Continuous Flow Synthesis of Propofol

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SUPPORTING INFORMATION

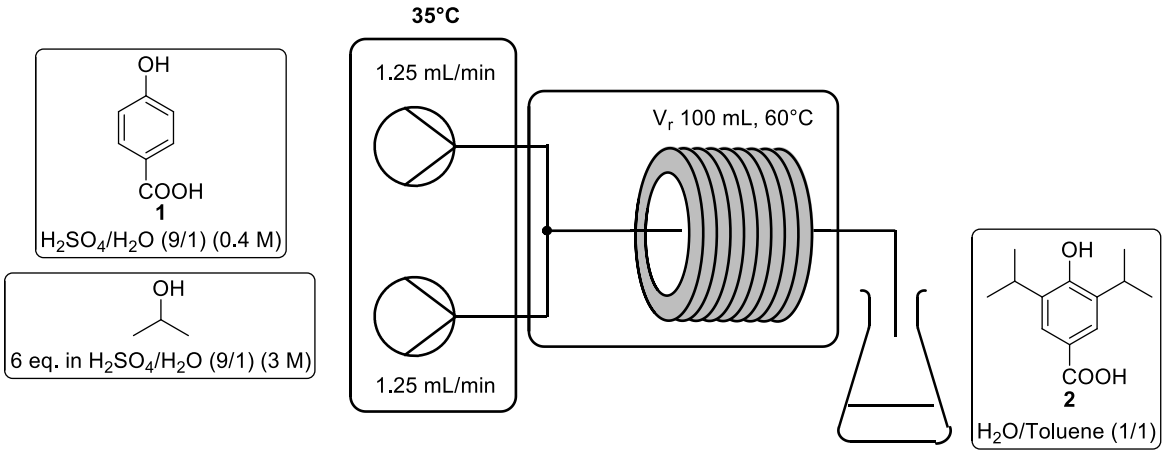
Table of contents

1. General methods

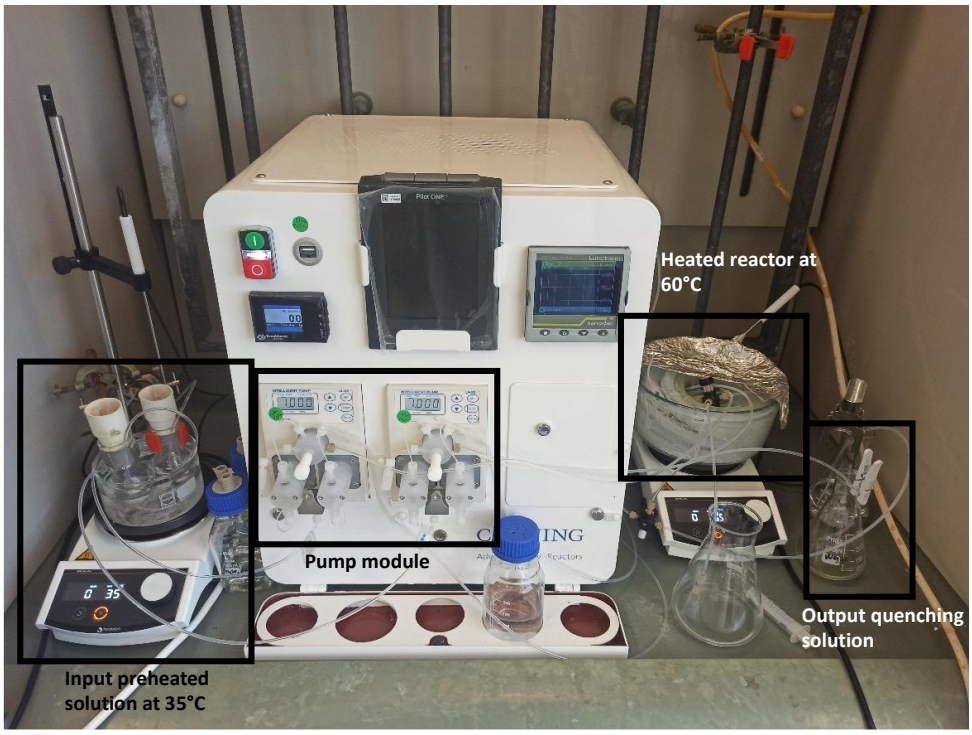
All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker Advance III 300 at 300 MHz and 76 MHz, respectively. Residual solvent peaks were used as the reference. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sex = sextet, sept = septet, m = multiplet), coupling constant (Hz) and integration). Chemical shifts are reported in ppm relative to the signals corresponding to residual non-deuterated ($CDCl_3$: δ = 7.26 ppm). Analyses were performed on GC-FID thermoscientific trace 1310 equipped with Durabond DB-5MS (30 m, 0.250 mm Ø narrowbore, 0.25 µm film), the He vector gas flow rate of 1ml.min-1 in split mode (50mL.min^{-1}) and the inlet injector temperature of 250 °C. As FID detector, the air flow rate is at 350 mL.min^{-1} with vector gas at 35 mL.min^{-1}. Samples analysis were done, after 2 minutes at 50 °C, at a temperature rate of 10 °C.min^{-1} for 20 minutes reaching 250 °C. All GC-sample were prepared using grade HPLC solvents from Ficher. Distillation were performed on a Büchi Kugelrohr. The flow reactor system is specified for each cases between the AFR™ Corning® module pump device, the Vapourtec® R4 heated system and R2S pump system.

