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ELECTRONIC SUPPLEMENTARY INFORMATION

Diphenylsilane as a Coupling Reagent for Amide Bond Formation

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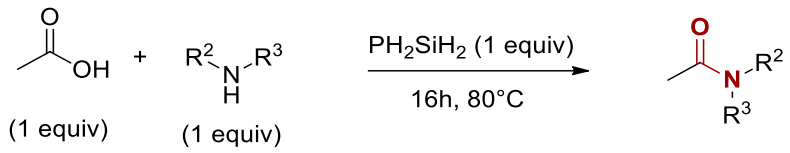
General information

Diphenylsilane and acids were obtained from commercial suppliers and used without further purification. Commercial amines were distilled over CaH_2 before use. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. All glassware was flamed-dried before use. Dichloromethane (DCM), toluene and acetonitrile (ACN) were obtained by filtration through drying columns on a filtration system. Tetrahydrofuran (THF) was freshly distilled over sodium and benzophenone. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by UV light (254 nm) and/or using ninhydrin stain. Flash column chromatographies were performed using flash silica gel (0.040-0.063 mm). Nuclear magnetic resonance spectra were recorded on an Avance AV400 MHz, Avance AV 300 MHZ, DRX400 MHz, or Avance 500 MHz spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million with the solvent resonance as the reference $CDCl_3$ (δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million using the central peak of $CDCl_3$ (δ = 77.16 ppm) as the reference. All ^{13}C NMR spectra were obtained with complete proton decoupling. All NMR yields were determined using ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. Infrared spectra were taken on a Bruker Vertex Series FTIR (neat) and are reported in reciprocal centimeters (cm^{-1}). High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal.

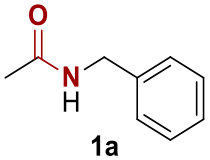
Experimental procedures and characterization data

General procedure A: Amine acetylation



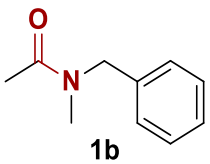
In a flame-dried sealed tube under argon, the acid (1 equiv), the amine (1 equiv) and diphenylsilane (1 equiv) were stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the crude was purified by flash column chromatography on silica gel.

Characterization data for amides with acetic acid as acid partner



1a

***N*-Benzylacetamide (1a).** Compound **(1a)** was synthesized using **general procedure A** with acetic acid (57.2 uL, 1.0 mmol), benzylamine (109.0 uL, 1.0 mmol) and diphenylsilane, 97% (192.0 uL, 1.0 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 2:8) to afford the desired product as a white solid (120 mg, 80% yield). Product in accordance with literature characterization data.[1] **Rf** = 0.16 (hexanes/EtOAc 4:6); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 2H), 7.31 – 7.26 (m, 3H), 5.86 (s, 1H), 4.42 (d, J = 5.7 Hz, 2H), 2.01 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.3, 138.4, 128.6, 127.7, 127.3, 43.5, 23.0.

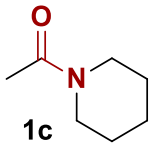


1b

***N*-Benzyl-*N*-methylacetamide (1b).** Compound **(1b)** was synthesized using **general procedure A** with acetic acid (57.2 uL, 1.0 mmol), *N*-benzylmethylamine (124.0 uL, 1.0

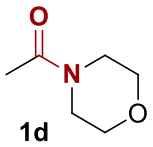
[1] Sanz Sharley, D. D.; Williams, J. M. J. *Chem. Comm.* **2017**, *53*, 2020-2023.

mmol) and diphenylsilane, 97% (192.0 uL, 1.0 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 1:1) to afford the desired product as a pale yellow oil (153 mg, 94% yield). Product in accordance with literature characterization data.[2] Rf = 0.15 (hexanes/EtOAc 1:1); 1.3:1 mixture of rotamers; *Major rotamer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.16 (m, 5H), 4.59 (s, 2H), 2.92 (s, 3H), 2.16 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7, 137.3, 128.5, 128.0, 126.3, 50.5, 35.5, 21.8. *Minor rotamer*: **^{1}H NMR** (400 MHz, $CDCl_3$) 7.39 – 7.16 (m, 5H), 4.52 (s, 2H), 2.94 (s, 3H), 2.15 (s, 3H); **^{13}C NMR** (101 MHz, CDCl3) δ 171.0, 136.5, 128.9, 127.6, 127.3, 54.2, 33.7, 21.4.



1c

1-(Piperidin-1-yl)ethanone (1c). Compound **(1c)** was synthesized using **general procedure A** with acetic acid (57.2 uL, 1.0 mmol), and diphenylsilane, 97% (192.0 uL, 1.0 mmol). The crude was purified by flash column chromatography on silica gel (100% EtOAc) to afford the desired product as a colourless oil (112 mg, 88% yield). Product in accordance with literature characterization data.[3] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.55 – 3.52 (m, 2H), 3.39 – 3.37 (m, 2H), 2.07 (s, 3H), 1.67 – 1.61 (m, 2H), 1.59 – 1.50 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.8, 47.5, 42.5, 26.5, 25.6, 24.6, 21.6.



1d

1-Morpholinoethanone (1d). Compound **(1d)** was synthesized using **general procedure A** with acetic acid (57.2 uL, 1.0 mmol), and diphenylsilane, 97% (192.0 uL, 1.0 mmol). The crude was purified by flash column chromatography on silica gel (100% EtOAc) to afford the desired product as a colourless oil (107 mg, 83% yield). Product in accordance with literature characterization data.[4] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.69 – 3.65 (m, 4H), 3.62 – 3.59 (m, 2H), 3.46 – 3.44 (m, 2H), 2.09 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2, 66.9, 66.7, 46.7, 41.8, 21.2.

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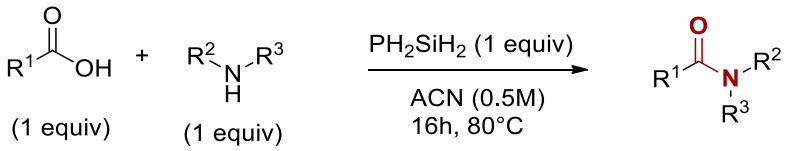
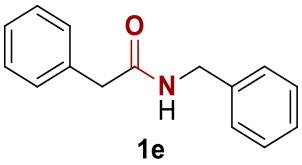
[2] Hanada, S.; Yuasa, A.; Kuroiwa, H.; Motoyama, Y.; Nagashima, H. *Eur. J. Org. Chem.* **2010**, *6*, 1021-1025.
[3] Chen, Z.; Fu, R.; Chai, W.; Zheng, H.; Sun, L.; Lu, Q.; Yuan, R. *Tetrahedron* **2014**, *70*, 2237-2245.
[4] Rao, C. B.; Rao, D. C.; Babu, D. C.; Venkateswarlu, Y. *Eur. J. Org. Chem.* **2010**, *15*, 2855-2859.

General procedure B: Amide synthesis



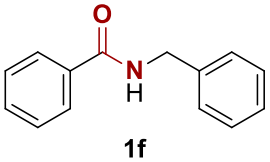
In a flame-dried sealed tube under argon, the acid (1 equiv) and the amine (1 equiv) were dissolved in ACN. Diphenylsilane (1 equiv) was added and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was filtered and concentrated under reduced pressure (or directly concentrated under reduced pressure depending on the amount of siloxane formed). The crude was purified by flash column chromatography on silica gel.

Characterization data for amides



1e

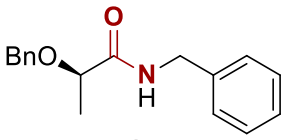
***N*-Benzyl-2-phenylacetamide (1e).** Compound **(1e)** was synthesized using **general procedure B** with phenylacetic acid (68.1 mg, 0.5 mmol), benzylamine (54.6 uL, 0.5 mmol) and diphenylsilane, 97% (96.0 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to afford the desired product as a white solid (95 mg, 84% yield). Product in accordance with literature characterization data.[1] **Rf** = 0.19 (hexanes/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.17 (m, 10H), 5.66 (s, 1H), 4.42 (d, *J* = 5.8 Hz, 2H), 3.64 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 138.2, 134.9, 129.6, 129.2, 128.8, 127.6, 127.5, 127.5, 44.0, 43.7.



