Microwave-assisted synthesis of 4-oxo-2-butenoic acids by aldol-condensation of glyoxylic acid

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1. Table S1. Optimisation of the transformation of 4-methoxyacetophenone into 1 via aldol-condensation.

![Chemical structure](image)

| Entry | Conditions | Yield after purification |
|-------|------------|--------------------------|
| 1     | 1.5 eq. glyoxylic acid monohydrate, 1.7 eq. NaH 60% dispersion in mineral oil, DMSO, 80 °C, 18 h | Low conversion<sup>1</sup> |
| 2     | 1.5 eq. glyoxylic acid monohydrate, 1.7 eq. NaH 60% dispersion in mineral oil, DMSO, 80 °C, 18 h, then 1.5 eq. NaH 60% dispersion in mineral oil, 1.5 eq. TsCl, 80 °C, 5 min | Low conversion<sup>1</sup> |
| 3     | 1.5 eq. glyoxylic acid monohydrate 1.7 eq. LiOH monohydrate MeOH, 80°C, 18h | Moderate conversion<sup>2</sup> |
| 4     | 3.0 eq. glyoxylic acid monohydrate, 1.0 eq. pyrrolidine, 1.0 eq. acetic acid, MeOH, MW, 80°C, 8 h | Moderate conversion<sup>2</sup> |
| 5     | 3.0 eq. glyoxylic acid monohydrate 3.0 eq. TsCl, dioxane, 80°C, 18 h | Moderate conversion<sup>2</sup> |
| 6     | 3.0 eq. glyoxylic acid monohydrate 3.0 eq. Tf<sub>2</sub>O, dioxane, 80°C, 18 h | No product |
| 7     | 3.0 eq. glyoxylic acid monohydrate 1.0 eq. TsOH monohydrate dioxane, 80°C, 48 h | 70% |

<sup>1</sup>Low conversion: < 10% desired product by UV and/or ELSD LC-MS analysis. <sup>2</sup>Moderate conversion: < 50% desired product by UV and/or ELSD LC-MS analysis.
2. Figure S1. Crude NMR of TsOH-promoted aldol-condensation on pentan-2-one. A mixture of desired product 15 and side-product 19 1:1.5 was obtained.
3. Table S2. Calculated HOMO and LUMO energies for different methyl ketone substrates and glyoxylic acid.

Calculations employed the RHF/6-31+G** level of theory in the Gaussian09 suite of programs. Geometries were optimised and frequencies computed to verify that they are minima.

| Methyl ketone substituent | Substituent class | ENOL HOMO | ENOL LUMO | ENOLATE HOMO | ENOLATE LUMO | ENAMINE_HOMO | ENAMINE_LUMO |
|---------------------------|-------------------|-----------|-----------|--------------|--------------|--------------|--------------|
| cyclohexyl                | aliphatic         | -0.33597  | 0.07163   | -0.08481     | 0.16325      | -0.29239     | 0.06944      |
| cyclopentyl               | aliphatic         | -0.32685  | 0.06935   | -0.08144     | 0.18209      | -0.2852      | 0.07097      |
| isopropyl                 | aliphatic         | -0.33841  | 0.07206   | -0.08243     | 0.18843      | -0.29357     | 0.07363      |
| n-propyl                  | aliphatic         | -0.33828  | 0.07428   | -0.08121     | 0.17438      | -0.29256     | 0.07546      |
| t-butyl                   | aliphatic         | -0.33857  | 0.07477   | -0.08406     | 0.18351      | -0.30383     | 0.07418      |
| p-methylphenyl            | aromatic          | -0.30309  | 0.06808   | -0.09087     | 0.14946      | -0.28913     | 0.07035      |
| p-ethylphenyl             | aromatic          | -0.30318  | 0.06618   | -0.09156     | 0.14344      | -0.296       | 0.06673      |
| p-fluorophenyl            | aromatic          | -0.31576  | 0.0643    | -0.09751     | 0.1698       | -0.29798     | 0.06697      |
| p-chlorophenyl            | aromatic          | -0.3168   | 0.06266   | -0.1016      | 0.1533       | -0.2998      | 0.06417      |
| p-methoxyphenyl           | aromatic          | -0.29375  | 0.06866   | -0.09049     | 0.14403      | -0.28246     | 0.06718      |
| p-cyanophenyl             | aromatic          | -0.33266  | 0.0507    | -0.11218     | 0.1525       | -0.31016     | 0.05943      |

