SOLID-SUPPORTED CYCLOHEXANE-1,3-DIONE (CHD): A ‘CAPTURE AND RELEASE’ REAGENT FOR THE SYNTHESIS OF AMIDES AND NOVEL SCAVENGER RESIN

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SUPPORTING INFORMATION

1 Synthesis of Resin Bound Cyclohexane-1,3-dione (CHD) 6

Resin IR spectra were recorded by swelling of beads in DCM between NaCl plates and viewed with a Perkin Elmer FT-IR Spectrometer. Resins were analysed by Magic Angle Spinning (MAS) probe on a Bruker AC600 Spectrometer. Microwave reactions were carried out in a CEM Discover Microwave Synthesiser with Explorer Carousel. A special setting on this microwave allows simultaneous microwave irradiation and cooling of samples in a stream of air thus enabling higher levels of irradiation throughout the time course of the reaction.

1.1 *N*-Methylaminomethyl polystyrene resin 2

Formylpolystyrene resin (purchased from Argonaut technologies, 20 g, 28.2 mmol), NaBH(OAc)₃ (29.9 g, 141 mmol) and methylamine hydrochloride (9.59 g, 141 mmol) were shaken for 18 hours in a conical flask with DMF (peptide synthesis grade) (196 mL) and AcOH (4 mL). The resin was filtered through a sintered filter funnel and washed with 2 × MeOH, 2 × DMF, 2 × MeOH, 2 × 10 % DIPEA in DMF, 2 × DMF and 2 × DCM then dried overnight in the vacuum oven. The resin gave a positive blue coloration with *p*-chloranil. δ_{H} (MAS, 600 MHz, CDCl₃); 1.5 (CH₂ PS), 1.8 (CH₂ PS), 2.4 (NCH₃), 3.6 (CH₂), 6.6 (ArH PS), 7.0 (ArH PS) ppm; ν_{max} (DCM); ~3300 (br, NH), 3100-2800 (br, CH), 1601 (Ar C=C) cm⁻¹.

1.2 1-Ethyl-3,5-dimethoxycyclohexa-2,5-dienecarboxylic acid 3

Ammonia (125 mL) was condensed into a 250 mL three-necked flask and 3,5-dimethoxybenzoic acid (10 g, 54.9 mmol) and anhydrous THF (100 mL) added to form a clear solution. The mixture was cooled to -78°C in a dry ice/acetone bath and lithium (0.96 g, 137.4 mmol) added portion-wise to form a highly coloured solution (red, green or blue). Bromoethane (4.31 mL, 60.4 mmol) was added dropwise to form a cloudy white solution. The solution was stirred at -78°C for one hour then warmed slowly to room temperature over a further 19 hours whilst the ammonia evaporated into water. The solution was concentrated *in vacuo* to remove the THF and the residue dissolved in chilled DCM (75 mL) and water (40 mL). The mixture was cooled in an ice bath, 2M HCl (75 mL) was added dropwise to pH 3 and the DCM layer separated. The aqueous layer was washed twice more with DCM (2×75 mL) and the combined organic layers washed with brine (50 mL), dried over anhydrous magnesium sulfate before being concentrated *in vacuo* to yield a pale yellow crystalline solid (11.6 g, 100 %). If necessary the crude mixture was recrystallised from dichloromethane:petroleum ether (1:1) to give a white crystalline solid. **rf** (10 % MeOH/DCM); 0.61; **mpt**; 132-136 $^{\circ}\text{C}$ (literature 141-144 $^{\circ}\text{C}$); δ_{H} (CDCl_3 , 200 MHz); 0.81 (3H, t, $^3J = 7.5$ Hz, $-\text{CH}_2\text{CH}_3$), 1.74 (2H, q, $^3J = 7.5$ Hz, $-\text{CH}_2\text{CH}_3$), 2.76 (2H, s, **H4**), 3.60 (6H, s, $2 \times \text{OCH}_3$), 4.65 (2H, s, **H2/H6**) ppm; δ_{C} (CDCl_3 , 93 MHz); 9.0 ($-\text{CH}_2\text{CH}_3$), 31.6 ($-\text{CH}_2\text{CH}_3$), 34.2 (**C4**), 50.8 (**C1**), 54.8 ($2 \times \text{OCH}_3$), 94.8 (**C2/C6**), 153.8 (**C3/C5**), 182.8 (**C=O**) ppm; ν_{max} (**nujol mull**); ~ 3500 (br, OH), 3000-2700 (br, CH), 1698 (**C=O**), 1685 (**C=O**), 1656 (**C=C**) cm^{-1} ; **m/z** found (FAB) $[\text{M}+\text{H}]^+$ 213.11271, $\text{C}_{11}\text{H}_{17}\text{O}_4$ requires 213.11268.

