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A novel and efficient green methodology for the synthesis of meso-substituted dipyrromethanes

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ABSTRACT

Meso-substituted dipyrromethanes were synthesized in excellent yields by the one-pot condensation of aldehyde/ketone and pyrrole in the presence of catalytic amount of the inexpensive, readily available and non-toxic inorganic acid in aqueous media at room temperature. In this reaction the products were obtained in short reaction time and easy operation under mild conditions without using any strong acid and minimize the organic solvents. Dipyrromethanes were filtered in high purity without use of flash chromatography.

Keywords: Meso-substituted dipyrromethane, pyrrole, carbonyl compound, green chemistry.

INTRODUCTION

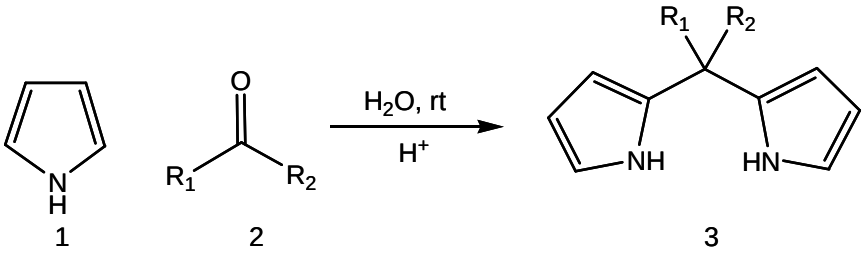
Polypyrrolic compounds are of wide interest in several areas, namely in porphyrins [1], materials science [2], optics [3], medicine [4] and related macrocycles [5]. Meso substituted dipyrromethanes are important building blocks for many of the structures of interest in the areas of organic synthesis and pharmaceuticals [6]. The stability of meso substituted dipyrromethane to oxidation, during the synthetic procedure, is always a cause for concern. The isolation and storage of such compounds under diverse conditions have been established allowing good to excellent yield of meso substituted dipyrromethane to be obtained in the case where adequate substituents are present on the pyrrole rings. Those substituents provide for the stability of both the pyrrole precursors and the product dipyrromethane [7,8].

Due to their great importance, a number of different synthetic routes have been developed for the synthesis and purification of dipyrromethanes in the last decades. Almost, all the methods to achieve the dipyrromethanes from the excess of pyrrole and carbonyl compounds in the presence of various strong acids such as $BF_3{\cdot}OEt_2$ [9], trifluoroacetic acid [10,11] (TFA), methane sulfonic acid [12,13] and hydrochloric acid [14]. All those methods required prolonged reaction time and exotic reaction conditions. They imply necessarily a delicate time control to stop the reaction when the dipyrromethane concentration is at its maximum and involve a final workup that requires, at least, the distillation of the excess pyrrole. These studies mostly afford low to moderate yields of meso-substituted dipyrromethanes. The yields are reduced due to the formation of oligomeric products, which make the purification of the dipyrromethanes from the reaction medium difficult. The direct synthesis of dipyrranes from aldehydes and pyrrole gives a mixture of oligopyrromethane and separation of each oligopyrromethane is difficult [15]. It is known that acid catalysed reactions of pyrroles are limited because of their sensitivity to acids. The reactions of nitrogen-containing compounds activated with a catalytic amount of conventional Lewis acids are also limited due to their deactivation by strong coordination to the Lewis acid, in many cases stoichiometric amounts of the acid are required [16]. However, the use of excess and even stoichiometric amount of acids with organic solvents makes such processes environmentally questionable.

To date, many more organic transformations have been carried out in water or aqueous media [17-19] but the purification of dipyrromethanes were little difficult [20,21]. Although, the purification of dipyrromethanes was done

by the use of flash chromatography which is environmentally questionable, in recent year, novel acid has gained special attention as a catalyst in organic synthesis because of many advantages such as excellent solubility in water, non-toxic, easy to handling, inexpensive, eco-friendly nature, readily available and high reactivity. Recently, synthetically useful organic transformation using inorganic novel acid as a catalyst has been reported in the literature [22].

Inspired by the early report and the critical role of inorganic acid in organic synthesis provoked us to examine the catalytic scope of novel inorganic acid in the synthesis of meso-substituted dipyrromethane. Herein, we report the high yield synthesis of meso-substituted dipyrromethane in the condensation of pyrrole **(1)** and cyclohexanone **(2)** by making use of novel acid as catalysts under stirring at room temperature reaction condition in a very short time <20 min (**Scheme 1 Table 3**). However, the reported catalysts require longer reaction time giving moderate yields of products for this conversion. The present procedure is superior in comparison with TFA, $InCl_3$, CH_3SO_3H and $BF_3O(Et)_2$ catalyzed reactions of carbonyl with pyrrole which generated several unexpected products [23]. Whereas expensive $InCl_3$, TFA, CH_3SO_3H and BF_3O $(Et)_2$ catalyzed reactions took a very long reaction time (5 h) [24].



