Supporting Information

Palladium-catalyzed C-H bond carboxylation of acetanilide: an efficient usage of *N, N*-dimethyloxamic acid as the carboxylate source

Yinuo Wu*, Cheng Jiang, Deyan Wu, Qiong Gu, Zhang-Yi Luo and Hai-Bin Luo*

School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China,

E-mail:wyinuo3@mail.sysu.edu.cn and luohb77@mail.sysu.edu.cn; Fax: + 86-20-3994 3000

Table of Contents

1. General considerations

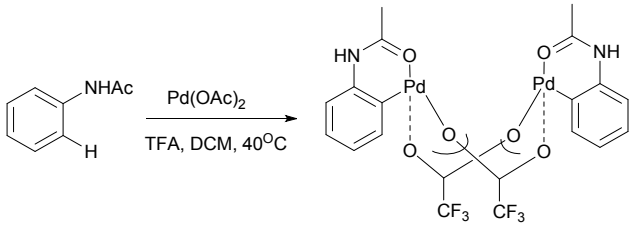
Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All the reactions were performed in Rotaflo®(England) resealable screw-cap Schlenk flask (approx. 20 mL volume) in the presence of Teflon coated magnetic stirrer bar (4 mm × 10 mm). 1, 2-Dichloroethane (DCE) and diglyme was distilled under calcium hydride under reduced pressure. Dioxane and toluene were distilled from sodium under nitrogen. Thin layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates. Silica gel (Merck, 70-230 and 230-400 mesh) was used for column chromatography. ^{1}HNMR spectra were recorded on a Bruker (400 MHz) spectrometer. Spectra were referenced internally to the residual proton resonance in DMSO-d_6 (δ 2.50 ppm), or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. ^{13}C NMR spectra were referenced to DMSO-d_6 (δ 39.5 ppm, the middle peak). Coupling constants (J) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a Shimadzu LCMS-IT-TOF. GC-MS analysis was conducted on a HP 5973 GCD system using a HP5MS column (30 m × 0.25 mm). The products described in GC yield were accorded to the authentic samples/dodecane calibration standard from HP 6890 GC-FID system. Compounds described in the literatures were characterized by comparison of their ^{1}H, and/or ^{13}C NMR spectra to the previously reported data.[1]

2. General procedures for reaction condition screenings and coupling reactions

General procedures for screening the carboxylation: The acetanilide (0.135 g, 1.0 mmol) and the metal complex (10 mol% or as indicated in Table 1) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar under air atmosphere. The solvent (2.0 mL) was added into the tube. The solution was stirred for about 1 to 2 minutes until the solid had been dissolved. Oxamic acids (2.0 mmol), oxidant (2.0 mmol) were loaded into the tube. The tube was stirred at room temperature or a preheated oil bath (rt - 120^{o}C) for 18 hours. After completion of reaction, the reaction tube was allowed to cool to room temperature. Ethyl acetate (~10 mL), dodecane (114 μL, internal standard) and water (~3 mL) were added. The organic layer was subjected to GC analysis. The GC yield obtained was previously calibrated by authentic sample/dodecane calibration curve.

General procedure for access to substituted anthranilic acid: Substituted acetanilides (1.0 mmol) and the $Pd(OAc)_2$ (22.4 mg, 0.1 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. DCE (2.0 mL) was added into the tube. The solution was stirred for about 1 to 2 minutes until the solid was dissolved. *N, N*-dimethyloxamic acid (2.0 mmol), $K_2S_2O_8$ (2.0 mmol), TFA(0.5 mmol)were loaded into the tube. The tube was stirred at 80^{o}C for 24 hours. After completion of reaction as judged by TLC analysis, the reaction was quenched with water and diluted with EtOAc. The organic layer was separated and the aqueous layer was washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

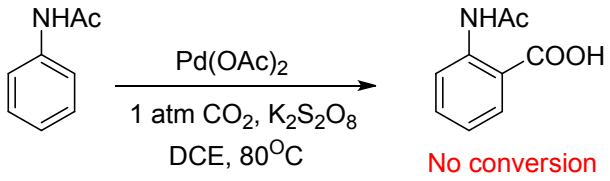
3. The synthesis of Complex P1



Complex 1

The complex **P1** was synthesized according to the literature method.[2] In a one-dram vial was added acetanilide (27.0 mg, 0.2 mmol), $Pd(OAc)_2$ (44.8 mg, 0.2 mmol), and dichloromethane (10 mL). Trifluoroacetic acid (22.8 mg, 0.2 mmol) was subsequently added into the vial and the resulting solution was heated to 40°C for 3h. After cooling to ambient temperature, the reaction mixture was concentrated in vacuo and the resulting residue was redissolved in hexanes (2 mL). After 2 h, precipitation of the desired complex occurred. The suspension was filtered through Celite and washed with hexanes. The residue was washed with dichloromethane and the wash solution was subsequently collected and concentrated in vacuo to afford the bimetallic palladacycle **P1** (58.2 mg, 82%) as a yellow solid.

4. Control experiments using CO_2 as the carboxylate reagent

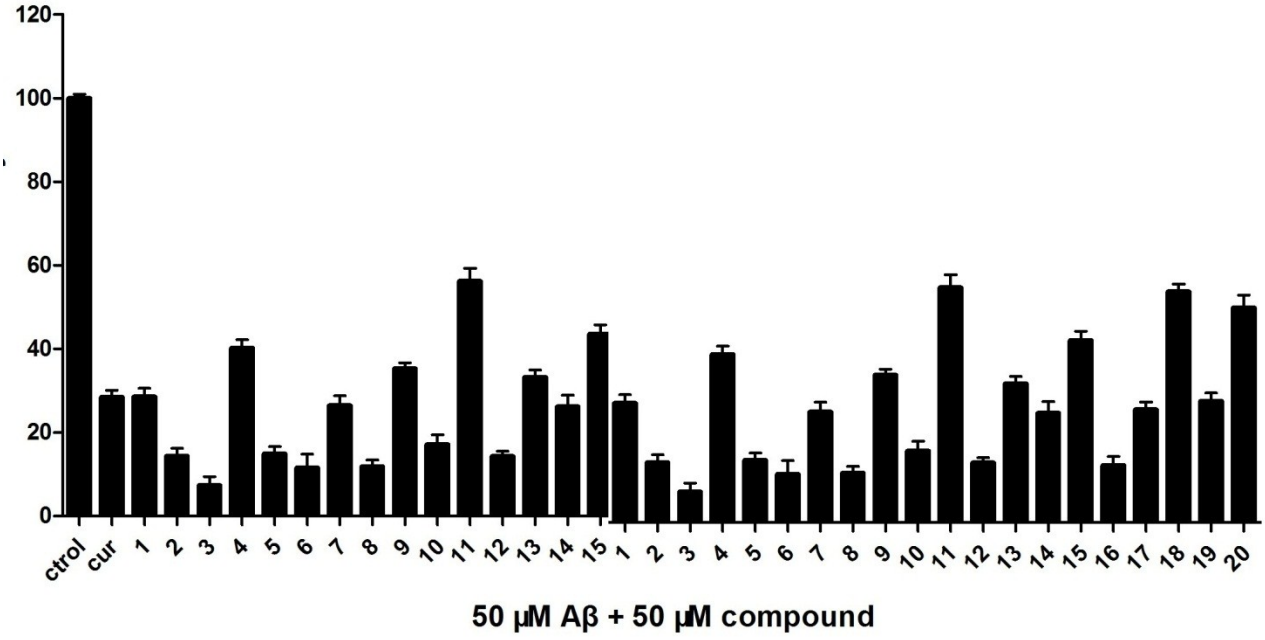


The acetanilide (0.135 g, 1.0 mmol) and the $Pd(OAc)_2$ (10 mol%) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The solvent DCE (2.0 mL) was added into the tube. The solution was stirred for about 1 to 2 minutes until the solid had been dissolved. $K_2S_2O_8$ (2.0 mmol) and TFA (0.5 mmol) were loaded into the tube. The Schlenk tube was degassed under vacuum and filled with carbon oxide from a balloon at room temperature. And then the mixture was stirred at 80°C for 18 hours. After completion of reaction, the reaction was quenched with water and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The crude products were analyzed on the GC-MS to detect the desired product.

5. The inhibitory Activity against *Aβ*42 aggregation

All the *N*-acyl-anthranilic acids obtained were evaluated for their inhibitory activities against A*β* 42 aggregation according to a ThT fluorescence assay. Curcumin (cur) was used as the positive control. As shown in SP Figure 1, all of them showed moderate to potent activity against A*β* aggregation and 9 of them showed better inhibitory activity of *β*-amyloid (A*β*) peptides than that of the positive control curcumin (EC_{50} 3.9 μM). The best one is compound 3, which may become a hit compound for further development for the treatment of Alzheimer's disease.

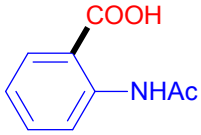
Experiment: A*β*42 was dissolved in 1% NH_3−H_2O (440 μM), and the test samples were dissolved in DMSO to give a concentration of 10 mM. Then, 100 μM A*β*42 was left untreated or mixed with equal amounts of these compounds and incubated at 37 °C for 48 h. After incubation, the samples were added to 96-well microplates to give a final volume of 200 μL with 50 mM glycine−NaOH buffer (pH = 8.5) containing 5 μM ThT. A Thermetype multifunctional microplate reader (Ruishi Di Ken) was used to measure the fluorescence at an excitation of 450 nm and an emission of 485 nm.[3]



SP Figure 1: Inhibition rate against A*β*42 aggregation by *N*-acyl-anthranilic acids and curcumin (cur) at 50μM

6. Characterization data of coupling products

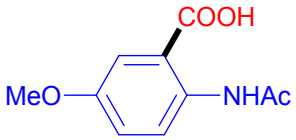
2-acetamidobenzoic acid (1)



1, 73%

DCM : MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.57 (s, 1H), 11.05 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.14 (t, J = 7.6 Hz, 1H), 2.14 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 169.44, 168.42, 140.84, 133.96, 131.02, 122.52, 119.93, 116.46, 24.98. HRMS: calcd. for C9 H9 N O3 [M+H]+: 180.0655, found 180.0660.

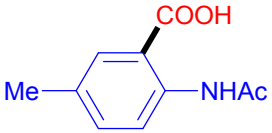
2-acetamido-5-methoxybenzoic acid (2)



2, 81%

DCM : MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.29 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 3.1 Hz, 1H), 7.18 (dd, J = 9.2, 3.1 Hz, 1H), 3.77 (s, 3H), 2.09 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 168.91, 167.97, 154.16, 134.01, 122.17, 119.90, 118.50, 114.63, 55.36, 24.67. HRMS: calcd. for C10 H11 N O4 [M+H]+: 210.0761, found 210.0764.

2-acetamido-5-methylbenzoic acid (3)

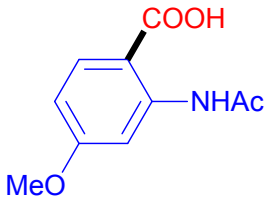


3, 80%

DCM : MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.33 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.38 (d, J = 8.5 Hz, 1H), 2.28 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.90, 168.68, 138.91, 134.93, 132.07, 131.48, 120.53, 116.95, 25.34, 20.61. HRMS: calcd.

for C10 H11 N O3 [M+H]+: 194.0812, found 194.0819.

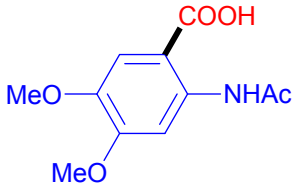
2-acetamido-4-methoxybenzoic acid (4)



4, 76%

DCM : MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.32 (s, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.94 (d, J = 8.9 Hz, 1H), 6.70 (dd, J = 8.9, 2.5 Hz, 1H), 3.81 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.88, 169.17, 164.06, 143.50, 133.48, 108.69, 108.62, 104.86, 55.87, 25.65. HRMS: calcd. for C10 H11 N O4 [M+H]+: 210.0761, found 210.0764.

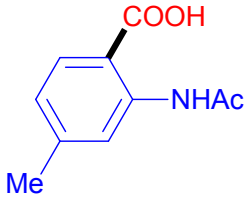
2-acetamido-4, 5-dimethoxybenzoic acid (5)



5, 77%

DCM : MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.26 (s, 1H), 7.43 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.67, 168.72, 153.57, 143.86, 137.29, 113.34, 108.00, 103.66, 56.08, 56.00, 25.52. HRMS: calcd. for C11 H13 N O5 [M+H]+: 240.0866, found 240.0868.

2-acetamido-4-methylbenzoic acid(6)

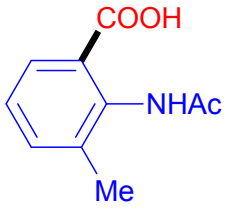


6, 71%

DCM : MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.34 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.02 – 6.89 (m, 1H), 2.34 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ

169.96, 168.84, 144.96, 141.48, 131.52, 123.77, 120.53, 113.99, 25.51, 22.06. HRMS: calcd. for C10 H11 N O3 [M+H]+: 194.0812, found 194.0820.

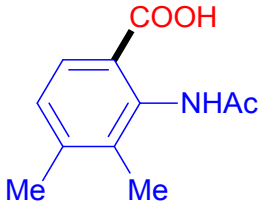
2-acetamido-3-methylbenzoic acid（7）



7, 52%

DCM: MeOH (10:1); R_f = 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 2.20 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.82, 168.43, 136.05, 134.92, 133.93, 129.53, 128.03, 126.08, 23.45, 18.48. HRMS: calcd. for C10 H11 N O3 [M+H]+: 194.0812, found 194.0820.

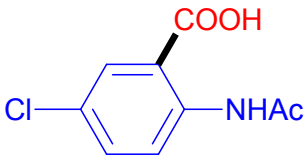
2-acetamido-3,4-dimethylbenzoic acid(8)



8, 50%

DCM: MeOH (10:1); R_f = 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 7.40 (d, J = 1.1 Hz, 1H), 7.23 (s, 1H), 2.29 (s, 3H), 2.15 (s, 3H), 1.99 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 168.77, 168.44, 135.92, 135.28, 134.47, 133.60, 129.30, 128.40, 23.42, 20.74, 18.40. HRMS: calcd. for C11 H13 N O3 [M+H]+: 208.0968, found 208.0973.

2-acetamido-5-chlorobenzoic acid(9)

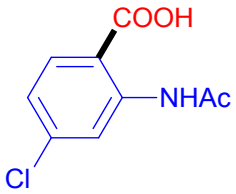


9, 70%

DCM: MeOH (10:1); R_f = 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.46 (d, J = 9.0 Hz,

1H), 7.90 (d, J = 2.6 Hz, 1H), 7.63 (dd, J = 9.0, 2.7 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.04, 168.60, 139.98, 134.00, 130.60, 126.63, 122.39, 118.99, 25.34. HRMS: calcd. for C9 H8 N O3 Cl [M+H]+: 214.0265, found 214.0264.

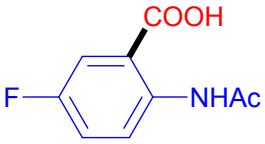
2-acetamido-4-chlorobenzoic acid(10)



10, 68%

DCM: MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 7.96 (s, 1H), 7.19 (d, J = 2.2 Hz, 1H), 2.15 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 169.41, 169.24, 142.35, 138.92, 133.23, 122.88, 119.52, 115.34, 25.47. HRMS: calcd. for C9 H8 N O3 Cl [M+H]+: 214.0265, found 214.0264.

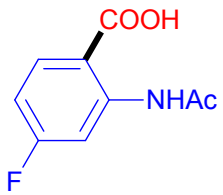
2-acetamido-5-fluorobenzoic acid(11)



11, 75%

DCM:MeOH (10:1); R_f= 0.4;^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.41 (dd, J = 9.2, 5.2 Hz, 1H), 7.66 (dd, J = 9.4, 3.2 Hz, 1H), 7.45 (ddd, J = 9.2, 8.1, 3.2 Hz, 1H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.91, 168.62 (d, J = 2.3 Hz), 158.36, 155.97, 137.56 (d, J = 2.4 Hz), 122.87 (d, J = 7.2 Hz), 121.15 (d, J = 22.0 Hz), 117.15 (d, J = 23.8 Hz), 25.16. HRMS: calcd. for C9 H8 N O3 F [M+H]+: 198.0561, found 198.0565.

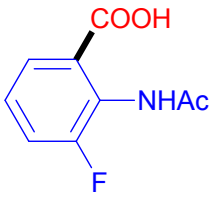
2-acetamido-4-fluorobenzoic acid(12)



12, 63%

DCM: MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.35 (dd, *J* = 12.3, 2.7 Hz, 1H), 8.06 (dd, *J* = 8.9, 6.8 Hz, 1H), 6.98 (ddd, *J* = 8.9, 8.0, 2.7 Hz, 1H), 2.17 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 174.09 (d, *J* = 19.7 Hz), 171.40, 168.92, 148.33 (d, *J* = 13.1 Hz), 139.04 (d, *J* = 11.1 Hz,), 117.67, 114.69 (d, *J* = 22.3 Hz), 111.35 (d, *J* = 28.2 Hz), 30.28. HRMS: calcd. for C9 H8 N O3 F [M+H]+: 198.0561, found 198.0565.

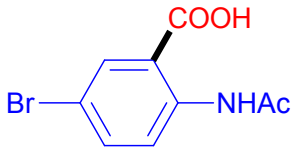
2-acetamido-3-fluorobenzoic acid(13)



13, 60%

DCM : MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 1H), 7.61 – 7.57 (m, 1H), 7.46 (ddd, *J* = 10.0, 8.3, 1.5 Hz, 1H), 7.34 (td, *J* = 8.1, 5.2 Hz, 1H), 2.02 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.84, 167.19 (d, *J* = 3.3 Hz, 5H), 158.47, 156.02, 130.66, 127.13 (d, *J* = 8.1 Hz), 126.01(d, *J* = 8.1 Hz), 119.44 (d, *J* = 21.1 Hz), 23.27. HRMS: calcd. for C9 H8 N O3 F [M+H]+: 198.0561, found 198.0563.

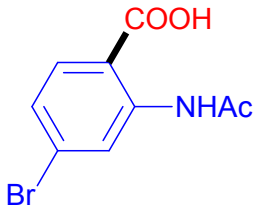
2-acetamido-5-bromobenzoic acid(14)



14, 62%

DCM: MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.40 (d, *J* = 9.0 Hz, 1H), 8.02 (d, *J* = 2.4 Hz, 1H), 7.74 (dd, *J* = 9.0, 2.4 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.07, 168.55, 140.38, 136.87, 133.50, 122.57, 119.17, 114.38, 25.39. HRMS: calcd. for C9 H8 N O3 Br [M+H]+: 257.9760, found 257.9758.

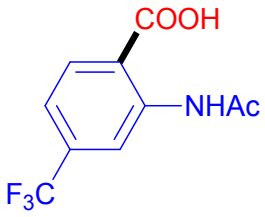
2-acetamido-4-bromobenzoic acid(15)



15, 52%

DCM: MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.34 (dd, J = 8.5, 2.0 Hz, 1H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.36, 169.33, 142.31, 133.27, 127.91, 125.86, 122.56, 115.87, 25.47. HRMS: calcd. for C9 H8 N O3 Br [M+H]+: 257.9760, found 257.9758.

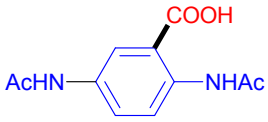
2-acetamido-4-(trifluoromethyl)benzoic acid(16)



16, 43%

DCM: MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 8.82 (d, J = 1.2 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.48 (dd, J = 8.3, 1.3 Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.56, 168.82, 141.45, 133.77, 133.45, 132.67, 120.67, 119.29 (d, J = 3.9 Hz), 116.79 (d, J = 4.2 Hz), 25.37 (s, 5H). HRMS: calcd. for C10 H8 N O3 F3 [M+H]+: 248.0529, found 248.0525.

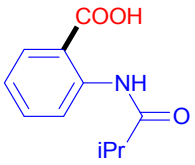
2, 5-diacetamidobenzoic acid(17)



17, 56%

DCM: MeOH (10:1); R_f= 0.4;^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H), 10.83 (s, 1H), 10.03 (s, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.26 (d, J = 2.6 Hz, 1H), 7.72 (dd, J = 9.0, 2.7 Hz, 1H), 2.10 (s, 3H), 2.03 (s, 3H).^{13}C NMR (101 MHz, DMSO) δ 169.17, 168.26, 168.10, 135.98, 134.14, 124.40, 121.12, 120.69, 117.13, 24.81, 23.86. HRMS: calcd. for C11 H12 N2 O4[M+H]+: 237.0857, found 237.0860.

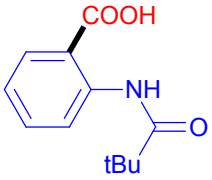
2-isobutyramidobenzoic acid(18)



18, 68%

DCM: MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.52 (dd, J = 8.4, 0.9 Hz, 1H), 7.99 (dd, J = 7.9, 1.6 Hz, 1H), 7.62 – 7.53 (m, 1H), 7.14 (dd, J = 11.0, 4.2 Hz, 1H), 2.56 (dd, J = 13.8, 6.9 Hz, 1H), 1.17 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.48, 170.13, 141.56, 134.49, 131.56, 122.91, 120.30, 116.80, 36.87, 19.68. HRMS: calcd. for C11 H13 N O3 [M+H]+: 208.0968, found 208.0975.

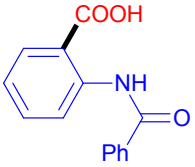
2-pivalamidobenzoic acid(19)



19, 51%

DCM: MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1H), 8.62 (d, J = 7.9 Hz, 1H), 8.00 (dd, J = 7.9, 1.5 Hz, 1H), 7.57 (s, 1H), 7.13 (d, J = 7.8 Hz, 1H), 1.24 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.15, 170.39, 141.96, 134.64, 131.61, 122.76, 119.95, 116.23, 27.62. HRMS: calcd. for C12 H15 N O3 [M+H]+: 222.1125, found 222.1127.

2-benzamidobenzoic acid(20)

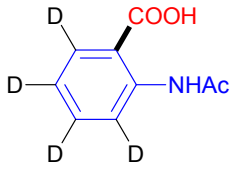


20, 42%

DCM: MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 8.72 (d, J = 8.2 Hz, 1H), 8.06 (dd, J = 7.9, 1.2 Hz, 1H), 7.96 (d, J = 7.1 Hz, 2H), 7.69 – 7.62 (m, 2H), 7.59 (t, J = 7.3 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.49, 165.17, 141.60, 135.00, 134.77, 132.62, 131.74, 129.43, 127.47, 123.39, 120.35, 116.95. HRMS: calcd. for C14 H11 N O3

[M+H]+: 242.0812, found 242.0817.

