A novel, efficient, and recyclable biocatalyst for Michael additions and its iron (III) complex as promoter for alkyl oxidation reactions

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Supporting Data

Apparatus and Instrumentation

Melting points were recorded on Gallenkamp apparatus and are reported uncorrected. The Fourier Transform Infrared (FTIR) spectra were recorded in KBr pellets on a JASCO FT-IR-6300, system at a resolution of 4 cm⁻¹ ranging 400-4000 cm⁻¹. NMR measurements were made using a Bruker DPX spectrometer, at 600 MHz for ¹H-NMR and 125 MHz for ¹³C-NMR, in DMSO-d₆ as solvent using TMS as internal standard. Solid state NMR spectra were recorded at 600 MHz Bruker Avance II spectrometer, 150 MHz for ¹³C NMR. Mass spectra were measured on a GCMS DFS-Therm spectrometer, with EI 70 eV. Elemental analyses were made by means of ELEMENTAR-VARIO MICROCUBE Elemental Analyzer.

1. Application of Cs-g-PCPA, graft copolymer, against unmodified chitosan beads, as a heterogeneous basic catalyst for Michael addition reactions

1.1 Reaction of 3 with dimedone 4

Mixtures of benzylidene-malononitrile 3 (1.54 g, 10.0 mmol) with dimedone 4 (10.0 mmol) in the presence of 50 mL absolute ethanol were stirred at reflux for 3 h. The solution contained 10%wt. of the catalyst (Method A using chitosan beads and Method B using Cs-g-PCPA (G% = 64%) beads). The solid product formed in this process was separated by filtration and recrystallized from ethanol.

2-aminomethyl-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile 5
The compound was obtained as colorless crystals; m.p. 230-231°C; Lit.\textsuperscript{1} 233-234°C. IR (KBr): \( \nu = 1691 \) (C=O), 2220 (CN), 3341, 3420 (NH\textsubscript{2}) cm\textsuperscript{-1}, \(^1\)H NMR (DMSO-d\textsubscript{6}): \( \delta = 0.96 \) (s, , 3H, CH\textsubscript{3}), 1.05 (s, , 3H, CH\textsubscript{3}), 2.09 – 2.24 (s, , 2H, CH\textsubscript{2}), 2.48 (s, , 2H, CH\textsubscript{2}), 4.14 (s, 1H, CH, C-4 pyran), 7.08 (s, 2H, NH\textsubscript{2}), 7.16 – 7.29 (m, 5H, phenyl-H); \(^13\)C NMR (DMSO-d\textsubscript{6}): \( \delta = 26.9 \) (CH\textsubscript{3}), 28.5 (CH\textsubscript{3}), 31.9 (C(CH\textsubscript{3})\textsubscript{2}), 35.7 (C-4, pyran), 40.1, 50.1 (CH\textsubscript{2}), 59.6 (CH\textsubscript{2}), 112.9, 118.7 (CN), 126.0, 126.7, 127.8, 143.8, 158.1, 162.7 (aromatic carbons), 195.0 (C=O); MS, m/z (%), 294.1 (M\textsuperscript{+}, 29), 217.1 (66), 55.1 (100). Anal. Calcd. for C\textsubscript{18}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.36; H, 6.10; N, 9.43. % Yields: Method A (Cs beads; %Yield = 75), Method B (Cs-g-PCPA beads; %Yield = 95).

### 1.2 Reaction of 3 with Barbituric and thiobarbituric acids

Mixtures of benzylidene-malononitrile 3 (10.0 mmol) and barbituric 6a and thiobarbituric acid 6b (10.0 mmol) in the presence of 50 mL absolute ethanol were stirred at reflux for 3 h. The solutions contained 10\%wt of the catalyst (Method A using chitosan beads and Method B using Cs-g-PCPA (G\% = 64\%) beads). The solid products formed in these processes were separated by filtration and recrystallized from ethanol.

**7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile 7a**

This compound was obtained as Pale yellow crystals; m.p. 207°C,\textsuperscript{2,3} IR(KBr): \( \nu = 1686, 1715 \) (C=O), 2190 (CN), 3305, 3390 (NH\textsubscript{2}) cm\textsuperscript{-1}, \(^1\)H NMR (DMSO-d\textsubscript{6}): \( \delta = 4.24 \) (s, 1H, H-4), 7.08 (s, 2H, NH\textsubscript{2}), 7.13 – 7.34 (m, 5H, Phenyl), 11.51 (s, 1H, NH), 12.07 (s, 1H, NH); \(^13\)C NMR (DMSO-d\textsubscript{6}): \( \delta = 33.7, 58.0, 82.4, 117.6 \) (CN), 126.8 (p-C, Phenyl), 127.1 (o-C, Phenyl), 128.4 (m-C, Phenyl), 144.8 (i-C, Phenyl), 124.1, 128.7, 129.0, 144.1, 152.2, 158.6 (C-2, C-6), 161.7, 184.3 (C=O); MS, m/z (%), 282.1 (M\textsuperscript{+}, 70), 77.1 (100). Anal. Calcd. for C\textsubscript{14}H\textsubscript{10}N\textsubscript{4}O\textsubscript{3}: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.49; H, 3.47; N, 19.68. % Yields: Method A (Cs beads; %Yield = 65), Method B (Cs-g-PCPA; %Yield = 80).