1f

***N*-Benzylbenzamide (1f).** Compound **(1f)** was synthesized using **general procedure B** with benzoic acid (61.1 mg, 0.5 mmol), benzylamine (54.6 uL, 0.5 mmol) and diphenylsilane, 97%

(96 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 8:2) to afford the desired product as a white solid (78 mg, 74% yield). Product in accordance with literature characterization data.[5] **Rf** = 0.42 (hexanes/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.78 (m, 2H), 7.53 – 7.28 (m, 8H), 6.41 (s, 1H), 4.66 (d, *J* = 5.7 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 138.3, 134.5, 131.6, 128.9, 128.7, 128.0, 127.7, 127.1, 44.2.

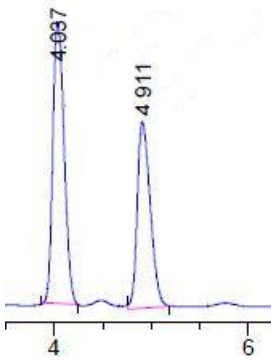


1g

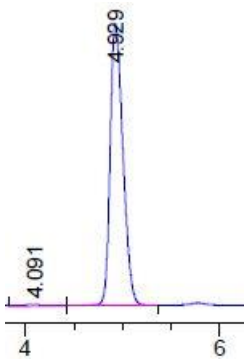
(R)-*N*-Benzyl-2-(benzyloxy)propanamide (1g). Compound **(1g)** was synthesized using **general procedure B** with (R)-(+)-2-(Benzyloxy)propionic acid (91.9 mg, 0.5 mmol), benzylamine (54.6 uL, 0.5 mmol) and diphenylsilane, 97% (96.0 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to afford the desired product as a colourless oil (88 mg, **65%** yield). Product in accordance with literature characterization data.[6] **Rf** = 0.41 (hexanes/EtOAc 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 5H), 7.28 – 7.26 (m, 5H), 6.93 (s, 1H), 4.63 – 4.39 (m, 4H), 4.04 (q, *J* = 6.8 Hz, 1H), 1.46 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.2, 138.3, 137.4, 128.9, 128.7, 128.2, 128.0, 127.8, 127.6, 76.4, 72.2, 43.0, 18.8.

SFC trace using a Chiralpak OJ-H, at 30°C, 150 bar, eluting in 5% MeOH.

Racemic



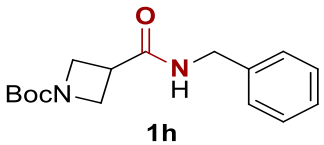
Compound **(1c)**



[5] Gockel, S. N.; Hull, K. L. *Org. Lett.* **2015**, *17*, 3236-3239.
[6] Aspin, S. J.; Taillemaud, S.; Cyr, P.; Charette, A. B. *Angew. Chem. Int. Ed.* **2016**, *55*, 13833-13837.

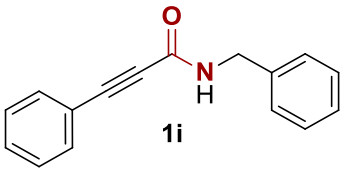
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.037	MM	0.1347	1.12022e4	1385.78503	56.5572
2	4.911	MM	0.1561	8604.63770	918.62268	43.4428

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.091	BV	0.2889	112.44040	4.70427	1.5581
2	4.929	VB	0.1441	7104.23193	766.56879	98.4419



1h

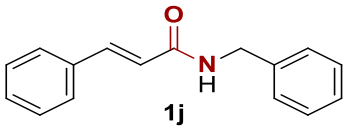
***tert*-Butyl 3-(benzylcarbamoyl)azetidine-1-carboxylate (1h).** Compound **(1h)** was synthesized using **general procedure B** with 1-boc-azetidine-3-carboxylic acid (101 mg, 0.5 mmol), benzylamine (54.6 uL, 0.5 mmol) and diphenylsilane, 97% (96.0 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 1:1) to afford the desired product as a colourless oil (104 mg, 72% yield). **Rf** = 0.14 (hexanes/EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 5.84 (s, 1H), 4.46 (d, *J* = 5.7 Hz, 2H), 4.14 – 4.11 (m, 2H), 4.06 – 4.01 (m, 2H), 3.22 – 3.14 (m, 1H), 1.43 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.6, 156.2, 138.0, 128.8, 127.9, 127.7, 79.8, 51.8, 43.8, 33.3, 28.4; **FTIR** (cm^{-1}) (neat) : 3297, 2975, 2886, 1700, 1650, 1545, 1407, 1366, 1242, 1136, 1031, 730, 699; **HRMS** (ESI, Pos) : calcd for $C_{16}H_{22}N_2O_3Na$ $[M+Na]^+$: 313.1523 *m/z*, found 313.1514 *m/z*.



1i

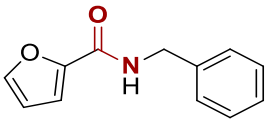
***N*-Benzyl-3-phenylpropiolamide (1i).** Compound **(1i)** was synthesized using **general procedure B** with phenylpropiolic acid (73.1 mg, 0.5 mmol) benzylamine (54.6 uL, 0.5 mmol) and diphenylsilane, 97% (96.0 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 8:2) to afford the desired product as a white solid (64 mg, 54% yield). Product in accordance with literature characterization data.[7] **Rf** = 0.33 (hexanes/EtOAc 7:3); 10:1 mixture of rotamers; *Major rotamer* : **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.51 (m, 2H), 7.44 – 7.29 (m, 8 H), 6.21 (s, 1H), 4.55 (d, *J* = 5.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.4, 137.4, 132.6, 130.2, 128.9, 128.6, 128.0, 127.3, 120.2, 85.2, 83.0, 44.0; *Minor rotamer* : **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.51 (m, 2H), 7.44 – 7.29 (m, 8 H), 6.01 (s, 1H), 4.71 (d, *J* = 6.7 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.3, 137.6, 132.7, 130.5, 129.0, 128.7, 128.1, 127.9, 120.1, 91.4, 80.8, 47.5.

[7] Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett.* **2014**, *16* 2018-2021.



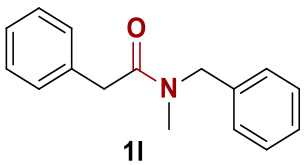
1j

(E)-*N*-Benzylcinnamamide (1j). Compound **(1j)** was synthesized using **general procedure B** with *trans*-cinnamic acid (74.1 mg, 0.5 umol), benzylamine (54.6 uL, 0.5 mmol) and diphenylsilane, 97% (96.0 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 8:2) to afford the desired product as a white solid (83 mg, 70% yield). Product in accordance with literature characterization data.[8] **Rf** = 0.33 (hexanes/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 15.6 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.38 – 7.27 (m, 8H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.07 (s, 1H), 4.57 (d, *J* = 5.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1, 141.3, 138.3, 134.9, 129.7, 128.9, 128.8, 127.9, 127.8, 127.5, 120.7, 43.8.



1k

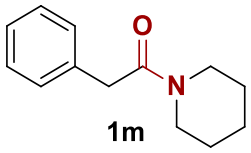
***N*-Benzylfuran-2-carboxamide (1k).** Compound **(1k)** was synthesized using **general procedure B** with 2-furoic acid (56.0 mg, 0.5 mmol), benzylamine (54.6 uL, 0.5 mmol) and diphenylsilane, 97% (96.0 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to afford the desired product as a pale yellow solid (71 mg, 70% yield). Product in accordance with literature characterization data.[9] **Rf** = 0.17 (hexanes/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.40 (m, 1H), 7.35 – 7.34 (m, 4H), 7.32 – 7.27 (m, 1H), 7.14 (d, *J* = 3.5 Hz, 1H), 6.67 (s, 1H), 6.50 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.61 (d, *J* = 5.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4, 148.0, 144.0, 138.1, 128.8, 127.9, 127.6, 114.4, 112.2, 43.2.



