Electronic Supplementary Information

Catalysis by Amberlyst A 21: A greener approach to 4,5,6,7-tetrahydro-1*H*-indazol-3(2*H*)-ones via efficient construction of cyclohexanone derivatives

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General methods: Unless stated otherwise, solvents and chemicals were obtained from commercial sources and were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ^1H and ^{13}C NMR spectra were determined in $\text{DMSO}-d_6$ solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using melting point B-540 apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. HRMS was determined using waters LCT premier XETOF ARE-047 apparatus. The ion exchange resin i.e. Amberlyst A-21 was purchased from Sigma-Aldrich and was used without any further purification.

Preparation of diethyl 4'-bromo-5-methyl-3-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2,6-dicarboxylate (3a)

To a solution of ethyl acetoacetate **2a** (2.2 mmol) and 4-bromobenzaldehyde **1a** (1.0 mmol) in *i*-PrOH (10 ml) was added Amberlyst A-21 (20% w/w) and the mixture was stirred at 80 °C for 15 h. After completion of the reaction as indicated by TLC the mixture was cooled to room temperature. The resin was separated by filtration and washed with warm *i*-PrOH (55-60 °C) to elute all the contaminated organic compounds from the resin. The combined filtrate was concentrated under low vacuum to reduce its volume and then cooled to give the desired product **3a** as a white solid; mp 150-151°C; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 7.48 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 4.97 (s, OH), 3.97-3.79 (m, 6H), 3.29 (d, $J = 8.0$ Hz, 1H), 2.92 (d, $J = 16.0$ Hz, 1H), 2.34 (d, $J = 16.0$ Hz, 1H), 0.96 (s, 3H), 0.88 (t, $J = 8.0$ Hz, 3H), 0.87 (t, $J = 8.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 200.7, 173.5, 167.4, 137.3, 131.7, 129.7, 121.6, 72.9, 62.2, 61.1, 60.9, 56.7, 52.6, 44.5, 28.5, 13.9, 13.6; IR (KBr): 3433, 1736, 1598, 1364, 1174, 775

cm⁻¹; HRMS (ESI): calcd for C₁₉H₂₄O₆Br (M+H)⁺ 427.0756, found 427.0736; MS (ESI): m/z ([M+H]⁺): 427.1

General procedure for the preparation of compound 5a-c

To a solution of ethyl acetoacetate **2a** (2.2 mmol) and aldehyde **1** (1.0 mmol) in ethanol (10 ml) was added Amberlyst A-21 (20% w/w) and the mixture was stirred at 80 °C for 15 h to ensure the completion of the reaction (monitored by TLC). The reaction mass was cooled to room temperature and hydrazine hydrate **4** (1.0 mmol) was added. The mixture was stirred at 80 °C for another 12 h. After completion of the reaction (confirmed by TLC) the resin was separated by filtration. The filtrate was concentrated under low vacuum to give the crude product that was purified by recrystallization from ethanol to afford the pure product **5a-c**.

Recovery of the catalyst: The recovered Amberlyst A21 resin, obtained by filtering off the reaction product, was washed successively with THF (5 mL) and EtOH (5 mL) thrice and dried at 100 °C for 2 h. The efficiency of the catalyst was not changed significantly on using for additional three consecutive times in the model reaction is shown in Table 1.

Ethyl 4-(4-bromophenyl)-6-hydroxy-6-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate (5a)

White solid; mp 303-304 °C; ¹H NMR (DMSO-*d*₆, 400 MHz): δ 11.1 (bs, NH), 9.05 (bs, NH), 7.39 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 4.50 (s, OH), 4.03 (d, *J* = 10.4 Hz, 1H), 3.96-3.88 (m, 2H), 2.76 (d, *J* = 15.6 Hz, 1H), 2.56-2.50 (m, 2H), 1.23 (s, 3H), 0.99 (t, *J* = 8.4 Hz, 3H); ¹³C NMR (DMSO-*d*₆, 100 MHz): δ 172.0, 158.0, 142.4, 138.9, 130.6 (2C), 130.5, 119.0, 99.0, 69.9, 59.5, 59.3, 38.8, 38.3, 36.5, 28.3, 14.0; IR (KBr): 3280, 1741, 1516, 1260, 806 cm⁻¹; HRMS (ESI): calcd for C₁₇H₂₀N₂O₄Br (M+H)⁺ 395.0606, found 395.0598; MS (ESI): m/z ([M+H]⁺): 395.0.