1.3 Resin-bound *bis*-enol ether 4

Crude acid **3** (10.9 g, 51.6 mmol) was dissolved in DMF (peptide synthesis grade) (94 mL) and DIC (8.08 mL, 51.6 mmol) was added dropwise. Meanwhile *N*-methyl aminomethyl resin **3** (18.7 g, 25.8 mmol) was swelled in DCM (94 mL). The contents of the first flask were transferred to the conical flask containing the resin. The resulting mixture was shaken at room temperature for 2 ½ hours and the resin filtered and washed with $2 \times \text{DMF}$, $2 \times \text{MeOH}$, $2 \times \text{DMF}$ and $4 \times \text{DCM}$. The coupling repeated was repeated for 2 ½ hours, the resin washed according to the same protocol and dried overnight in the vacuum oven. The resin gave a negative colourless result with *p*-chloranil.

δ_{H} (MAS, 600 MHz, CDCl_3); 0.7 (CH_2CH_3), 1.4 (CH_2 PS), 1.8 (CH_2 PS and CH_2CH_3), 2.7 (**H4**), 2.8 (NCH_3), 3.2-3.6 ($2 \times \text{OCH}_3$), 4.5 (**H2/H6** and NCH_2), 6.5 (ArH PS), 7.0 (ArH PS) ppm; ν_{max} (**DCM**); 3100-2800 (br, CH), 1690 (**C=O** tert amide), 1636 (Ar **C=C**), 1602 (Ar **C=C**) cm^{-1} .

1.4 3-Methoxycyclohexen-1-one (MCH) resin 5

Bis-enol ether resin **4** (50 g) was shaken with TFA (45 mL), water (2.5 mL) and DMF (2.5 mL) for 2 ½ hours at room temperature. The resin was filtered and washed with 2 × DMF, 2 × MeOH, 2 × DMF and 4 × DCM then dried overnight in the vacuum oven. δ_{H} (MAS, 600 MHz, CDCl_3); 0.9 (CH_2CH_3), 1.4 (CH_2 PS), 1.8 (CH_2 PS and CH_2CH_3), 2.4 (CH_2), 2.9 (NCH_3), 3.1 (CH_2), 3.6 (OCH_3), 4.5 (NCH_2), 5.4 (**H4**), 6.6 (ArH PS), 7.0 (ArH PS) ppm; ν_{max} (DCM); 3200-2800 (br, CH), 1631(C=C enol), 1602 (Ar C=C) cm^{-1} ;

1.5 Cyclohexane-1,3-dione (CHD) resin 6

3-Methoxy cyclohexen-1-one resin **5** (1 g) was stirred with TFA (1.67 mL), water (1.67 mL) and DMF (1.67 mL) in the microwave synthesiser at 110 °C (50 W) for 10 minutes. The resin was filtered and washed with 2 × DMF, 2 × MeOH then shaken in $n\text{BuNH}_2$ for five minutes to remove any TFA enol ester ($\nu_{\text{max}} = 1781 \text{ cm}^{-1}$). The resin was further washed with 2 × DMF, 2 × MeOH, 2 × DMF and 4 × DCM then dried overnight in the vacuum oven. The resin gave a positive brown colouration with 1M $\text{FeCl}_3 \cdot \text{H}_2\text{O}$ aqueous solution indicating 1,3-diketone formation. δ_{H} (MAS, 600 MHz, CDCl_3); 0.8 (CH_2CH_3), 1.4 (CH_2 PS), 1.8 (CH_2 PS and CH_2CH_3), 1.9 (CH_2), 2.8 (NCH_3), 2.9 (CH_2), 4.5 (broad NCH_2), 5.0 (**H2**), 6.6 (ArH PS), 7.0 (ArH PS) ppm; ν_{max} (DCM); 3200-2800 (br, CH), 1715 (small, C=O keto), 1674 (C=O enol), 1631(C=C enol), 1602 (Ar C=C) cm^{-1} .

