Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Development of a Solid-Compatible Continuous Flow Reactor for the Paraformaldehyde Slurry Mediated α-hydroxymethylation of Methyl Vinyl Ketone

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CONTENT

Hydroxymethylation in continuous flow

General information

All reagents (methyl vinyl ketone, paraformaldehyde, DABCO, 1,3,5-trimethoxybenzene etc.) were purchased from Fisher Scientific and used as such. NMR spectra were measured with a Bruker Avance Nanobay III NMR spectrometer. The components were dissolved in deuterated DMSO-d_6 and tetramethylsilane (TMS) as an internal standard.

Hydroxymethylation in batch

In a vial (20 mL) equipped with a magnetic stirrer, 200 mg of methyl vinyl ketone (2.85 mmol) is combined with 1.4 equivalents of paraformaldehyde (120 mg, 3.99 mmol), 0.05 equivalents of DABCO (16 mg, 0.14 mmol), and 0.48 mL ethanol (2.9 equivalents). The vial is tightly sealed and placed in a pre-heated oil bath at 100 °C for 8 minutes while stirring. Subsequently, ^{1}H-NMR analysis is conducted using 1,3,5-trimethoxybenzene as the internal standard, and both the conversion and NMR yield are determined. When the isolated yield was determined, the mixture was purified by column chromatography (diethylether/pentane: 50/50). The underlined peaks were used to determine conversion and NMR yield. Experiments with other solvents or different time/temperature conditions were conducted in a similar manner.

^{1}H-NMR (400MHz, DMSO-d_6): δ = 2.30 (3H, s, C$\underline{H_3}$), 4.10 (2H, dt, C_{quat}-C$\underline{H_2}$), 4.94 (1H, t, O$\underline{H}$), 5.99 (1H, s, C$\underline{H_a}H_b$), 6.18 (1H, s, $CH_a\underline{H_b}$) ppm (isolated)

^{13}C-NMR (100MHz, DMSO-d_6): δ = 26.78 ($\underline{C}H_3$), 59.46 (HO-$\underline{C}H_2$), 124.62 (C_{quat}-$\underline{C}H_2$), 148.77 ($\underline{C_{quat}}$), 199.67 ($\underline{C}$=O) ppm

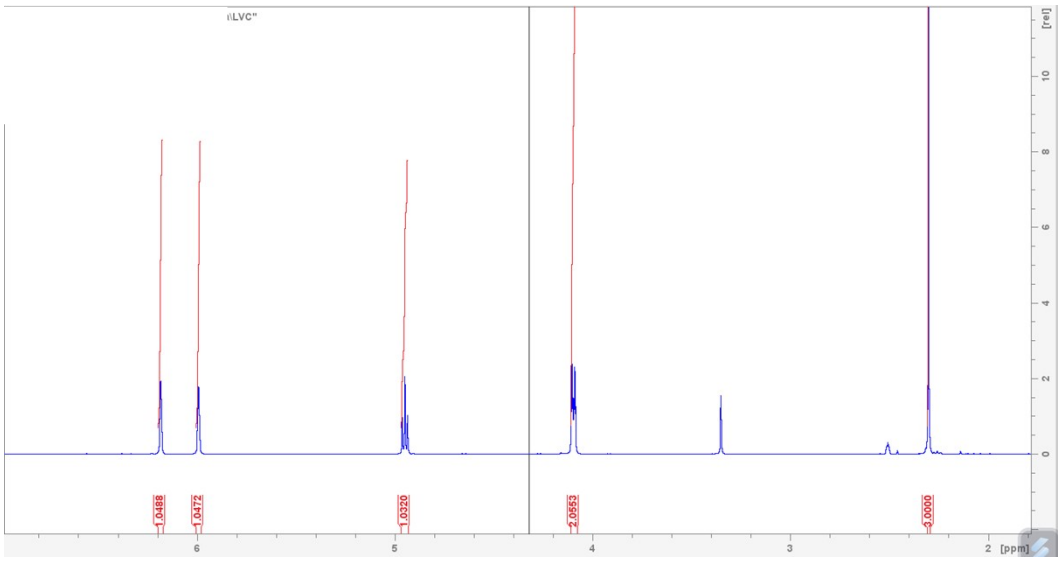


Figure S1. ^{1}H-NMR of 3-(hydroxymethyl)but-3-en-2-one in DMSO (isolated).