1l

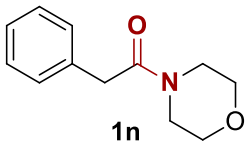
[8] Zhang, B.; Feng, P.; Cuia, Y.; Jiao, N. *Chem. Commun.* **2012**, *48*, 7280-7282.
[9] Green, R. A.; Pletcher, D.; Leach, S. G.; Brown, R. C. D. *Org. Lett.* **2016**, *18*, 1198-1201.

***N*-Benzyl-*N*-methyl-2-phenylacetamide (1l).** Compound **(1l)** was synthesized using **general procedure B** with phenylacetic acid (68.1 mg, 0.5 mmol), *N*-benzylmethylamine (61.8 uL, 0.5 mmol) and diphenylsilane, 97% (96 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to afford the desired product as a pale yellow oil (84 mg, 70% yield). Product in accordance with literature characterization data.[10] **Rf** = 0.36 (hexanes/EtOAc 6:4); 1.4:1 mixture of rotamers; *Major rotamer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 9H), 7.10 (d, *J* = 6.9 Hz, 1H), 4.61 (s, 3H), 3.79 (s, 2H), 2.90 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.2, 137.4, 135.1, 128.9, 128.8, 128.7, 128.2, 127.0, 126.5, 51.1, 41.3, 35.3; *Minor rotamer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 9H), 7.10 (d, *J* = 6.9 Hz, 1H), 4.53 (s, 2H), 3.76 (s, 2H), 2.96 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.6, 136.6, 135.2, 129.0, 128.9, 128.8, 127.8, 127.5, 126.9, 53.8, 41.0, 34.2.



1m

2-Phenyl-1-(piperidin-1-yl)ethanone (1m). Compound **(1m)** was synthesized using **general procedure B** with phenylacetic acid (68.1 mg, 0.5 mmol), piperidine (49.4 uL, 0.500 mmol) and diphenylsilane, 97% (96 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to afford the desired product as a light yellow oil (78 mg, 77% yield). Product in accordance with literature characterization data.[11] **Rf** = 0.29 (hexanes/EtOAc 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 5H), 3.73 (s, 2H), 3.58 – 3.56 (m, 2H), 3.38 – 3.35 (m, 2H), 1.61 – 1.49 (m, 4H), 1.37 – 1.33 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 135.5, 128.8, 128.7, 126.7, 47.4, 43.0, 41.3, 26.3, 25.6, 24.5.

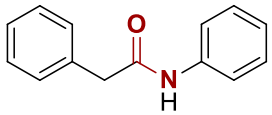


1n

1-Morpholino-2-phenylethanone (1n). Compound **(1n)** was synthesized using **general procedure B** with phenylacetic acid (68.1 mg, 0.5 mmol), morpholine (43.1 uL, 0.5 mmol) and diphenylsilane, 97% (96 uL, 0.5 mmol). The crude was purified by flash column

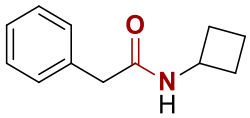
[10] Nordstrøm, L. U.; Vogt, H.; Robert Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672-17673.
[11] Albert-Soriano, M.; M. Pastor, I. M. *Eur. J. Org. Chem.* **2016**, *30*, 5180-5188.

chromatography on silica gel (hexanes/EtOAc 7:3) to afford the desired product as a colourless oil (93 mg, 91% yield). Product in accordance with literature characterization data.[5] **Rf** = 0.12 (hexanes/EtOAc 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 2H), 7.28 – 7.24 (m, 3H), 3.74 (s, 2H), 3.65 (s, 4H), 3.48 (d, *J* = 5.0 Hz, 2H), 3.44 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.8, 134.9, 128.9, 128.6, 127.0, 66.9, 66.6, 46.7, 42.3, 41.0.



1o

***N*,2-Diphenylacetamide (1o).** Compound **(1o)** was synthesized using **general procedure B** with phenylacetic acid (68.1 mg, 0.5 mmol), aniline (45.7 uL, 0.5 mmol) and diphenylsilane, 97% (96.0 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 8:2) to afford the desired product as a white solid (48 mg, 46% yield). Product in accordance with literature characterization data.[12] **Rf** = 0.28 (hexanes/EtOAc 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 4H), 7.35 – 7.33 (m, 3H), 7.30 – 7.28 (m, 2H), 7.14 (s, 1H), 7.08 (t, J = 7.4 Hz, 1H), 3.74 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2, 137.7, 134.6, 129.7, 129.4, 129.1, 127.8, 124.6, 119.9, 45.0.



1p

***N*-Cyclobutyl-2-phenyl-ethanamide (1p).** Compound **(1p)** was synthesized using **general procedure B** with phenylacetic acid (68.1 mg, 0.5 mmol), cyclobutylamine (42.7 uL, 0.5 mmol) and diphenylsilane, 97% (96.0 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to afford the desired product as a white solid (95 mg, **67%** yield). **Mp**: 84 - 86 °C; **Rf** = 0.19 (hexanes/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H), 5.47 (s, 1H), 4.36 (sp, *J* = 8.0 Hz, 1H), 3.53 (s, 2H), 2.31 – 2.26 (m, 2H), 1.77 – 1.60 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1, 135.1, 129.5, 129.1, 127.4, 44.9, 43.8, 31.2, 15.1; **FTIR** (cm^{-1}) (neat): 3266, 3065, 2977, 2939, 1640, 1549, 1498, 1338, 1263, 703, 579; **HRMS** (ESI, Pos): calcd for $C_{12}H_{15}NOH$ $[M+H]^+$ 190.1226 *m/z*, found 190.1219 *m/z*.

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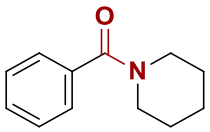
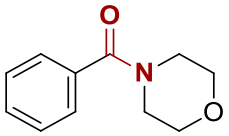
[12] MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. *Green Chem.* **2013**, *15*, 596-600.



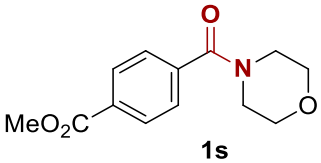
1q

Phenyl(piperidin-1-yl)methanone (1q). Compound **(1q)** was synthesized using **general procedure B** with benzoic acid (61.1 mg, 0.5 mmol), piperidine (49.4 uL, 0.500 mmol) and diphenylsilane, 97% (96 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to afford the desired product as a colourless oil (46 mg, 49% yield). Product in accordance with literature characterization data.[13] **Rf** = 0.33 (hexanes/EtOAc 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (s, 5H), 3.53 (d, *J* = 151.1 Hz, 4H), 1.67 – 1.51 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 136.7, 129.4, 128.5, 126.9, 48.9, 43.2, 26.7, 25.8, 24.7.



1r

Morpholino(phenyl)methanone (1r). Compound **(1r)** was synthesized using **general procedure B** for 42 h instead of 16 h, with benzoic acid (61.1 mg, 0.5 mmol), morpholine (43.1 uL, 0.5 mmol) and diphenylsilane, 97% (96 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 1:1) to afford the desired product as a colourless oil (60 mg, 67%). Product in accordance with literature characterization data.[13] **Rf** = 0.36 (hexanes/EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (s, 5H), 3.75 – 3.44 (m, 8H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 135.4, 129.9, 128.6, 127.2, 67.0, 48.3, 42.7.



