Supplementary Information

Amidation of phenol derivatives: a direct synthesis of paracetamol (acetaminophen) from hydroquinone

Roxan Joncour,[a] Nicolas Duguet,[a] Estelle Métay,[a] Amadéo Ferreira[b] and Marc Lemaire*[a]

[a] Laboratoire de CAtalyse SYnthèse et ENvironnement (CASYEN), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), CNRS, UMR-5246, Université Claude Bernard Lyon 1, 43 boulevard du 11 novembre 1918, Bât. Curien/CPE, 69622, Villeurbanne, France. E-mail: marc.lemaire.chimie@univ-lyon1.fr; Fax: +33-472-43-14-08; Tel: +33-472-43-14-07.

[b] Minakem SAS, 145 chemin des Lilas, 59310 Beuvry-la-Forêt, France.

Table of contents

1. Calculation of theoretical atom-economies and E factors

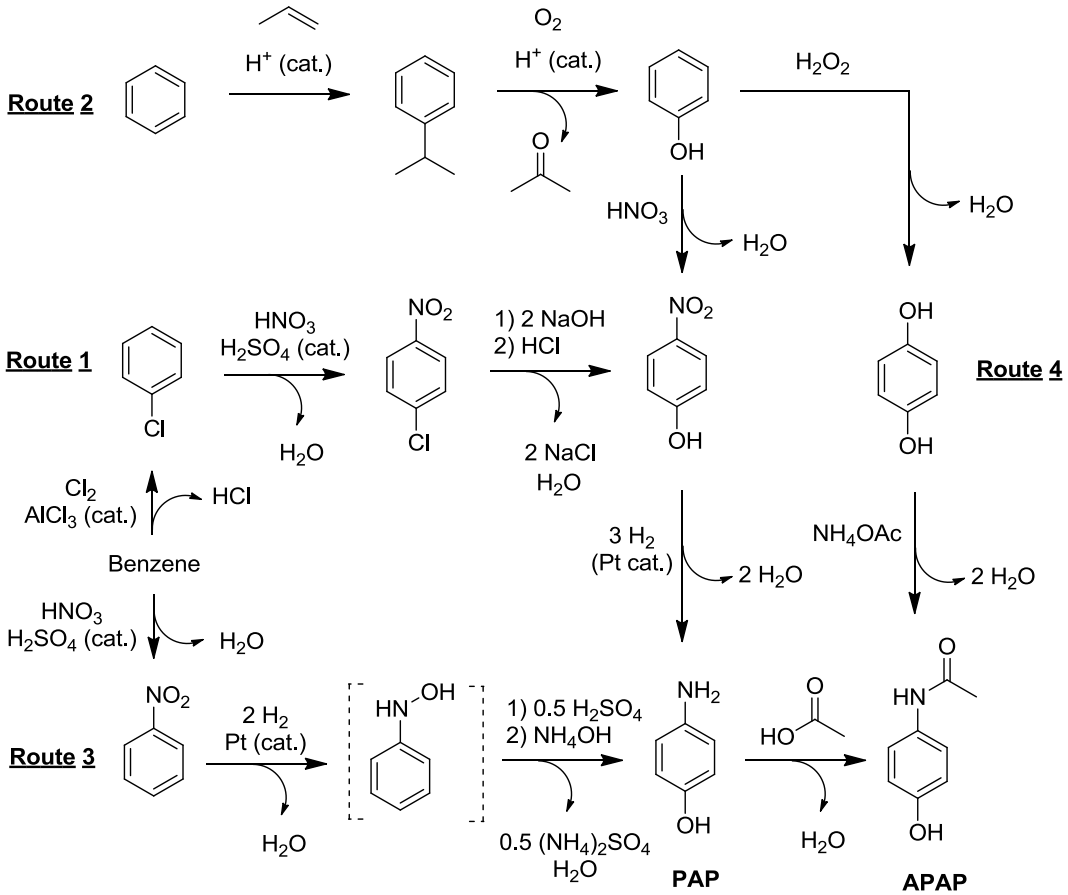
Theoretical atom-economies (AE) and E factors were calculated for the production of paracetamol (M = 151.16 g.mol^{-1}) in accordance with Trost's definition[1] of atom-economy and with Sheldon's definition[2] of E factor. These indicators were calculated using the following relations:

$$\text{AE} = \frac{\text{mol. wt. of desired product}}{\text{mol. wt. of all product}} \text{ x } 100\% = \frac{151.16}{151.16 + \text{mol. wt. of waste}} \text{x } 100\%$$

$$\text{E factor} = \frac{\text{mol. wt. of waste}}{\text{mol. wt. of desired product}} \text{ x } 100\% = \frac{\text{mol. wt. of waste}}{151.16} \text{x } 100\%$$

Four different routes were evaluated for the industrial production (or considered as such) of paracetamol from benzene (Scheme A).

- **Route 1:** Nitration of chlorobenzene.
- **Route 2:** Nitration of phenol.
- **Route 3:** Reduction of nitrobenzene.
- **Route 4:** Acetamidation of hydroquinone (this work).



Scheme A. Routes for paracetamol synthesis

[1] a) B. M. Trost, *Science,* **1991**, *254*, 1471-1477. b) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995***, 34*, 259–281. c) C.-L. Li and B. M. Trost, *PNAS* **2008**, *105*, 13197-13202.

[2] a) R. A. Sheldon, *Chem. Ind.* **1992**, 903-906. b) R. A. Sheldon, *C. R. Acad. Sci. Paris,* IIc **2000**, Chemistry 3, 541-551.

The results of theoretical atom-economies and E factors are compiled in Table A.

Table A. AE and E factor of considered routes for paracetamol synthesis from benzene

Route	Considered waste (equiv.)	Waste mol. wt. (g/mol)	AE (%)	E factor[3]
1	H_2O (5) NaCl (2) HCl (1)	18.02 (x5) 58.44 (x2) 36.46	**38**	**1.61**
2	H_2O (4) Acetone (1)	18.02 (x4) 58.08	**54**	**0.86**
3	H_2O (4) $(NH_4)_2SO_4$ (0.5)	18.02 (x4) 132.14 (x0.5)	**52**	**0.91**
4	H_2O (3) Acetone (1)	18.02 (x3) 58.08	**57**	**0.74**

From these figures, it appears that the route 1 (nitration of chlorobenzene) is the least attractive in terms of atom economy and E factor. The small differences between the routes 2, 3 and 4 are not significant to draw any conclusions. Moreover, these values are obviously not sufficient for selecting the "true" best method. Several parameters should also be considered: yields, selectivities, solvents (reaction, work-up or purification), energy, potential recycling, valorisation of by-product, etc.

Calculating and comparing the practical atom-economies and E factors of the four routes is not viable because of the existence of a huge number of patents and publications for each steps. The selection of a particular method would necessarily influence the result. Moreover, data from manufacturers who sell paracetamol are of course highly confidential.

Nevertheless, each route has inherent drawbacks and some of them are listed in Table B.

