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

SUPPORTING INFORMATION

Design and Development of 3D Printed Catalytically-Active Stirrers for Chemical Synthesis

Matthew R. Penny[a] *and Stephen T. Hilton**[a]

Abstract: In this present study, we describe the novel design, preparation and evaluation of catalyst-impregnated stirrer beads for chemical synthesis. Using a low-cost SLA 3D printer and freeware design software, a high surface area holder for a magnetic stirrer bead was developed and 3D printed containing p-toluenesulfonic acid. The devices were used to efficiently catalyze Mannich reactions in excellent yields and it was demonstrated that the devices can be re-used up to 5-times with excellent reproducibility.

[a] Dr M.R. Penny, Dr S.T. Hilton
UCL School of Pharmacy
University College London
29-39 Brunswick Square, London, WC1N 1AX, United Kingdom
E-mail: s.hilton@ucl.ac.uk

Supporting information for this article is given via a link at the end of the document.

Table of Contents

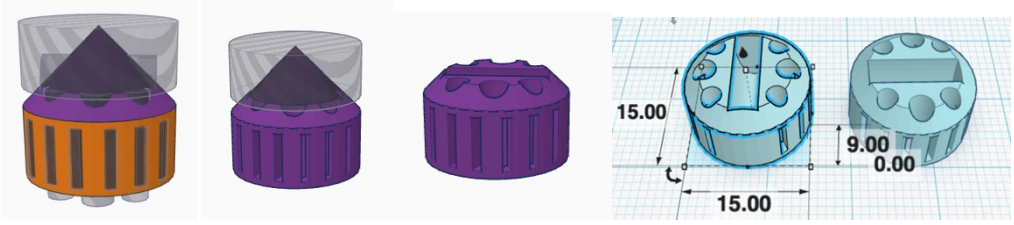
S1. Design and Development of Stirrer Device

S1.1. Design Software

The stirrer bar holders and other objects were designed using the web-based freeware design program - Tinkercad (www.tinkercad.com) which is able to export models in .STL file format for use with a 3D printer.

S1.2. Device Design

The stirrer bar holder design was based upon a commercial overhead stirrer (www.silverson.com/us/products/ultramix-mixers) with a large surface area which, when spun at high speeds, would cause 1) a high flow of liquid over the surface of the stirrer and 2) high turbulence to ensure efficient mixing. A slot to hold a 10 mm x 3 mm magnetic flea was added to the design in order to use it with batch reactions. Stirrers were designed via combining and subtracting a range of shapes in Tinkercad in order to create vertical columns and horizontal channels to increase mixing of the reaction with the final design being 15 mm x 15 mm around and 9 mm high. Once combined, the shape was exported as an STL file ready for printing.



Supplementary Figure 1. Development of Stirrer Device.

Initial prototypes were designed around a single stirrer bead which could be housed in the centre as shown below (Supplementary Figure 2). Following iterative development, it was clear that in order to catalyse a reaction, the stirrer device needed a larger surface area. The third row clearly highlights the difference that an increased size of device can bring (Supplementary Figure 2).

Supplementary Figure 1. Development of Stirrer Device.

2. Preparation of Photopolymerisable Resin

S2.1. Preparation of catalyst-loaded photopolymerizable resin

Freshly ground *p*-toluene sulfonic acid monohydrate (5% w/v) and diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (2% w/w) were dissolved in isobornyl acrylate (33% w/w) in the absence of light with the aid of sonication. Trimethylolpropane triacrylate (15% w/w) and bisphenol A ethoxylate diacrylate (50% w/w) were added and the mixture stirred for 15 hours. The photopolymerizable resin thus prepared was then poured into the tray of a Formlabs Form 1+ SLA 3D printer prior to printing.

S2.3. Device Printing and Fabrication

The photopolymerizable resin was poured into the tray of the Formlabs Form 1+ SLA 3D printer. The .STL file of the model was loaded using the PreForm software for use with a Formlabs 3D printer. The stirrer bar holders were printed with a layer height of 0.1 mm using the Clear02 resin setting. After printing, objects were removed, soaked in isopropanol for 10 minutes and left to dry and finish curing in natural light for 24 hours. A magnetic flea (10 mm x 3 mm) was added and to secure it, additional catalyst-doped photopolymerizable resin added and the objects placed in natural sunlight for 24 hours to cure. The objects were finally rinsed with isopropanol, dried and stored at room temperature prior to use.

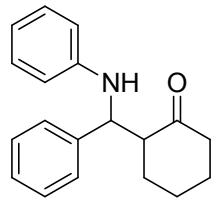
S2.4. Estimation of the amount of *p*TsOH content per device

Following the printing of the stirrer bead devices, each device was weighed and the average weight obtained, providing a total mass of 1.31 g per device. Therefore, each device can be expected to contain 0.065 g/ 0.34 mmol of *p*TsOH. Whilst it is difficult to estimate or quantify the amount of catalyst at the surface, from the literature, it has been reported that the amount of surface that is exposed in a reaction is 70 microns.[1] However, this is based on a very different system, meaning that these two results are not directly comparable. The surface area of the 3D printed stirrer device is approximately 1380 mm^2 with an overall volume of 815 mm^3 before reaction and on exposure to solvent, if we assume the loss/ reactivity of the first 100 microns of the surface, this leads to an overall reduction in volume of the device of approximately 8%. Using the w/w calculation, this equates to an overall amount of 0.005 g/ 0.027 mmol of *p*TsOH available per reaction.

S3.1. General Procedure for Mannich Reactions

The catalytically active stirrer bar holder containing a magnetic flea was added to a 25 mL round bottom flask along with ethanol (4 mL) and placed above a stirrer hotplate. With the stirrer at maximum speed, benaldehyde (2 mmol), aniline (2 mmol) and ketone (3 mmol) were added successively and the reaction was monitored by thin layer chromatography. Upon completion, the reaction was concentrated in vacuo and the crude material purified by flash column chromatography (hexane/EtOAc) to afford the Mannich adduct. In the case of compound **6** deionised water (8 mL) was added and the precipitate filtered off under vacuum, washed with EtOH/H_2O (2:1) and dried.

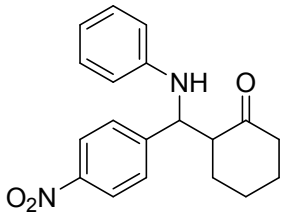
2-(Phenyl(phenylamino)methyl)cyclohexan-1-one[2]



6

According to the general procedure compound **6** was obtained as a colourless solid (508 mg, 91%); m.p. 107-109 ºC; *syn/anti* 33:67; IR (thin film) ν_{max} 3379, 2943, 1692, 1601, 1510, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60-2.06 (m, 6H), 2.31-2.36 (m, 1H), 2.42-2.46 (m, 1H), 2.74-2.79 (m, 1H), 4.63 (d, J = 7.1 Hz, 0.67H), 4.69 (brs, 1H), 4.81 (d, J = 4.3 Hz 0.33H), 6.52-6.57 (m, 2H), 6.61-6.67 (m, 1H), 7.05-7.10 (m, 2H), 7.20-7.24 (m, 1H), 7.28-7.33 (m, 2H). 7.35-7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*anti*) 23.7, 27.9, 31.3, 41.8, 57.5, 58.0, 113.6, 117.5, 127.2, 127.3, 128.5, 129.1, 141.6, 147.2, 212.9; (*syn*) 24.9, 27.0, 26.7, 42.4, 56.6, 57.2, 114.1, 117.7, 127.0, 127.5, 128.4, 129.0, 141.5, 147.5, 211.3; HRMS (ESI) *m/z* calc for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found: 280.1695.

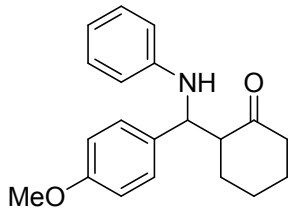
2-((4-Nitrophenyl)(phenylamino)methyl)cyclohexan-1-one[3]



18

According to the general procedure compound **18** was obtained as an orange gum (579 mg, 89%); *syn/anti* 36:64; IR (thin film) ν_{max} 3387, 2936, 1703, 1598, 1511, 1340 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58-1.84 (m, 3H), 1.94-2.04 (m, 3H), 2.30-2.48 (m, 2H), 2.84-2.88 (m, 1H), 4.59 (br. s, 0.7 H), 4.72 (d, J = 5.3 Hz, 0.3H), 4.86 (br. s, 1H), 6.50-6.52 (m, 2H), 6.86-6.71 (m, 1H), 7.07-7.11 (m, 2H), 7.53-7.60 (m, 2H), 8.14-8.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*anti*) 25.0, 27.0, 29.1, 42.5, 56.2, 57.3, 114.1, 118.4, 123.6, 128.6, 129.2, 146.6, 149.5, 210.6; (*syn*) 24.5, 27.8, 32.0, 42.3, 57.1, 57.8, 113.5, 118.2, 123.7, 128.2, 129.3, 147.1, 149.8, 211.7; HRMS (ESI) *m/z* calc for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.1547, found: 325.1548.

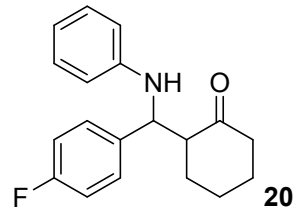
2-((4-Methoxyphenyl)(phenylamino)methyl)cyclohexan-1-one[4]



19

According to the general procedure compound **19** was obtained as a colourless solid (440 mg, 71%); *syn/anti* 31:69; IR (thin film) ν_{max} 3359, 2935, 1658, 1591, 1555, 1505, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55-2.09 (m, 6H), 2.27-2.48 (m, 2H), 2.69-2.80 (m, 1H), 3.78 (s, 3H), 4.60 (d, J = 7.3 Hz, 1.5H), 4.73 (d, J = 4.5 Hz, 0.5H), 6.53-6.57 (m, 2H), 6.61-6.67 (m, 1H), 6.81-6.86 (m, 2H), 7.04-7.10 (m, 2H), 7.26-7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*anti*) 23.5, 27.9, 31.1, 41.7, 55.2, 56.9, 57.6, 113.7, 113.9, 117.5, 128.27, 129.0, 133.6, 147.3, 158.7, 213.0; (*syn*) 24.8, 27.0, 29.0, 42.4, 55.2, 56.6, 57.4, 113.7, 114.1, 117.6, 128.6, 129.0, 133.4, 147.5, 158.5, 211.6; HRMS (ASAP) *m/z* calc for $C_2H_{22}NO_2$ $[M-H]^-$ 308.1651, found: 308.1647.

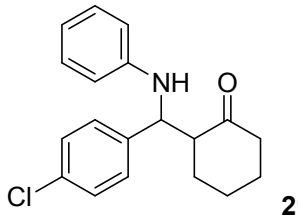
2-((4-Fluorophenyl)(phenylamino)methyl)cyclohexan-1-one[3]



20

According to the general procedure compound **20** was obtained as a colourless solid (508 mg, 85%); m.p. 111-113 ºC; *syn/anti* 32:68; IR (thin film) ν_{max} 3376, 2951, 1690, 1602, 1506, 1224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57-2.08 (m, 6H), 2.31-2.45 (m, 1H), 2.40-2.45 (m, 1H), 2.71-2.81 (m, 1H), 4.61-4.76 (m, 2H), 6.50-6.55 (m, 2H), 6.63-6.69 (m, 1H), 6.96-7.02 (m, 2H), 7.06-7.11 (m, 2H), 7.32-7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*anti*) 23.9, 27.8, 31.4, 42.0, 57.4, 57.5, 113.6, 115.3 (d, J = 21.2 Hz), 117.7, 128.8 (d, J = 8.0 Hz), 129.1, 137.4 (d, J = 2.9 Hz), 147.1, 161.9 (d, J = 245.2 Hz), 212.5; (*syn*) 24.9, 27.0, 29.0, 42.5, 56.5, 56.9, 114.1, 115.2 (d, J = 21.2 Hz), 117.9, 129.1, 129.1 (d, J = 8.1 Hz), 137.1 (d, J = 3.7 Hz), 147.2, 161.9 (d, J = 245.2 Hz), 211.3; HRMS (ESI) *m/z* calc for $C_{19}H_{21}FNO$ $[M+H]^+$ 298.1602, found: 298.1602.

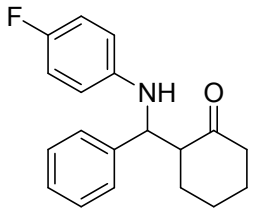
2-((4-Chlorophenyl)(phenylamino)methyl)cyclohexan-1-one[5]



21

According to the general procedure compound **21** was obtained as a colourless oil (440 mg, 70%); *syn/anti* 40:60; IR (thin film) ν_{max} 3398, 2938, 1704, 1602, 1502, 1316 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58-2.06 (m, 6H), 2.25-2.35 (m, 1H), 2.37-2.43 (m, 1H), 2.70-2.79 (m, 1 H), 4.53 (brs, 0.3 H), 4.58 (d, J = 6.3 Hz, 0.7 H), 4.7 (brs, 1H), 6.48-6.52 (m, 2H), 6.61-6.67 (m, 1H), 7.04-7.09 (m, 2H), 7.23-7.26 (m, 2 H), 7.28-7.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 27.0, 29.0, 29.7, 42.4, 56.4, 57.0, 114.1, 118.0, 128.5, 129.0, 132.7, 140.0, 147.1, 211.1; HRMS (ESI) *m/z* calc for $C_{19}H_{21}ClNO$ $[M+H]^+$ 314.1306, found: 314.1306.