2. Synthetic procedures

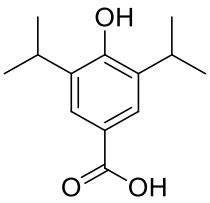
a) Preparation of 3,5-diisopropyl-4-hydroxybenzoic acid (2)



PFA reactor and channels, 1,6mmØ, AFR Corning pump module, T shape mixer, elution system H_2SO_4/H_2O (9/1)



A stock solution of 4-hydroxybenzoic acid (**1**) (200 mmol, 27.6 g) in H_2SO_4/H_2O (9:1, 440 mL/55 mL, 0.5 M) and a stock solution of isopropyl alcohol (6 eq., 1.2 mol, 71.5 g, 91.3 mL) in H_2SO_4/H_2O (9:1, 363 mL/40.7 mL) were heated at 35°C and pumped using the AFR™ Corning® module pump at a flow rate of 1.25 mL.min^{-1} for each solution through a T-mixer heated at 60 °C and a 100 mL coil PFA reactor also heated at 60 °C. The output of the reactor was collected into a stirred solution of H_2O/toluene (1:1) at room temperature. The setup was eluted by a solution of H_2SO_4/H_2O (9:1). The layers were separated and the aqueous phase was extracted with toluene. The combined organics phases were washed with brine, dried with $MgSO_4$ and concentrated under vacuum. Flash chromatography afforded the desired product **2** as a white solid (84%, 168 mmol, 37.3 g).