Table B. Comparison of the four routes to paracetamol

Route 1	Steps: 5 steps from benzene, 4 from chlorobenzene Key-steps: nitration of chlorobenzene, reduction of *para*-nitrophenol Drawbacks: Formation of *ortho*-chloronitrobenzene from the nitration of chlorobenzene, Neutralization of nitrophenol.
Route 2	Steps: 5 steps from benzene, 3 from phenol Key-steps: nitration of phenol, reduction of *para*-nitrophenol Drawbacks: Formation of *ortho*-aminophenol from the nitration of phenol.
Route 3	Steps: 4 steps from benzene, 3 from nitrobenzene Key-steps: Hydrogenation of nitrobenzene, Bamberger rearrangement of phenylhydroxylamine Drawbacks: Formation of *ortho*-aminophenol and aniline from the Bamberger rearrangement, production of ammonium sulfate, sensitivity to catalyst poisons
Route 4	Steps: 4 steps from benzene, 2 from phenol Key-steps: Oxidation of phenol, amidation of hydroquinone Drawbacks: Formation of cathecol from the oxidation of phenol, low productivity for the production of hydroquinone

[3] Water was considered as a waste for the calculation of theoretical E factors.

2. General information

Hydroquinone (HQ, 99.5% from Sigma-Aldrich), ammonium acetate (98% from Sigma-Aldrich), acetamide (99% from Lancaster) and acetic acid (100% from VWR) were used without further purification. NMR spectra were acquired on DRX Bruker 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75 MHz) at 293 K. Shifts are referenced relative to the deuterated solvent residual peak. The chemical shifts (δ) are expressed in ppm and the coupling constants (*J*) are given in Hz. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublets of doublets, m = multiplet, br = broad. Electrospray ionization (ESI) mass spectra (MS) were recorded in the positive mode using a LCQ Advantage-Thermofinnigan spectrometer. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel Merck 60 F254 (0.25 mm). Flash column chromatography was performed with silica gel Merck Si 60 (40–63 μm). Infrared (IR) spectra were recorded in a SMART iTR-Nicolet iS10 spectrometer using Attenuated Total Reflectance (ATR) and the wavenumbers (ν max) are expressed in cm^{-1}. Melting points were measured using a Kofler Heizbank apparatus and noted in °C.

3. HPLC method for the amidation of hydroquinone

HPLC analyses of the crude reaction mixtures were run using a PerkinElmer Series 200 apparatus fitted with a manual injector, a pump and a UV/Vis detector.

- Column C18 (250 x 4.6 mm, particule size 0.5 μm)
- Mobile phase: (H_2O + CH_3CN) + 0.1 % v/v H_3PO_4
- Flow-rate: 1.0 $mL.min^{-1}$.
- Wavelength: 254 or 290 nm.
- Temperature: 20 °C

The above gradient of acetonitrile was used to separate the crude reaction mixtures (Figure A). For practical reasons, hydroquinone and paracetamol were detected at 290 nm whereas *para*-aminophenol was detected at 254 nm (Table B).

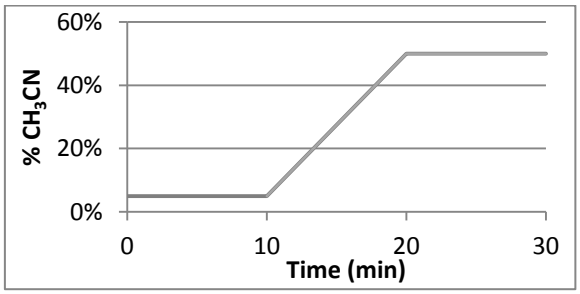


Figure A. Gradient for HPLC experiments

Products separation is presented in Table C and an example resulting of HPLC chromatogram is shown in Figure B.

Table C. Retention and detection wavelength of measured compounds

Compound	Retention time	Detection wavelength
p-Aminophenol	2.6-2.7 min	254 nm
Hydroquinone	7.0-7.5 min	290 nm
Paracetamol	12.0-12.7 min	290 nm

The yields of hydroquinone, *para*-aminophenol and paracetamol were calculated from calibration curves.

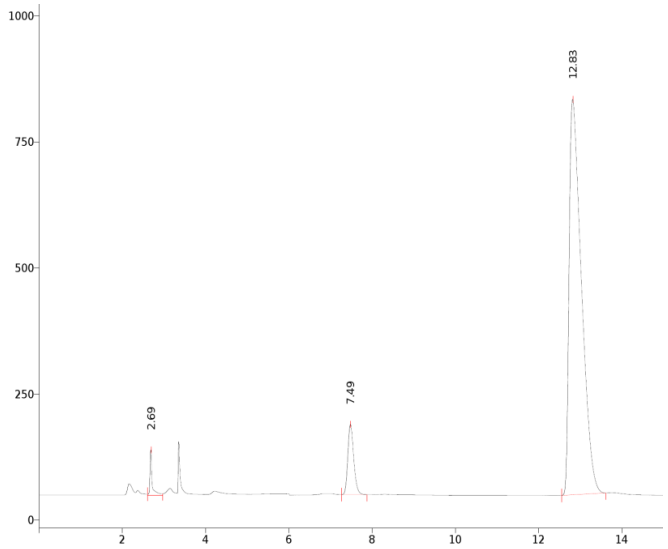


Figure B. Example of a HPLC chromatogram of a crude mixture.

4. General procedures

a. General procedure for scope and optimization (**procedure a**)

A phenol derivative (40 mmol, 1 equiv), ammonium acetate (6.3 g, 80 mmol, 2 equiv) and acetic acid (11.5 mL, 200 mmol, 5 equiv) were successively added in a 30-mL steel reactor equipped with an inner glass tube and an inner temperature sensor. The reactor was purged with argon and heated to 160 °C (graphite bath) before stirring. The temperature was then increased to 220 °C and the mixture was stirred at this temperature for 15 hours.

For optimization reactions, the mixture was diluted with methanol and water, poured into a 250-mL volumetric flask and completed to 250 mL with water and methanol. The reaction was finally analysed by HPLC.

For the scope, the mixture was diluted with water (75 mL) and neutralized with sodium carbonate (Na_2CO_3, 22 g) and extracted three times with ethyl acetate (EtOAc, 3 × 75 mL). The organic layers were combined and the solvent was removed under reduce pressure (60 °C, 8 mbar). The crude product was purified by column chromatography (cyclohexane / EtOAc).

b. Medium-scale preparation of paracetamol (**procedure b**)

Hydroquinone (44.0 g, 0.4 mol, 1 equiv), ammonium acetate (63.0 g, 0.8 mol, 2 equiv) and acetic acid (114 mL, 2 mol, 5 equiv) were added in a 300-mL Parr Instrument reactor equipped with a temperature sensor and a mechanical stirrer. The autoclave was purged with argon and heated to 160 °C (heating mantle) before stirring. The temperature was further increased to 230 °C and the mixture was stirred at this temperature for 15 hours. The reactor was cooled down to room temperature and the homogeneous mixture was transferred to a 250-mL flask (a sample was taken at that stage in order to run HPLC analyses). A distillation set-up was then installed and acetic acid was evaporated under reduced pressure. A total amount of 98 mL was recovered which corresponds to a 85% recovery. The reaction mixture was cooled down to room temperature and the precipitate was filtered, washed twice with water (2 × 20 mL) and dried to give paracetamol (53.0 g, 88%) as a white solid. HPLC analysis revealed a 99% purity.

5. Characterization data of the products

***N*-(4-Hydroxy-phenyl)-acetamide** [103-90-2]. The title compound was prepared from hydroquinone (44.0 g, 0.4 mol) following the procedure **b** to give paracetamol (53.0 g, 88% yield) as a white solid. M.p. 170 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 2.08 (s, 3H), 6.72 (d, 2H, J = 8.7), 7.30 (d, 2H, J = 8.7); ^{13}C NMR (75 MHz, CD_3OD): δ 23.5 (CH_3), 116.2 (2 CH^{Ar}), 123.4 (2 CH^{Ar}), 131.5 (Cq^{Ar}), 155.3 (Cq^{Ar}), 171.4 ($Cq^{C=O}$); IR (ATR) ν max: 3322, 3160, 1651; MS (ESI^+): 110.1 ([HO-C_6H_4-NH_3]$^+$, 9), 152.1 ([M+H]$^+$, 100).

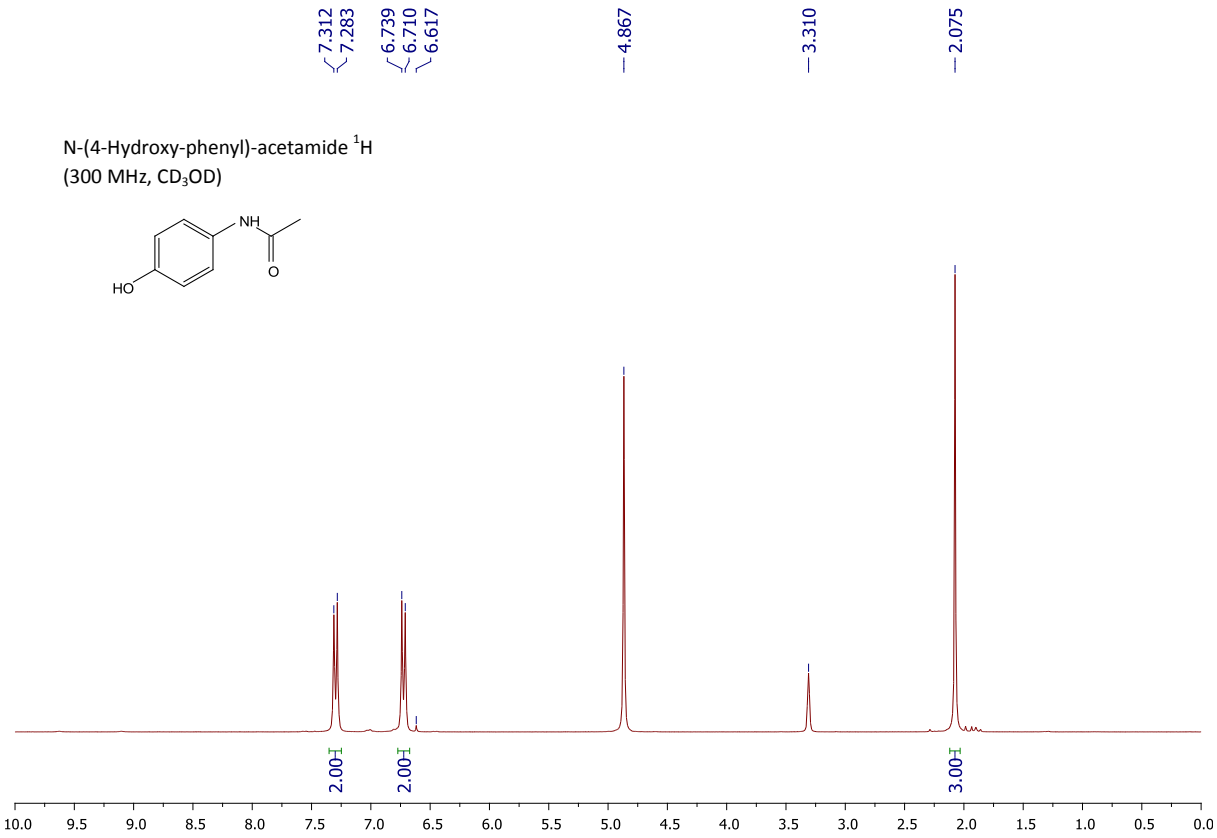
***N*-(3-Hydroxy-phenyl)-acetamide** [621-42-1]. The title compound was prepared from resorcinol (4.40 g, 40 mmol) following the procedure **a**. The crude product was purified by column chromatography (cyclohexane / EtOAc 90 : 10) to give *N*-(3-hydroxy-phenyl)-acetamide (3.01 g, 50% yield) as a white solid. M.p. 148 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 2.09 (s, 3H), 6.53 (ddd, 1H, J = 8.1, 2.4, 0.9), 6.91 (ddd, 1H, J = 8.1, 2.1, 0.9), 7.08 (t, 1H, J = 8.1), 7.17 (t, 1H, J = 2.1); ^{13}C NMR (75 MHz, CD_3OD): δ 23.8 (CH_3), 108.4 (CH^{Ar}), 112.1 (CH^{Ar}), 112.3 (CH^{Ar}), 130.5 (CH^{Ar}), 140.9 (Cq^{Ar}), 158.8 (Cq^{Ar}), 171.6 ($Cq^{C=O}$); IR (ATR) ν max: 3322, 3058, 1604; MS (ESI^+): 110.1 ([HO-C_6H_4-NH_3]$^+$, 18), 152.1 ([M+H]$^+$, 100), 174.1 ([M+Na]$^+$, 28).

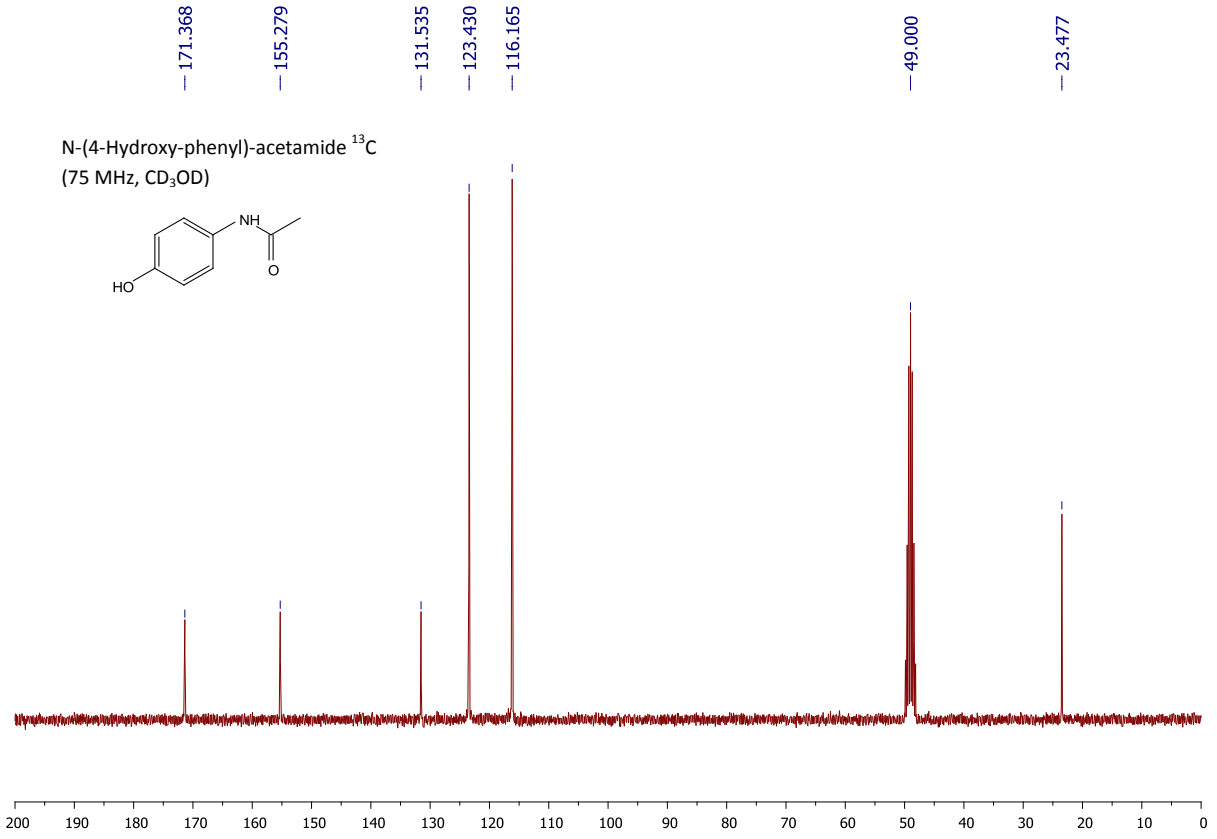
***N*-(2-Hydroxy-phenyl)-acetamide** [614-80-2]. The title compound was prepared from catechol (4.40 g, 40 mmol) following the procedure **a**. The crude product was purified by column chromatography (cyclohexane / EtOAc 60 : 40) to give *N*-(2-hydroxy-phenyl)-acetamide (0.52 g, 9% yield) as a grey solid. M.p. 207 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 2.17 (s, 3H), 6.80 (td, 1H, J = 7.7, 1.5), 6.85 (dd, 1H, J = 7.8, 1.5), 6.99 (td, 1H, J = 7.8, 1.5); ^{13}C NMR (75 MHz, d_6-DMSO): δ 23.6 (CH_3), 116.0 (CH^{Ar}), 119.0 (CH^{Ar}), 122.4 (CH^{Ar}), 124.7 (CH^{Ar}), 126.4 (Cq^{Ar}), 147.9 (Cq^{Ar}), 169.0 ($Cq^{C=O}$); IR (ATR) ν max: 3400, 3031, 1656; MS (ESI^+): 110.1 ([HO-C_6H_4-NH_3]$^+$, 25), 152.0 ([M+H]$^+$, 100), 174.0 ([M+Na]$^+$, 19).

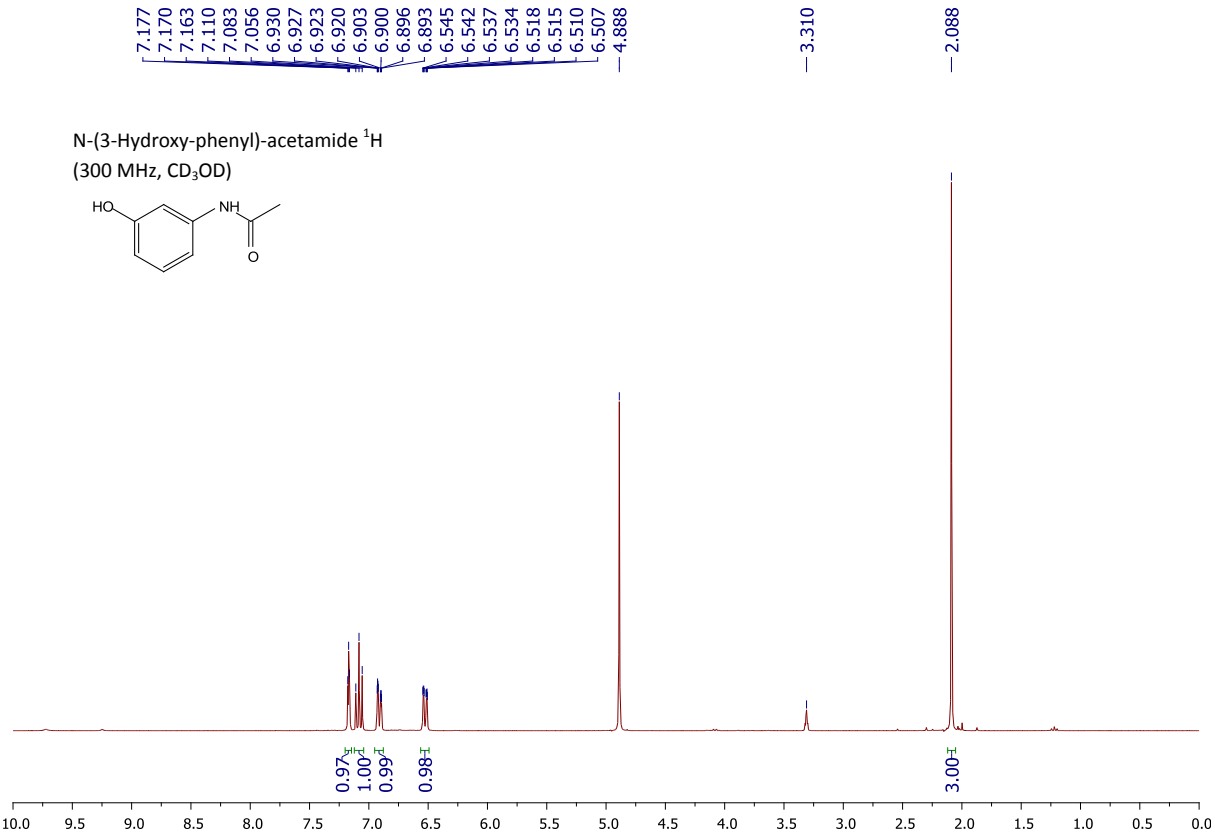
***N*-Naphthalen-1-yl-acetamide** [575-36-0]. The title compound was prepared from 1-naphthol (5.77 g, 40 mmol) following the procedure **a**. The crude product was purified by column chromatography (cyclohexane / EtOAc 95 : 5) to give *N*-naphthalen-1-yl-acetamide (2.70 g, 36% yield) as an orange solid. M.p. 160 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ 2.20 (s, 3H), 7.48 (t, 1H, J = 7.8), 7.52-7.56 (m, 2H), 7.71 (d, 1H, J = 7.5), 7.75 (d, 1H, J = 8.1), 7.92-7.95 (m, 1H), 8.08-8.11 (m, 1H), 9.93 (*br* s, 1H, NH); ^{13}C NMR (75 MHz, d_6-DMSO): δ 23.5 (CH_3), 121.5 (CH^{Ar}), 122.7 (CH^{Ar}), 125.0 (CH^{Ar}), 125.6 (CH^{Ar}), 125.7 (CH^{Ar}), 126.0 (CH^{Ar}), 127.7 (Cq^{Ar}), 128.1 (CH^{Ar}), 133.7 (2 Cq^{Ar}), 168.9 ($Cq^{C=O}$); IR (ATR) ν max: 3269, 1654, 1540; MS (ESI^+): ([$C_{10}H_7NH_3$]$^+$, 37), 186.1 ([M+H]$^+$, 100).

***N*-Naphthalen-2-yl-acetamide** [581-97-5]. The title compound was prepared from 2-naphthol (5.77 g, 40 mmol) following the procedure **a**.The crude product was purified by column chromatography (cyclohexane / EtOAc 95 : 5) to give *N*-naphthalen-2-yl-acetamide (4.12 g, 56% yield) as a white solid. M.p. 130 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 2.15 (s, 3H), 7.32-7.43 (m, 2H), 7.52 (dd, 1H, J = 8.9, 2.0), 7.71-7.77 (m, 3H), 8.18 (d, 1H, J = 1.8); ^{13}C NMR (75 MHz, CD_3OD): δ 23.9 (CH_3), 117.7 (CH^{Ar}), 121.2 (CH^{Ar}), 125.9 (CH^{Ar}), 127.4 (CH^{Ar}), 128.5 (2 CH^{Ar}), 129.5 (CH^{Ar}), 132.0 (Cq^{Ar}), 135.2 (Cq^{Ar}), 137.3 (Cq^{Ar}), 171.8 ($Cq^{C=O}$); IR (ATR) ν max: 3281, 1685, 1547; MS (ESI^+): 144.2 ([$C_{10}H_7NH_3$]$^+$, 34), 186.1 ([M+H]$^+$, 100).

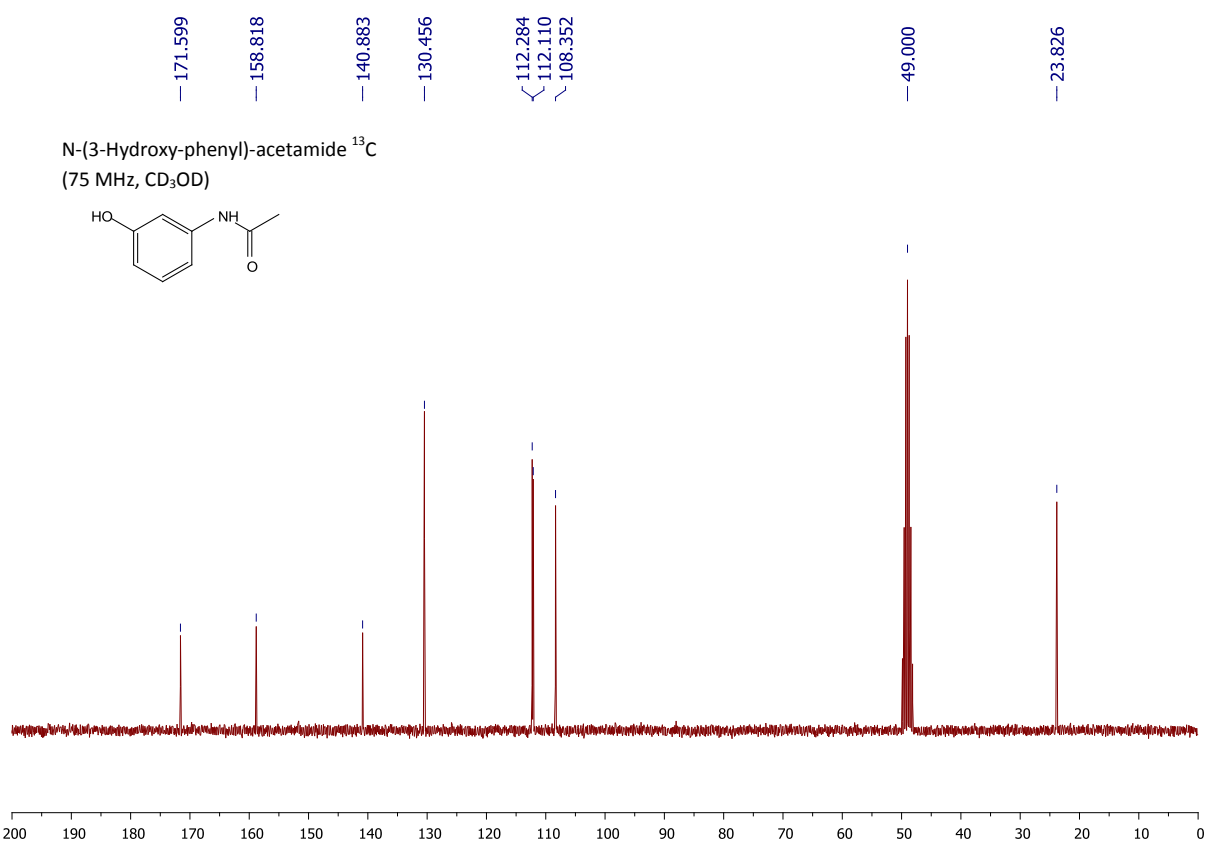
6. ^{1}H and ^{13}C spectra



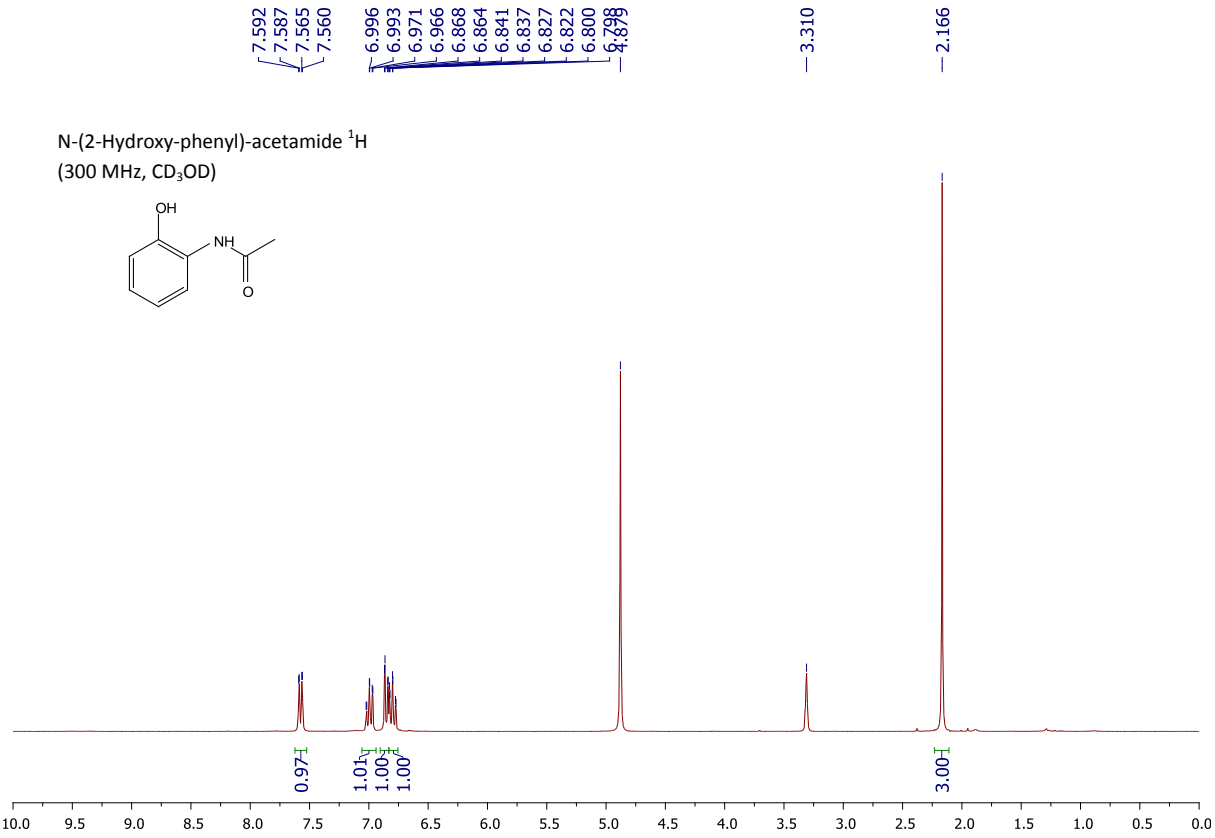


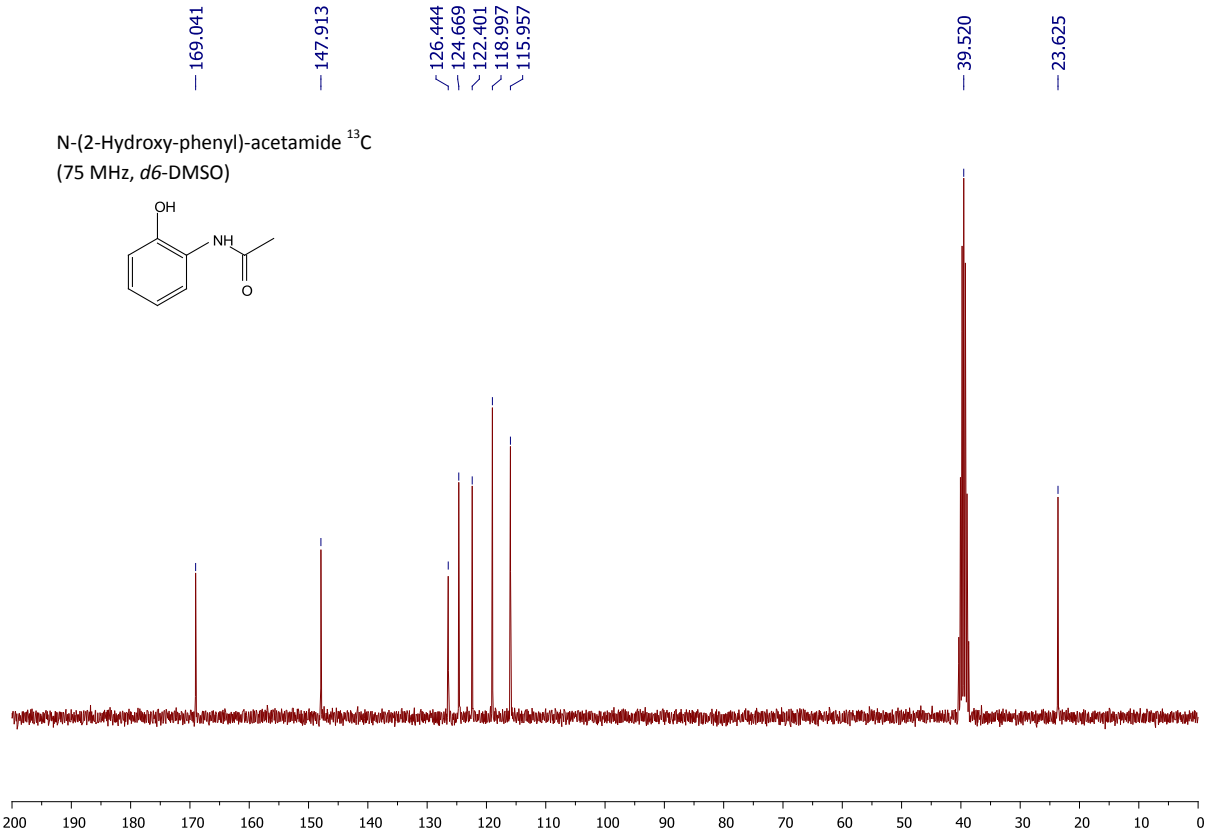


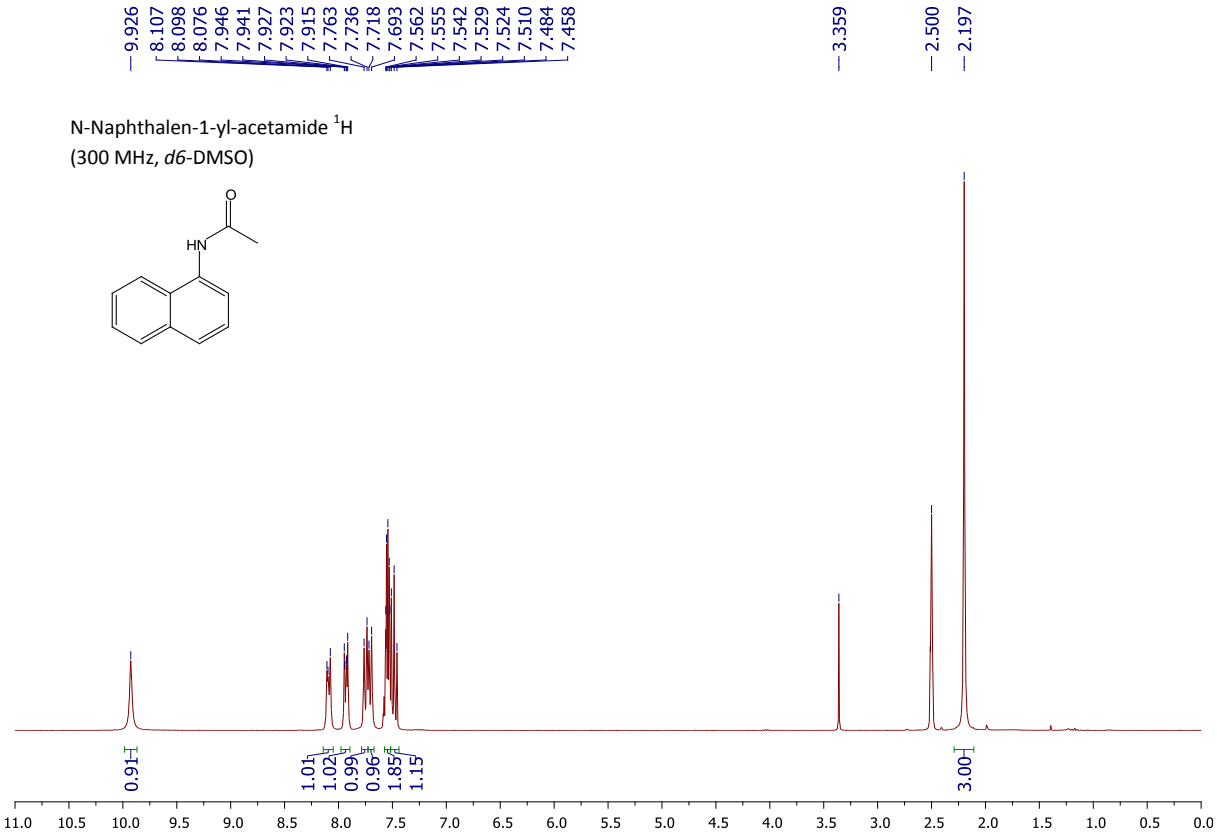
N-(3-Hydroxy-phenyl)-acetamide ^{1}H
(300 MHz, CD_3OD)



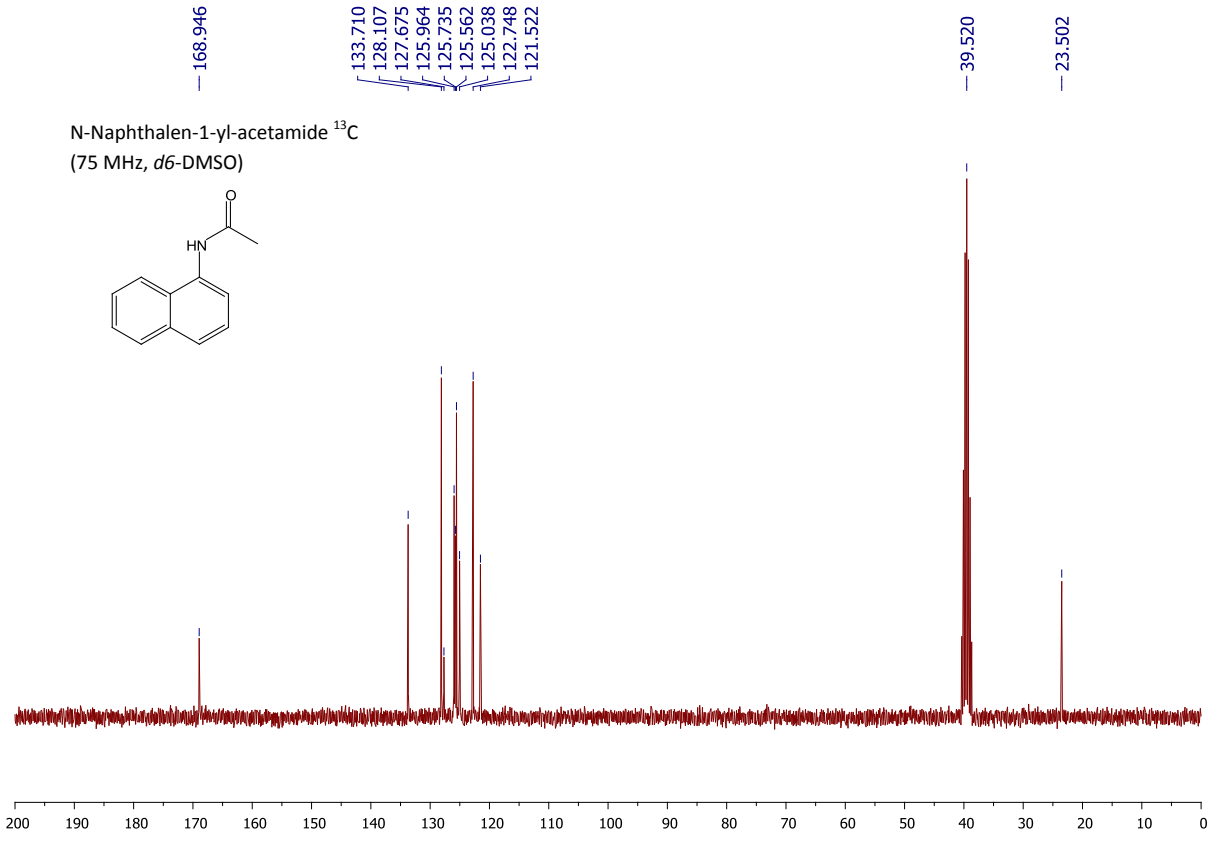
N-(3-Hydroxy-phenyl)-acetamide ^{13}C
(75 MHz, CD_3OD)


7.592
7.587
7.565
7.560
6.996
6.993
6.971
6.966
6.868
6.864
6.841
6.837
6.827
6.822
6.800
6.798
4.879
3.310
2.166
N-(2-Hydroxy-phenyl)-acetamide 1H
(300 MHz, CD3OD)
OH
NH
O
0.97
1.01
1.00
1.00
3.00
10.0
9.5
9.0
8.5
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