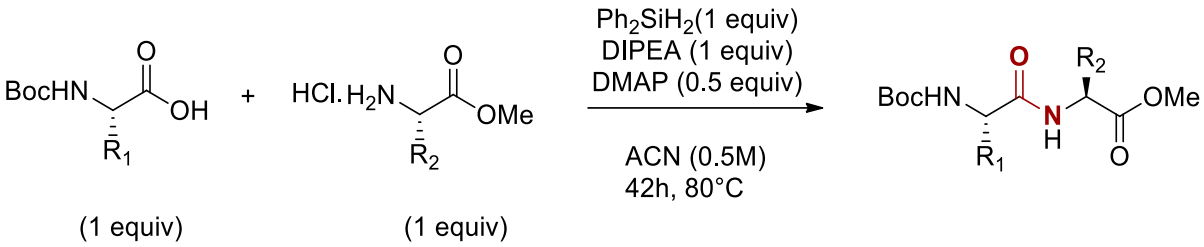
1s

Methyl 4-(morpholine-4-carbonyl)benzoate (1s). Compound **(1s)** was synthesized using **general procedure B** with mono-methyl terephthalate, 97% (90.1 mg, 0.5 mmol), morpholine (43.1 uL, 0.5 mmol) and diphenylsilane, 97% (96 uL, 0.5 mmol). The crude was

[13] Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944-2945.

purified by flash column chromatography on silica gel (hexanes/EtOAc 6:4) to afford the desired product as a white solid (79 mg, 63% yield). Product in accordance with literature characterization data.[5] **Rf** = 0.13 (hexanes/EtOAc 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 3.93 (s, 3H), 3.79 – 3.39 (m, 8H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 166.2, 139.6, 131.4, 129.9, 127.1, 66.8, 52.4, 48.1, 42.5.

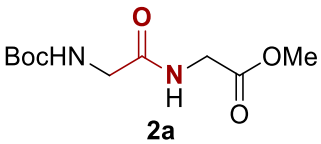
General procedure C: Peptide and lactams synthesis



(1 equiv) (1 equiv)

In a flame-dried sealed tube under argon, the acid (1 equiv), the amine HCl salt (1 equiv) and 4-dimethylaminopyridine (DMAP) (0.5 equiv) were dissolved in ACN. *N*,*N*-diisopropylethylamine (DIPEA) (1 equiv) and diphenylsilane (1 equiv) were added and the reaction mixture was stirred at 80 °C for 42 h. The reaction mixture was filtered and concentrated under reduced pressure (or directly concentrated under reduced pressure depending on the amount of siloxane formed). The crude was purified by flash column chromatography on silica gel.

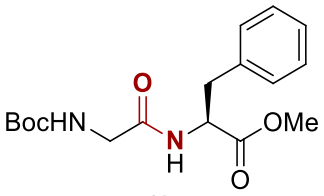
Characterization data for peptides and lactams



2a

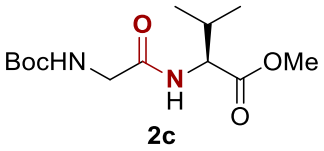
Methyl 2-(2-((*tert*-butoxycarbonyl)amino)acetamido)acetate (2a). Compound (2a) was synthesized using **general procedure C** for 16 h instead of 42 h, with boc-glycine (43.8 mg, 0.25 mmol), glycine ester hydrochloride (31.4 mg, 0.25 mmol), 4-dimethylaminopyridine (15.3 mg, 0.125 mmol), *N*,*N*-diisopropylethylamine (41.3 uL, 0.25 mmol) and diphenylsilane, 97% (46.5 uL, 0.250 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 7:3) to afford the desired product as a pale yellow oil (56 mg, 91% yield).

Product in accordance with literature characterization data.[14] **Rf** = 0.18 (hexanes/EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.55 (s, 1H), 5.09 (s, 1H), 4.07 (d, *J* = 5.3 Hz, 2H), 3.85 (d, *J* = 5.9 Hz, 2H), 3.76 (s, 3H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.3, 170.0, 156.2, 80.4, 52.5, 44.3, 41.2, 28.4.



2b

(*S*)-Methyl 2-(2-((tert-butoxycarbonyl)amino)acetamido)-3-phenylpropanoate (2b). Compound **(2b)** was synthesized using **general procedure C** with boc-glycine (350.4 mg, 2 mmol), L-phenylalanine methyl ester hydrochloride (431.4 mg, 2 mmol), 4-dimethylaminopyridine (122.2 mg, 1 mmol), *N*,*N*-diisopropylethylamine (330.5 uL, 2 mmol) and diphenylsilane, 97% (372.3 uL, 2 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 1:1) to afford the desired product as a pale yellow oil (566 mg, 84**%** yield). Product in accordance with literature characterization data.[15] **Rf** = 0.44 (hexanes/EtOAc 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 3H), 7.11 – 7.09 (m, 2H), 6.64 (s, 1H), 5.20 (s, 1H), 4.85 – 4.90 (m, 1H), 3.86 – 3.72 (m, 2H), 3.70 (s, 3H), 3.19 – 3.01 (m, 2H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.8, 169.3, 156.0, 135.8, 129.3, 128.7, 127.2, 80.3, 53.2, 52.4, 44.3, 38.0, 28.4.



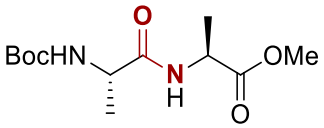
2c

(*S*)-Methyl 2-(2-((*tert*-butoxycarbonyl)amino)acetamido)-3-methylbutanoate (2c). Compound **(2c)** was synthesized using **general procedure C** with boc-glycine (43.8 mg, 0.25 mmol), L-valine methyl ester hydrochloride (41.9 mg, 0.25 mmol), 4-dimethylaminopyridine (15.3 mg, 0.125 mmol), *N*,*N*-diisopropylethylamine (41.3 uL, 0.25 mmol) and diphenylsilane, 97% (46.5 uL, 0.250 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 6:4) to afford the desired product as a

[14] Grauer, A.; Riechers, A.; Ritter, S.; Koenig, B. *Chem. Eur. J.* **2008**, *14*, 8922-8927

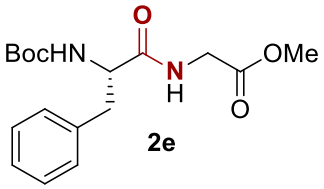
[15] Leleu, S.; Penhoat, M.; Bouet, A.; Dupas, G.; Papamicaël, C.; Marsais, F.; Levacher, V. *J. Am. Chem. Soc.* **2005**, *127*, 15668-15669.

pale yellow oil (59 mg, 81% yield). **Rf** = 0.30 (hexanes/EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.57 (s, 1H), 5.10 (s, 1H), 4.56 (dd, J = 9.0, 4.9 Hz, 1H), 3.89 – 3.79 (m, 2H), 3.74 (s, 3H), 2.18 (m, 1H), 1.46 (s, 9H), 0.94 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3, 169.6, 156.2, 134.5, 80.5, 57.1, 52.3, 44.6, 31.4, 28.4, 19.0, 17.8; **FTIR** (cm^{-1}) (neat) : 3325, 2967, 2934, 2876, 1740, 1718, 1665, 1513, 1437, 1392, 1366, 1249, 1208, 1164, 1051, 1026, 941, 865, 765, 587; **HRMS** (ESI, Pos) : calcd for $C_{13}H_{24}N_2O_5H$ $[M+H]^+$ 289.1758 *m/z*, found 289.1766 *m/z* ; $[\alpha]_D^{20}$ = +33.7 °(*c* 0.92, $CHCl_3$).



