Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

For the article

60-Times Faster Digital-Discovery-Compatible Reaction Setup with Enhanced Safety for Chemical Applications

Andrey N. Lebedev,[a] Konstantin S. Rodygin,[a] Svetlana A. Vakhrusheva,[a] Valentine P. Ananikov [a,b]*

[a] Saint Petersburg State University, Universitetskaya Emb. 7/9, Saint Petersburg, 199034, Russia

[b] N. D. Zelinsky Institute of Organic Chemistry, Leninsky pr. 47, Moscow, 119991, Russia; E-mail: val@ioc.ac.ru

Table of contents

1. General information

Calcium carbide (≥75%), triethylamine, cyclohexanone, 4-chlorothiophenol, 2-methyltetrahydrofuran, thiourea, di-tert-butyl dicarbonate, amines for N-acylation (excluding deithylamine), citronellol, carboxylic acid chlorides for N-acylation, benzyl alcohol and potassium fluoride were obtained from Sigma Aldrich. Solvents such as THF, DCM, DMSO, acetone, EtOAc, CH_3CN, EtOH, chloroform, dioxane, xylene, diethyl ether, toluene, diethylamine, and morpholine were obtained from the local supplier “Vecton”. In the case of work with organometallic compounds, THF was first dried over Na and distilled in an inert atmosphere.

The “Maestro Solo” printer was used for 3D printing. All plastics used were purchased from «Bestfilament» and were predried at 40 °C for 12 hours before use. 3D printing was carried out using the FDM method with a nozzle with a diameter of 0.4 mm. A solution of polymeric filament in an appropriate solvent was used as glue to seal the capsule.

Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker 300 MHz DPX NMR spectrometer.

The determination of capsule tightness was evaluated using a Shimadzu GCMS QP-2010 SE gas chromatography–mass spectrometer (electron ionization method).

2. 3D design of capsules

To select the appropriate design of capsules for storing reagents, the ratio of the free internal volume to the surface area of a capsule and the possibility of printing should be considered. To quantify the rationality of each shape, a coefficient K_i was introduced. K_i is the ratio of the free internal volume of a capsule to its surface area. The surface area is directly proportional to the consumption of plastic. Therefore, the smaller the surface area and the larger the internal space are, the better the form. Thus, spheres, cubes and cylinders were selected as the simplest forms for further calculations. Although the sphere has the largest usable internal space ($K_{sphere} > K_i$) (**1**), internal and external supports were needed when 3D printing. The cylinder shape was more attractive since, at a fixed plastic consumption, its useful internal volume is greater than that of the cube ($K_{cylinder} > K_{cube}$) (*cf*. **2** and **3**).

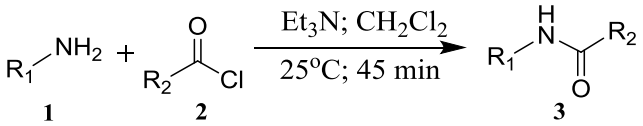
$$K_{sphere} = \frac{V_{sph}}{S_{sph}^{surf}} = \frac{^4/_3 \pi r^3}{4\pi r^2} = \frac{r}{3} = \frac{a}{3}, if\ (r = a) \quad \textbf{1}$$

$$K_{cylinder} = \frac{V_{cul.}}{S_{cul.}^{surf}} = \frac{\pi r^2 h}{2\pi r h + 2\pi r^2} = \frac{r}{4} = \frac{a}{4}, if\ \ r = h = a \quad \textbf{2}$$

$$K_{cube} = \frac{V_{cube}}{S_{cube}^{surf}} = \frac{a^3}{6a^2} = \frac{a}{6} \quad \textbf{3}$$

3. General procedure for the selected chemical reactions

3.1 Typical procedure for the N-acylation reaction.

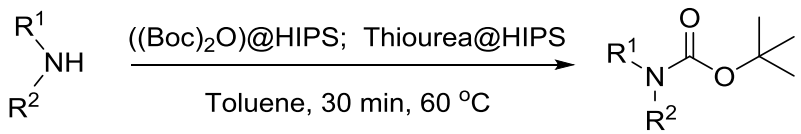


12.5 mmol of triethylamine, 11 mmol of the corresponding amine (**1a-1n**) and 10 mmol of acyl halide **2** were separately sealed in PLA capsules. The total amount of PLA was 550 mg. Then, 20 mL of DCM was added to a round-bottom flask. Then, plastic capsules with triethylamine and acyl halide were immersed in the reaction mixture. When stirring for 1 min, the capsules were completely dissolved, and the reagents were released. The resulting mixture was stirred at room temperature for 45 min. Then, 20 mL of DCM (or EtOAc, MeCN, or 2-Me-THF) was added to the flask and mixed with 50 mL of 1 M HCl in a separating funnel. The organic layer was separated and evaporated to a minimum volume. Then, 50 mL of diethyl ether was added to the resulting residue. In this case, the PLA precipitated and was then filtered through cotton wool. The filtrate was dried over anhydrous sodium sulfate, filtered and removed from the solvent. A colorless amide powder was obtained.

In the case of obtaining N-(pyridin-4-yl)benzamide **3f**, after 45 min of stirring, the mixture was transferred to a separating funnel, and 50 mL of 1 M HCl solution was added. The organic (lower) phase was drained off, and the dichloromethane was evaporated. In the dry residue, pure PLA was quantitatively obtained. The remaining white aqueous layer was saturated with NaCl. The resulting suspension of amide in water was filtered and washed with cold water and cold dichloromethane.

In the case of obtaining N,N'-ethanediyl-bis-benzamide **3h** obtaining, after the addition of 50 mL of 1 M HCl solution, the organic (lower) phase was removed, and the dichloromethane was evaporated. In the dry residue, pure PLA was quantitatively obtained. The aqueous phase was filtered on a filter. Since the amide is insoluble in neither dichloromethane nor water, the precipitate obtained on the filter was washed consequently with warm dichloromethane and water.

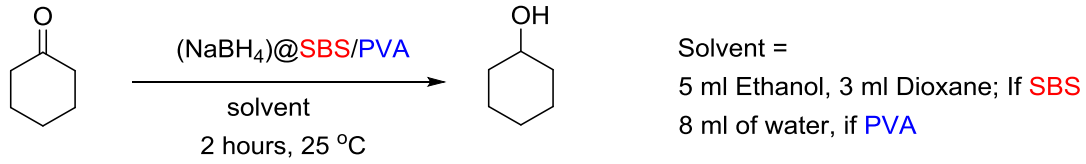
3.2 Typical procedure for the Boc-protection of amines



15.2 mg (0.2 mmol) of thiourea and 436.5 mg (2.0 mmol) of $(Boc)_2O$ were encapsulated in HIPS capsules, separately. The total amount of HIPS was 350 mg. Then, 2.0 mmol of the amine

(aniline or morpholine), capsules with thiourea and $(Boc)_2O$ were placed in a round-bottom flask with 10 mL of toluene. Within 5 min, the plastic capsules were completely dissolved, and the reagents were completely released. The mixture was stirred at 60 °C for 30 min. After filtration, the solvent was evaporated, and the viscous residue was purified by column chromatography with silica gel. Elution was performed using a mixture of EtOAc with hexane (1:1). After evaporation of the solvents, a colorless solid was obtained.

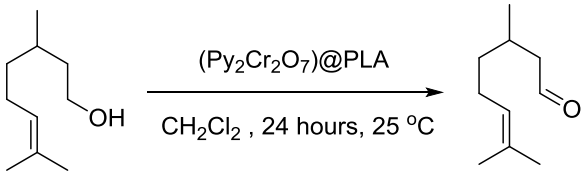
3.3 Procedure for the reduction of a ketone with sodium borohydride



With SBS capsules. First, 190.0 mg (5 mmol) of $NaBH_4$ was encapsulated in SBS. The total amount of SBS plastic was 110 mg. Capsules with a reducing agent were mixed with 5 mL of ethanol and 3 mL of dioxane. Then, 981.5 mg (10 mmol) of cyclohexanone was added, and the mixture was stirred for 2 hours at 25 °C. The reaction mixture was then evaporated and mixed with 20 mL of water. The resulting suspension was extracted with ether (3*20 mL). The organic phases were combined, washed with brine solution and dried over anhydrous $NaSO_4$. After solvent evaporation, the residue was distilled in vacuo.

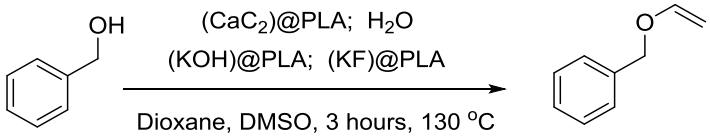
With PVA capsules. 190.0 mg (5 mmol) of $NaBH_4$ was encapsulated in PVA. The total amount of PVA plastic was 120 mg. Distilled water (8 mL) was utilized as the solvent. Then, 981.5 mg (10 mmol) of cyclohexanone was added, and the mixture was stirred for 2 hours at 25 °C. The resulting turbid solution was extracted with ether (3*20 mL). The organic phases were combined, washed with brine solution and dried over anhydrous $NaSO_4$. After solvent evaporation, the residue was distilled in vacuo.

3.4 Procedure for the oxidation reaction with pyridinium dichromate.



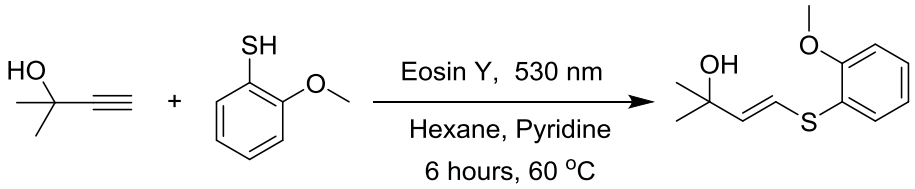
733 mg (2.0 mmol) of pyridinium dichromate was encapsulated in PLA. The total amount of PLA was 310 mg. Encapsulated pyridinium dichromate and 200 mg (1.3 mmol) of citronellol were then placed in 2 mL of DCM. Within 2 min, the plastic capsule was completely dissolved, and the reagents were completely released. The reaction mixture was stirred for 24 hours at room temperature. The solution was filtered through a plug of silica gel and washed with 50 mL of diethyl ether. The combined organic phases were washed with 1 M HCl and then with brine. After solvent evaporation, the residue was distilled in *vacuo*.

3.5 Procedure for the nucleophilic addition (vinylation) reaction.



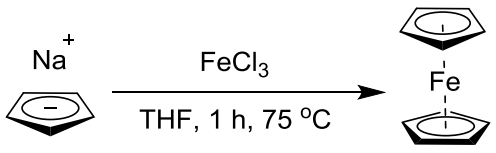
512.0 mg (8.0 mmol) of CaC_2, 255.2 mg (4.4 mmol) of KF and 246.4 mg (4.4 mmol) of KOH were separately encapsulated in PLA. The total amount of PLA was 820 mg. Encapsulated reagents with 433.0 mg (4.0 mmol) of benzyl alcohol and 576.0 mg (32.0 mmol) of H_2O were dissolved in a mixture of 25 mL of DMSO with 5 mL of dioxane. The flask was sealed, and the mixture was heated at 130 °C for 3 h with vigorous stirring. After completion of the reaction, the mixture was filtered and saturated with NaCl, and the vinyl ether was extracted with hexane. Then, the organic phases were combined and dried over anhydrous $NaSO_4$. After evaporation of hexane, the vinylated product was obtained in high purity.

3.6 Procedure for light-mediated thiol–yne click reaction.



189 µL (2.0 mmol) of 2-methylbut-3-yn-2-ol and 270 µL (2.2 mmol) of 2-methoxybenzenethiol were separately encapsulated in PLA. The total amount of PLA was 382 mg. Encapsulated reagents with 4.0 mg (6 µmol) of Eosin Y were dissolved in a mixture of 400 µL of hexane with 400 µL of pyridine. The test tube was irradiated by a LED beam (λ=530 nm) under open air. Irradiation was carried out for 6 hours at a temperature of 60 °C. After completion of the reaction, the solvents were evaporated. The target substance was purified by column chromatography.

3.7 Ferrocene generation via the encapsulation technique/Schlenk technique/open-air procedure.



<u>Warnings:</u> Sodium cyclopentadienide solution is extremely pyrophoric. Handling it in the open air requires special care!

Sodium cyclopentadienide (NaCp) was obtained according to the standard method.[1]

To obtain a solution of iron chloride in THF, 2.7 g (16.6 mmol) of anhydrous $FeCl_3$ was added into a vial with a septum, and under ice cooling, 20 mL of dry THF was added dropwise.

Each of the three techniques of ferrocene synthesis involves the mixing of two solutions: $FeCl_3$ and NaCp. Purification was carried out identically for each method.

1) Reaction in open air using the encapsulation technique.

THF solutions of ferric chloride (0.83 M) and NaCp (3.3 M) were placed in HIPS capsules separately and sealed in an inert atmosphere. To check the stability of the compounds inside the capsules, they were placed in a refrigerator at 5 °C for a day.

Capsules with solutions of $FeCl_3$ and NaCp were placed into a flask containing 20 mL of dry THF under rapid stirring and cooled to 0 °C. After the capsules were added, the flask was loosely capped to minimize the evaporation of THF and prevent saturation of the reaction mixture with atmospheric oxygen. The reaction mixture was stirred for an hour at 75 °C and then poured into a beaker with 100 mL of 5% HCl. The solid phase (amorphous heterogeneous precipitate) was filtered through a Schott filter with a porosity of 40 μm, boiled with 100 mL of acetone, cooled to room temperature, and filtered through Celite. Then, the dried precipitate was distilled in *vacuo* at 200-230 °C. The yield of ferrocene was 76%.

2) Reaction in open air without encapsulation.

Attempts have been made to mix solutions of $FeCl_3$ and NaCp both by instantaneous mixing and dropwise mixing. However, the reaction mixture was periodically ignited, which led to a significant loss of reagents. After the standard purification technique, the yield of ferrocene was only 5%.

3) Reaction in an inert atmosphere using the Schlenk technique.

The $FeCl_3$ and NaCp solutions were prepared in an inert atmosphere using a Schlenk manifold. The $FeCl_3$ addition to the NaCp was carried out dropwise through a septum under argon flow. The mixture was stirred for an hour at 75 °C and then purified according to the aforementioned procedure. The yield of ferrocene was 81%.

4. Spectroscopic data of products 3-9

N,N-diethylbenzamide (3a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 3.52 (br s, 2H), 3.22 (br s, 2H), 1.21 (br s, 3H), 1.08 (br s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.02, 137.09, 128.85, 128.15, 126.02, 43.07, 39.02, 13.97, 12.70.

HRMS (EI, m/z) calcd. for $[C_{11}H_{15}NO+H]^+$, 178.1226; found 178.1226.

N-Hexylbenzamide (3b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 6.93 (br s, 1H), 3.35 (dd, *J* = 13.3, 7.0 Hz, 2H), 1.61 – 1.48 (m, 2H), 1.36 – 1.16 (m, 6H), 0.84 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.69, 134.84, 131.11, 128.33, 126.98, 40.14, 31.49, 29.57, 26.67, 22.52, 13.97.

HRMS (EI, m/z) calcd. for $[C_{13}H_{19}NO+H]^+$, 206.1539; found 206.1542.

4-Benzoylmorpholine (3c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 5H), 3.57 (s, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.01, 135.10, 129.54, 128.24, 126.80, 66.52, 47.88, 42.28.

HRMS (EI, m/z) calcd. for $[C_{11}H_{13}NO_2+H]^+$, 192.1019; found 192.1022.

N-*tert*-butylbenzamide (3d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 2H), 7.48 – 7.38 (m, 3H), 5.93 (br s, 1H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.00, 135.99, 131.08, 128.48, 126.78, 51.63, 28.92.

HRMS (EI, m/z) calcd. for $[C_{11}H_{15}NO+H]^+$, 178.1226; found 178.1228.

N-(2,4,6-trimethylphenyl)benzamide (3e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.56 (m, 1H), 7.48 (m, 2H), 7.39 (s, 1H), 6.93 (s, 2H), 2.30 (s, 3H), 2.24 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.18, 137.19, 135.43, 134.79, 131.82, 131.37, 129.13, 128.85, 127.34, 21.09, 18.50.

HRMS (EI, m/z) calcd. for $[C_{16}H_{17}NO+H]^+$, 240.1383; found 240.1385.

N-(pyridin-4-yl)benzamide (3f)

^{1}H NMR (400 MHz, DMSO) δ 12.04 – 11.92 (m, 1H), 8.76 (d, *J* = 7.1 Hz, 2H), 8.49 (d, *J* = 7.1 Hz, 2H), 8.15 (d, *J* = 7.8 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.58 (dd, *J* = 7.8 Hz, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 167.31, 153.49, 141.95, 133.04, 132.86, 128.58, 115.26.

HRMS (EI, m/z) calcd. for $[C_{12}H_{10}N_2O+H]^+$, 199.0866; found 199.0867.

N-benzoyltryptamine (*N-(2-(1H-indol-3-yl)ethyl)benzamide*) (3g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 7.69 (d, *J* = 7.3 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.41 – 7.33 (m, 3H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 1.6 Hz, 1H), 6.37 (br s, 1H), 3.80 (dd, *J* = 12.7, 6.6 Hz, 2H), 3.09 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.73, 136.60, 134.74, 131.46, 128.62, 127.42, 126.96, 122.33, 122.26, 119.54, 118.79, 112.89, 111.49, 40.45, 25.38.

HRMS (EI, m/z) calcd. for $[C_{17}H_{16}N_2O+Na]^+$, 287.1155; found 287.1159.

N,N'-ethanediyl-*bis*-benzamide (3h)

^{1}H NMR (400 MHz, DMSO) δ 8.59 (br s, 2H), 7.88 – 7.82 (m, 4H), 7.55 – 7.49 (m, 2H), 7.49 – 7.42 (m, 4H), 3.49 – 3.42 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 166.50, 134.53, 131.06, 128.20, 127.16, 39.73.

HRMS (EI, m/z) calcd. for $[C_{16}H_{16}N_2O_2+H]^+$, 269.1285; found 269.1287.

N,N-Diethyl-*p*-toluamid (3i)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 3.53 (br s, 2H), 3.30 (br s, 2H), 2.38 (s, 3H), 1.18 (br s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.58, 139.15, 134.54, 129.07, 126.47, 43.38, 39.34, 21.43, 14.27, 13.13.

HRMS (EI, m/z) calcd. for $[C_{12}H_{17}NO+H]^+$, 192.1383; found 192.1383.

4-*tert*-butyl-*N,N*-diethylbenzamide (3j)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 3.53 (br s, 2H), 3.29 (br s, 2H), 1.32 (s, 9H), 1.16 (br s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.51, 152.25, 134.41, 126.21, 125.29, 43.32, 39.24, 34.75, 31.29, 14.31, 12.95.

HRMS (EI, m/z) calcd. for $[C_{15}H_{23}NO+H]^+$, 234.1852; found 234.1854.

3,4-dichloro-*N,N*-diethylbenzamide (3k)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.20 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.51 (br s, 2H), 3.24 (br s, 2H), 1.21 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.90, 137.11, 133.60, 132.98, 130.68, 128.71, 125.81, 43.47, 39.67, 14.32, 12.92.