1 2 3

3a. $R_1 = R_1 = -(CH_2)_5$
3b. $R_1 = R_2 = CH_3$
3c. $R_1 = CH_3$, $R_2 = C_2H_5$
3d. $R_1 = R_2 = C_2H_5$
3e. $R_1 = R_2 = CH_2CH_2CH_3$
3f. $R_1 = R_1 = -(CH_2)_4$
3g. $R_1 = CH_3$, $R_2 = C_6H_5$
3h. $R_1 = CH_3$, $R_2 = p\text{-}NO_2C_6H_4$
3i. $R_1 = CH_2CH_2CH_3$, $R_2 = C_6H_5$
3j. $R_1 = R_2 = C_6H_5$
3k. $R_1 = H$, $R_2 = C_6H_5$
3l. $R_1 = H$, $R_2 = C_6F_5$
3m. $R_1 = H$, $R_2 = 4\text{-}C(CH_3)_3C_6H_4$
3n. $R_1 = CH_3$, $R_2 = C_6H_5$
3o. $R_1 = H$, $R_2 = 4\text{-}OCH_3C_6H_4$
3p. $R_1 = H$, $R_2 = 3,5\text{-}(C(CH_3)_3)\text{-}4\text{-}OH\text{-}C_6H_2$
3q. $R_1 = H$, $R_2 = 3,5\text{-}(OCH_3)_2\text{-}4\text{-}OH\text{-}C_6H_2$
3r. $R_1 = H$, $R_2 = 2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$

Scheme1: Synthesis of meso-substituted dipyrromethanes

MATERIALS AND METHODS

The melting points of compounds are uncorrected, expressed in degree centigrade and recorded using Thomas Hoover Unimelt capillary melting point apparatus. Perkin-Elmer FT-2000 spectrometer was used for recording infrared spectra (ν_{max} in cm^{-1}). NMR spectra were obtained on a Jeol-delta-400 spectrometer. The tetramethylsilane (TMS) was used as an internal standard and the chemical shifts (δ) are expressed in ppm. ESI-MS were recorded by LC-TOF (KC-455) mass spectrometer of Waters. TGA/DTA was recorded by Perkin-Elmer Diamond 1100. HPLC analysis was performed on Waters 2998 Photodiode Array Detector on a Waters PAH C18 HPLC column (4.6×250 mm) using methanol as the eluent. The starting materials were purchased from Spectrochem Chemicals India. The pyrrole was distilled prior to use and the solvents used were of analytical reagent grade. The compounds synthesized were characterized by melting points, ^1H NMR, ^{13}C NMR, IR and ESI-MS techniques.

Synthesis of meso-substituted dipyrromethanes (3)

To a stirred solution of cyclohexanone (1 mmol) and pyrrole (2 mmol) in 25 ml of water, acid catalyst (100 mg) was added at room temperature. The reaction mixture was stirred for appropriate time given in table 3 and progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of reaction the reaction mixture was stirred for 1/2h more and desired product was solidified in the round bottom flask. The solid precipitate as a desire dipyrromethane was collected by simple filtration followed by washing with water (3×100 ml). Finally the product

was dried at room temperature. The purity of the product was checked by TLC and HPLC in methanol/ water (1:1, v/v) as solvent, by comparing the retention time with authentic samples **(supplementary data Figure S3)**. As the meso substituted dipyrromethanes undergo slow polymerization upon standing at room temperature.

5-spirocyclohexyldipyrromethane (3a): Physical state: off white solid; mp: 122-124 ºC (lit [25] 104-106 ºC); R_f : 0.59 (1:1 $CHCl_3$: Hexane, v/v); IR (KBr, cm^{-1}): 3443, (-NH) 2976 (-CH_3), 1548, 1443, 1025, 723 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$, 25 ˚C) δ = 1.56 (m, 24H, -CH_2), 2.06 (m, 16H, -CH_2) 6.10 (m, 4H, *β*-pyrrolic CH) 6.56 (d, *J* = 1.12 Hz, 2H, *α*-pyrrolic CH) 7.66 (br s, 2H, NH); ^{13}C NMR (100MHz, $CDCl_3$, 25 ˚C) δ = 22.74, 25.90, 37.20 (-CH_2, cyclohexyl-C), 39.78(meso-C), 104.23, 107.80 (*β*-pyrrolic -C), 116.66, 137.81 (*α*-pyrrolic -C); ESI-MS : m/z = Calculated ($C_{14}H1_8N_2$), 214.1470: Observed (M^+) 214.5705; HPLC retention time: 2.1 min.

