An efficient synthesis of tri and tetrasubstituted imidazoles from benzils using functionalised chitosan as biodegradable solid acid catalyst

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2. Experimental

2.1. General

Melting points of all the synthesized compounds were taken in a Riechert Thermover instrument and are uncorrected. Microwave irradiation was done using Microwave Synthesis Reactor, monowave 300 (Anton paar) (power 5-10 watt). The IR spectra were recorded on Perkin Elmer RXI spectrometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-d_6/$CDCl_3$ as solvent. Mass spectra were recorded on Micromass Quattro II (ESI) spectrometer. Elemental analyses (C, H and N) were conducted using the Elemental vario EL III elemental analyser and their results were found to be in agreement with the calculated values. The SEM and EDX characterization of the catalyst was performed on JEOL JSM 6510LV FEG from JEOL Japan. All reagents were purchased from Merck, Aldrich and were used without further purification. The purity of compounds was checked by thin layer chromatography (TLC) on glass plates coated with silica gel and visualized by iodine vapours.

2.2. Preparation of chitosan supported sulphuric acid

To a magnetically stirred suspension of chitosan (1.00 g) in dry dichloromethane (10 mL), chlorosulfonic acid (2 mL) was added drop wise at 0 °C during 1 h. After its complete addition, the mixture was stirred for another 2 h at room temperature until HCl was removed from reaction vessel. Then, the mixture was filtered and washed several times with methanol until a neutral pH level is achieved, then dried at room temperature to obtain chitosan sulphuric acid as white powder.

2.3. Determination of H^+ ion concentration of chitosan sulphuric acid

H^+ ion concentration of the catalyst was determined by neutralization titration analysis. 100 mg of catalyst was stirred in 20 mL of 0.1 N NaOH solution for 30 min in an Erlenmeyer

flask. The excess amount of base was then neutralized by the addition of 0.1 N HCl solution to the equivalence point of titration.

2.4. General procedure for the preparation of 2,4,5-trisubstituted imidazoles, 4a-f.

For trisubstituted imidazole derivatives, benzil (1 mmol), different aldehydes (1 mmol), and ammonium acetate (4.0 mmol) were dissolved in 5.0 mL of EtOH in a 100 mL round bottom flask containing a magnetic stir bar. Then 100 mg of the CTSA was added to the reaction mixture and the reaction mixture was refluxed while stirring for stipulated time period. In case of microwave irradiation, the reaction mixture was taken in a 10 mL reaction vial containing a magnetic stir bar. The reaction vessel was heated in the microwave reactor cavity for specified time period at 100 °C. After the completion of the reaction, the reaction mixture was filtered to separate the catalyst. The filtrate was added to ice cold water to get the solid product. This crude product was filtered and washed several times with water and dried. The crude product was further crystallized from methanol. The recovered catalyst was washed with ethanol and acetone and then air dried and reused in subsequent cycles.

2.5. General procedure for the preparation of 1,2,4,5-tetrasubstituted imidazole, 6a-f, 7a-d.

Benzil (1 mmol), different aldehydes (1 mmol), ammonium acetate (3.0 mmol) and different substituted amines (1mmol) were dissolved in 5.0 mL of EtOH in a 100 mL round bottom flask containing a magnetic stir bar. Then 100 mg of the CTSA was added to the reaction mixture and the reaction mixture was refluxed while stirring for appropriate time period. In case of microwave irradiation, the reaction mixture was taken in a 10 mL reaction vial containing a magnetic stir bar. The reaction vessel was heated in the microwave reactor cavity for specified time period at 100 °C. After the completion of the reaction, the reaction mixture was filtered to separate the catalyst. The filtrate was added to ice cold water to get the solid product. This crude product was filtered and washed several times with water and

dried. The crude product was further crystallized from methanol. The recovered catalyst was washed with ethanol and acetone and then air dried and reused in subsequent cycles.