HRMS (EI, m/z) calcd. for $[C_{11}H_{13}Cl_2NO+H]^+$, 246.0444; found 246.0446.

***N,N*-diethylpropanamide (3l)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (q, *J* = 7.0 Hz, 2H), 3.27 (q, *J* = 7.0 Hz, 2H), 2.29 (q, *J* = 7.4 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.74, 41.72, 39.93, 26.13, 14.18, 12.99, 9.49.

HRMS (EI, m/z) calcd. for $[C_7H_{15}NO+H]^+$, 130.1226; found 130.1227.

***N,N*-diethyl-*N′,N′*-dimethylurea (3m)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (q, *J* = 7.1 Hz, 4H), 2.76 (s, 6H), 1.08 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.38, 42.07, 38.80, 13.35.

HRMS (EI, m/z) calcd. for $[C_7H_{16}N_2O+H]^+$, 145.1335; found 145.1340.

***N,N*-diethyl-4-methylbenzenesulfonamide (3n)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 3.21 (q, *J* = 7.2 Hz, 4H), 2.40 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.00, 137.52, 129.67, 127.11, 42.10, 21.54, 14.23.

HRMS (EI, m/z) calcd. for $[C_{11}H_{17}NO_2S+H]^+$, 228.1053; found 228.1058.

***Tert*-butyl phenylcarbamate (4)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.28 (m, 2H), 7.03 (m, 1H), 6.49 (br s, 1H), 1.52 (s, 9H). Cf. lit data.[2]

Tert-butyl morpholine-4-carboxylate (5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (m, J = 4.8 Hz, 4H), 3.41 (m, 4H), 1.46 (s, 9H). Cf. lit data.[2]

Cyclohexanol (6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (m, 1H), 2.16 (m, 1H), 1.85 (m, 2H), 1.69 (m, 2H), 1.51 (m, 1H), 1.33 – 1.04 (m, 5H). Cf. lit data.[3]

Benzyl vinyl ether (8)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H), 6.58 (dd, *J* = 14.3, 6.8 Hz, 1H), 4.78 (s, 2H), 4.32 (dd, *J* = 14.3, 2.1 Hz, 1H), 4.10 (dd, *J* = 6.8, 2.1 Hz, 1H). Cf. lit data.[4]

(E)-4-((2-Methoxyphenyl)thio)-2-methylbut-3-en-2-ol (9)

^{1}H NMR (400 MHz, Acetone-d6) δ 7.37 – 7.13 (m, 2H), 7.03 – 6.86 (m, 2H), 6.42 (d, J = 15.1 Hz, 1H), 6.12 (d, J = 15.1 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 1H), 1.32 (s, 3H), 1.32 (s, 3H). Cf. lit data.[5]

Ferrocene (10)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (s, 10H). Cf. lit data.[6]

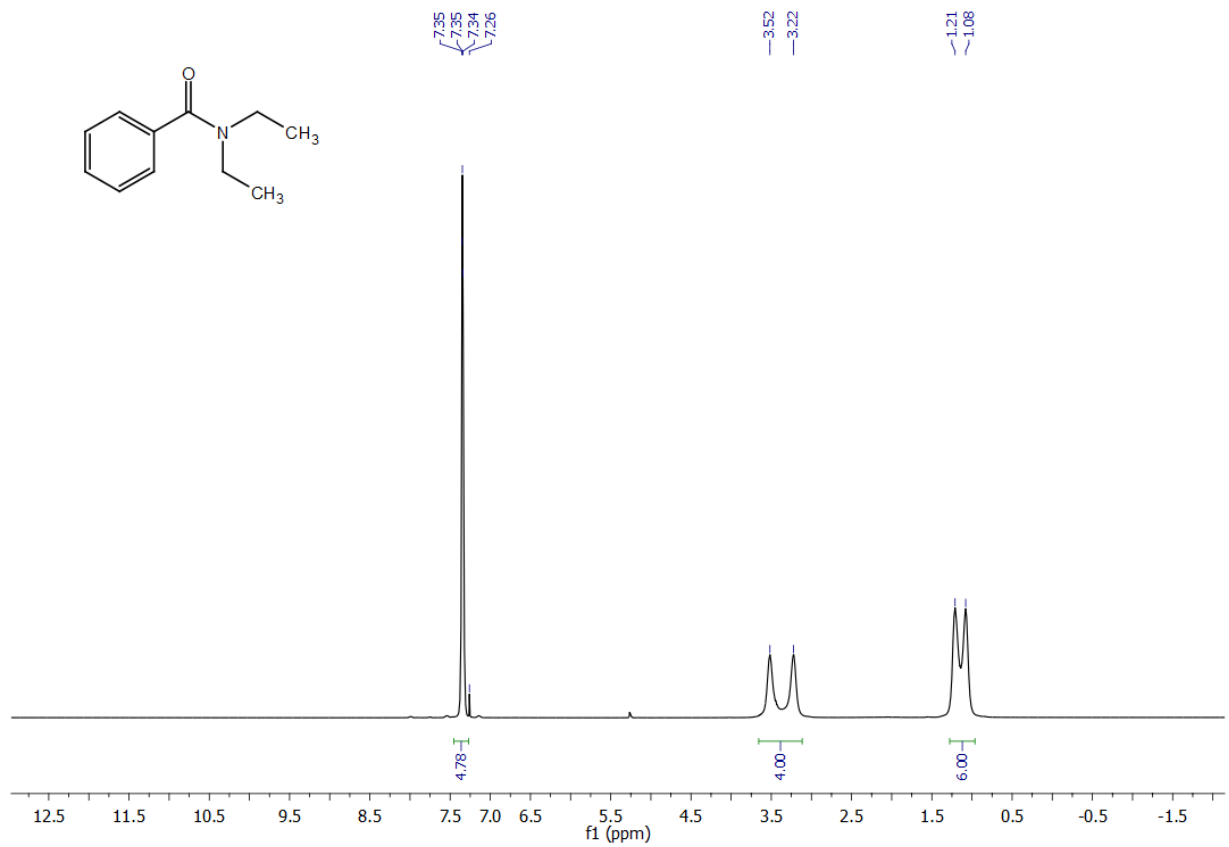


Figure S1. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of N,N-diethylbenzamide (**3a**).

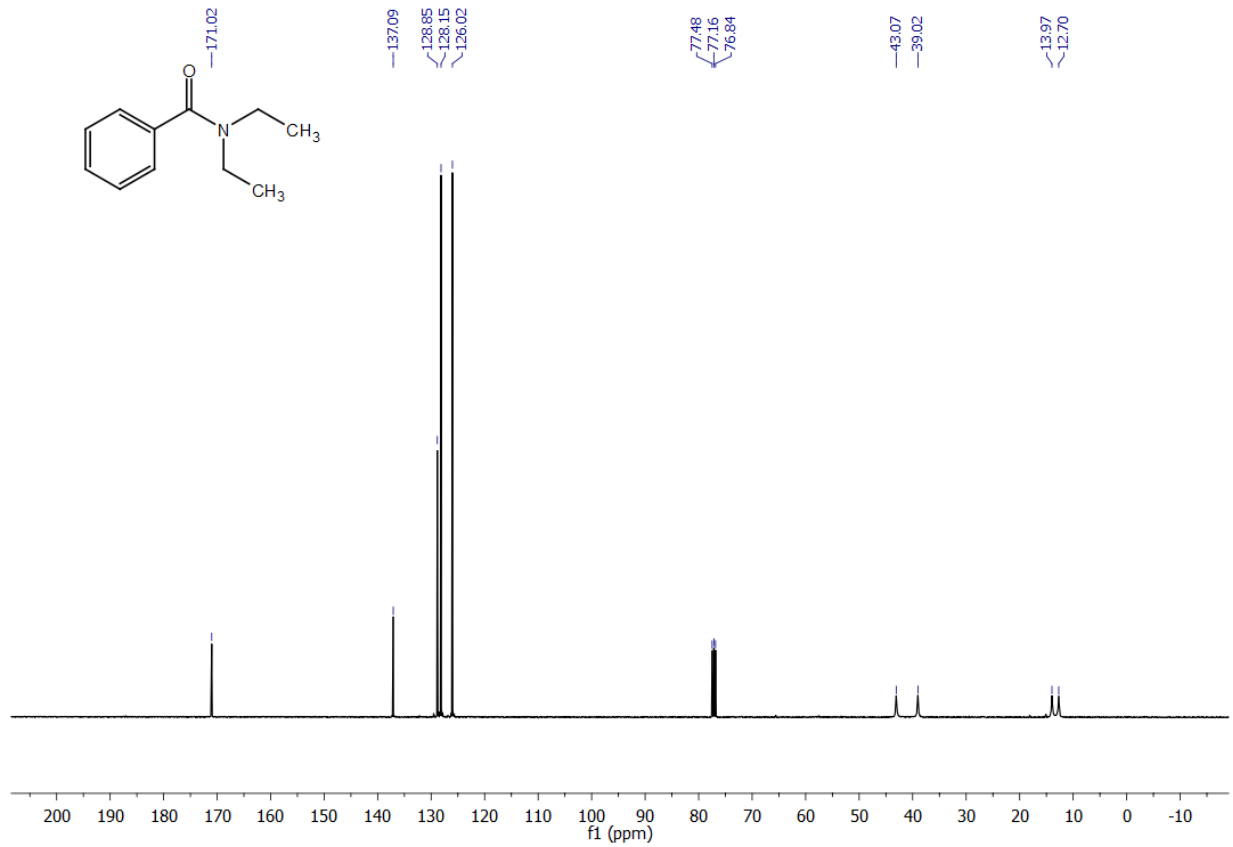


Figure S2. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of N,N-diethylbenzamide (**3a**).

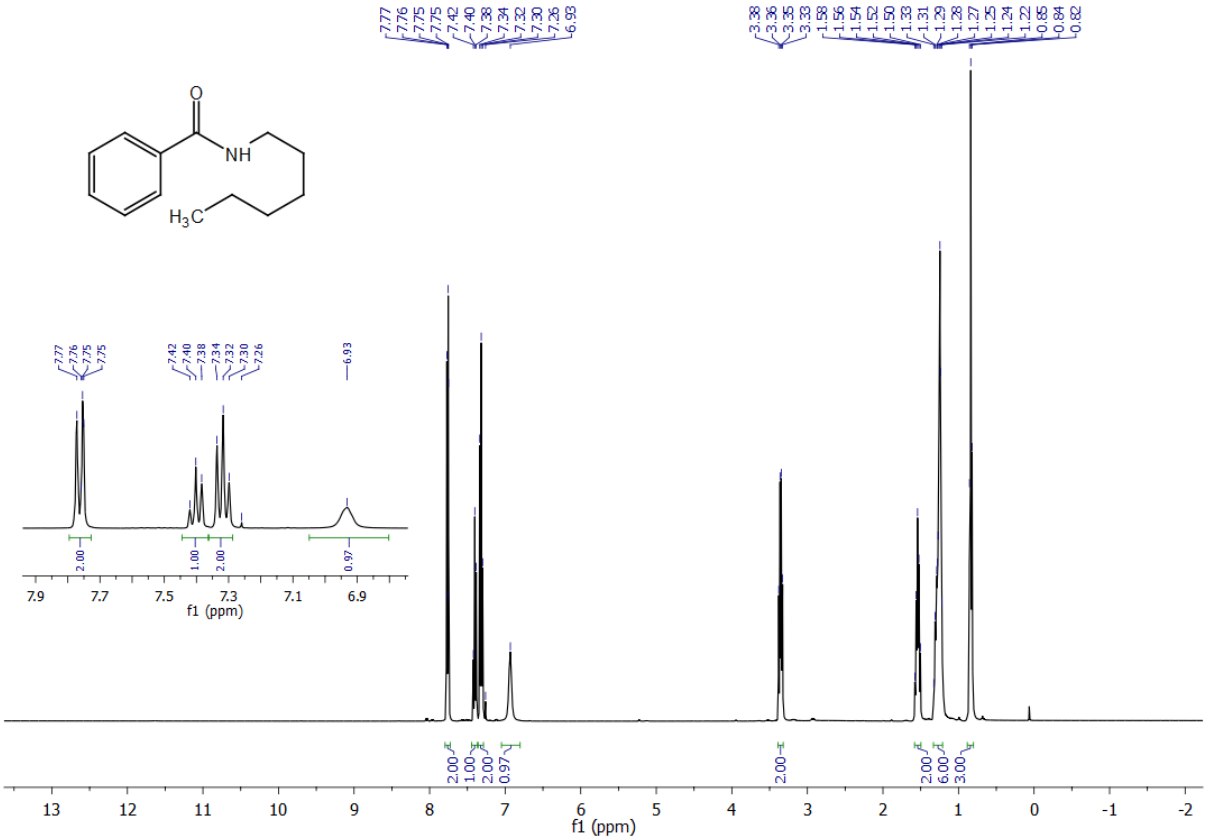


Figure S3. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of N-hexylbenzamide (**3b**).

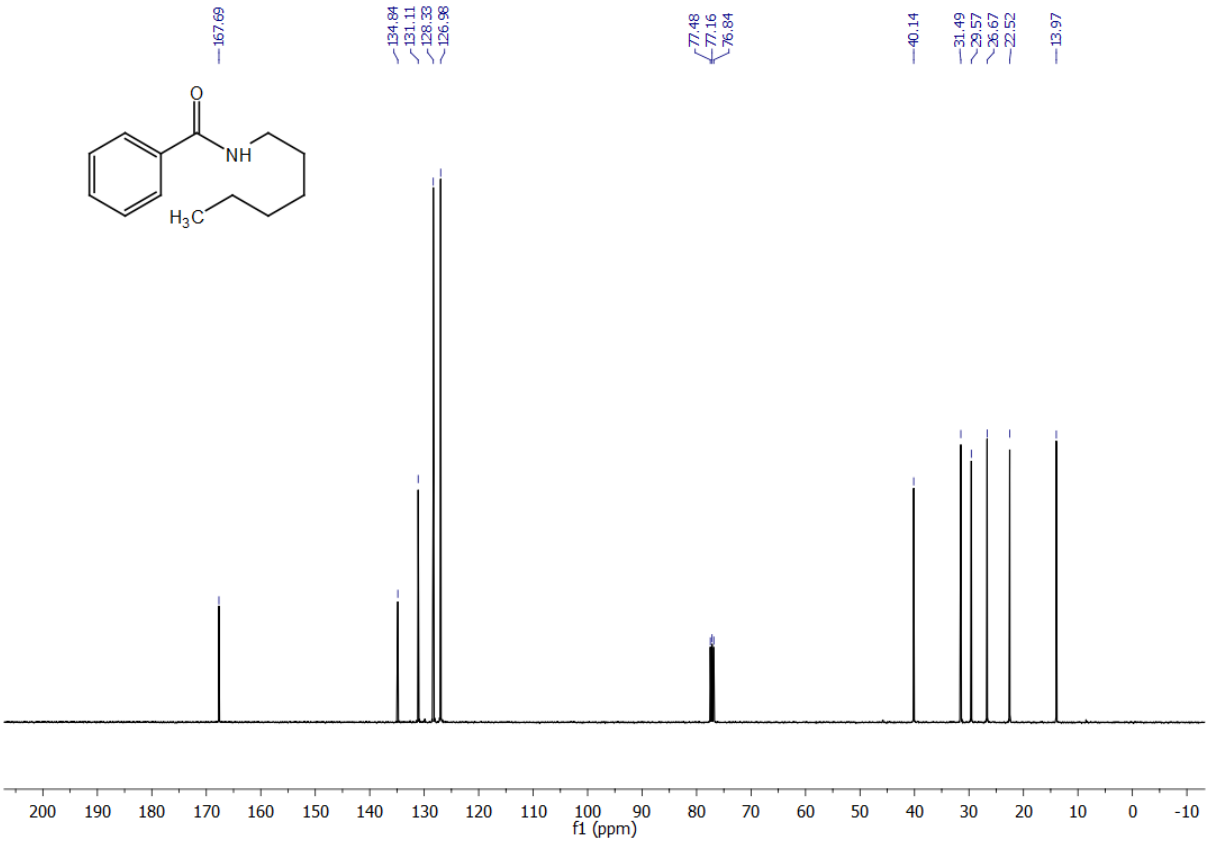


Figure S4. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of N-hexylbenzamide (**3b**).

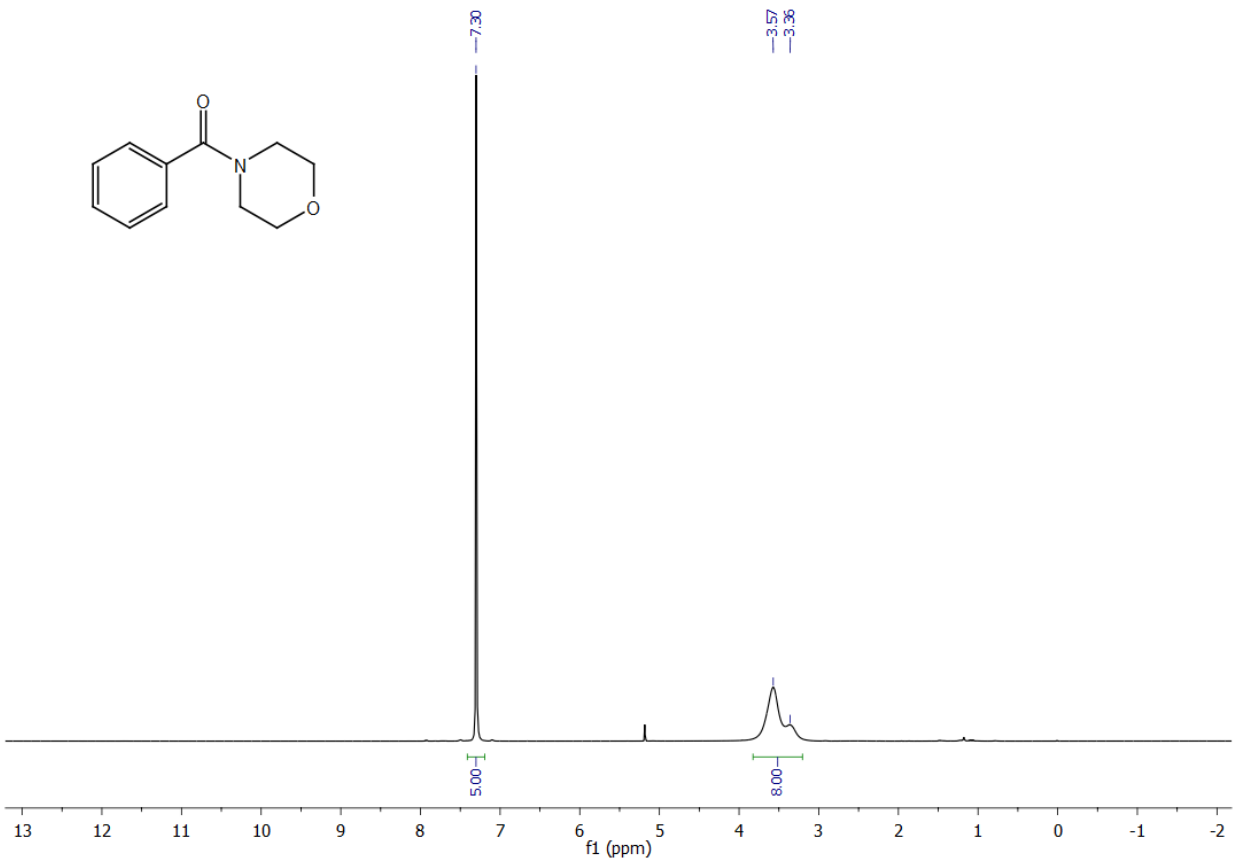


Figure S5. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of 4-benzoylmorpholine (**3c**).