5,5-Dimethyldipyrromethane (3b): Physical state: white solid; mp: 55 ºC (lit [26] 54-56ºC); R_f: 0.40 (1:1 $CHCl_3$: hexane, v/v), IR (KBr, cm^{-1}): 3429, (-NH) 2979 (-CH_3), 1554, 1445, 1025, 720 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$, 25 ˚C) δ = 1.61, (s, 6H, -CH_3), 5.91 (d, *J* = 2.9 Hz, 2H, *β*-pyrrolic CH), 6.10 (m, 2H, *β*-pyrrolic CH), 6.57 (d, *J* = 2.2 Hz 2H, *α*-pyrrolic CH), 7.62 (br s, 2H, NH). ^{13}C NMR (100MHz, $CDCl_3$, 25 ˚C) δ = 29.26 (-CH_3), 35.26 (*meso*-C), 103.71, 107.62 (*β*-pyrrrolic-C), 117.07, 139.07 (*α*-pyrrrolic-C); ESI-MS : m/z = Calculated ($C_{11}H_{14}N_2$), 174.1157: Observed (M + Na) 197.1128; HPLC retention time: 2.9 min.

5-Ethyl-5-methyl dipyrromethane (3c): Physical state: brownish solid; mp: 102 ºC; R_f: .40 (1:1 $CHCl_3$: pet ether, v/v); mp: 102 ºC; IR (KBr, cm^{-1}): 3348 (-NH), 2931 (-CH_3) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$, 25 ˚C) δ = 0.77 (t, 3H, -CH_3), 1.53 (s, 3H, -CH_3), 1.97 (q, 2H, -CH_2), 6.10 (m, 4H, *β*-pyrrolic -CH), 6.56 (d, *J* = 2.2 Hz, 2H, *α*-pyrrolic CH) 7.56 (br s, 2H, pyrrolic-NH); ^{13}C NMR (100MHz, $CDCl_3$, 25 ˚C) δ = 8.77 (-CH_3), 25.51 (-CH_3), 33.43 (-CH_2), 39.20 (meso-C), 104.65, 107.44 (*β*-pyrrolic, -C), 116.96, 138.63 (*α*-pyrrolic, -C); ESI-MS : m/z = Calculated ($C_{12}H_{16}N_2$), 188.1313: Observed (M+Na) 211.1215.

5,5-Diethyldipyrromethane (3d): Physical state: white solid; mp: 112 ºC (lit [27]110-112ºC); R_f: .60 (1:1 $CHCl_3$: hexane, v/v), IR (KBr, cm^{-1}): 3363 (-NH), 2943 (-CH_3) cm^{-1}, ^1H NMR (400MHz, $CDCl_3$, 25 ˚C) δ = 0.84, (t, 3H, -CH_3), 1.9 (q, 2H, -CH_2) 6.11 (m, 4H, *β*-pyrrolic CH), 6.61(s, 2H, *α*-pyrrolic CH), 7.66 (br s, 2H, pyrrolic-NH); ^{13}C NMR (100MHz, $CDCl_3$, 25 ˚C) δ = 28.77 (-CH_3), 30.51 (-CH_2CH_3), 36.20 (meso-C), 103.65, 107.24 (*β*-pyrrolic, -C), 116.86, 140.13 (*α*-pyrrolic, -C); ESI-MS : m/z = Calculated ($C_{13}H1_8N_2$), 202.1470: Observed (M^+) 202.2541.

5,5-Dipropyldipyrromethane (3e): Physical state: yellowish solid; R_f: 0.60 (1:1 $CHCl_3$: pet ether, v/v); IR (KBr, cm^{-1}): 3358 (-NH), 2932 (-CH_3) cm^{-1}; ^1H NMR (400MHz, $CDCl_3$, 25˚C) δ = 0.84 (t, 3H, -CH_3) 1.04 (q, 2H, -CH_2) 1.85 (q, 2H, -CH_2) 6.09 (m, 4H, β-pyrrole CH) 6.54 (d, 2H, α-pyrrole CH) 7.53 (br s, 2H, NH); ^{13}C NMR (100MHz, $CDCl_3$, 25˚C) δ = 14.38 (CH_3), 17.33 (-CH_2), 39.68 (-CH_2CH_2-), 42.59 (meso-C), 105.51,107.16 (*β*-pyrrolic-C), 116.84, 137.31 (*α*-pyrrolic-C); ESI-MS : m/z = Calculated ($C_{15}H_{22}N_2$), 230.1783: Observed (M+1) 231.1599.