**7-amino-4-oxo-5-phenyl-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile 7b**

This compound was obtained as pale yellow crystals; m.p. 190°C; IR(KBr): \( \nu = 1690 \) (C=O), 2192 (CN), 3280, 3310 (NH\textsubscript{2}) cm\textsuperscript{-1}, \(^1\)H NMR (DMSO-d\textsubscript{6}): \( \delta = 4.22 \) (s, 1H, H-5),
7.09 (s, 2H, NH₂), 7.11-7.27 (m, 5H, phenyl), 10.86 (s, 1H, NH), 12.03 (s, 1H, NH); \[^{13}\text{C}\] NMR (DMSO-d6): \(\delta = 36.1, 59.7, 87.7, 118.4, 118.7, 128.9, 130.6, 142.2, 149.0, 151.9, 158.0, 163.1\); MS, m/z (%), 298.1 (M⁺, 37), 77.1 (100). Anal. Calcd. for C\(_{14}\)H\(_{10}\)N\(_4\)O\(_2\)S: C, 56.37; H, 3.38; N, 18.78; S, 10.75. Found: C, 56.11; H, 3.16; N, 18.60; S, 10.67. %Yields: Method A (Cs beads; %Yield = 60), Method B (Cs-g-PCPA; %Yield = 76).

1.3 Gewald's reaction of 3-oxoalkanenitriles

To mixtures of 3-oxoalkanenitriles \(9a, b\) (4.0 mmol) in dry 1,4-dioxane (15.0 mL) were added sulfur (4.8 mmol, 154 mg), methyl cyanoacetate \(10\) (4.0 mmol, 396 mg, 350 mL). The solutions also contained 10%wt of the catalyst (Method A using chitosan beads and Method B using Cs-g-PCPA (G% = 64%) beads). The mixtures were then stirred at reflux for 8 h, filtered to remove the solid catalyst and extracted with chloroform (2 x 10 mL). The combined organic layers were washed with brine, dried with anhydrous MgSO\(_4\) and evaporated giving the solid products, which were recrystallized from ethanol.

**Methyl-2-amino-5-cyano-4-phenylthiophene-3-carboxylate 11a**

This compound was obtained as yellow solid; M.p. 110°C (Lit.\(^2,3\) m.p. 109-111°C). IR(KBr): \(\nu = 1668\) (C=O), 2230 (CN), 3310 (br , NH\(_2\) groups) cm\(^{-1}\); \[^1\text{H}\] NMR (DMSO-d6): \(\delta = 3.64\) (s, 3H, CO\(_2\)CH\(_3\)), 5.22 (br s, 2H, NH\(_2\)), 7.29 – 7.87 (m, 5H, Phenyl); \[^{13}\text{C}\] NMR (DMSO-d6): \(\delta = 26.7\) (CO\(_2\)CH\(_3\)), 127.8, 130.1, 139.6, 141.3, 151.9, 159.0, 169.0; MS, m/z (%), 259.1 (M⁺, 12), 195.1 (100). Anal. Calcd. for C\(_{13}\)H\(_{10}\)N\(_2\)O\(_2\)S: C, 60.45; H, 3.90; N, 10.85; S, 12.41. Found: C, 60.31; H, 3.72; N, 10.57; S, 12.14. %Yields: Method A (Cs beads; %Yield = 50), Method B (Cs-g-PCPA; %Yield = 75).

**Methyl-2-amino-5-cyano-4-(1-methyl-1H-pyrrol-2-yl)thiophene-3-carboxylate 11b**

This compound was obtained as Orange solid; M.p. 139°C (Lit.\(^2,3\) m.p. 138-142°C). IR(KBr): \(\nu = 1658\) (C=O), 2236 (CN), 3325 (NH\(_2\) groups) cm\(^{-1}\); \[^1\text{H}\] NMR (DMSO-d6): \(\delta = 1.34\) (s, 3H, CH\(_3\), ester), 3.14 (s, 3H, N-CH\(_3\)), 3.81 (s, 2H, CH\(_2\), ester), 4.42 (br s, 2H, NH\(_2\)), 6.19 (m, 1H, H-4\'), 7.05 (d, 1H, J = 2.5 Hz, H-5\'), 7.24 (d, 1H, J = 2.5, H-3'); \[^{13}\text{C}\] NMR (DMSO-d6): \(\delta = 23.2\) (CO\(_2\)CH\(_3\)), 29.7 (N-CH\(_3\)), 105.8, 113.1, 115.8, 116.9, 118.5, 131.0, 145.1, 158.0, 160.3, 169.8; MS, m/z (%), 262.1 (M⁺, 18), 195.1 (100). Anal. Calcd. for C\(_{12}\)H\(_{11}\)N\(_2\)O\(_2\)S: C, 55.16; H, 4.24; N, 16.08; S, 12.27. Found: C, 55.04; H, 3.97; N, 15.87; S, 12.05. %Yields: Method A (Cs beads; %Yield = 60%), Method B (Cs-g-PCPA; %Yield = 80).
1.4 Reaction of enamino-nitriles 12a,b with dimeredone 4