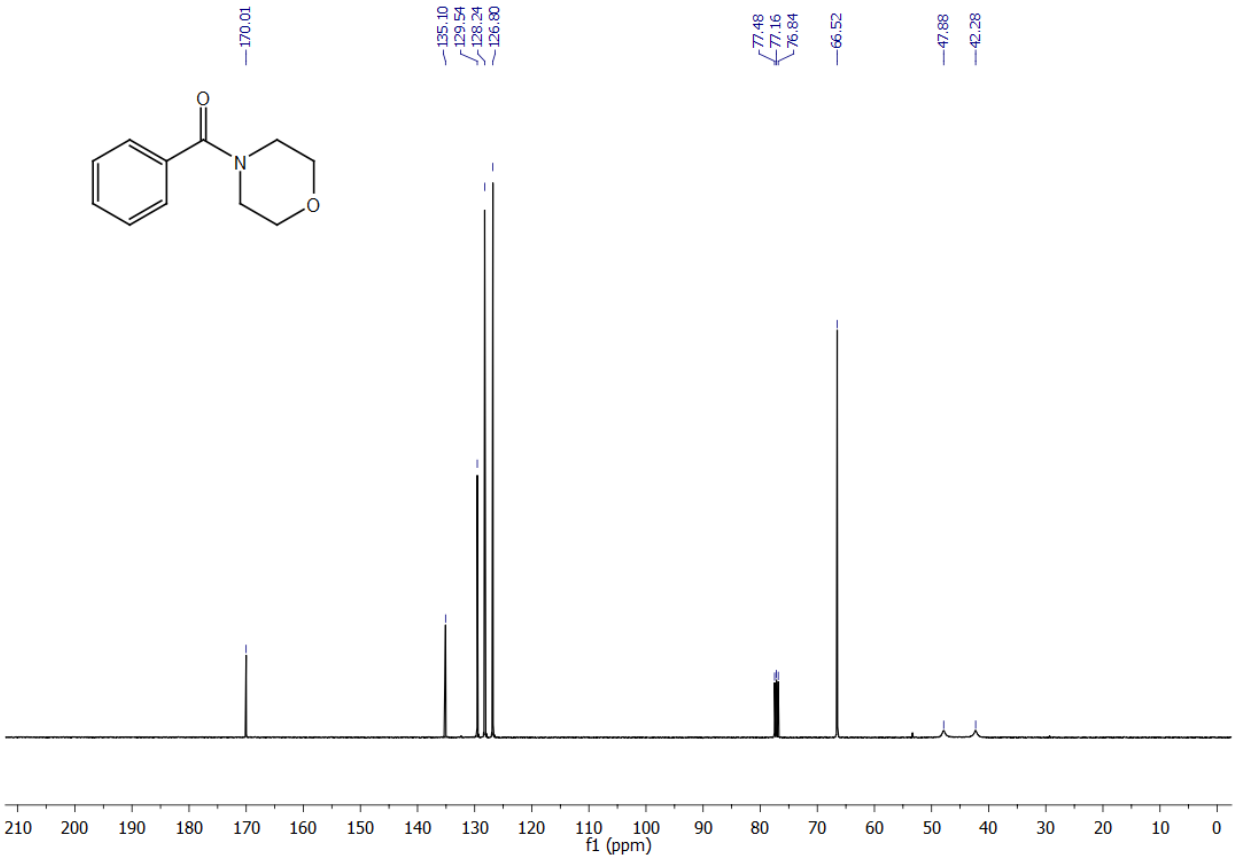


Figure S6. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of 4-benzoylmorpholine (**3c**).

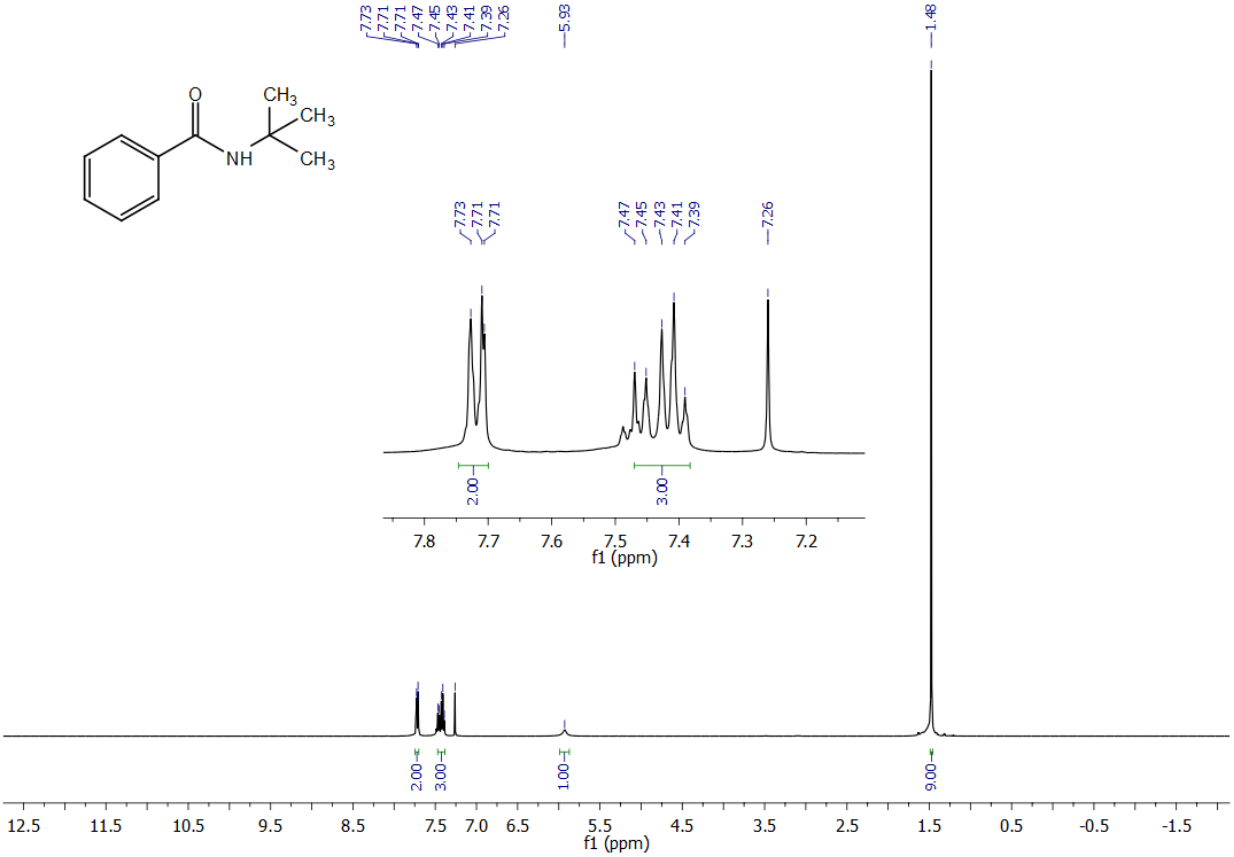


Figure S7. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of N-*tert*-butylbenzamide (**3d**).

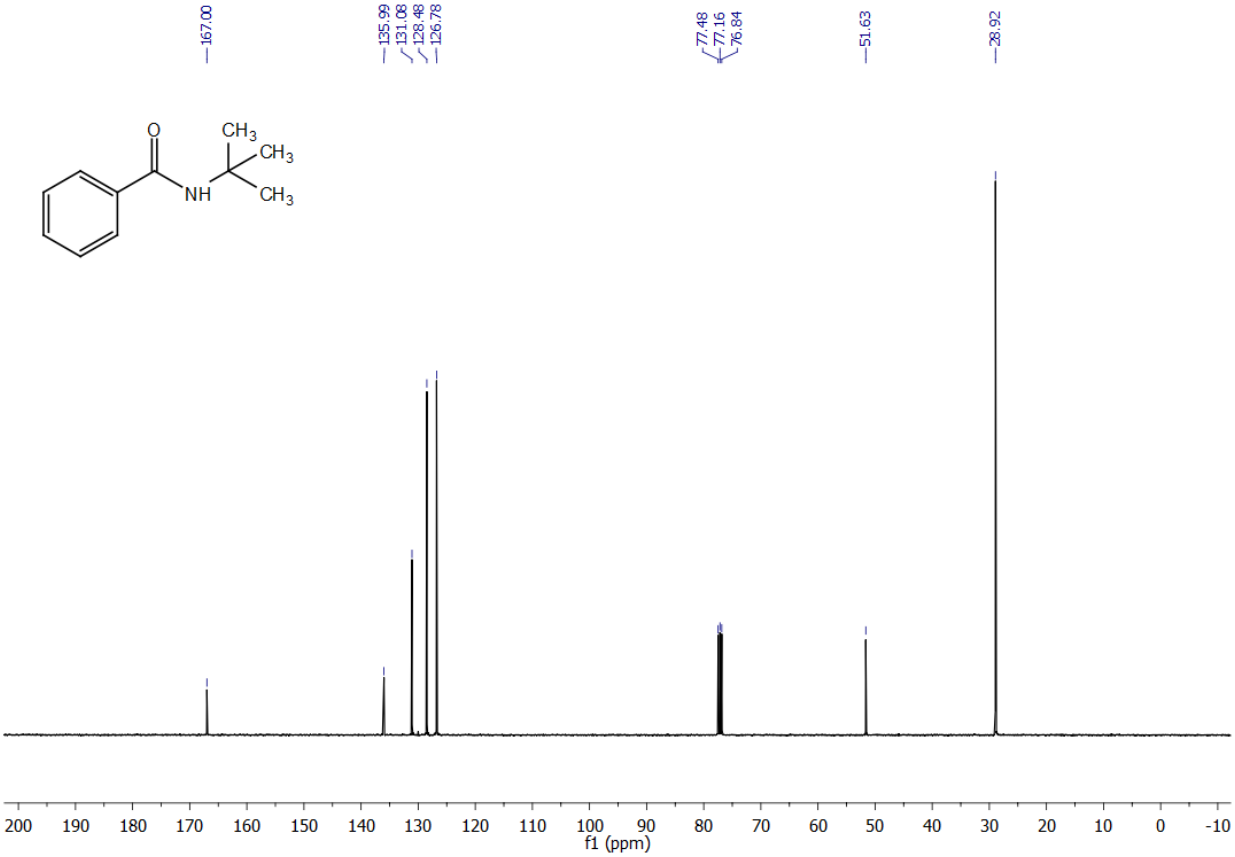


Figure S8. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of N-*tert*-butylbenzamide (**3d**).

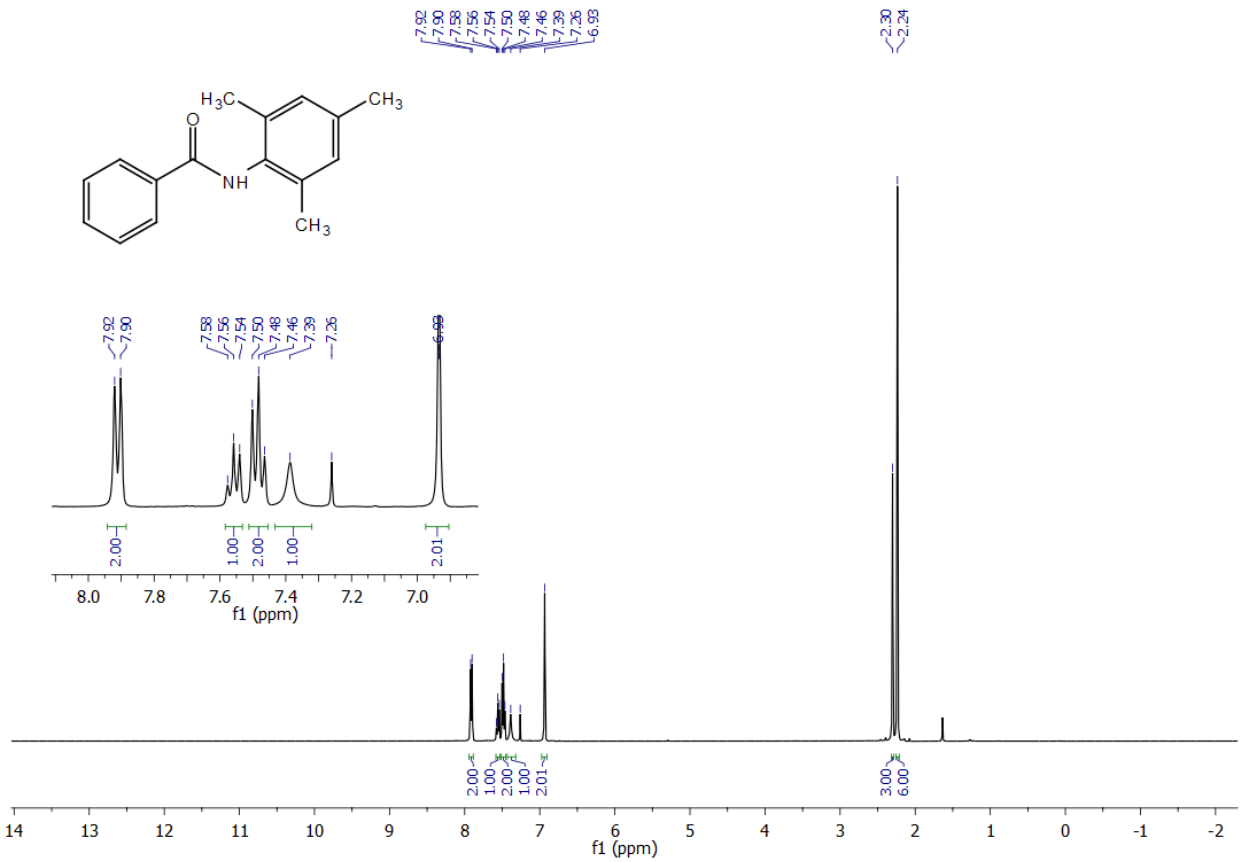


Figure S9. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of N-(2,4,6-trimethylphenyl)benzamide (**3e**).

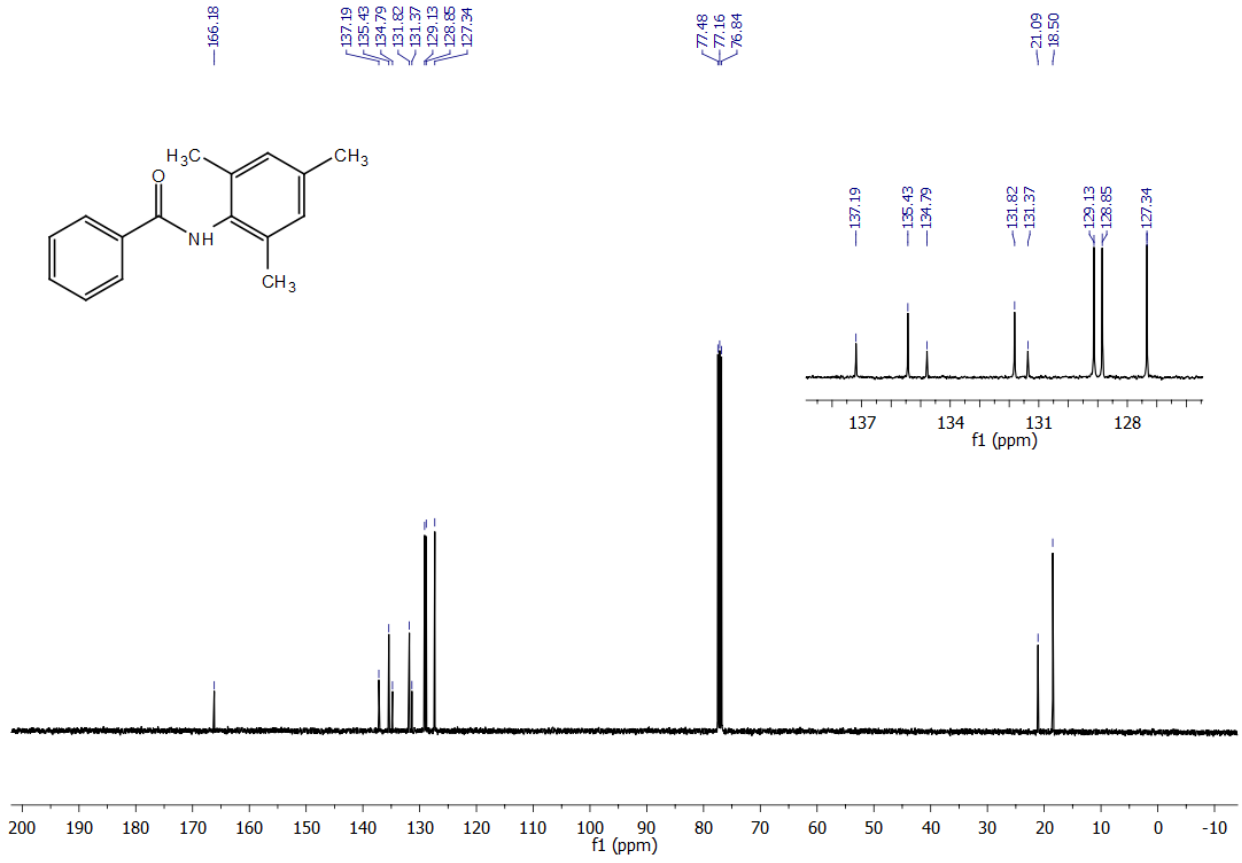


Figure S10. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of N-(2,4,6-trimethylphenyl)benzamide (**3e**).