Continuous flow setup

Figure S2 illustrates a schematic overview of the continuous flow setup, denoted as the CØPE reactor. The setup comprises two flows merged via a T-mixer positioned after the pulsator. Two SF-10 pumps facilitate the conveyance of both the paraformaldehyde slurry and the MVK liquid into the reactor. The system pressure is indicated by these pumps on the display interface. Adjustments of the pulsator amplitude can be made using the rotary knob, ranging from 0.0 to 0.95 in increments of 0.05. These values correspond to a percentage of the maximum stroke volume, which is 0.76 mL/stroke (or a maximum stroke amplitude of 0.38 mL/stroke). The frequency of the strokes is controlled using the Danfoss VLT® Midi Drive FC 280 frequency controller. N_2 gas from an external gas tank pressurizes the cylindrical BPR to achieve the desired system pressure.

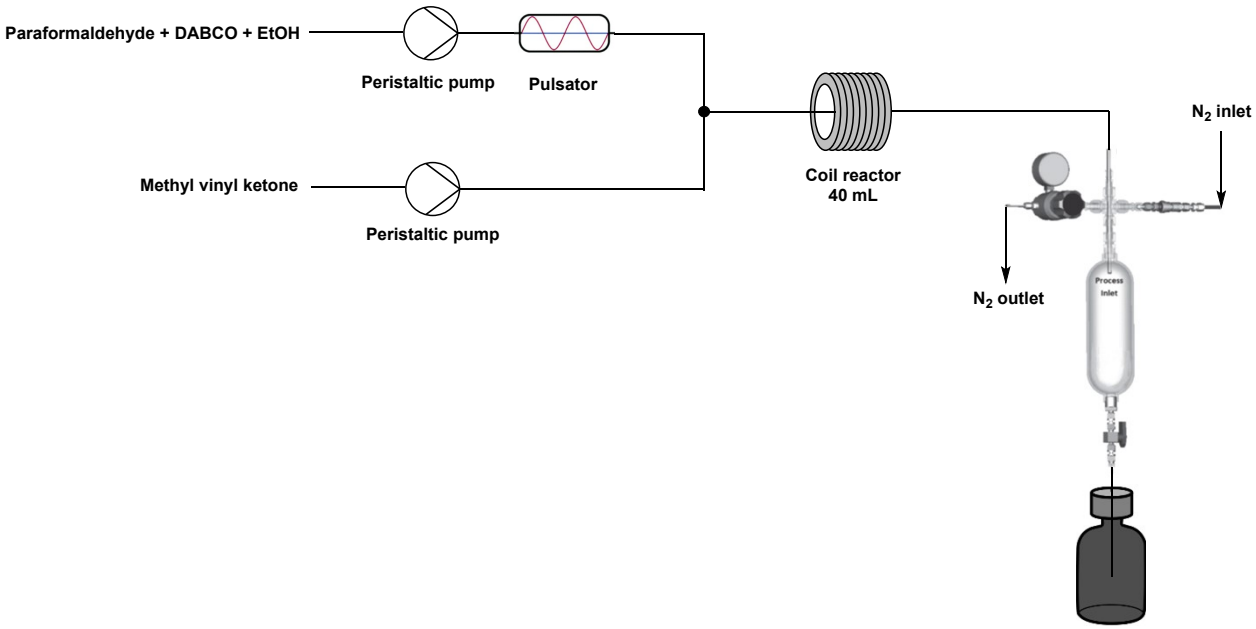


Figure S2. Schematic overview of the continuous flow setup (CØPE reactor).