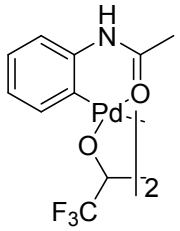
2-acetamidobenzoic acid-*d4* (1D)



1D

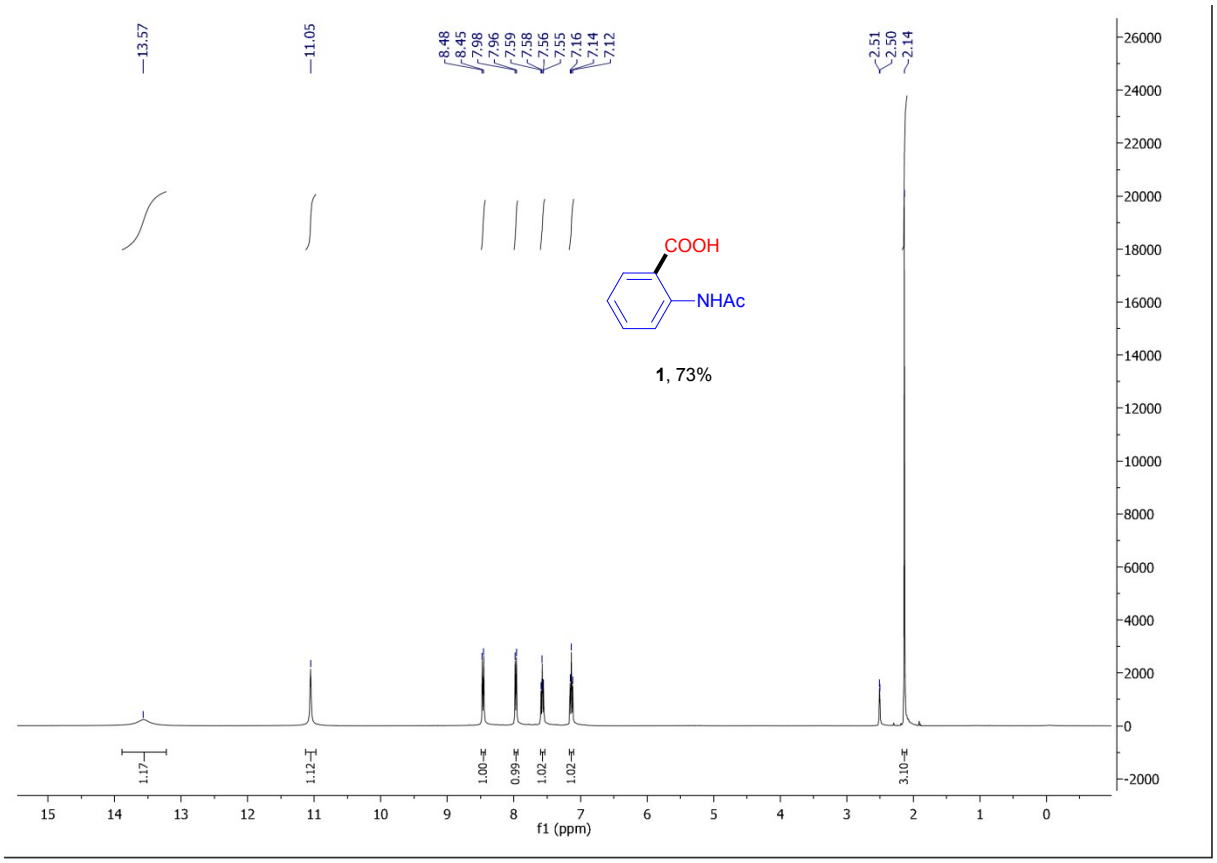
DCM: MeOH (10:1); R_f= 0.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.44, 168.40, 140.74, 116.46, 24.97.

Bimetallic Palladium Complex P1

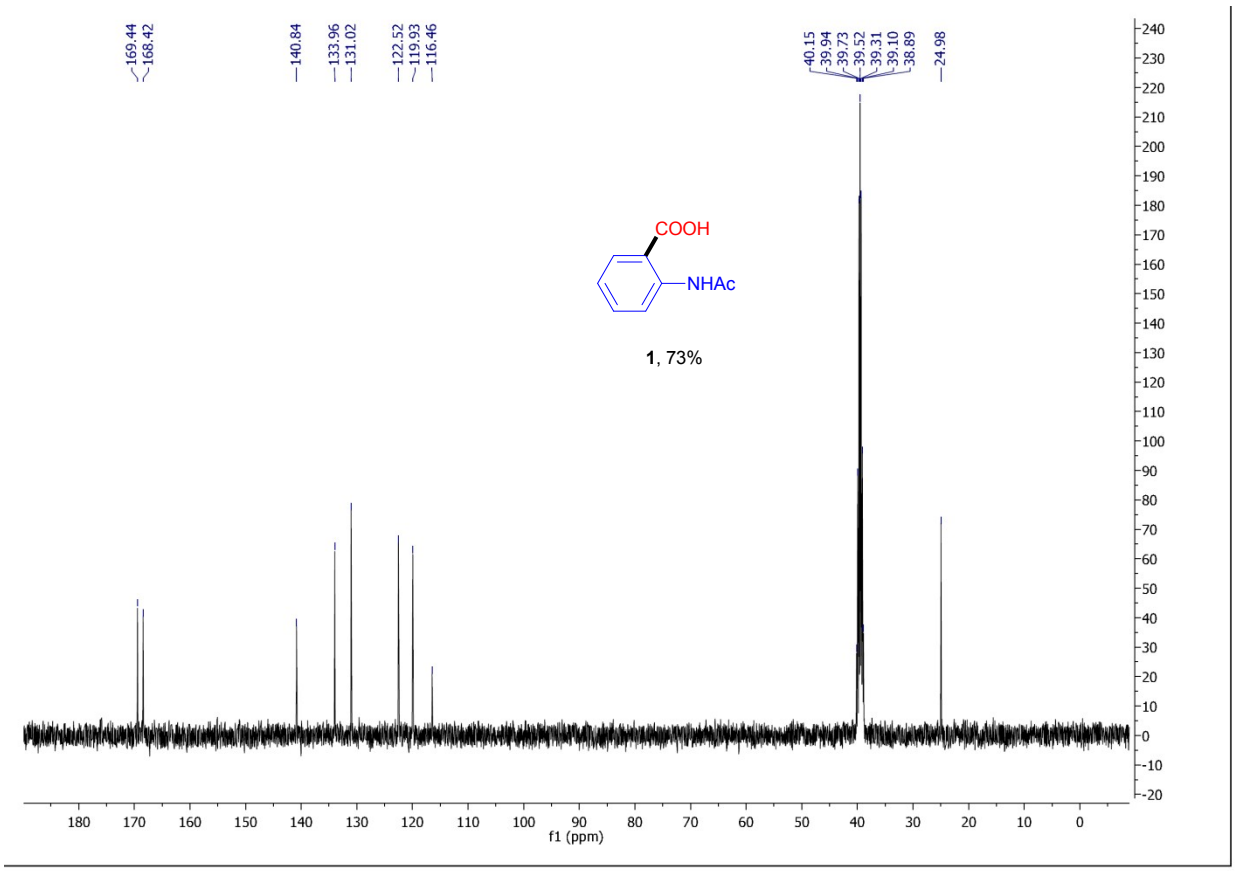


^{1}H NMR (400 MHz, MeOD) δ 7.06 – 6.99 (m, 2H), 6.88 (d, *J* = 7.5 Hz, 2H), 6.81 (d, *J* = 7.6 Hz, 4H), 1.96 (s, 6H).^{13}C NMR (101 MHz, MeOD) δ 167.72, 133.95, 132.45, 126.50, 123.86, 116.97, 20.48.^{19}F NMR (376 MHz, MeOD) δ -77.20.

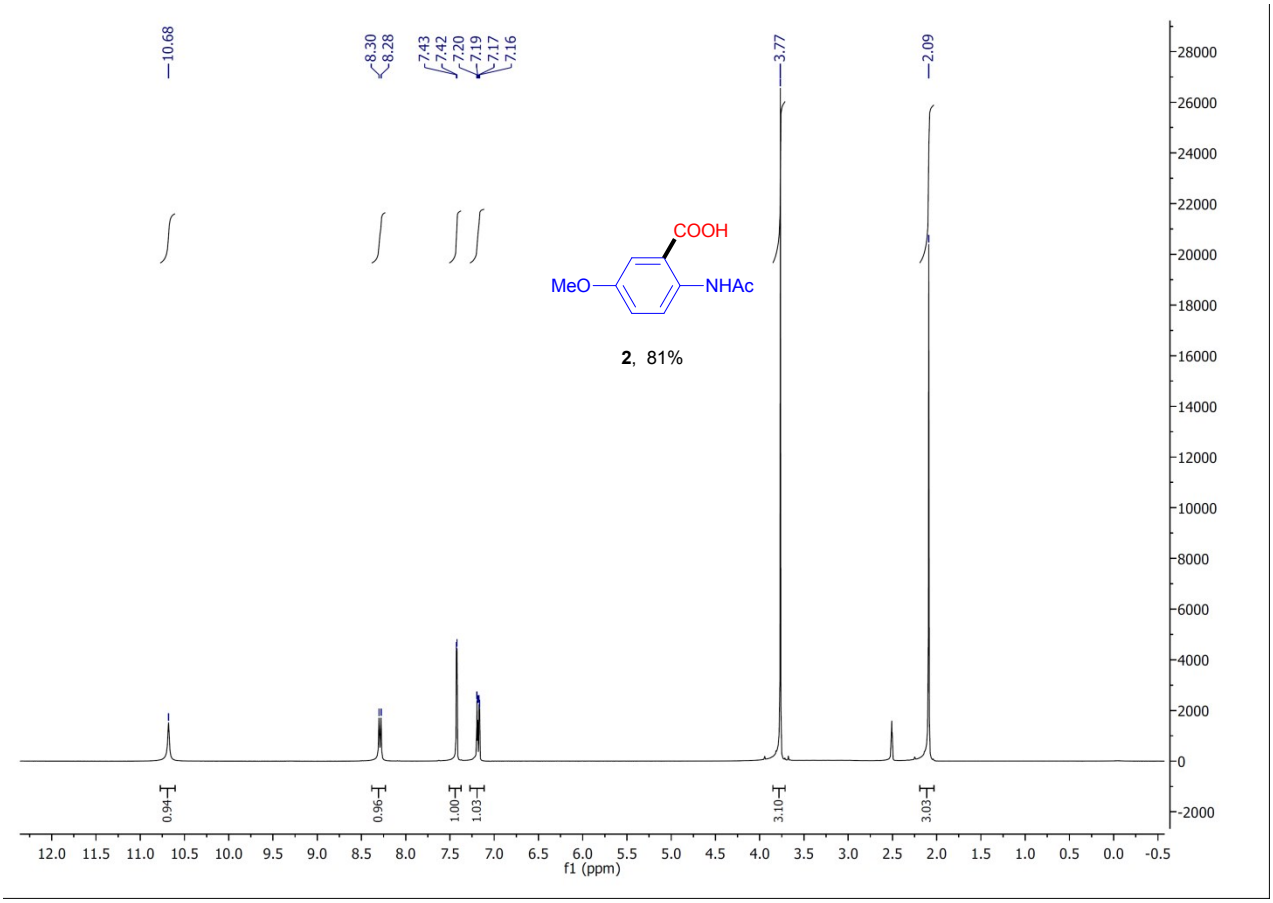
7. ^{1}H and ^{13}C NMR


13.57
11.05
8.48
8.45
7.98
7.96
7.59
7.58
7.56
7.55
7.16
7.14
7.12
2.51
2.50
2.14
COOH
NHAc
1.17
1.12
1.00
0.99
1.02
1.02
3.10
f1 (ppm)

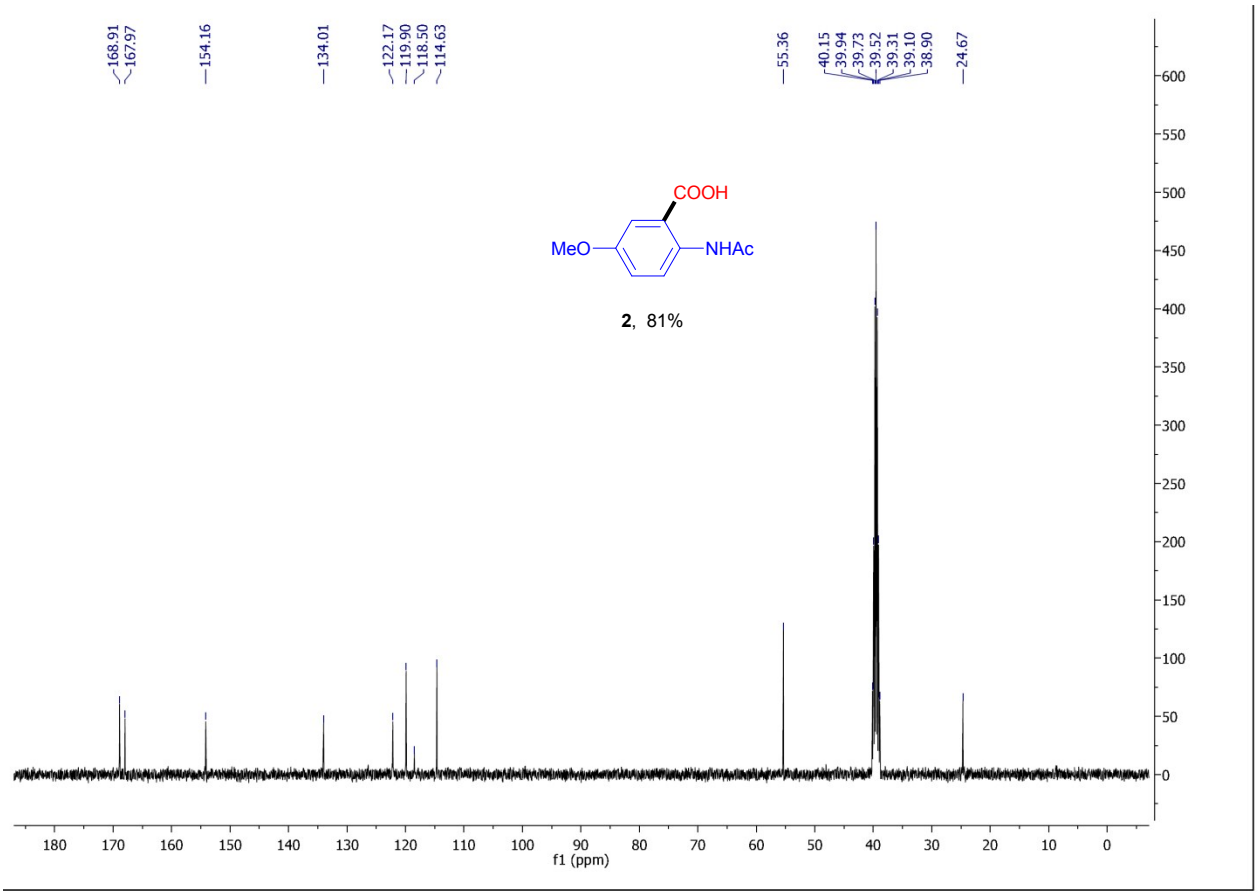
1, 73%


169.44
168.42
140.84
133.96
131.02
122.52
119.93
116.46
40.15
39.94
39.73
39.52
39.31
39.10
38.89
24.98
COOH
NHAc
f1 (ppm)

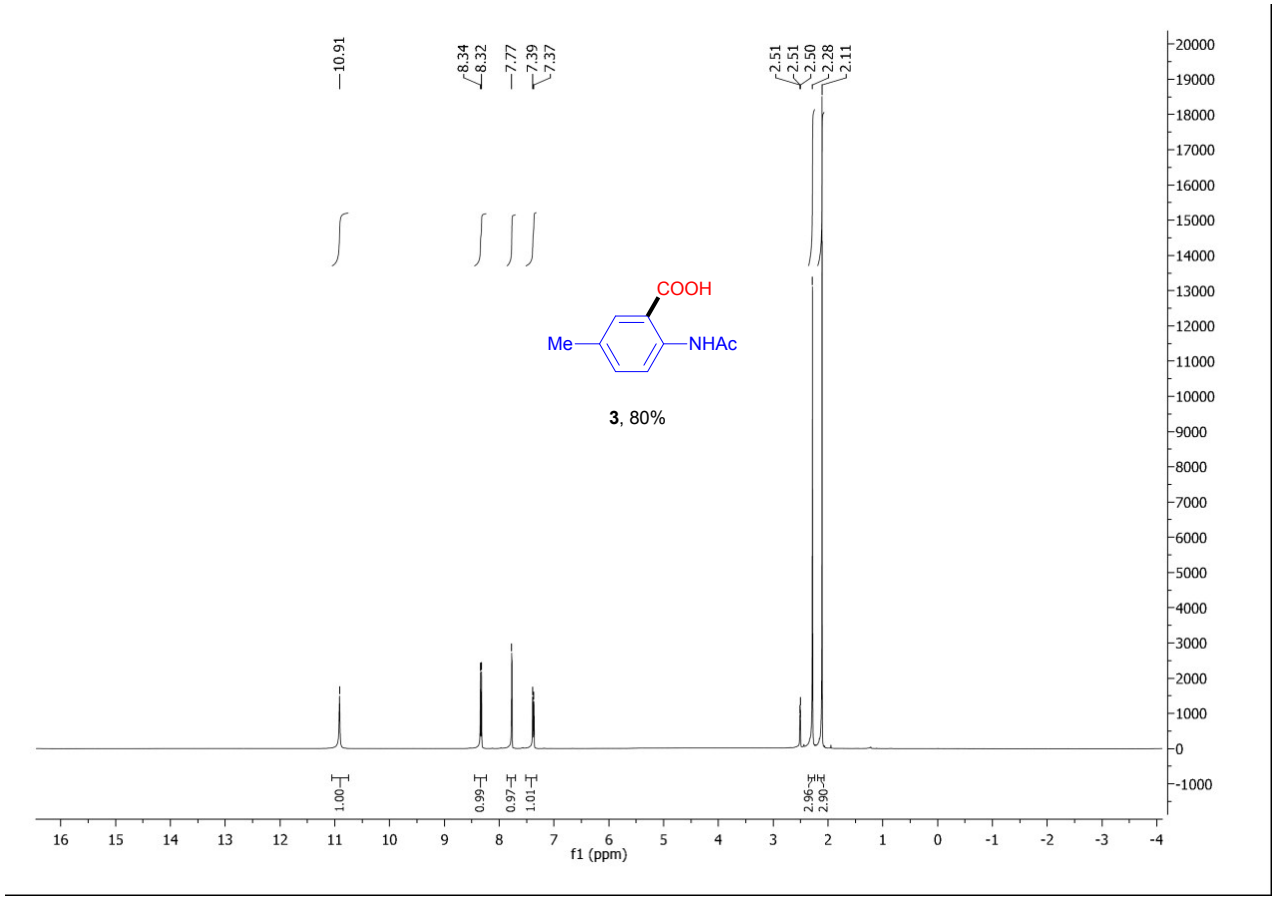
1, 73%


10.68
8.30
8.28
7.43
7.42
7.20
7.19
7.17
7.16
3.77
2.09
COOH
MeO
NHAc
0.94
0.96
1.00
1.03
3.10
3.03
f1 (ppm)

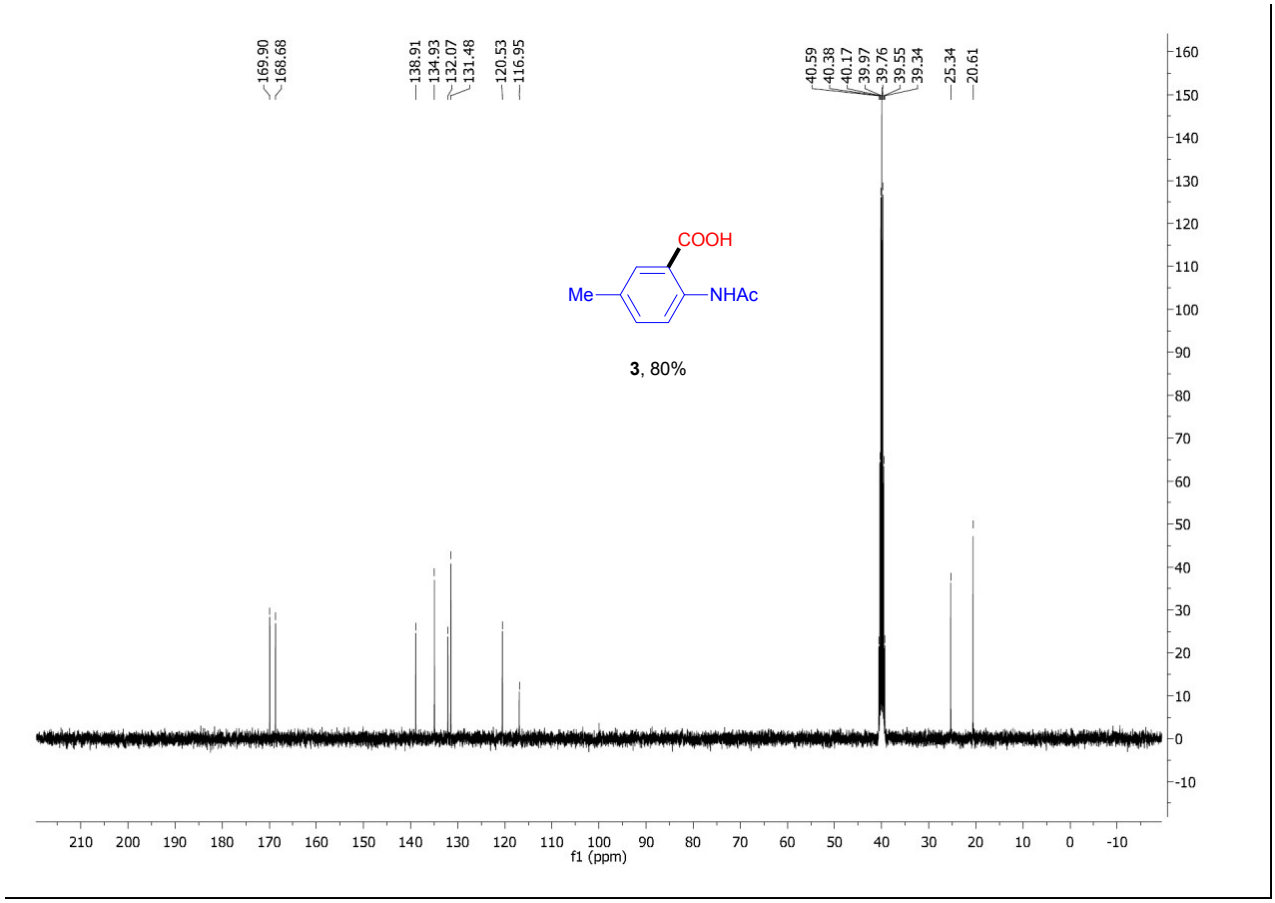
2, 81%


168.91
167.97
154.16
134.01
122.17
119.90
118.50
114.63
55.36
40.15
39.94
39.73
39.52
39.31
39.10
38.90
24.67
COOH
MeO
NHAc
f1 (ppm)