2 Capture and Release at Room Temperature

2.1 Resin bound benzoyl enol ester **7a**

Resin bound enol ester **7a** was prepared by the reaction of CHD resin **6** (1 g, 0.69 mmol) with acid chloride (3.45 mmol) and acetic acid (197 μ L, 3.45 mmol) in DCM (4 mL) and shaken on a blood rotator at room temperature overnight. The resin was filtered and washed with $2 \times$ DMF, $2 \times$ MeOH, $2 \times 10\%$ DIPEA in DMF, $2 \times$ DMF and $4 \times$ DCM and dried overnight in the vacuum oven.

2.2 Benzoyl benzamide **8a**

Resin bound benzoyl enol ester **7a** (0.1 g, 0.02 mmol wrt capture and release) was reacted with amine (0.4 mmol) in MeOH (1 mL) and shaken on a blood rotator at room temperature overnight. Dowex-50WX (0.25 g, 1.2 mmol) was added to the reaction mixture and the suspension stirred at room temperature for 2 hours. The resin was filtered and washed with $2 \times$ MeOH (2×1 mL), $2 \times$ DCM (2×1 mL) and $1 \times$ MeOH (1 mL). The filtrate was concentrated *in vacuo* to give a white crystalline solid (4.3 mg, 100 %). The product was analysed by LC-MS at 220 nm using an acetonitrile (0.1 % TFA)/water (0.1 % TFA) gradient over 30 minutes on a C18 Luna Phenomenex column as found to be 100 % the required product. **m/z** found (ES^+) 212 $[\text{M}+\text{H}]^+$, $\text{C}_{14}\text{H}_{14}\text{NO}$ requires 212.

3 Capture and Release under Microwave Irradiation

3.1 Resin-bound enol esters **7 a-e**

Resin bound enol esters **7 a-e** were prepared by the reaction of CHD resin **6** (1 g, 0.69 mmol) with acid chloride (3.45 mmol) and acetic acid (197 μ L, 3.45 mmol) in DCM (4 mL) and stirred in the microwave synthesiser at 110 °C (300 W) for 10 minutes. The resin was filtered and washed with 2 $\times$ DMF, 2 $\times$ MeOH, 2 $\times$ 10 % DIPEA in DMF, 2 $\times$ DMF and 4 $\times$ DCM. The coupling was repeated in the microwave for a further 10 minutes and the resin washed using the same protocol and dried overnight in the vacuum oven.

Resin bound benzoyl enol ester 7a: δ_{H} (MAS, 600 MHz, CDCl_3); 0.9 (CH_2CH_3), 1.4 (CH_2 PS), 1.8 (CH_2 PS and CH_2CH_3), 1.9 (CH_2), 2.8 (NCH_3), 2.9 (CH_2), 4.8 (NCH_2), 6.1 (**H2**), 6.6 (ArH PS), 7.0 (ArH PS), 8.1 (ArH) ppm; ν_{max} (DCM); 3200-2800 (br, CH), 1738 (C=O enol ester), 1673 (C=O enol), 1632 (C=C enol), 1602 (Ar C=C) cm^{-1} .

Resin bound 4-methoxybenzoyl enol ester 8b: δ_{H} (MAS, 600 MHz, CDCl_3); 0.9 (CH_2CH_3), 1.4 (CH_2 PS), 1.8 (CH_2 PS and CH_2CH_3), 2.0 (CH_2), 2.8 (NCH_3), 2.9 (CH_2), 4.8 (NCH_2), 6.0 (**H2**), 6.6 (ArH PS), 7.0 (ArH PS), 8.0 (ArH) ppm; ν_{max} (DCM); 3200-2800 (br, CH), 1731 (C=O enol ester), 1674 (C=O enol), 1631 (C=C enol), 1603 (Ar C=C) cm^{-1} .