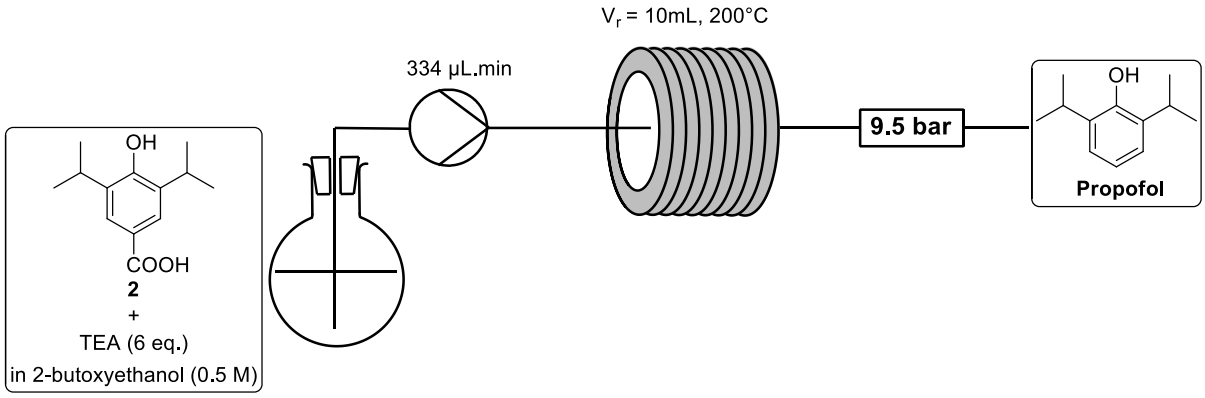


2

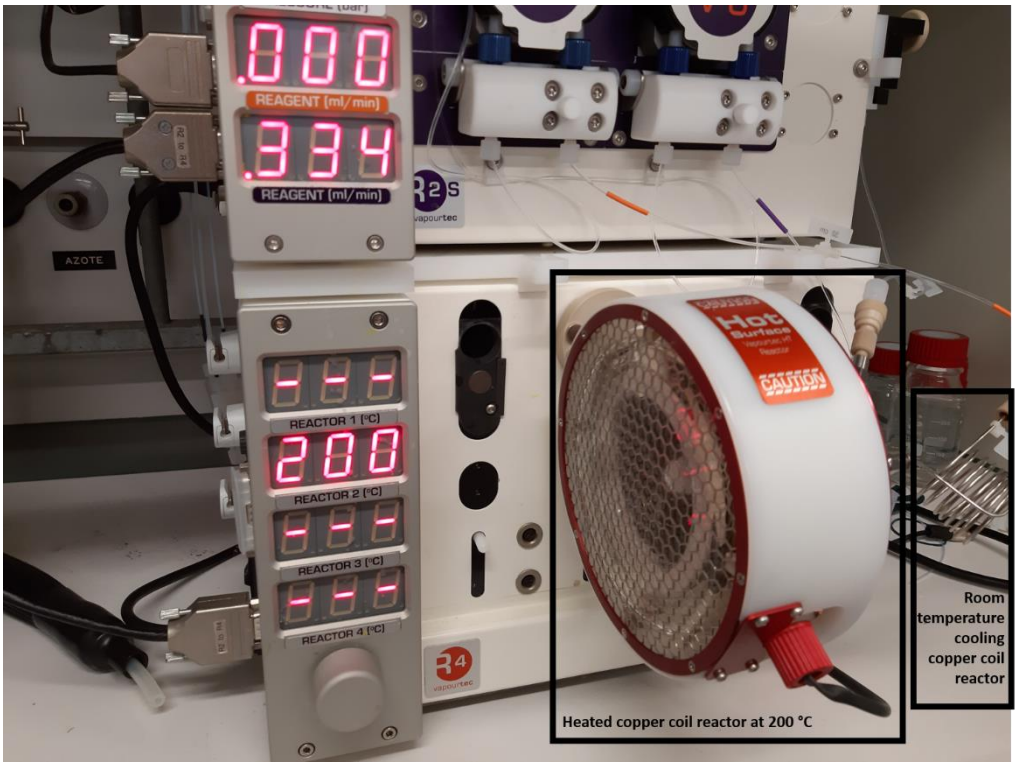
3,5-diisopropyl-4-hydroxybenzoic acid (2): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.87 (s, 2H), 3.17 (hept, *J* = 6.9 Hz, 2H), 1.31 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 172.64, 155.15, 133.73, 126.50, 121.47, 27.22, 22.60. Melting point: 139-142°C. GC retention time: 19.02 minutes. Data were in accordance with those in literature.[1]

[1] Pramanik, C.; Kotharkar, S.; Patil, P.; Gotrane, D.; More, Y.; Borhade, A.; Chaugule, B.; Khaladkar, T.; Neelakandan, K.; Chaudhari, A.; Kulkarni, M. G.; Tripathy, N. K.; Gurjar, M. K. *Org. Process Res. Dev.* **2014**, *18*, 152–156.