| Glyoxylic acid | HOMO   | LUMO   |
|----------------|--------|--------|
| Neutral        | -0.45302 | 0.05375     |
| Protonated     | -0.72186 | -0.2152    |
4. General Information for the Synthesis
Chemicals were purchased from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed on aluminium plates coated with 60 F254 silica from Merck. Flash chromatography was carried out using a Biotage SP4, Biotage Isolera or Varian automated flash system with Silicycle or GraceResolve normal phase silica gel pre-packed columns. Fractions were collected at 254 nm or if necessary on all wavelengths between 200 and 400 nm. Microwave irradiation was performed in a Biotage Initiator Sixty in sealed vials (Biotage microwave vials, Type I, Class A borosilicate, 28 mm outer diameter, 26 mm inner diameter, 83 mm long, round-bottom for 5-20 mL of total reaction volume; Biotage microwave vials, 16 mm outer diameter, 14 mm inner diameter, 83 mm long, round-bottom for 2-5 mL of total reaction volume). Reactions were irradiated at 2.45 GHz and were able to reach temperatures between 60 and 250 °C. Heating was at a rate of 2-5 °C/s and the pressure was able to reach 20 bars.

5. Analytical Equipment
Melting points were measured using a Stuart automatic melting point SMP40 apparatus or a Shanghai ShenGuang WRR apparatus. Fourier Transform InfraRed (FTIR) spectra were measured using an Agilent Cary 630 FTIR or a Bruker TENSOR II FTIR Spectrometer as a neat sample tableting with KBr. The abbreviations for peak description are as follows: b = broad; w = weak; m = medium and s = strong. Ultraviolet (UV) spectra were recorded on a Hitachi U-2900 spectrophotometer or an Agilent Cary 100 UV-Vis spectrophotometer and were performed in ethanol. High resolution mass spectrometry (HRMS) was provided by the ESPRC National Mass Spectrometry Service, University of Wales, Swansea, or the Mass Spectrometry Service, Department of Pharmacy, Naval Medical University and performed by Diya Lyu on an Agilent Technologies 6550 iFunnel Q-TOF LC-MS, or conducted using an Agilent 6550 iFunnel QTOF LC-MS with an Agilent 1260 Infinity UPLC system. The sample was eluted on Acquity UPLC BEH C18 (1.7μm, 2.1 x 50mm) with a flow rate of 0.7 mL/min and run at a gradient of 1.2 min 5-95% 0.1% aq. HCOOH in MeCN.
LC-MS analyses were conducted using a Waters Acquity UPLC system with photo diode array (PDA) and evaporating light scattering detector (ELSD) or using the ESI mass spectra which were performed by Zichao Ding on an Agilent Technologies 6120 Quadrupole LC-MS. When a 2 min gradient was used, the sample was eluted on an Acquity UPLC BEH C18, 1.7μm, 2.1 x 50mm, with a flow rate of 0.6 ml/min using 5-95% 0.1% HCOOH in MeCN. Analytical purity of compounds was determined using Waters X Terra RP18, 5 μm (4.6 × 150 mm) column at 1 ml/min using either 0.1% aq. ammonia and MeCN or 0.1% aq. HCOOH and MeCN with a gradient of 5-100% over 15 min. When a 12 min gradient was used, the sample was eluted on ZORBAX Eclipse XDB-C18, 3.5 μm, 4.6 x 100 mm, with a flow rate of 0.4 ml/min using 30-70% 0.1% HCOOH in MeCN.