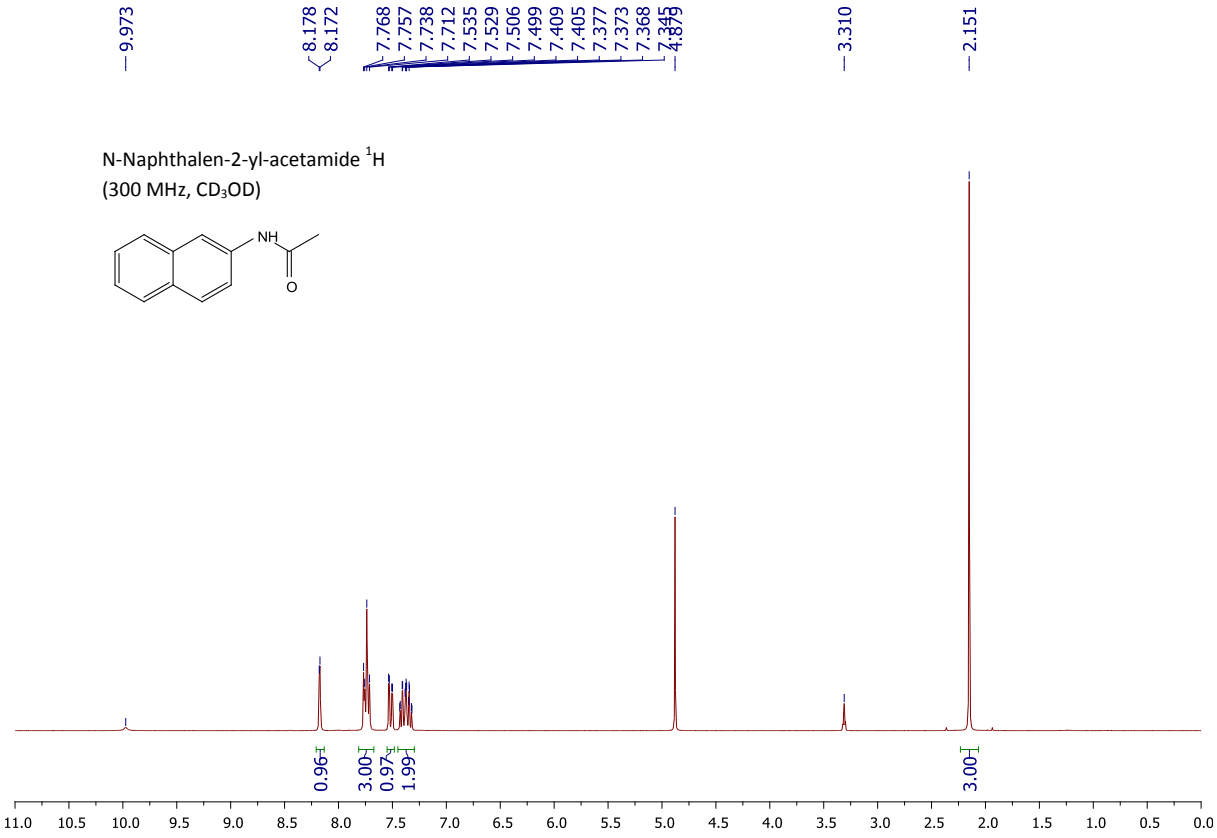

169.041
147.913
126.444
124.669
122.401
118.997
115.957
39.520
23.625
N-(2-Hydroxy-phenyl)-acetamide 13C
(75 MHz, d6-DMSO)
OH
NH
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

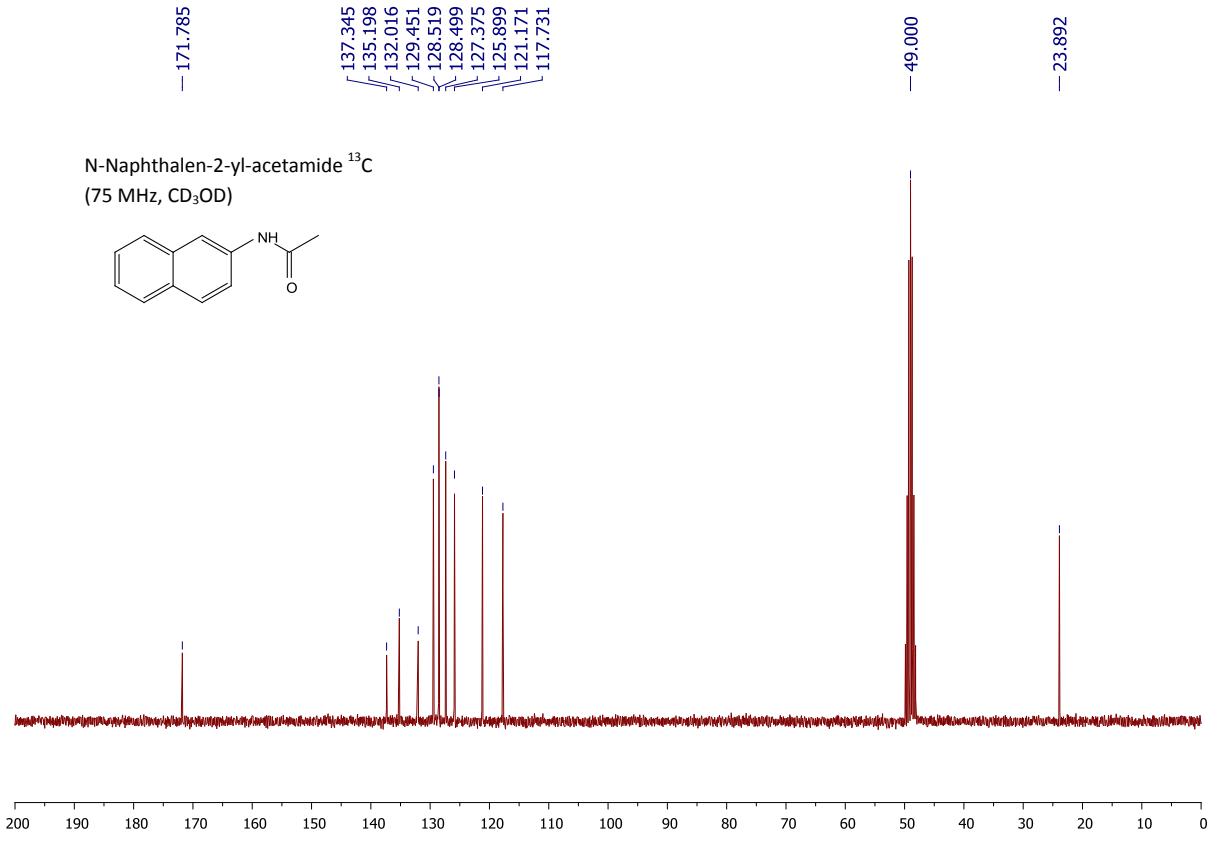


N-Naphthalen-1-yl-acetamide ^{1}H
(300 MHz, *d6*-DMSO)



N-Naphthalen-1-yl-acetamide ^{13}C
(75 MHz, *d6*-DMSO)


9.973
8.178
8.172
7.768
7.757
7.738
7.712
7.535
7.529
7.506
7.499
7.409
7.405
7.377
7.373
7.368
7.345
4.879
3.310
2.151
N-Naphthalen-2-yl-acetamide 1H
(300 MHz, CD3OD)
NH
O
0.96
3.00
0.97
1.99
3.00
11.0 10.5 10.0 9.5 9.0 8.5 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


171.785
137.345
135.198
132.016
129.451
128.519
128.499
127.375
125.899
121.171
117.731
49.000
23.892
N-Naphthalen-2-yl-acetamide 13C
(75 MHz, CD3OD)
NH
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0