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Challenges in the development of bio-based solvents: a case study on methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate as an alternative aprotic solvent

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1 Experimental Process

Materials

DL-1,2-Isopropylideneglycerol (solketal) 98%, dimethyl carbonate 99%, 4-methoxyacetophenone 99%, anhydrous anisole 99.7%, acetic anhydride ⩾99%, anhydrous ytterbium(III) chloride (99.9%), 3-buten-2-one 99%, 2,3-dimethyl-1,3-butadiene 98%, anhydrous acetonitrile 99.8%, anhydrous cyclohexane 99.5%, anhydrous diethyl ether ⩾99%, anhydrous propylene carbonate 99.7%, iron (III) chloride 97%, anhydrous ethyl acetate 99.8%, methanol 99.9%, dichloromethane 99.8%, acetone 99.9%, dimethyl sulfoxide 99.9%, Nile red ⩾98%, 4-nitroaniline ⩾99%, chloroform 99.9% and chloroform-d ($CDCl_3$, 99.8% D) were purchased from Sigma-Aldrich. QUANTOFIX® Peroxide 100 was purchased from Macherey-Nagel. Ames MPF 98/100 kits, 2-nitrofluorene and 4-nitroquinoline-*N*-oxide were purchased from Xenometrix. TA98 and TA100 were stored at -70 °C. Anhydrous potassium carbonate was purchased from Fisher Scientific. *N,N*-diethyl-4-nitroaniline was purchased from VWR.

Experiment process for synthesis and purification of methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC)

After optimising the reaction conditions (process as shown in Table S1., Table S2. and Table S3.), to a 200 mL round bottom flask of a multi-point reflux reactor (Radleys, RR98073) was added 5 mL solketal (0.040 mol), 5.5 mg K_2CO_3 (0.04 mmol), 67.4 mL (0.8 mol) dimethyl carbonate (DMC) and magnetic stirring bar. The mixture was then agitated and heated up to DMC reflux temperature for 20 h. After cooling down, the crude product mixture was filtered, and DMC with by-product methanol was removed by rotary evaporator under reduced pressure. Finally, 6.94 g colourless MMC (purity of 99% by GC, 91% isolated yield) was then purified by micro distillation (BÜCHI, Glass Oven B-585 Kugelrohr) under reduced pressure. GC, GC-MS, ^{1}H NMR (400 MHz) and ^{13}C NMR (400 MHz) of MMC were all analysed. MMC: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.37-4.31(m, 1H), 4.18-4.16 (m, 2H), 4.10-4.06(m, 1H), 3.80-3.76 (m, 4H), 1.43 (s, 3H), 1.36 (s, 3H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 155.5, 109.8, 73.2, 67.8, 66.1, 54.9, 26.6, 25.2 pp. GC-MS (relative intensity, 70 eV) m/z: 175 (100), 133, 115, 101, 77, 71, 59, 57, 43.

Experiment process for solvent test in the synthesis of 4-methoxyacetophenone (4-MAP) from anisole and acetic anhydride catalysed by $FeCl_3$

Typically, into a 3 ml sample bottle was added 5.4 μL (0.05 mmol) anisole, 8.1 mg (0.05 mmol) $FeCl_3$, 4.7 μL (0.05 mmol) acetic anhydride and 0.5 mL related solvent. The sample bottle was sealed as a closed system for 2 hours and agitated by a roller (Stuart, roller mixer SRT6) at room temperature. GC and GC-MS were utilised for the monitor of all the reactions.

The product was proved to be 4-MAP by comparing to commercial 4-MAP by GC. 4-MAP: GC-MS (relative intensity, 70 eV) m/z: 150 (M^+), 135, 107, 92, 77, 64, 63, 62, 51, 50, 43 (100), 42.

Experiment process for solvent test in the synthesis of 1-(3,4-dimethylcyclohex-3-enyl) ethanone (DE) from 3-buten-2-one and 2,3-dimethylbuta-1,3-diene (diene) catalysed by anhydrous $YbCl_3$

Generally, into a 3 mL sample bottle was placed 10 mg anhydrous $YbCl_3$ (0.036 mmol), 0.5 mL corresponding solvent, 29 μL 3-buten-2-one (0.358 mmol), 40 μL diene (0.358 mmol). After that, the argon gas protected sample bottle was then sealed and agitated for 16 hours on a roller (Stuart, roller mixer SRT6) at room temperature. GC and GC-MS were utilised to monitor all the reactions. 1-(3,4-dimethylcyclohex-3-enyl) ethanone (DE) was isolated by distillation after filtration of the reaction mixture and its GC, GC-MS, ^{1}H NMR (400 MHz) and ^{13}C NMR (400 MHz) were all analysed. DE: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59-2.48 (m, 1H), 2.14 (s, 3H), 2.12-1.85(m, 5H), 1.60 (s, 3H), 1.58 (s, 3H), 1.55-1.43 (m, 1H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 18.8, 19.0, 25.3, 27.9, 31.2, 33.0, 48.2, 123.9, 125.3, 211.8 ppm. GC-MS (relative intensity, 70 eV) m/z: 152 (M^+), 137, 119, 109 (100), 107, 95, 93, 91, 81, 79, 77, 67, 55, 43.