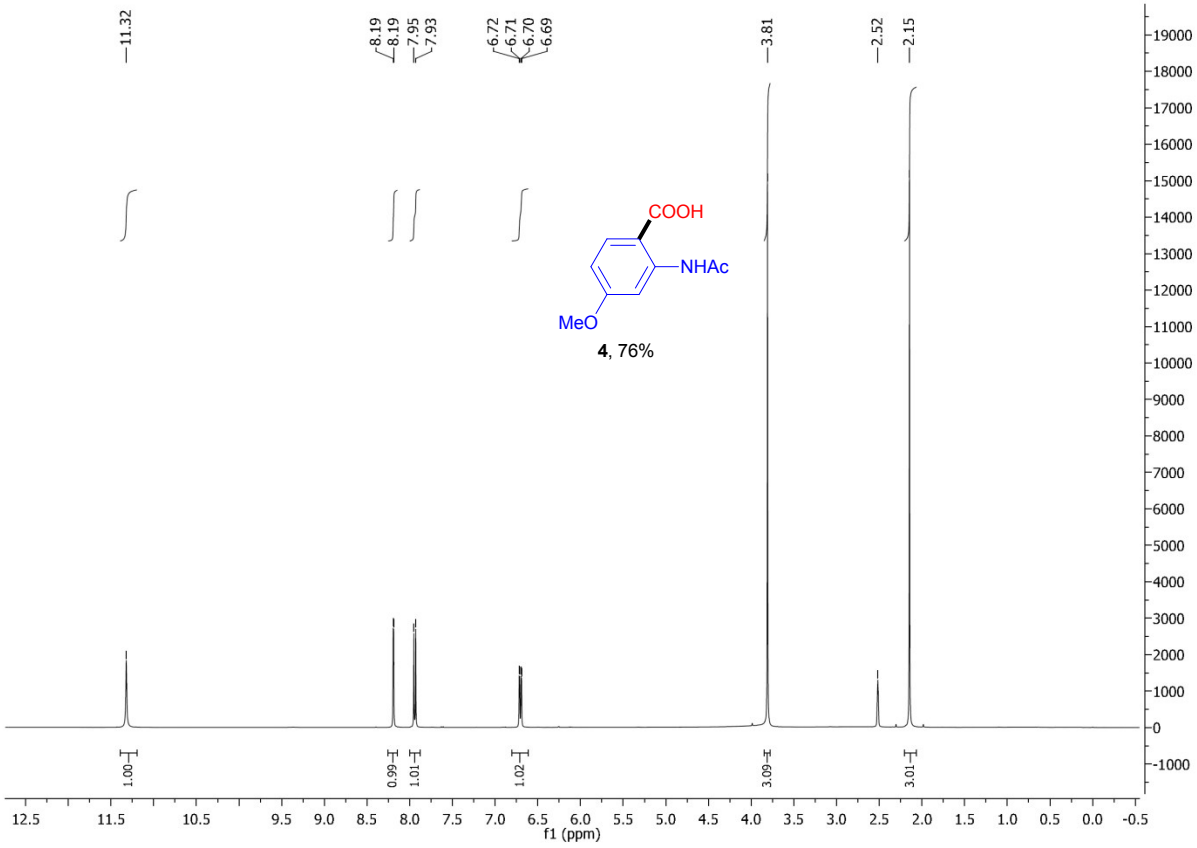
2, 81%

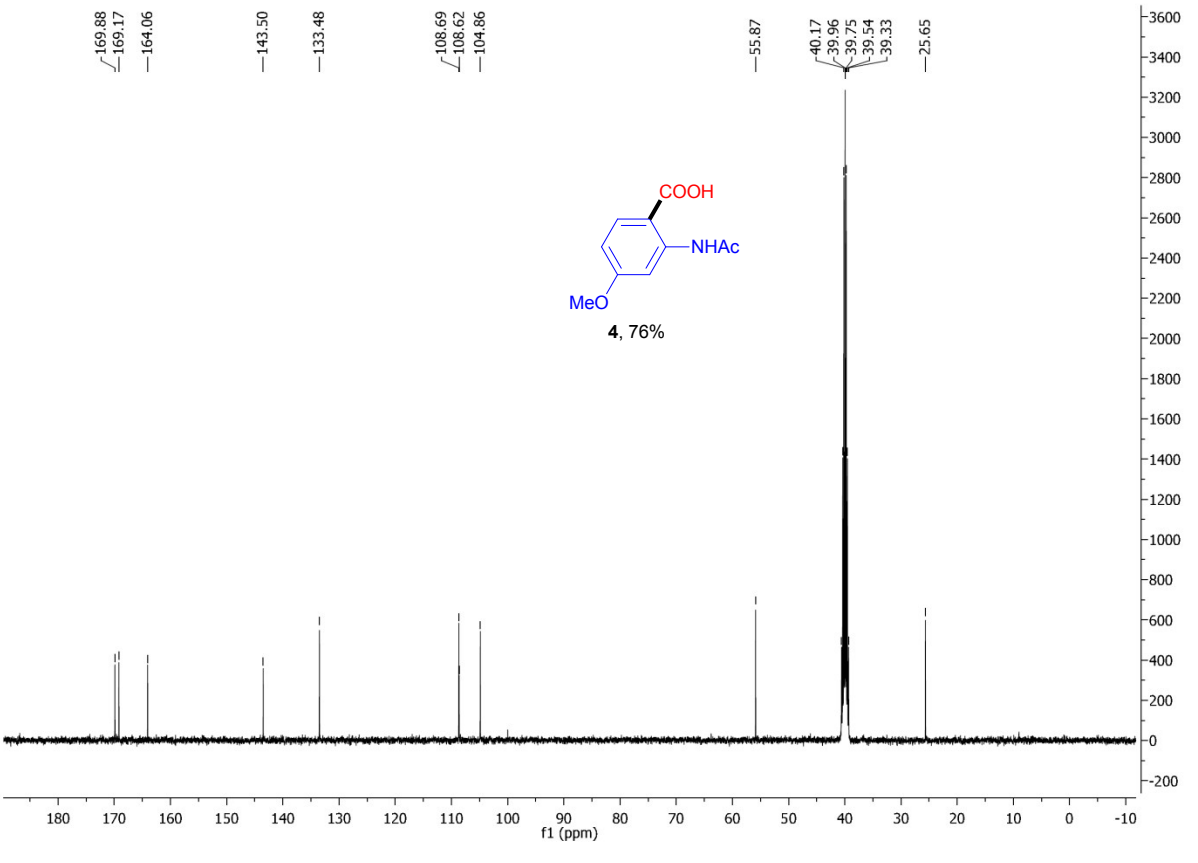

10.91
8.34
8.32
7.77
7.39
7.37
2.51
2.51
2.50
2.28
2.11
COOH
Me
NHAc
1.00
0.99
0.97
1.01
2.96
2.90
f1 (ppm)

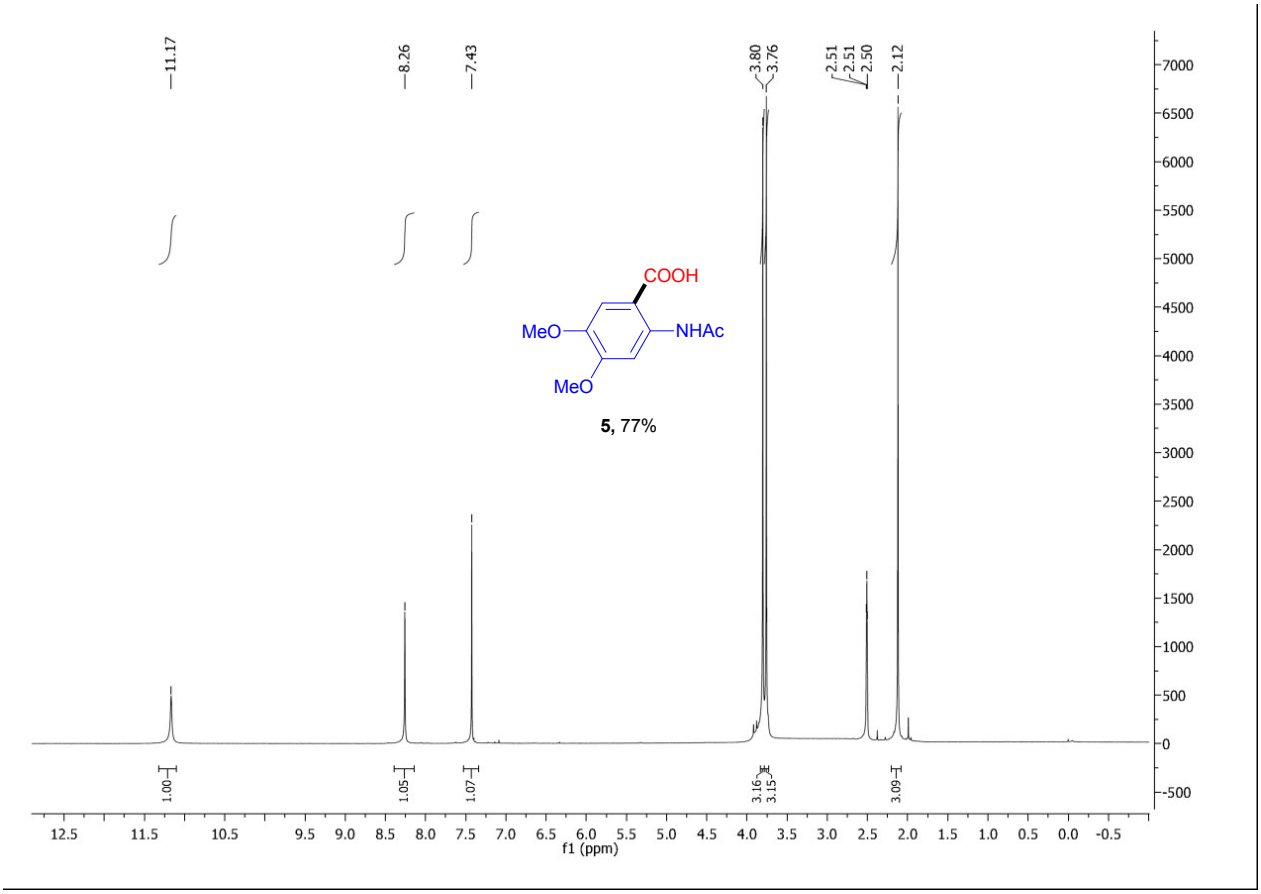
3, 80%


169.90
168.68
138.91
134.93
132.07
131.48
120.53
116.95
40.59
40.38
40.17
39.97
39.76
39.55
39.34
25.34
20.61
COOH
Me
NHAc
f1 (ppm)

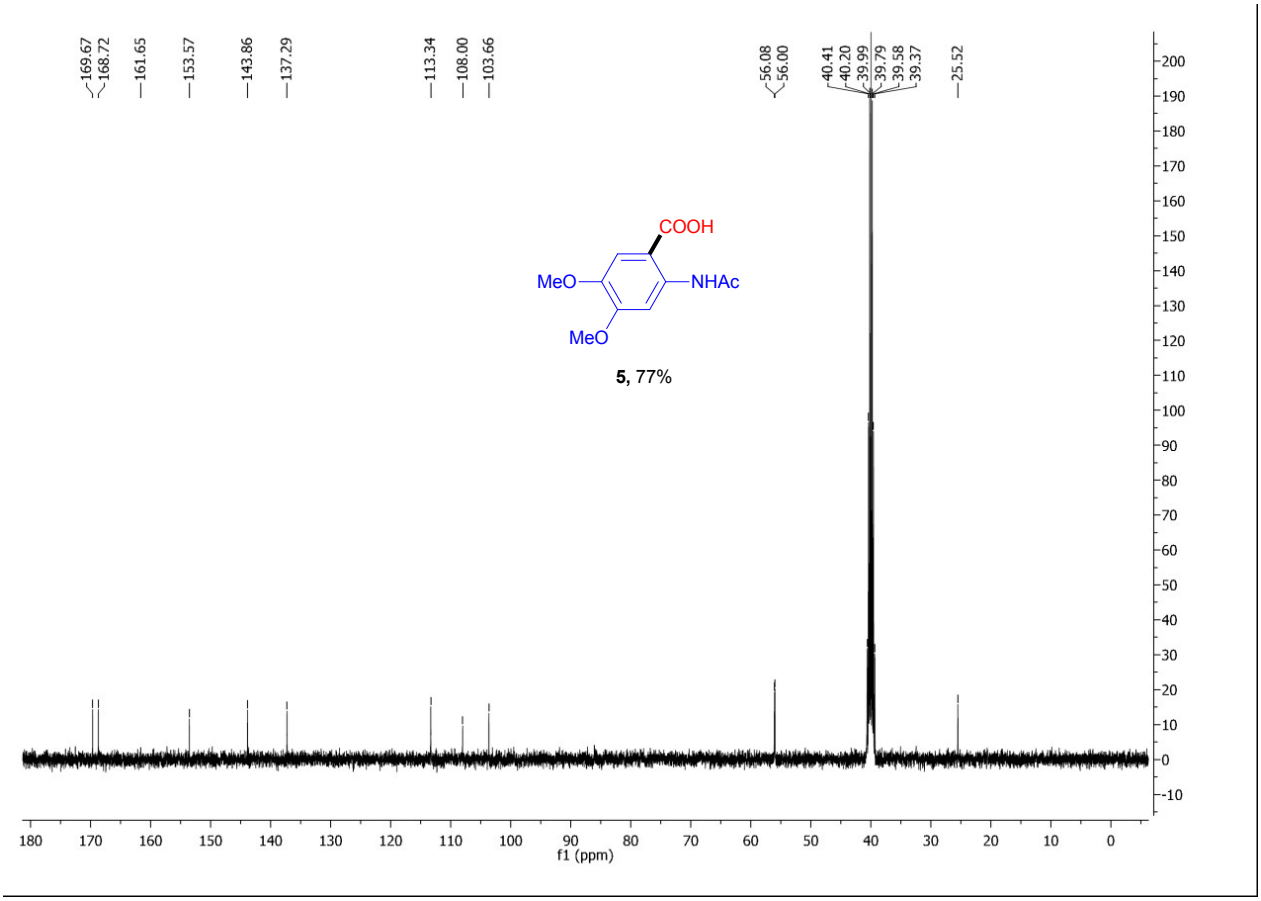
3, 80%


11.32
8.19
8.19
7.95
7.93
6.72
6.71
6.70
6.69
3.81
2.52
2.15
COOH
NHAc
MeO
4, 76%
1.00
0.99
1.01
1.02
3.09
3.01
f1 (ppm)

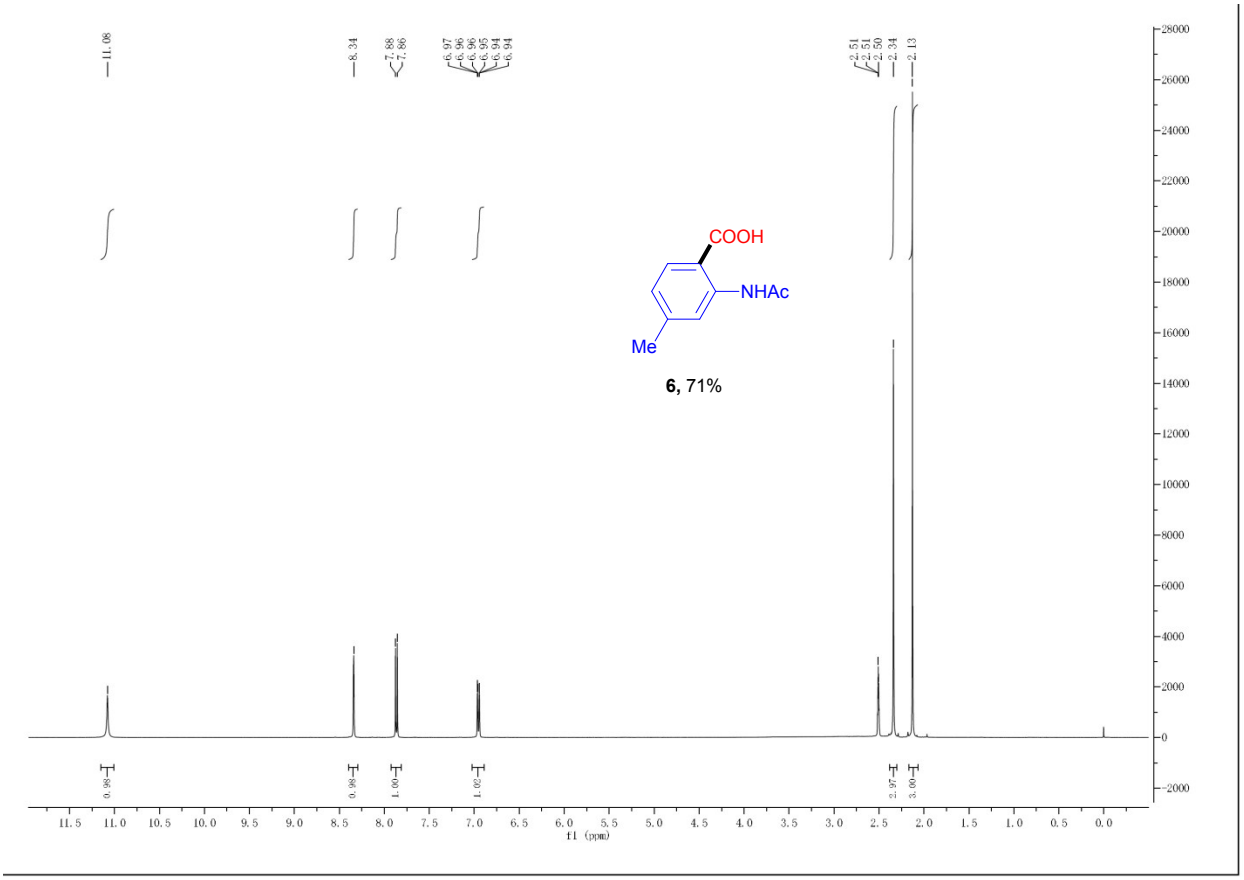

169.88
169.17
164.06
143.50
133.48
108.69
108.62
104.86
55.87
40.17
39.96
39.75
39.54
39.33
25.65
COOH
NHAc
MeO
4, 76%
f1 (ppm)


11.17
8.26
7.43
3.80
3.76
2.51
2.51
2.50
2.12
COOH
MeO
NHAc
MeO
1.00
1.05
1.07
3.16
3.15
3.09
f1 (ppm)

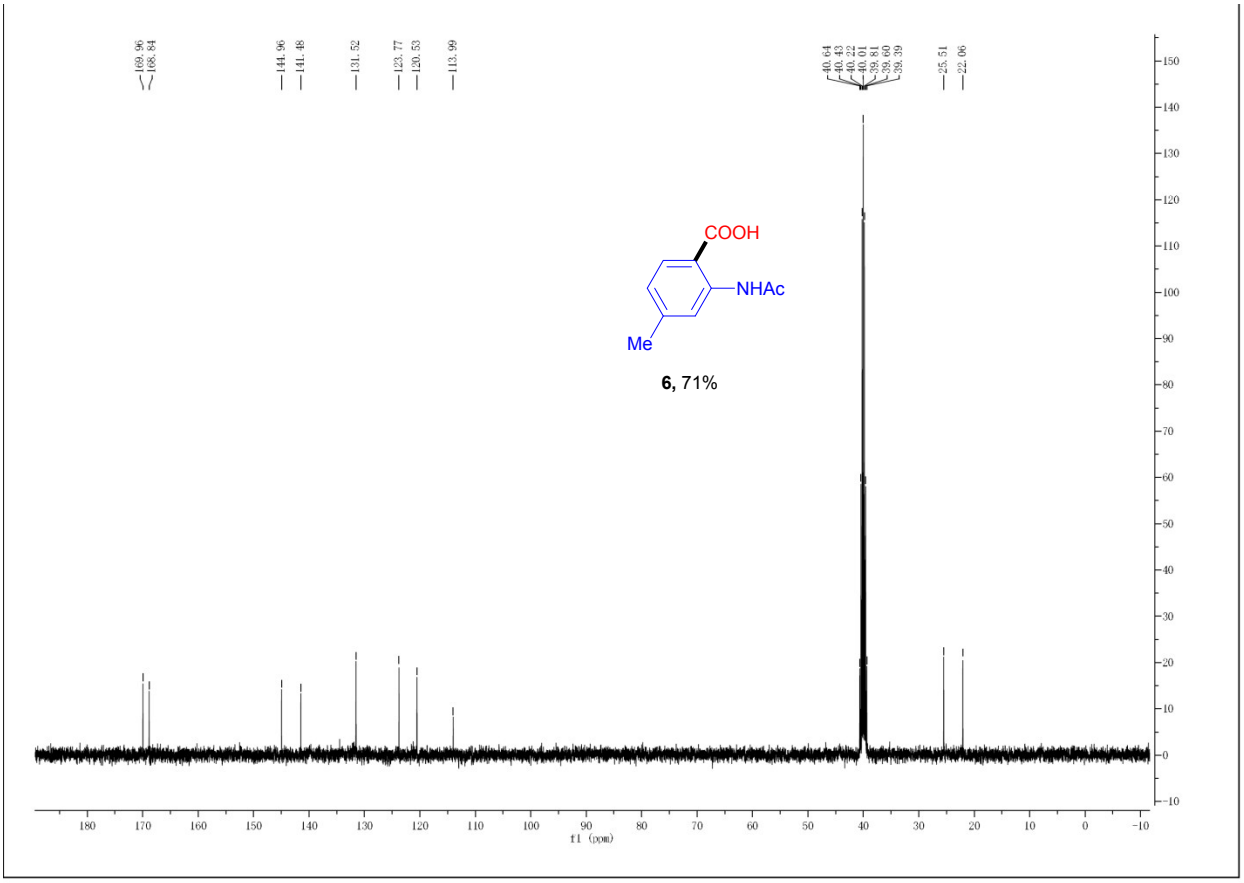
5, 77%


169.67
168.72
161.65
153.57
143.86
137.29
113.34
108.00
103.66
56.08
56.00
40.41
40.20
39.99
39.79
39.58
39.37
25.52
COOH
MeO
NHAc
MeO
f1 (ppm)

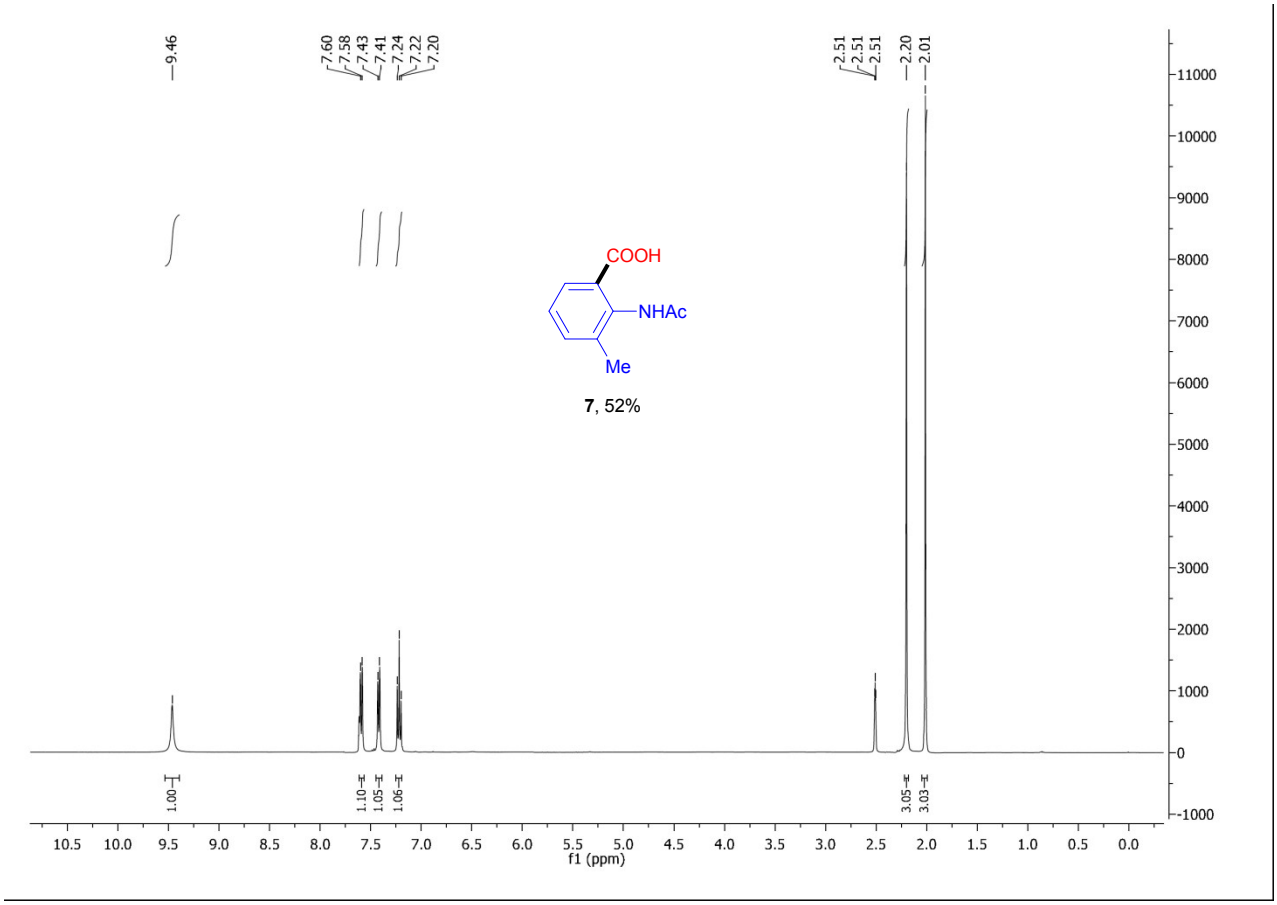
5, 77%


11.08
8.34
7.88
7.86
6.97
6.96
6.96
6.95
6.94
6.94
2.51
2.51
2.50
2.34
2.13
COOH
NHAc
Me
0.98
0.98
1.00
1.02
2.97
3.00
f1 (ppm)