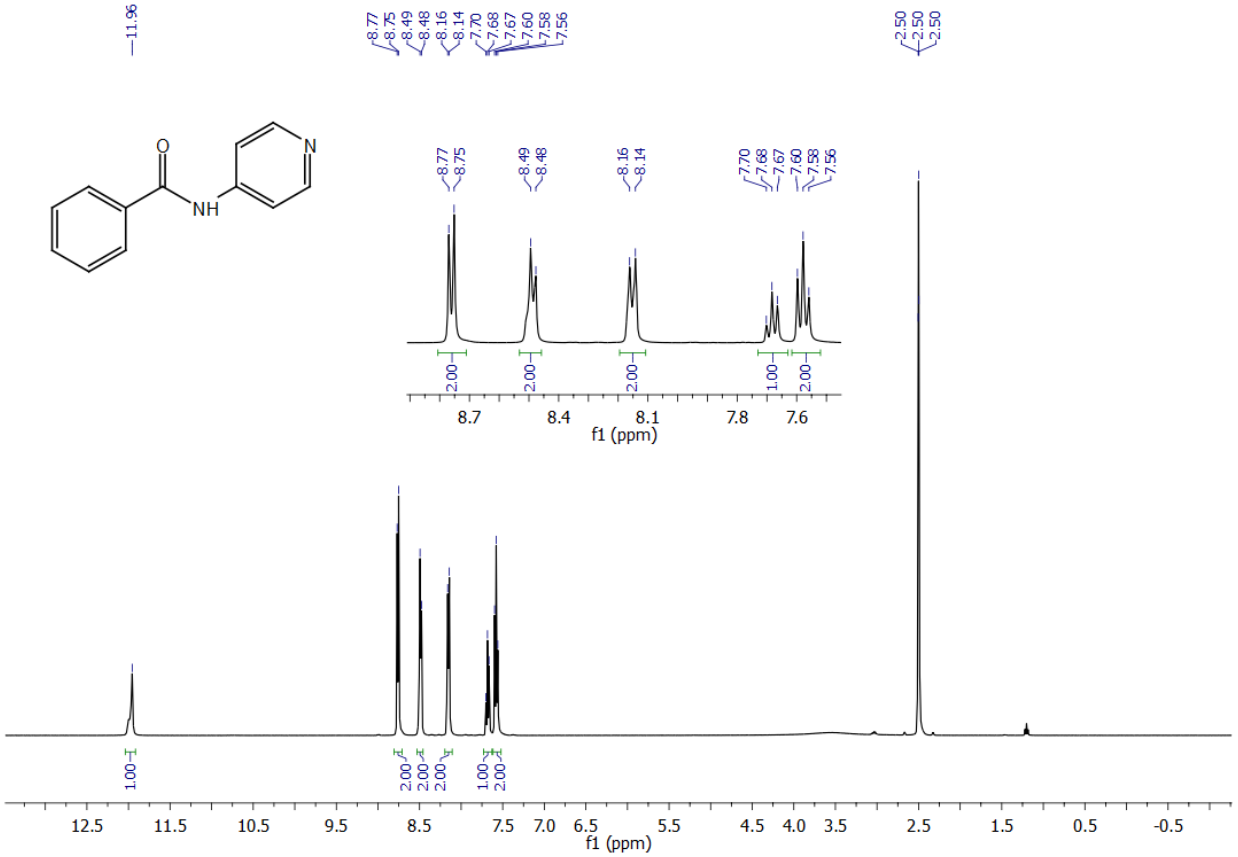


Figure S11. NMR ^{1}H spectrum ($(CD_3)_2SO$, 400 MHz) of N-(pyridin-4-yl)benzamide (**3f**).

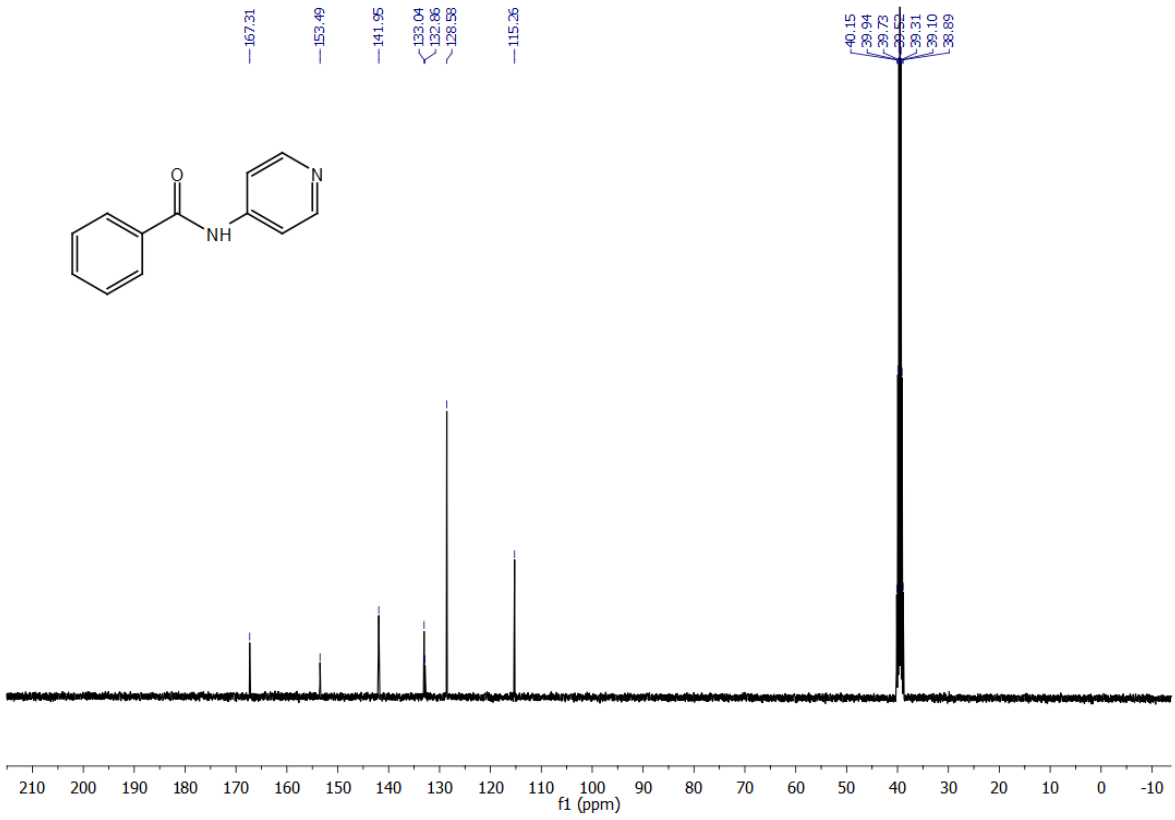


Figure S12. NMR ^{13}C spectrum ($(CD_3)_2SO$, 101 MHz) of N-(pyridin-4-yl)benzamide (**3f**).

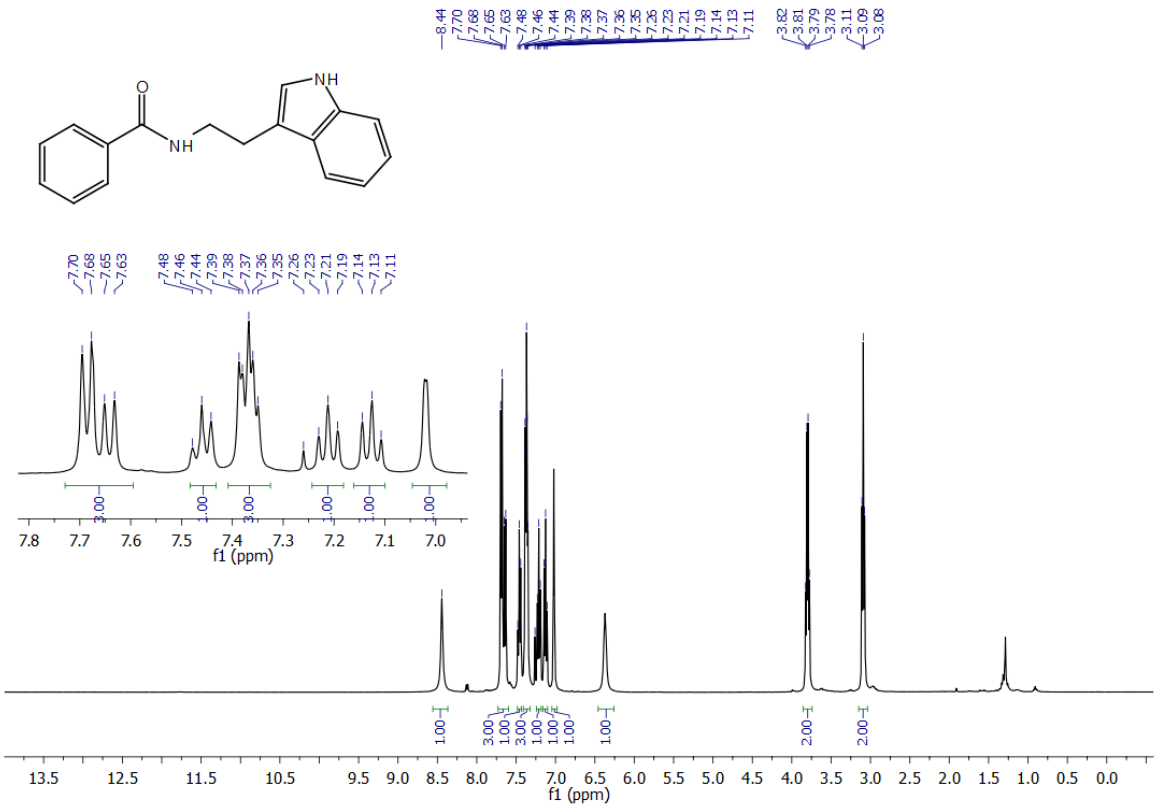


Figure S13. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of N-benzoyltryptamine (N-(2-(1H-indol-3-yl)ethyl)benzamide) (**3g**).

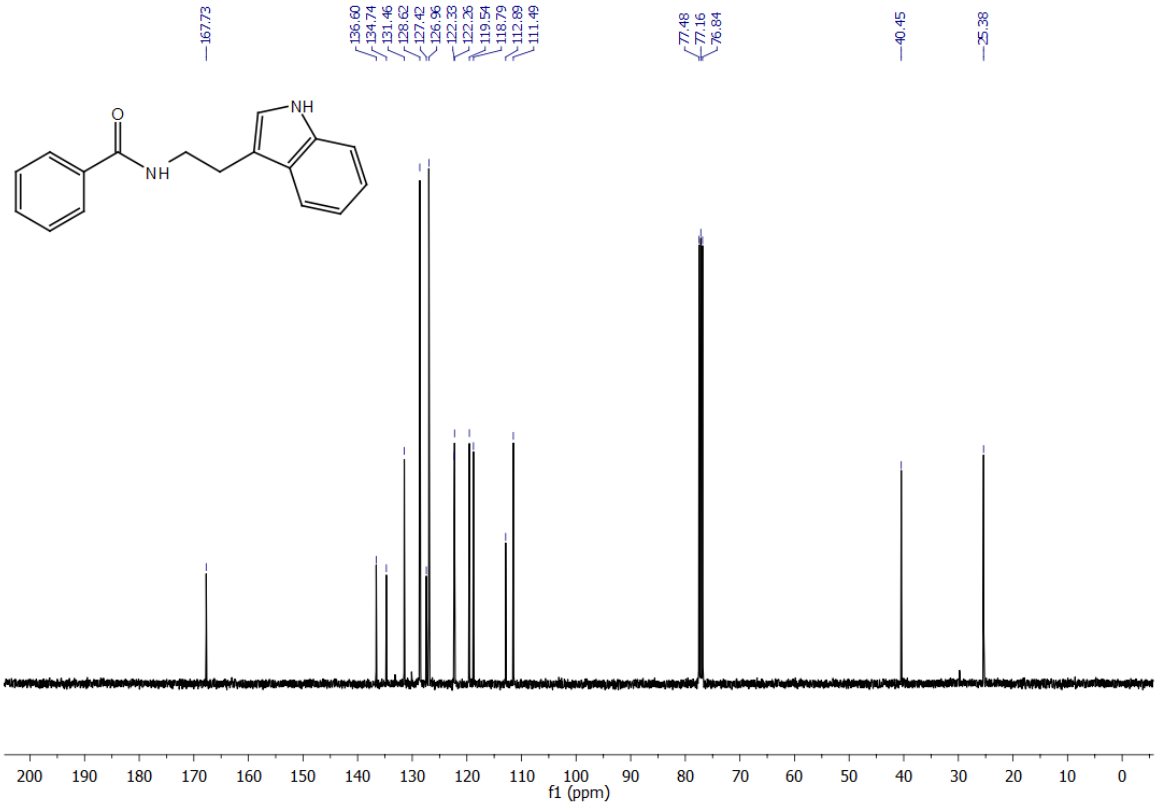


Figure S14. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of N-benzoyltryptamine (N-(2-(1H-indol-3-yl)ethyl)benzamide) (**3g**).

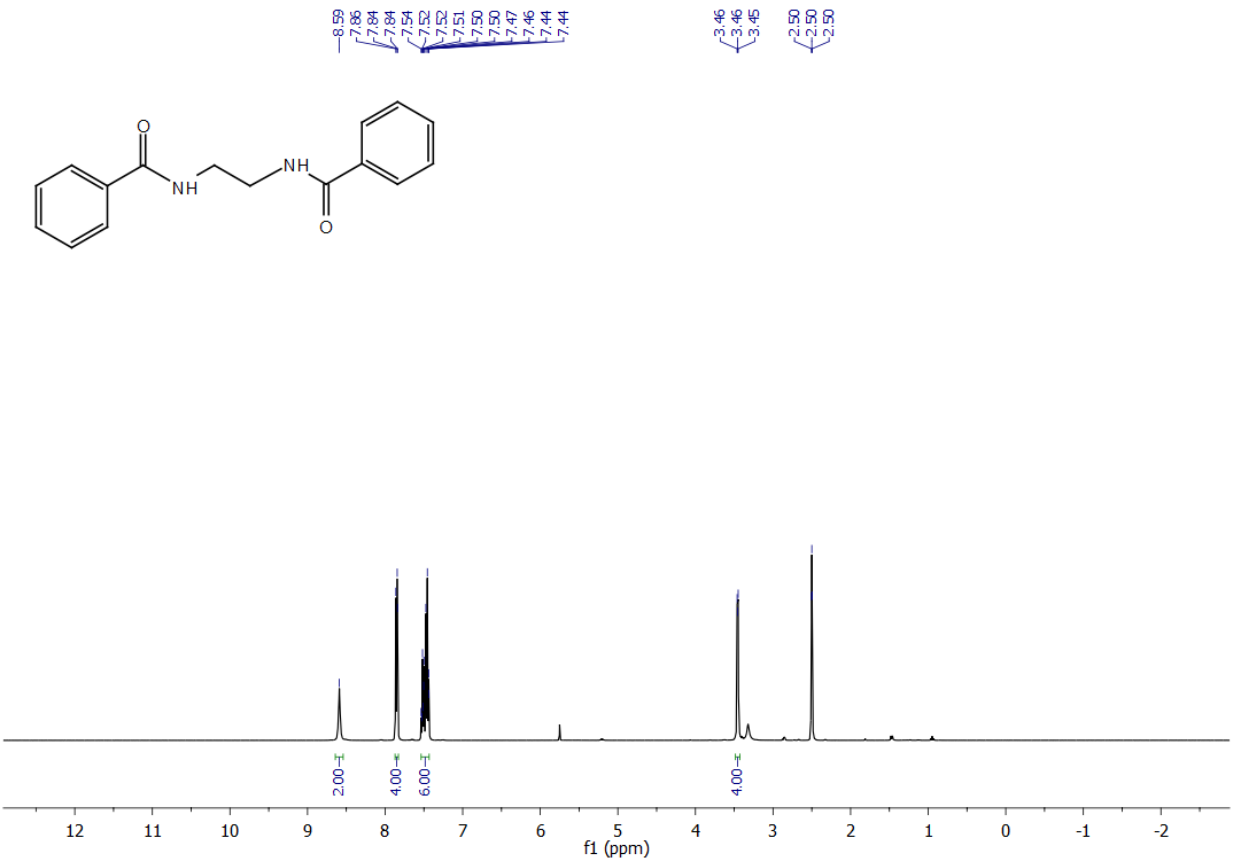


Figure S15. NMR ^{1}H spectrum ($(CD_3)_2SO$, 400 MHz) of N,N'-ethanediyl-bis-benzamide (**3h**).

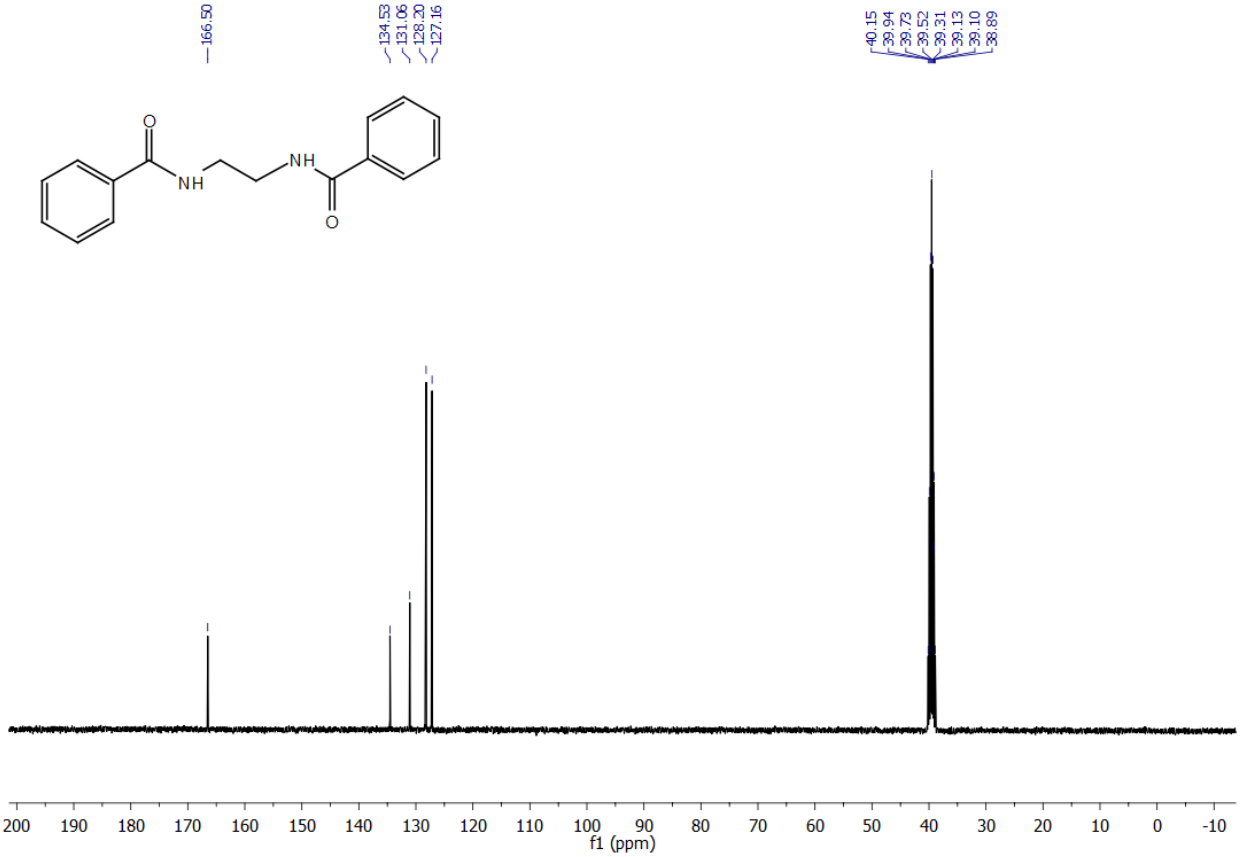


Figure S16. NMR ^{13}C spectrum ($(CD_3)_2SO$, 101 MHz) of N,N'-ethanediyl-bis-benzamide (**3h**).