GC-FID analysis

An Agilent 6890N gas chromatography equipped with a flame ionisation detector (GC-FID) was utilised for the analysis of the reaction results. The GC-FID has a ZB5HT capillary column (30 m×250 µm×0.25 µm nominal, max temperature 400 °C) at 20.2 psi constant pressure. The carrier gas in the GC-FID was helium with flow rate at 2.0 mL/min in constant flow mode. The split ratio used was set as 5:1. Generally, the starting oven temperature was at 50 °C for 4 minutes. Following this, the temperature was then increasing by 10 °C/min to 300 °C and maintained at 300 °C for 10 minutes. The temperature of the injector was at 300 °C, and the temperature of the flame ionisation detector was held at 340 °C. Each of the GC samples consisted of 20-40 mg product mixture and 1.5 mL dichloromethane or acetone as GC solvent.

GC-MS analysis

A gas chromatograph-mass spectrometry (GC-MS) proceeded on a Perkin Elmer Clarus 500 GC along with a Clarus 560 S quadrupole mass spectrometer. The equipment was equipped with a DB5HT capillary column (30 m×250 µm×0.25 µm nominal, max temperature 430 °C). The carrier gas utilised in GC-MS was helium with flow rate at 1.0 mL/min, and the split ratio used was 10:1. The injector temperature was 330 °C. During the GC-MS test, the initial temperature of the oven was at 50 °C for 4 minutes. After that, the temperature increased with a rate of 10 °C/min to 300 °C and held for 10 minutes. The Clarus 500 quadrupole mass spectrum was conducted in electron ionisation (EI) mode at 70 eV with the source temperature and the quadrupole both at 300 °C. The m/z mass scan was in the range of 40 to 640 m/z. The data was collected by the PerkinElmer enhanced TurboMass (Ver. 5.4.2) chemical software. Each GC-MS sample consisted of 20-40 mg product mixture and 1.5 mL

DCM or acetone as GC-MS solvent.

^{1}H NMR and ^{13}C NMR analysis

The ^{1}H NMR and ^{13}C NMR spectrum results in this work were recorded by a JEOL JNM-ECS 400 MHz spectrometer. During preparation, 100 mg sample from the experiment was dissolved in 1 mL chloroform-d. 16 scans were utilised for ^{1}H NMR analysis, and 256 scans were utilised for ^{13}C NMR analysis. The NMR data was processed and analysed by ACD/NMR Processor Academic Edition software (Ver. 12.01).

HSPiP software predictions

HSPiP (4th Edition 4.1.04), developed by Abbott, Hansen and Yamamoto, is a software which can be employed to predict the Hansen solubility parameters (HSPs) and the other various chemical and physical properties of a given chemical. In this study, HSPiP was used to calculate the HSPs of MMC and also predict its physical properties *via* using Y-MB method (Dr. Hiroshi Yamamoto's neural network molecular breaking technique). HSPiP also provided a 3D Hansen space diagram for MMC and other conventional solvents investigated. The simplified molecular-input line-entry system (SMILES) of MMC is COC(=O)OCC1COC(C)(C)O1. The position of MMC and other nearby conventional solvents in the 3D Hansen space can be seen in the figure S2.

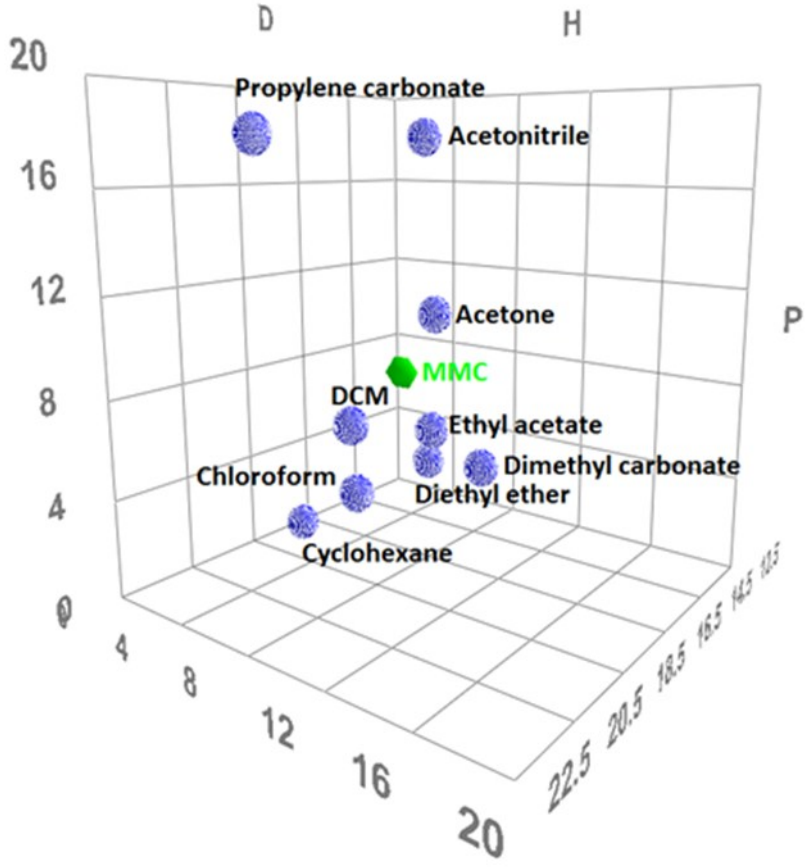

Figure S1. HSPiP map showing the position of MMC in relation to a selection of traditional solvents.