Ethyl 6-hydroxy-6-methyl-4-(4-nitrophenyl)-3-oxo-3,3a,4,5,6,7-hexahydro-2H-indazole-5-carboxylate (5b)

White solid; mp 293-294 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 10.9 (bs, NH), 9.4 (bs, NH), 8.11 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 4.60 (s, OH), 4.21 (d, J = 10.8 Hz, 1H), 3.96-3.84 (m, 2H), 2.82 (d, J = 16.0 Hz, 1H), 2.63 (d, J = 10.8 Hz, 1H), 2.55 (d, J = 16.0 Hz, 1H), 1.25 (s, 3H), 0.97 (t, J = 8.0 Hz, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 171.6, 157.9, 151.5, 146.0, 138.9, 129.6 (2C), 123.0 (2C), 98.6, 69.9, 59.6, 58.8, 38.8, 36.5, 28.2, 14.0; IR (KBr): 3501, 1597, 1347, 1180, 775 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{20}\text{N}_3\text{O}_6$ ($\text{M}+\text{H}$) $^+$ 362.1352, found 362.1356; MS (ESI): m/z ($[\text{M}+\text{H}]^+$): 362.2.

Ethyl 4-(4-cyanophenyl)-6-hydroxy-6-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate (5c)

White solid; mp 292-293 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 11.2 (bs, NH), 9.1 (bs, NH), 7.69 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.56 (s, OH), 4.13 (d, J = 10.8 Hz, 1H), 3.94-3.87 (m, 2H), 2.79 (d, J = 16.0 Hz, 1H), 2.60 (d, J = 10.8 Hz, 1H), 2.58 (d, J = 16.0 Hz, 1H), 1.24 (s, 3H), 0.96 (t, J = 8.0 Hz, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 171.7, 157.8, 149.1, 138.9, 131.7 (2C), 129.4 (2C), 119.0, 108.8, 98.6, 69.9, 59.5, 58.8, 38.8, 36.5, 28.2, 13.9; IR

(KBr): 3440, 1598, 1363, 775 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{20}\text{N}_3\text{O}_4$ $(\text{M}+\text{H})^+$ 342.1454, found 342.1448; MS (ESI): m/z $([\text{M}+\text{H}]^+)$: 342.2.

General procedure for the preparation of compound 3d-i

To a solution of ethyl acetoacetate **2a** (2.2 mmol) and aldehyde **1** (1.0 mmol) in *i*-PrOH (10 ml) was added Amberlyst A-21 (20% w/w) and the mixture was stirred at 80 °C for 15 h. After completion of the reaction as indicated by TLC the mixture was cooled to room temperature. The resin was separated by filtration and washed with warm *i*-PrOH (55-60 °C) to elute all the contaminated organic compounds from the resin. The combined filtrate was concentrated under low vacuum to reduce its volume and then cooled to give the desired product.

Diethyl 4-hydroxy-4-methyl-6-oxo-2-(*p*-tolyl)cyclohexane-1,3-dicarboxylate (3d)

White solid; mp 131-132 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 7.10 (q, J = 8.0 Hz, 4H), 4.08-3.97 (m, 3H), 3.91-3.82 (m, 2H), 3.70 (bs, OH), 3.63 (d, J = 12.4 Hz, 1H), 3.01 (d, J = 12.4 Hz, 1H), 2.70 (d, J = 14.4 Hz, 1H), 2.49 (d, J = 14.4 Hz, 1H), 2.29 (s, 3H), 1.33 (s, 3H), 1.06 (t, J = 8.0 Hz, 3H), 0.82 (t, J = 8.0 Hz, 3H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ 203.5, 170.6, 168.2, 136.9, 135.9, 128.5 (2C), 128.2, 72.5, 62.0, 59.9, 59.4, 56.3, 54.0, 43.6, 38.8, 28.2, 20.6, 13.8, 13.7; IR (KBr): 3434, 1710, 1598, 1352, 774 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{27}\text{O}_6$ $(\text{M}+\text{H})^+$ 363.1808, found 363.1819; MS (ESI): m/z $([\text{M}+\text{H}]^+)$: 363.2.