Spectral Data of synthesized compounds

2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-4,5-diphenylimidazole(4a)

Nature of compound: White solid; m. p. 105 ˚C, IR (KBr) cm^{-1} : 1500 (C=N), 1600 (C=C), 3435 (NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.75 (s, 1H, CH_3), 7.33-7.43 (m, 5H, arom.H), 7.42-7.46 (m, 2H, arom.H), 7.47-7.51 (m, 3H, arom.H), 7.53-7.59 (m, 2H, arom.H), 7.66-7.71 (m, 3H, arom.H), 9.43 (br, s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.55, 110.00, 123.61, 125.15, 127.83, 128.55, 129.17, 137.71, 138.73, 149.79; ESI-MS: (*m/z*) 411.1 (M^+ +1). Elemental analysis for $C_{25}H_{19}ClN_4$: C, 73.07; H, 4.66; N, 13.66. Found C, 73.10; H, 4.68; N, 13.67.

2-(4-Chlorocoumarin-3-yl)-4,5-diphenylimidazole(4b)

Nature of compound: Yellow crystalline solid; m. p. 305 °C, IR (KBr) cm^{-1}: 1497 (C=N), 1601 (C=C), 1726 (C=O), 3445 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.27-7.31 (m, 2H, arom.H), 7.39-7.44 (m, 6H, arom.H), 7.45-7.49 (m, 4H, arom.H), 7.56-7.60 (m, 1H, arom.H), 8.01-8.04 (m, 1H, arom.H), 12.23 (br, s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 116.36, 120.63, 123.32, 124.13, 124.87, 127.70, 127.94, 128.67, 128.79, 132.50, 145.21, 153.09, 162.01; ESI-MS: (*m/z*) 399.7 (M^+ +1). Elemental analysis $C_{25}H_{19}ClN_4$: C, 73.07; H, 4.66; N, 13.66. Found C, 73.10; H, 4.68; N, 13.67.

2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-1,4,5-triphenylimidazole(6a)

Nature of compound: Cream crystalline solid; m. p. 305 °C, IR (KBr) cm^{-1}: 1496(C=N), 1597(C=C).^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.10 (s, 3H, CH_3), 7.08-7.11 (m, 2H,

arom.H), 7.18-7.26 (m, 5H, arom.H), 7.27-7.33 (m, 6H, arom.H), 7.43-7.54 (m, 7H, arom.H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 12.82, 124.59, 111.05, 126.53, 126.87, 127.61, 128.00, 128.35, 128.43, 128.68, 129.07, 129.95, 130.79, 149.31; ESI-MS: (*m/z*) 487.2 (M^+ +1). Elemental analysis: $C_{31}H_{23}ClN_4$: C, 76.45; H, 4.76; N, 11.50. Found C, 76.43; H, 4.78; N, 11.53.

1-(4-methoxyphenyl)-2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-4,5-diphenylimidazole(6b)

Nature of compound: Cream crystalline solid; m. p. 345 °C, IR (KBr) cm^{-1}: 1501(C=N), 1596(C=C).^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.12(s, 3H, CH_3), 3.71(s, 1H, O-CH_3), 6.79-6.81(m, 2H, arom.H), 7.00-7.03 (m, 2H, arom.H), 7.18-7.16 (m, 1H, arom.H), 7.21-7.24 (m, 4H, arom.H), 7.30-7.31(m, 3H, arom.H), 7.42-7.53(m, 7H, arom.H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 12.87, 55.09, 110.34, 113.74, 124.52, 126.30, 126.53, 126.87, 127.91, 128.11, 128.22, 128.33, 128.36, 128.68, 128.99, 130.18, 130.74, 134.29, 137.36, 137.45, 138.20, 149.32, 158.62; ESI-MS: (*m/z*) 517.2 (M^+ +1). Elemental analysis: $C_{32}H_{25}ClN_4O$: C, 74.33; H, 4.87; N, 10.83. Found C, 74.33; H, 4.88; N, 10.85.