Mixtures of the 3-(piperidinyl-1-yl)acrylonitrile 12a, 3-morpholino-acrylonitrile 12b, (10.0 mmol) and dimeredone 4 (10 mmol) in 30 mL absolute ethanol containing the catalyst (10%wt.) (Method A using chitosan beads and Method B using Cs-g-PCPA (G% = 64%) beads). The mixtures were stirred at reflux for 5 h and filtered to give solids, which were recrystallized from ethanol.

7,7-Dimethyl-2-(piperidine-1-yl)-7,8-dihydroquinolin-5(6H)-one 13a

The compound was obtained as colorless crystals. m.p.: 145°C. Anal. Calcd. for C_{16}H_{22}N_{2}O: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.48; H, 8.52; N, 10.73. % Yields: Method A (Cs beads; %Yield = 80), Method B (Cs-g-PCPA; %Yield = 90). The crystal structure data has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 824677.

7,7-Dimethyl-2-morpholino-7,8-dihydroquinolin-5(6H)-one 13b

The compound was obtained as colorless crystals. m.p.: 129°C. Anal. Calcd. for C_{15}H_{20}N_{2}O_{2}: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.23; H, 7.68; N, 10.64. %Yields: Method A (Cs beads; %Yield = 65), Method B (Cs-g-PCPA; %Yield = 85). The crystal structure data has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 824678.

2. Application of the Cs-g-PCPA/Fe(III) chelate as an oxidizing catalyst

(Oxidation of methyl pyridazinone)

Hydrogen peroxide (30%, 5 mmol) was added carefully to a pre-heated solutions of methyl pyridazinones 14a,b (1 mmol) in glacial acetic acid (5 mL) containing 10%wt of the Cs-g-PCPA(G=64%)/Fe(III) chelate. The mixtures were then stirred at reflux until thin layer chromatography indicated that the reactions were complete. The crude product mixtures were poured into 20 mL ice/water mixture and an stirred for 30 min. Extraction with CH_{2}Cl_{2} gave organic layers that were dried over anhydrous Na_{2}SO_{4} and concentrated under reduced pressure to yield analytically pure products 15a,b.

7-amino-2-phenylfuro[3,4-d]pyrazin-1(2H)-one 15a
The compound was obtained as yellow powder. (%Yield: 72%; m.p. 198°C). IR (KBr, cm$^{-1}$): $\nu = 3350$ and 3330 (NH$_2$), 1660 (CO). $^1$H NMR (400 MHz, DMSO-d$_6$, $\delta = 6.07$ (s, 2H, NH$_2$), 7.46 (s, 1H, pyridazinone), 7.51 (m, 5H, phenyl), 8.14 (s, 1H, furan). $^{13}$C NMR (125 MHz, DMSO-d$_6$, $\delta = 114.1$, 121.6, 126.8, 130.7, 131.2, 139.9, 140.8, 144.0, 147.2 (aromatic carbons), 168.2 (C=O). MS (m/z (%)): 227.1 (M+, 12), 77.1 (100). Anal. Calcd. for C$_{12}$H$_9$N$_3$O$_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.28; H, 3.78; N, 18.29.

7-amino-2-(4-chlorophenyl)furo[3,4-d]pyridazin-1(2H)-one 15b

The compound was obtained as pale yellow powder. (%Yield: 66%; m.p. 215°C). IR (KBr, cm$^{-1}$): $\nu = 3360$ and 3330 (NH$_2$), 1668 (CO). $^1$H NMR (400 MHz, DMSO-d$_6$, $\delta = 6.29$ (s, 2H, NH$_2$), 7.25 (d, 2H, o-H, $J = 8.00$ Hz, aryl), 7.69 (d, 2H, m-H, $J = 8.00$ Hz, aryl), 8.26 (s, 1H, furan). $^{13}$C NMR (125 MHz, DMSO-d$_6$), $\delta = 113.1$, 124.4, 126.9, 128.6, 129.0, 133.1, 139.1, 151.7, 155.9 (aromatic carbons), 171.9 (C=O). MS (m/z (%): 261.1 (M+, 4), 111.1 (100). Accurate Mass; 261.0298 (C$_{12}$H$_8$O$_2$N$_3$Cl$_1$).

References:

