Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.
This journal is © The Royal Society of Chemistry 2015

# Supporting Information

# Continuous Photochemistry: The Flow Synthesis of Ibuprofen via a Photo-Favorskii Rearrangement

Marcus Baumann, and Ian R. Baxendale*

Department of Chemistry, University of Durham, South Road, Durham, DH1 3LE, UK.

## Table of contents:

## 1. Materials and methods:

Unless otherwise stated, all solvents were purchased from Fisher Scientific and used without further purification. Substrates and reagents were purchased from Alfa Aesar or Sigma Aldrich and used as received.

$^{1}$H-NMR spectra were recorded on a Bruker Avance-400 instrument and are reported relative to residual solvent: $CHCl_3$ (δ 7.26 ppm). $^{13}$C-NMR spectra were recorded on the same instrument and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for $^{1}$H-NMR are reported as follows: chemical shift (δ/ ppm) (integration, multiplicity, coupling constant (Hz)). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br. s = broad singlet, app = apparent. Data for $^{13}$C-NMR are reported in terms of chemical shift (δ/ ppm) and multiplicity (C, CH, $CH_2$ or $CH_3$). IR spectra were obtained by use of a Perkin Elmer RX1 spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21-70% of tallest signal) or strong (s, >71% of tallest signal). Low and high resolution mass spectrometry was performed using the indicated techniques on either Waters LCT Premier XE or Waters TQD instruments equipped with Acquity UPLC and a lock-mass electrospray ion source. For accurate mass measurements the deviation from the calculated formula is reported in ppm. Melting points were recorded on an Optimelt automated melting point system with a heating rate of 1 °C/min and are uncorrected.

## 2. Preparation of 2-chloro-4'-isobutylpropiophenone 5:

A stirred solution of isobutylbenzene (6.7 g, 50 mmol, 1. 0 equiv) in dichloroethane (35 mL, 1.43 M) was cooled to 0 °C with an ice bath. Powdered $AlCl_3$ (13.2 g, 100 mmol, 2.0 equiv) was added portionwise to this solution resulting in a yellow solution within 10 minutes. Using a dropping funnel a solution of chloropropionyl chloride (7.6 g, 60 mmol, 1.2 equiv) in dichloroethane (10 mL, 6 M) was added over a period of 25 minutes. After a further hour the reaction mixture was allowed to warm to room temperature and kept stirring for a total of 6 h, after which $^1$H-NMR analysis indicated full conversion of the starting material. The crude reaction mixture was quenched by pouring onto crushed ice (~250 g) and subsequently extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered over a pad of silica (~20 g) resulting in a light brown liquid after evaporation of the volatiles.

Isolated yield: 10.6 g (47.3 mmol, 95%)

Purity by $^1$H-NMR: >95%

**Spectroscopic data:**

**$^1$H-NMR (400 MHz, $CDCl_3$):** δ/ppm 7.96 (2H, d, *J* = 8.3 Hz), 7.28 (2H, d, *J* = 8.3 Hz), 5.27 (1H, q, *J* = 6.7 Hz), 2.56 (2H, d, *J* = 7.2 Hz), 1.87-1.98 (1H, m), 1.76 (3H, d, *J* = 6.7 Hz), 0.93 (6H, d, *J* = 6.6 Hz).

**$^{13}$C-NMR (101 MHz, $CDCl_3$):** δ/ppm 193.3 (C), 148.5 (C), 131.8 (C), 129.5 (2CH), 129.0 (2CH), 52.8 (CH), 45.4 ($CH_2$), 30.1 (CH), 22.4 ($CH_3$), 22.3 ($CH_3$), 20.1 ($CH_3$).

**IR (neat):** ν/$cm^{-1}$ 2957 (m), 1687 (s), 1606 (s), 1252 (m), 954 (s), 857 (m), 739 (m), 632 (m).

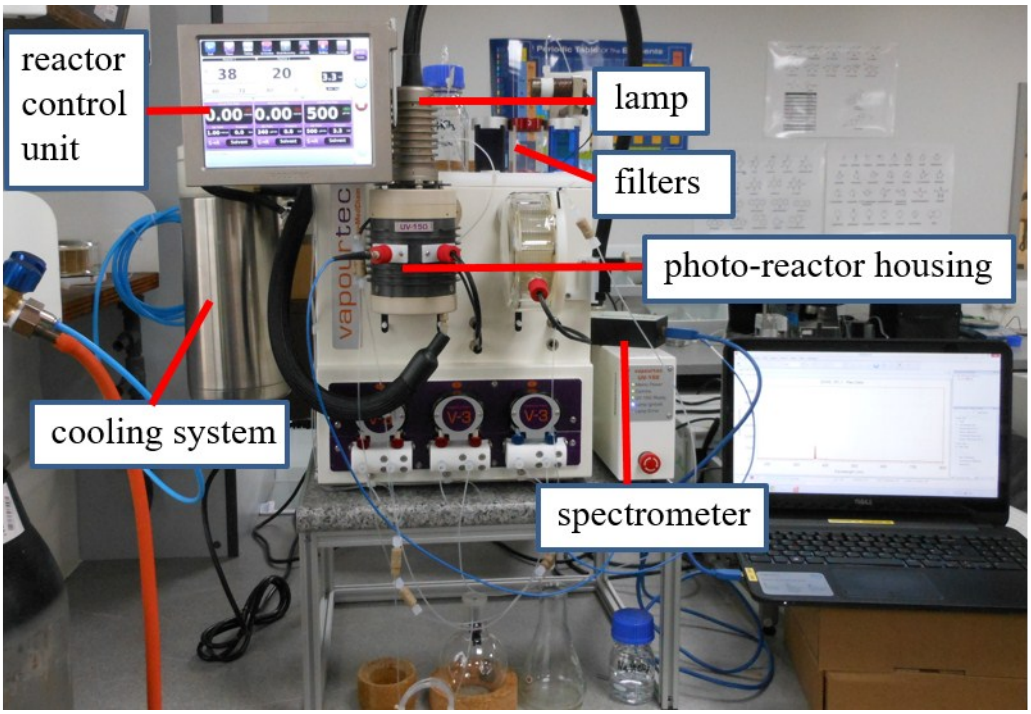
**LC-MS (ESI-TOF):** 246.9 (M+Na).

**HR-MS (ESI-TOF):** calculated for $C_{13}H_{18}ClO$ 225.1046, found 225.1039 (Δ -3.1 ppm).

$^1$H-NMR and IR data are consistent with reported values: Giordano, C.; Castaldi, G.; Casagrande, F.; Belli, A. Esters of α-Arylalkanoic Acids from 'Masked' α-Halogenalkyl Aryl Ketones and Silver Salts: Synthetic, Kinetic, and Mechanistic Aspects. *J. Soc. Chem. Perkin Trans. 1* **1982**, *11*, 2575-2581.