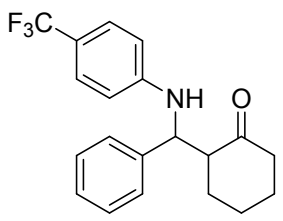
2-(((4-Fluorophenyl)amino)(phenyl)methyl)cyclohexan-1-one[6]



22

According to the general procedure compound **22** was obtained as a colourless solid (502 mg, 84%); m.p. 92-94 ºC; *syn/anti* 29:71; IR (thin film) ν_{max} 3402, 2932, 1698, 1509, 1448, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56-2.06 (m, 6H), 2.32-2.37 (m, 1H), 2.42-2.48 (m, 1H), 2.72-2.82 (m, 1H), 4.55 (d, J = 7.3 Hz, 0.7H), 4.59 (br. s, 1H), 4.76 (d, J = 4 Hz, 0.3 H), 6.45-6.51 (m, 2H), 6.74-6.81 (m, 2H), 7.21-7.25 (m, 1H), 7.29-7.38 (m, 4H); ^{13}C NMR (100 MHz, $CHCl_3$) δ (syn) 24.9, 27.0, 28.4, 42.4, 56.0, 57.9, 115.1 (d, J = 8.1 Hz), 115.4 (d, J = 22.7 Hz), 127.1, 127.5, 128.5, 141.3, 143.9 (d, J = 2.2 Hz), 157.2 (d, J = 235.7 Hz), 211.5; (anti) 23.8, 28.0, 31.5, 41.9, 57.5, 58.8, 114.7 (d, J = 7.3 Hz), 115.4 (d, J = 22.7 Hz), 127.3, 127.3, 128.5, 141.5, 143.6 (d, J = 1.5 Hz), 155.5 (d, J = 234.9 Hz), 212.9; HRMS (ESI) *m/z* calc for $C_{19}H_{21}FNO$ $[M+H]^+$ 298.1602, found: 298.1602.

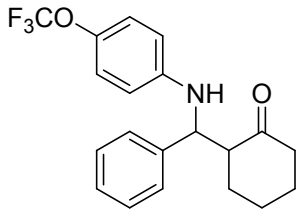
2-(Phenyl((4-(trifluoromethyl)phenyl)amino)methyl)cyclohexan-1-one[7]



23

According to the general procedure compound **23** was obtained as a colourless solid (415 mg, 60%); m.p. 141-142 ºC; *syn/anti* 53:47; IR (thin film) ν_{max} 3397, 2950, 1700, 1615, 1538, 1516, 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57-1.69 (m, 3H), 1.91-1.93 (m, 1H), 2.03-2.09 (m, 2 H), 2.29-2.37 (m, 1H), 2.42-2.47 (m, 1H), 2.80-2.85 (m, 1H), 4.83 (m, 1H), 4.92 (br. s, 0.5H), 4.94 (br. s, 0.4H), 6.56 (d, J = 8.6 Hz, 2H), 7.22-7.26 (m, 1H), 7.30-7.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.8, 28.6, 42.4, 56.2, 57.0, 113.1, 126.4, 126.4, 127.3, 127.5, 128.7, 140.6, 149.9, 211.2; HRMS (ESI) *m/z* calc for $C_{20}H_{21}F_3NO$ $[M+H]^+$ 348.1570, found: 348.1567.

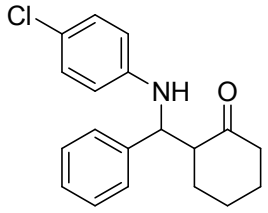
2-(Phenyl((4-(trifluoromethoxy)phenyl)amino)methyl)cyclohexan-1-one[7]



24

According to the general procedure compound **24** was obtained as a colourless solid (632 mg, 87%); m.p. 96-97 ºC; *syn/anti* 53:47; IR (thin film) ν_{max} 3390, 2937, 1699, 1608, 1517, 1225, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59-2.07 (m, 6H), 2.32-2.39 (m, 1H), 2.41-2.47 (m, 1H), 2.74-2.81 (m, 1H), 4.56 (d, J = 7.1 Hz, 0.6H), 4.63 (br. s, 0.3H), 4.78 (d, J = 3.8 Hz, 0.4H), 4.86 (br. s, 0.6H), 6.48-6.53 (m, 2H), 1.94 (m, 2H), 7.23-7.27 (m, 1H), 7.31-7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 23.9, 28.0, 31.6, 42.0, 57.4, 58.5, 113.9, 121.1 (q, J = 255.4 Hz), 122.2, 127.2, 127.4, 128.6, 140.5 (q, J = 2.2), 141.3, 146.1, 212.8; δ (minor) 24.9, 27.0, 28.4, 42.4, 56.5, 57.6, 114.3, 121.1 (q, J = 255.4 Hz), 112.13, 127.22, 127.4, 128.5, 140.7 (q, J = 2.2 Hz), 141.0, 146.3, 211.3; HRMS (ESI) *m/z* calc for $C_{20}H_{21}F_3NO_2$ $[M+H]^+$ 364.1519, found: 364.1517.

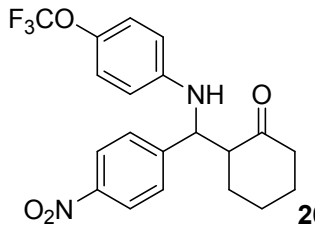
2-(((4-Chlorophenyl)amino)(phenyl)methyl)cyclohexan-1-one[7]



25

According to general procedure compound **25** was obtained as a colourless solid (450 mg, 72%); m.p. 113-115 ºC; *syn/anti* 38:62; IR (thin film) ν_{max} 3410, 2957, 1698, 1598, 1496, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58-2.07 (m, 6H), 2.31-2.38 (m, 1H), 2.41-2.46 (m, 1H), 2.74-2.82 (m, 1H), 4.57 (d, J = 6.7 Hz, 0.7H), 4.76 (m, 1.2H), 6.45-6.50 (m, 2H), 6.99-7.04 (m, 2H), 7.21-7.26 (m, 1H), 7.29-7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (syn) 24.9, 26.9, 28.5, 42.4, 56.4, 57.5, 115.2, 122.3, 127.2, 127.5, 128.5, 128.8, 141.0, 146.1, 211.3; (anti) 23.9, 27.9, 31.6, 42.0, 57.4, 58.4, 114.8, 122.1, 127.2, 127.3, 128.6, 128.9, 141.3, 145.9, 212.7; HRMS (ESI) *m/z* calc for $C_{19}H_{21}ClNO$ $[M+H]^+$ 314.1306, found: 314.1308.

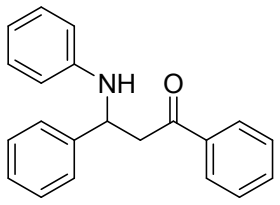
2-((4-Nitrophenyl)((4-(trifluoromethoxy)phenyl)amino)methyl)cyclohexan-1-one



26

According to the general procedure compound **26** was obtained as an orange solid (740 mg, 91%); m.p. 125-127 ºC; *syn/anti* 52:48; IR (thin film) ν_{max} 3422, 2944, 1710, 1608, 1512, 1345, 1250, 1200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59-1.81 (m, 3H), 1.94-2.09 (m, 3H), 2.30-2.49 (m, 2H), 2.84-2.88 (m, 1H), 4.65 (br.d, J = 5.1 Hz, 1H), 4.83 (br.s, 0.5H), 4.99 (br. s, 0.5 H), 6.44-6.48 (m, 2H), 6.93-6.96 (m, 2H), 7.54-7.59 (m, 2H), 8.15-8.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 24.9, 27.0, 27.9, 28.8, 32.3, 42.4, 42.6, 57.0, 57.4, 58.2, 113.8, 114.4, 122.3, 122.4, 123.8, 123.8, 128.2, 128.5, 141.1, 140.9, 145.4, 145.5, 147.2, 147.2, 148.9, 149.3, 211.8, 210.6; HRMS (ESI) *m/z* calc for $C_{20}H_{22}F_3N_2O_4$ $[M+H]^+$ 409.1370, found: 409.1367.

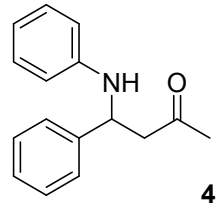
1,3-Diphenyl-3-(phenylamino)propan-1-one[4]



27

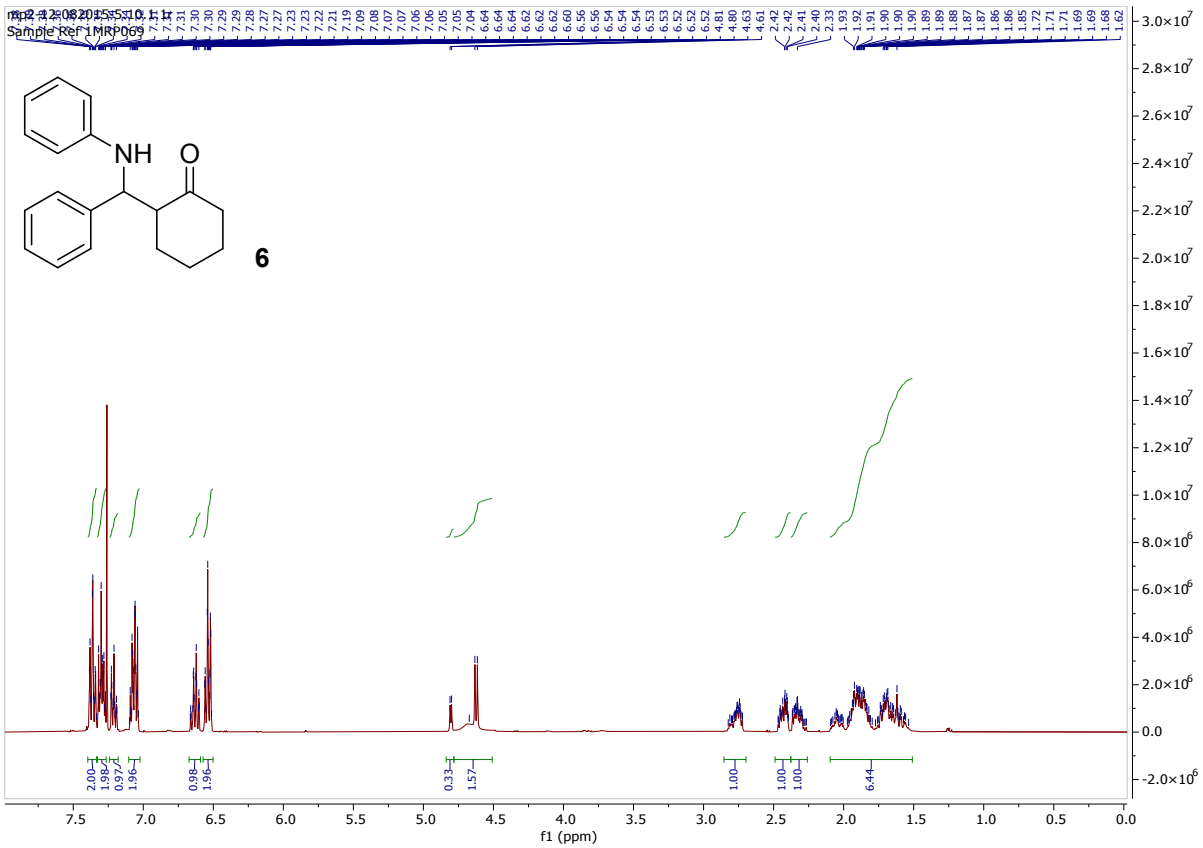
According to the general procedure compound **27** was obtained as a colourless solid (314 mg, 52%); m.p. 168-170 ºC; IR (thin film) ν_{max} 3; IR (thin film) ν_{max} 3383, 3023, 1668, 1596, 1509, 1492, 1288 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.48 (ddd, J = 15.1, 7.8, 5.1 Hz, 2 H), 4.56 (br. s, 1H), 5.02 (dd, J = 7.3, 5.6 Hz, 1H), 6.55-6.58 (m, 2H), 7.08-7.12 (m, 2H), 7.22-7.26 (m, 1H), 7.32-7.35 (m, 2H), 7.44-7.48 (m, 4H), 7.55-7.60 (m, 1H), 7.91-7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.3, 54.8, 113.8, 117.8, 126.4, 127.4, 128.2, 128.7, 128.8, 129.1, 133.4, 136.7, 143.1, 147.0, 198.3; HRMS (ESI) *m/z* calc for $C_{21}H_{20}NO$ $[M+H]^+$ 302.1539, found: 302.1538.