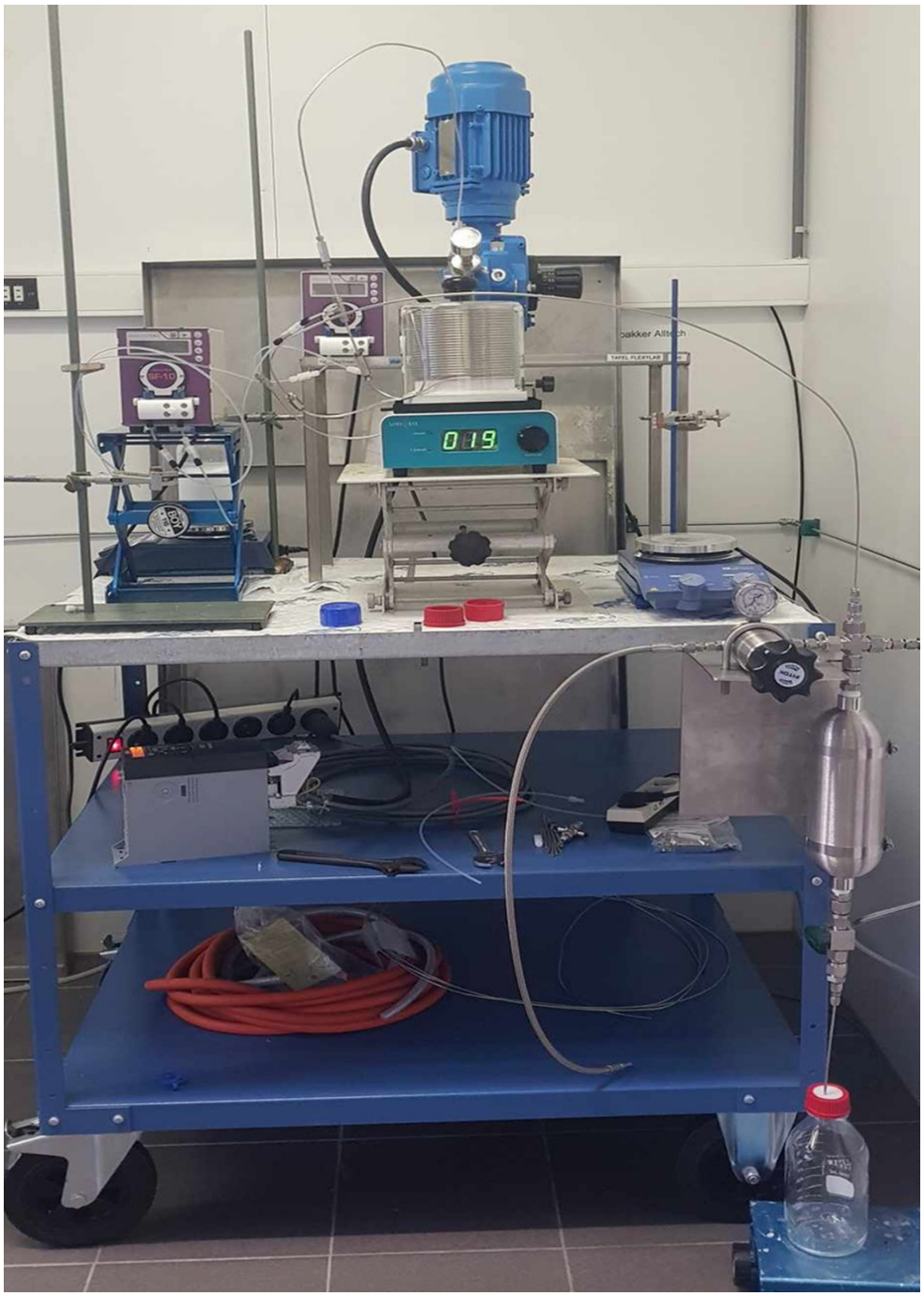


Figure S3. Photograph of the continuous flow setup (CØPE Reactor).

Residence time distribution

Residence time distribution experiments were conducted using a slightly modified reactor setup (see Figure S4). Thymol blue served as a tracer within an ethanol solution (± 10^{-4}M concentration). The tracer flow was introduced into the system via a T-mixer (with a check valve) positioned between the pulsator and the reactor, within a carrier stream of ethanol. After the reactor, an in-line UV-VIS flow cell was installed, connected to an Ocean Optics DH-

2000-BAL light source and an Ocean Optics HDX miniature spectrometer. RTD curves were generated through a step experiment approach. Regression analysis was applied to the acquired data, and the derivative of this function yielded the residence time distribution