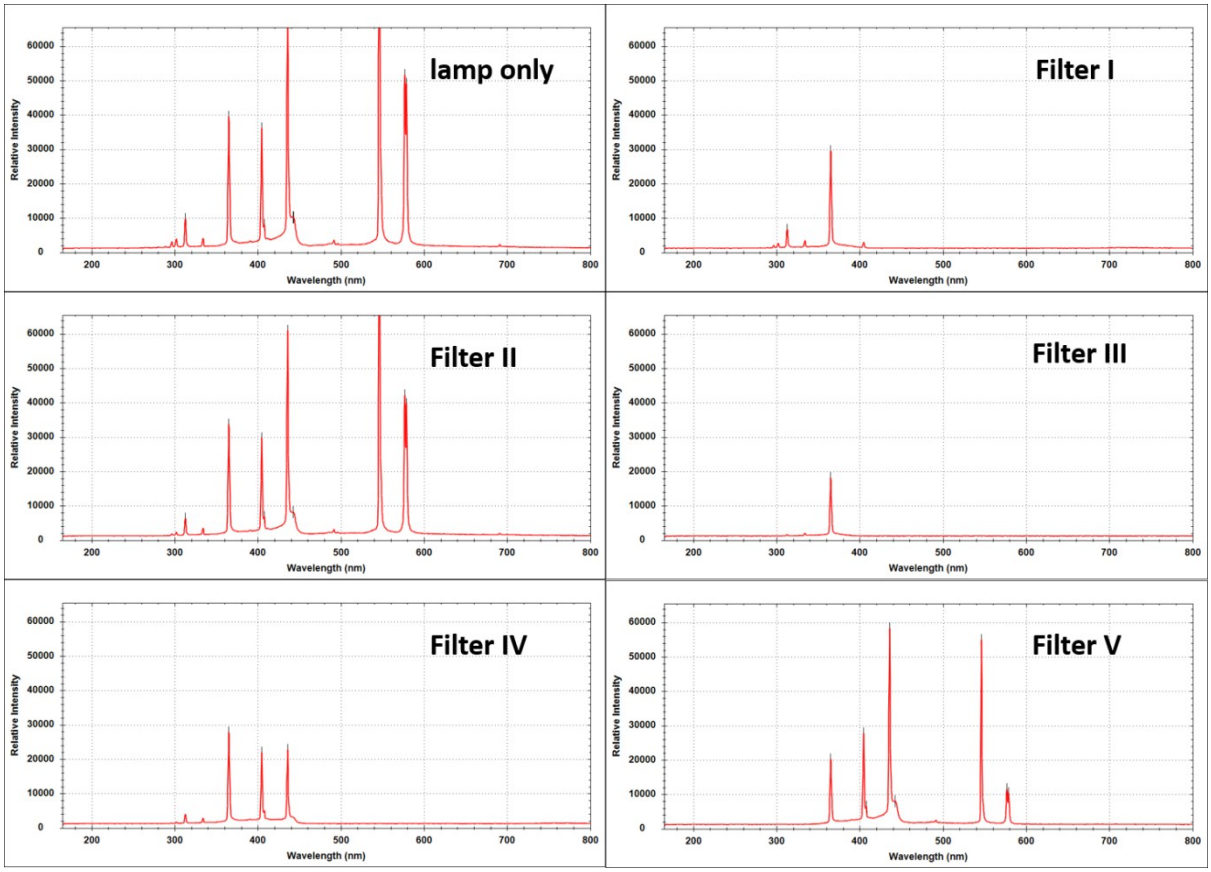
## 3. Photo-reactor set-up:

For performing all of the reactions a commercially available Vapourtec E-series system comprising of three peristaltic pumps and a UV-150 photo-reactor was used. Temperature control of the photo-reactor was achieved via an attached Dewar filled with solid $CO_2$ and attached to a $N_2$-cylinder (see image below). The photochemical reactions were monitored via a portable ExemplarLS spectrometer providing information through continuous recording of emission/transmission spectra. Different filters (see next page for details) were used and placed in between the high intensity medium pressure lamp and the reactor coil (10 mL volume).



## 4. Emission spectra of different filters used

Emission spectra recorded for various filters using water as solvent at 50% lamp power setting (80 W) using a portable ExemplarLS spectrometer:



## 5. Flow procedure for preparing ibuprofen

For a reaction on 1 mmol scale a stock solution was prepared containing chloropropiophenone **5** (224 mg, 1 mmol), propylene oxide (0.2 mL) in a mixture of acetone (9 mL) and water (1 mL). The photo-flow reactor was configured placing the appropriate filter into the reactor housing. The stock solution was then pumped through the reactor (10 mL) with a chosen flow rate, temperature and lamp power setting. After collecting the crude product solution, the solvents were evaporated allowing to record $^{1}$H-NMR spectra of the crude mixture. In order to isolate pure ibuprofen, this crude mixture was dissolved in DCM (~10 mL) and extracted with aqueous NaOH solution (2 M). The aqueous layer was separated from the organic and subsequently acidified by adding 5 M HCl until the pH reached 3. After extraction with DCM (3x10 mL) the combined organic layers were collected and dried over anhydrous sodium sulfate, filtered and subjected to solvent evaporation generating ibuprofen initially as a light yellow oil. Trituration of this oil from hexanes at 0 °C led to the isolation of ibuprofen as white amorphous powder.