1-(4-chlorophenyl)-2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-4,5-diphenylimidazole(6c)

Nature of compound: White crystalline solid; m. p. 306 °C, IR (KBr) cm^{-1}: 1500(C=N), 1599(C=C).^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.15(s, 3H, CH_3), 7.08-7.10 (m, 2H, arom.H), 7.22-7.25 (m, 3H, arom.H), 7.31-7.34 (m, 5H, arom.H), 7.45-7.52 (m, 7H, arom.H), 7.53-7.63(m, 2H, arom.H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.02, 110.21, 121.11, 124.58, 126.48, 127.33, 128.00, 129.09, 129.11, 129.26, 130.79, 133.61, 137.41, 137.90, 138.6, 149.61; ESI-MS: (*m/z*) 521.2 (M^+ +1). Elemental analysis: $C_{31}H_{22}Cl_2N_4$: C, 71.40; H, 4.25; N, 10.74. Found C, 71.38; H, 4.43; N, 10.70.

1-(p-tolyl)-2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-4,5-diphenylimidazole(6d)

Nature of compound: Cream crystalline solid; m. p. 337 °C, IR (KBr) cm^{-1}: 1498(C=N), 1601(C=C).^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 2.25(s, 3H, CH_3), 2.08(s, 1H, CH_3), 6.96-6.99 (m, 2H, arom.H), 7.07-7.09 (m, 2H, arom.H), 7.17-7.25 (m, 5H, arom.H), 7.30-7.32 (m, 3H, arom.H), 7.46-7.48(m, 7H, arom.H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 13.02, 22.11, 110.01, 123.10, 124.58, 126.48, 127.33, 128.00, 129.10, 129.20, 129.17, 130.79, 134.61, 137.41, 138.90, 144.61, 148.81; ESI-MS: (*m/z*) 501.3 (M^+ +1). Elemental analysis: $C_{32}H_{25}ClN_4$: C, 76.71; H, 5.02; N, 11.18. Found C, 76.73; H, 5.00; N, 11.19.

1-(4-hydroxyphenyl)-2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-4,5-diphenylimidazole(6e)

Nature of compound: Cream crystalline solid; m. p. 329 °C, IR (KBr) cm^{-1}: 1511(C=N), 1599(C=C). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 2.10(s, 3H, CH_3), 2.08(s, 1H, CH_3), 6.61-6.64 (m, 2H, arom.H), 6.64-6.87(m, 2H, arom.H), 7.21-7.23 (m, 5H, arom.H), 7.30-7.32 (m, 3H, arom.H), 7.46-7.53(m, 7H, arom.H), 9.63(OH). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 12.89, 110.43, 115.16, 124.54, 126.50, 127.92, 128.05, 128.33, 128.62, 129.03, 130.74, 134.36, 137.20, 138.20, 149.29, 157.00; ESI-MS: (*m/z*) 503.6 (M^+ +1). Elemental analysis: $C_{31}H_{23}ClN_4O$: C, 79.02; H, 4.60; N, 11.13. Found C, 79.02; H, 4.62; N, 11.13.

1-Benzyl-2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-4,5-diphenylimidazole(6f)

Nature of compound: Pinkish crystalline solid; m. p. 330 °C, IR (KBr) cm^{-1}: 1498(C=N), 1601(C=C).^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 2.16(s, 3H, CH_3), 4.04(2H, s, CH_2), 7.19-7.46 (12H, m, arom.H), 7.47-7.61 (8H, m, arom.H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 13.23, 48.71, 110.91, 124.67, 125.22, 126.24, 127.07, 127.35, 127.48, 127.89, 128.14, 128.35, 128.96, 130.99, 135.04, 136.89, 137.62, 137.73, 148.64. ESI-MS: (*m/z*) 501.3 (M^+ +1). Elemental analysis: $C_{35}H_{25}ClN_4$: C, 78.27; H, 4.69; N, 10.43. Found C, 78.26; H, 4.65; N, 10.41.