2d

(*S*)-Methyl 2-((S)-2-((tert-butoxycarbonyl)amino)propanamido)propanoate (2d). Compound **(2d)** was synthesized using **general procedure C** with boc-L-alanine (47.3 mg, 0.25 mmol), alanine methyl ester hydrochloride (34.9 mg, 0.25 mmol), 4-dimethylaminopyridine (15.3 mg, 0.125 mmol), *N*,*N*-diisopropylethylamine (41.3 uL, 0.25 mmol) and diphenylsilane, 97% (46.5 uL, 0.250 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 1:1) to afford the desired product as a white solid (42 mg, 54% yield). Product in accordance with literature characterization data.[16] **Rf** = 0.45 (hexanes/EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.60 (s, 1H), 4.98 (s, 1H), 4.57 (p, *J* = 7.3 Hz, 1H), 4.16 (m, 1H), 3.74 (s, 3H), 1.44 (s, 9H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.36 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.3, 172.3, 155.6, 80.2, 52.6, 50.1, 48.1, 28.4, 18.5.

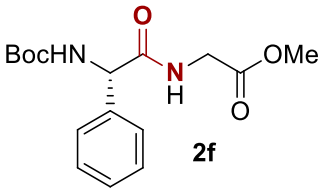


2e

(*S*)-Methyl 2-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)acetate (2e). Compound **(2e)** was synthesized using **general procedure C** with boc-L-phenylalanine (66.3 mg, 0.25 mmol), glycine ester hydrochloride (31.4 mg, 0.25 mmol), 4-dimethylaminopyridine (15.3 mg, 0.125 mmol), *N*,*N*-diisopropylethylamine (41.3 uL, 0.25 mmol) and diphenylsilane,

[16] Anderson, R. J.; Groundwater, P. W.; Huang, Y.; James, A. L.; Orenga, S.; Rigby, A.; Roger-Dalbert, C.; Perry, J. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 832-835.

97% (46.5 uL, 0.250 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 1:1) to afford the desired product as a pale yellow oil (48 mg, 57% yield). Product in accordance with literature characterization data.[17] **Rf** = 0.43 (hexanes/EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 –7.28 (m, 2H), 7.26 –7.18 (m, 3H), 6.39 (s, 1H), 4.97 (s, 1H), 4.40 (s, 1H), 4.07 – 3.90 (m, 2H), 3.73 (s, 3H), 3.14 – 3.04 (m, 2H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.8, 170.0, 155.6, 136.7, 129.4, 128.7, 127.0, 80.4, 55.7, 52.5, 41.3, 38.5, 28.3.

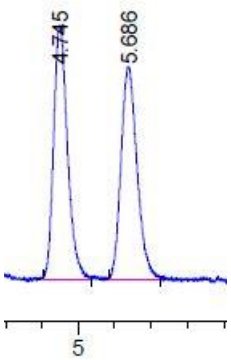


2f

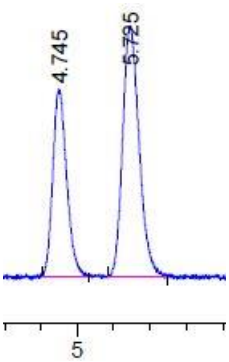
(*S*)-Methyl 2-(2-((tert-butoxycarbonyl)amino)-2-phenylacetamido)acetate (2f). Compound **(2f)** was synthesized using **general procedure C** with 2-((*tert*-Butoxycarbonyl)amino)-2-phenylacetic acid (62.8 mg, 0.25 mmol), glycine ester hydrochloride (31.4 mg, 0.25 mmol), 4-dimethylaminopyridine (15.3 mg, 0.125 mmol), *N*,*N*-diisopropylethylamine (41.3 uL, 0.25 mmol) and diphenylsilane, 97% (46.5 uL, 0.250 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 1:1) to afford the desired product as a white solid (42 mg, 52% yield). Product in accordance with literature characterization data.[18] **Rf** = 0.41 (hexanes/EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 6.29 (s, 1H), 5.71 (s, 1H), 5.20 (s, 1H), 4.03 (ddd, *J* = 44.7, 18.4, 5.1 Hz, 2H), 3.73 (s, 3H), 1.41 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.6, 170.0, 155.3, 138.1, 129.1, 128.6, 127.4, 80.3, 58.6, 52.5, 41.5, 28.4.

SFC trace using a Chiralpak AD-H, at 30°C, 150 bar, eluting in 10% MeOH.

Racemic



Compound **(2f)**



[17] Pan, Jia; Devarie-Baez, N. O.; Xian, M. *Org. Lett.* **2011**, *13*, 1092-1094.
[18] Yang, K.S.; Rawal, V. H. *J. Am. Chem. Soc.* **2014**, *136*, 16148-16151.

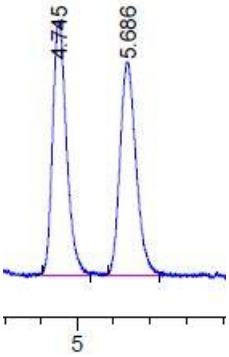
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.745	BB	0.2043	620.11877	46.88760	50.7544
2	5.686	BB	0.2207	601.68335	39.28406	49.2456

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.745	BB	0.1967	454.47809	33.82792	38.8010
2	5.725	BB	0.2447	716.82648	45.26966	61.1990

Compound **(2f)** was also synthesized using **general procedure C** with pyridine (10.1 uL, 125 mmol) instead of 4-dimethylaminopyridine to afford the desired product as a white solid (42 mg, 52% yield).

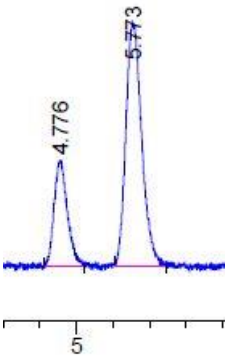
SFC trace using a Chiralpak AD-H, at 30°C, 150 bar, eluting in 10% MeOH.

Racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.745	BB	0.2043	620.11877	46.88760	50.7544
2	5.686	BB	0.2207	601.68335	39.28406	49.2456

Compound **(2f)**



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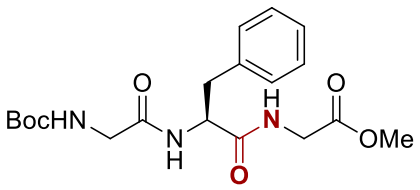
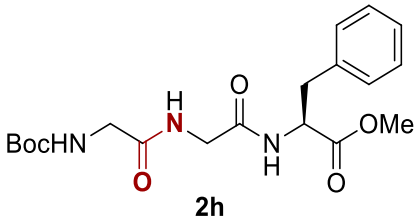


2g

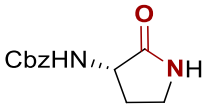
(*S*)-Methyl 9-benzyl-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (2g). Compound **(2g)** was synthesized using **general procedure C** with **(4a)** (80.6 mg, 250 umol), glycine ester hydrochloride (31.4 mg, 0.25 mmol), 4-dimethylaminopyridine (15.3 mg, 0.125 mmol), *N*,*N*-diisopropylethylamine (41.3 uL, 0.25 mmol) and diphenylsilane, 97% (46.5 uL, 0.250 mmol). The crude was purified by flash column chromatography on silica gel (100% EtOAc) to afford the desired product as a white solid (50 mg, 51% yield). **Mp**: 78 – 80 °C; **Rf** = 0.35 (100% EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 5H), 6.86 (s, 2H), 5.27 (s, 1H), 4.77 (q, *J* = 7.3 Hz, 1H), 3.94 (ddd, *J* = 55.1, 18.0, 5.5 Hz, 2H), 3.76 (m, 2H), 3.70 (s, 3H), 3.10 (d, *J* = 6.7 Hz, 2H), 1.41 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.2, 170.0, 169.8,

156.3, 136.4, 129.4, 128.8, 127.1, 80.5, 54.2, 52.4, 44.5, 41.3, 38.1, 28.4; **FTIR** (cm^{-1}) (neat) : 3293, 3066, 2978, 2932, 1749, 1650, 1518, 1438, 1392, 1367, 1246, 1208, 1167, 1049, 918, 863, 732, 700, 571; **HRMS** (ESI, Pos) : calcd for $C_{19}H_{27}N_3O_6H$ $[M+H]^+$: 394.1973 *m/z*, found 394.1992 *m/z*; $[\alpha]_D^{20}$ = -16.5 ° (*c* 0.85, $CHCl_3$).