**Spectroscopic data:**

**$^{1}$H-NMR (400 MHz, $CDCl_3$):** δ/ppm 7.27 (2H, d, *J* = 8.1 Hz), 7.15 (2H, d, *J* = 8.1 Hz), 3.75 (1H, q, *J* = 7.1 Hz), 2.50 (2H, d, *J* = 7.2 Hz), 1.89 (1H, sept, *J* = 6.8 Hz), 1.55 (3H, d, *J* = 7.1 Hz), 0.95 (6H, d, *J* = 6.6 Hz).

**$^{13}$C-NMR (101 MHz, $CDCl_3$):** δ/ppm 181.2 (C), 140.9 (C), 137.0 (C), 129.4 (2CH), 127.3 (2CH), 45.1 ($CH_2$), 45.0 (CH), 30.2 (CH), 22.4 ($2CH_3$), 18.1 ($CH_3$).

**IR (neat):** ν/$cm^{-1}$ 2500-3200 (broad), 2955 (m), 2868 (m), 1710 (s, broad), 1507 (m), 1420 (m), 1231 (s), 1184 (m), 1074 (m), 936 (m), 866 (m), 780 (s), 668 (m), 522 (m).

**LC-MS (ESI-TOF):** 207.1 (M+H).

**HR-MS (ESI-TOF):** calculated for $C_{13}H_{19}O_2$ 207.1385, found 207.1393 (Δ 3.9 ppm).

**Melting point (hexanes):** 73.1-75.1 °C (lit.: 73-75 °C).

**Elemental analysis:** calculated for $C_{13}H_{18}O_2$: C: 75.69%, H: 8.80%; found C: 75.45%, H: 8.77%.

Spectroscopic data is consistent with reported values: Metzger, A., Bernhardt, S., Manolikakes, G. and Knochel, P., $MgCl_2$-Accelerated Addition of Functionalized Organozinc Reagents to Aldehydes, Ketones, and Carbon Dioxide. *Angew. Chem. Int. Ed.* **2010**, *49*, 4665–4668.

## 6. Characterisation of compounds 8-11

**2-Phenylacetic acid, 8:**

Spectroscopic data:

**$^{1}$H-NMR (400 MHz, $CDCl_3$):** δ/ppm 7.25-7.40 (5H, m), 3.68 (2H, s). **$^{13}$C-NMR (101 MHz, $CDCl_3$):** δ/ppm 177.9 (C), 133.3 (C), 129.4 (2CH), 128.7 (2CH), 127.4 (CH), 41.1 ($CH_2$). **LC-MS (ESI-TOF):** 135.1 (M-H). **HR-MS (ESI-TOF):** calculated for $C_8H_7O_2$ 135.0446, found 135.0435.

**2-(*p*-Tolyl)propanoic acid, 9:**

Spectroscopic data:

**$^{1}$H-NMR (400 MHz, $CDCl_3$):** δ/ppm 7.24 (2H, d, *J* = 8.1 Hz), 7.16 (2H, d, *J* = 8.1 Hz), 3.73 (1H, q, *J* = 7.2 Hz), 2.35 (3H, s), 1.52 (3H, d, *J* = 7.2 Hz). **$^{13}$C-NMR (101 MHz, $CDCl_3$):** δ/ppm 181.1 (C), 137.1 (C), 136.8 (C), 129.4 (2CH), 127.5 (2CH), 45.0 (CH), 21.1 ($CH_3$), 18.1 ($CH_3$). **LC-MS (ESI-TOF):** 163.1 (M-H). **HR-MS (ESI-TOF):** calculated for $C_{10}H_{11}O_2$ 163.0747, found 163.0759.