Kamlet-Taft solvatochromic parameters testing of MMC

The Kamlet-Taft (KT) solvatochromic parameters of MMC were measured by UV-vis. spectra (JENWAY, 6705 UV/Vis. Spectrophotometer) of different dyes of Nile red (NR), 4-nitroaniline (NA) and *N,N*-diethyl-4-nitroaniline (NN) respectively dissolved in MMC in quartz cuvettes at 25 °C. When the ν_{max} of these dyes was determined, then KT parameters α,[1] β,[2] and π^*,[2] can be obtained based on Equation 1-3 as shown below.

$$\alpha = \textbf{Error!} \quad (1)$$

$$\beta = \textbf{Error!} \quad (2)$$

$$\pi^* = \textbf{Error!} \quad (3)$$

Where $\nu_{max\ in\ NR}$, $\nu_{max\ in\ NA}$ and $\nu_{max\ in\ NN}$ represent the wavenumbers at maximum absorbance on the UV-vis. spectra for NR, NA and NN, respectively.

Differential scanning calorimetry (DSC) analysis for MMC

The melting point and crystallisation point of MMC were determined by DSC (TA Instruments, Q2000) to be -7°C and -50 °C as shown in Fig. S2, respectively. During the testing, 8.1 mg MMC was hermetically-sealed in Tzero aluminium DSC pan. The dynamic run proceeded at a rate of 5 °C/min from 25 °C to –90 °C.

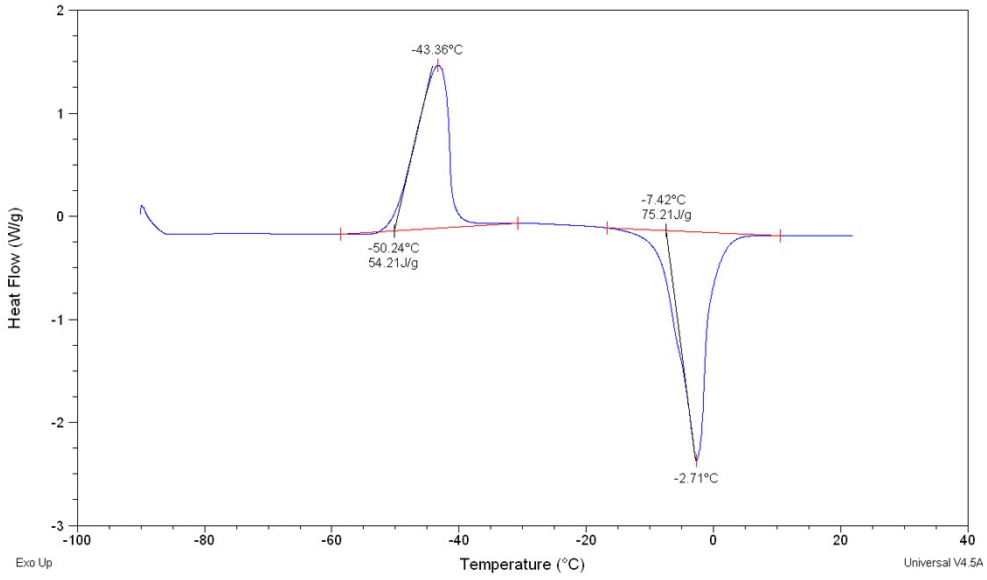

Figure S2. The DSC of MMC

Ames test for MMC

The experiment procedure was based on manufacturer's guidelines as follows:[3] TA98 and TA100 were tested at 6 different concentrations (0.16 mg/mL, 0.31 mg/mL, 0.63 mg/mL,

1.25 mg/mL, 2.5 mg/mL, 5 mg/mL) of MO, as well as a positive (concentration of 2 μg/mL for 2-nitrofluorene (2-NF) and 0.1 μg/mL for 4-nitroquinoline-*N*-oxide (4-NQO)) and a negative (dimethyl sulfoxide (DMSO) solvent) control. They grew in a medium including sufficient histidine for 90 minutes to conduct about twice cell division. After the exposure, these cultures were diluted in pH indicator medium without histidine and then aliquoted into 48 wells of a 384-well plate. After 48 hours at 37 °C, the wells including bacteria conducted reversion to return to His^+ changed the colour from purple to yellow since pH of the medium was decreased by the metabolism of the His^+ strains. The number of the wells changed colour were counted manually for each dose, which was tested in three times to obtain the average value.