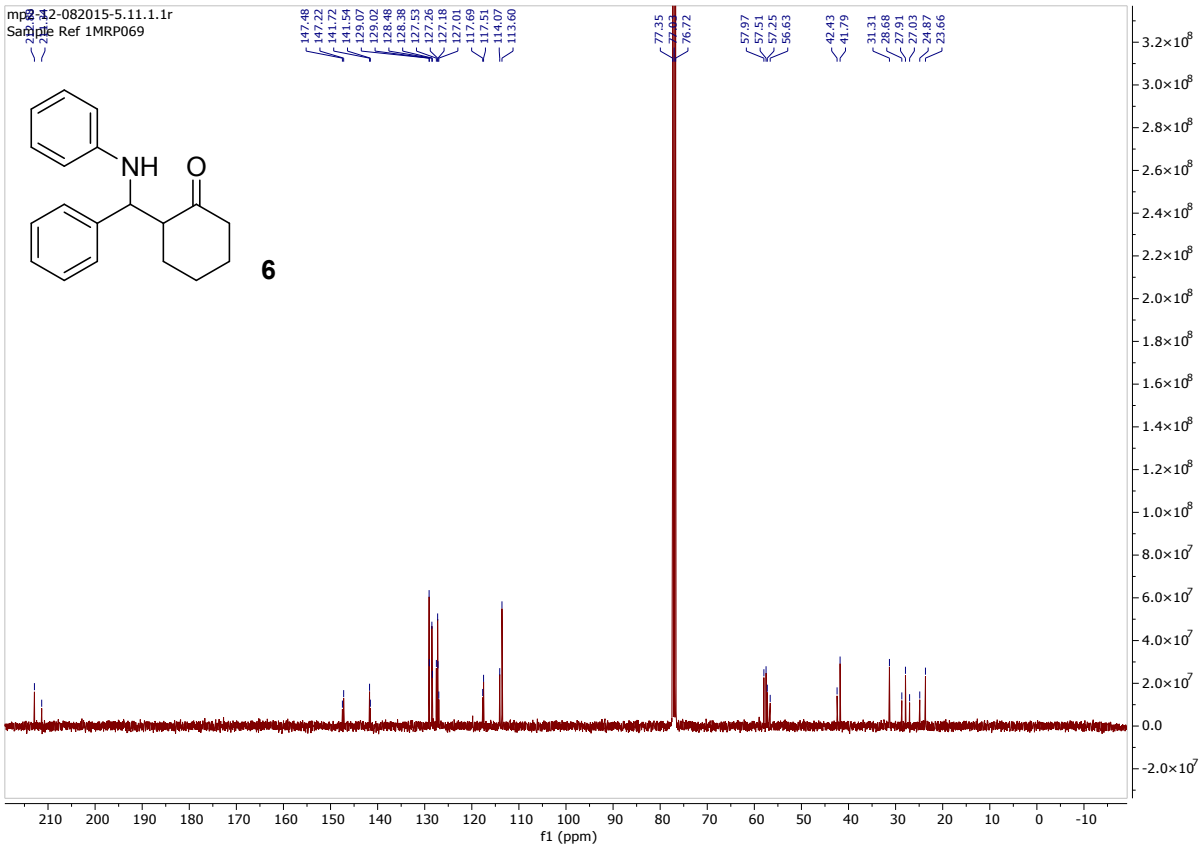
4-Phenyl-4-(phenylamino)butan-2-one[8]

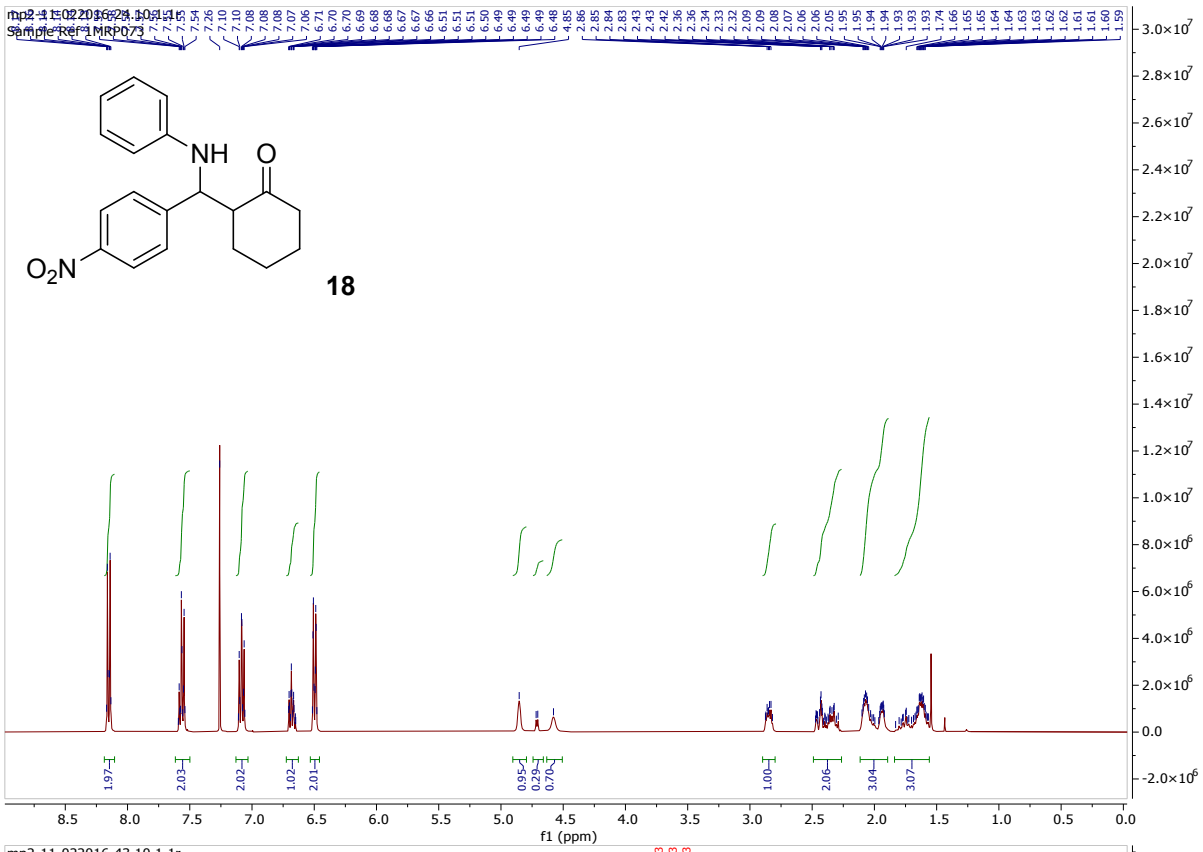


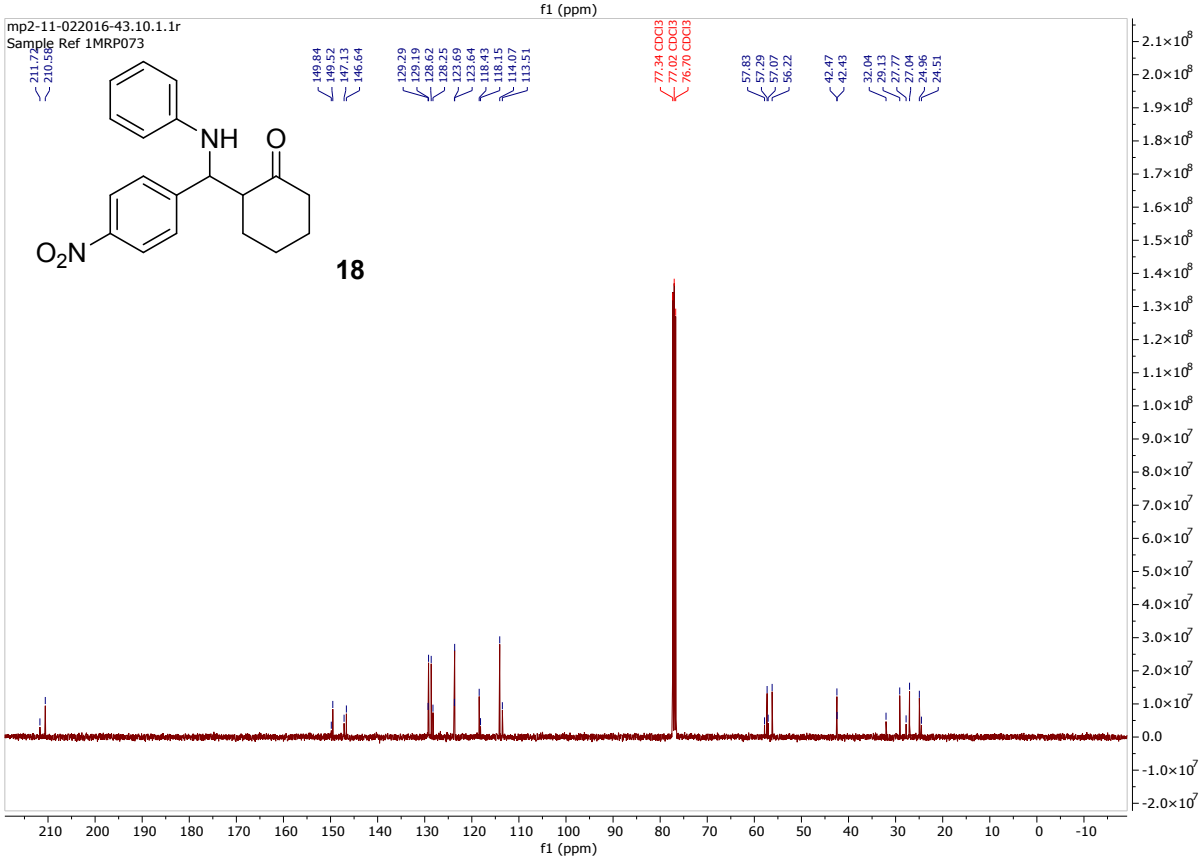
4

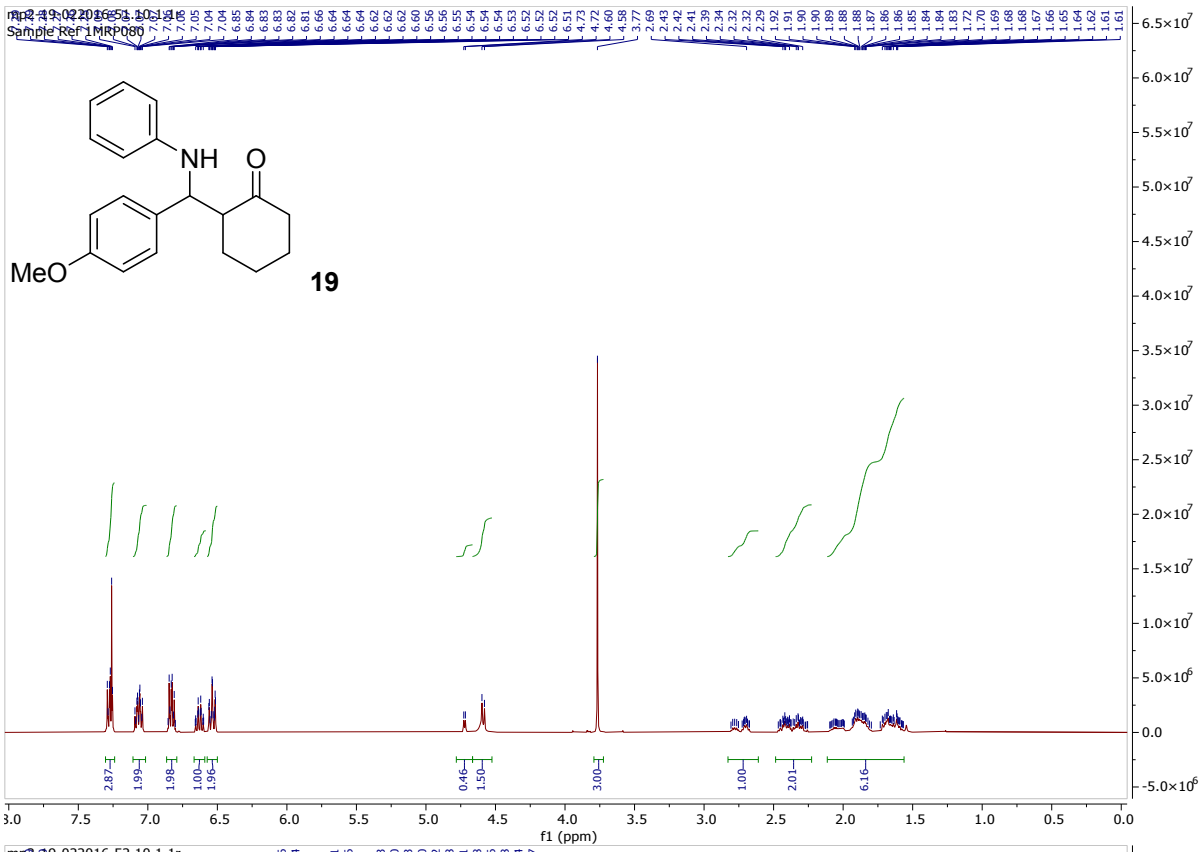
According to the general procedure compound **4** was obtained as a colourless solid (310 mg, 65%); m.p. 88-89 ºC; IR (thin film) ν_{max} 3368, 2934, 1706, 1602, 1511, 1493, 1280 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.94 (d, J = 6.3 Hz, 2H), 4.46 (br. s, 1H), 4.86 (t, J = 6.3 Hz, 1H), 6.55-6.58 (m, 2H), 6.67-6.71 (m, 1H), 7.09-7.13 (m, 2H), 7.23-7.27 (m, 1H), 7.32-7.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8, 51.3, 54.4, 113.8, 117.9, 126.3, 127.4, 128.8, 129.2, 142.5, 146.8, 207.2; HRMS (ESI) *m/z* calc for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1383, found: 240.1383.