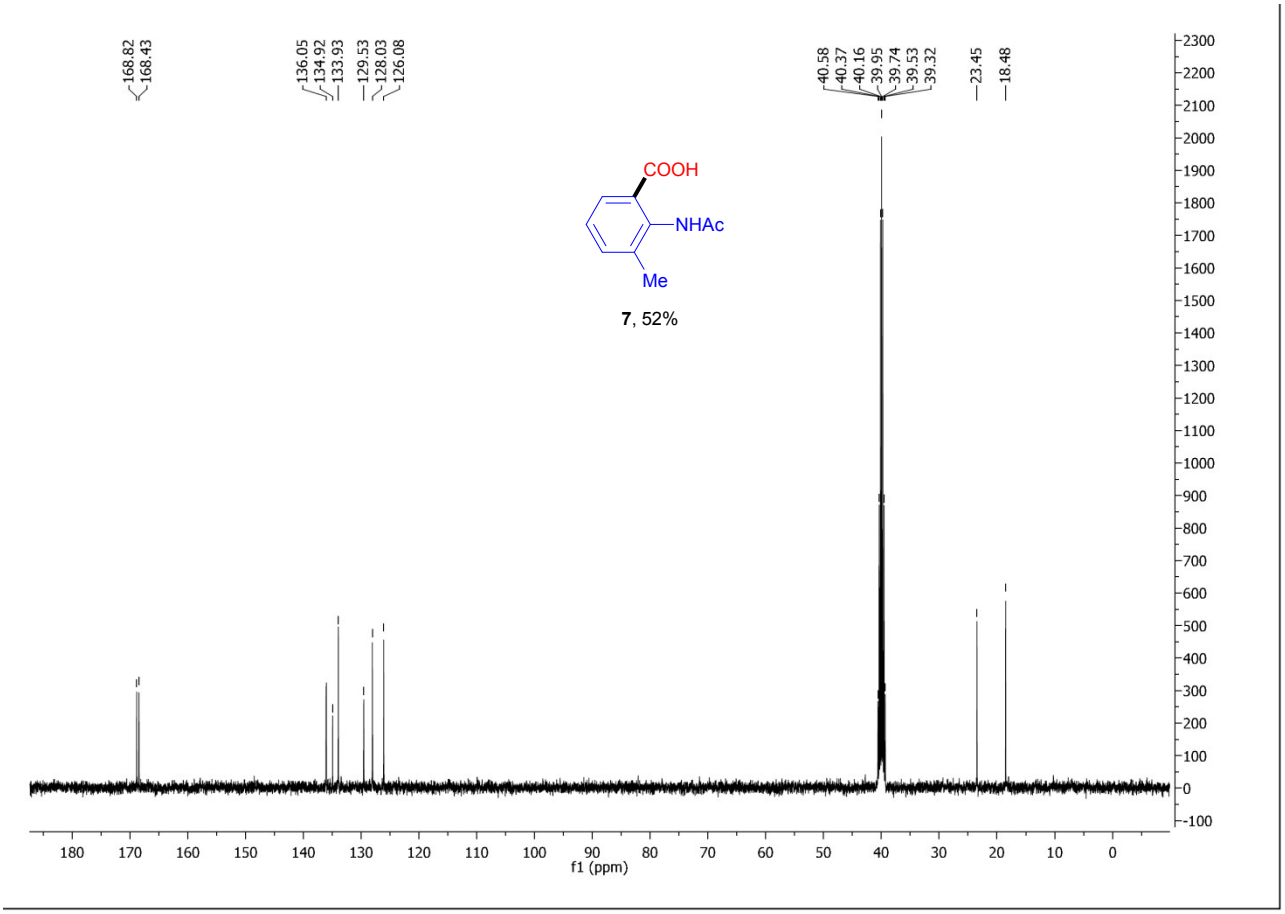
6, 71%


169.96
168.84
144.96
141.48
131.52
123.77
120.53
113.99
40.64
40.43
40.22
40.01
39.81
39.60
39.39
25.51
22.06
COOH
NHAc
Me
f1 (ppm)

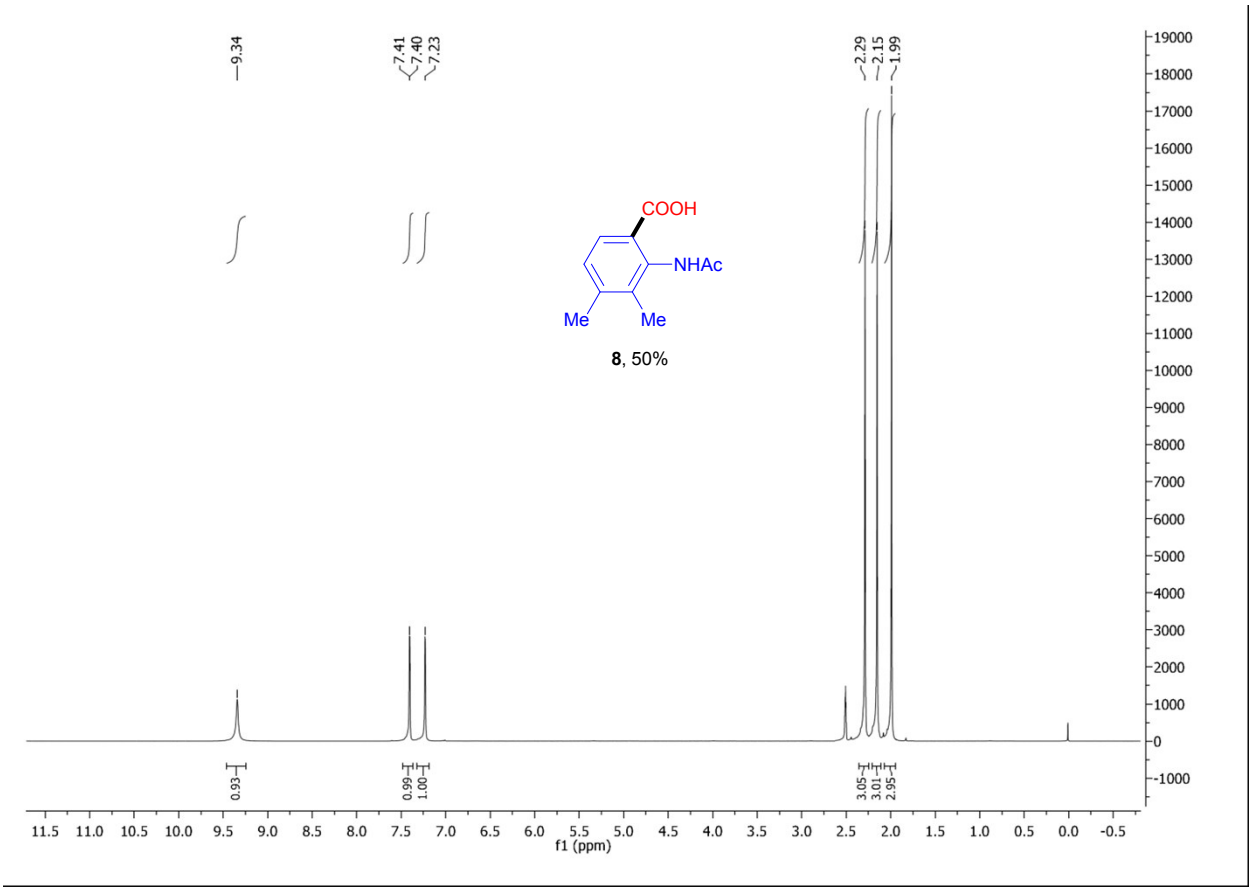
6, 71%


9.46
7.60
7.58
7.43
7.41
7.24
7.22
7.20
2.51
2.51
2.51
2.20
2.01
COOH
NHAc
Me
1.00
1.10
1.05
1.06
3.05
3.03
f1 (ppm)

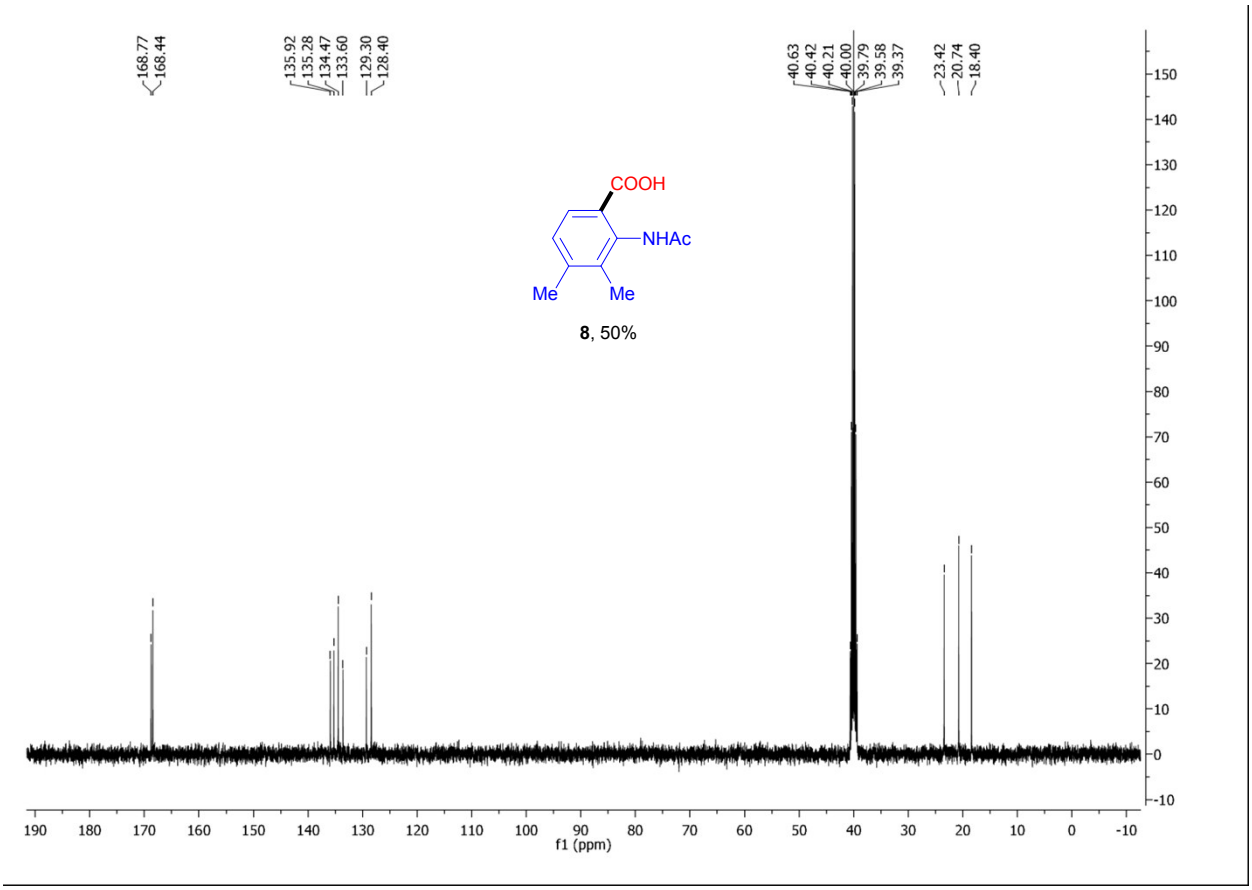
7, 52%


168.82
168.43
136.05
134.92
133.93
129.53
128.03
126.08
40.58
40.37
40.16
39.95
39.74
39.53
39.32
23.45
18.48
COOH
NHAc
Me
f1 (ppm)

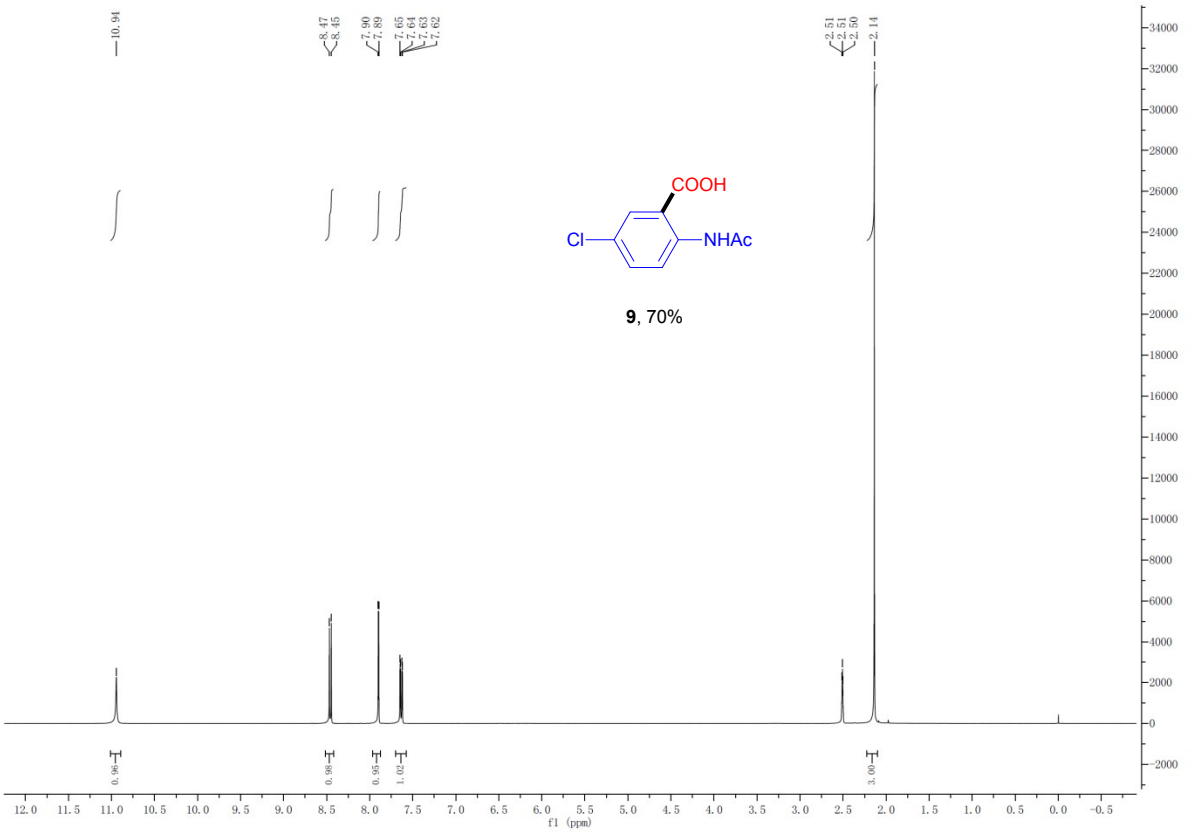
7, 52%


9.34
7.41
7.40
7.23
2.29
2.15
1.99
COOH
NHAc
Me
Me
0.93
0.99
1.00
3.05
3.01
2.95
f1 (ppm)

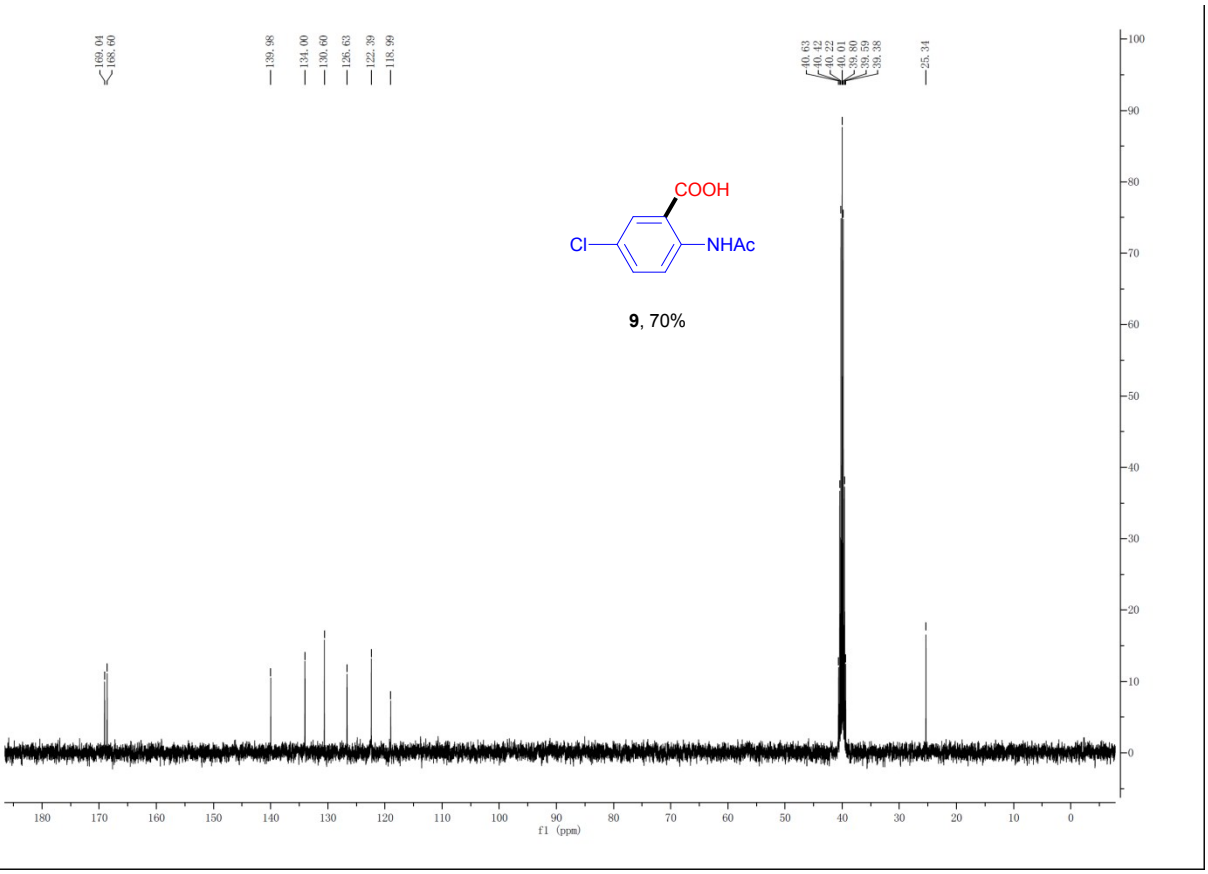
8, 50%


168.77
168.44
135.92
135.28
134.47
133.60
129.30
128.40
40.63
40.42
40.21
40.00
39.79
39.58
39.37
23.42
20.74
18.40
COOH
NHAc
Me
Me
f1 (ppm)

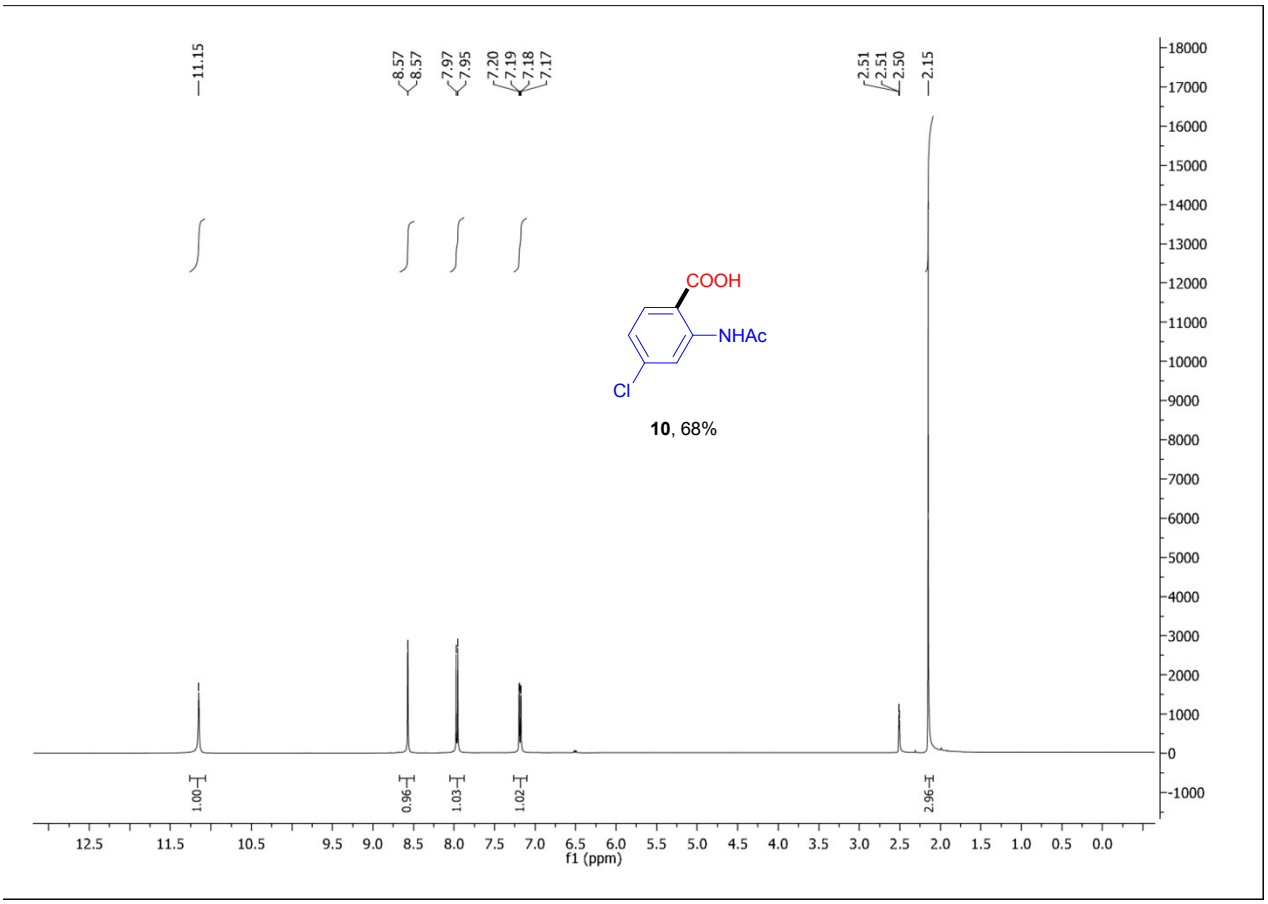
8, 50%


10.94
8.47
8.45
7.90
7.89
7.65
7.64
7.63
7.62
2.51
2.51
2.50
2.14
COOH
Cl
NHAc
0.96
0.98
0.95
1.02
3.00
f1 (ppm)

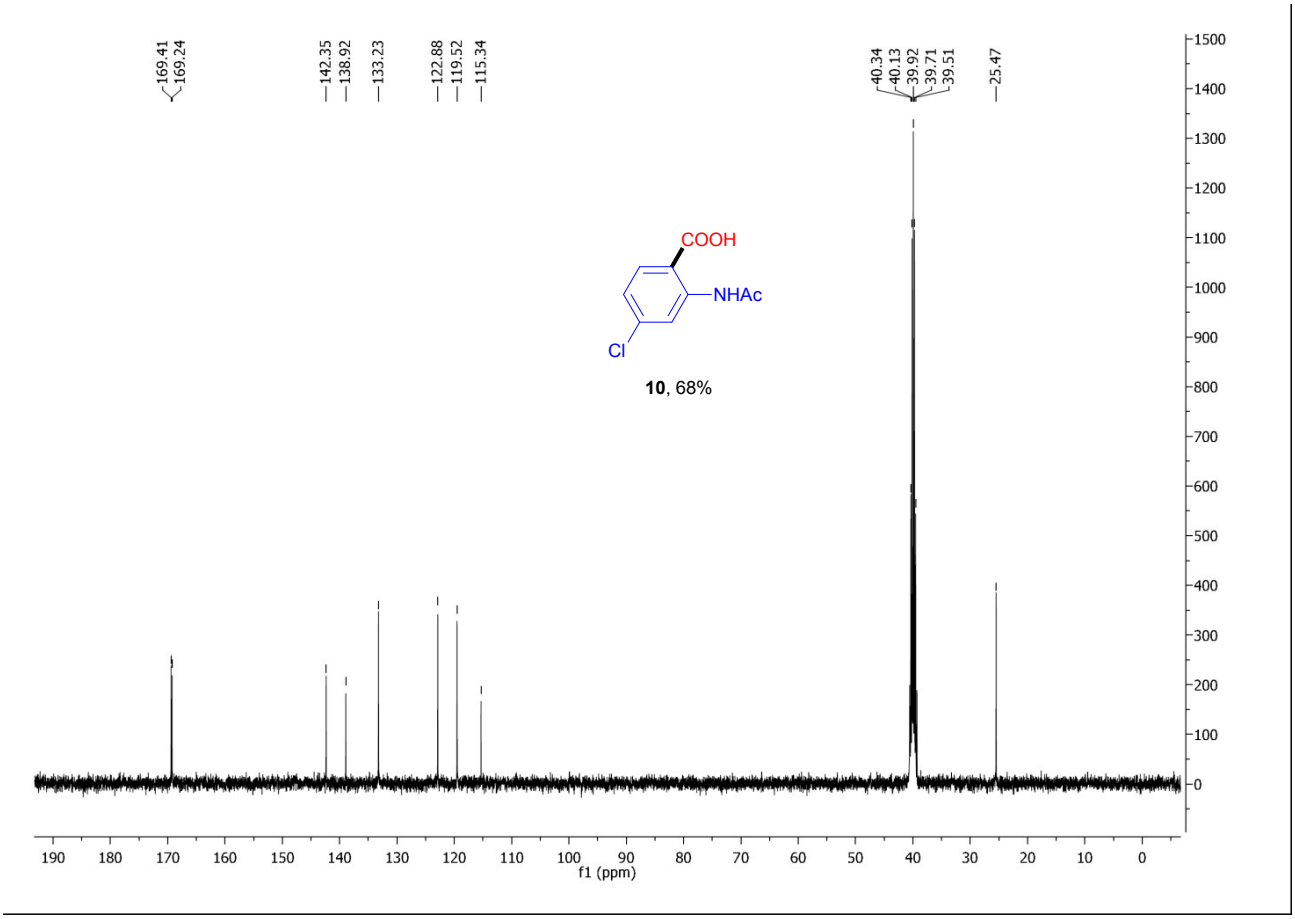
9, 70%


169.04
168.60
139.98
134.00
130.60
126.63
122.39
118.99
40.63
40.42
40.22
40.01
39.80
39.59
39.38
25.34
COOH
Cl
NHAc
f1 (ppm)