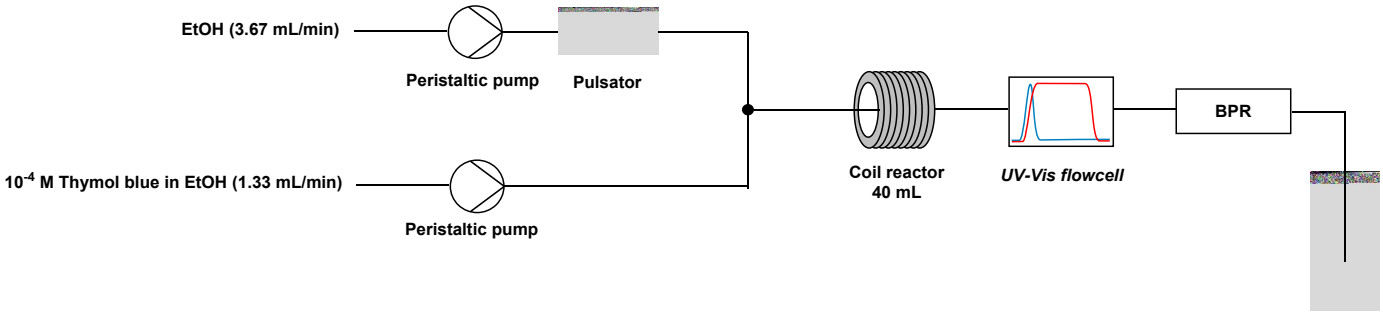


Figure S4. Continuous flow setup for the determination of the residence time distribution.

The oscillation Reynolds number (Re_{Osc}) is calculated according to Equation S1.

$$Re_{Osc} = \frac{2\pi f x_0 \rho D_h}{\mu} \qquad D_h = \frac{4A}{P}$$

Equation S1. Calculation of the oscillating Reynolds number: ρ = density of the fluïdum [kg/m³], D_h = characteristic length [m], μ = dynamic viscosity of the fluïdum [Pa*s], f = frequency of the oscillation [Hz], x_0 = amplitude of the oscillation [m], A = area [m²], P = wetted Perimeter [m].

The plug-flow behaviour of the reactor can be quantified using the Bodenstein number (Bo). This dimensionless number is the ratio of the rate of transport by convection to the rate of transport by diffusion and dispersion. A Bodenstein number of 0 corresponds to full back mixing (ideal for a CSTR), while Bo = ∞ corresponds to no back mixing and an ideal plug flow, desired in a flow channel. It can be calculated from the average residence time ($\bar{t}$) and variance (σ^2) obtained from the RTD according to the equation below.

$$\frac{\sigma^2}{\bar{t}^2} = \sigma_\theta^2 = \frac{2}{Bo} + \frac{8}{Bo^2} => Bo = \frac{1 + \sqrt{1 + 8 * \sigma_\theta^2}}{\sigma_\theta^2}$$

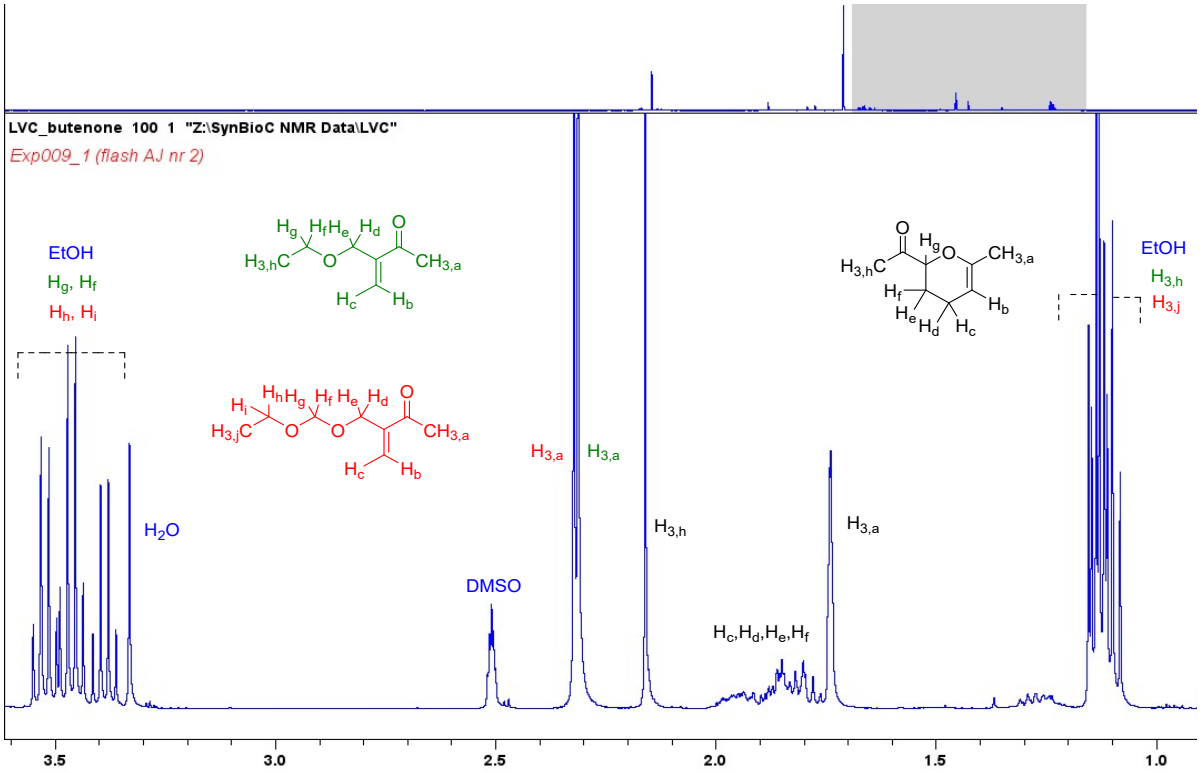
Equation S2. Calculation of the Bodenstein number.