Diethyl 2-(2-formylphenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3e)

White solid; mp 180-182 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 10.4 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.26 (m, 2H), 7.01 (d, J = 8.0 Hz, 1H), 5.97 (d, J = 5.2 Hz, 1H), 5.46 (d, J = 5.2 Hz, 1H), 4.94 (s, OH), 4.42 (d, J = 11.6 Hz, 1H), 4.18 (q, J = 8.0 Hz, 2H) 3.97 (q, J = 8.0 Hz, 2H), 3.01 (d, J = 11.6 Hz, 1H), 2.62 (d, J = 15.2 Hz, 1H), 2.44 (d, J = 15.2 Hz, 1H), 1.24 (t, J = 8.0 Hz, 6H), 1.03 (t, J = 8.0 Hz, 3H); ^{13}C NMR (CDCl₃, 100 MHz): δ 206.2, 188.0, 171.7, 170.3, 144.2, 143.0, 128.7, 127.8, 125.6, 123.9, 78.0, 72.5, 68.7, 60.8, 60.0, 55.8, 28.1, 22.5, 14.2, 13.8; IR (KBr): 3433, 1710, 1694, 1598, 1362, 775 cm^{-1} ; HRMS (ESI): calcd for C₂₀H₂₅O₇ (M+H)⁺ 377.1600, found 377.1611; MS (ESI): m/z ([M+H]⁺): 377.2.

Diethyl 2-(4-chlorophenyl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3f)

White solid; mp 154-156 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 7.38-7.31 (m, 4H), 4.97 (s, OH, 1H), 3.97-3.79 (m, 6H), 3.31 (d, J = 8.0 Hz, 1H), 2.93 (d, J = 11.2 Hz, 1H), 2.35 (d, J = 11.2 Hz, 1H), 1.24 (s, 3H), 0.96 (t, J = 8.0 Hz, 3H), 0.87 (t, J = 8.0 Hz, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 203.1, 170.4, 168.1, 139.0, 131.5, 130.2, 128.0 (2C), 72.5, 61.6, 60.0, 59.6, 56.0, 54.1, 43.5, 38.8, 28.2, 13.8, 13.7; IR (KBr): 3480, 2831, 1738, 1597, 1365, 1174, 1016, 776 cm^{-1} ; HRMS (ESI): calcd for C₁₉H₂₄O₆Cl (M+H)⁺ 383.1261, found 383.1266; MS (ESI): m/z ([M+H]⁺): 383.1.

Diethyl 2-([1,1'-biphenyl]-4-yl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3g)

White solid; mp 188-189 °C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 7.64 (dd, J = 8.2 Hz, 4H), 7.46-7.34 (m, 5H), 4.93 (s, OH), 4.02 (d, J = 12.2 Hz, 1H), 3.95-3.86 (m, 3H), 3.82 (q, J = 8.0 Hz, 2H), 3.36 (d, J = 12.0 Hz, 2H), 2.96 (d, J = 14.0 Hz, 1H), 2.36 (d, J = 14.0 Hz, 1H), 1.26 (s, 3H), 0.97 (t, J = 8.0 Hz, 3H), 0.83 (t, J = 8.0 Hz, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 203.4, 170.6, 168.2, 139.6, 139.2, 138.6 (2C), 128.9 (2C), 127.3, 126.4 (2C), 126.2 (2C), 72.6, 61.7, 59.9, 59.5, 56.2, 54.1, 43.7, 38.8, 28.2, 13.8, 13.7; IR (KBr): 3426, 2983, 1717, 1586, 1375, 1159, 764 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{29}\text{O}_6$ ($\text{M}+\text{H}$) $^+$ 425.1964, found 425.1967; MS (ESI): m/z ($[\text{M}+\text{H}]^+$): 425.2

Diethyl 2-(furan-2-yl)-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3h)

Light yellow liquid; ^1H NMR (CDCl_3 , 400 MHz) δ 7.35 (d, J = 14.0 Hz, 1H), 6.30 (d, J = 14.0 Hz, 1H), 6.06 (d, J = 12.4 Hz, 1H), 5.98 (s, 1H), 4.21 (q, J = 8.0 Hz, 4H), 4.01 (t, J = 8.0 Hz, 1H), 3.86-3.81 (m, 1H), 3.68-3.62 (m, 1H), 2.83 (dd, J = 4.8 Hz, 1H), 2.69-2.59 (m, 1H), 2.02 (s, 3H), 1.25 (t, J = 8.0 Hz, 3H), 1.11 (t, J = 8.0 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 206.6, 176.6, 170.5, 155.1, 141.7, 110.1, 106.0, 61.4, 61.2, 60.2, 56.6, 51.9, 51.0, 22.9, 22.0, 14.0, 13.9; IR (KBr): 2957, 1733, 1672, 1215, 758 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{23}\text{O}_7$ ($\text{M}+\text{H}$) $^+$ 339.1444, found 339.1447; MS (ESI): m/z ($[\text{M}-17]^+$): 321.1.