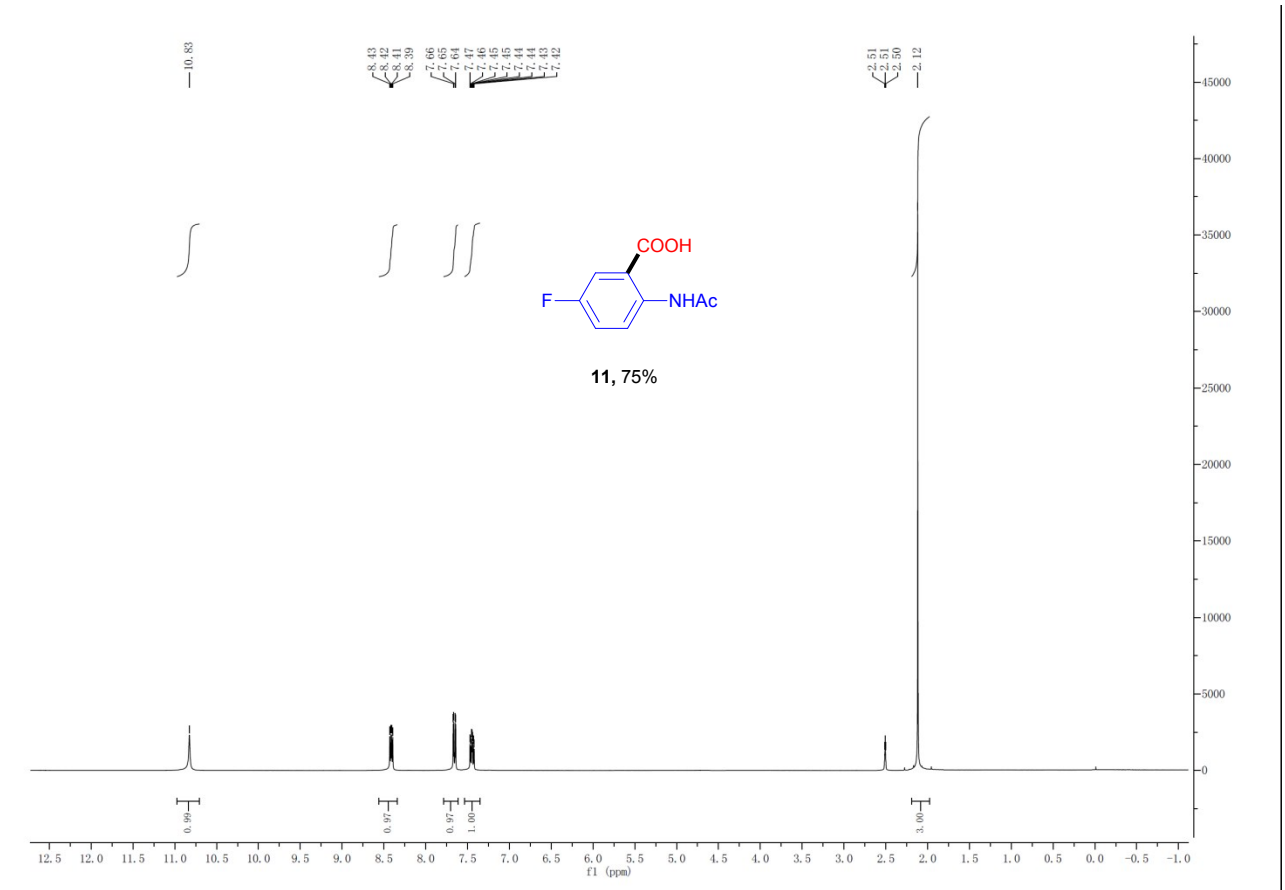
9, 70%


11.15
8.57
8.57
7.97
7.95
7.20
7.19
7.18
7.17
2.51
2.51
2.50
2.15
COOH
NHAc
Cl
1.00
0.96
1.03
1.02
2.96
f1 (ppm)

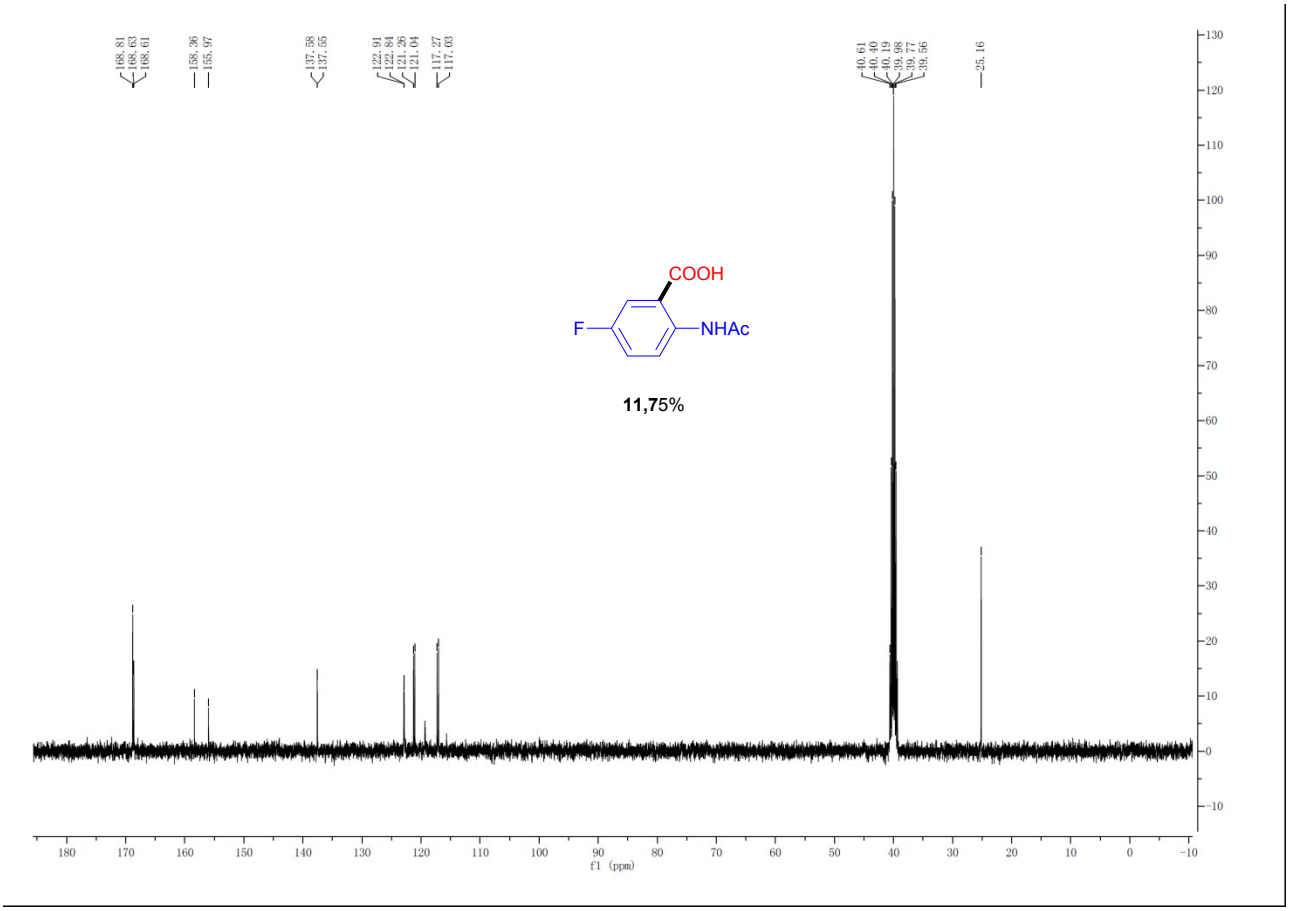
10, 68%


169.41
169.24
142.35
138.92
133.23
122.88
119.52
115.34
40.34
40.13
39.92
39.71
39.51
25.47
COOH
NHAc
Cl
f1 (ppm)

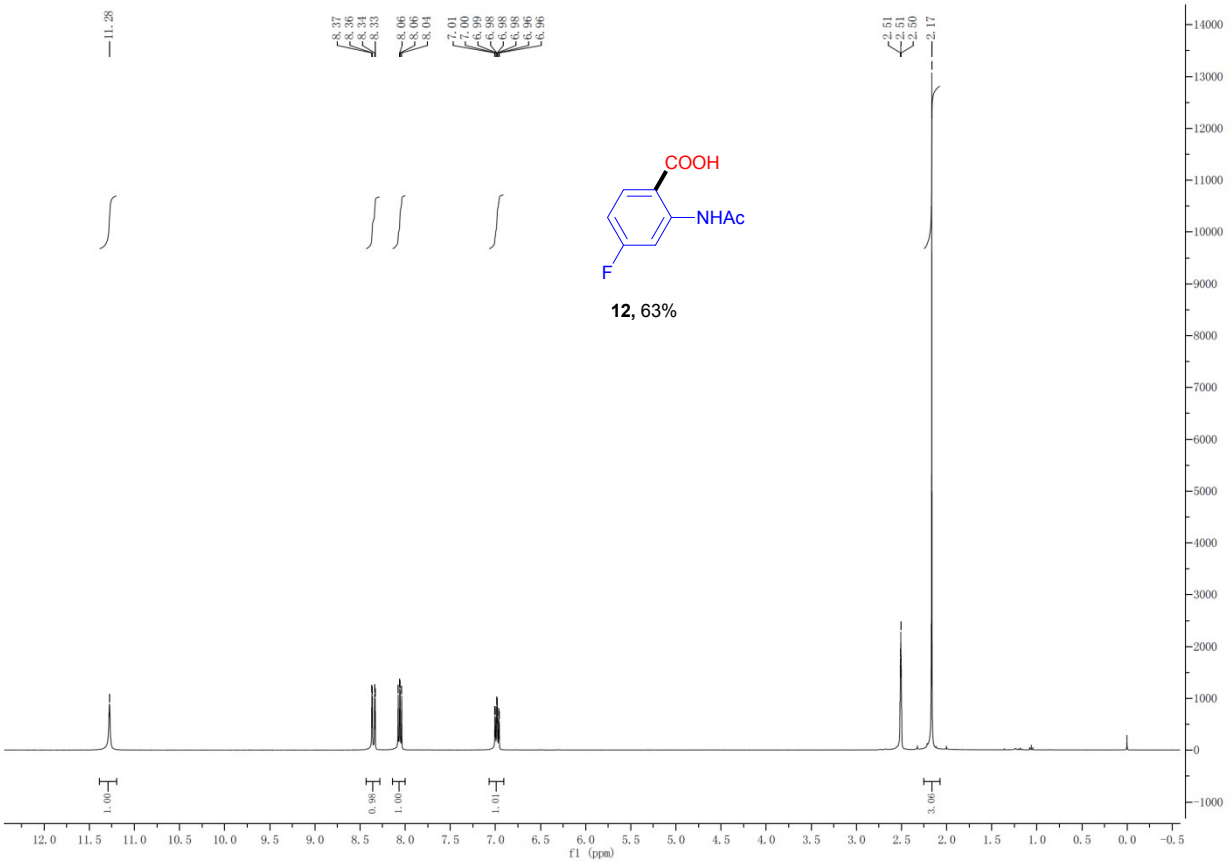
10, 68%


10.83
8.43
8.42
8.41
8.39
7.66
7.65
7.64
7.47
7.46
7.45
7.45
7.44
7.44
7.43
7.42
2.51
2.51
2.50
2.12
COOH
F
NHAc
0.99
0.97
0.97
1.00
3.00
f1 (ppm)

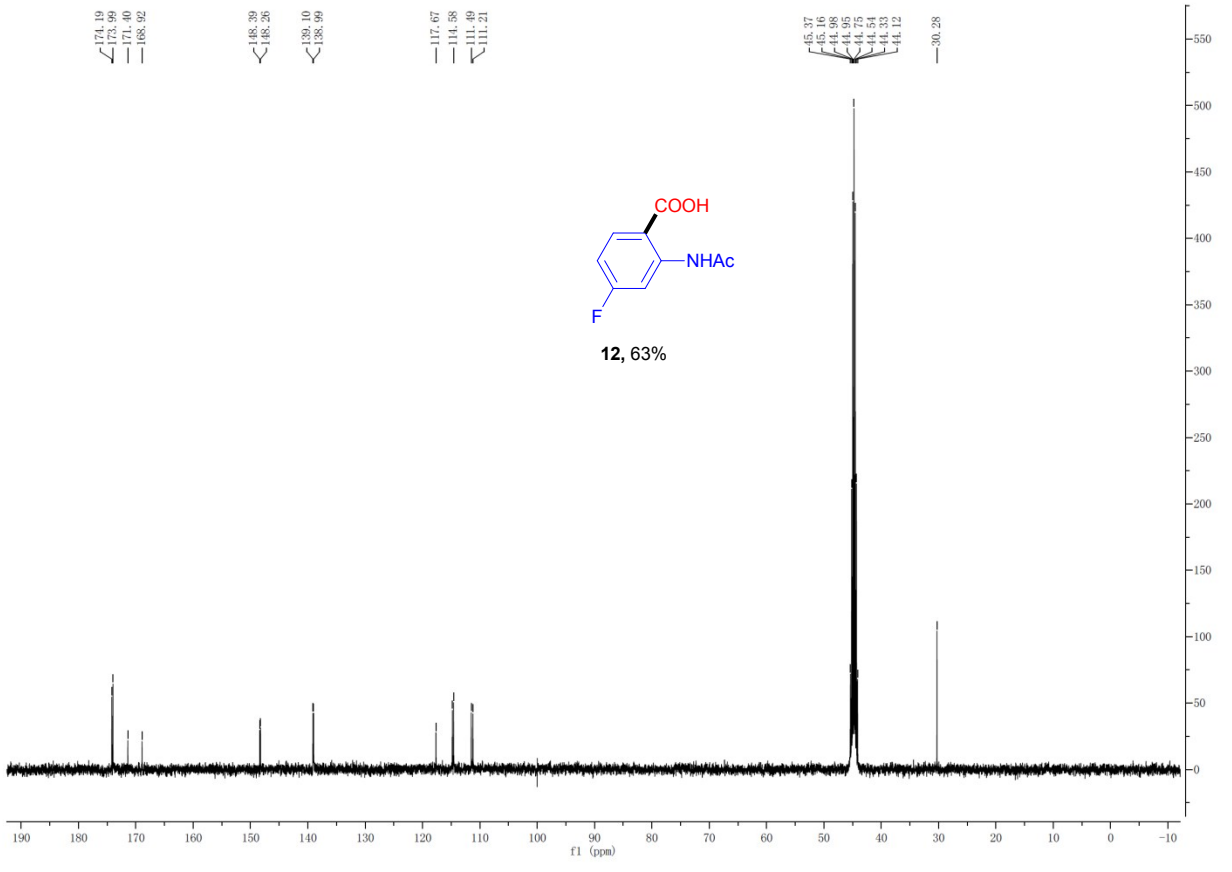
11, 75%


168.81
168.63
168.61
158.36
155.97
137.58
137.55
122.91
122.84
121.26
121.04
117.27
117.03
40.61
40.40
40.19
39.98
39.77
39.56
25.16
COOH
F
NHAc
f1 (ppm)

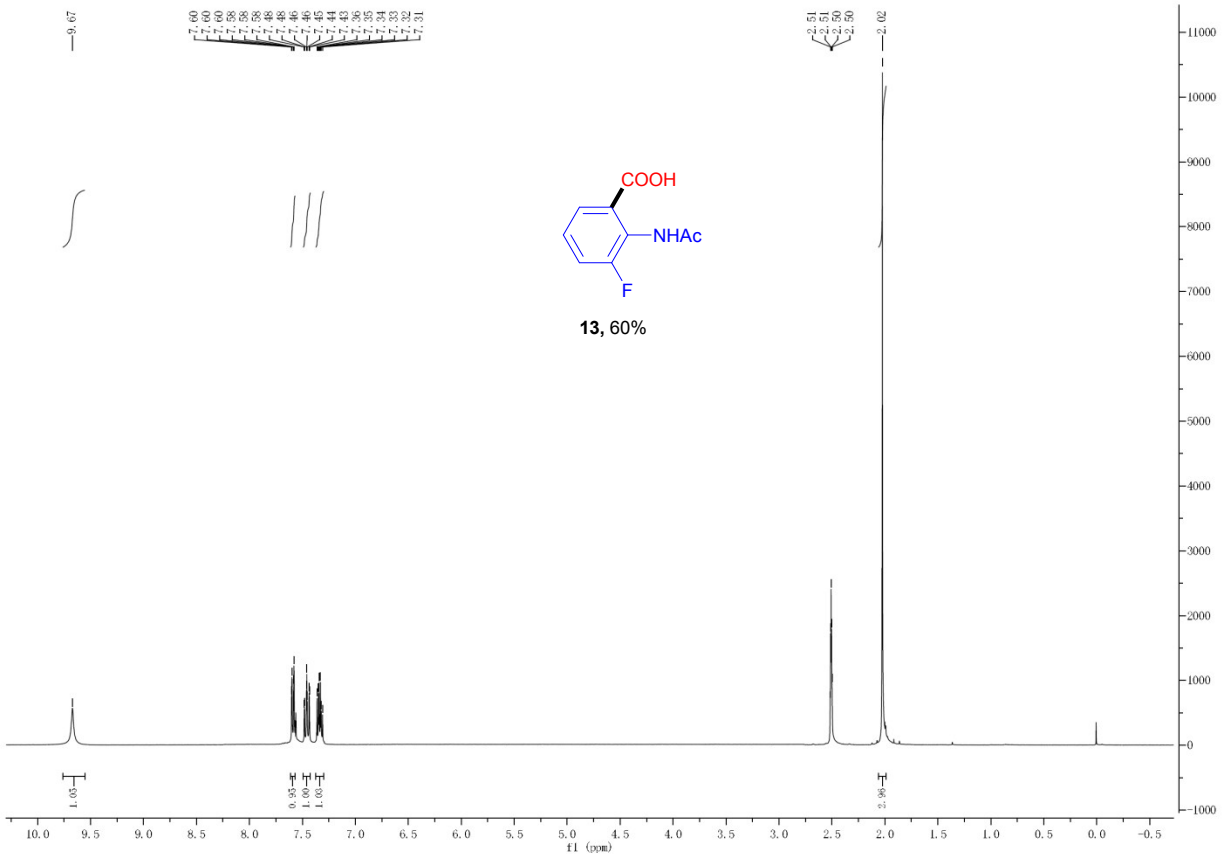
11,75%


11.28
8.37
8.36
8.34
8.33
8.06
8.06
8.04
7.01
7.00
6.99
6.98
6.98
6.96
6.96
2.51
2.51
2.50
2.17
COOH
NHAc
F
1.00
0.98
1.00
1.01
3.06
f1 (ppm)

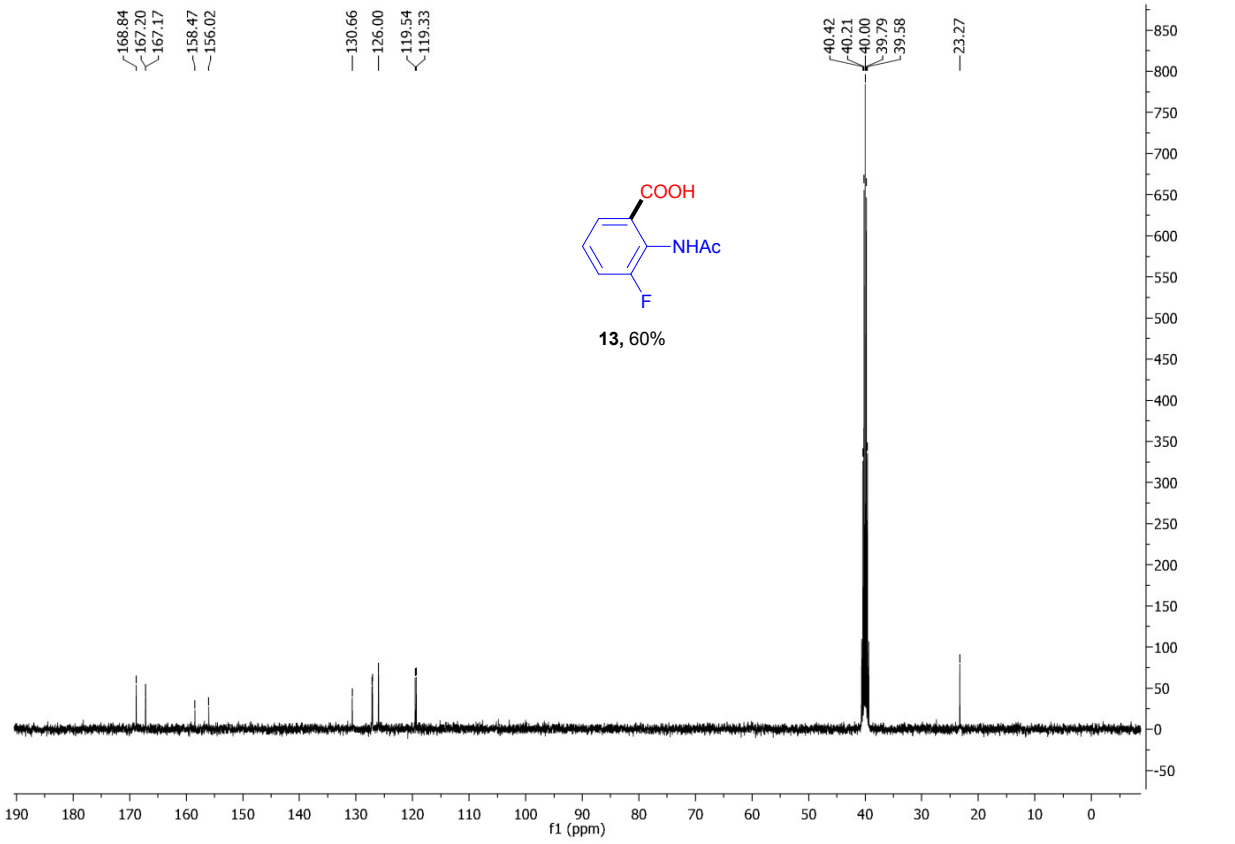
12, 63%


174.19
173.99
171.40
168.92
148.39
148.26
139.10
138.99
117.67
114.58
111.49
111.21
45.37
45.16
44.98
44.95
44.75
44.54
44.33
44.12
30.28
COOH
NHAc
F
f1 (ppm)