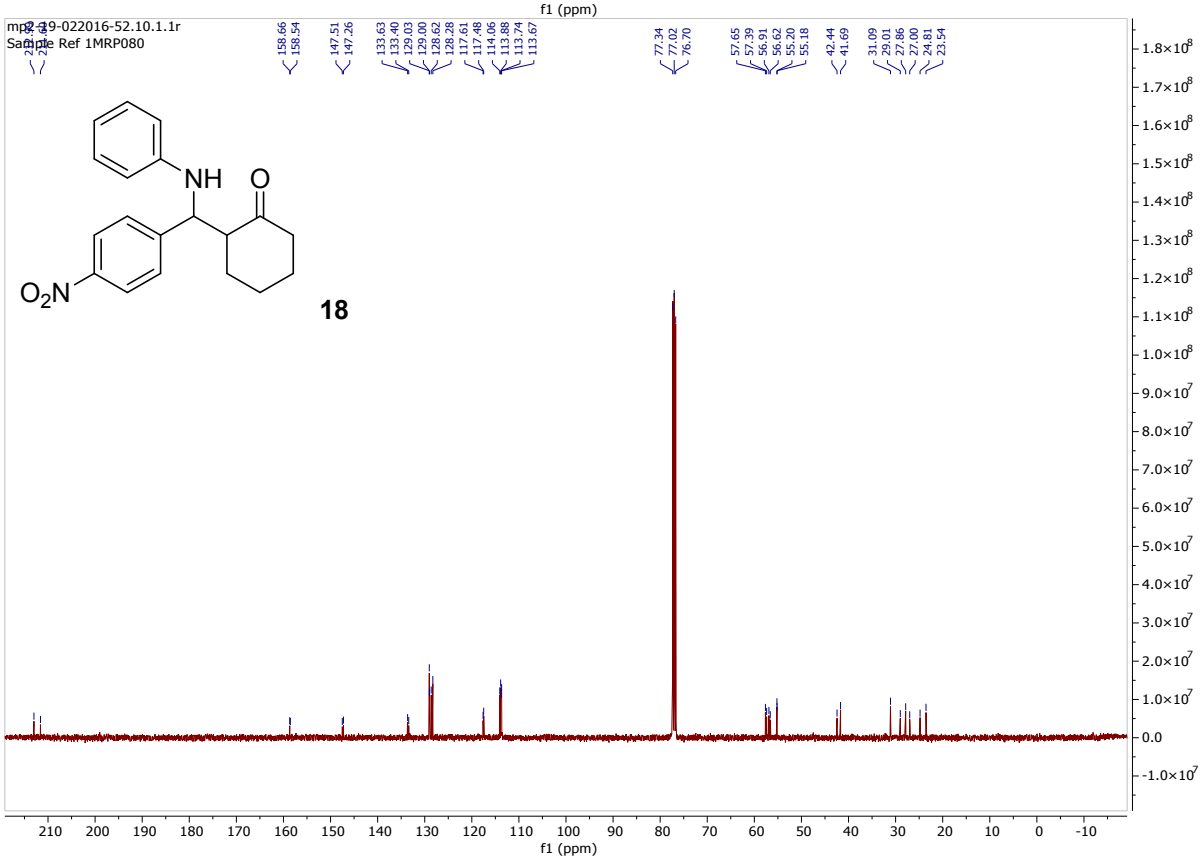

Sample Ref 1MRP069
NH
O
6
f1 (ppm)

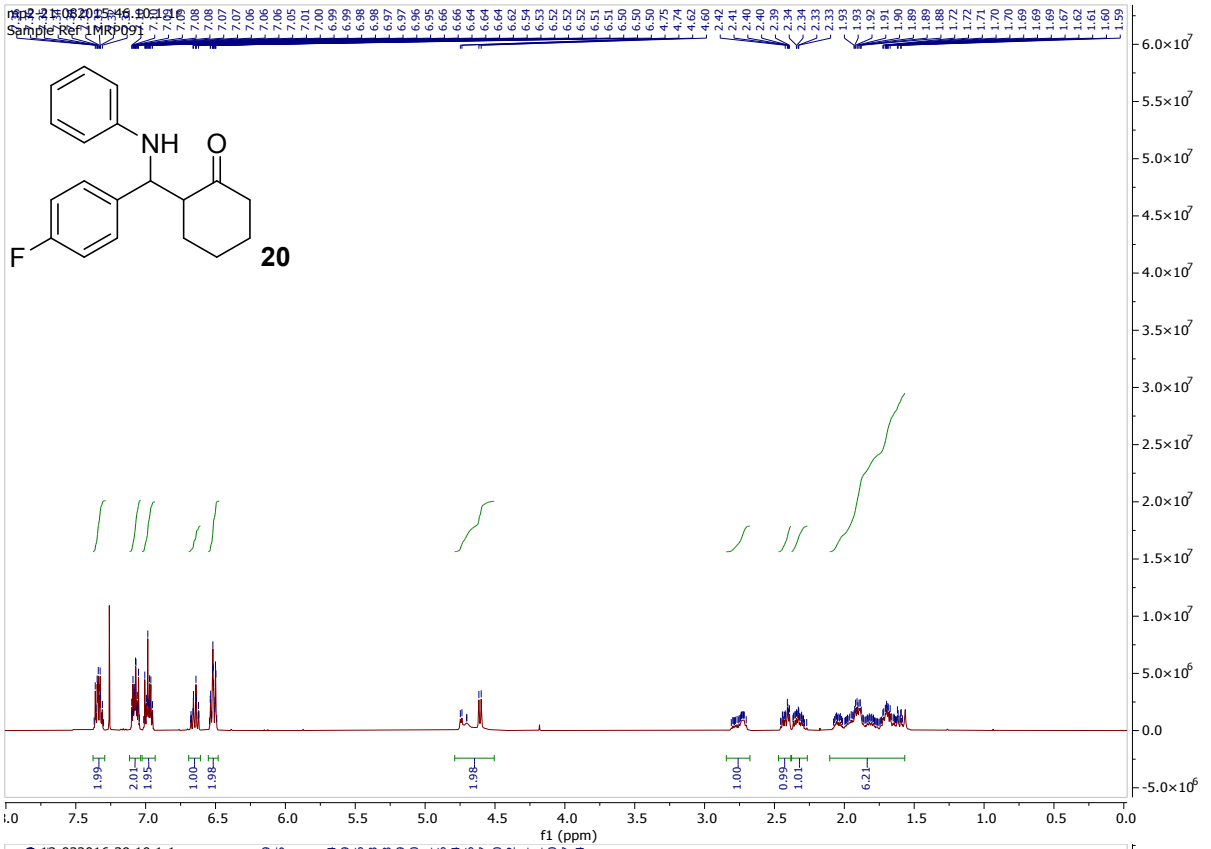

Sample Ref 1MRP069
NH
O
6
f1 (ppm)

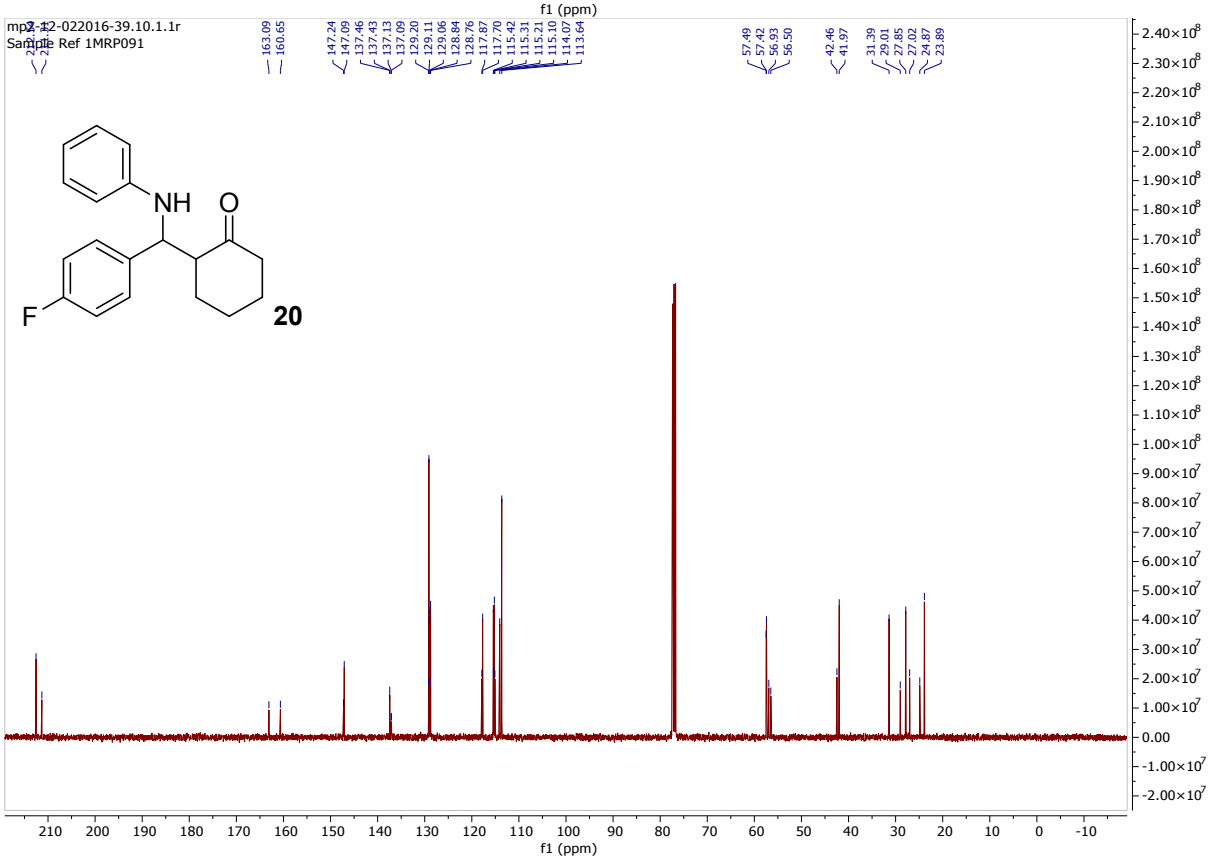

mp2-11-022016-24.10.1.1r
Sample Ref 1MRP073
NH
O
O_2N
18
f1 (ppm)