5-spirocyclopentyldipyrromethane (3f): Physical state: white solid; R_f: 0.51 (1:1 $CHCl_3$: hexane, v/v); IR (KBr, cm^{-1}): 3433, (-NH) 2974 (-CH_3), cm^{-1}; ^1H NMR (400MHz, $CDCl_3$, 25 ˚C) δ = 1.76 (m, 16H, -CH_2), 2.10 (m, 16H, -CH_2), 6.11 (m, 4H, *β*-pyrrolic CH), 6.55(brs, 2H, *α*-pyrrolic CH), 7.57 (br s, 2H, NH); ^{13}C NMR (100MHz, $CDCl_3$, 25 ˚C) δ = 23.64, 39.15 (-CH_2, cyclopentyl-C), 46.95 (meso-C), 104.17, 107.37 (*β*-pyrrolic-C), 117.17, 137.58 (*α*-pyrrolic-C); ESI-MS : m/z = Calculated ($C_{13}H_{16}N_2$), 200.1313: Observed (M+K) 239.1001.

5-Methyl-5-phenyldipyrromethane (3g): Physical state: white solid; mp: 104 ºC (lit [28]106 ºC); R_f : 0.52 (1:1 $CHCl_3$: hexane, v/v); IR (KBr, cm^{-1}): 3375 (-NH) 2942 (-CH_3); ^1H NMR (400MHz, $CDCl_3$, 25˚C) δ = 2.05 (s, 3H, -CH_3), 5.97 (d, 2H, *β*-pyrrolic CH) 6.13 (m, 2H, *β*-pyrrolic CH) 6.67 (d, *J* = 2.2 Hz 2H, *α*-pyrrolic CH) 7.12 (m, 5H. Ar-H), 7.37 (br s, 2H, NH); ESI-MS : m/z = Calculated ($C_{16}H_{16}N_2$), 236.1313: Observed (M+2) 238.5668.

5-methyl-5-(4-nitrophenyl)dipyrromethane (3h): Physical state: yellow solid; mp: 140 ˚C, (lit [29] 142-144 ˚C); R_f: .61 (1:1 Ethyl acetate: Hexane, v/v); IR (KBr pellet, cm-1): 3402 (-NH), 3103, 2927, 1515 (-NO_2 antisymmetric), 1343 (-NO_2 symmetric), 1099, 726 cm^{-1}; ^1H NMR δ (400MHz, $CDCl_3$, 25 ˚C) δ = 5.94 (d, 2H, *β*-pyrrolic CH), 7.19 (m, 2H, *β*-pyrrolic CH), 7.70 (brs, 2H, *α*-pyrrolic CH), 8.08 (d, *J* = 8.8 Hz, 2H, phenyl), 7.87 (br s, 2H, NH), 8.08 (d, *J* = 8.4 Hz, 2H, phenyl), and 8.08 (d, 2H, phenyl); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ˚C) δ = 28.43 (-CH_3), 47.52 (meso-C), 106.00, 106.81 (*β*-pyrrolic -C), 124.55, 128.67 (*α*-pyrrolic -C),136.09, 136.62 (Ar-C), 145.66, 152.59 (Cq); ESI-MS : m/z = Calculated ($C_{16}H_{15}N_3O_2$), 281.1164: Observed (M+Na) 304.2086.

5-Phenyl-5-propyldipyrromethane (3i): Physical state: brownish viscous liquid; IR (KBr, cm^{-1}): 3433 (-NH) 2948 (-CH_3), 1456, 1256, 1096, 1115, 1023, 735, 726; R_f: 0.40 (1:1 $CHCl_3$: pet ether, v/v); ^1H NMR (400MHz, $CDCl_3$, 25˚C) δ = 1.78, (s, 3H, -CH_3) 2.37 (t, 2H, -CH_2) 2.59 (t, 2H, -CH_2) 6.21 (dd, 4H, β-pyrrole CH) 6.65 (d, 2H, α-

pyrrole CH) 7.29 (m, 5H, phenyl -CH) 7.59 (br s, 2H, NH); ^{13}C NMR (100MHz, $CDCl_3$, 25˚C) δ = 25.99, 3069, 38.79, 42.90, 104.74, 107.30, 17.15, 125.55, 128.10, 128.19, 137.57, 142.38; ESI-MS : m/z = Calculated ($C_{18}H_{20}N_2$), 264.1626: Observed (M+Na) 287.1617.