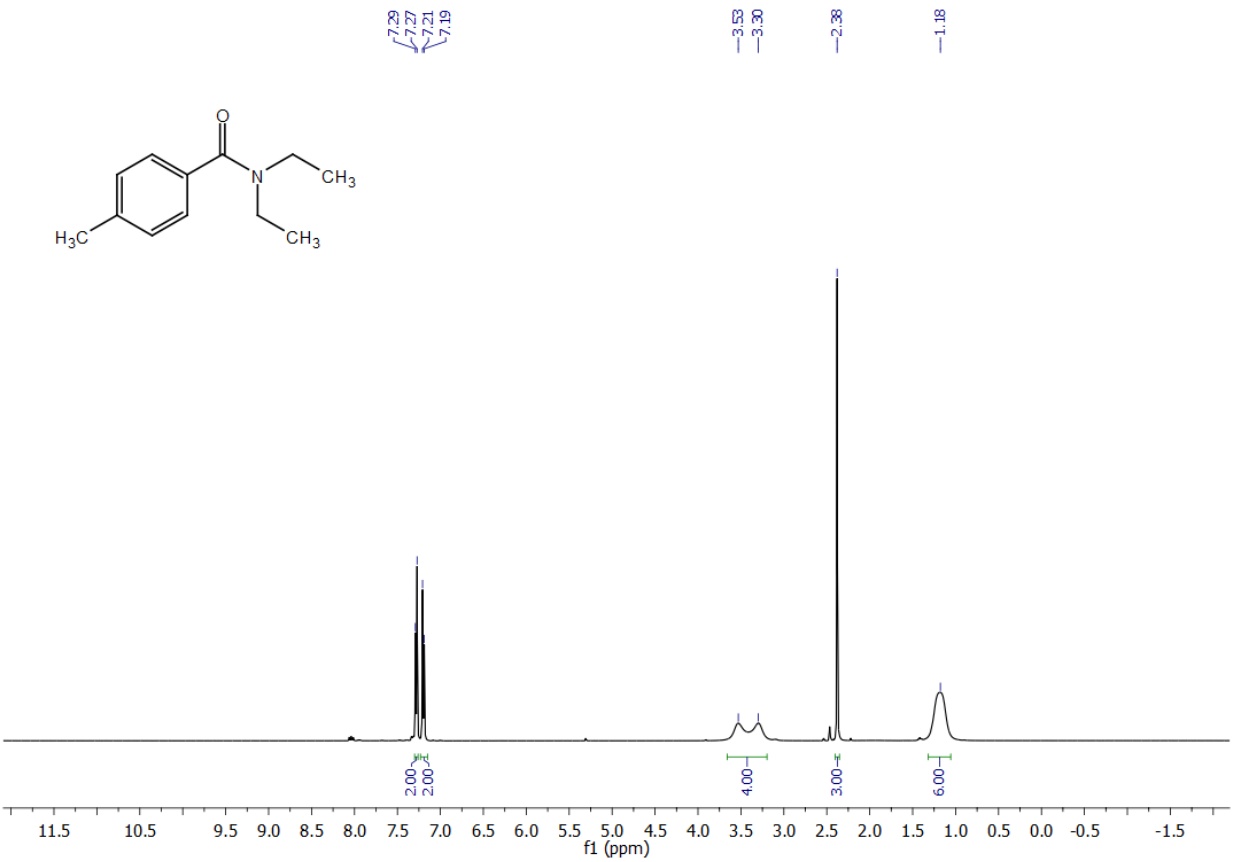


Figure S17. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of N,N-diethyl-*p*-toluamide (**3i**).

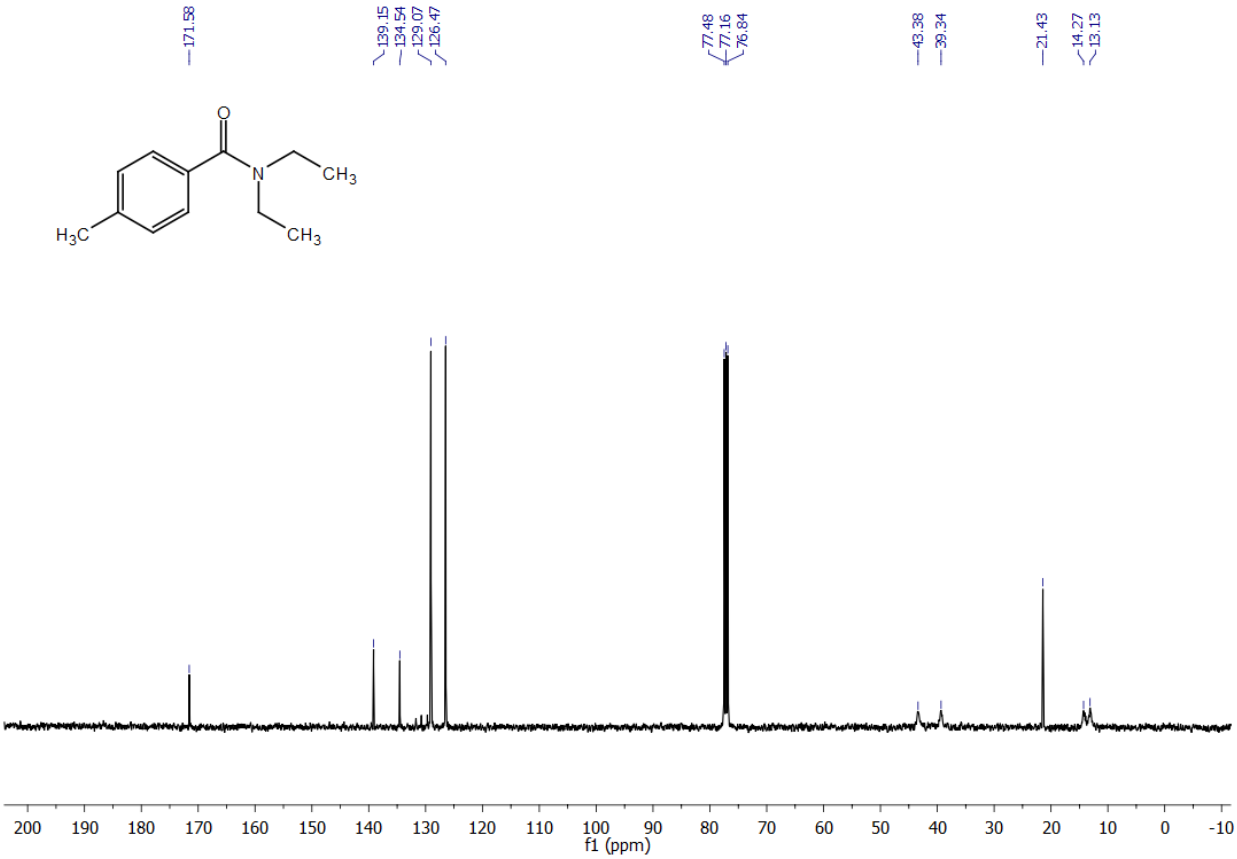


Figure S18. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of N,N-diethyl-*p*-toluamide (**3i**).

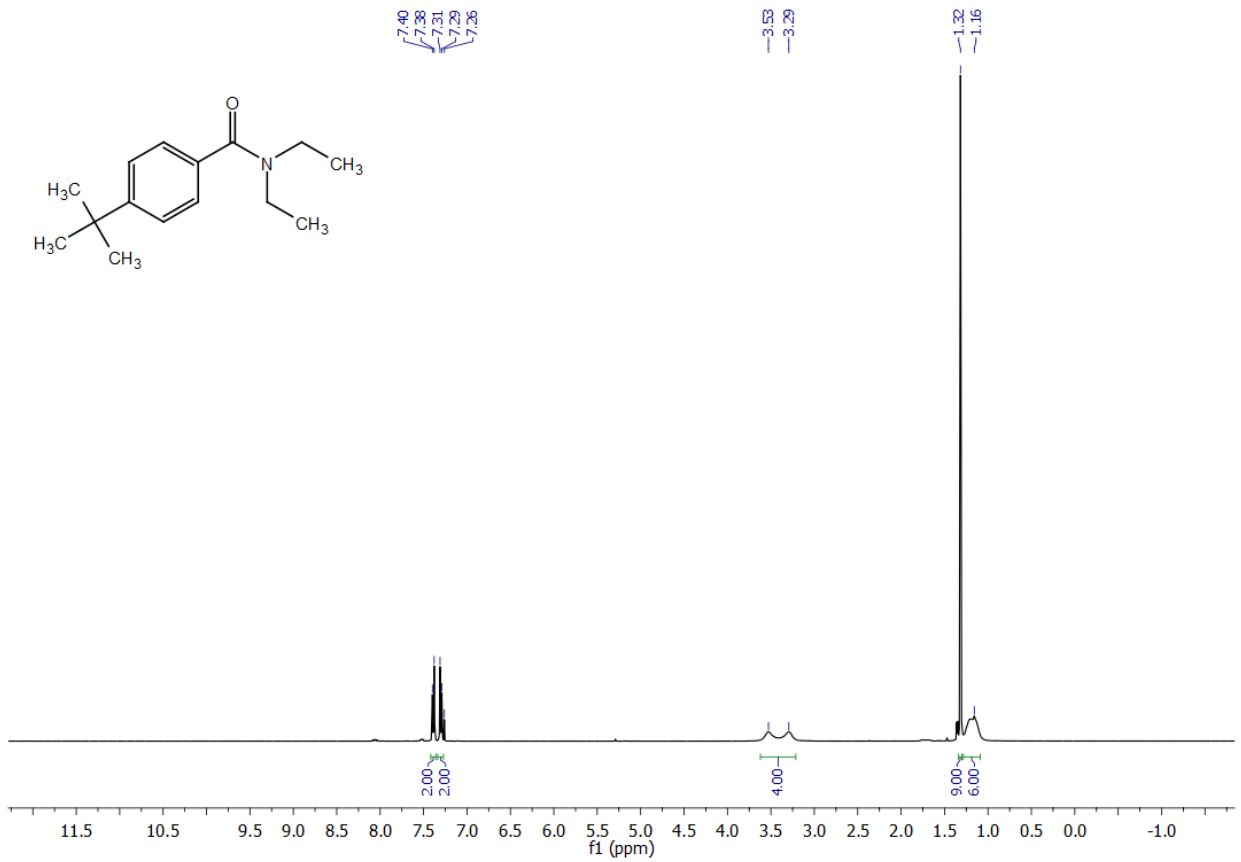


Figure S19. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of 4-*tert*-butyl-N,N-diethylbenzamide (**3j**).

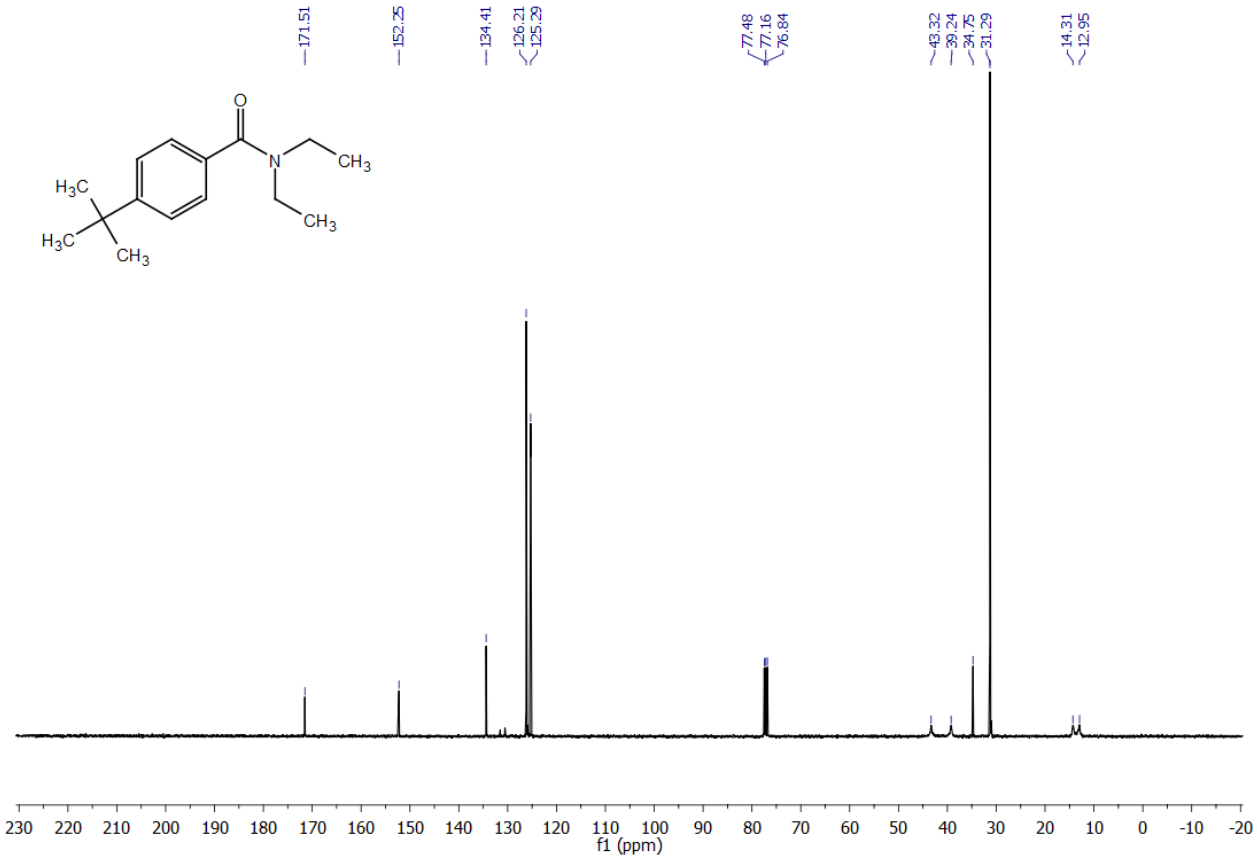


Figure S20. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of 4-*tert*-butyl-N,N-diethylbenzamide (**3j**).

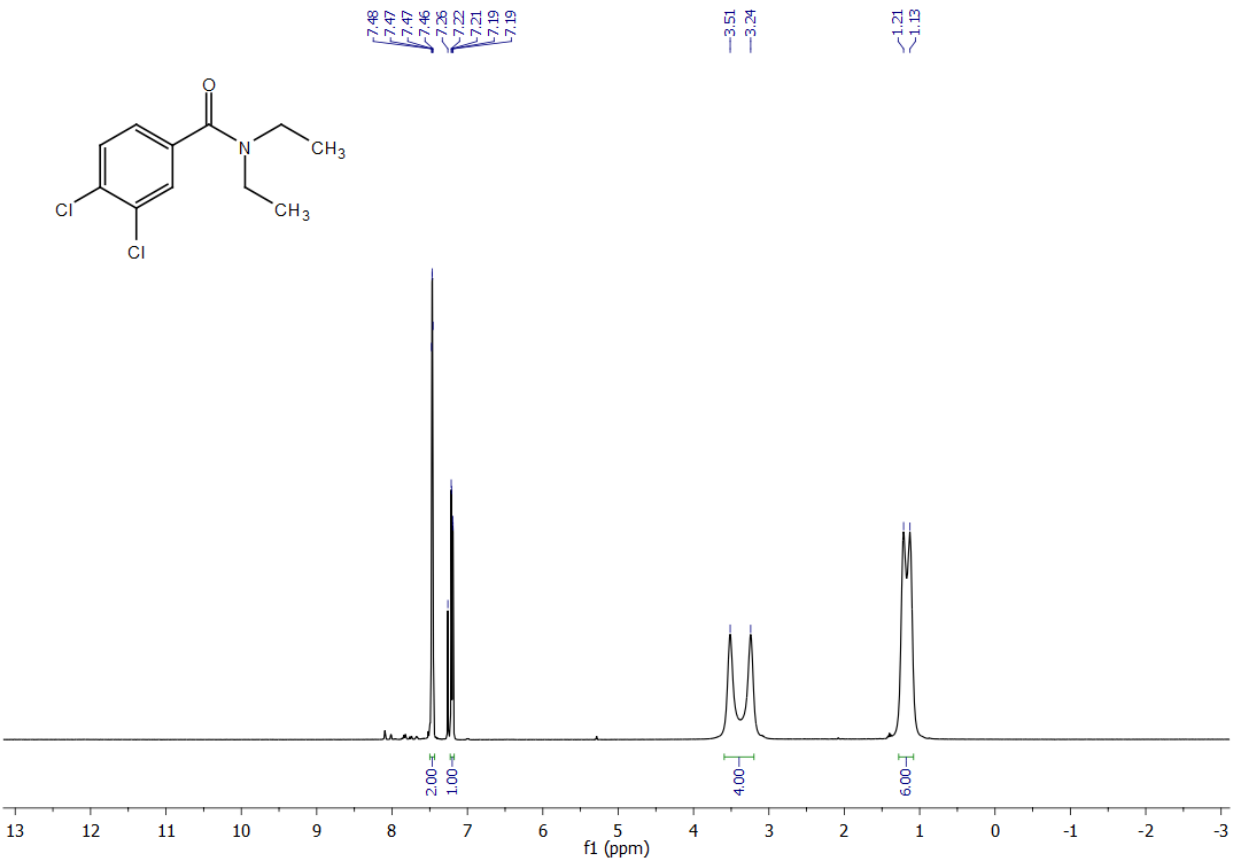


Figure S21. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of 3,4-dichloro-N,N-diethylbenzamide (**3k**).

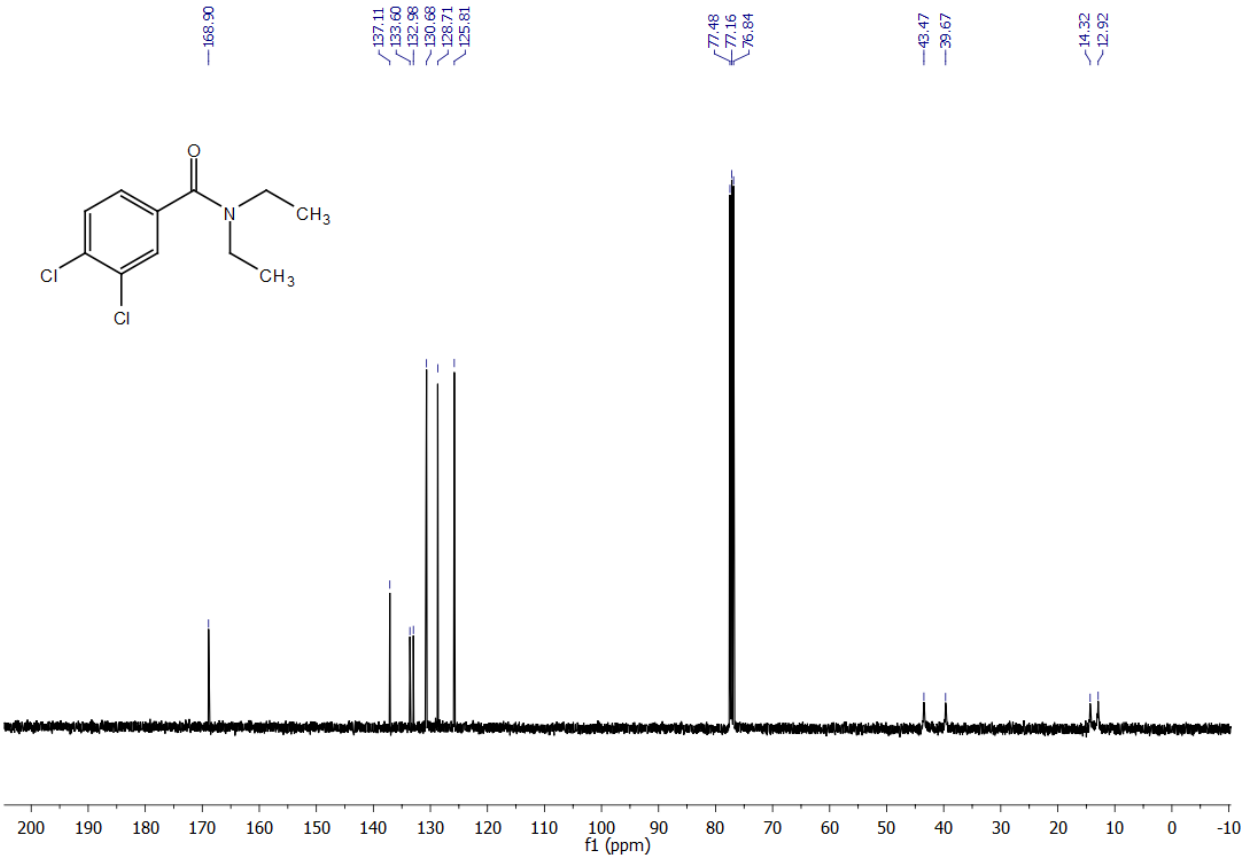


Figure S22. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of 3,4-dichloro-N,N-diethylbenzamide (**3k**).