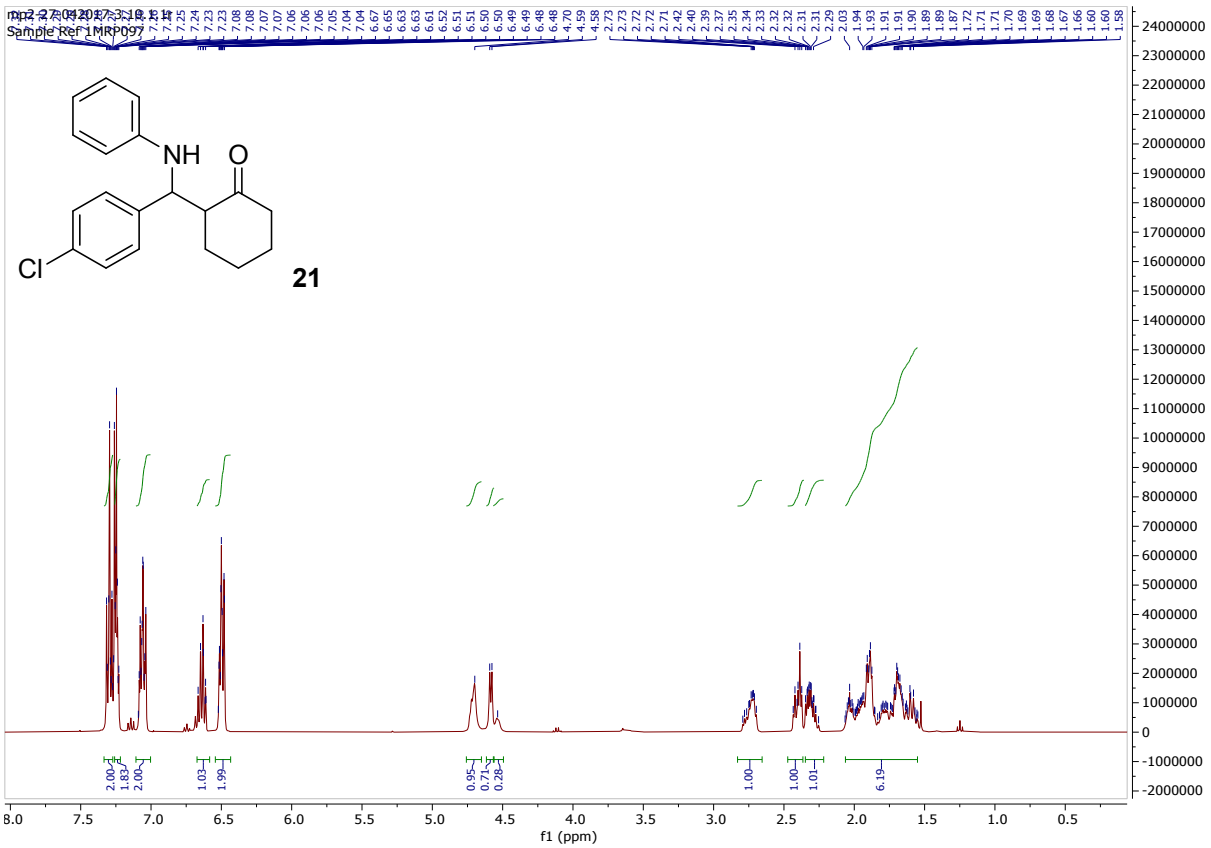

mp2-11-022016-43.10.1.1r
Sample Ref 1MRP073
NH
O
O_2N
18
f1 (ppm)

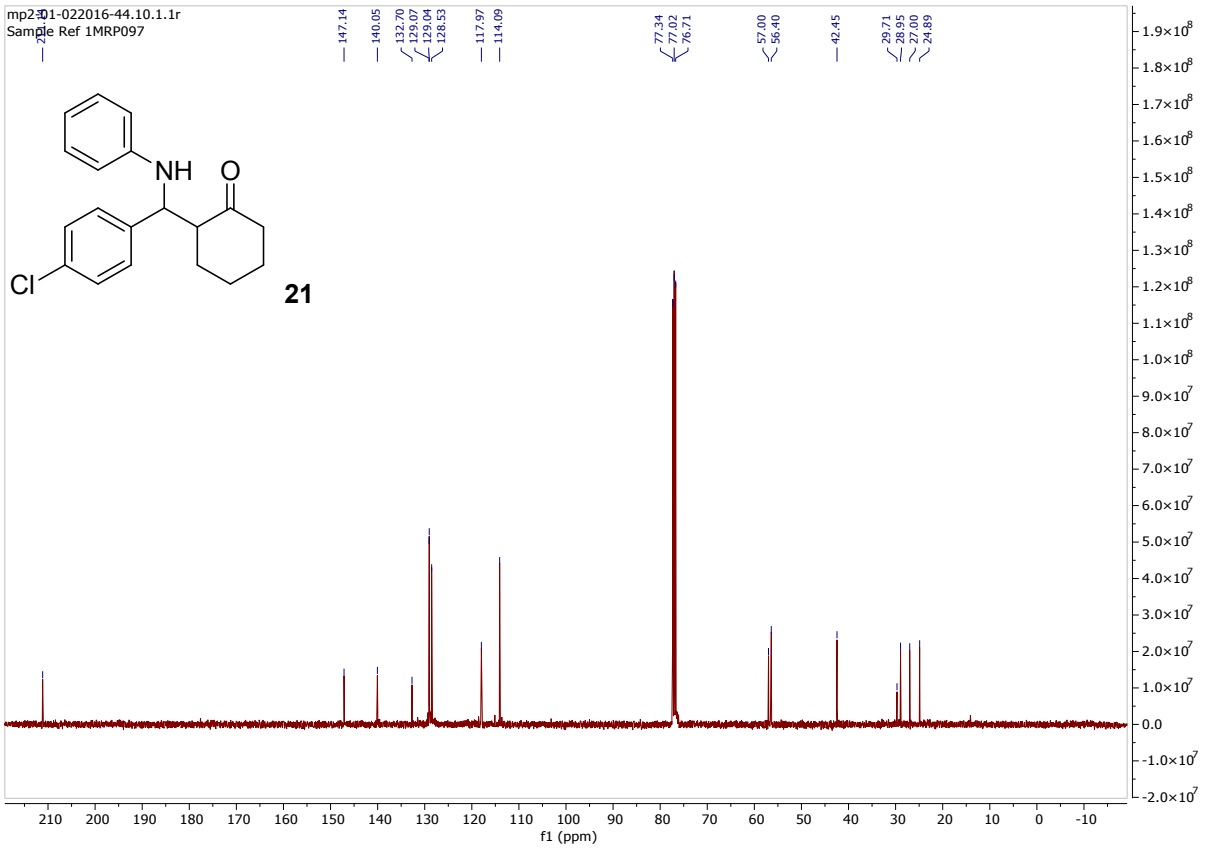

mp2-19-022016-51.10.1.1r
Sample Ref 1MRP080
NH
O
MeO
19
f1 (ppm)

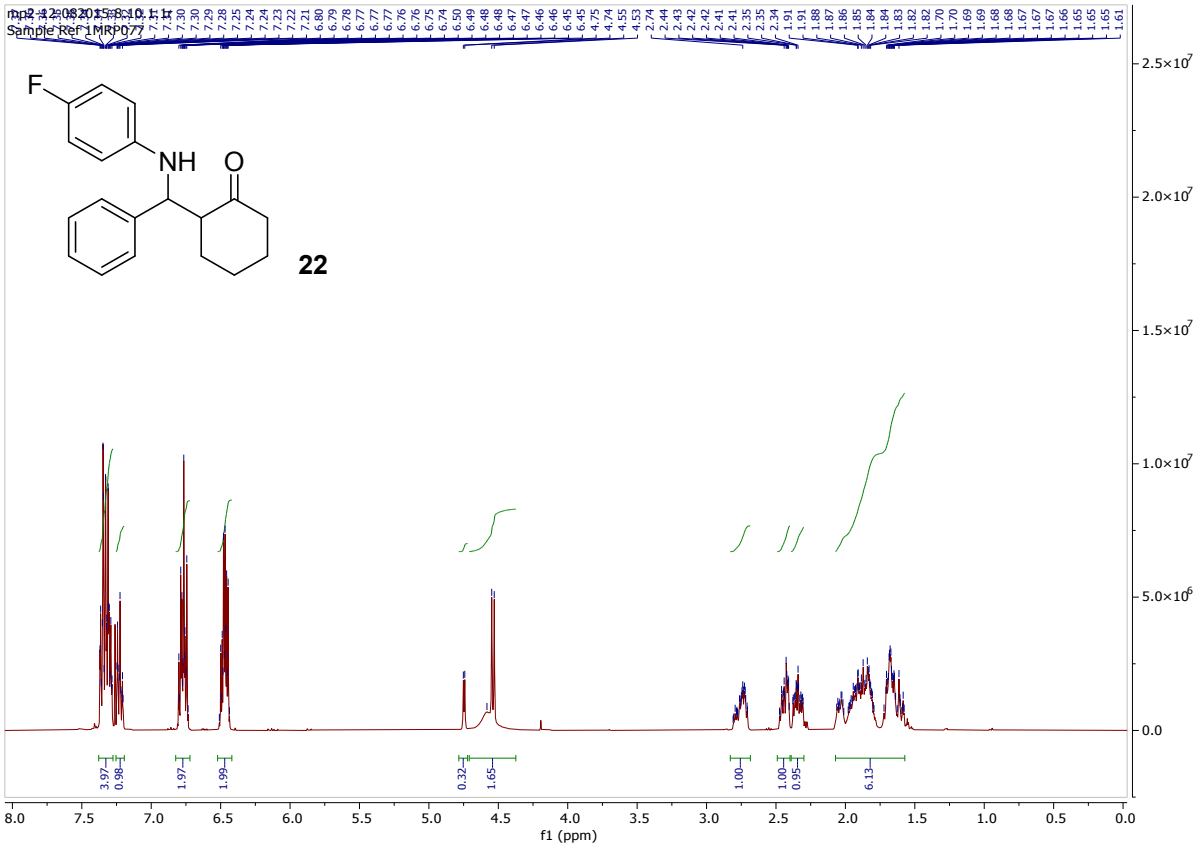

mp2-19-022016-52.10.1.1r
Sample Ref 1MRP080
NH
O
O_2N
18
f1 (ppm)

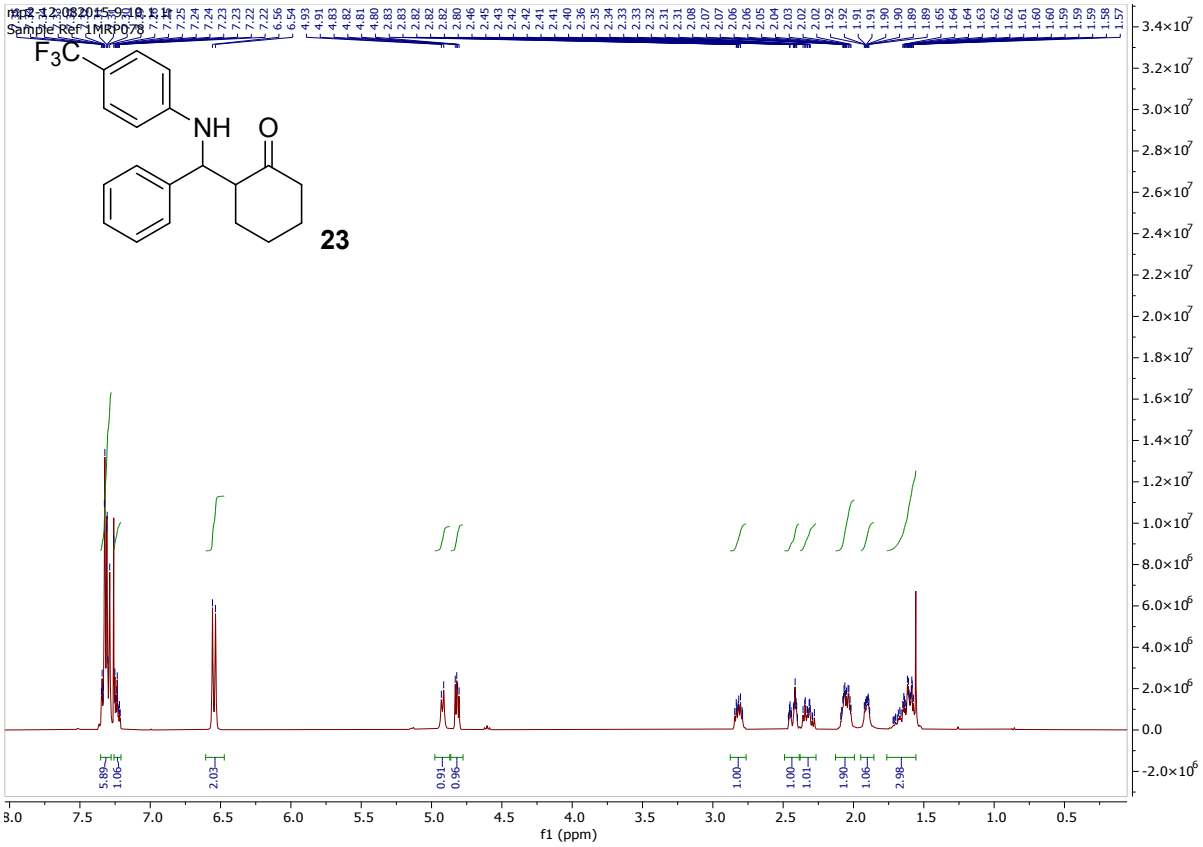

Sample Ref 1MRP091
NH
O
F
20
f1 (ppm)