5,5-diphenyl dipyrromethane (3j) Physical state: Grey needles; m.p: 262 °C (lit [30] 260 °C); **R_f:** 0.39 (1:1 $CHCl_3$: hexane, v/v); ^{1}H NMR δ (400MHz, $CDCl_3$, 25 ˚C) δ = 5.94 (m, 2H, *β*-pyrrolic-H), 6.15 (m, 2H, *β*-pyrrolic-H), 6.71 (m, 2H, *α*-pyrrolic-H), 7.02 (d, *J* = 8.08 Hz, 4H, Ar-H), 7.16 (m, 6H, Ar-H), 7.86 (brs, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ˚C) δ = 55.60 (meso-C), 107.94, 109.55 (*β*-pyrrolic -C), 117.37, 129.22 (*α*-pyrrolic -C),126.76, 127.86 (Ar-C), 145.66, 152.59 (Cq); ESI-MS : m/z = Calculated ($C_{21}H_{18}N_2$), 298.1470: Observed (M^+) 298.0950.

5-phenyl dipyrromethane (3k): Physical state: white solid; mp: 100-101 ˚C. (lit. [31]101 ˚C); R_f: 0.47 (1:1 chloroform: hexane, V/V); IR (KBr pellet, cm^{-1}): 3343, 3057, 1457, 1258, 1095, 1114, 1026, 738, 725; ^{1}H NMR (400MHz, $CDCl_3$, 25˚C) δ = 5.45 (s, 1H, CH), 5.93 (s, 2H, *β*-pyrrolic-CH), 6.18 (m, 2H, *β*-pyrrolic-CH), 6.66 (m, 2H, *α*-pyrrolic-CH), 7.22 (m, 5H, Ar-H), 7.82 (s 2H, NH); ^{13}C NMR (100MHz, $CDCl_3$, 25˚C) δ = 43.84, (meso-C), 107.04, 108.29 (*β*-pyrrolic-C), 117.19, 126.88 (*α*-pyrrolic-C), 128.33, 128.55 (Ar-C), 132.47, 142.02 (Cq); ESI-MS : m/z = Calculated ($C_{15}H_{14}N_2$), 222.1157: Observed (M+Na) 214.1089.

5-pentafluorophenyldipyrromethane (3l) : Physical state: Gray solid; mp: 130 °C (lit 131-132 °C); R_f: 0.46 (chloroform); IR (KBr pellet, cm^{-1}): 3343, 2956, 1460, 1255, 1117, 853, 731, 727; ^{1}H NMR (400MHz, $CDCl_3$, 25˚C) δ = 5.87 (s, 1H, CH), 6.00 (s, 2H, *β*-pyrrolic, CH) 6.13-6.16 (m, 2 H, *β*-pyrrolic, CH), 6.70 (d, *J* = 1.84 Hz, 2H, *α*-pyrrolic, CH), 8.14 (br s, 2H, NH); ESI-MS : m/z = Calculated ($C_{15}H_9F_5N_2$), 312.0686: Observed (M+1) 313.1068.

5-(4-*tert*-butyl-phenyl)dipyrromethane (3m): Physical state: colorless crystal; mp: 165 °C (lit [32] 160 °C); R_f : 0.57 (1:1 chloroform: pet. Ether, v/v); IR (KBr pellet, cm^{-1}): 3343, 2956, 1460, 1255, 1117, 853, 731, 727; ^{1}H NMR (400MHz, $CDCl_3$, 25˚C) δ = 1.28 (s, 9H, -$(C(CH_3)_3)$), 5.43 (s, 1H, CH), 5.90 (s, 2H, *β*-pyrrolic CH), 6.13 (d, *J*= 2.92 Hz, 2H, *β*-pyrrolic CH), 6.66 (s, 2H, *α*-pyrrolic CH) 7.11 (d, J = 8.08 Hz, 2H. Ar-H), 7.29 (d, J = 8.08 Hz, 2H. Ar-H), 7.93 (br s, 2H, NH); ^{13}C NMR (100MHz, $CDCl_3$, 25˚C) δ = 31.33 (CH_3), 43.48 ($C(CH_3)_3$, 53.41 (-C), 107.03, 108.34 27 (*β*-pyrrolic-C), 117.05, 125.54 (*α*-pyrrolic-C), 127.96, 132.69 (Ar-C), 138.92, 149.76 (Cq); ESI-MS : m/z = Calculated ($C_{19}H_{22}N_2$), 278.1783: Observed (M^+) 301.4315.