$^1$H and $^{13}$C NMR spectra were obtained using a Bruker Avance III 500 spectrometer using a frequency of 500 MHz, and 123 MHz, respectively, or using a Bruker Avance III 600 spectrometer operating at a frequency of 600 MHz, and 150 MHz, respectively. $^{19}$F NMR spectra were acquired using the Bruker Avance III 300 spectrometer using a frequency of 282 MHz. The abbreviations for spin multiplicity are as follows: s = singlet; d = doublet; t = triplet; q = quartet, p = quintuplet, h = sextuplet and m = multiplet. Combinations of these abbreviations are employed to describe more complex splitting patterns (e.g. dd = doublet of doublets).

6. NMR spectra
Compound 2
Compound 2

![Chemical Structure](image)

**Bruker Data Parameters**

- **NAME**: MD-466-123-F4
- **EXPN** 21
- **PROCNO** 1

**Acquisition Parameters**

- **DATE**: 20200214
- **TIME**: 4:41
- **INSTRUM**: spect
- **DDBB**: 8 mm DABRO B8
- **PULPROG**: gppg90
- **ID**: 65596
- **SOLVENT**: MeOD
- **NS**: 256
- **DS**: 1
- **SNR**: 29761.904 Hz
- **FIDRES**: 0.454131 Hz
- **AQ**: 1.2010048 sec
- **RG**: 456
- **DM**: 16,890 usec
- **DE**: 7.65 usec
- **TE**: 298.2 K
- **TD1**: 1,000,000,000 sec
- **TD1**: 9.9999999 sec
- **TD0**: 1

**Channel 1**

- **SF01**: 115.813151 MHz
- **ND1**: 1417
- **P1**: 9.90 usec
- **PLW1**: 81.3899999 W

**Channel 2**

- **SF02**: 500.30200012 MHz
- **ND2**: 1417
- **CPDPRG[2]**: walt16
- **P2**: 80.00 usec
- **PLW2**: 19.8000000 W
- **PLW1**: 0.78978902 W
- **PLW1**: 0.39725000 W

**Processing Parameters**

- **ST**: 65596
- **SF**: 115.800545 MHz
- **TD**: 0
- **GB**: 1.00 Hz
- **PC**: 1.40
Compound 3
zqj-Aldol-11

Br

O

O

10

Bruker

Current Data Parameters
NAME  zqj-Aldol-11
EXPNM  2
PROCNO  1

F2 - Acquisition Parameters
Date  20210413
Time  2.18
INSTRUM  spect
DDOBB  6 mm DABCO BB-
PULPROG  zgppg20
TD  373.7
SOLVENT  DMSO
NS  604
DS  8
SWN  37978.789 Hz
FIDRES  1.000126 Hz
AQ  0.4999966 sec
RG  2050
DR  14.000 usec
DE  6.80 usec
TE  201.0 K
DD1  1.0000000 sec
DD2  9.0000000 sec
TD0  1

Z = 1

== CHANNEL f1 ==
SF01  150.9178950 MHz
NUC1  1H
P1  9.00 usec
PLW1  41.50000000 W

== CHANNEL f2 ==
SF02  600.1240058 MHz
NUC2  1H
CPSFID[2]  waltz16
CPDRX  70.00 usec
PLW2  19.4000015 W
PLW12  1.01040006 W
PLW18  0.49509999 W

F2 - Processing parameters
SF  65536
CF  150.9028112 MHz
GSW  1H
SSB  0
LB  3.00 Hz
GB  0
PC  1.40
Compound 6
Compound 19

Bruker NMR Spectrogram

Current Data Parameters
- INSTRUM: 8 mm DABBO BB-
- SPCP: 9990
- SOLVENT: MeOD
- DS: 16
- SNR: 10360.973 Hz
- FIDRES: 0.187691 Hz
- AQ: 8.2714458 sec
- RG: 2.07
- DM: 49.300 usec
- TD: 291.6 usec
- TE: 1.0000000 sec

Channel 1
- BF: 500.300000 MHz
- UFL: 16.190 MHz
- PLM1: 19.5000000 W

Processing parameters
- BF: 500.300000 MHz
- NDW: -1
- SB: 0
- LB: 0.90 Hz
- PB: 1.00