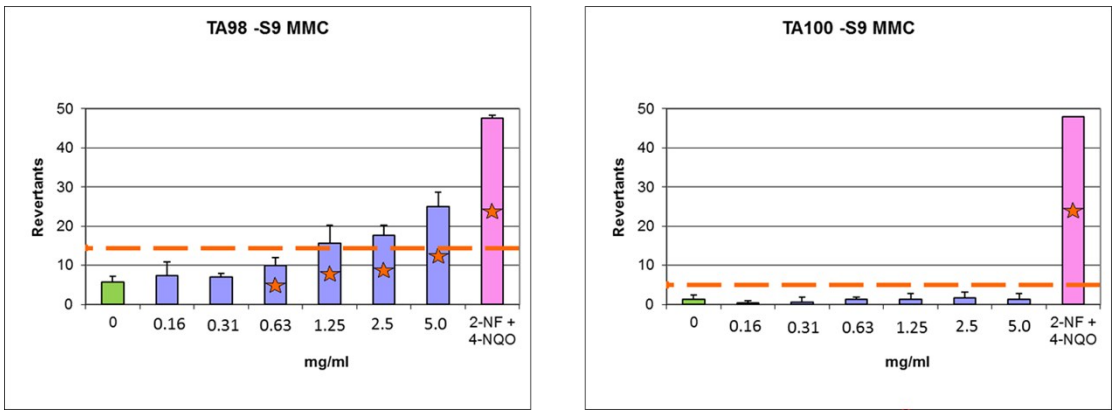

Figure S3. Peroxide test for MMC

An initial investigation to monitor the formation of peroxides in MMC was carried out using a peroxide test strip (Macherey-Nagel, QUANTOFIXR Peroxide-100). Monitoring of 7.5 mL of MMC was carrying out over a period of 224 days under standard atmospheric conditions in absence of antioxidants or stabilisers. The approach of test was following the manufacture's instruction: A drop from the 6 mL MMC solvent was added to the test pad of the peroxide test strip and was allowed to evaporate. After evaporation, a drop of distilled water was added to the test pad, and the colour of the test pad was compared to peroxide colourimetric card in order to attain the concentration value of the peroxide in the MMC solvent.

2 Optimisation of synthesis of MMC

The effect of reaction time on the synthesis of MMC

To investigate the effect of reaction time on the synthesis of MMC from solketal and DMC catalysed by K_2CO_3, reaction time from 1 h to 50 h was selected and the reaction was monitored by GC. Table S1. indicates that the yield of MMC increased gradually from 42% to97% (entry 1-6, Table S1.). Nevertheless, when the reaction time was longer than 20 h, the yield of MMC remained 97% (entry 6-8, Table S1.), which demonstrated that 20 h is the optimised reaction time for this process. Meanwhile, the selectivity towards MMC maintained very high (99%) in all cases, which indicated that this reaction had a high selectivity towards MMC.

Table S1. The effect of the reaction time on the synthesis of MMC[a]

Entry	Time	Selectivity (%)[b]	GC yield (%)
1	1 h	>99	42
2	2 h	>99	61
3	5 h	>99	84
4	10 h	>99	92
5	15 h	>99	96
6	**20 h**	**>99**	**97**
7	25 h	>99	97
8	50 h	>99	97

[a] Reaction conditions: solketal/DMC/K_2CO_3 = 6 mmol : 240 mmol : 7.2 mmol; *T* = 90 °C. [b] Selectivity towards MMC.

The effect of catalytic loading on the synthesis of MMC

For the purpose of optimisation of catalytic loading (K_2CO_3/solketal mole ratio) in the synthesis, K_2CO_3/solketal mole ratios from 2.0000 to 0.0000 were investigated as shown in Table S2. Potassium carbonate had a very high catalytic performance during this reaction. Even when only 0.001 equivalent K_2CO_3 was applied in the process, the yield of MMC still remained very high (96%) (entry 10, Table S2.). When 0.0005 equivalent of K_2CO_3 was applied in the reaction, the yield of MMC dropped down to only 40% (entry 11, Table S2.). Furthermore, when 0.0001 catalytic equivalent was employed in the reaction, the yield of MMC fell to only 3% (entry 12, Table S2.). Specifically, the control experiment (entry 13, Table S2.) demonstrated that if the catalyst does not exist in the reaction system, the carboxymethylation reaction between solketal and DMC will not conduct. During this investigation, the selectivity towards MMC still remained very high (99%). As a result, 0.001 K_2CO_3 equivalent was selected as an optimised reaction condition. This was an amazing result since only tiny amount of potassium carbonate was required in this process.

Table S2. The effect of catalytic loading on the synthesis of MMC[a]

Entry	K_2CO_3/solketal mole ratio	Selectivity (%)[b]	GC yield (%)
1	2.0000	>99	97
2	1.2000	>99	97
3	0.8000	>99	97
4	0.4000	>99	96
5	0.1000	>99	97
6	0.0500	>99	97
7	0.0300	>99	98
8	0.0100	>99	98
9	0.0050	>99	97
10	**0.0010**	**>99**	**96**
11	0.0005	>99	40
12	0.0001	>99	3
13	0.0000	>99	0

[a] Reaction conditions: solketal/DMC = 6 mmol : 240 mmol; *T* = 90 °C; Reaction time was 20 h. [b] Selectivity towards MMC.

The effect of DMC/solketal mole ratio on the synthesis of MMC

By using the optimised conditions as mentioned above, the effect of mole ratio of DMC to solketal was discovered from the range of 5:1 to 40:1, and these results are listed in Table S3. When DMC to solketal mole ratio increases, selectivity and GC yield towards MMC improved from 90% to 99% and 90% to 96%, respectively (entry 1-5, Table S3.). 20:1 of mole ratio of DMC to solketal was proved to be the optimised reaction condition.