5-(4-methylphenyl)dipyrromethane (3n): Physical state: colorless crystal; mp: 114 °C (lit [33]110-111 °C); R_f : 0.57 (1:1 chloroform: pet. Ether, v/v); IR (KBr pellet, cm^{-1}): 3343, 2956, 1460, 1255, 1117, 853, 731, 727; ^{1}H NMR (400MHz, $CDCl_3$, 25˚C) δ = 2.05 (s, 3H, -CH_3), 5.97 (d, 2H, *β*-pyrrolic CH) 6.13 (m, 2H, *β*-pyrrolic CH) 6.67 (d, *J* = 2.2 Hz 2H, *α*-pyrrolic CH) 7.12 (m, 5H. Ar-H), 7.37 (br s, 2H, NH); ^{13}C NMR (100MHz, $CDCl_3$, 25˚C) δ = 21.07 (CH_3), 43.61 (meso-C), 107.02, 108.27 (*β*-pyrrolic-C), 117.87, 128.21 (*α*-pyrrolic-C), 129.32, 132.76 (Ar-C), 136.25, 138.19 (Cq); ESI-MS : m/z = Calculated ($C_{16}H_{16}N_2$), 236.1313: Observed (M^+) 236.5767.

5-(4-methoxyphenyl)dipyrromethane (3o): Physical state: white solid; mp: 98-99 °C (lit [34] 99 °C.); R_f : 0.37 (1:1 chloroform: pet. Ether, v/v), IR (KBr pellet, cm^{-1}): 3345, 3092, 1610, 1513, 1460, 1255, 1176, 1111, 1032, 843, 737, 726;^{1}H NMR (400MHz, $CDCl_3$, 25˚C) δ = 3.89 (s, 3H, OCH_3), 5.50 (s, 1H CH), 6.01 (s, 2H, *β*-pyrrolic-CH), 6.25 (m, 2H, *β*-pyrrolic-CH), 6.76 (m, 2H α-pyrrolic-CH), 6.94 (d, *J* = 8.8, Hz, 2H Ar-H), 7.21 (d, *J* = 8.04, Hz, 2H Ar-H), 8.00 (brs, 2H, NH); ^{13}C NMR (100MHz, $CDCl_3$, 25 ˚C) δ: 43.05 (meso-C), 55.24 (-OCH_3)107.00, 108.31 (*β*-pyrrolic -C), 113.91, 117.09 (*α*-pyrrolic C), 129.34 132.84 (Ar-C), 134.17, 158.44 (Cq); ESI-MS : m/z = Calculated ($C_{14}H_{16}N_2O$), 252.1263: Observed (M+Na) 275.1198.

5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)dipyrromethane (3p): Physical state: white transparent crystal; R_f: 0.33(1:1 chloroform: pet. Ether, v/v); IR (KBr, cm^{-1}): 3450 (-OH), 3369 (-NH) 2955, 2871, 1433, 1233, 1148, 1031, 731, 717; ^{1}H NMR (400MHz, $CDCl_3$, 25 ˚C) δ = 1.41 (s, 18H, -$C(CH_3)_3$), 5.14 (s, 1H, phenolic-OH), 5.36 (s, 1H, meso-CH), 5.93 (s, 2H, *β*-pyrrolic -CH), 6.17 (m, 2H, *β*-pyrrolic -CH), 7.67 (d, *J* = 2.2 Hz, 2H, *α*-pyrrolic -CH), 7.02 (s, 2H, Ar-H) and 7.87 (br s, 2H, pyrrolic-NH); ^{13}C NMR (100MHz, $CDCl_3$, 25 ˚C) δ: 30.28 (-CH_3), 34.30 (-$C(CH_3)_3$), 43.86 (meso-C), 106.96, 108.23 (*β*-pyrrolic -C), 116.89, 124.96 (*α*-pyrrolic C), 132.31 (Ar-C), 133.27, 135.83, 152.60 (Cq); ESI-MS : m/z = Calculated ($C_{23}H_{30}N_2O$), 250.2358: Observed (M^+) 250.0105.

