation of pyrrole compound **4b**, which was on reduction with $SnCl_2{\cdot}2H_2O$ produced compound **4a**.

Based on the above mechanism, it assumed that a formation of imine bond was a driving force for the formation of compound **4b**, whereas, in the case of 2,5-dimethoxytetrahydrofuran this type of imine bond formation was not possible. This might be the reason for the failure of reaction of *o*-nitroaniline with 2,5-dimethoxytetrahydrofuran under identical conditions. Similarly, by adopting this methodology, synthesis of N-substituted pyrrole derivative NB-64 (entry 8, Table-2) as novel human immunodeficiency virus type 1 entry inhibitor in high yields



Scheme-III: Preparation of pyrrole from *o*-nitro aniline

(82 %) was achieved by treating 2-chloro-5-nitrobenzoic acid with 2,5-dimethoxytetrahydrofuran under identical reaction conditions (**Scheme-V**). ^{1}H NMR analysis of this compound showed a characteristic pyrrole protons which appeared at δ 6.27 and 7.10 as triplets with coupling constant (*J*) value of 2.07 Hz.

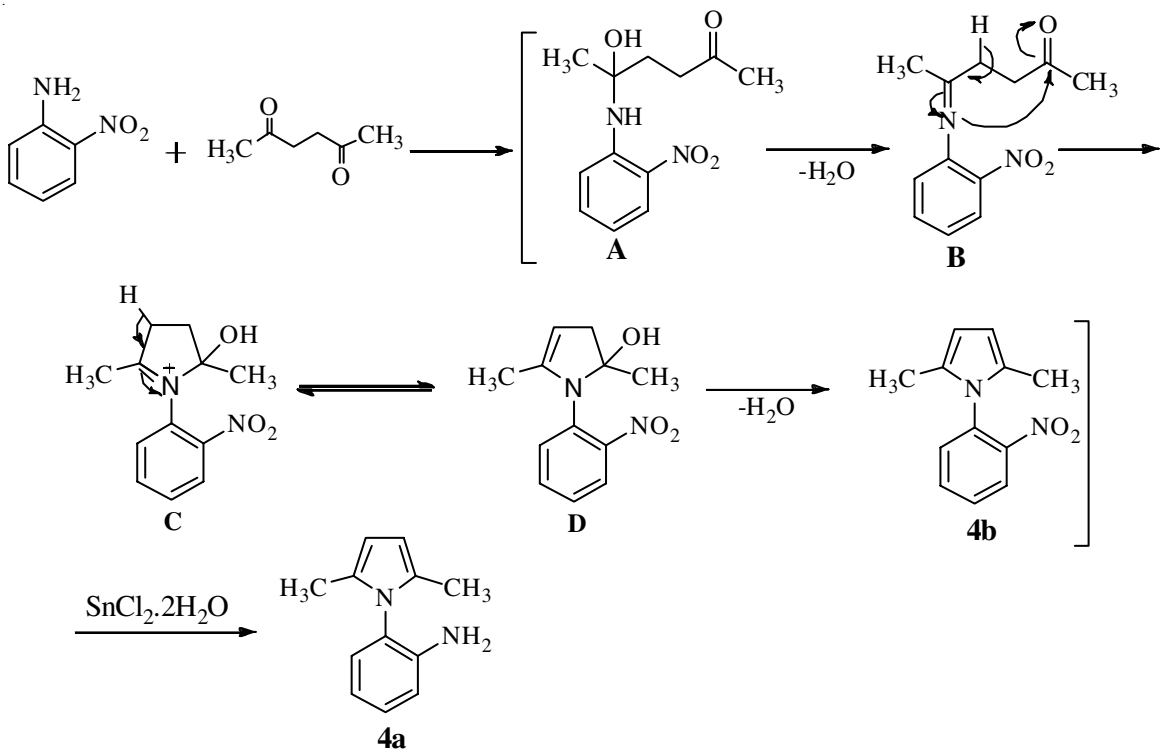


Scheme-V: Synthesis of pyrrole derivative NB-64

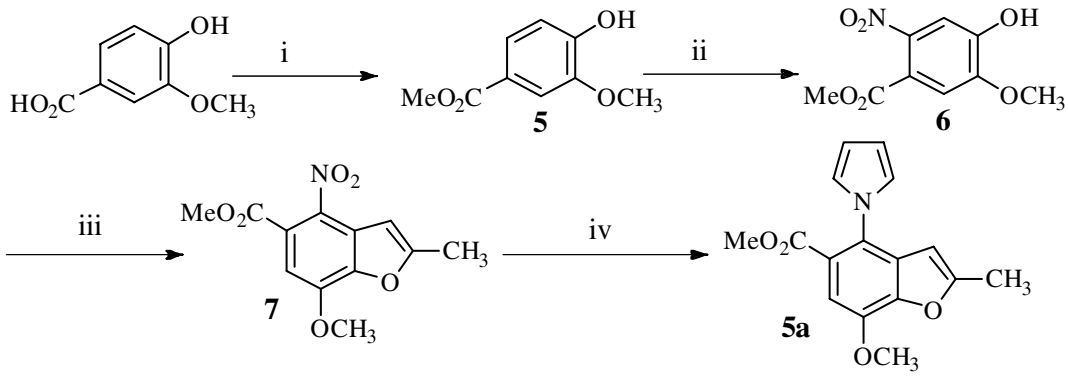
Encouraged by these results, this methodology was further extended for the synthesis of novel hybrid molecules (incorporation of two or more pharmacophores in a single moiety). Recently, hybrid drug approach has gained impetus due to its overwhelming success, exemplified by RSNOs (S-nitrosothiols)-β-receptor blocker hybrids, RSNOs-NSAIDs hybrids [33], distamycin-Hoechst 33258 hybrids [34], CBI-PBD conjugates [35], Uramustine-distamycin A hybrids [36], 5-fluorouracil-distamycin A hybrids [37], *etc*. This approach led to the development of more sequence-selective, highly potent and selective-tumor candidates. Another advantage of hybrid molecules is the fact that the intake of one hybrid drug is better for patients' compliance. By adopting this methodology, a series of novel hybrid molecules containing *N*-aryl pyrrole hybrid molecules (entries **5a**, **5b**, **5c** and **5d**) were synthesized.

Synthesis of compound 5a: The synthesis began with the esterification of commercially available vanillic acid with CH_3OH in the presence of conc. H_2SO_4 to afford compound **5**. Ester **5** was nitrated with a mixture of fuming HNO_3 and $SnCl_4$ at -20 ºC (dry ice/CCl_4) in CH_2Cl_2. The resulted nitro compound **6** was subjected to Claisen rearrangement by treating with propargyl bromide in the presence of K_2CO_3 under microwave irradiation for 7 min in a sealed tube to afford cyclized product **7** in good yield. Resulted benzofuran compound **7** was treated with 2,5-dimethoxytetrahydrofuran in the presence of $SnCl_2{\cdot}2H_2O$ in H_2O at 55 ºC for 60 min to afford target compound **5a** in 85 % yield (**Scheme-VI**). ^{1}H NMR analysis of this compound showed three singlets at δ 2.46, 3.65 and 4.06 corresponding to -CH_3, -OCH_3 and -CO_2CH_3, respectively. The protons of pyrrole ring appeared at δ 6.22 and 6.71 as triplets with coupling constant value (*J*) of 2.08 Hz and the proton of furan ring appeared at δ 6.29 as singlet. In the ESI-MS spectra the (M+H) peak appeared at 268.

Synthesis of compounds 5c and 5d: Coupling of 4-methylbenzoyl chloride with 2-nitroaniline afforded corresponding amide **8**, which was converted to thioamide **9** by treating with Lawesson′s reagent (**Scheme-VII**). Thioamide **9** was cyclized

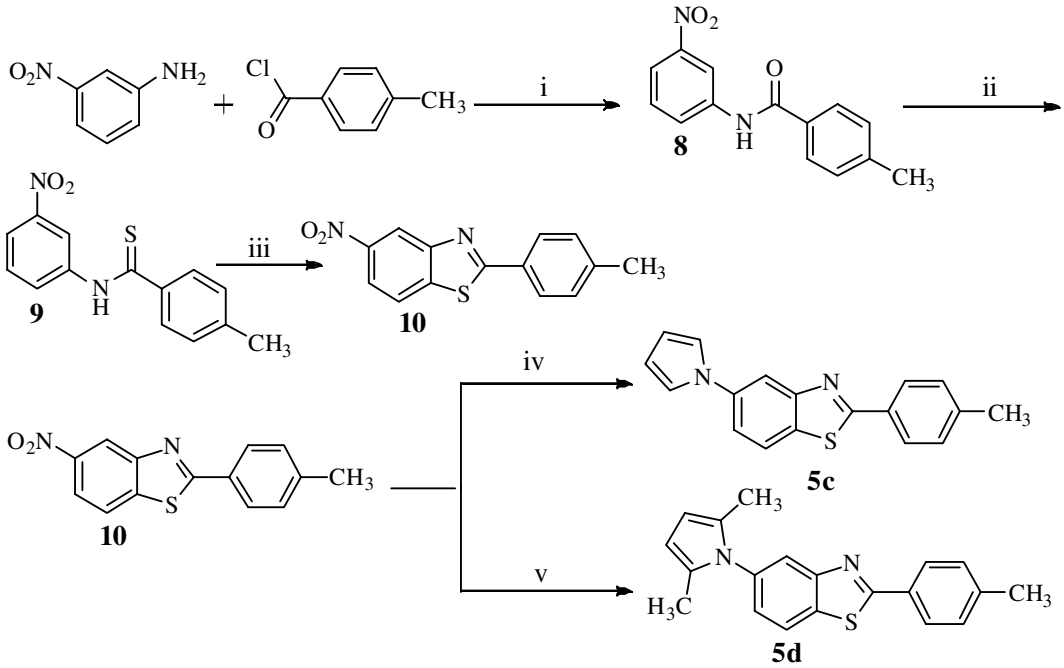


Scheme-IV: Plausible mechanism for formation of **4a**



Reagents and conditions: (i) Conc. H_2SO_4, CH_3OH, reflux, 10 h (ii) $SnCl_4$, fuming HNO_3, CH_2Cl_2, -20 ^{0}C, 10 min (iii) K_2CO_3, propargyl bromide, N,N-diethylaniline, MW, 7 min (iv) 2,5-dimethoxytetrahydrofuran, $SnCl_2.2H_2O$, H_2O, reflux, 1 h

Scheme-VI: Synthesis of benzoxazole-pyrrole hybrid molecule **5a**



Reagents and Condtions: (i) Et_3N, CH_2Cl_2, r.t., 8 h (ii) Lawesson's reagent, dry toluene, reflux, 3 h (iii) DDQ, CH_3OH, r.t. 20 min (iv) 2,5-dimethoxytetrahydrofuran, $SnCl_2.2H_2O$, H_2O, reflux, 1 h (v) 2,5-hexanedione, $SnCl_2.2H_2O$, H_2O, reflux, 1 h

Scheme-VII: Synthesis of benzothiazole-pyrrole hybrid molecules **5c** and **5d**

with DDQ in CH_3OH at room temperature to yield compound **10**. Compound **10** on reaction with 2,5-dimethoxytetrahydrofuran and 2,5-hexanedione in the presence of $SnCl_2{\cdot}2H_2O$ to afford compounds **4c** and **4d**, respectively in good yield (81 and 80 %, respectively). Compound **4b** was also synthesized by adopting the same synthetic scheme and the structure of these compounds satisfactorily ascertained by ^{1}H NMR, ^{13}C NMR and ESI-MS.

Conclusion

We have built up a basic method for the union of *N*-functionalized pyrroles from nitro benzenes in great yield utilizing a cheap, monetarily accessible synthon. The proficient convention portrayed here speaks to the briefest course accessible to get to an assortment of substituted pyrroles is operationally straight-forward and gives a noteworthy improvement over existing techniques for the arrangement of this class.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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