Resin bound 3,5-dichlorobenzoyl enol ester 8c: δ_{H} (MAS, 600 MHz, CDCl_3); 0.9 (CH_2CH_3), 1.4 (CH_2 PS), 1.9 (CH_2 PS), 2.0 (CH_2CH_3), 1.9 (CH_2), 2.8 (NCH_3), 2.9 (CH_2), 4.8 (NCH_2), 6.1 (**H2**), 6.6 (ArH PS), 7.0 (ArH PS), 7.5 (ArH), 8.0 (ArH) ppm; ν_{max} (DCM); 3200-2800 (br, CH), 1739 (C=O enol ester), 1673 (C=O enol), 1626 (C=C enol), 1601 (Ar C=C) cm^{-1} ;

Resin bound butyryl enol ester 8d: δ_{H} (MAS, 600 MHz, CDCl_3); 0.9 ($\text{CH}_3\text{CH}_2\text{CH}_2$), 1.0 (CH_2CH_3), 1.4 (CH_2 PS), 1.7 ($\text{CH}_3\text{CH}_2\text{CH}_2$), 1.8 (CH_2 PS and CH_2CH_3), 1.9 (CH_2), 2.3 ($\text{CH}_3\text{CH}_2\text{CH}_2$), 2.8 (NCH_3), 2.9 (CH_2), 4.8 (NCH_2), 6.1 (**H2**), 6.6 (ArH PS), 7.0 (ArH PS) ppm; ν_{max} (DCM); 3200-2800 (br, CH), 1731 (C=O enol ester), 1674 (C=O enol), 1632 (C=C enol), 1601 (Ar C=C) cm^{-1} .

Resin bound isobutyryl enol ester 8e: δ_{H} (MAS, 600 MHz, CDCl_3); 0.9 (CH_2CH_3), 1.2 (Me_2CH), 1.4 (CH_2 PS), 1.8 (CH_2 PS and CH_2CH_3), 1.9 (CH_2), 2.6 (Me_2CH), 2.8 (NCH_3), 2.9 (CH_2), 4.8 (NCH_2), 6.2 (**H2**), 6.6 (ArH PS), 7.0 (ArH PS) ppm; ν_{max} (DCM); 3200-2800 (br, CH), 1739 (C=O enol ester), 1674 (C=O enol), 1632 (C=C enol), 1602 (Ar C=C) cm^{-1} .

3.2 Release of amides **8 a-p**

Resin bound enol esters **7 a-e** (0.1 g, 0.02 mmol wrt capture and release) were reacted with amine (0.4 mmol) in MeOH (1 mL) and stirred in the microwave synthesiser at 125 °C (200 W) for 30 minutes on constant irradiation. Dowex-50WX (0.25 g, 1.2 mmol) was added to the reaction mixture and the suspension stirred at room temperature for 2 hours. The resin was filtered and washed with 2 $\times$ MeOH (2 $\times$ 1 mL), 2 $\times$ DCM (2 $\times$ 1 mL) and 1 $\times$ MeOH (1 mL). The filtrate was concentrated *in vacuo* and

the yield calculated from the weight of product. The product was analysed by LC-MS at 220 nm using an acetonitrile (0.1 % TFA)/water (0.1 % TFA) gradient over 30 minutes on a C18 Luna Phenomenex column.

4 Allyl Cation Scavenging

4.1 *O*-Alloc deprotection in the absence of scavenger

In the absence of scavenger, the benzyl alcohol formed reacts with allyl cations to give allyl benzyl ether.

O-Alloc benzyl alcohol **11** (0.5 g, 2.60 mmol) was dissolved in THF (13 ml) and tetrakis(triphenylphosphine) palladium (0) (150 mg, 0.13 mmol) added in one portion. The mixture was stirred at room temperature under argon for 30 mins. The mixture was concentrated *in vacuo* and purified by column chromatography on silica eluting with 20 % ethyl acetate in petroleum ethers (40 – 60 °C) to yield a clear colourless oil (162 mg, 42 %). δ_{H} (CDCl₃, 200 MHz) 4.12 (2H, d, $^3J = 5.5$ Hz, CH₂CH=CH₂), 4.61 (2H, s, CH₂Ph), 5.32 (1H, d, $^3J = 10.0$ Hz, CH=CH₂ cis), 5.42 (1H, d, $^3J = 17.0$ Hz, CH=CH₂ trans), 6.04 (1H, m, CH=CH₂), 7.43 (5H, m, ArH) ppm.