2h

(*S*)-Methyl 12-benzyl-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (2h). Compound **(2h)** was synthesized using **general procedure C** with boc-glycine (43.8 mg, 0.25 mmol), **(4b)** (87.6 mg, 250 umol), 4-dimethylaminopyridine (15.3 mg, 0.125 mmol), *N*,*N*-diisopropylethylamine (41.3 uL, 0.25 mmol) and diphenylsilane, 97% (46.5 uL, 0.250 mmol). The crude was purified by flash column chromatography on silica gel (100% EtOAc) to afford the desired product as a pale yellow oil (50 mg, 50% yield). Product in accordance with literature characterization data.[19] **Rf** = 0.24 (100% EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 3H), 7.11 – 7.09 (m, 2H), 6.69 (s, 1H), 6.43 (s, 1H), 5.09 (s, 1H), 4.85 (dd, *J* = 13.9, 6.1 Hz, 1H), 4.99 – 3.87 (m, 2H), 3.81 (d, *J* = 5.8 Hz, 2H), 3.72 (s, 3H), 3.12 (ddd, *J* = 30.6, 13.9, 6.0 Hz, 2H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9, 170.1, 168.6, 156.2, 135.9, 129.3, 128.7, 127.3, 80.5, 53.5, 52.5, 44.3, 43.0, 37.9, 28.4.

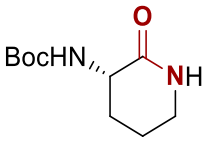


3a

(*S*)-Benzyl (2-oxopyrrolidin-3-yl)carbamate (3a). Compound **(3a)** was synthesized using **general procedure C** with N-alpha-Benzyloxycarbonyl-D-2,4-diaminobutyric acid (126 mg, 500 umol), 4-dimethylaminopyridine (30.5 mg, 0.25 mmol), *N*,*N*-diisopropylethylamine (87.1 uL, 0.5 mmol) and diphenylsilane, 97% (95.7 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (MeOH/DCM 15:85) to afford the desired product as a white solid (91 mg, 78 % yield). Product in accordance with literature characterization data.[20] **Rf** = 0.43 (MeOH/DCM, 15:85); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.34 (m, 4H), 7.33 – 7.30 (m, 1H), 6.18 (s, 1H), 5.40 (s, 1H), 5.12 (s, 2H), 4.26 – 4.20 (s, 1H), 3.37– 3.33 (m, 2H),

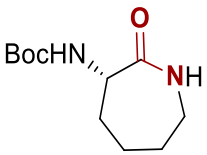
[19] Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150-12154.
[20] Long, B.; Tang, S.; Chen, L.; Qu, S.; Chen, B.; Liu, J.; Maguire, A. R.; Wang, Z.; Liu, Y.; Zhang, H.; Xu, Z.; Ye, T. *Chem. Comm.* **2013**, *49*, 2977-2979.

2.71 (s, 1H), 2.04 – 1.94 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6, 156.6, 136.4, 128.6, 128.3, 128.2, 67.1, 52.0, 39.1, 30.1.



3b

(*S*)-*tert*-Butyl (2-oxopiperidin-3-yl)carbamate (3b). Compound **(3b)** was synthesized using **general procedure C** with Nalpha-Boc-L-ornithine, 95% (116 mg, 0.5 mmol), 4-dimethylaminopyridine (30.5 mg, 0.25 mmol), *N*,*N*-diisopropylethylamine (87.1 uL, 0.5 mmol) and diphenylsilane, 97% (95.7 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (100 % EtOAc) to afford the desired product as a pale yellow oil (96 mg, 90% yield). Product in accordance with literature characterization data.[21] **Rf** = 0.19 (100 % EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.43 (s, 1H), 4.05 – 4.01 (m, 1H), 3.34 – 3.30 (m, 2H), 2.51 – 2.46 (m, 1H), 1.94 – 1.86 (m, 2H), 1.64 – 1.54 (m, 1H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.0, 156.0, 79.7, 51.6, 41.8, 28.5, 28.0, 21.1.



3c

(*S*)-*tert*-Butyl (2-oxoazepan-3-yl)carbamate (3c). Compound **(3c)** was synthesized using **general procedure C** with Boc-D-Lys-OH (123 mg, 0.5 mmol), 4-dimethylaminopyridine (30.5 mg, 0.25 mmol), *N*,*N*-diisopropylethylamine (87.1 uL, 0.5 mmol) and diphenylsilane, 97% (95.7 uL, 0.5 mmol). The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 1:1) to afford the desired product as a white solid (82 mg, 72% yield). Product in accordance with literature characterization data.[22] **Rf** = 0.21 (hexanes/EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 5.90 (d, J = 5.1 Hz, 1H), 4.28 (dd, J = 10.5, 6.1 Hz, 1H), 3.30 – 3.18 (m, 2H), 2.04 (dd, J = 29.5, 13.7 Hz, 2H), 1.84 – 1.72 (m, 2H), 1.59 – 1.49 (m, 1H), 1.44 (s, 9H), 1.40 – 1.25 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.0, 155.3, 79.5, 53.3, 42.2, 32.3, 29.0, 28.5, 28.2.

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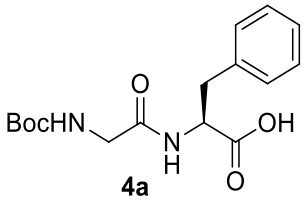
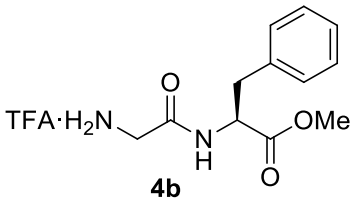
[21] Yu, K.-L.; Rajakumar, G.; Srivastava, L. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1988**, *31*, 1430-1436.
[22] Sudakow, A.; Papke, U.; Lindel, T. *Chem. Eur. J.* **2014**, *20*, 10223-10226.

Peptide deprotection: procedures and characterization data



4a

(*S*)-2-(2-((*tert*-Butoxycarbonyl)amino)acetamido)-3-phenylpropanoic acid (4a). In a flame-dried round bottom flask, **(2b)** (260 mg, 0.77 mmol) was dissolved in THF (8 mL) and cooled down to 0 °C. A solution of lithium hydroxide monohydrate (259 mg, 10.8 mmol) in H_2O (8 mL) was cooled down to 0 °C and added to the first solution. The reaction was allowed to reach room temperature and stirred overnight. A solution of 3 M HCl was added (untill pH was acidic). The reaction was diluted in ethyl acetate and brine was added. The mixture was then extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford compound **(4a)** (196 mg, 79 **%** yield) as a white solid. The crude material was used without purification. Product in accordance with literature characterization data.[23] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 – 7.14 (m, 5H), 6.78 (s, 1H), 5.38 (s, 1H), 4.84 (s, 1H), 3.86 (dd, *J* = 17.0, 6.0 Hz, 1H), 3.67 (dd, *J* = 16.8, 5.2 Hz, 1H), 3.18 – 2.84 (m, 2H), 1.43 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.0, 170.0, 156.5, 135.9, 129.5, 128.7, 127.2, 80.8, 53.2, 44.1, 37.6, 28.4.