Table S3. The effect of DMC/solketal mole ratio on the synthesis of MMC[a]

Entry	DMC/solketal mole ratio	Selectivity (%)[b]	GC yield (%)
1	5:1	90	90
2	10:1	96	94
3	15:1	97	94
4	**20:1**	**>99**	**96**
5	40:1	>99	96

[a] Reaction conditions: solketal/K_2CO_3 = 6 mmol : 0.006 mmol; *T* = 90 °C; Reaction time was 20 h. [b] Selectivity towards MMC.

In summary, reaction time 20 h, 0.001 equivalent catalytic loading of K_2CO_3 and 20:1 of mole ratio of DMC to solketal was found to be the optimised reaction condition for the synthesis of MMC from DMC and solketal catalysed by potassium carbonate and were used for the production of MMC.

3 Characterisation

GC-MS EI mass spectrum of MMC

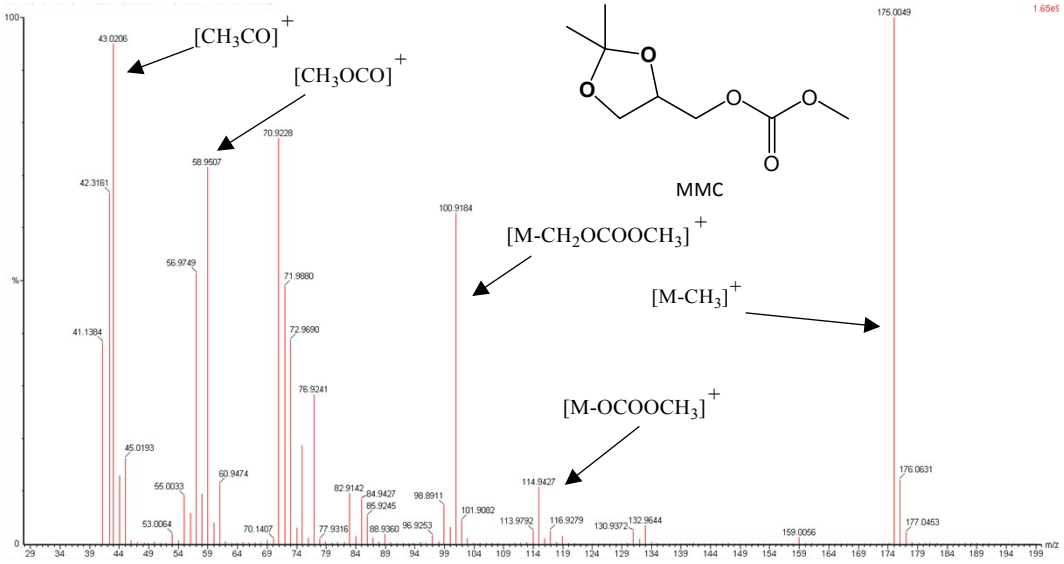

Figure S3. Mass spectrum (EI) of MMC

^{1}H NMR of MMC

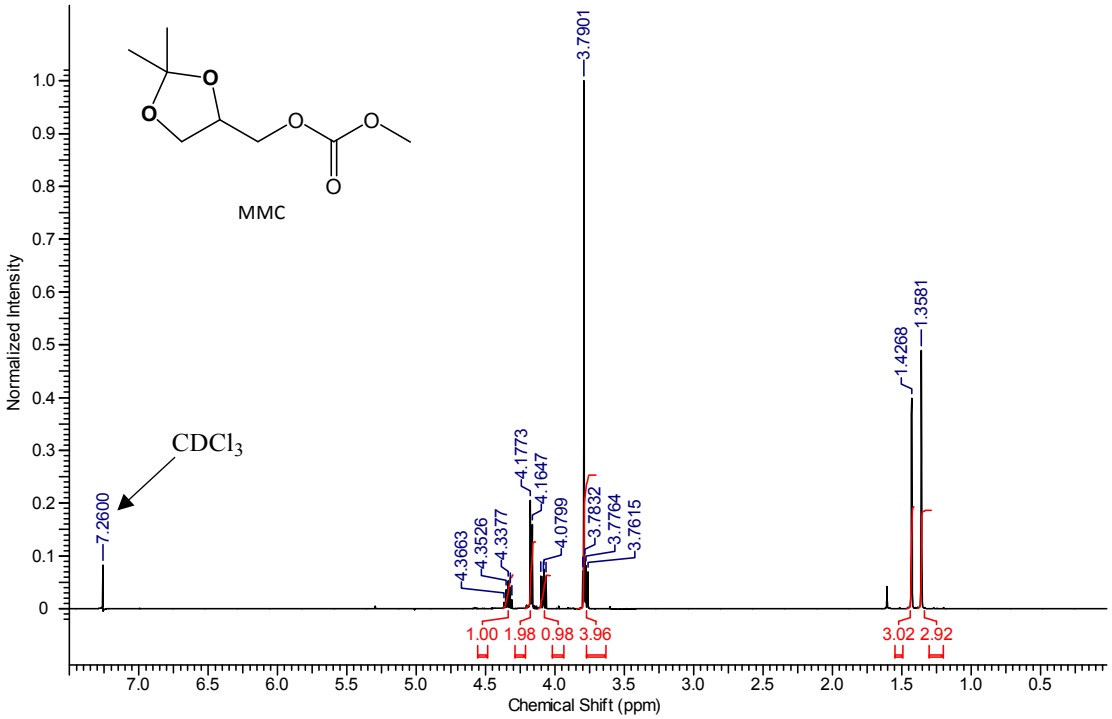

Figure S4. ^{1}H NMR of MMC

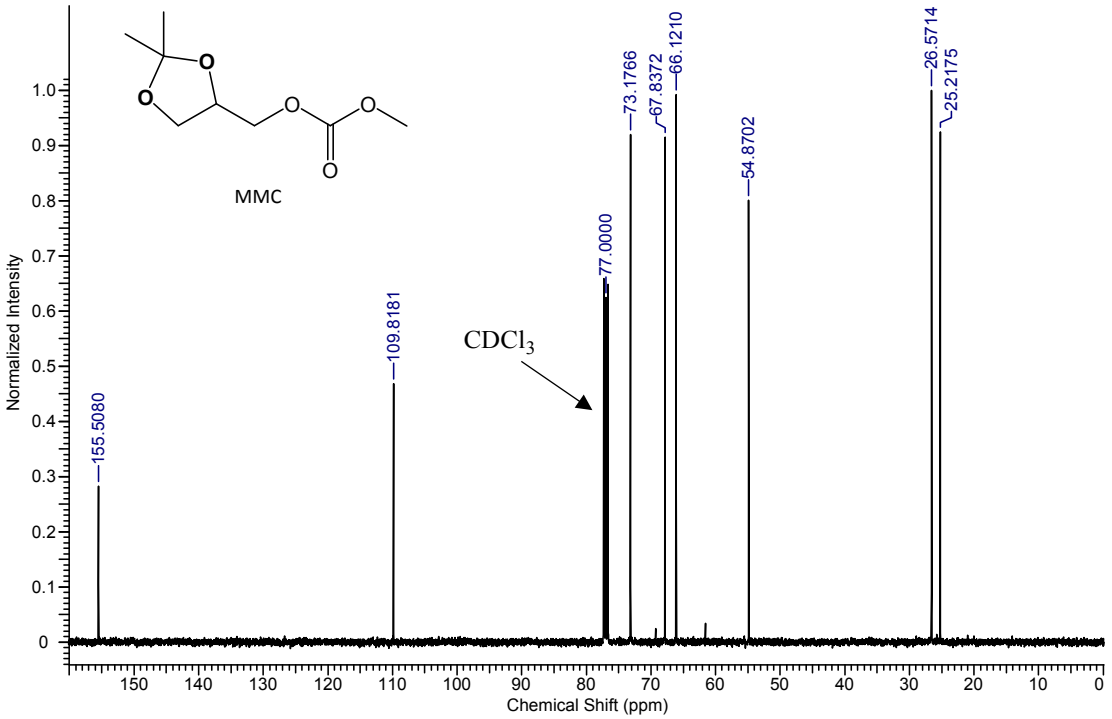

Figure S5. ^{13}C NMR of MMC

GC-MS EI mass spectrum of 4-methoxyacetophenone (4-MAP)

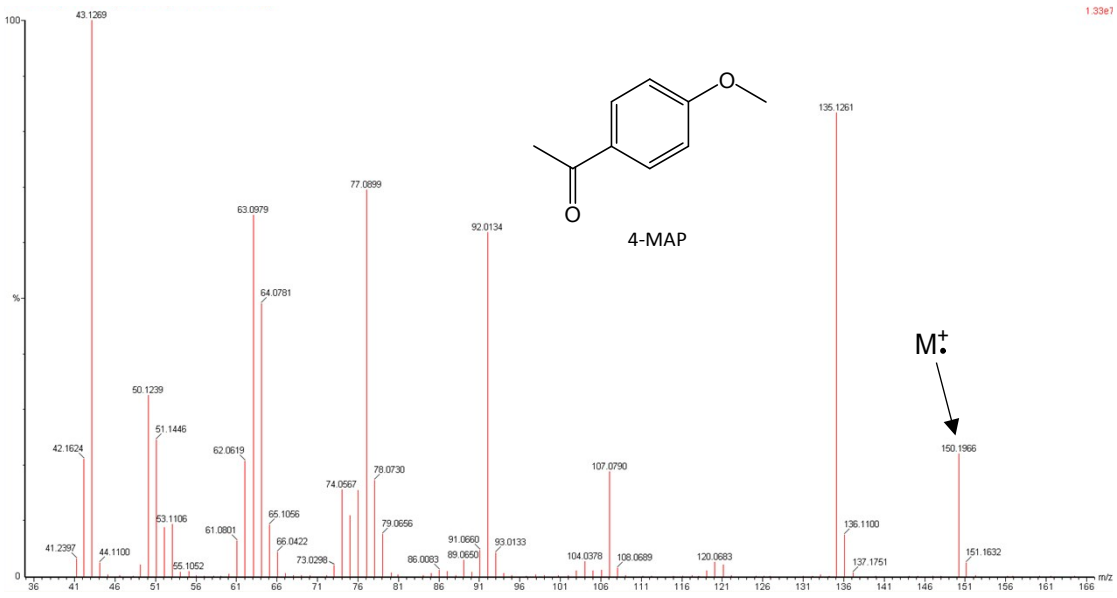

Figure S6. Mass spectrum (EI) of 4-MAP

This mass spectrum (EI) of 4-MAP synthesised in this experiment was also in accordance with the standard mass spectrum mentioned in the literature.[4]