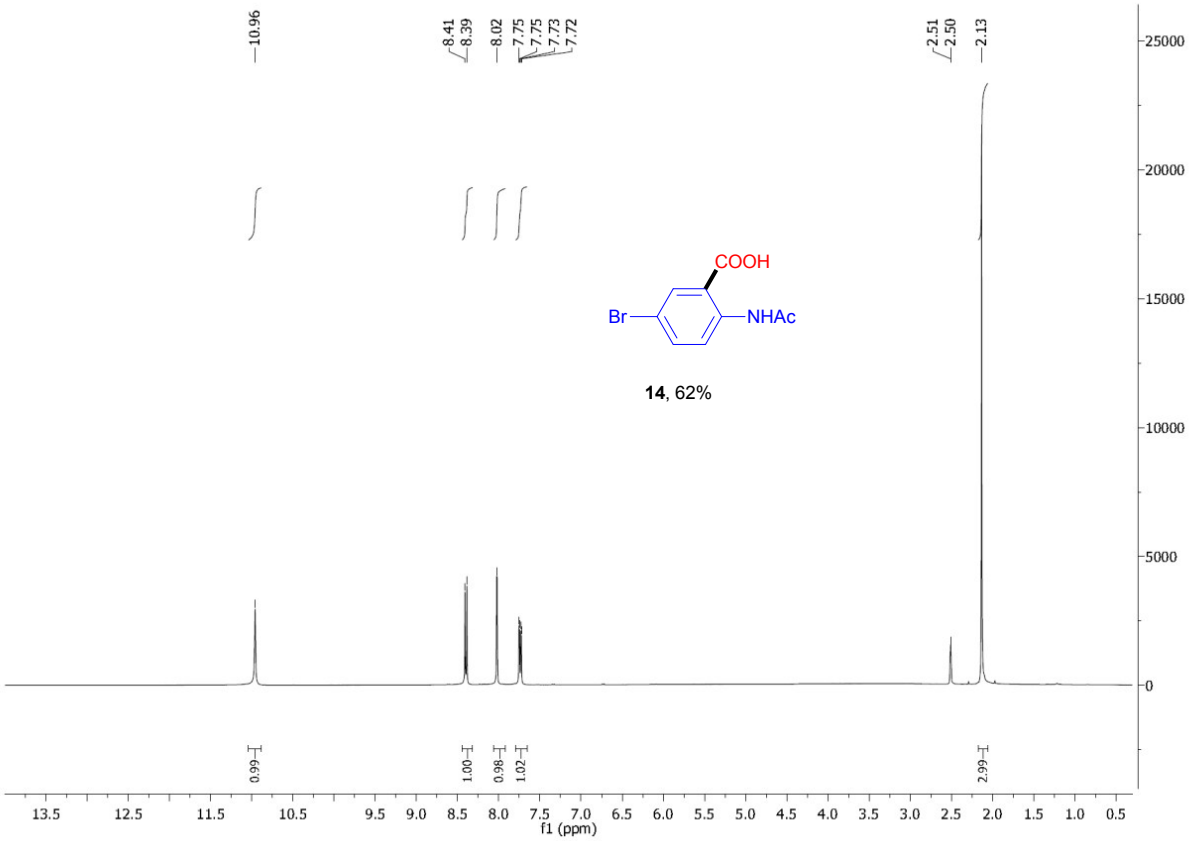
12, 63%


9.67
7.60
7.60
7.60
7.58
7.58
7.58
7.48
7.48
7.46
7.46
7.45
7.44
7.43
7.36
7.35
7.34
7.33
7.32
7.31
2.51
2.51
2.50
2.50
2.02
COOH
NHAc
F
1.03
0.95
1.00
1.03
2.96
f1 (ppm)

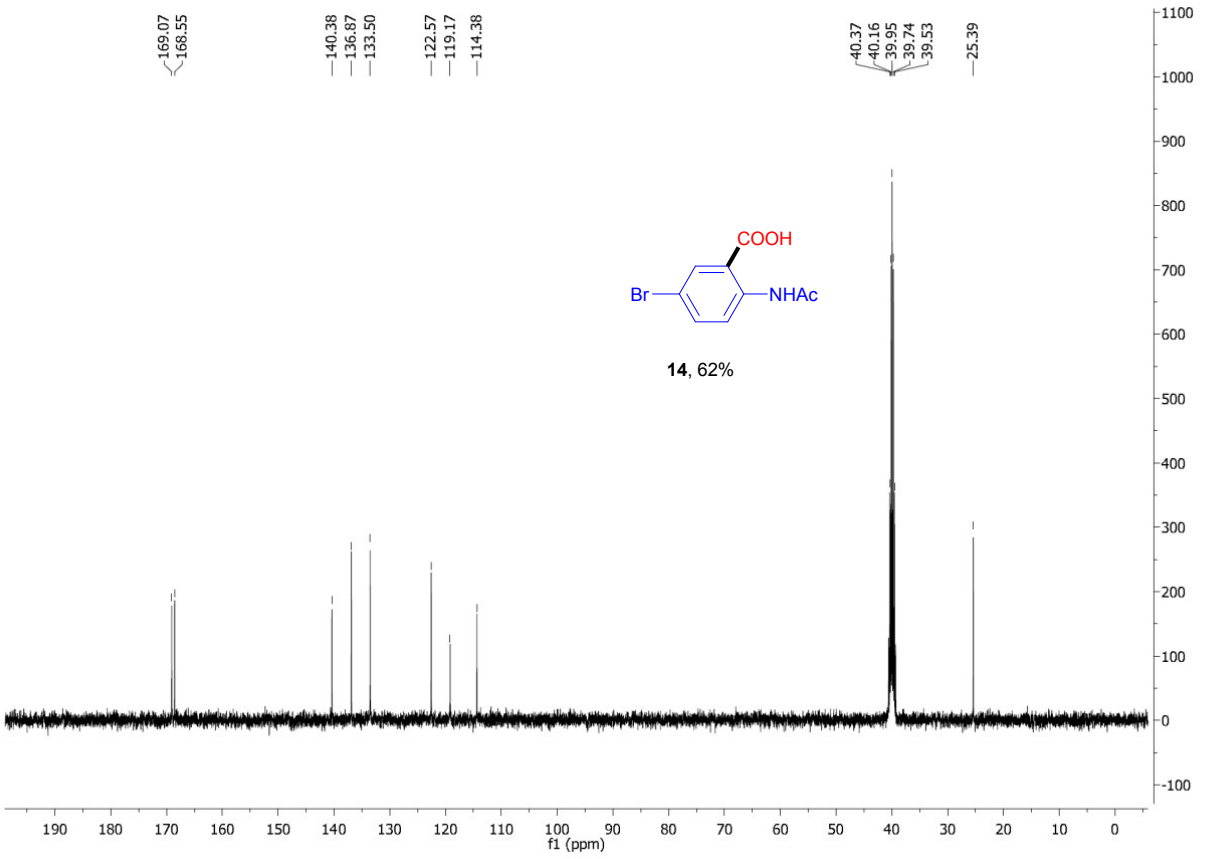
13, 60%


168.84
167.20
167.17
158.47
156.02
130.66
126.00
119.54
119.33
40.42
40.21
40.00
39.79
39.58
23.27
COOH
NHAc
F
f1 (ppm)

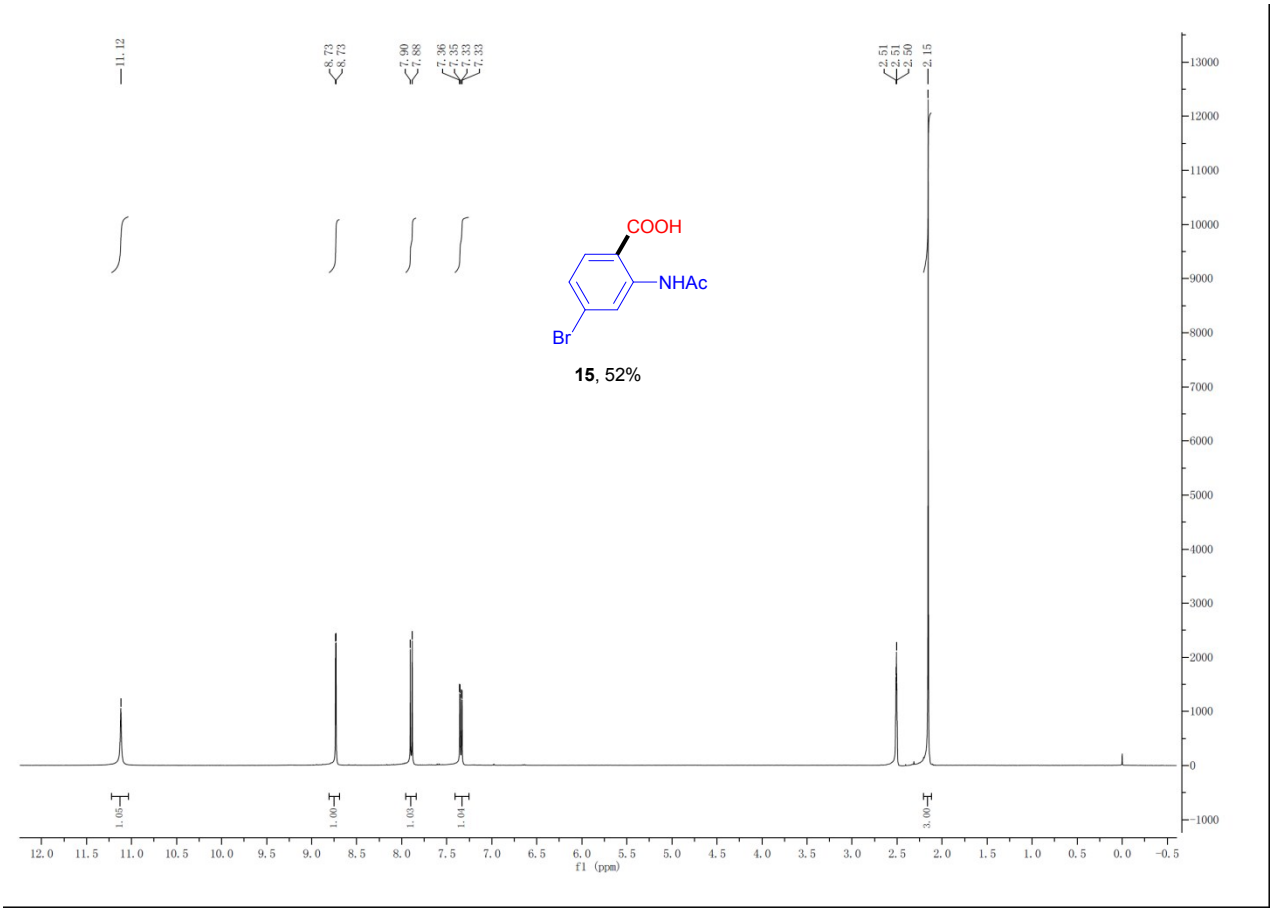
13, 60%


10.96
8.41
8.39
8.02
7.75
7.75
7.73
7.72
2.51
2.50
2.13
COOH
Br
NHAc
0.99
1.00
0.98
1.02
2.99
f1 (ppm)

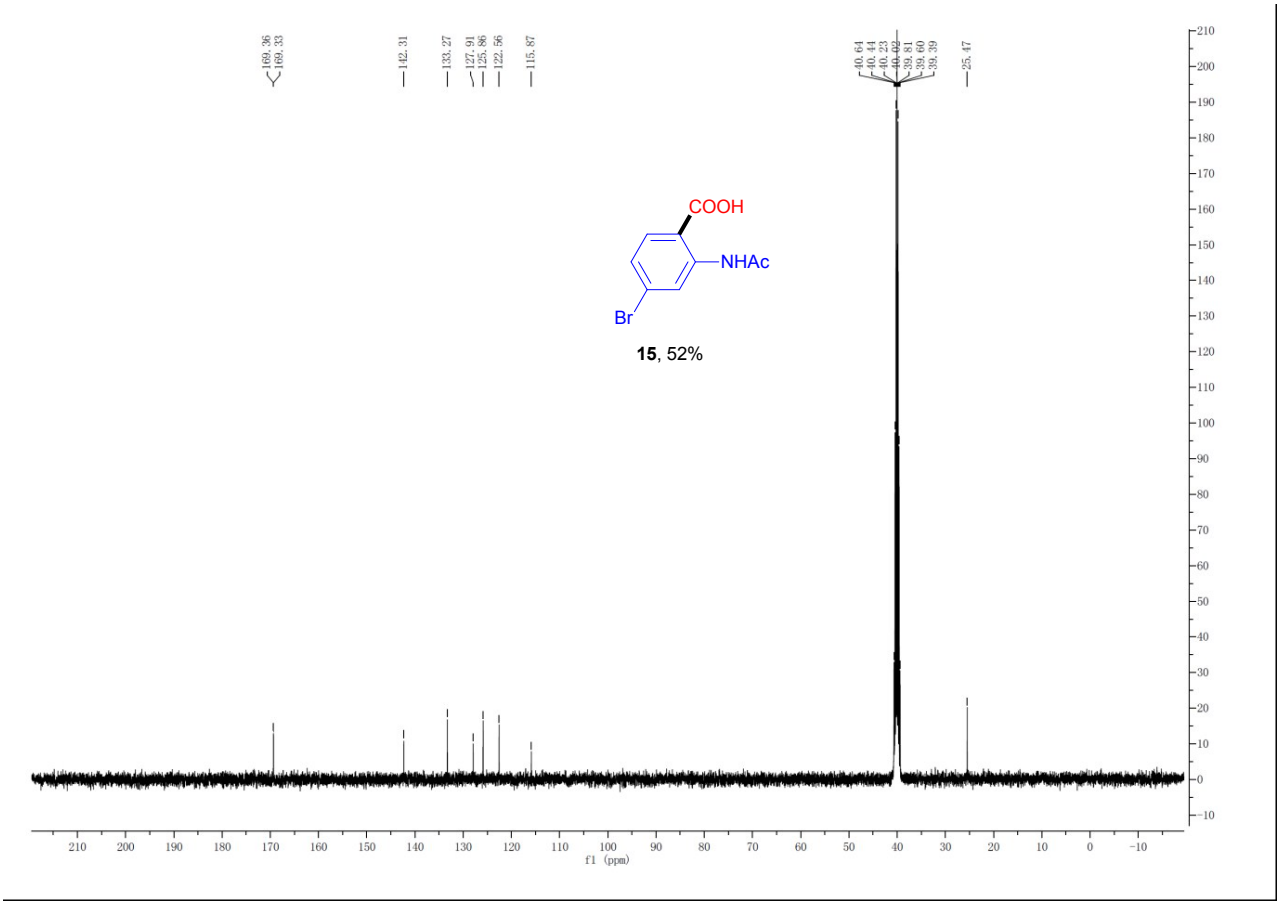
14, 62%


169.07
168.55
140.38
136.87
133.50
122.57
119.17
114.38
40.37
40.16
39.95
39.74
39.53
25.39
COOH
Br
NHAc
f1 (ppm)

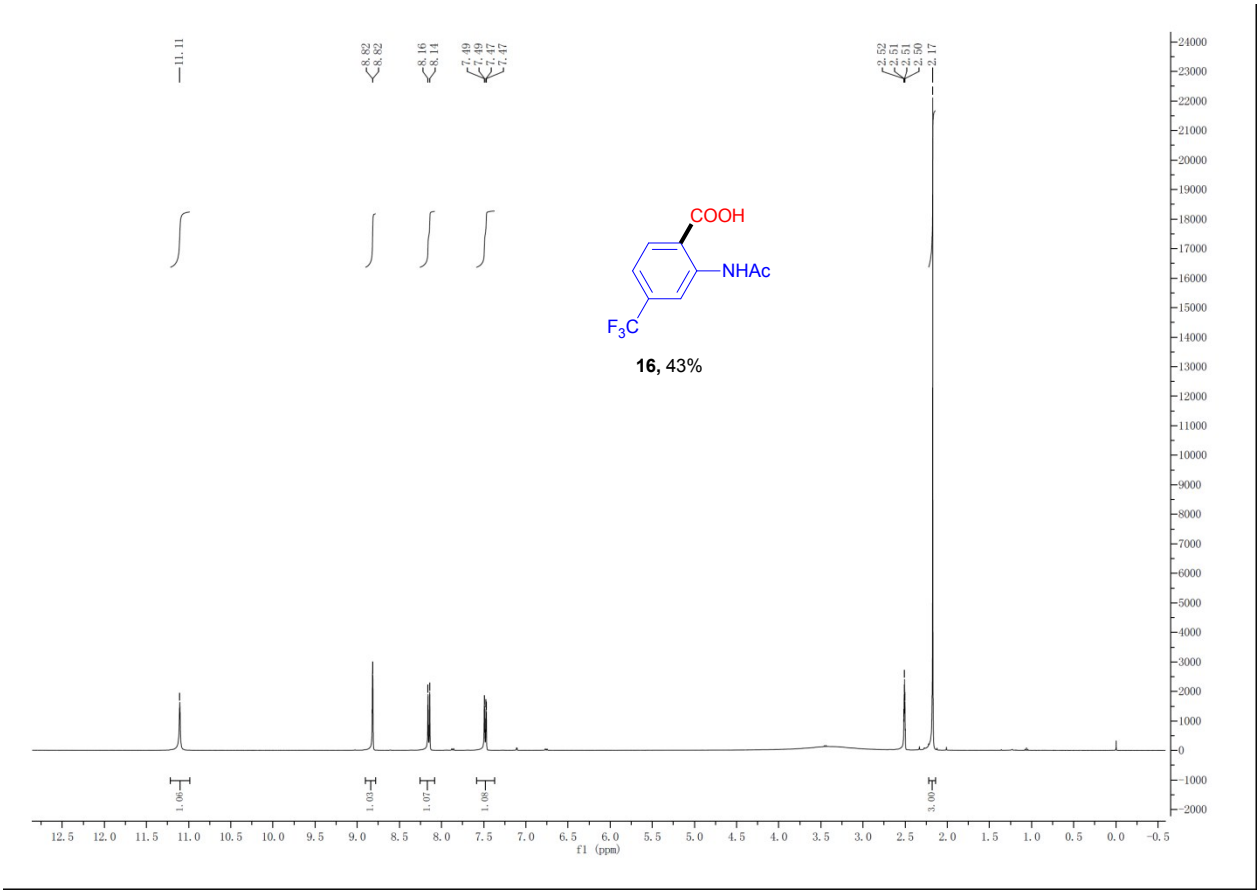
14, 62%


11.12
8.73
8.73
7.90
7.88
7.36
7.35
7.33
7.33
2.51
2.51
2.50
2.15
COOH
NHAc
Br
1.05
1.00
1.03
1.04
3.00
f1 (ppm)

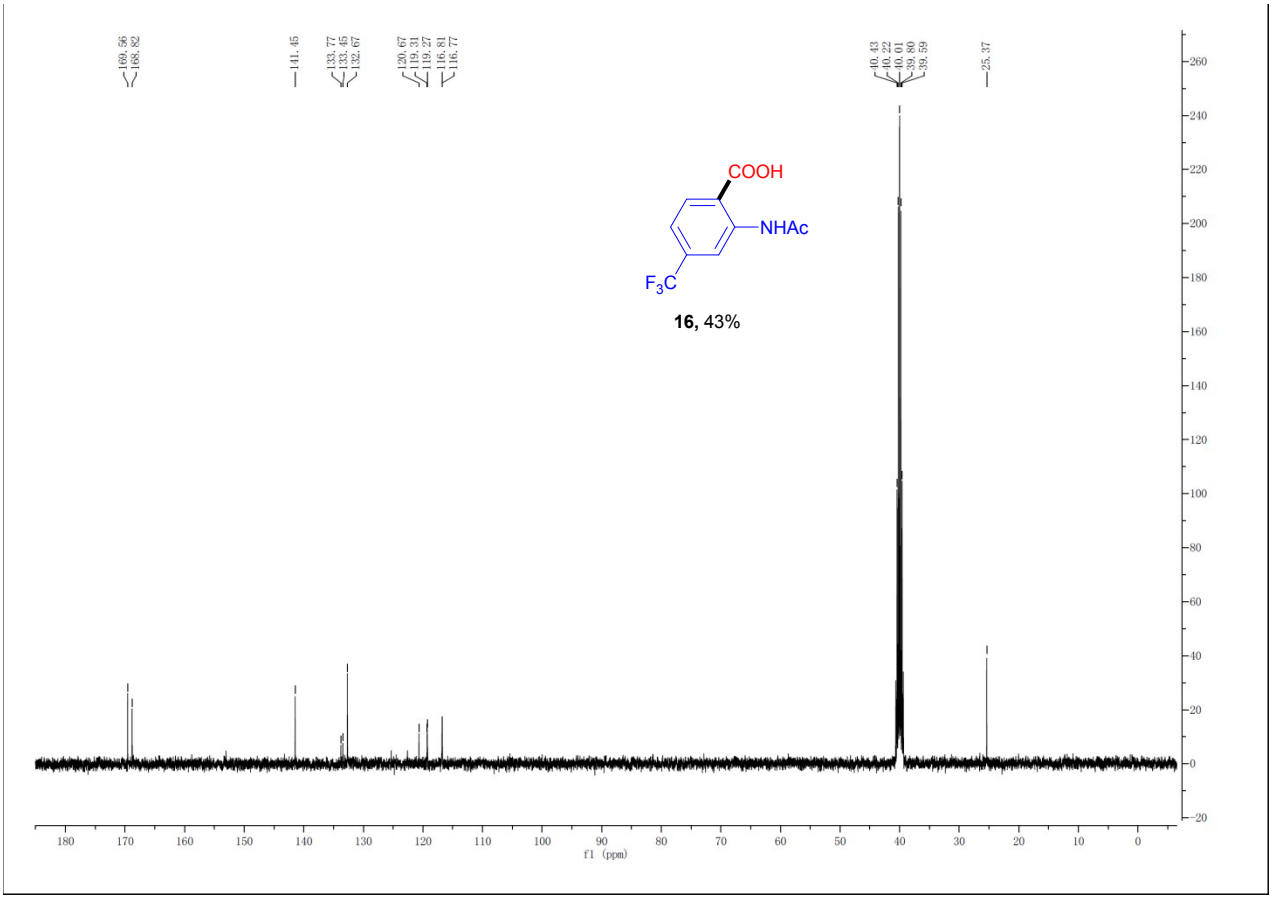
15, 52%


169.36
169.33
142.31
133.27
127.91
125.86
122.56
115.87
40.64
40.44
40.23
40.02
39.81
39.60
39.39
25.47
COOH
NHAc
Br
f1 (ppm)

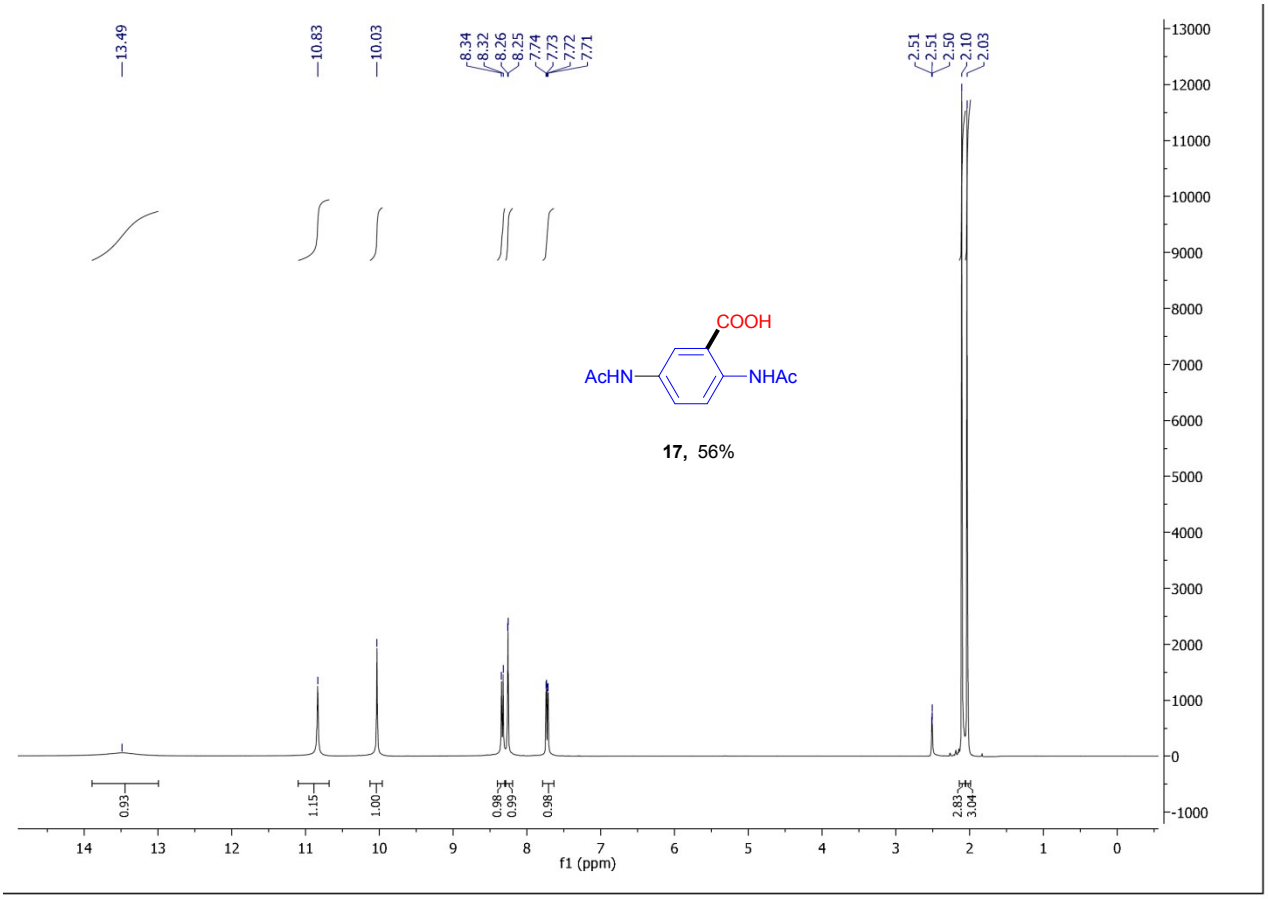
15, 52%


11.11
8.82
8.82
8.16
8.14
7.49
7.49
7.47
7.47
2.52
2.51
2.51
2.50
2.17
COOH
NHAc
F3C
1.06
1.03
1.07
1.08
3.00
f1 (ppm)