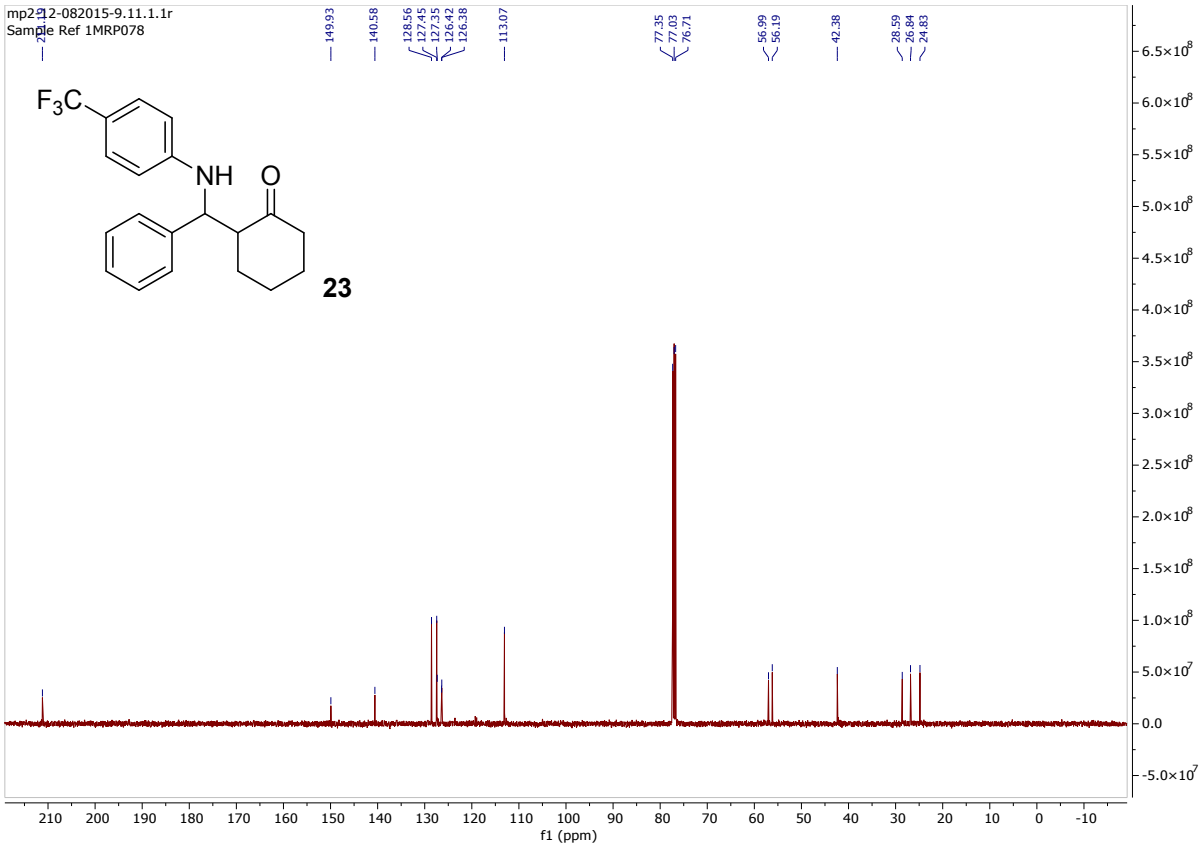

Sample Ref 1MRP091
NH
O
F
20
f1 (ppm)

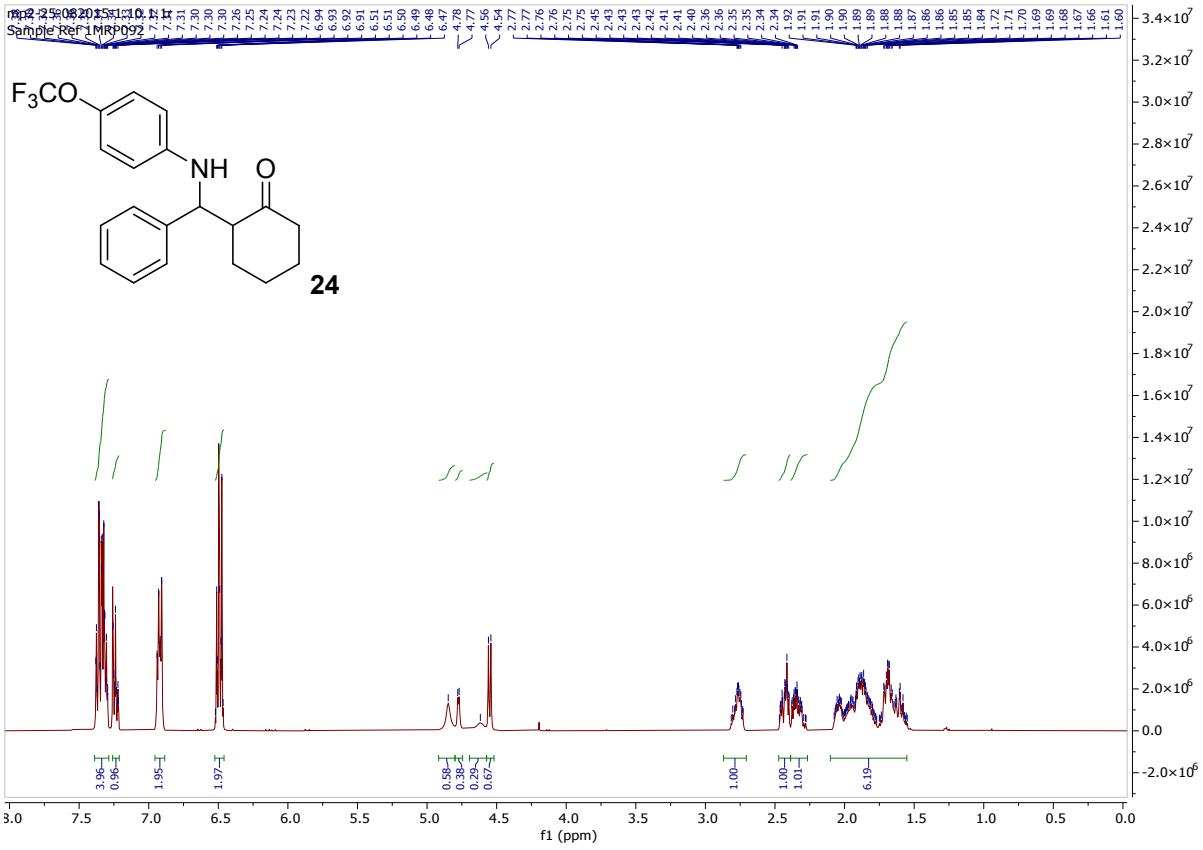

Sample Ref 1MRP097
NH
O
Cl
21
f1 (ppm)

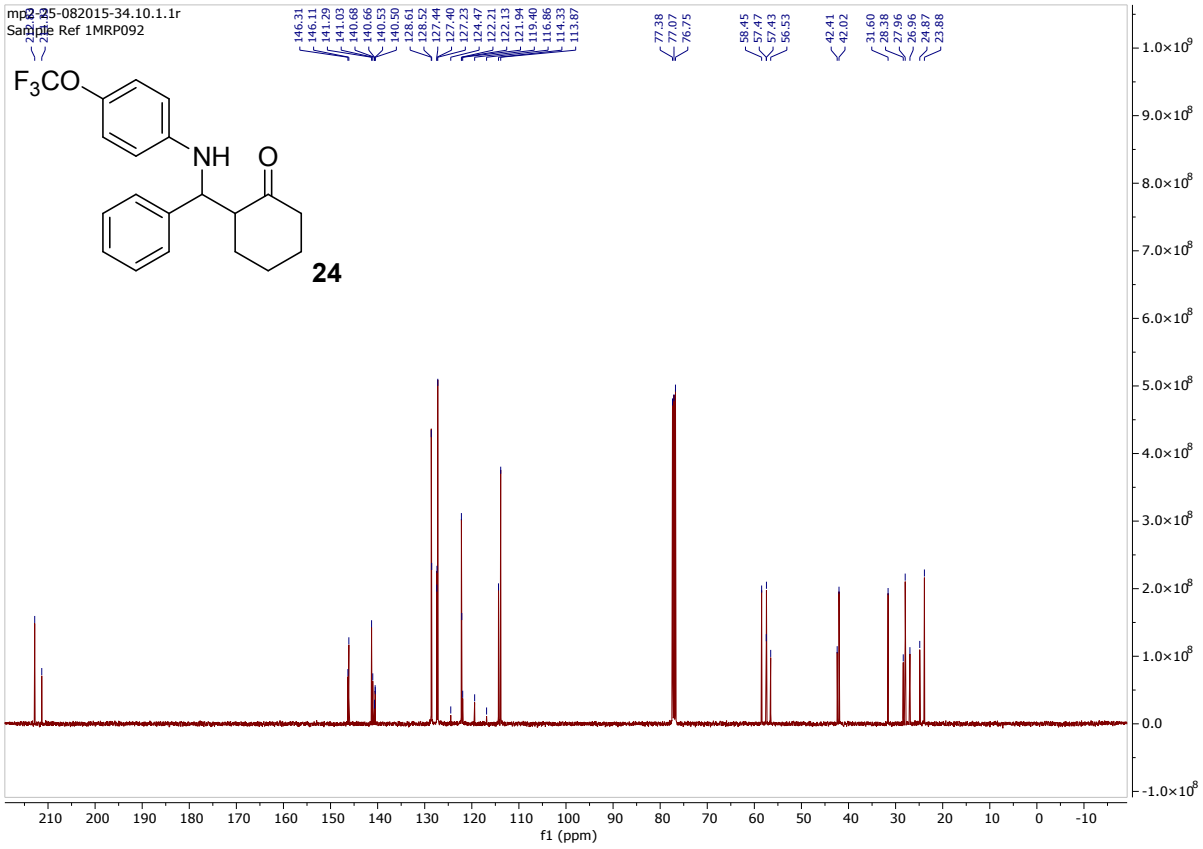

Sample Ref 1MRP097
147.14
140.05
132.70
129.07
129.04
128.53
117.97
114.09
77.34
77.02
76.71
57.00
56.40
42.45
29.71
28.95
27.00
24.89
NH
O
Cl
21
f1 (ppm)

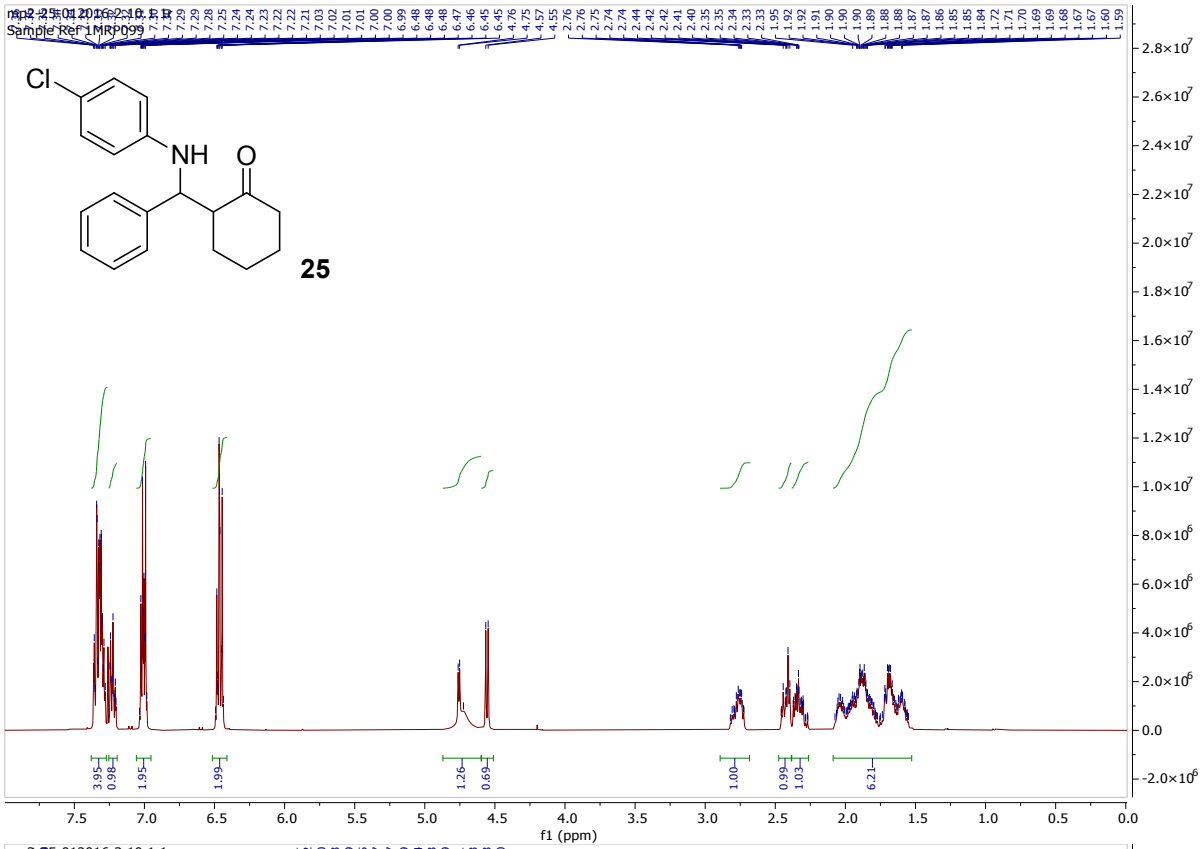

Sample Ref 1MRP077
F
NH
O
22
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
3.97
0.98
1.97
1.99
0.32
1.65
1.00
1.00
0.95
6.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