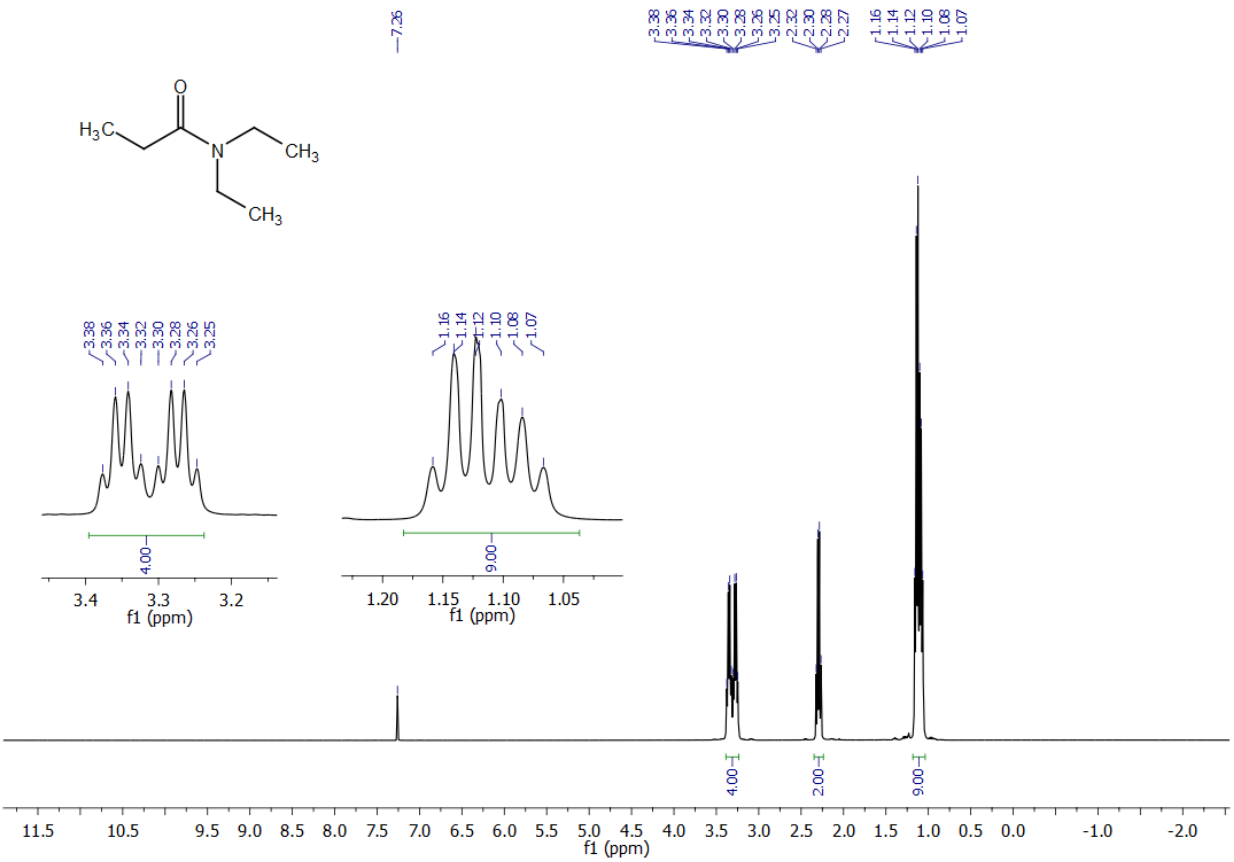


Figure S23. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of N,N-diethylpropanamide (**3l**).

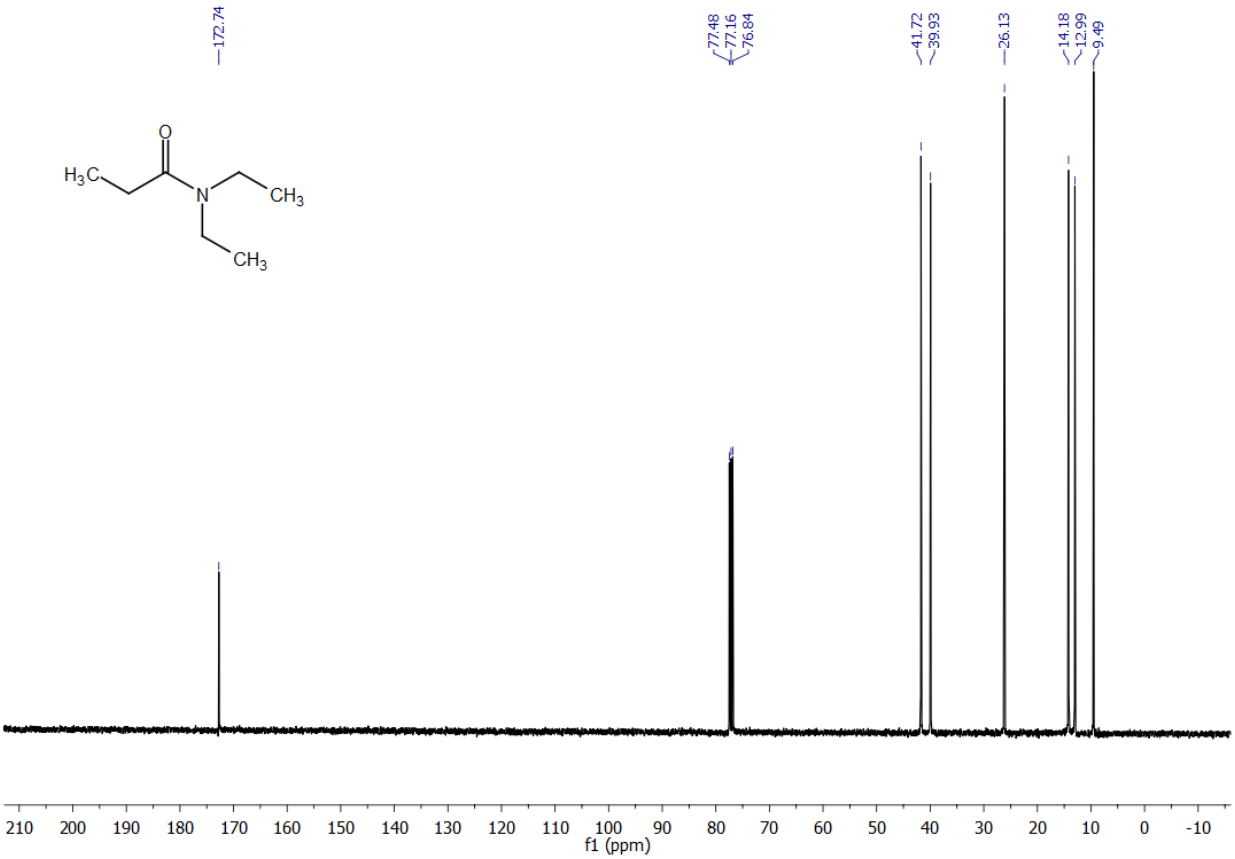


Figure S24. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of N,N-diethylpropanamide (**3l**).

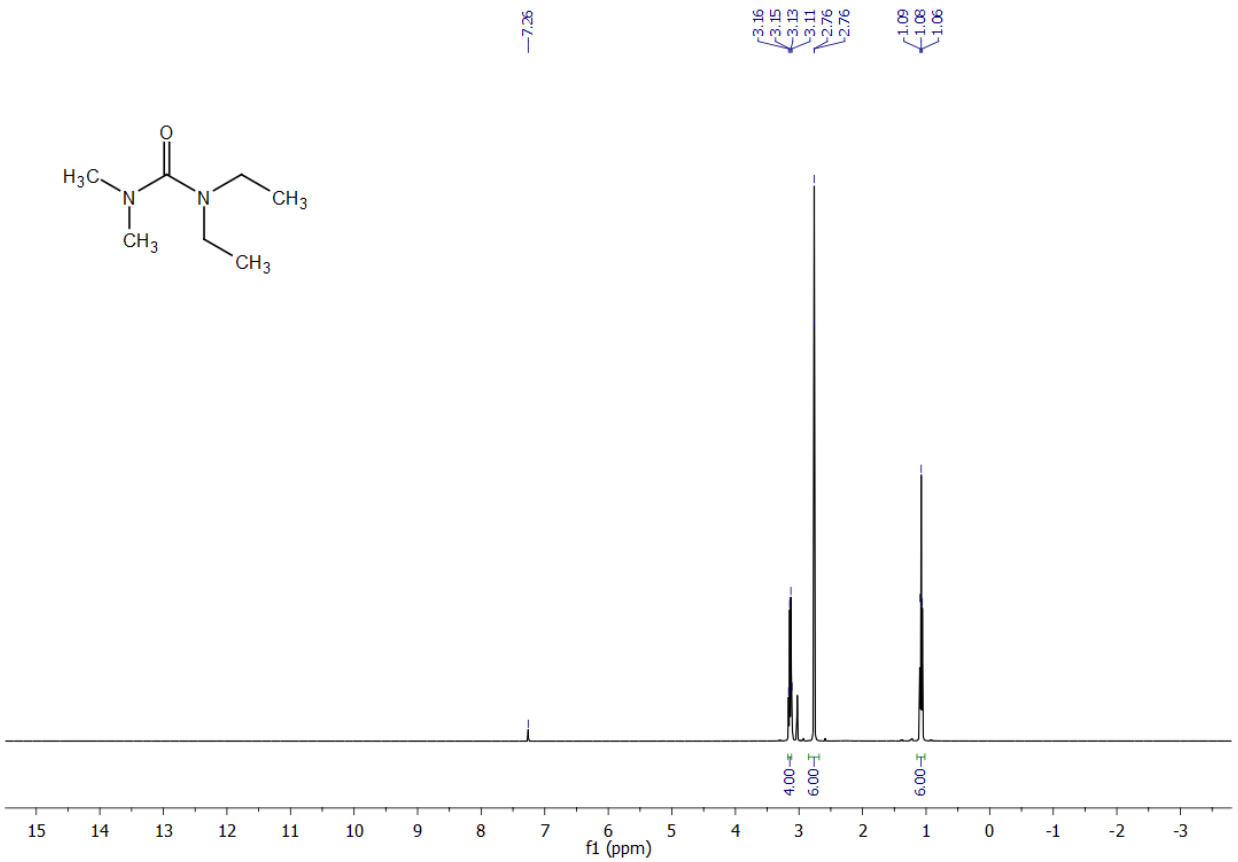


Figure S25. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of N,N-diethyl-N',N'-dimethylurea (**3m**).

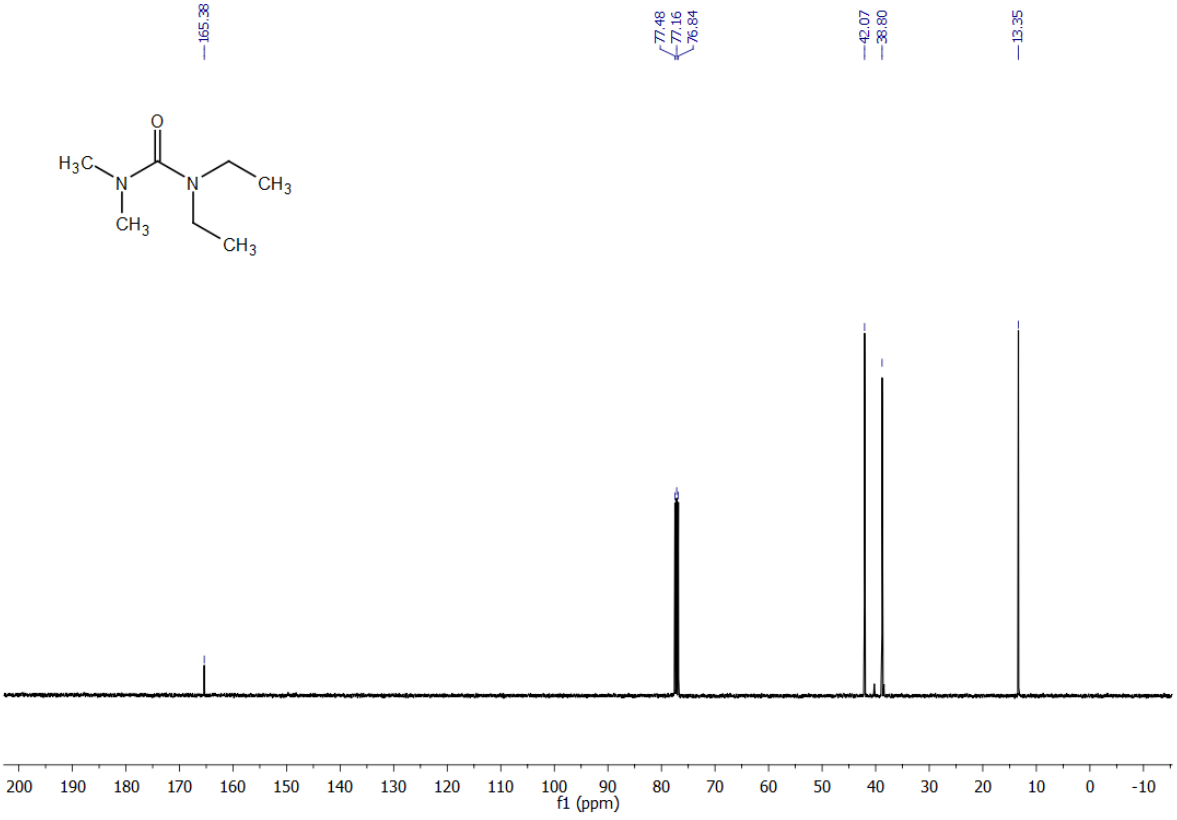


Figure S26. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of N,N-diethyl-N',N'-dimethylurea (**3m**).

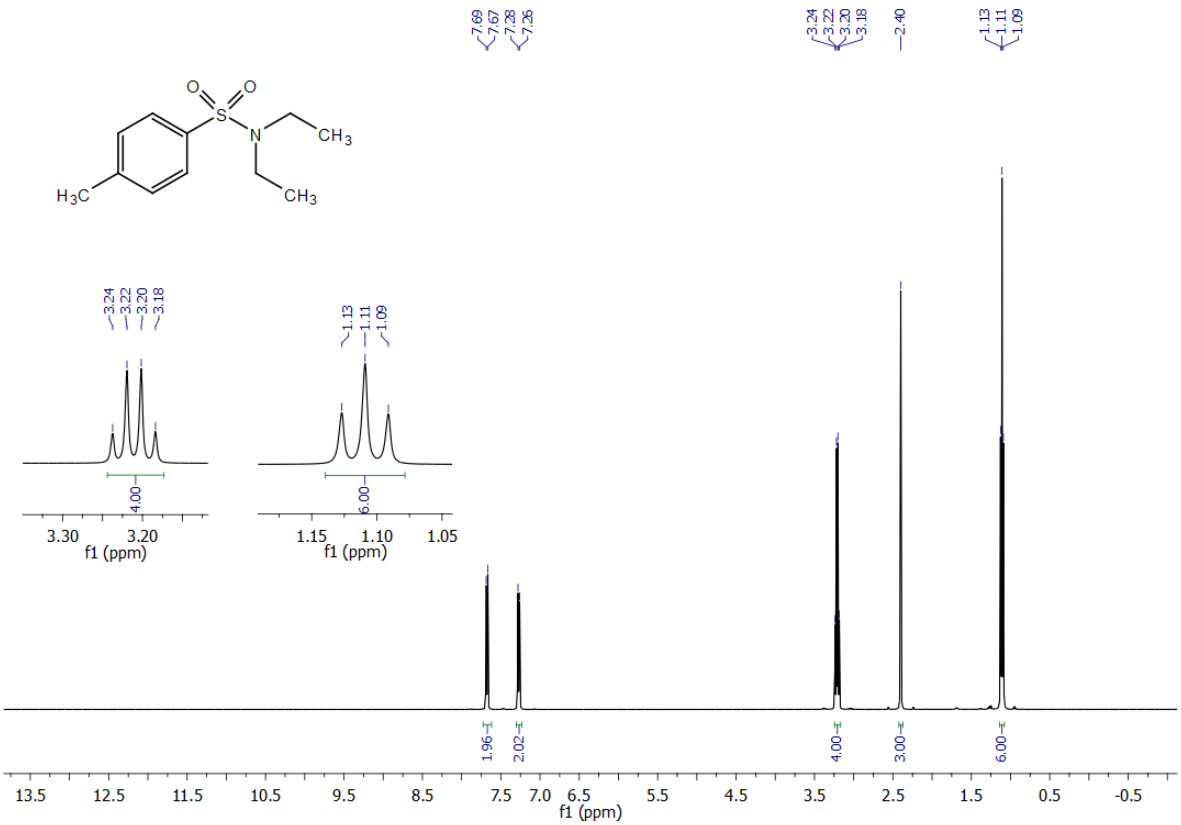


Figure S27. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of N,N-diethyl-4-methylbenzenesulfonamide (**3n**).