Data is consistent with literature: *J. Label. Compd. Radiopharm.* **2006**, *49*, 903.

**Methyl 2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)acetate, 10:**

Spectroscopic data:

**$^{1}$H-NMR (400 MHz, $CDCl_3$):** δ/ppm 9.80 (1H, s, NH), 7.14 (1H, s), 7.05 (1H, d, *J* = 7.2 Hz), 7.00 (1H, d, *J* = 7.2 Hz), 3.70 (3H, s), 3.64 (2H, s). **$^{13}$C-NMR (101 MHz, $CDCl_3$):** δ/ppm 172.1 (C), 156.1 (C), 144.0 (C), 128.8 (C), 128.6 (C), 125.2 (CH), 111.1 (CH), 110.0 (CH), 53.3 ($CH_3$), 40.9 ($CH_2$). **LC-MS (ESI-TOF):** 208.0 (M+H). **HR-MS (ESI-TOF):** calculated for $C_{10}H_{10}NO_4$ 208.0610, found 208.0592.

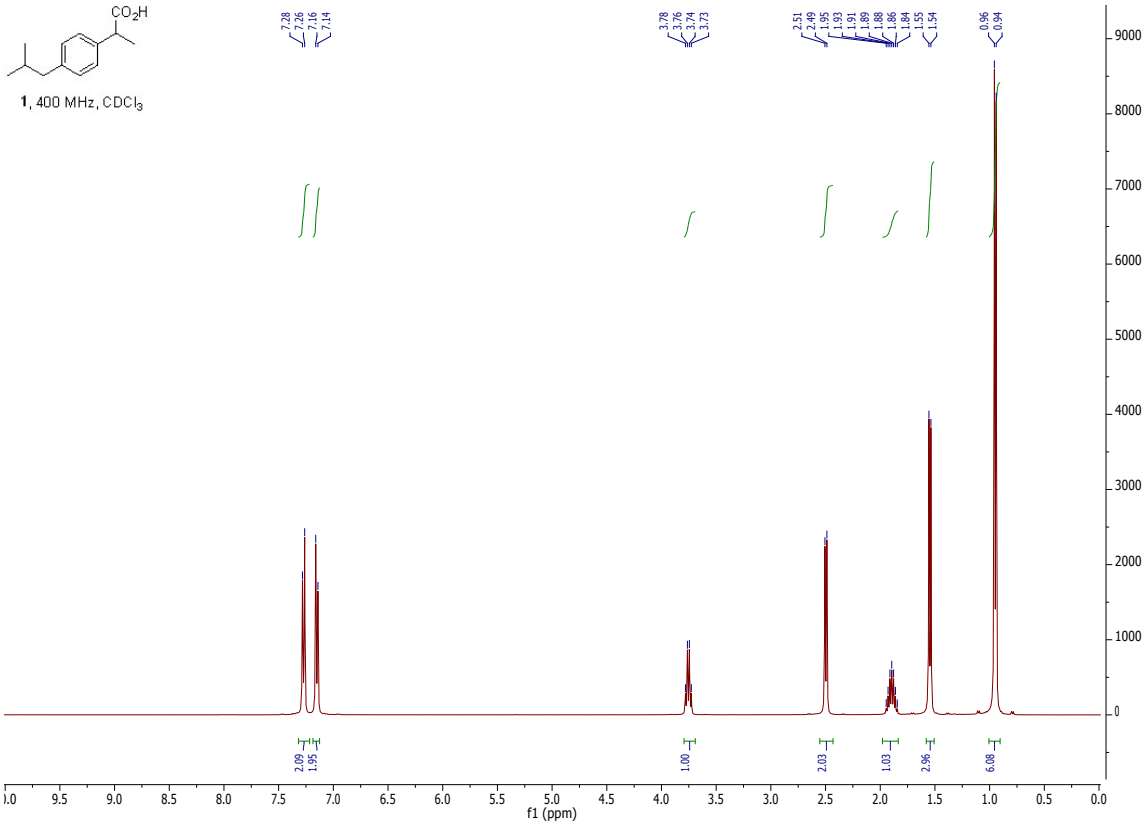
**Ethyl 2-(p-tolyl)propanoate, 11:**

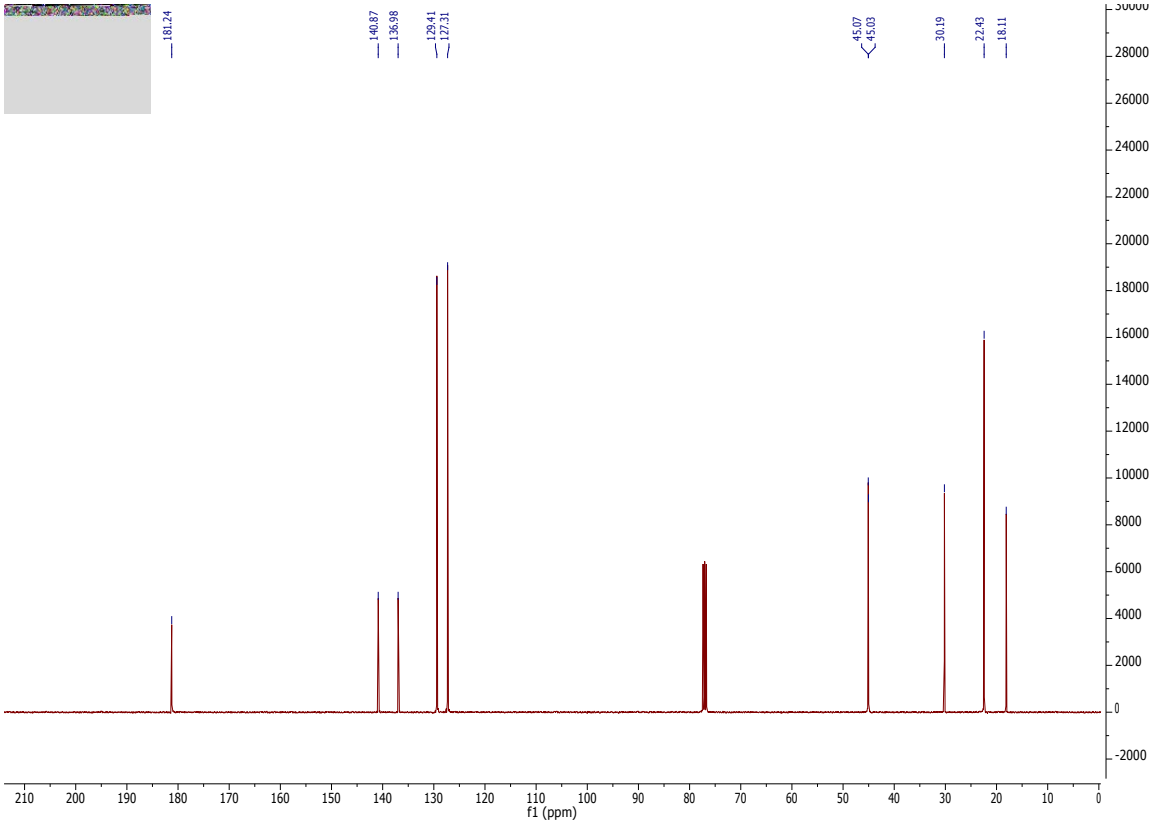
Spectroscopic data:

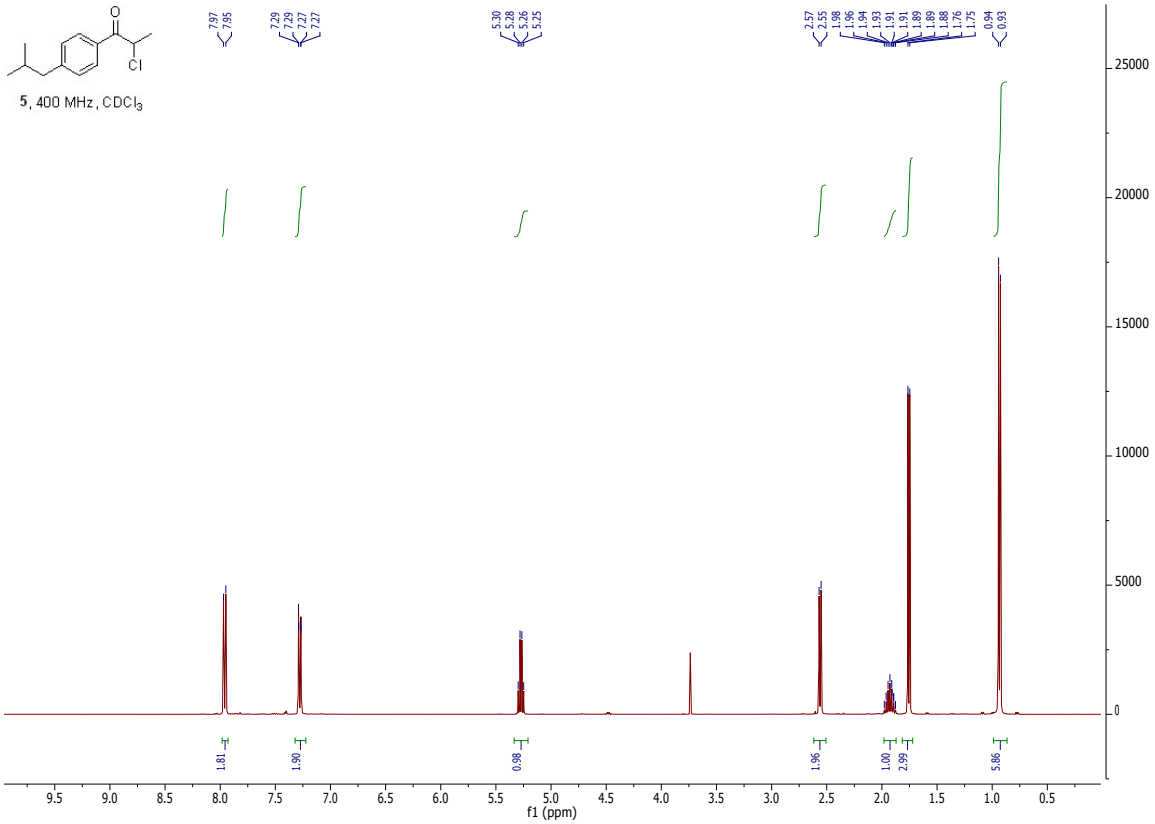
**$^{1}$H-NMR (400 MHz, $CDCl_3$):** δ/ppm 7.19 (2H, d, *J* = 7.2 Hz), 7.13 (2H, d, *J* = 7.2 Hz), 4.05-4.20 (2H, m), 3.67 (1H, q, *J* = 7.2 Hz), 2.33 (3H, s), 1.47 (3H, d, *J* = 7.2 Hz), 1.21 (3H, t, *J* = 7.2 Hz). **$^{13}$C-NMR (101 MHz, $CDCl_3$):** δ/ppm 174.7 (C), 137.7 (C), 136.7 (C), 129.3 (2CH), 127.3 (2CH), 60.7 ($CH_2$), 45.2 (CH), 21.1 ($CH_3$), 18.7 ($CH_3$), 14.1 ($CH_3$). **LC-MS (ESI-TOF):** 193.0 (M+H). **HR-MS (ESI-TOF):** calculated for $C_{12}H_{17}O_2$ 193.1229, found 193.1216.