GC-MS EI mass spectrum of 1-(3,4-dimethylcyclohex-3-enyl) ethanone (DE)

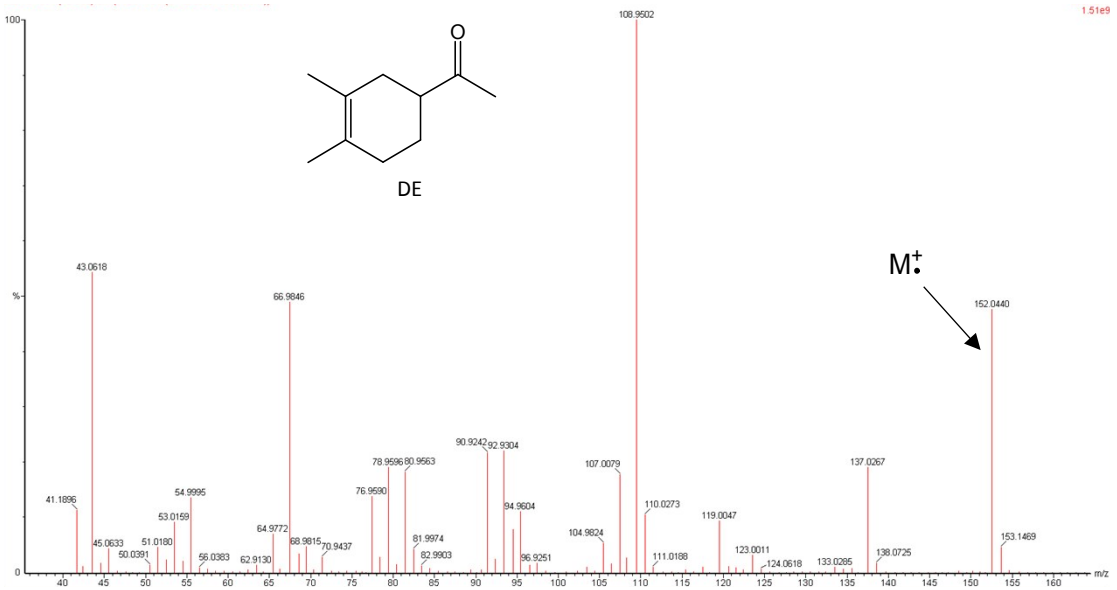

Figure S7. Mass spectrum (EI) of DE

This mass spectrum (EI) of DE synthesised in this experiment was also in accordance with the standard mass spectrum mentioned in the literature.[5]