Diethyl 2-ethyl-4-hydroxy-4-methyl-6-oxocyclohexane-1,3-dicarboxylate (3i)

Light yellow liquid; ^1H NMR (CDCl_3 , 400 MHz) δ 5.96 (s, OH), 4.21 (p, $J = 8.0$ Hz, 4H), 3.26 (d, $J = 11.6$ Hz, 1H), 3.13 (d, $J = 11.6$ Hz, 1H), 2.61 (q, $J = 8.0$ Hz, 1H), 2.40 (q, $J = 8.0$ Hz, 1H), 2.18-2.12 (m, 1H), 1.47 (q, $J = 8.0$ Hz, 2H), 1.38 (s, 3H), 1.17 (t, $J = 8.0$ Hz, 3H), 0.96 (t, $J = 8.0$ Hz, 3H), 0.82 (t, $J = 8.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 197.9, 170.8, 155.7, 60.9, 60.1, 52.2, 50.4, 39.6, 38.8, 26.2, 22.6, 20.7, 13.9, 13.9, 10.7; IR (KBr): 3391, 3019, 1728, 1664, 1215, 758 cm^{-1} ; HRMS (ESI): calcd for $\text{C}_{15}\text{H}_{25}\text{O}_6$ ($\text{M}+\text{H}$) $^+$ 301.1651, found 301.1664; MS (ESI): m/z ($[\text{M}+\text{H}]^+$): 301.2.

General procedure for the preparation of compounds **5d** and **5f**

To a solution of compound **3d** or **3f** (1.0 mmol) in ethanol (10 ml) was added hydrazine hydrate **4** (1.0 mmol). The mixture was stirred at 80 $^\circ\text{C}$ for another 12 h. After completion of the reaction (confirmed by TLC) the reaction mixture was concentrated under low vacuum to give the crude product that was purified by recrystallization from ethanol to afford the pure product.

Ethyl 6-hydroxy-6-methyl-3-oxo-4-*p*-tolyl-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate

(5d)

^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 11.1 (bs, NH), 9.1 (bs, NH), 7.43 (d, $J = 8.2$ Hz, 2H), 7.03 (d, $J = 8.2$ Hz, 2H), 4.50 (s, OH), 4.07 (d, $J = 10.1$ Hz, 1H), 3.94-3.85 (m, 2H), 2.75 (d, $J = 15.4$ Hz, 1H), 2.56-2.47 (m, 2H), 2.21 (s, 3H), 1.24 (s, 3H), 0.97 (t, $J = 8.0$ Hz, 3H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ 172.5, 158.4, 143.1, 138.2, 131.5, 129.8 (2C), 119.2, 98.2, 69.6, 58.7, 58.3, 37.8, 37.2, 36.4, 28.3 (2C), 14.3; IR (KBr): 3275, 1746, 1513, 1256 cm^{-1} ; MS (ESI): m/z ($[\text{M}+\text{H}]^+$): 331.4

Ethyl 4-(4-chlorophenyl)-6-hydroxy-6-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazole-5-carboxylate (5f)

^1H NMR (DMSO- d_6 , 400 MHz): δ 11.0 (bs, NH), 9.07 (bs, NH), 7.41 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 4.52 (s, OH), 4.05 (d, J = 10.1 Hz, 1H), 3.95-3.87 (m, 2H), 2.77 (d, J = 15.5 Hz, 1H), 2.55-2.49 (m, 2H), 1.24 (s, 3H), 0.99 (t, J = 8.2 Hz, 3H); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 172.1, 158.5, 142.7, 139.2, 131.4, 130.9 (2C), 119.4, 99.2, 69.8, 59.6, 59.5, 38.9, 38.5, 36.7, 28.2, 14.1; IR (KBr): 3278, 1745, 1515, 1257 cm^{-1} ; MS (ESI): m/z ($[\text{M}+\text{H}]^+$): 351.9.