5-(3,5-di-methoxy-4-hydroxyphenyl)dipyrromethane (3q): Physical state: white crystals; R_f : 0.33 (8:2 $CHCl_3$: CH_3OH, v/v); mp: 148-150 °C; IR (KBr) 3451 (-OH), 3425 (-NH), 2953, 1636, 1485, 1242, 1090, 1023, 966, 715, 555 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$, 25˚C) δ = 3.78 (s, 6H, -OCH_3), 5.36 (s, 1H, phenolic-OH), 5.43 (s, 1H, -CH), 5.93 (d, 2H, β-pyrrole CH), 6.16 (m, 2H, β-pyrrole CH), 6.44 (s, 2H, phenyl), 6.68 (m, 2H, α-pyrrole CH), 7.98 (br s, 2H, NH); ^{13}C NMR (100MHz, $CDCl_3$, 25˚C) δ = 43.93 (*meso*-C), 56.17 (OCH_3), 105.10, 107.03(*β*-pyrrolic-C), 108.28, 117.11(α-pyrrolic-C), 132.51, 133.10 (aryl-c), 133.47, 146.00 (aryl Cq); ESI-MS : m/z = Calculated ($C_{17}H_{18}N_2O_3$), 298.1317: Observed (M+Na) 321.1323

5-(2,4,6-trimethylphenyl)dipyrromethane (3r): Physical state: Grey solid; mp: 170 °C (lit[35] 170-171 °C); R_f: 0.69 (1:1 chloroform: pet. Ether, v/v); IR (KBr pellet, cm^{-1}): 3343, 2956, 1460, 1255, 1117, 853, 731, 727; ^{1}H NMR (400MHz, $CDCl_3$, 25˚C) δ = 2.05 (s, 6 H, CH_3), 2.27 (s, 3H, CH_3), 5.91 (s, 1H, CH), 6.00 (s, 2H, *β*-pyrrolic, CH) 6.15-6.18 (m, 2 H, *β*-pyrrolic, CH), 6.65 (s, 2 H, *α*-pyrrolic, CH), 6.86 (s, 2H, Ar-H), 7.93 (br s, 2H, NH); ESI-MS : m/z = Calculated ($C_{18}H_{20}N_2$), 264.1626: Observed (M+1) 265.1892.

RESULTS AND DISCUSSION

Novel inorganic acid was synthesized by minor modification of known procedure (See Supplementary data). The identity of novel acid was unambiguously confirmed by DTA/TGA analysis and FT-IR spectrum. The catalytic reaction was performed in homogeneous phase due to the solubility of the solid acid in the reaction system. The activities of the solid acids prepared at various amounts of acids and calcination temperatures are summarized in (**Table 1**) in which n_P, n_B and n_S denote molar ratio of phosphoric, boric and sulfuric acid used in the preparation process. As a result, no activity for the synthesis reaction was presented without H_2SO_4 added during the preparation of the catalyst (**Table 1, Entry 1**), and the conversion of cyclohexanone was evidently. The catalyst prepared at n_P:n_B:ns = 1:2:3 and calcinated at temperature of 100 °C, the conversion of carbonyl compounds reached to maximum 99% which is almost the maximum conversion using novel inorganic acids as catalysts that have been reported so far (**Table 1, Entry 4**).

Table 1: Condensation of pyrrole and cyclohexanone in different molar ratio of novel acid catalyst[a]

Entry	Catalysts	Time (min.)	Conversion of pyrrole (%)	Isolated Yield of DPM (3) (%)
1	n_P:n_B:n_S = 1:1:0	20	0	0
2	n_P:n_B:n_S = 1:1:1	20	80	80
3	n_P:n_B:n_S = 1:1:2	20	90	90
4	n_P:n_B:n_S = 1:2:3	20	99	99
5	n_P:n_B:n_S = 1:2:1	20	80	80
6	n_P:n_B:n_S = 1:3:1	20	75	75
7	H_2SO_4	600	50	30
8	H_3PO_4	600	20	10
9	H_3BO_3	600	30	20

[a]Reaction conditions: reaction temperature 25 °C, cyclohexanone (10 mmol); pyrrole (20 mmol), acid catalyst (100 mg); solvent (25 mL) water,

The *meso*-substituted dipyrromethanes were synthesized by the reaction of pyrrole with aryl aldehydes/ ketones in the presence of catalytic amount of novel inorganic acid in good to excellent yields (**Table 2**) in water at room temperature. The structure of *meso*-substituted dipyrromethanes was characterized by ^{1}H NMR spectroscopic and mass spectrometric techniques (**data in the supplementary information**). The mixture was stirring at room temperature for appropriate time given in table 3 and the product was isolated by simple filtration. The purity of dipyrromethane was confirmed by HPLC in methanol/ water (1:1, v/v) as solvent, by comparing the retention time with authentic samples. **(Supplementary data, Figure S3)**. However, no product formation was observed in absence of novel inorganic acid.

The synthesis of dipyrromethanes in various solvent has been done but it takes longer time for completion and yield of the product was also low due to the formation of side products like (tripyrromethane and polypyrrole)**.** In chloroform solvent a black tarry side product polypyrrole was also observed. The best solvent for the formation of dipyrromethane was a solvent which provide hydrogen bonding with novel acid i.e. methanol/ethanol and water (**Table 2**).

Table 2: novel inorganic acid catalyzed synthesis of dipyrromethanes in various solvent[a]

Entry	Solvent	Time (min)	Product 3	Isolated yields of 3 (%)[c]
1	$CHCl_3$	30	3a	60
2	CH_2Cl_2	30	3a	70
3	EtOAc	45	3a	60
4	THF	40	3a	65
5	C_6H_6	45	3a	50
6	Toluene	45	3a	50
7	MeOH (EtOH)	20	3a	80
8	Hexane	60	3a	40
9	H_2O	20	3a	99

[a]Reaction conditions: ketone (10 mmol), pyrrole (20 mmol), acid catalyst (100 mg), water (25 ml), [b]Catalyst was prepared by usual method. [c]Isolated yield.

This high yield formation of 5-aryldipyrromethane and 5,5-disubstituted dipyrromethanes in the presence of novel acid prompted us to examine the reaction in water of other carbonyl compounds (**2a-2r)** with pyrrole. The reaction products and yields are given in (**Table 3**).

Table 3: Reaction of different aldehydes and ketones with pyrrole in water, catalyzed by novel inorganic acid[a]

Entry	Aldehydes and ketones	Time (min)	Product 3	Isolated yields of 3 (%)[c]
1	2a	20	3a	99
2	2b	20	3b	95
3	2c	20	3c	93
4	2d	20	3d	91
5	2e	20	3e	85
6	2f	20	3f	93
7	2g	25	3g	91
8	2h	40	3h	85[d]
9	2i	30	3i	90
10	2j	40	3j	70[d]
11	2k	20	3k	98
12	2l	20	3l	92
13	2m	20	3m	97
14	2n	20	3n	96
15	2o	20	3o	90
16	2p	20	3p	86
17	2q	20	3q	82
18	2r	30	3r	80

[a]Reaction conditions: arylaldehydes and ketones (10 mmol), pyrrole (20 mmol), acid catalyst (100 mg), water (25 ml), [b]Catalyst was prepared by usual method. [c]isolated yield, [d]reflex temperature.

Meso substituted dipyrromethanes are formed in almost quantitative yields when pyrrole was react with various aldehydes/ketones in the presence of a catalytic amount of inorganic acid in water. The electrophilic substitution reaction of pyrrole with aldehyde proceeded smoothly at room temperature. The results summarized in (**Table 3**), clearly indicate the scope of the reaction as the reactions of aromatic aldehydes as well as aromatic, aliphatic and alicyclic ketones (**Entries 3a-3r**). A variety of substituted aromatic aldehydes with pyrrole in the presence of a catalytic amount of inorganic acid in water gave the corresponding meso substituted dipyrromethanes in excellent yields. It is reported that aromatic aldehydes and ketones with strong electron withdrawing substituent on the ring require longer reaction time giving comparatively low to moderate yields of the corresponding meso substituted dipyrromethane. In this context the present protocol is note worthy because even nitro substituted aromatic ketone underwent smooth reactions with pyrrole giving excellent yield of products under stirring and neutral conditions in a very short time (< 40 min). The immense advantage of the novel acid catalyst is for both the aldehydes and ketones.
Although the working action of novel inorganic acid, leading to meso-substituted dipyrromethane in excellent yields, is not very clear at this stage, the preliminary experimental results dictate that excellent yield synthesis of meso-substituted dipyrromethane is not only possible but also quite acceptable with green chemistry.

CONCLUSION

We have optimized a convenient methodology for the synthesis of 5-aryldipyrromethanes, 5-aryl-5-alkyldipyrromethanes and 5,5-dialkyldipyrromethanes in aqueous medium. A little or no work-up (simple filtration from the reaction mixture) was required. The synthetic route is based on the condensation of aromatic aldehydes and ketones with pyrrole (2equiv.) in aqueous medium and catalyzed by novel acid. This method appears to be quite general and by careful control of the reaction time, which is strongly dependent on the nature of the aldehyde and ketones the dipyrromethanes can be obtained in a very selective way. Essentially no tripyrromethane or other oligomeric side products was obtained. This ‘green’ synthetic route toward dipyrromethanes in water at present, has been (and will be) an impulse for research toward oligopyrrolic macromolecules.

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