4b

(*S*)-Methyl 2-(2-aminoacetamido)-3-phenylpropanoate trifluoroacetate salt (4b). In a flame-dried round bottom flask, **(2b)** (260 mg, 0.77 mmol) was dissolved in DCM (8 mL). Trifluoroacetic acid (591 uL, 7.7 mmol) was added and the reaction mixture was stirred overnight at room temperature. After completion, (reaction monitored by TLC) the reaction mixture was concentrated under reduced pressure, followed by azeoptroping with toluene to remove residual trifluoroacetic acid, to afford compound **(4b)** (268 mg, 99 % yield) as an orange oil. The crude material was used without purification. Product in accordance with

[23] Gamon, L. F.; Nathanael, J. G.; Taggert, B. I.; Henry, F. A.; Bogena, J.; Wille, U. *Chem. Eur. J.* **2015**, *21*, 14924-14930.

literature characterization data.[23] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (s, 2H), 7.65 (s, 1H), 7.23 – 7.15 (m, 3H), 7.08 – 7.06 (m, 2H), 4.75 (s, 1H), 3.80 (m, 1H), 3.70 – 3.54 (m, 1H), 3.63 (s, 3H), 3.07 – 3.03 (m, 1H), 2.96 – 2.91 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3, 166.5, 136.0, 129.3, 128.7, 127.2, 54.2, 52.5, 40.9, 37.6.

Control experiments

Reaction of diphenylsilane with benzylmethylamine

When mixing benzylamine with diphenylsilane in the reaction conditions, immediate H_2 release is observed. However, no new species are visible by ^{1}H NMR, only integration of peaks changes which suggests an equilibrium where starting materials are favored (*Figure 1.*). ^{29}Si NMR (*Figure 2.*) suggests that intermediate **2** is more likely as identical ^{29}Si spectra are obtained when using 1 or 2 equivalents of amine.

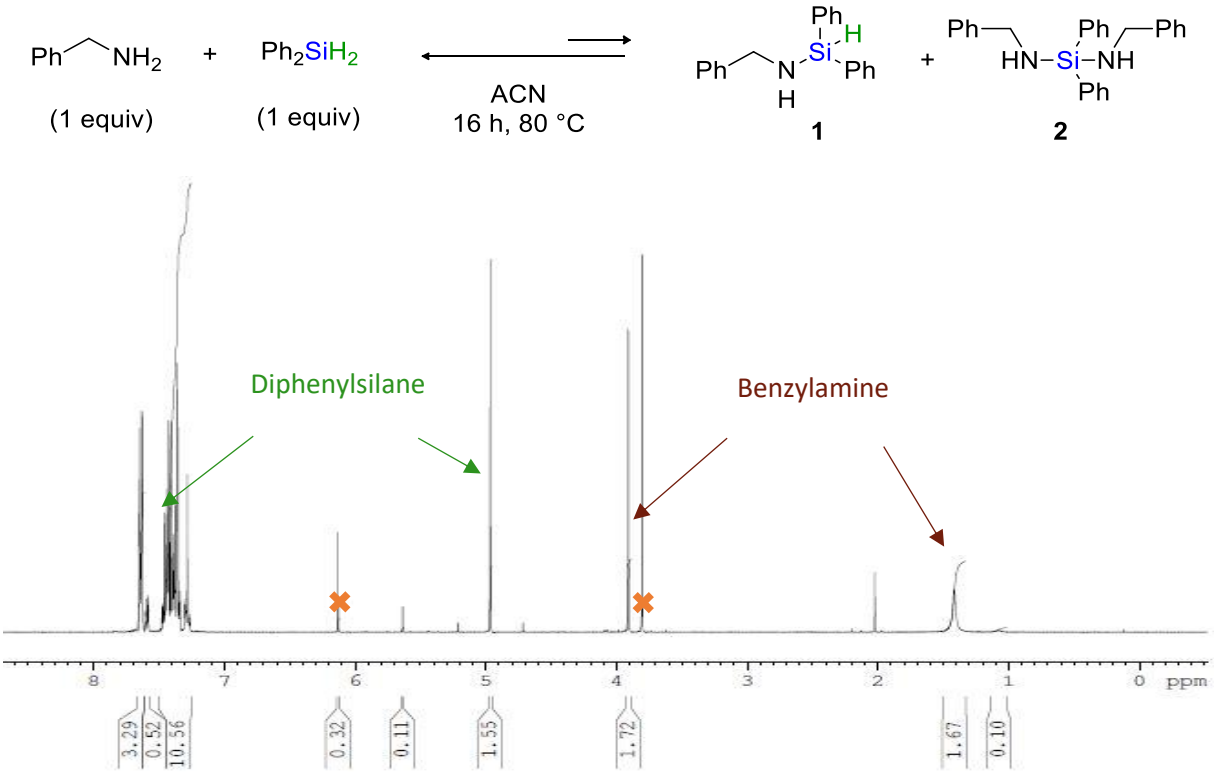


Figure 1. ^{1}H NMR spectrum of crude from reaction between benzylamine and diphenylsilane. Orange crossed peaks correspond to 1,3,5-trimethoxybenzene used as internal standard.

(a) -33.4 Ph_2SiH_2

(b) -33.4 Ph_2SiH_2

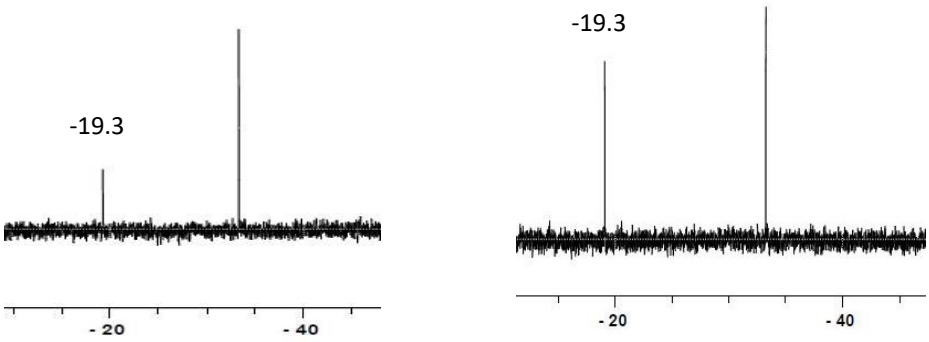


Figure 2. (a) ^{29}Si NMR, 1 equivalent of diphenylsilane and 1 equivalent of benzylamine (ACN, 16 h, 80 °C) (b) ^{29}Si NMR, 1 equivalent of diphenylsilane and 2 equivalents of benzylamine (CAN, 16 h, 80 ° C)

After one night, 1 equivalent of benzoic acid was added and the desired amide was obtained in 71% yield, comparable to the obtained yield for the one pot reaction (74%), which suggests that the reaction can go through the proposed chemical ligation pathway.

Reaction of diphenylsilane with benzoic acid

When mixing benzoic acid with diphenylsilane, no reaction occurs. When adding 1 equivalent of DIPEA, H_2 release is observed. ^{1}H NMR (*Figure 3.*) shows a proton at 5.90 ppm (in red) corresponding to the proton linked on the silicon in intermediate **1**. **1** has also been observed in GC (observed mass: 305.0). Protons that belong to diphenylsilane are still present (in green), showing an incomplete reaction.