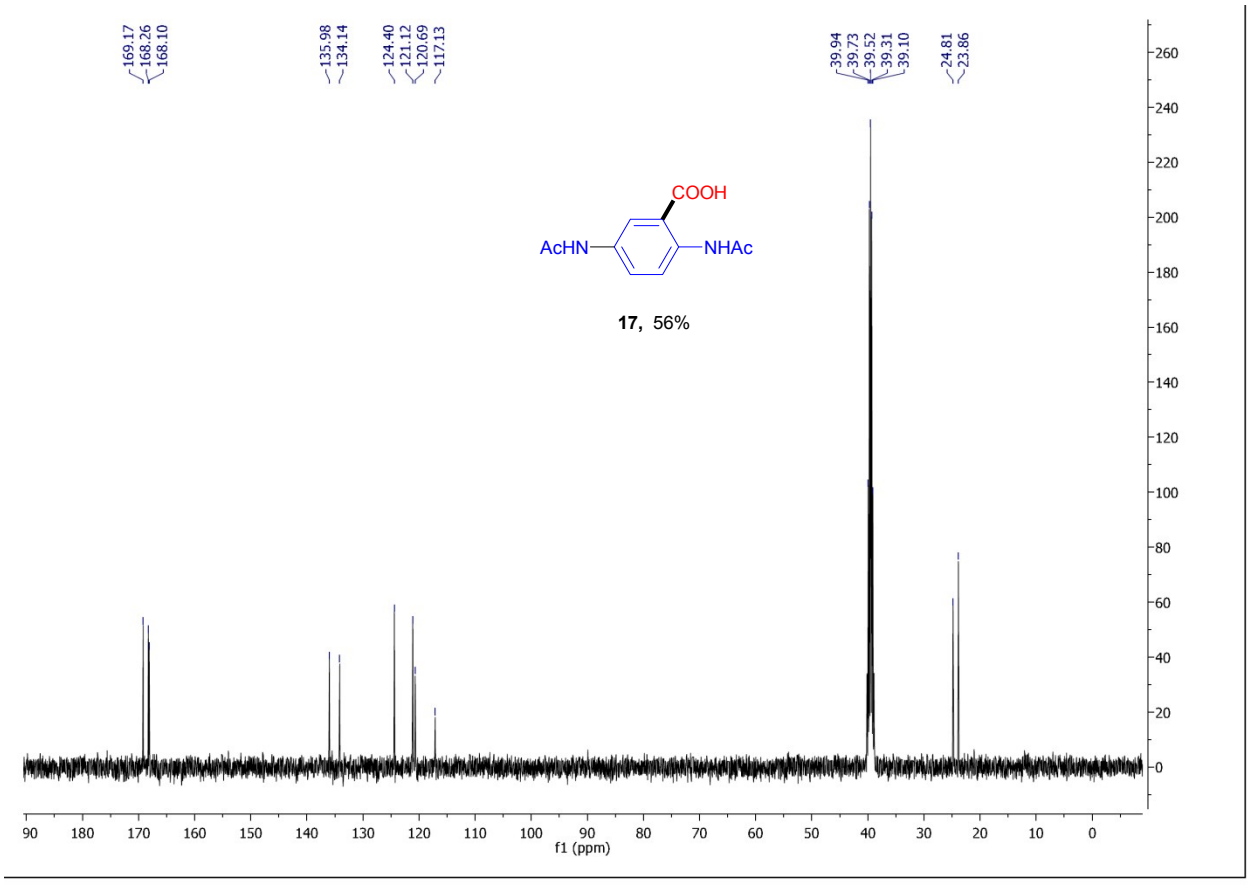
16, 43%


169.56
168.82
141.45
133.77
133.45
132.67
130.67
119.31
119.27
116.81
116.77
40.43
40.22
40.01
39.80
39.59
25.37
COOH
NHAc
F3C
f1 (ppm)

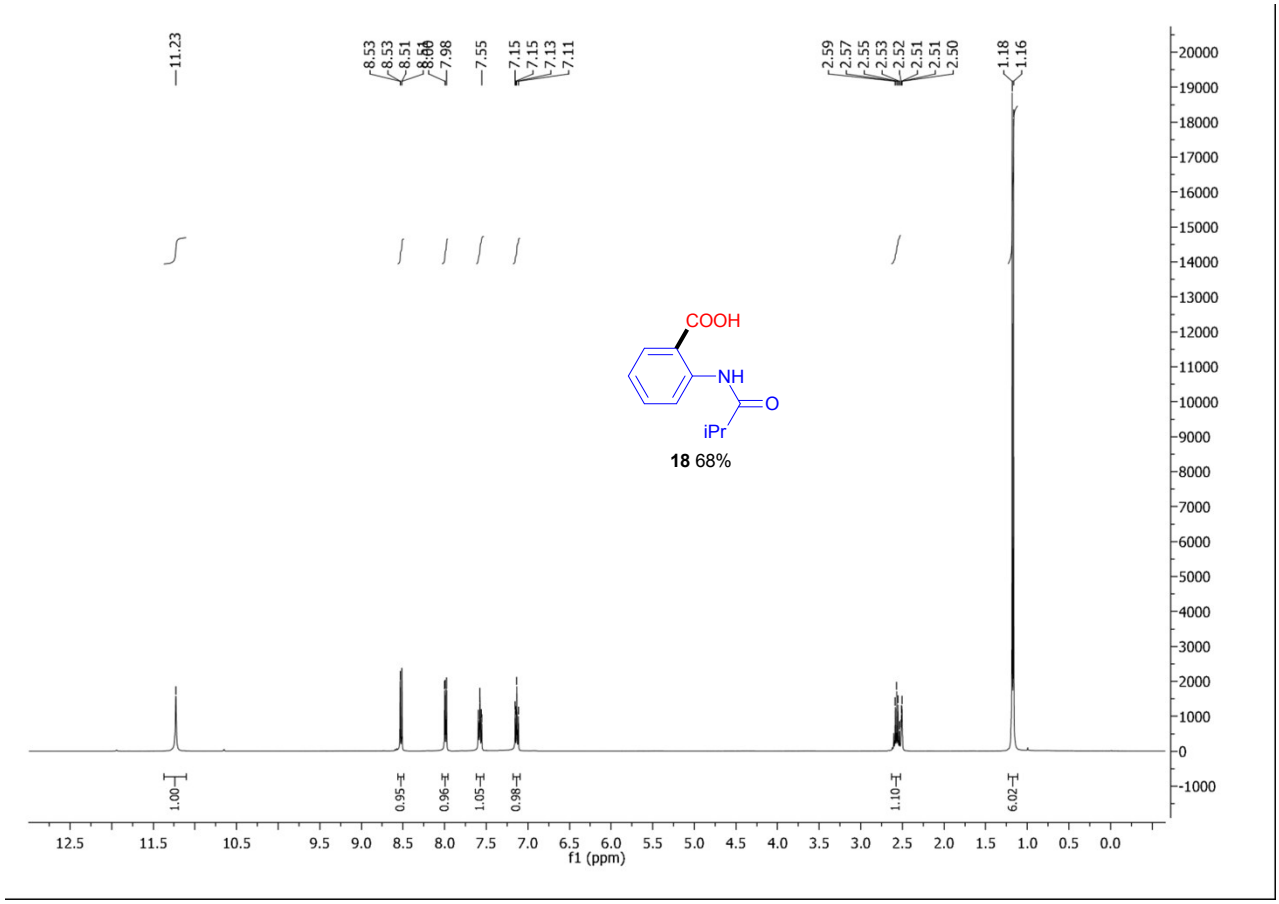
16, 43%


13.49
10.83
10.03
8.34
8.32
8.26
8.25
7.74
7.73
7.72
7.71
2.51
2.51
2.50
2.10
2.03
COOH
AcHN
NHAc
0.93
1.15
1.00
0.98
0.99
0.98
2.83
3.04
f1 (ppm)

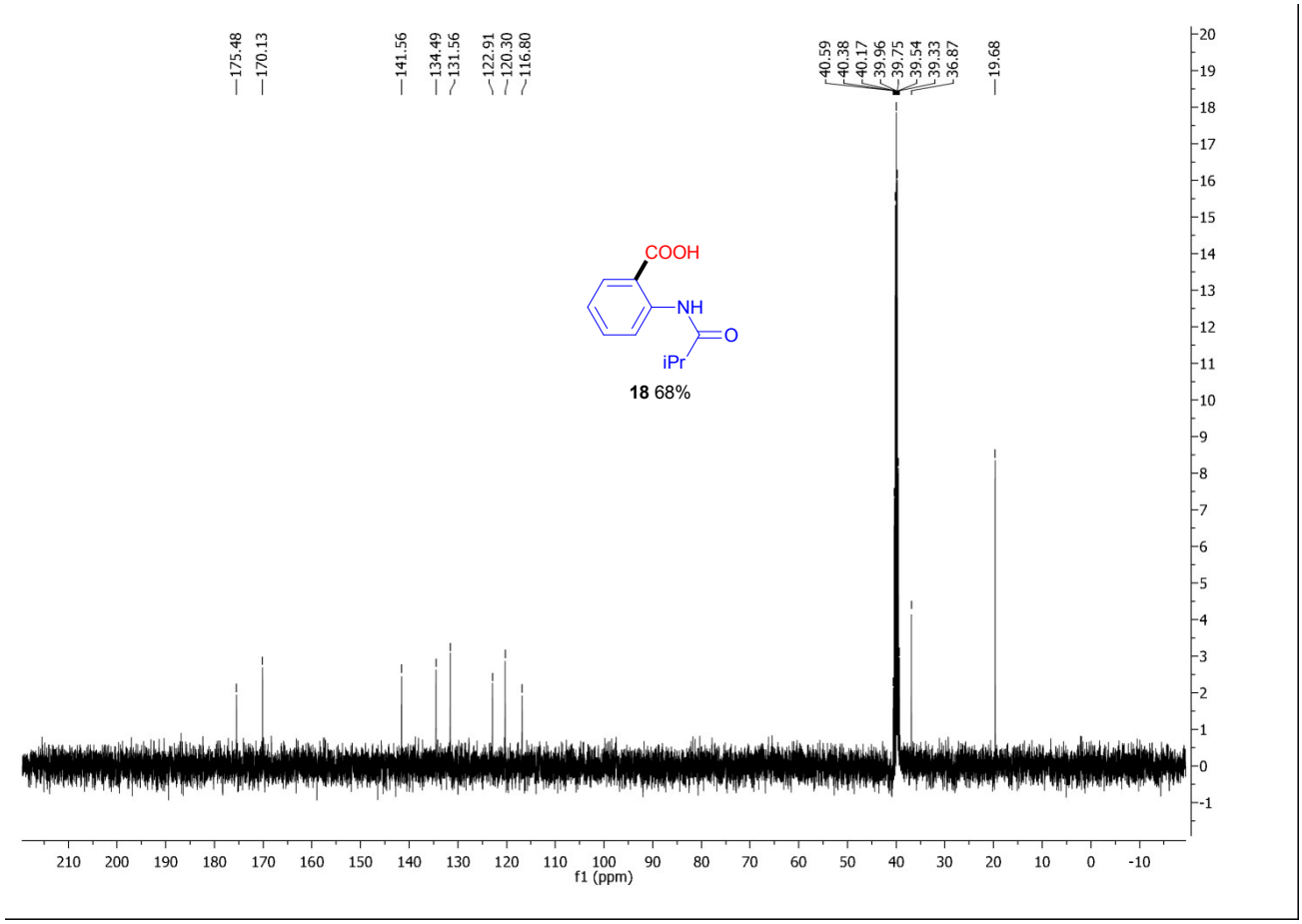
17, 56%


169.17
168.26
168.10
135.98
134.14
124.40
121.12
120.69
117.13
39.94
39.73
39.52
39.31
39.10
24.81
23.86
COOH
AcHN
NHAc
f1 (ppm)

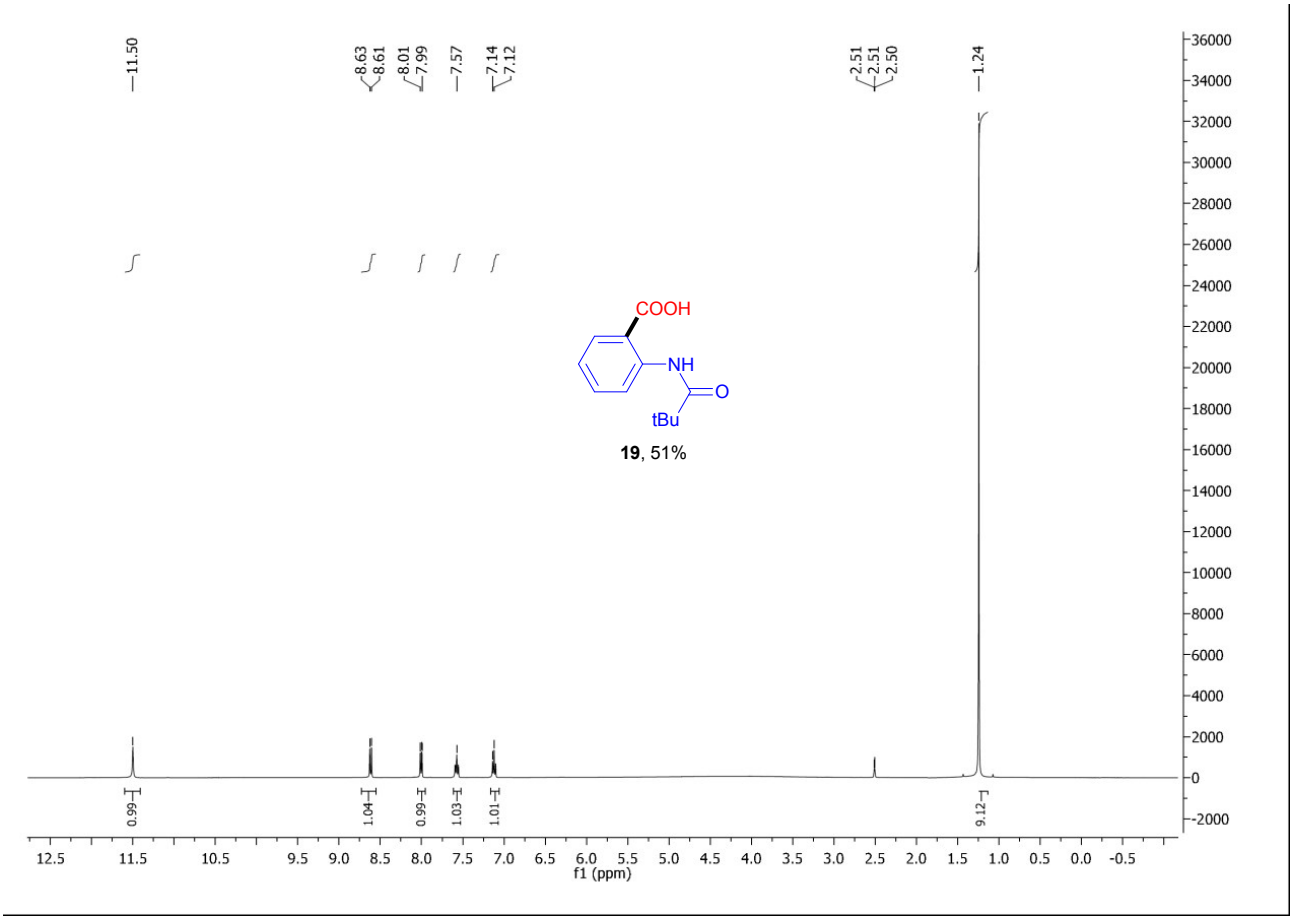
17, 56%


11.23
8.53
8.53
8.51
8.51
7.98
7.55
7.15
7.15
7.13
7.11
2.59
2.57
2.55
2.53
2.52
2.51
2.51
2.50
1.18
1.16
COOH
NH
O
iPr
1.00
0.95
0.96
1.05
0.98
1.10
6.02
f1 (ppm)

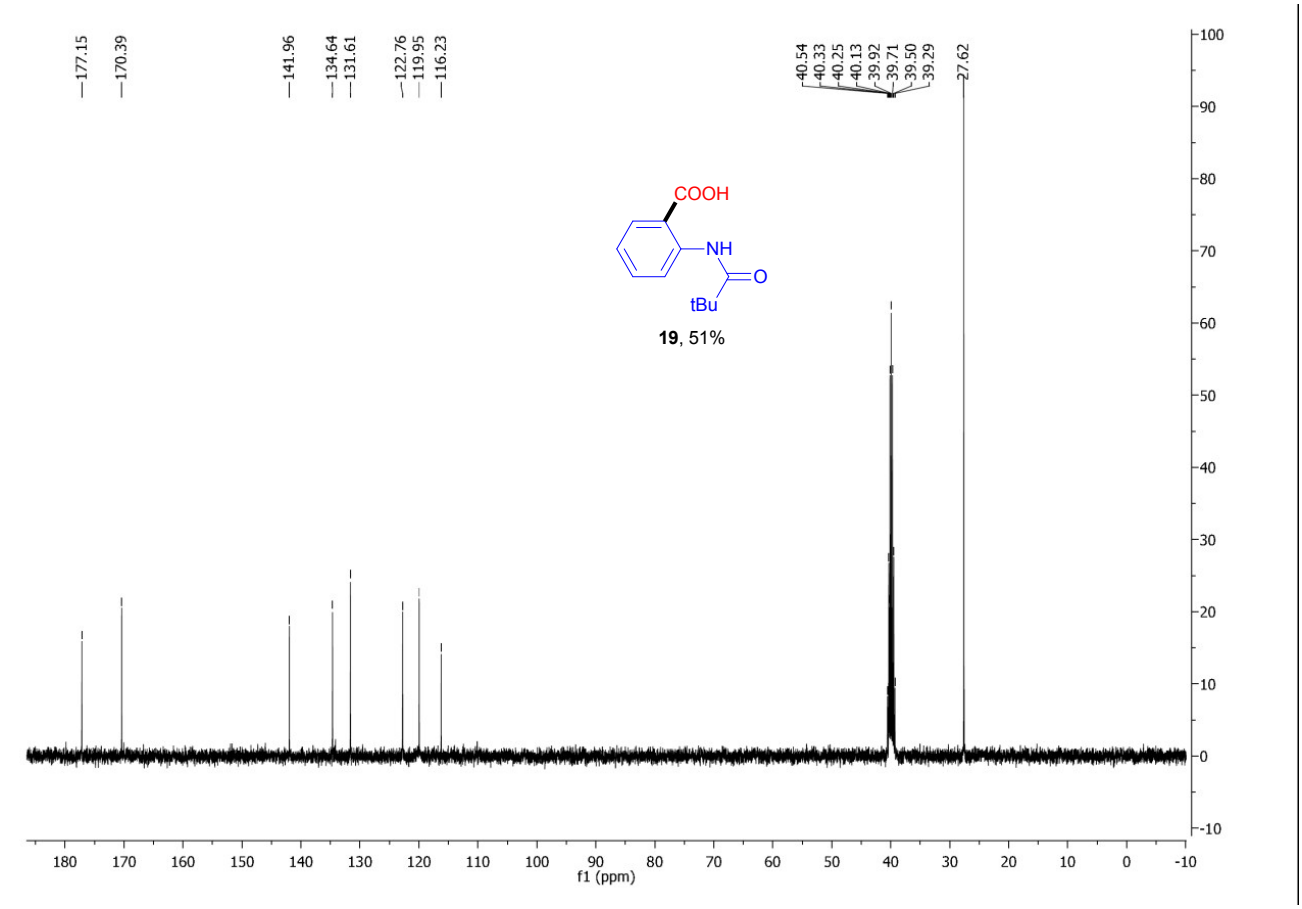
18 68%


175.48
170.13
141.56
134.49
131.56
122.91
120.30
116.80
40.59
40.38
40.17
39.96
39.75
39.54
39.33
36.87
19.68
COOH
NH
O
iPr
f1 (ppm)

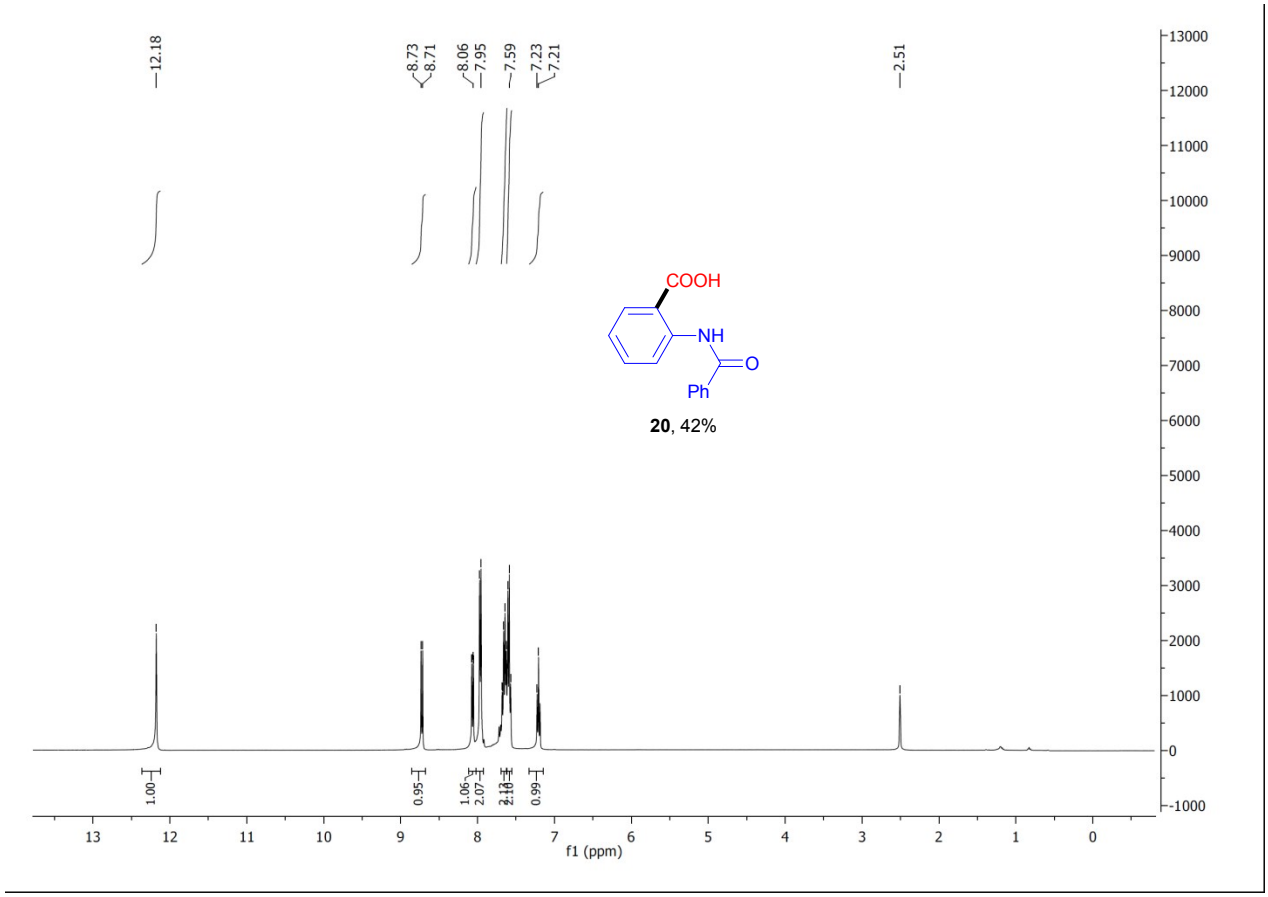
18 68%


11.50
8.63
8.61
8.01
7.99
7.57
7.14
7.12
2.51
2.51
2.50
1.24
COOH
NH
O
tBu
0.99
1.04
0.99
1.03
1.01
9.12
f1 (ppm)