Hydroxymethylation in continuous flow

Initially, feed vessel 1 is prepared by mixing 134.5 grams of paraformaldehyde (equivalent to 4.48 mol), 17.9 grams of DABCO (0.16 mol), and 542 mL of ethanol (9.28 mol). The mixture

undergoes vigorous stirring for one hour before being used to disrupt large paraformaldehyde clusters/clumps. Feed vessel 2 contains pure methyl vinyl ketone. Before the reaction is started, the system undergoes ethanol flushing and pressurization to 5 bar. A flow rate of 3.59 mL/min is set for feed vessel 1 (containing the slurry), and 1.41 mL/min for feed vessel 2. This configuration results in a total flow of 5 mL/min, translating to a residence time of 8 minutes given a reactor volume of 40 mL. Upon reaching steady state after three times the residence time, the cylindrical collection vessel is emptied to prevent contamination of the samples. Subsequently, two samples are collected and analyzed using the same analytical procedure as in the batch process. The reported conversion and NMR yield represent the average of both samples.

To identify the most significant byproduts, the reaction mixture at sub-optimal reaction conditions (extended residence times and elevated temperatures) was analysed after column chromatography (^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, HMBC). Figure S5 shows the characterisation of a mixture of these byproducts on ^{1}H-NMR.



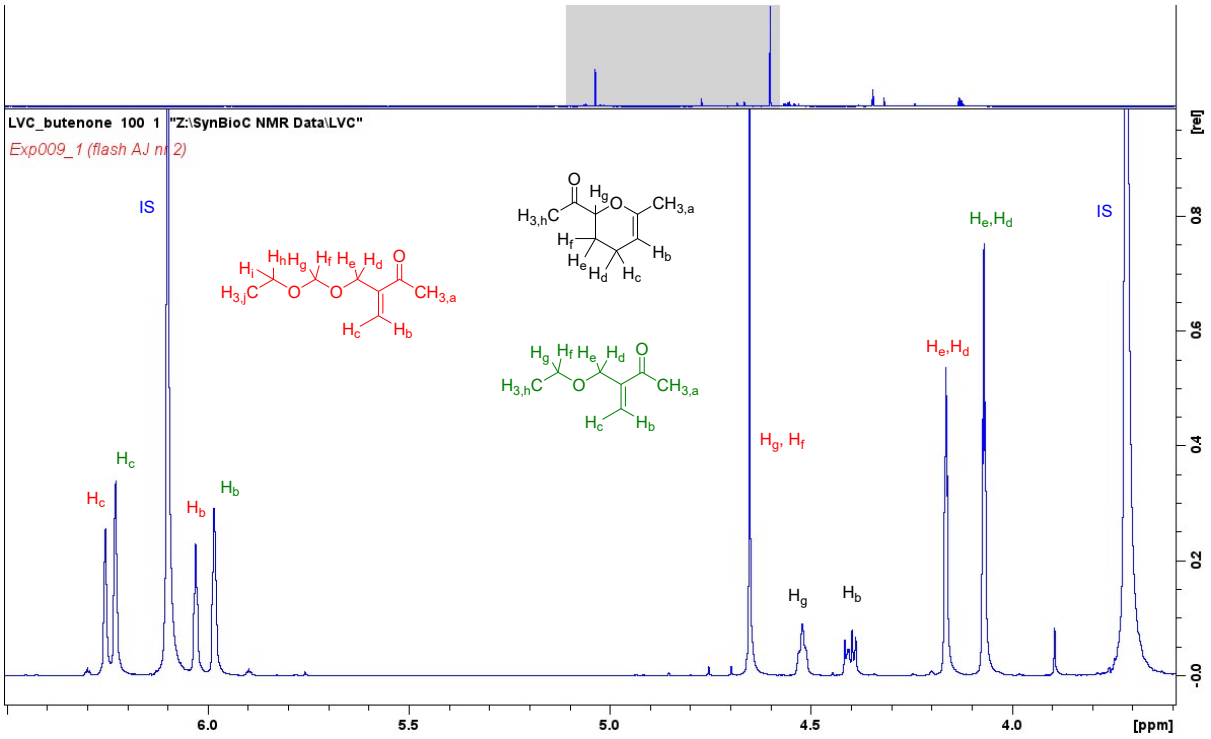


Figure S5. Characterisation and identification of the most significant byproducts on ^{1}H-NMR .

3-((ethoxymethoxy)methyl)but-3-en-2-one (red)