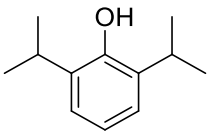
b) Preparation of Propofol



PFA channel, copper reactor, 1mmØ, Vapourtec R4 and R2S



To a stock solution of 3,5-diisopropyl-4-hydroxybenzoic acid (**2**) (0.5 mmol, 111 mg, 1 eq.) in 2-butoxyethanol (500 µL) was added triethylamine (3 mmol, 500 µL, 6eq.). The mixture was stirred at room temperature and pumped by R2S Vapourtec® pump device at a flow rate of 334 µL.min^{-1} through a 10 mL copper coil reactor at 200 °C and a 1 mL copper coil reactor at room temperature. The setup was eluted by 2-butoxyethanol. The output of the reactor was collected into a stirred solution of brine/cyclohexane. The organic layer was dried with $MgSO_4$ and concentrated under vacuum to afford the crude Propofol with an excellent purity. A subsequent bulb to bulb distillation of this residue (140°C, 5 mbar) is possible to further purify the Propofol, which is obtained as a colourless liquid. (58% yield)

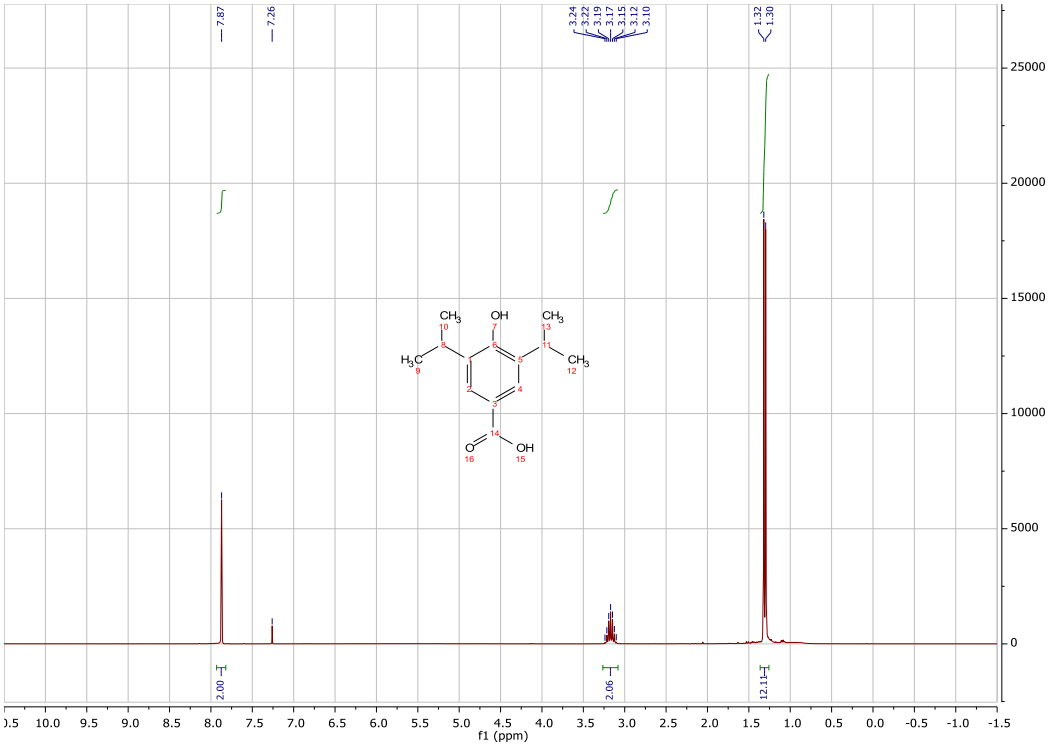


Propofol

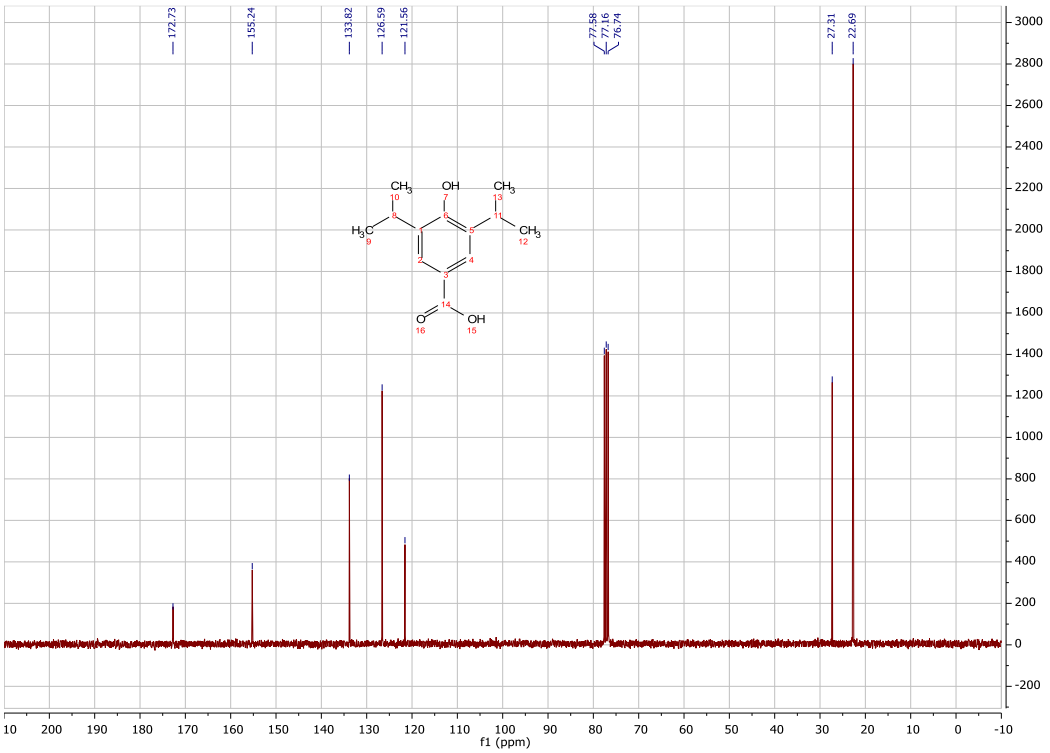
Propofol: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.07 (dd, *J* = 7.6, 0.5 Hz, 2H), 6.96 – 6.85 (m, 1H), 4.78 (s, 1H), 3.17 (hept, *J* = 6.8 Hz, 2H), 1.28 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 149.97, 133.66, 123.48, 120.66, 27.18, 22.78. GC retention time: 13.70 minutes. Data were in accordance with those in literature.[1]