^{1}H NMR of DE

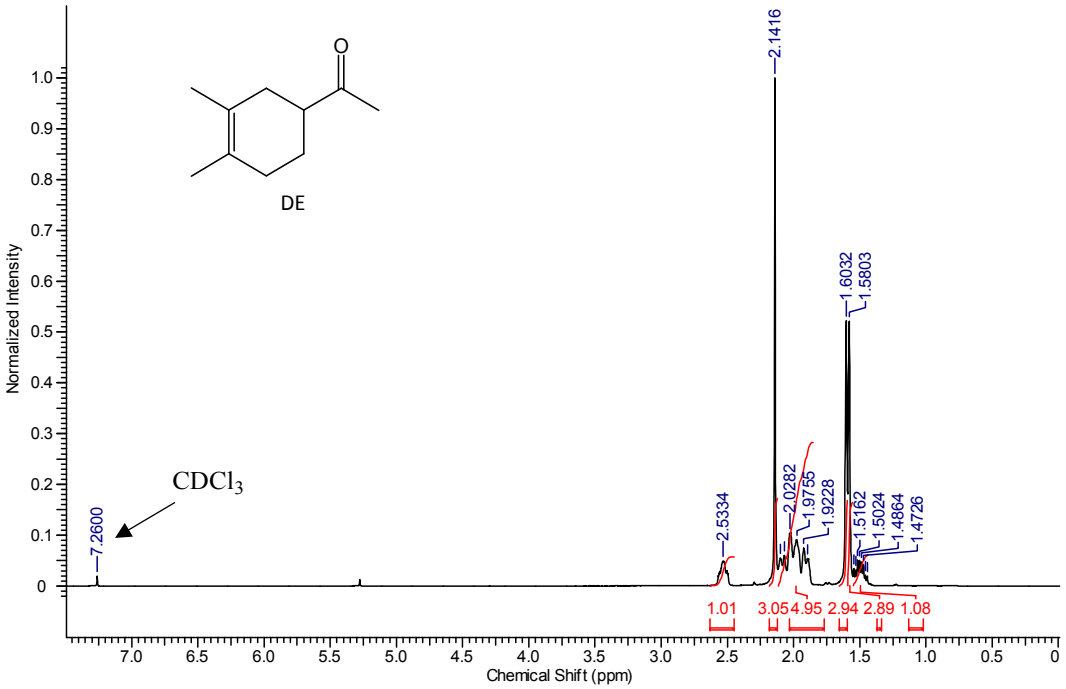

Figure S8. ^{1}H NMR of DE

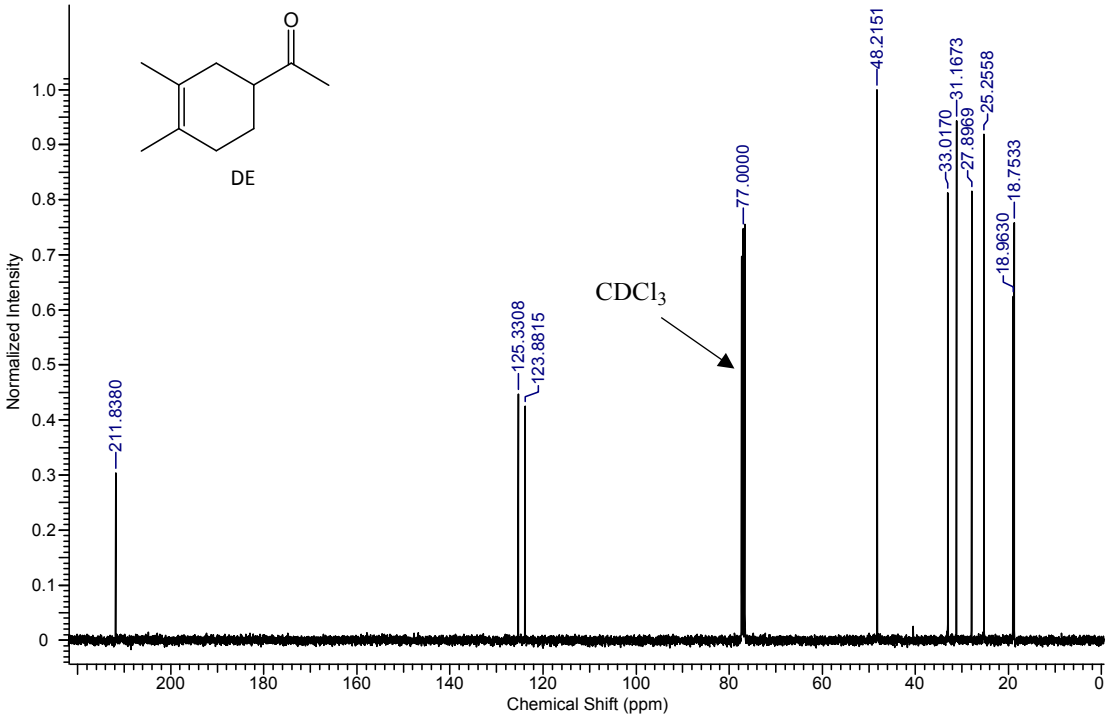

Figure S9. ^{13}C NMR of DE

GC-MS EI mass spectrum of (4,4-dimethyl-1,3-dioxolan-2-yl)methyl (2,2-dimethyl-1,3-dioxolan-4-yl)methyl carbonate (diMMC)

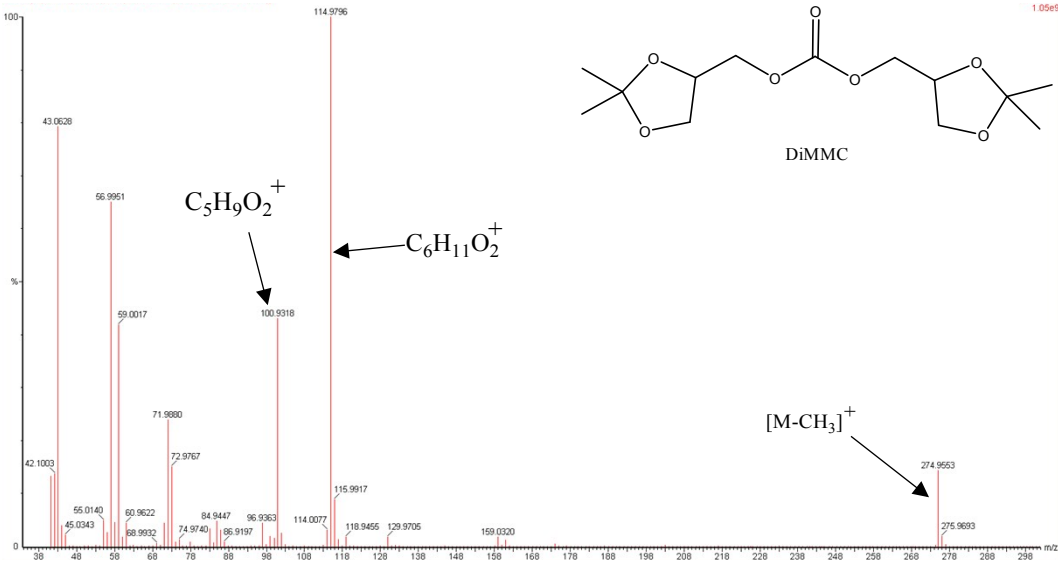

Figure S10. The mass spectrum (EI) of diMMC

References

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3 Ames MPF Microplate Format Mutagenicity Assay Short Procedure. Available online at http://www.xenometrix.ch/res/files/Ames%20MPF%20Short%20Instruction.pdf (accessed May 2016).

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