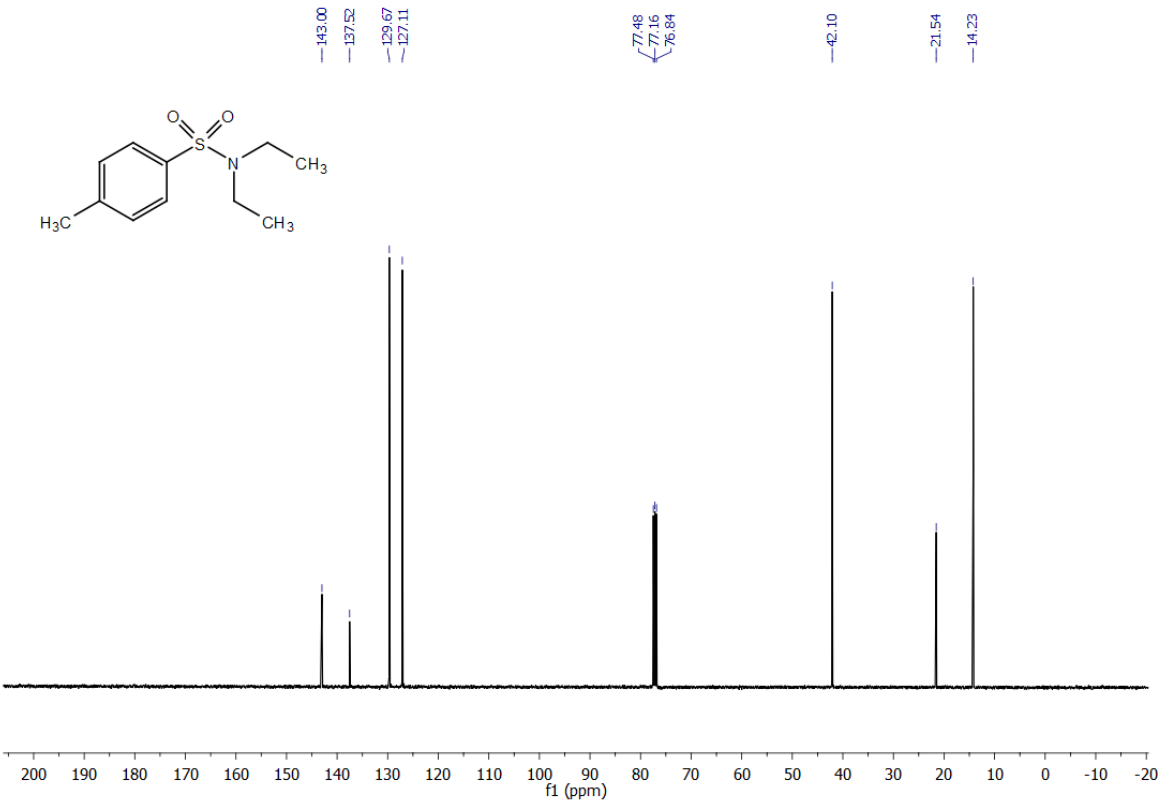


Figure S28. NMR ^{13}C spectrum ($CDCl_3$, 101 MHz) of N,N-diethyl-4-methylbenzenesulfonamide (**3n**).

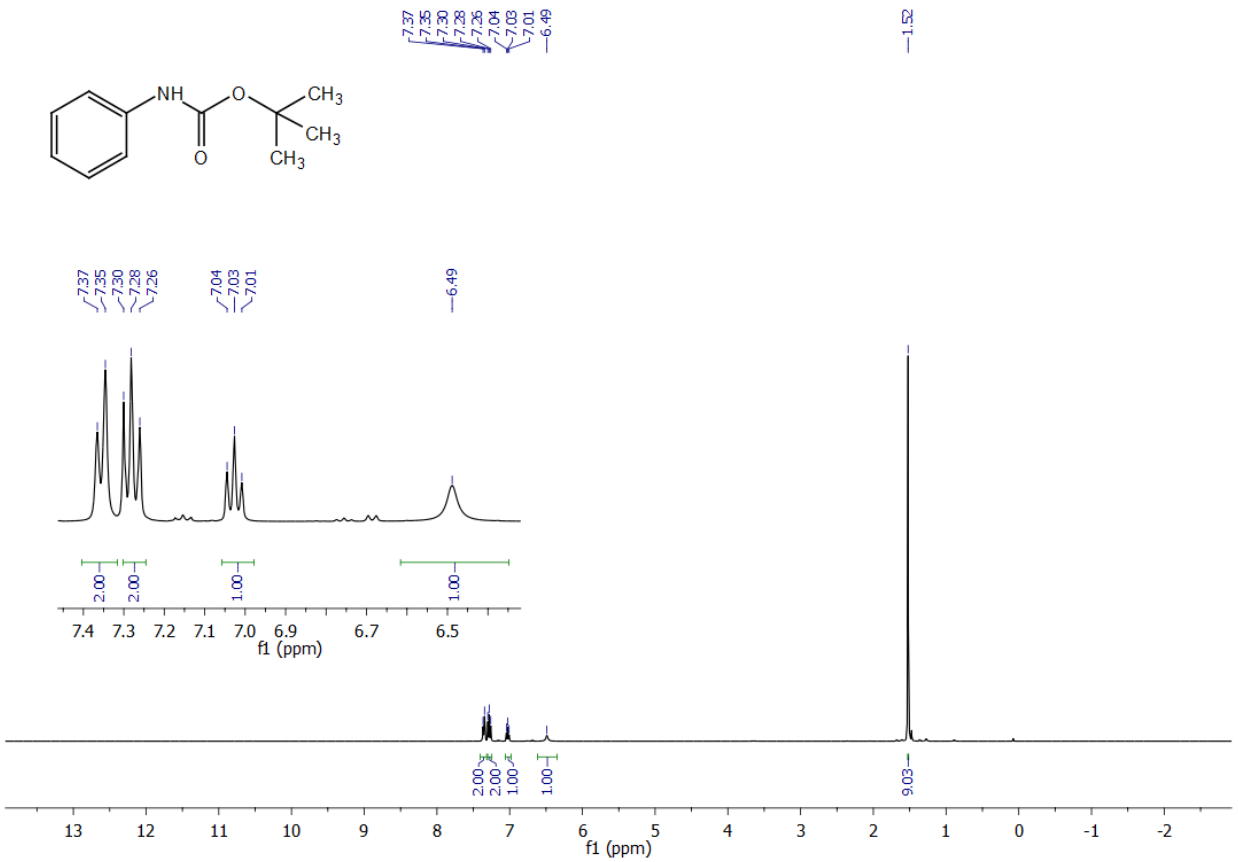


Figure S29. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of *tert*-butylphenylcarbamate (**4**).

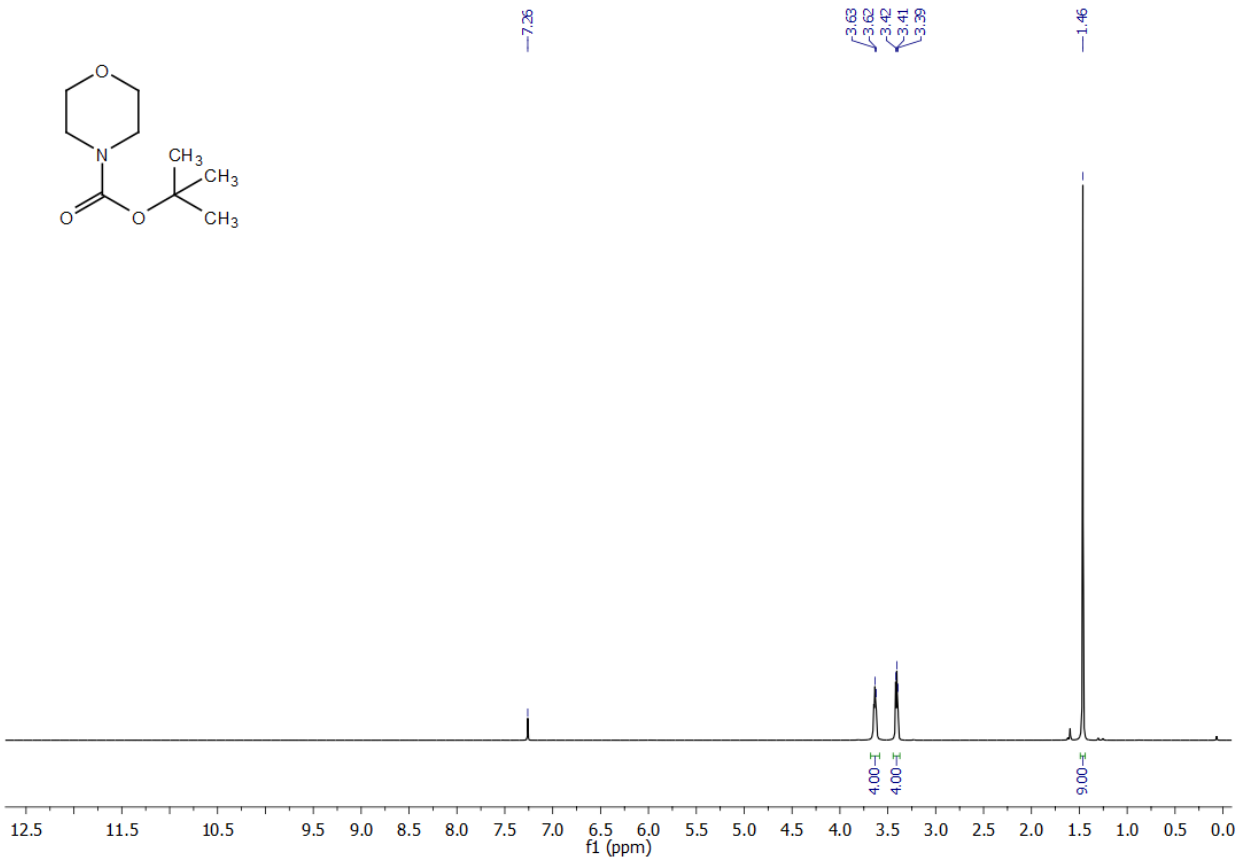


Figure S30. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of *tert*-butyl morpholine-4-carboxylate (**5**).

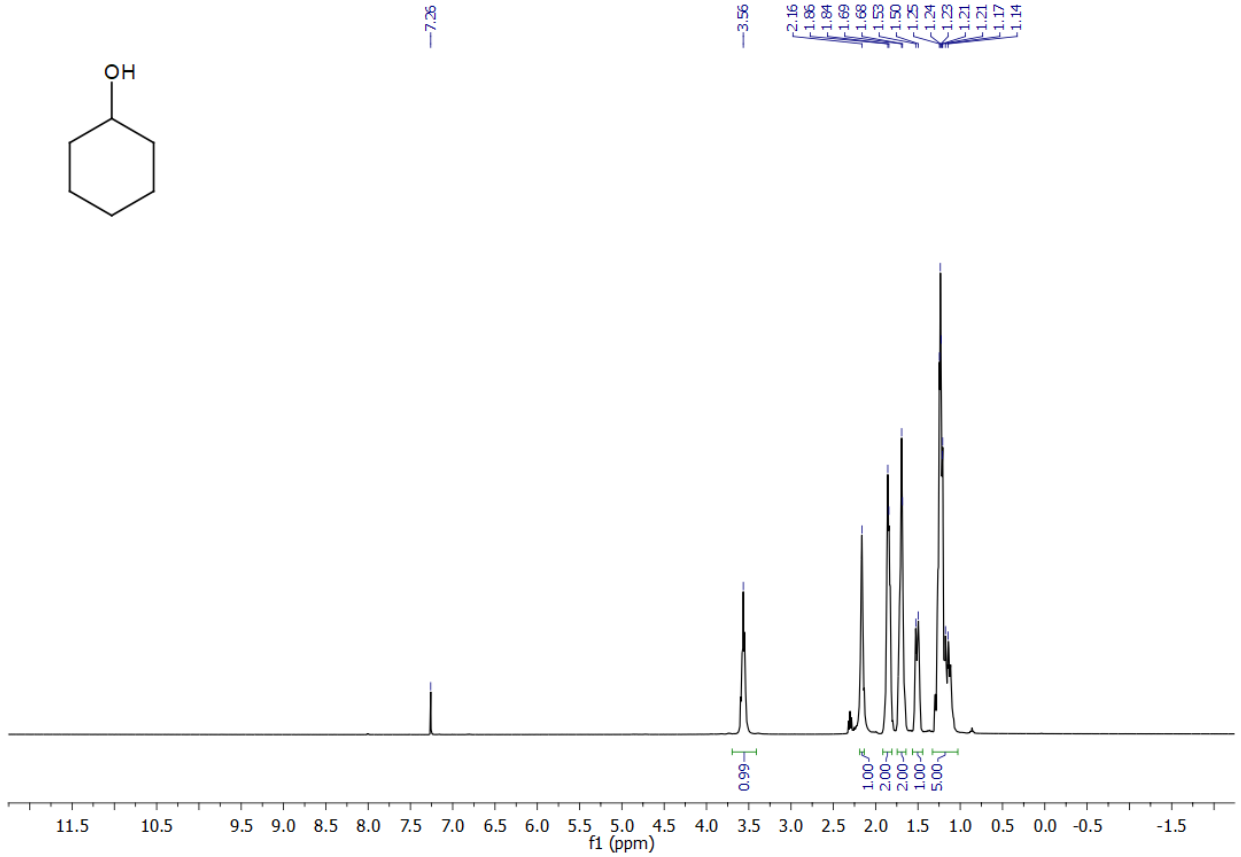


Figure S31. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of cyclohexanol (**6**).

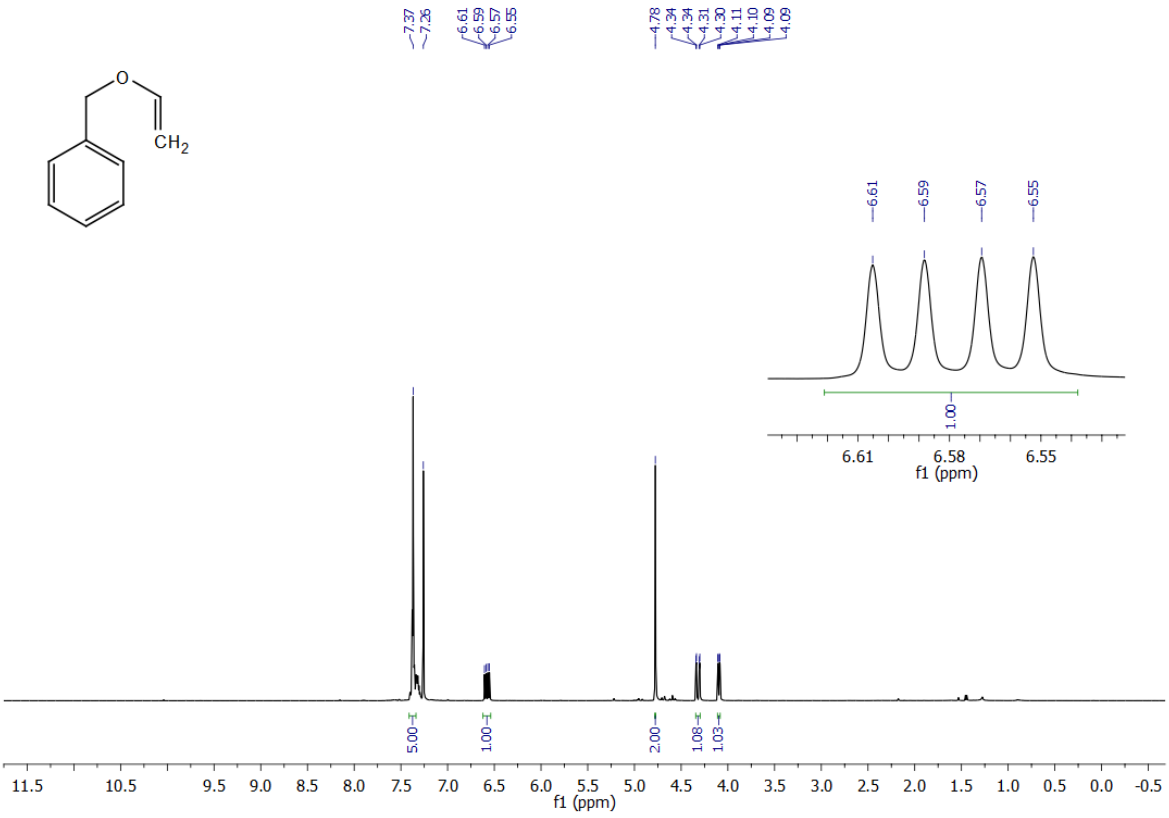


Figure S32. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of benzyl vinyl ether (**8**).

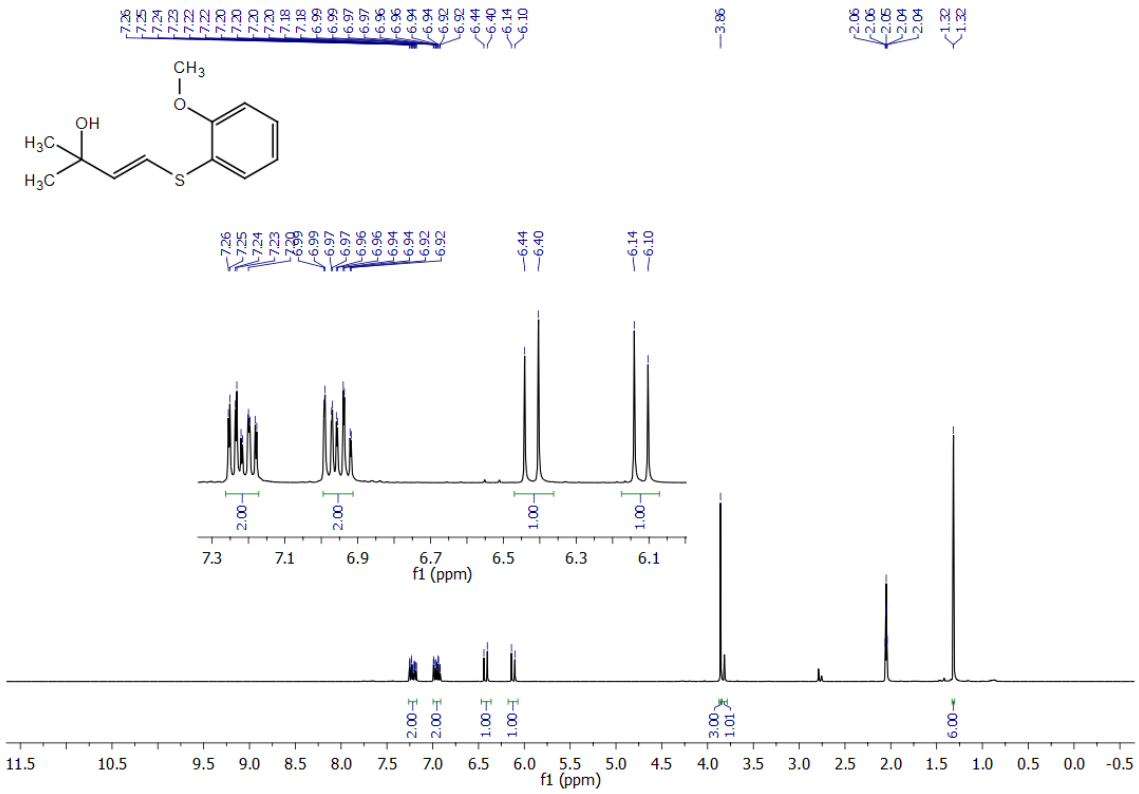


Figure S33. NMR ^{1}H spectrum (acetone-d_6, 400 MHz) of (E)-4-((2-methoxyphenyl)thio)-2-methylbut-3-en-2-ol **(9)**.