3. Characterizations

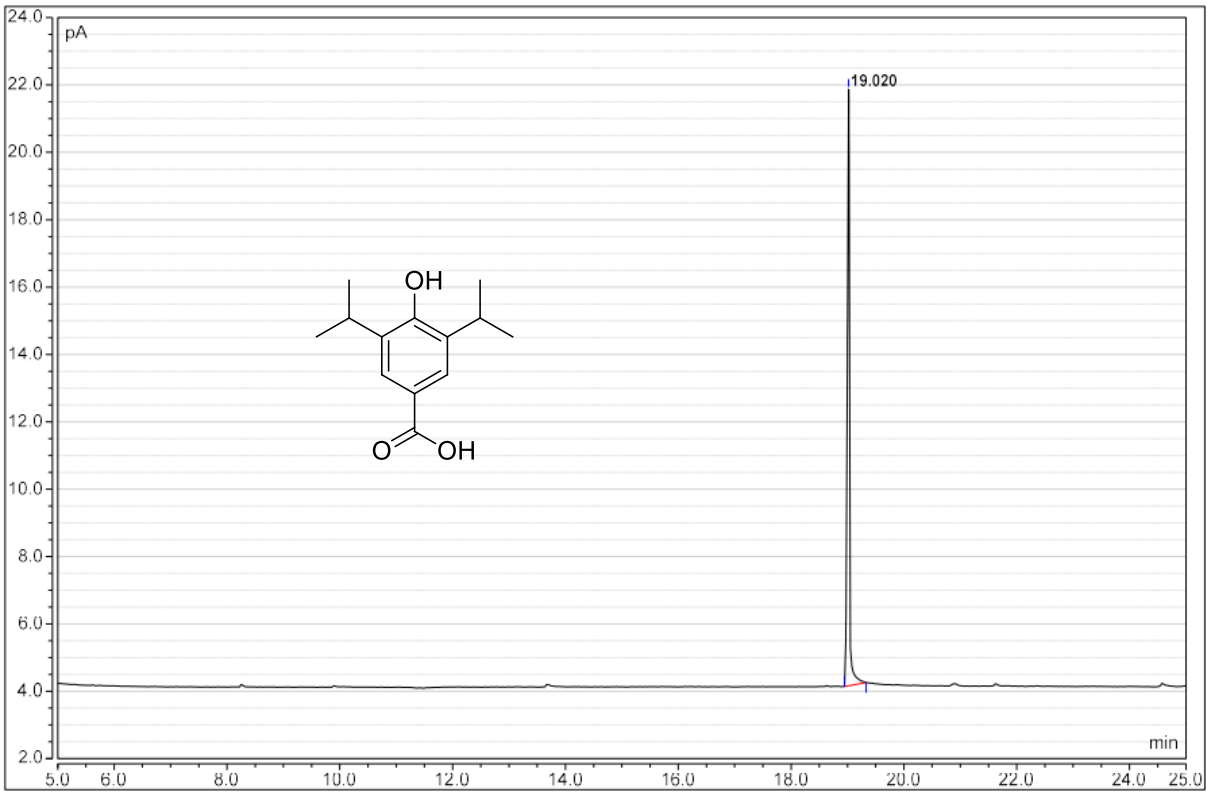
^{1}H NMR spectra of **2**



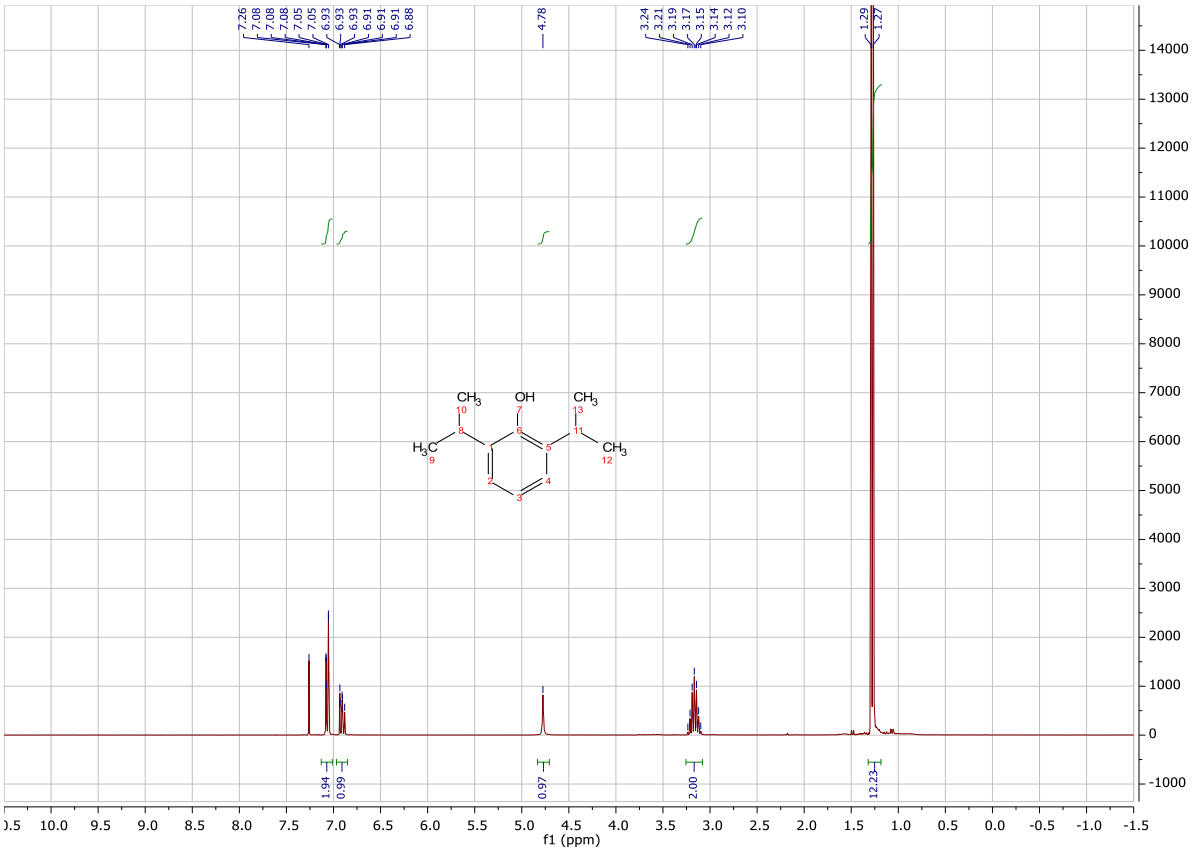