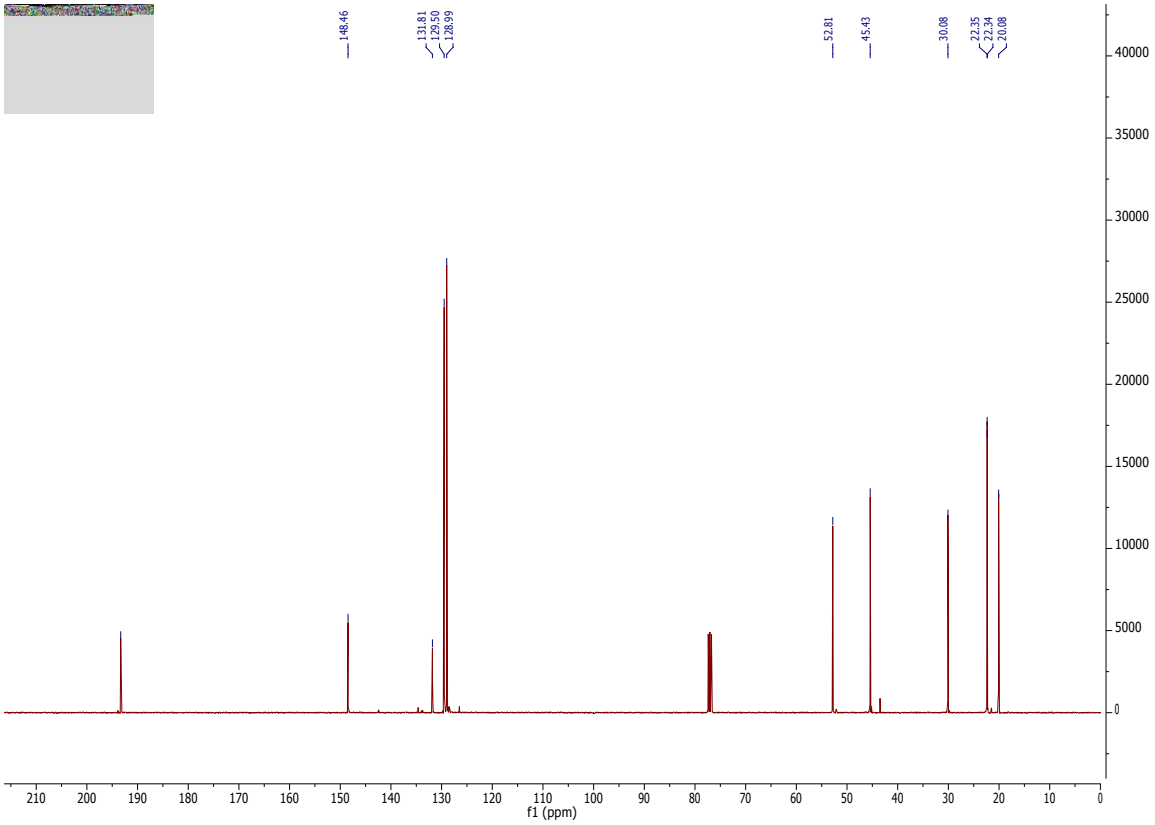
Data is consistent with literature: *J. Label. Compd. Radiopharm.* **2006**, *49*, 903.

## 7. Copies of NMR spectra for 1 and 5




181.24
140.87
136.98
129.41
127.31
45.07
45.03
30.19
22.43
18.11
f1 (ppm)


O
Cl
5, 400 MHz, CDCl3
7.97
7.95
7.29
7.29
7.27
7.27
5.30
5.28
5.26
5.25
2.57
2.55
1.98
1.96
1.94
1.93
1.91
1.91
1.89
1.88
1.76
1.75
0.94
0.93
1.81
1.90
0.98
1.96
1.00
2.99
5.86
f1 (ppm)


148.46
131.81
129.50
128.99
52.81
45.43
30.08
23.35
22.34
20.08
40000
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)