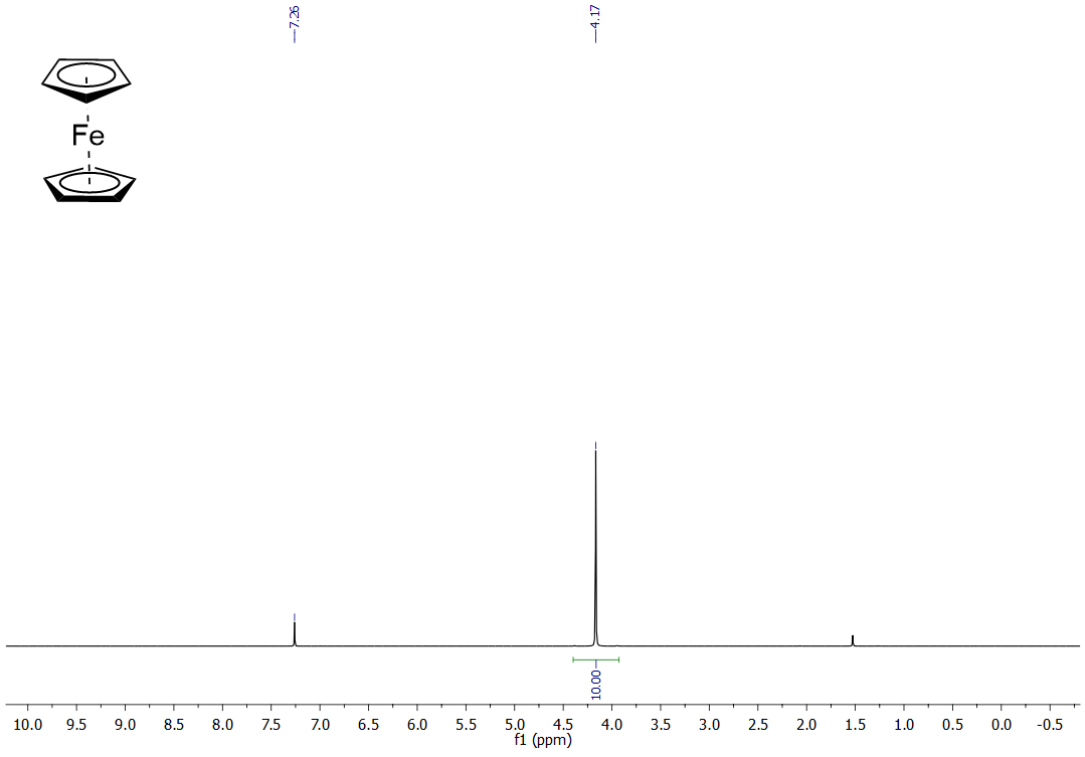


Figure S34. NMR ^{1}H spectrum ($CDCl_3$, 400 MHz) of ferrocene (**10**).

5. Method for determining the tightness of capsules

The tightness of the 3D-printed capsules was evaluated using GC-MS method. For the experiment, 10 glass vials were prepared. Five of them contained 10 mg of 4-chlorothiophenol encapsulated and sealed in a PLA capsule. The other 5 vials contained 10 mg of 4-chlorothiophenol too, but without encapsulation. The content of each vial was subjected by GC-MS to evaluate the 4-chlorothiophenol concentration in the gas phase in the specimens. The thiol concentration in the capsules containing samples was so low that only noise was observed in the spectrum (see Fig. S34). For the samples in which the thiol was not encapsulated, the signal intensity in the spectrum was 60000 times greater than the noise signal (see Fig. S35). Thus, the use of capsules reduces the evaporation of 4-chlorothiophenol by more than 60000 times.

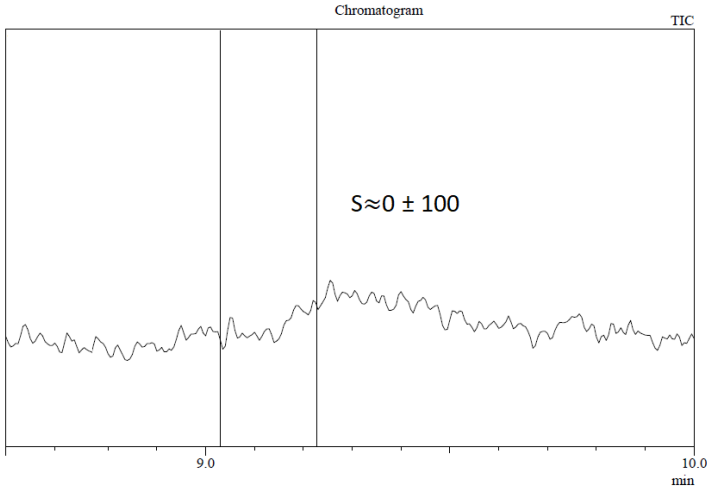


Figure S35. Chromatogram of the gas under the PLA capsule with 10 mg of 4-chlorothiophenol. The noise intensity is approximately 100 relative units.

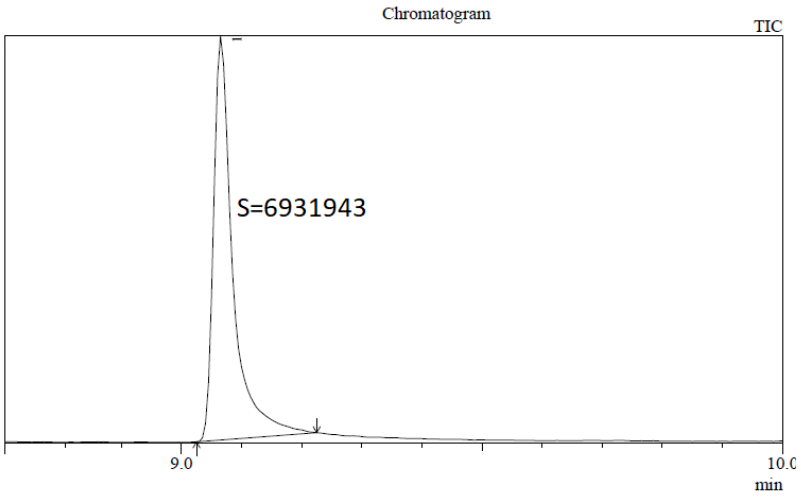


Figure S36. Chromatogram of the gas with 10 mg of 4-chlorothiophenol without encapsulation. The 4-chlorothiophenol signal intensity is approximately 69,000 relative units.

6. Photos of the capsule manufacturing process and its use

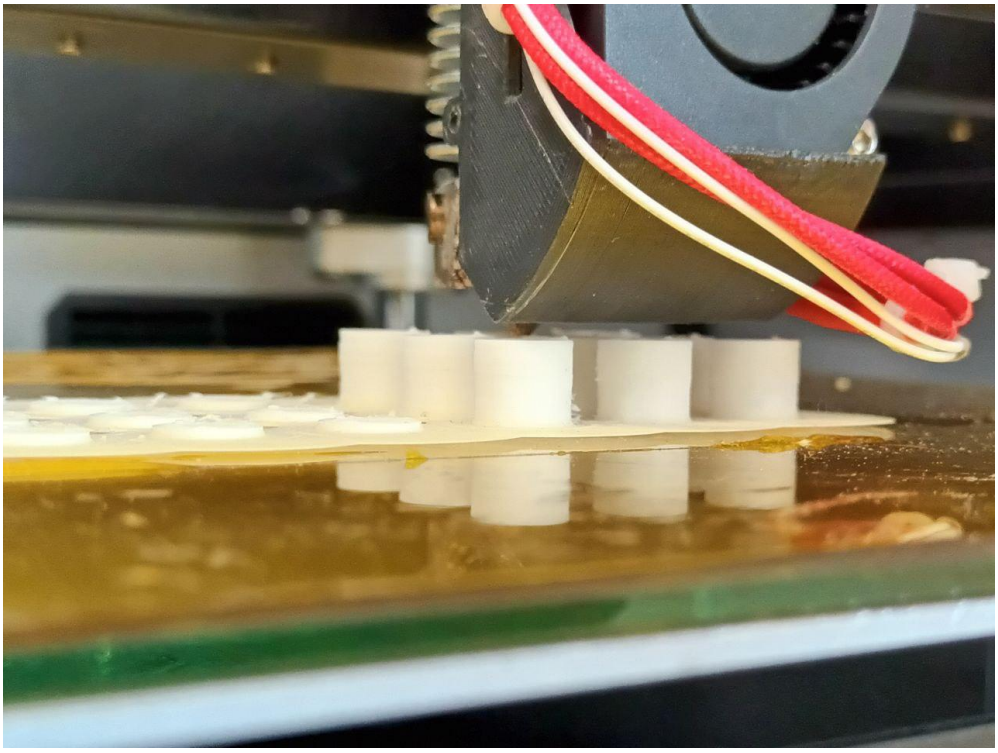


Figure S37. Uncolored (white) PLA cylinders 3D printing process.

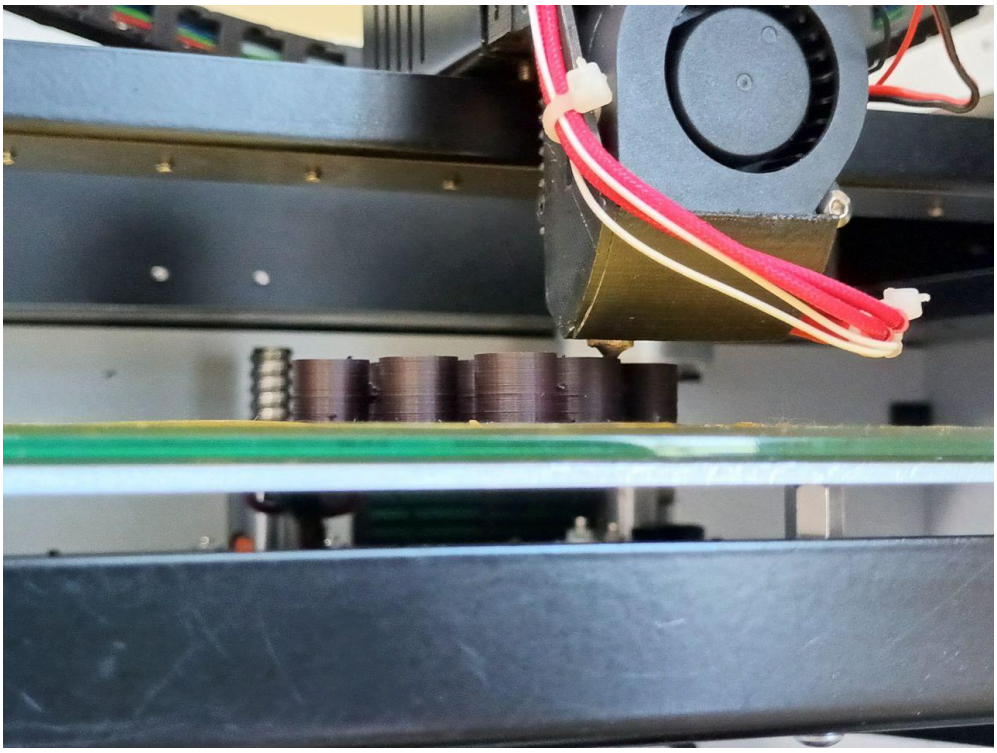


Figure S38. Colored PLA cylinders 3D printing process.

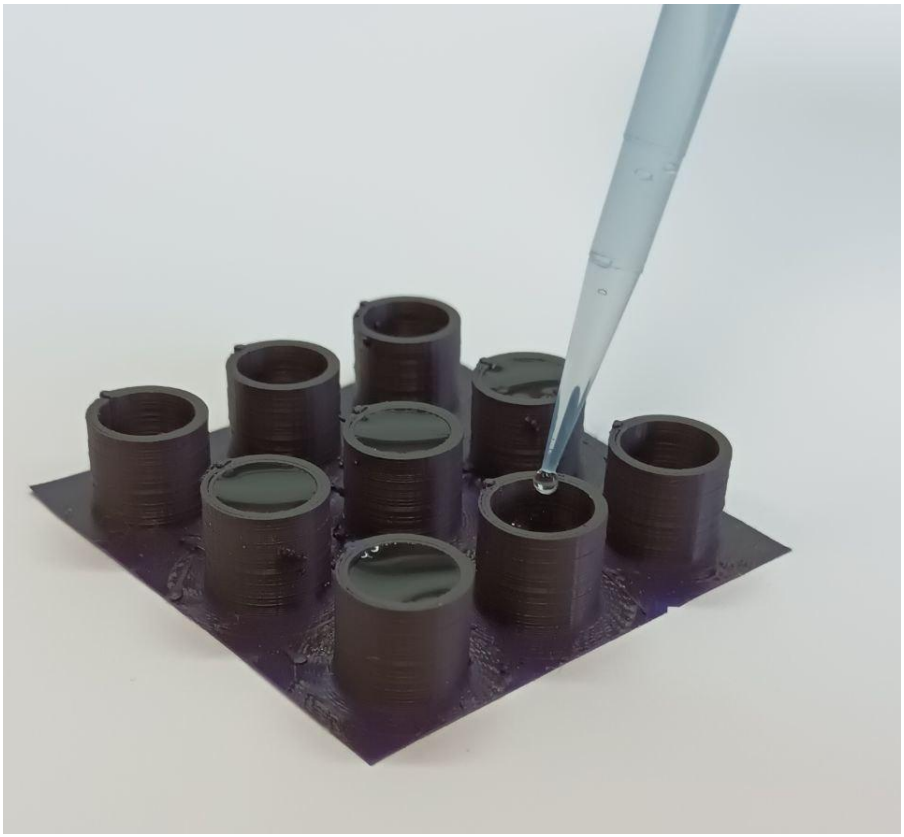


Figure S39. Photo of sequential filling of vials with reagents.

Figure S40. Photo of sealing of filled vials with caps using glue; the glue was made from the same plastic and an appropriate solvent.

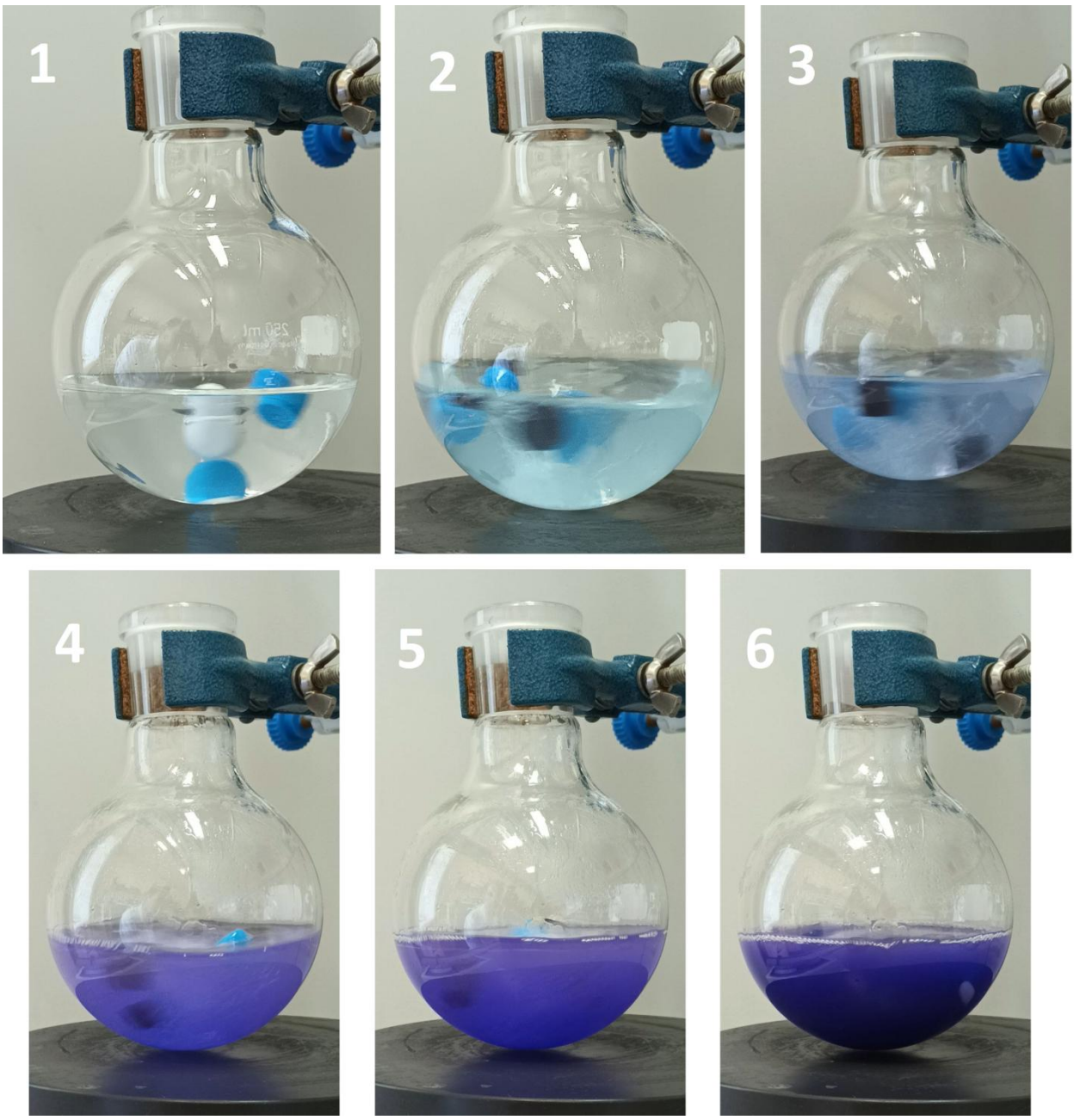


Figure S41. Photos of the sequential addition and dissolution of capsules with reagents in CH_2Cl_2.

7. Recycling remark

The nature of polymeric plastic cylinders significantly differs from the monomeric nature of reagents and products. Thus, standard procedures can separate both materials efficiently. Polymers can be dissolved while target substances are extracted with solvents such as ether, ethyl acetate or water. Conversely, these polymers precipitate once methanol is introduced.

Following this procedure, we successfully re-extracted PLA from capsules following the N-acylation of amines. After the reaction, the solvent was evaporated, and the ether was added. This led to the precipitation of the polymer as large flakes while the desired substance (amide) remained dissolved. After filtering out the plastic, the amide was purified using standard methods. The recovered PLA was then dried, re-extruded as per conventional procedures, and subsequently turned into filament wire for 3D printing. This regenerated PLA was shaped into new cylinders, which were repurposed in subsequent reactions without any noticeable decline in the product yield. Hence, these plastic cylinders are recyclable, and their isolation procedures are seamlessly compatible with those of the intended products.

The potential possibility of the recycling of polymeric capsules was demonstrated. Unless specially equipped, regular recycling procedure probably should not be performed directly in a laboratory. During chemical reactions, toxic compounds may contaminate polymers as a result of absorption. Therefore, as a general rule, the recycling procedure should be performed in special appropriate places as a part of global waste management. After synthetic procedures, the material from plastic capsules should be collected and transferred for recycling. Nevertheless, demonstration of a principal possibility of recycling is important for sustainability reasons.

8. References

1 G. Wilkinson, *Org. Synth.*, 1956, **36**, 31.

2 A. P. Ingale, V. K. More, U. S. Gangarde and S. V Shinde, *New J. Chem.*, 2018, **42**, 10142–10147.

3 L. Shi, Y. Liu, Q. Liu, B. Wei and G. Zhang, *Green Chem.*, 2012, **14**, 1372–1375.

4 R. Matake, Y. Adachi and H. Matsubara, *Green Chem.*, 2016, **18**, 2614–2618.

5 S. S. Zalesskiy, N. S. Shlapakov and V. P. Ananikov, *Chem. Sci.*, 2016, **7**, 6740–6745.

6 H. Ritter, B. Knudsen and V. Durnev, *Beilstein J. Org. Chem.*, 2013, **9**, 1278–1284.