^{13}C NMR spectra of **2**



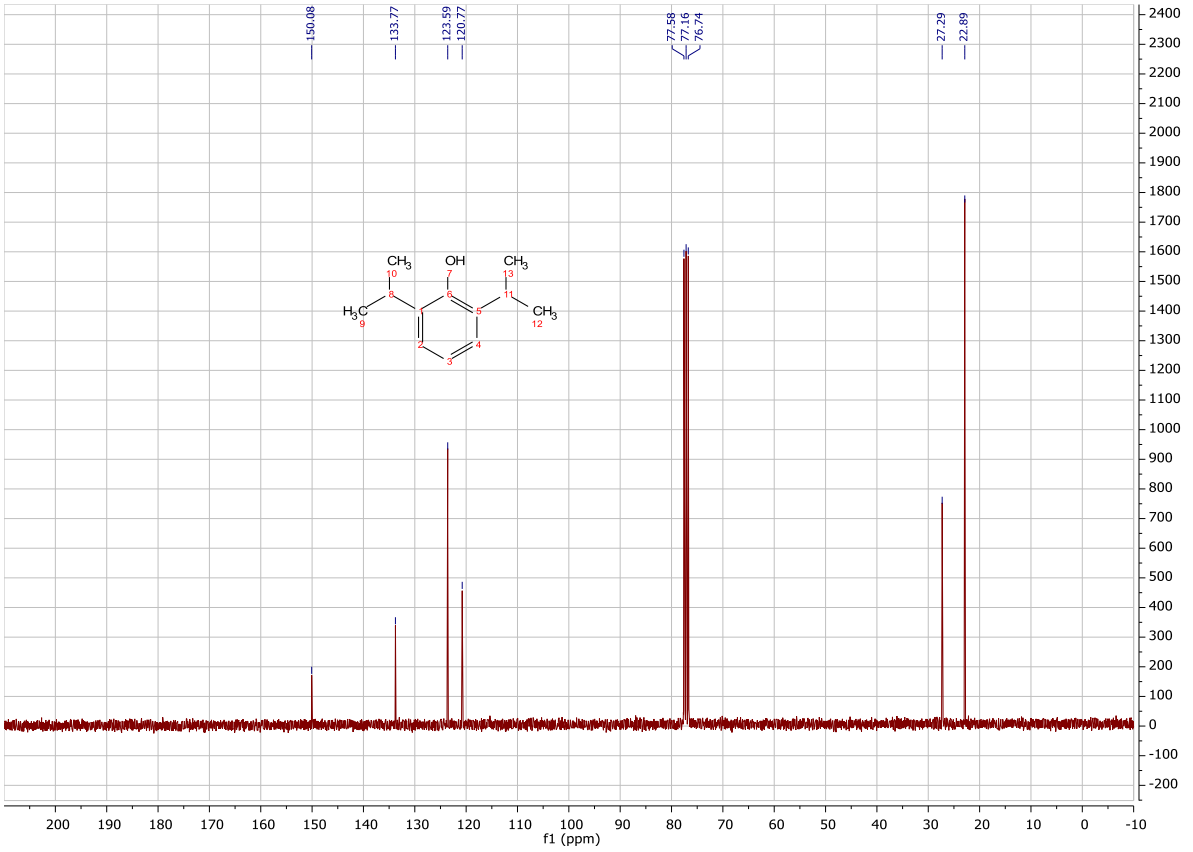
GC chromatograph of **2**



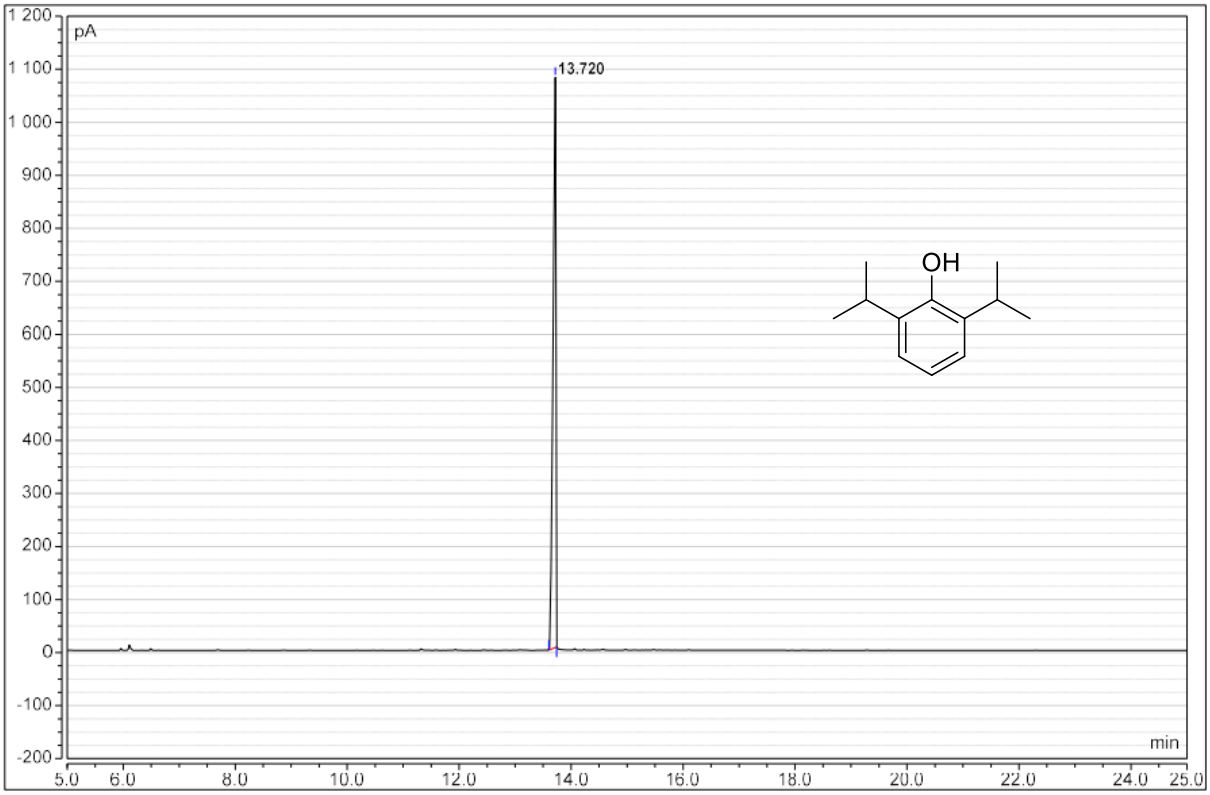
^{1}H NMR spectra of **propofol**



^{13}C NMR spectra of **propofol**



GC chromatograph of **propofol**



GC chromatogram of crude mixture of **propofol**