^{1}H-NMR (400MHz, DMSO-d_6): δ = 1.12 (3H, t, CH_2-C$\underline{H_3}$), 2.31 (3H, s, C$\underline{H_3}$-C=O), 3.52 (2H, q, O-C$\underline{H_2}$-CH_3), 4.16 (2H, t, C_{quat}-C$\underline{H_2}$-O), 4.65 (2H, s, O-C$\underline{H_2}$-O), 6.03 (1H, s, C_{quat}=C$\underline{H_a}$$H_b$), 6.25 (1H, s, C_{quat}=$CH_a$$\underline{H_b}$) ppm

^{13}C-NMR (100MHz, DMSO-d_6): δ = 15.50 (CH_2-C$\underline{H_3}$), 26.47 (C$\underline{H_3}$-C=O), 63.10 (O-C$\underline{H_2}$-CH_3), 65.21 (C_{quat}-C$\underline{H_2}$-O), 94.68 (O-C$\underline{H_2}$-O), 126.2 C_{quat}=C$\underline{H_2}$), 145.15 (C$\underline{_{quat}}$), 199.1 (C$\underline{}$=O) ppm

3-(ethoxymethyl)but-3-en-2-one (green)

^{1}H-NMR (400MHz, DMSO-d_6): δ =1.13 (3H, t, CH_2-C$\underline{H_3}$), 2.31 (3H, s, C$\underline{H_3}$-C=O), 3.46 (2H, q, O-C$\underline{H_2}$-CH_3), 4.06 (2H,t, C_{quat}-C$\underline{H_2}$-O), 5.98 (1H, s, C_{quat}= C$\underline{H_a}$$H_b$), 6.23 (1H, s, C_{quat}= $CH_a$$\underline{H_b}$) ppm

^{13}C-NMR (100MHz, DMSO-d_6): δ = 15.59 (CH_2-C$\underline{H_3}$), 26.51 (C$\underline{H_3}$-C=O), 65.87 (O-C$\underline{H_2}$-CH_3), 67.97 (C_{quat}-C$\underline{H_2}$-O), 126.01 (C_{quat}=C$\underline{H_2}$), 145.37 (C$\underline{_{quat}}$), 199.2 (C$\underline{}$=O) ppm

1-(6-methyl-3,4-dihydro-2H-pyran-2-yl)ethan-1-one (black)

^{1}H-NMR (400MHz, DMSO-d_6): δ =1.74 (3H, br s, C$\underline{H_3}$-C=O), 1.75-2.00 (4H, m, C$\underline{H_2}$- C$\underline{H_2}$), 2.16 (3H,s, C$\underline{H_3}$-C_{quat}), 4.37-4.43 (1H,m, C_{quat}=C$\underline{H}$-CH_2), 4.52 (1H,t, C_{quat}-C$\underline{H}$-O) ppm

^{13}C-NMR (100MHz, DMSO-d_6): δ = 18.03 (CH_2- $\underline{C}H_2$), 20.13 (C_{quat}-$\underline{C}H_3$), 23.12 ($\underline{C}H_2$- CH_2), 26.19 ($\underline{C}H_3$-C=O), 79.76 (C_{quat}=$\underline{C}$H- CH_2), 96.50 (C_{quat}-$\underline{C}$H-O), 149.69 ($\underline{C_{quat}}$), 208.00 ($\underline{C}$=O) ppm