2-(Indol-3-yl)-1,4,5-triphenylimidazole(7a)

Nature of compound: White solid; m. p. 314 °C, IR (KBr) cm^{-1}: 1498(C=N), 1601(C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.23(1H, s, CH), 7.12-7.17(3H, m, arom.H), 7.22-7.26(7H, m, arom.H) 7.33-7.36(3H, m, arom.H), 7.40-7.43(3H, m, arom.H), 7.59-7.61(2H, m, arom.H), 8.53-8.56(1H, m, arom.H), 11.03(1H, s, N-H).^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 106.81, 111.36, 121.91, 122.17, 122.29, 124.23, 126.09, 127.11, 129.10, 129.31, 129.17, 130.33, 130.78, 130.97, 131.11, 135.40, 135.81, 136.03, 137.19, 139.13, 144.04. ESI-MS: (*m/z*) 412.13 (M^+ +1). Elemental analysis: $C_{29}H_{21}N_3$: C, 84.64; H, 5.14; N, 10.21. Found C, 84.60; H, 5.15; N, 10.21.

1-(4-methoxyphenyl)-2-(Indol-3-yl)-4,5-diphenylimidazole(7b)

Nature of compound: White solid; m. p. 332 °C, IR (KBr) cm^{-1}: 1496(C=N), 1604(C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.78(3H, s, OCH_3), 6.24(1H, s, CH), 6.93-6.96(2H, m, arom.H), 7.12-7.17(3H, m, arom.H) 7.22-7.29(9H, m, arom.H), 7.35-7.37(1H, m, arom.H), 7.57-7.60(2H, m, arom.H), 8.58-8.60(1H, m, arom.H), 11.02(1H, s, N-H).^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 55.11, 107.01, 110.46, 121.01, 122.77, 122.30, 124.23, 125.99, 127.11, 129.10, 129.34, 129.16, 130.33, 131.78, 131.97, 132.11, 135.44, 135.71, 136.13, 137.09, 139.12, 144.94. ESI-MS: (*m/z*) 442.1 (M^+ +1). Elemental analysis: $C_{30}H_{23}N_3O$: C, 81.60; H, 5.25; N, 9.51. Found C, 81.62; H, 5.23; N, 9.55.

1-(4-chlorophenyl)-2-(Indol-3-yl)-4,5-diphenylimidazole(7c)

Nature of compound: White crystalline solid; m. p. 315 °C, IR (KBr) cm^{-1}: 1495(C=N), 1607(C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.35(1H, s, CH), 7.12-7.18(3H, m, arom.H), 7.22-7.31(7H, m, arom.H) 7.35-7.38(3H, m, arom.H), 7.42-7.45(2H, m, arom.H), 7.58-7.60(2H, m, arom.H), 8.49-8.51(1H, m, arom.H), 11.08(1H, s, N-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 106.60, 112.34, 121.91, 122.17, 122.09, 124.23, 126.09, 127.11,

129.10, 129.31, 129.16, 130.33, 130.98, 131.17, 132.11, 135.47, 135.71, 136.09, 137.10, 138.94, 145.00. ESI-MS: (*m/z*) 446.1 (M^+ +1). Elemental analysis: $C_{29}H_{20}ClN_3$: C, 78.10; H, 4.52; N, 9.42. Found C, 78.13; H, 4.50; N, 9.44.