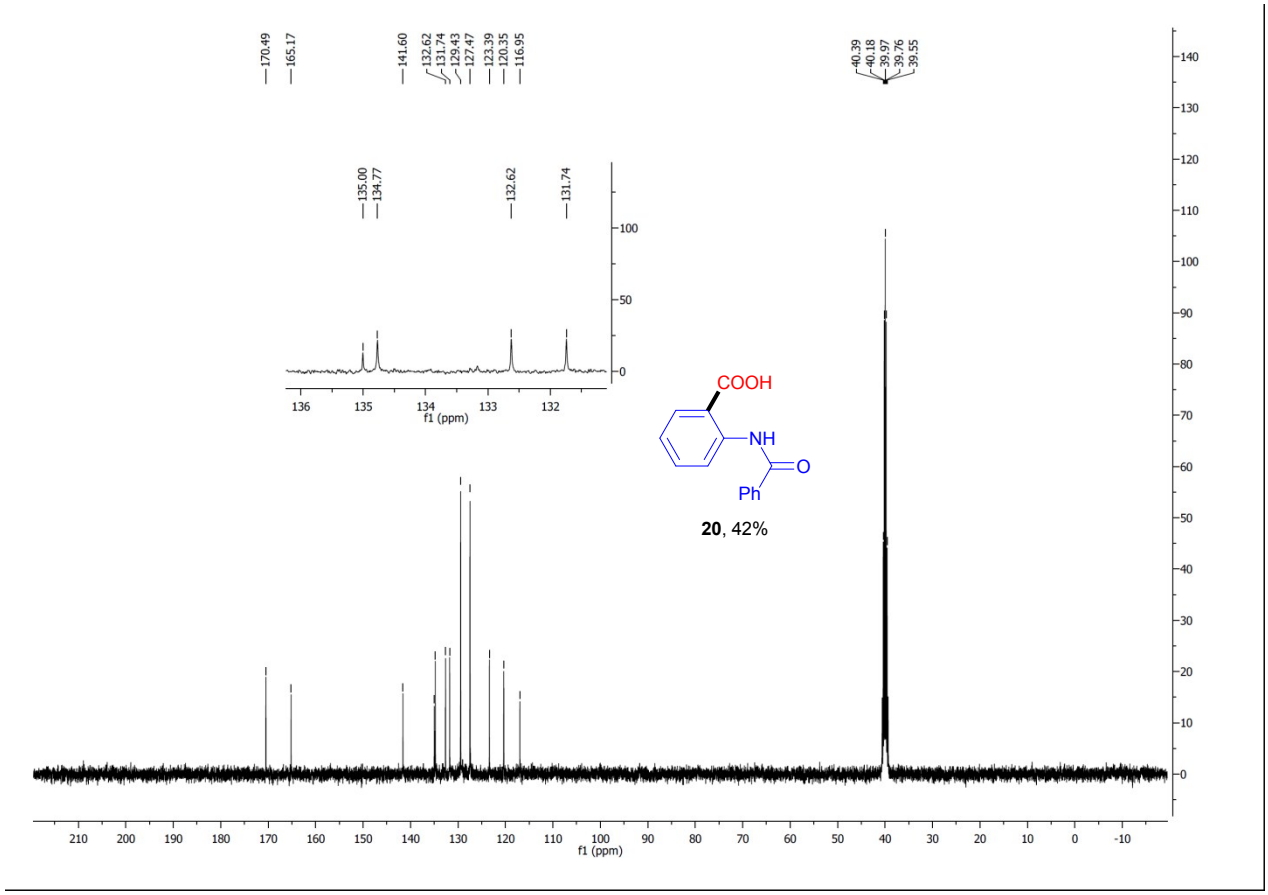
19, 51%


177.15
170.39
141.96
134.64
131.61
122.76
119.95
116.23
40.54
40.33
40.25
40.13
39.92
39.71
39.50
39.29
27.62
COOH
NH
O
tBu
f1 (ppm)

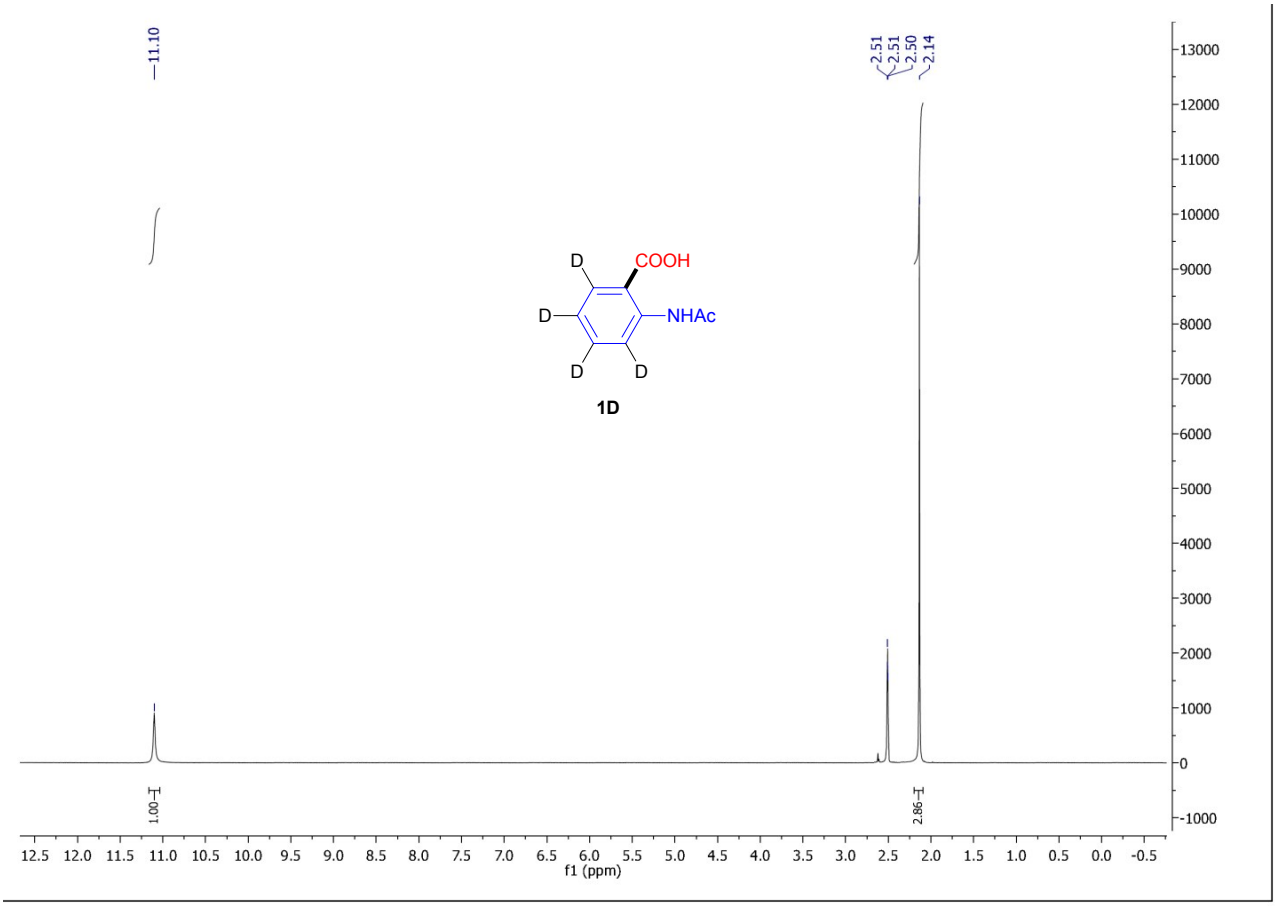
19, 51%


12.18
8.73
8.71
8.06
7.95
7.59
7.23
7.21
2.51
COOH
NH
O
Ph
1.00
0.95
1.06
2.07
2.13
0.99
f1 (ppm)

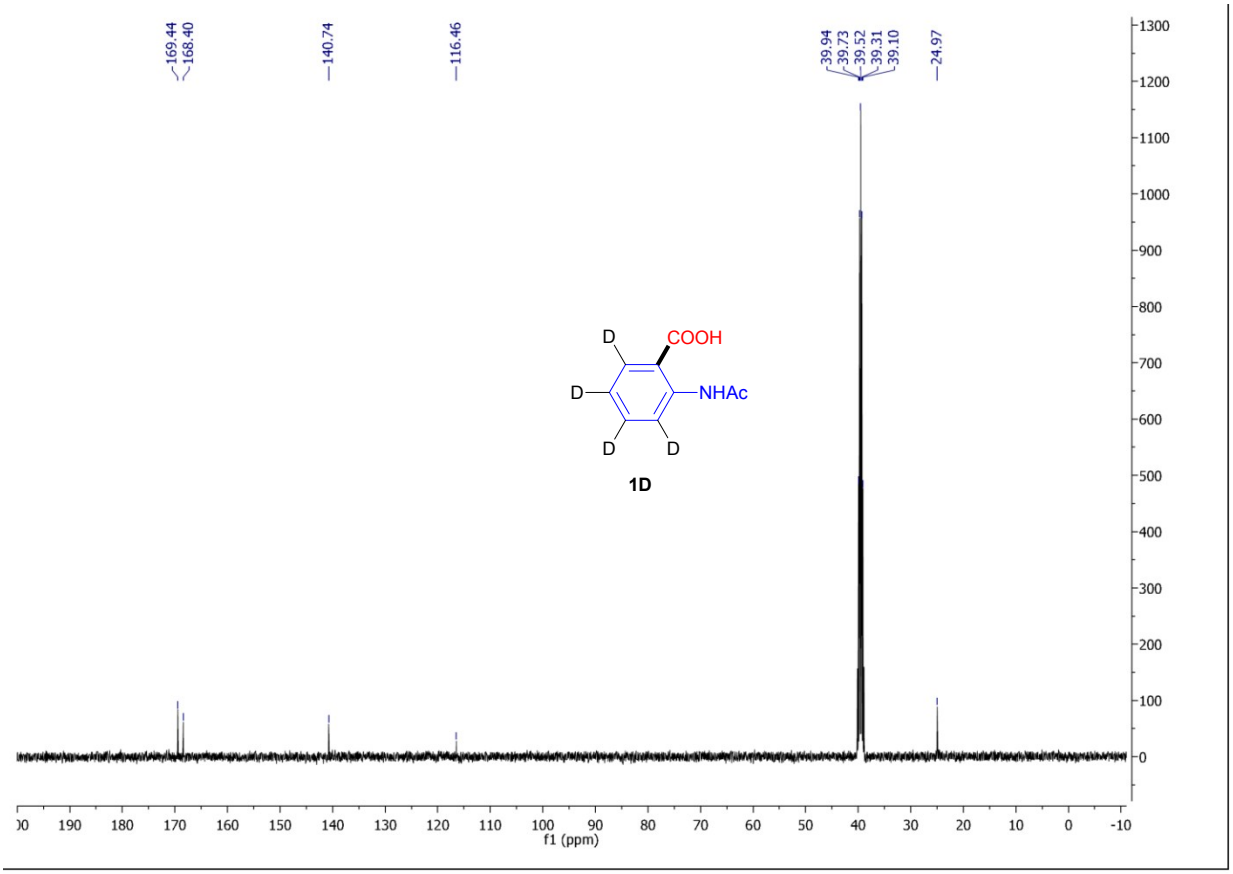
20, 42%


170.49
165.17
141.60
132.62
131.74
129.43
127.47
123.39
120.35
116.95
40.39
40.18
39.97
39.76
39.55
135.00
134.77
132.62
131.74
COOH
NH
O
Ph
f1 (ppm)

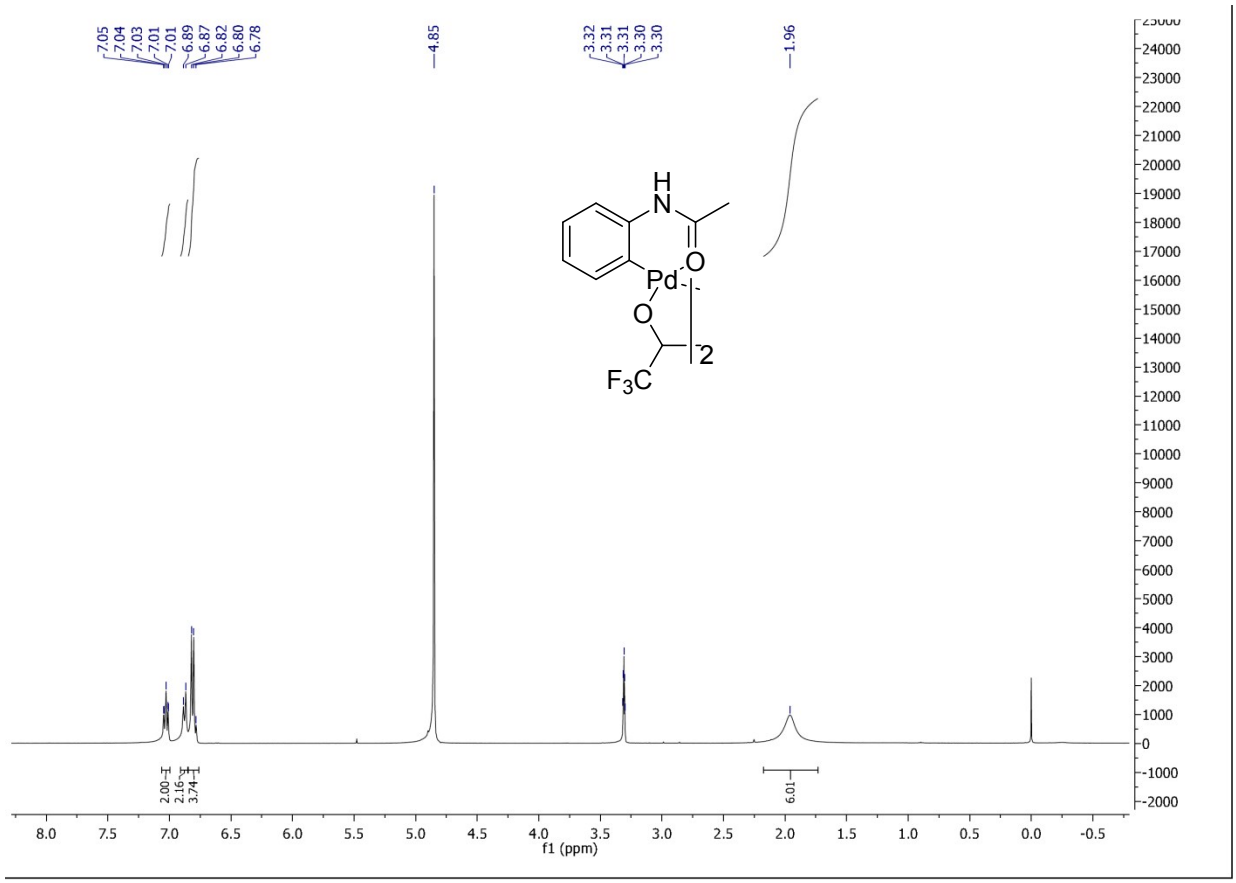
20, 42%

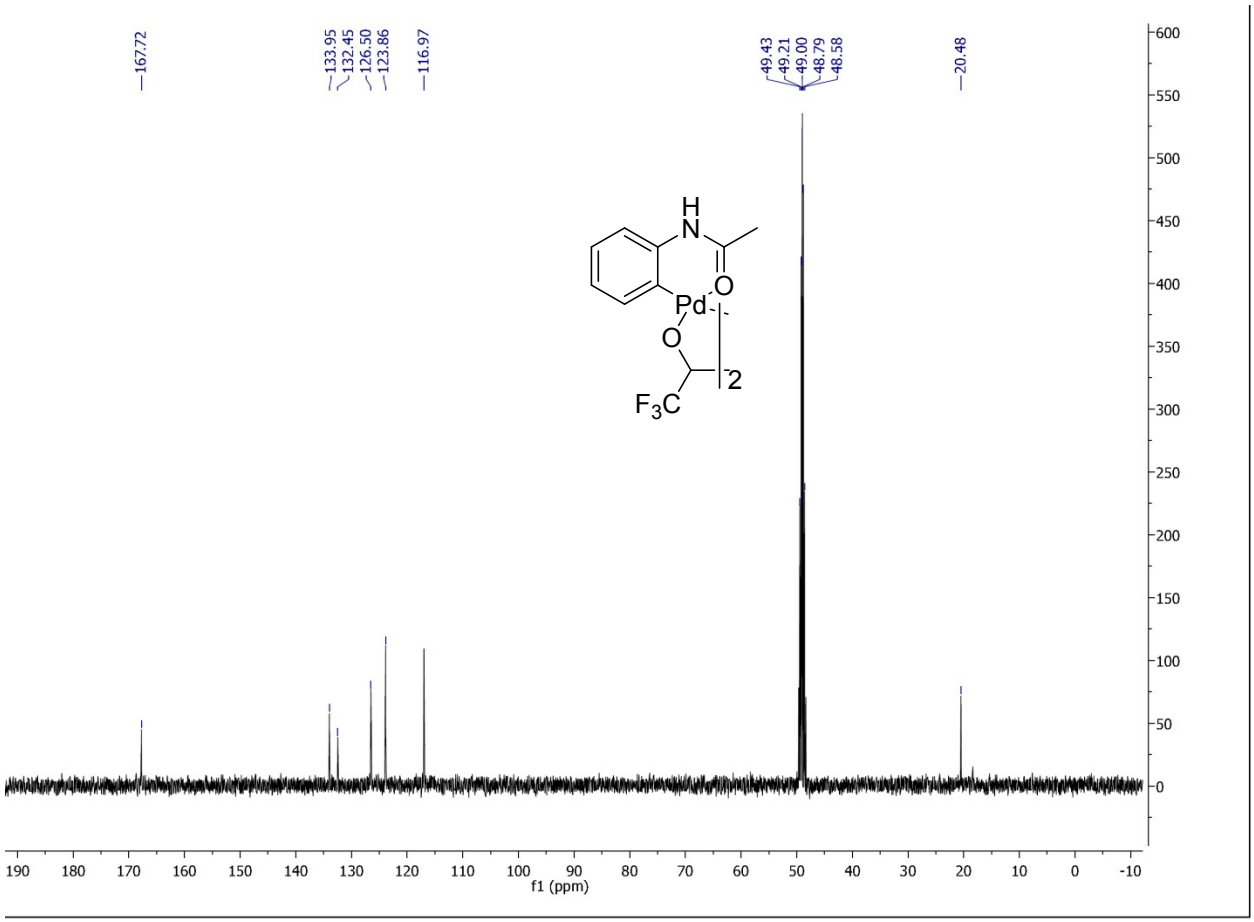

11.10
2.51
2.51
2.50
2.14
D
COOH
D
NHAc
D
D
1.00
2.86
f1 (ppm)

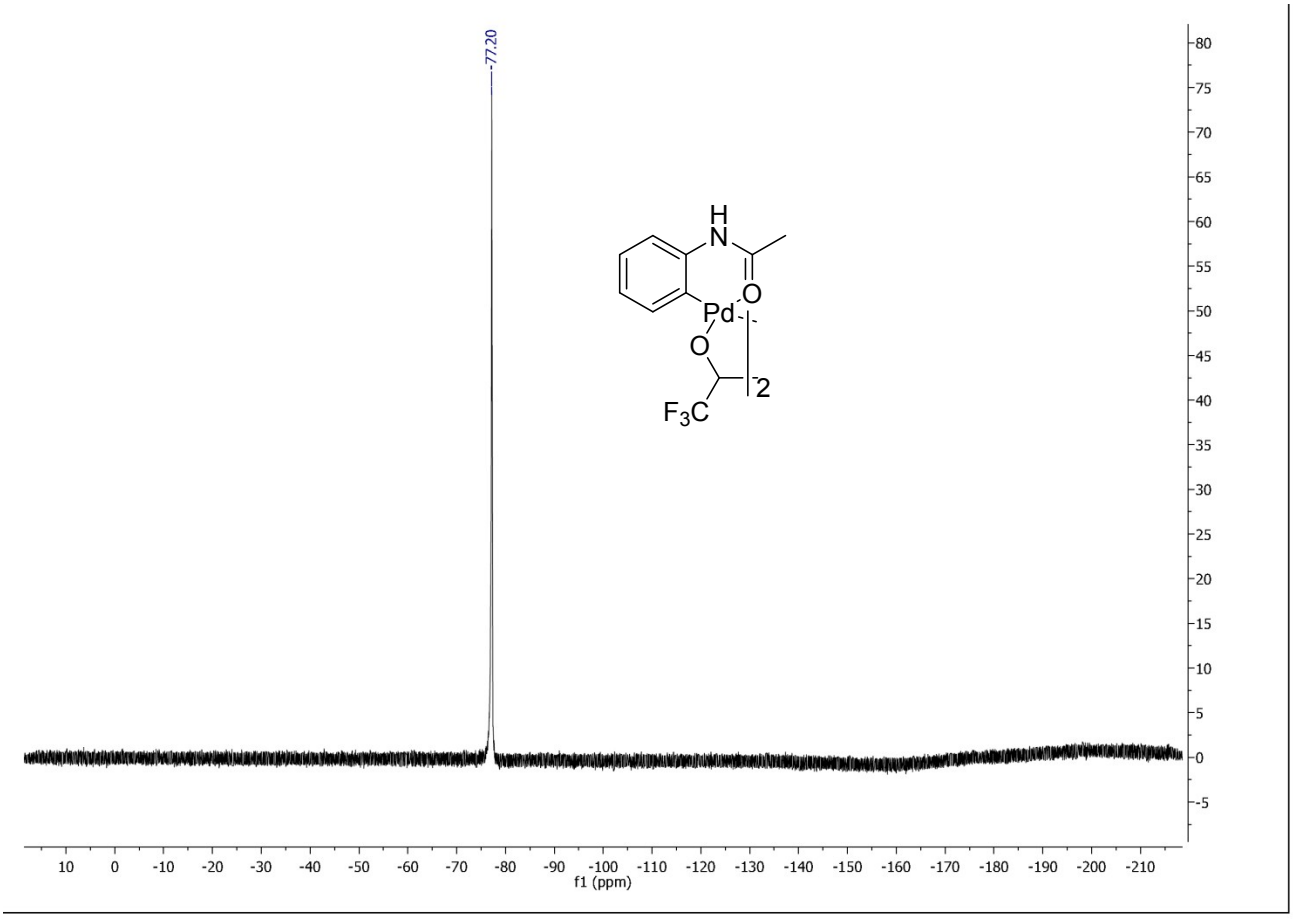
1D


169.44
168.40
140.74
116.46
39.94
39.73
39.52
39.31
39.10
24.97
D
COOH
D
NHAc
D
D
f1 (ppm)

1D


7.05
7.04
7.03
7.01
7.01
6.89
6.87
6.82
6.80
6.78
4.85
3.32
3.31
3.31
3.30
3.30
1.96
H
N
O
Pd
O
2
F3C
2.00
2.16
3.74
6.01
f1 (ppm)


167.72
133.95
132.45
126.50
123.86
116.97
49.43
49.21
49.00
48.79
48.58
20.48
H
N
O
Pd
O
2
F3C
f1 (ppm)



8. References

[1] R. Giri, J. K. Lam, and J.-Q. Yu, *J. Am. Chem. Soc.* 2010, **132**, 686.

[2] F. Luo, J. Yang, Z. Li, H. Xiang and X. Zhou, *E. J. Org. Chem.* 2015, 2463

[3] T. Wu, C. Jiang, L. Wang, S. L. Morris-Natschke, H. Miao, L. Gu, J. Xu, K.-H. Lee, and Q. Gu, *J. Nat. Prod*., 2015, **78**. 1593.