4.2 *O*-Alloc deprotection with dimedone **1** scavenger

Dimedone **1** (1.09 g, 7.81 mmol) was dissolved in THF (6 mL) and *O*-alloc benzyl alcohol **11** (0.3 g, 1.56 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at room temperature under argon while tetrakis(triphenylphosphine) palladium (0) (90 mg, 0.078 mmol) added in one portion. The mixture was stirred at room temperature for 30 minutes then concentrated *in vacuo* to yield a yellow solid. The crude material was purified by column chromatography on silica eluting with 20 % ethyl acetate in petroleum ethers (40 – 60 °C) increasing to 30 % ethyl acetate to yield benzyl alcohol **12** as a clear colourless oil (160 mg, 95 %). δ_{H} (CDCl₃, 200 MHz) 2.66 (1H, br s, OH), 4.71 (2H, s, CH₂), 7.43 (5H, m, ArH) ppm. Di-allyl dimedone was obtained as yellow crystals (68.8 mg, 20 %). δ_{H} (CDCl₃, 200 MHz) 0.97 (6H, s, 2 × CH₃), 2.47 (2H, s, CH₂), 2.51 (2H, s, CH₂), 2.54 (4H, s, 2 × CH₂CH=CH₂), 5.06 (2H, dd, $J = 10.0$ and 1.0 Hz, 2 × CH=CH₂ cis), 5.13 (2H, dd, $J = 20.0$ and 2.0 Hz, 2 × CH=CH₂ trans), 6.04 (2H, m, CH=CH₂), 7.43 (5H, m, ArH) ppm.

trans), 5.58 (2H, m, $2 \times \text{CH}=\text{CH}_2$) ppm; δ_{C} (CDCl_3 , 63 MHz) 28.6 ($2 \times \text{CH}_3$), 30.6 (C5), 38.7 (CH_2), 51.9 (CH_2), 119.3 ($\text{CH}=\text{CH}_2$), 132.2 ($\text{CH}=\text{CH}_2$), 208.6 (C=O) ppm; ν_{max} (thin film) 3079 (CH), 3013 (CH), 2956 (CH) 2928 (CH) 2871 (CH) 1726 (C=O) 1696 ($\text{CH}=\text{CH}_2$) 1639 (C=C) cm^{-1} ; m/z found (ES^+) $[\text{M}+\text{H}]^+$ 221 $\text{C}_{14}\text{H}_{21}\text{O}_2$ requires 221.

4.3 *O*-Alloc deprotection with dendritic CHD resin **10**

CHD resin **10** was prepared according to procedures 1.3 and 1.4 shown above. CHD resin **10** (1 g, 2.78 mmol) was swollen in THF (8 mL) and *O*-alloc benzyl alcohol **11** (214 mg, 1.11 mmol) in THF (2 mL) added dropwise. The mixture was stirred at room temperature under argon while tetrakis(triphenylphosphine) palladium (0) (1.28 mg, 1.11×10^{-3} mmol) added in one portion. The mixture was stirred at room temperature overnight then concentrated *in vacuo* to yield a clear colourless oil. (104 mg, 87 %). δ_{H} (CDCl_3 , 200 MHz) 2.25 (1H, br s, OH), 4.77 (2H, s, CH_2), 7.42 (5H, m, ArH) ppm. δ_{H} (Resin-MAS, 600 MHz, CDCl_3); 0.8 (CH_2CH_3), 1.5 (CH_2 PS), 1.8 (CH_2 PS and CH_2CH_3), 2.39 (CH_2), 2.84 ($\text{CH}_2\text{CH}=\text{CH}_2$), 3.64 (residual OMe), 5.09 ($\text{CH}=\text{CH}_2$), 5.75 ($\text{CH}=\text{CH}_2$), 6.6 (ArH PS), 7.1 (ArH PS) ppm.