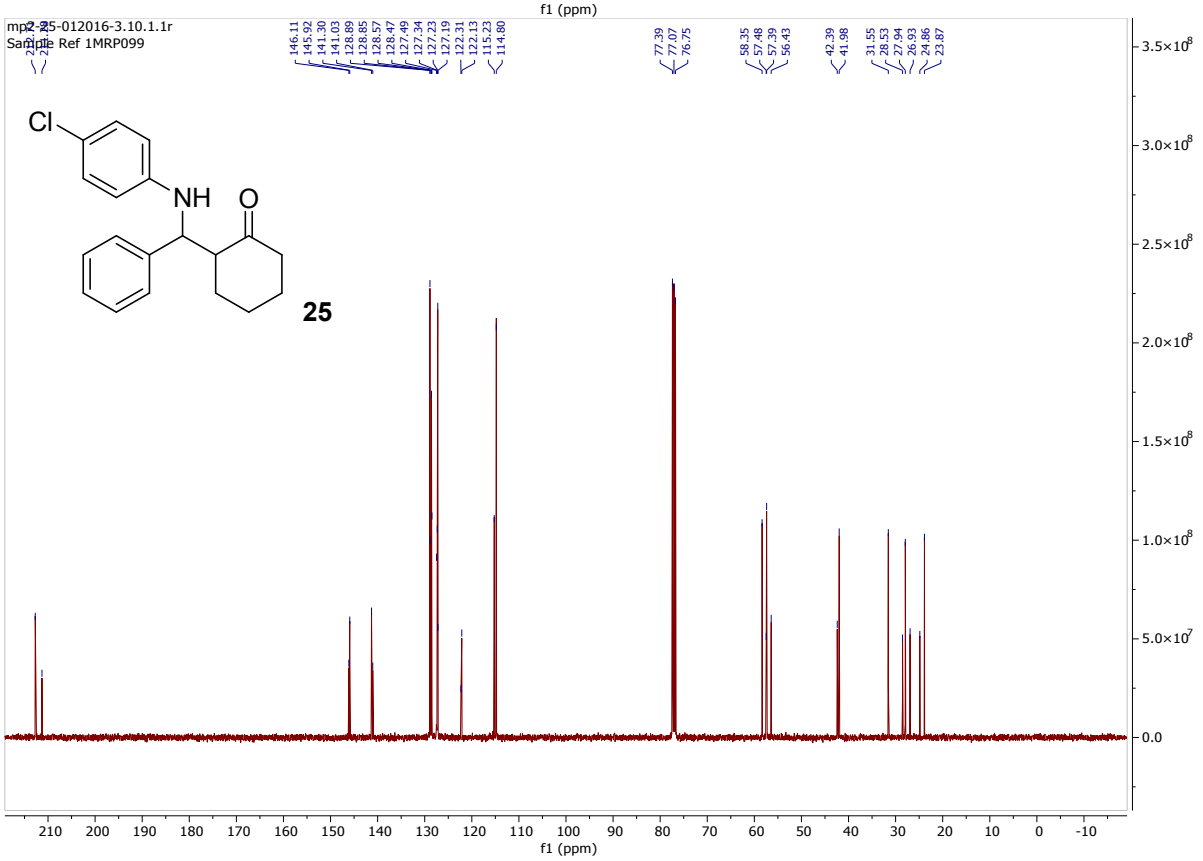

Sample Ref 1MRP078
F3C
NH
O
23
f1 (ppm)

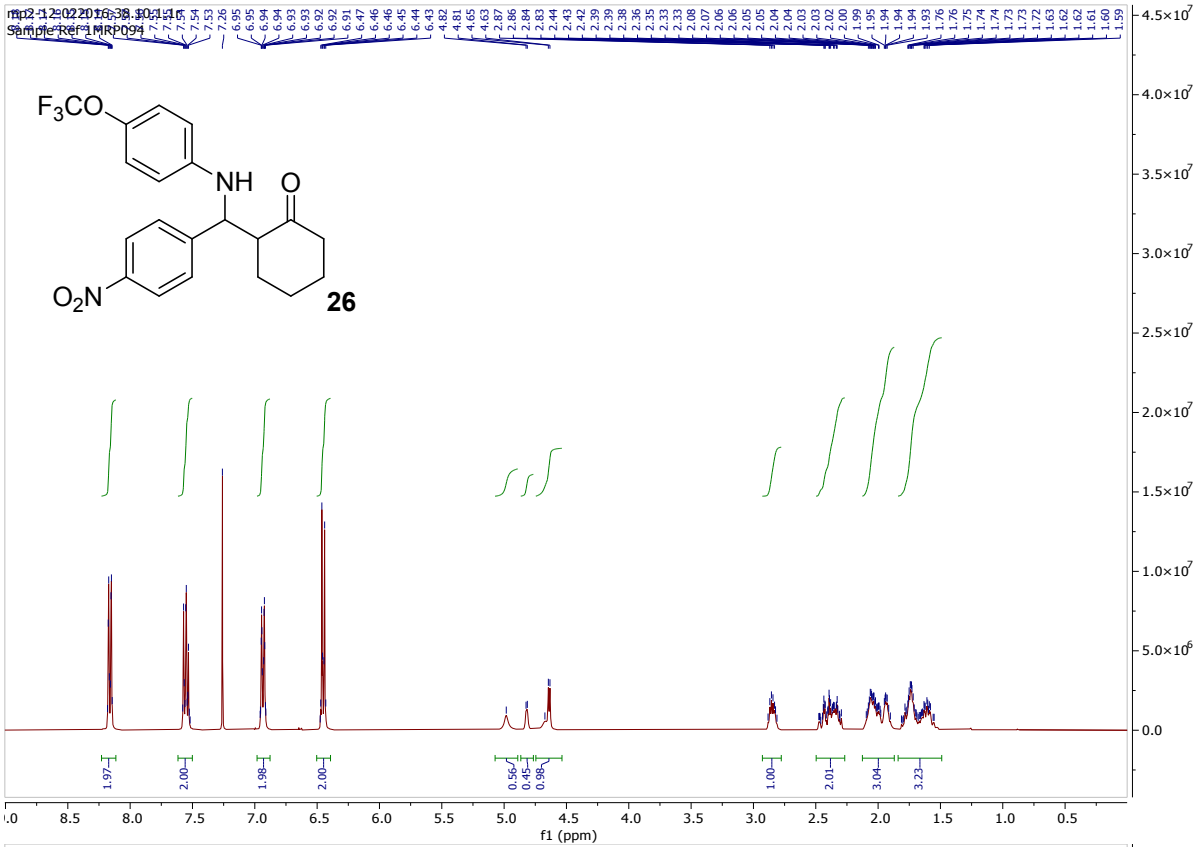

Sample Ref 1MRP078
F3C
NH
O
23
f1 (ppm)

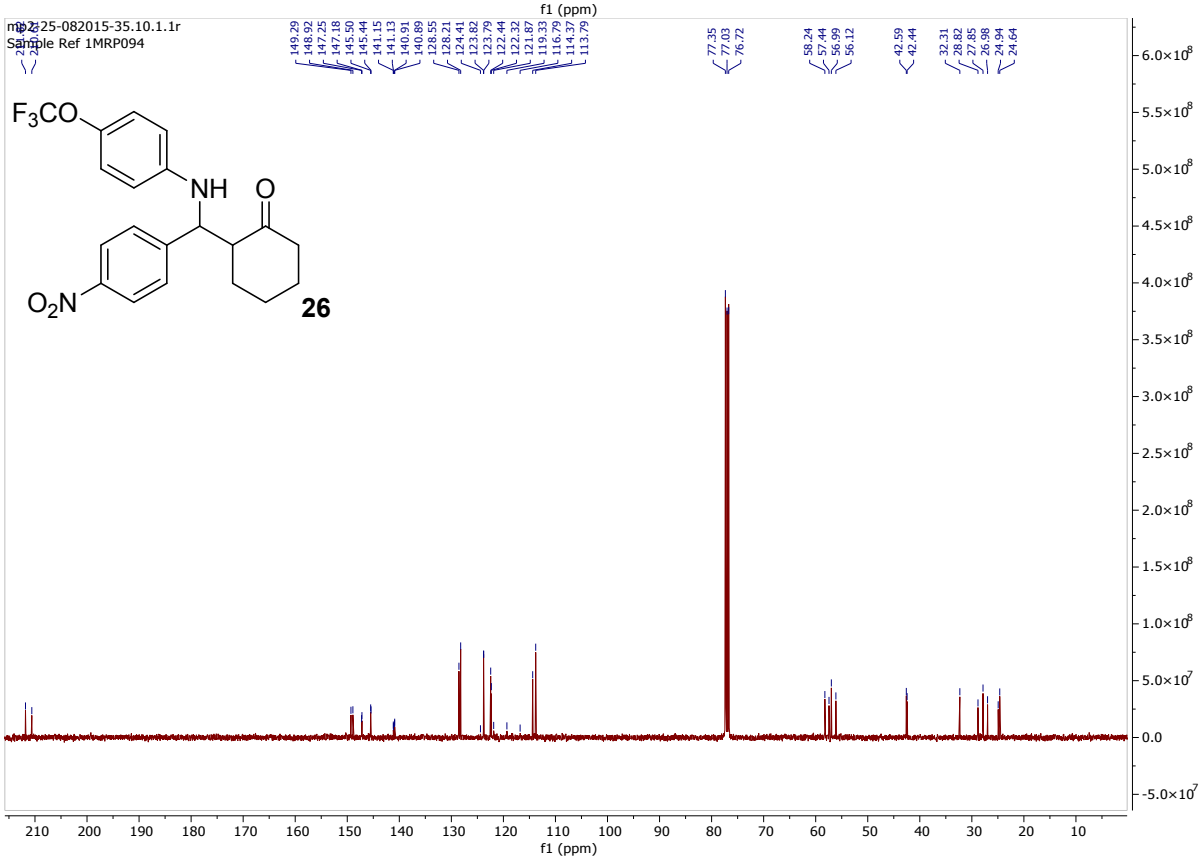

mp2-25-082015-1.10.1.1r
Sample Ref 1MRP092
F3CO
NH
O
24
f1 (ppm)

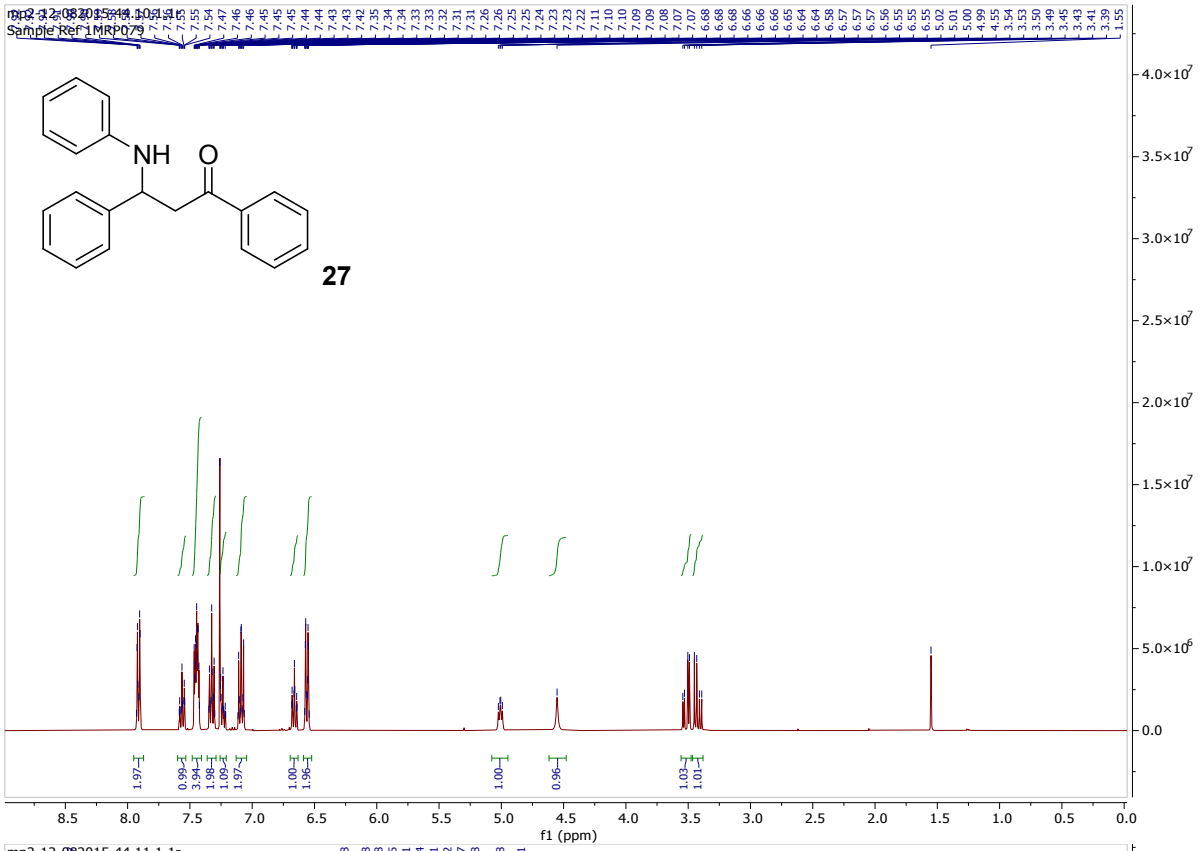

mp2-25-082015-34.10.1.1r
Sample Ref 1MRP092
F3CO
NH
O
24
f1 (ppm)