1-(4-hydroxyphenyl)-2-(Indol-3-yl)-4,5-diphenylimidazole(7d)

Nature of compound: Light pink solid; m. p. 308 °C, IR (KBr) cm^{-1}: 1499(C=N), 1611(C=C). ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.26(1H, s, CH), 6.76-6.79(2H, m, arom.H), 7.12-7.17(5H, m, arom.H) 7.22-7.32(7H, m, arom.H), 7.34-7.37(1H, m, arom.H), 7.57-7.59(2H, m, arom.H), 8.59-8.61(1H, m, arom.H), 9.77(1H, s, O-H), 11.06(1H, s, N-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 106.42, 111.31, 114.51, 119.98, 121.79, 122.91, 123.41, 126.9, 129.10, 127.11, 129.36, 129.79, 130.88, 131.33, 134.61, 136.47, 138.71, 138.99, 139.60, 144.66, 159.10. ESI-MS: (*m/z*) 428.1 (M^+ +1). Elemental analysis: $C_{29}H_{21}N_3O$: C, 81.47; H, 4.95; N, 9.82. Found C, 81.45; H, 4.98; N, 9.80.

2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-4,5-di-p-tolyl-1H-imidazole (4a')

Nature of compound: White solid; m. p. 93 ˚C, IR (KBr) cm^{-1} : 1500 (C=N), 1599 (C=C), 3434 (NH), ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.01 (s, 1H, CH_3), 2.35 (s, 1H, CH_3), 2.65 (s, 1H, CH_3), 7.13-7.15 (m, 4H, arom.H), 7.39-7.49 (m, 5H, arom.H), 7.52-7.55 (m, 4H, arom.H), 8.29 (br, s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.31, 20.9, 21.27, 110.02, 123.89, 125.11, 127.65, 128.49, 129.12, 129.29, 129.70, 129.90, 130.01, 137.16, 137.14 138.21, 149.71; ESI-MS: (*m/z*) 439.1 (M^+ +1). Elemental analysis for $C_{27}H_{23}ClN_4$: C, 73.87; H, 5.28; N, 12.76. Found C, 73.86; H, 5.29; N, 12.67.

1-(p-tolyl)-2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)- 4,5-di-p-tolyl-1H-imidazole (6g)

Nature of compound: Cream crystalline solid; m. p. 332 °C, IR (KBr) cm^{-1}: 1512(C=N), 1597 (C=C).^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.19 (s, 3H, CH_3), 2.12(s, 3H, CH_3), 2.27(s, 3H, CH_3), 2.31(s, 3H, CH_3), 7.04-7.12 (m, 8H, arom.H), 7.33-7.38 (m, 4H, arom.H), 7.45-

7.47 (m, 3H, arom.H), 7.51-7.53 (m, 2H, arom.H), ; ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.91, 20.91, 21.30, 110.20, 115.61, 125.41, 126.11, 127.80, 128.71, 129.01, 129.11, 130.10, 130.44, 134.61, 134.83, 137.41, 138.13, 138.9, 149.11; ESI-MS: (*m/z*) 529.01 (M^+ +1). Elemental analysis: $C_{34}H_{29}ClN_4$: C, 77.18; H, 5.52; N, 10.59. Found C, 77.17; H, 5.53; N, 10.60.

1-(4-chlorophenyl)-2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-4,5-di-p-tolyl-1H-imidazole (6h)

Nature of compound: White crystalline solid; m. p. 310 °C, IR (KBr) cm^{-1}: 1494(C=N), 1596 (C=C).^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.07 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.94-6.96 (m, 2H, arom.H), 7.03-7.10 (m, 8H, arom.H), 7.35-7.37 (m, 2H, arom.H), 7.45-7.47 (m, 3H, arom.H), 7.50-7.51(m, 2H, arom.H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 14.24, 20.89, 21.23, 110.12, 123.51, 123.81, 125.01, 127.70, 128.45, 129.15, 129.09, 129.68, 129.77, 129.87, 130.12, 133.66, 136.19, 137.21, 137.15, 138.31, 149.71; ESI-MS: (*m/z*) 549.2 (M^+ +1). Elemental analysis: $C_{33}H_{26}Cl_2N_4$: C, 72.13; H, 4.76; N, 10.19. Found C, 72.14; H, 4.77; N, 10.20.