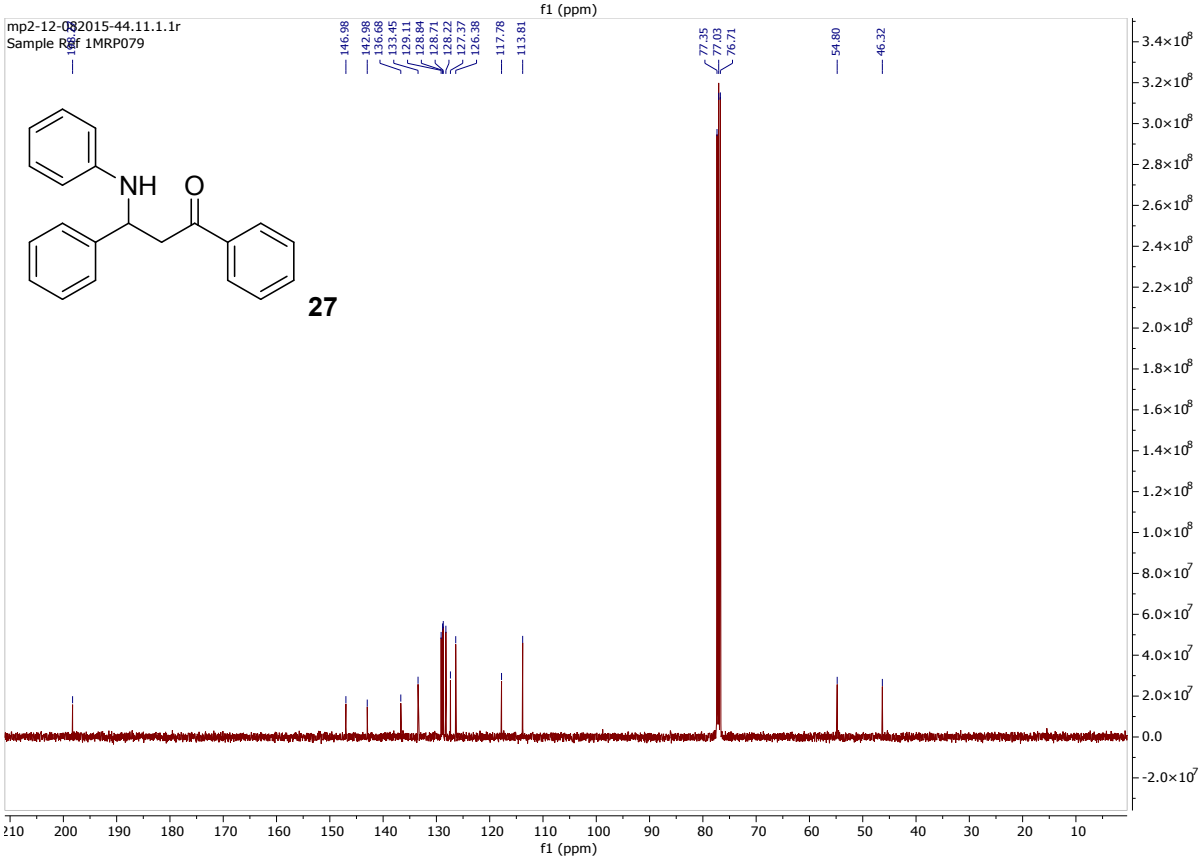

Sample Ref 1MRP099
Cl
NH
O
25
f1 (ppm)

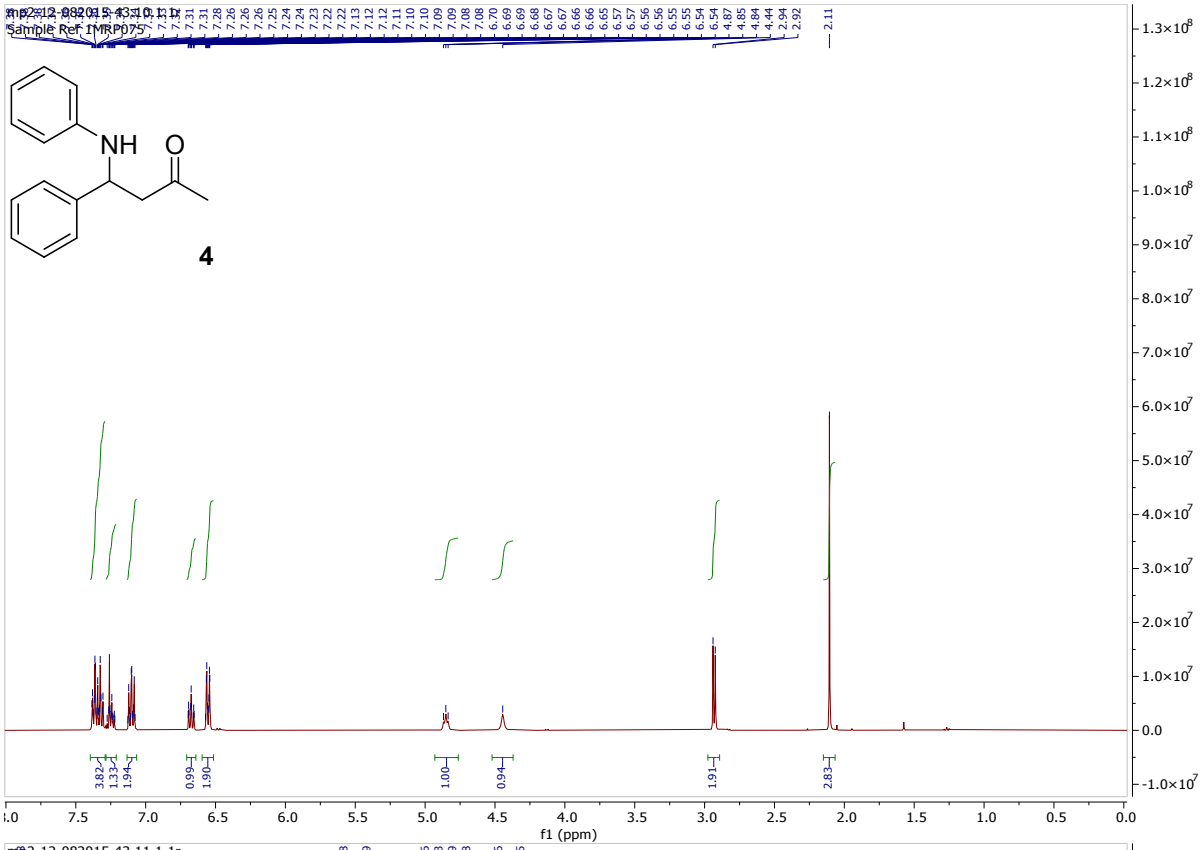

Sample Ref 1MRP099
Cl
NH
O
25
f1 (ppm)

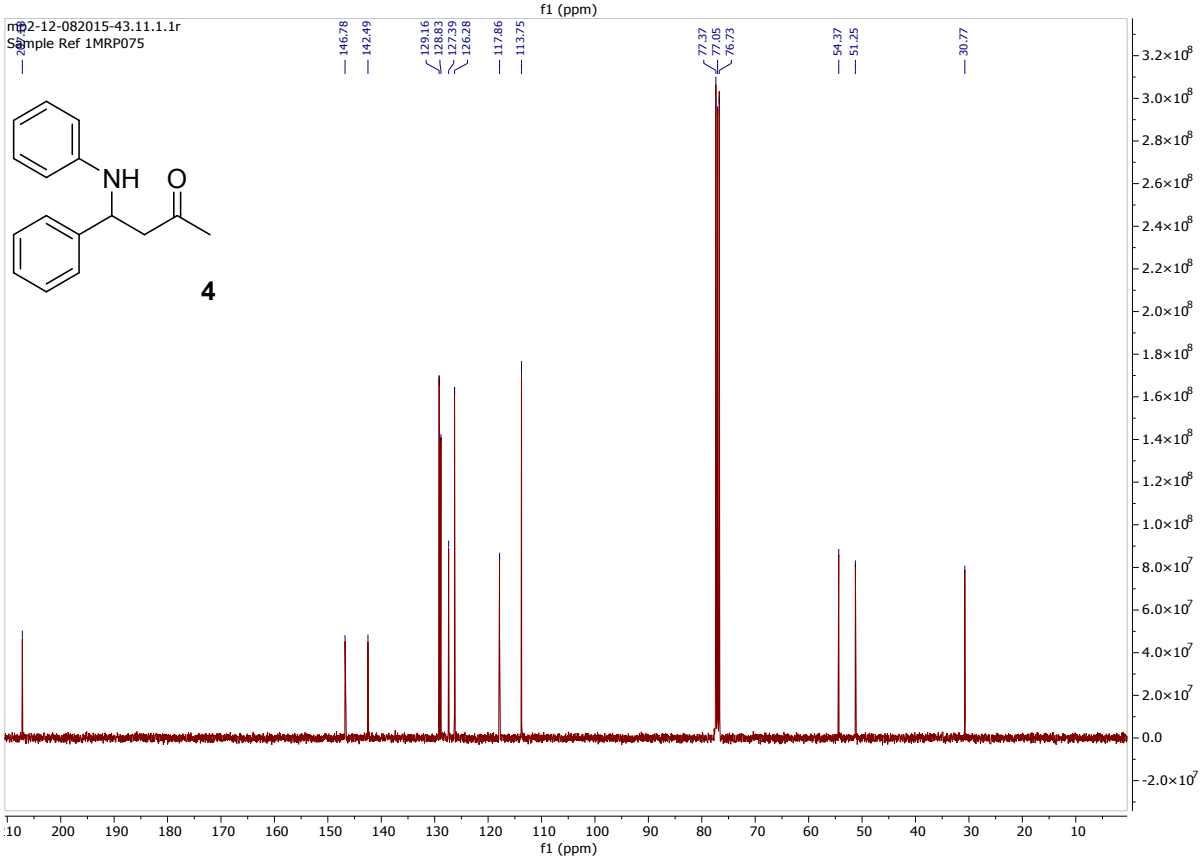

F3CO
NH
O
O2N
26
f1 (ppm)


F3CO
NH
O
O2N
26
f1 (ppm)


Sample Ref 1MRP079
NH
O
27
f1 (ppm)


mp2-12-082015-44.11.1.1r
Sample Ref 1MRP079
NH
O
27
f1 (ppm)


mp2-12-082015-43.10.1.1r
Sample Ref 1MRP075
NH
O
4
f1 (ppm)


mp2-12-082015-43.11.1.1r
Sample Ref 1MRP075
146.78
142.49
129.16
128.83
127.39
126.28
117.86
113.75
77.37
77.05
76.73
54.37
51.25
30.77
NH
O
4
f1 (ppm)

S4. References

[1] J. S. Manzano, Z. B. Weinstien, A. S. Sadow, I. I. Slowing, *ACS Catal*. **2017**, *7*, 7567-7577.
[2] M. Bandini, P. G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva, A. Umani-Ronchi, *J. Org. Chem.* **2002**, *67*, 3700-3704
[3] A. Pettignano, L. Bernardi, M. Fochi, L. Geraci, M. Robitzer, N. Tanchoux, F. Quignard, *New. J. Chem.* **2015**, *39*, 4222-4226
[4] N. Tanaka, Y. Masaki, *Synlett* **2000**, 406-408
[5] B. C. Ranu, S. Samanta, S. K. Guchhait, *Tetrahedron*, **2002**, *58*, 983-988
[6] S. Sukumari, I. A. Azath, K. Pitchumani, *Synlett* **2012**, *23*, 2328-2332
[7] A. Yanagisawa, Y. Lin, R. Miyake, K. Yoshida, *Org. Lett.* **2014**, *16*, 86-89
[8] X-D. Jia, X-E. Wang, C-X. Yang, C-D. Huo, W-J. Wang, Y. Ren, X-C. Wang, *Org. Lett.* **2010**, *12*, 732-735

Author Contributions

Dr Matthew R. Penny – Device design and chemical reactions, Dr Stephen T. Hilton - funding acquisition, project administration, writing of original draft with equal contribution.