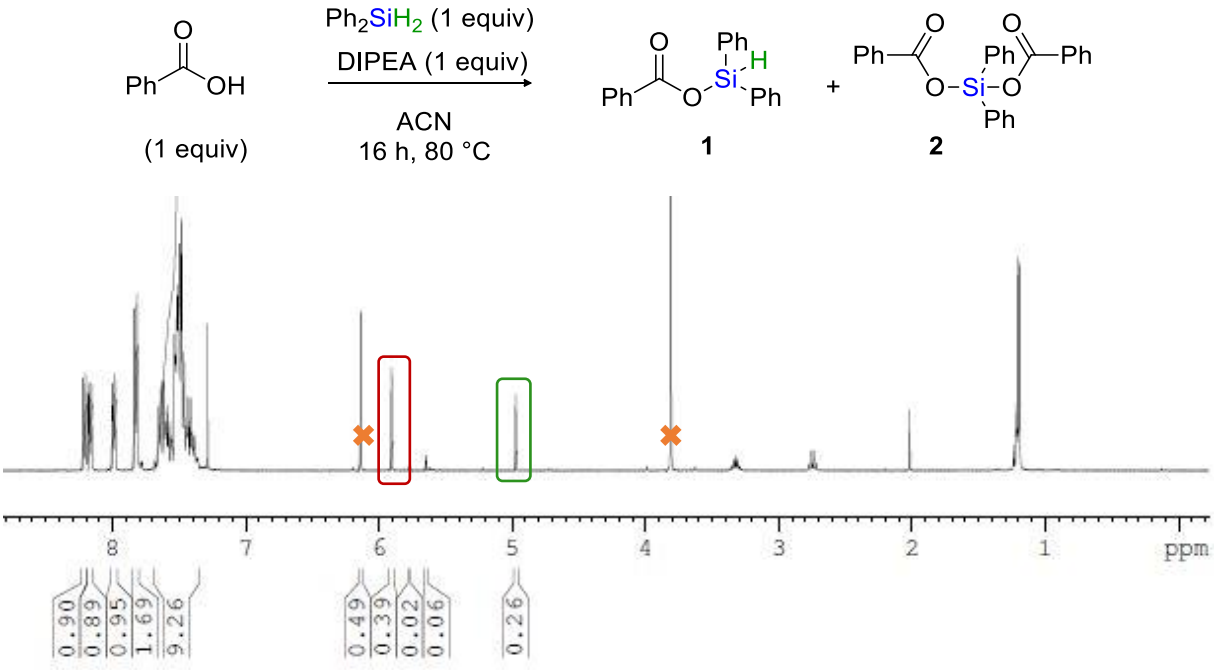


Figure 3. ^{1}H NMR spectrum of crude from reaction between benzoic acid and diphenylsilane. Orange crossed peaks correspond to 1,3,5-trimethoxybenzene used as internal standard.

After one night, 1 equivalent of benzylamine was added and the desired amide was obtained in 75% yield, comparable to the obtained yield for the one pot reaction (74%).

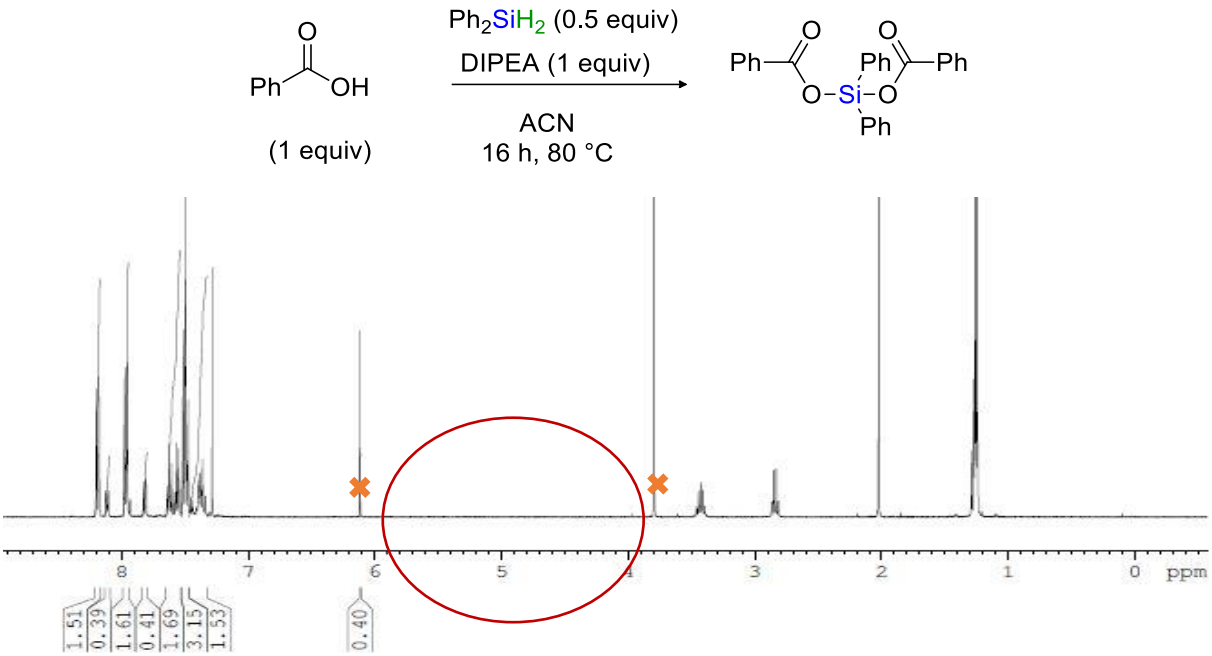
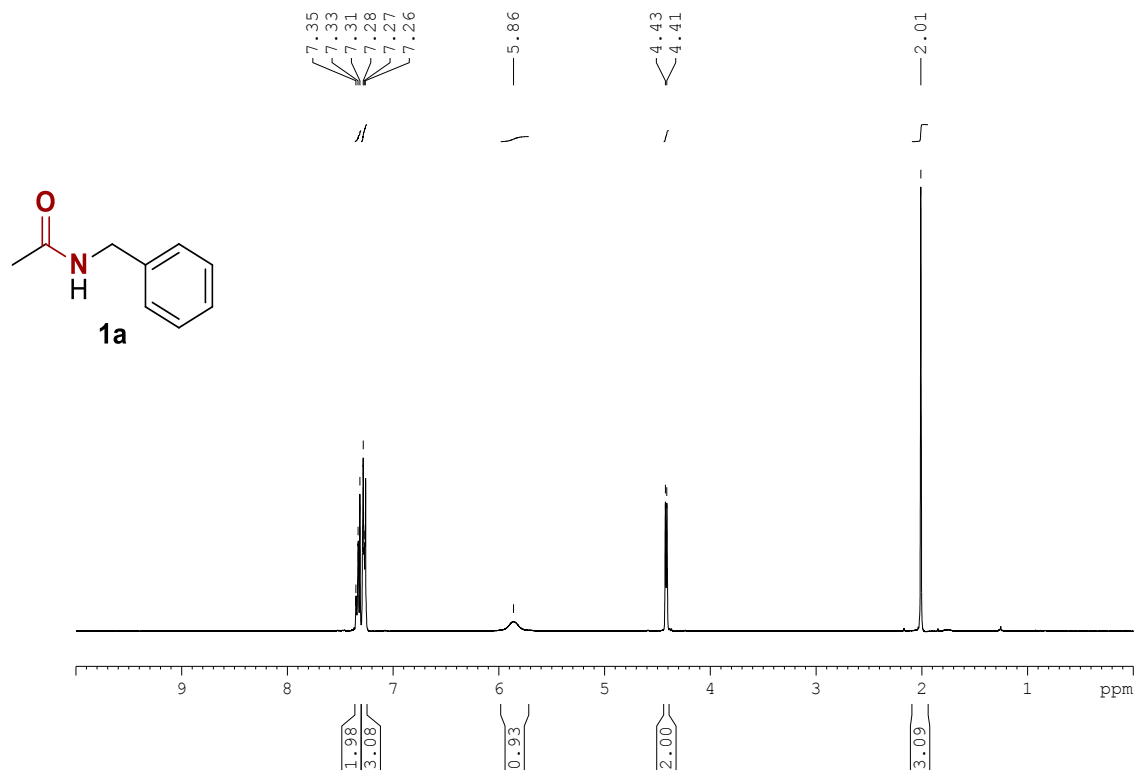


Figure 4. ^{1}H NMR spectrum of crude from reaction between benzoic acid and diphenylsilane. Orange crossed peaks correspond to 1,3,5-trimethoxybenzene used as internal standard.

^{1}H and ^{13}C NMR spectra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7
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5
4
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2
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ppm
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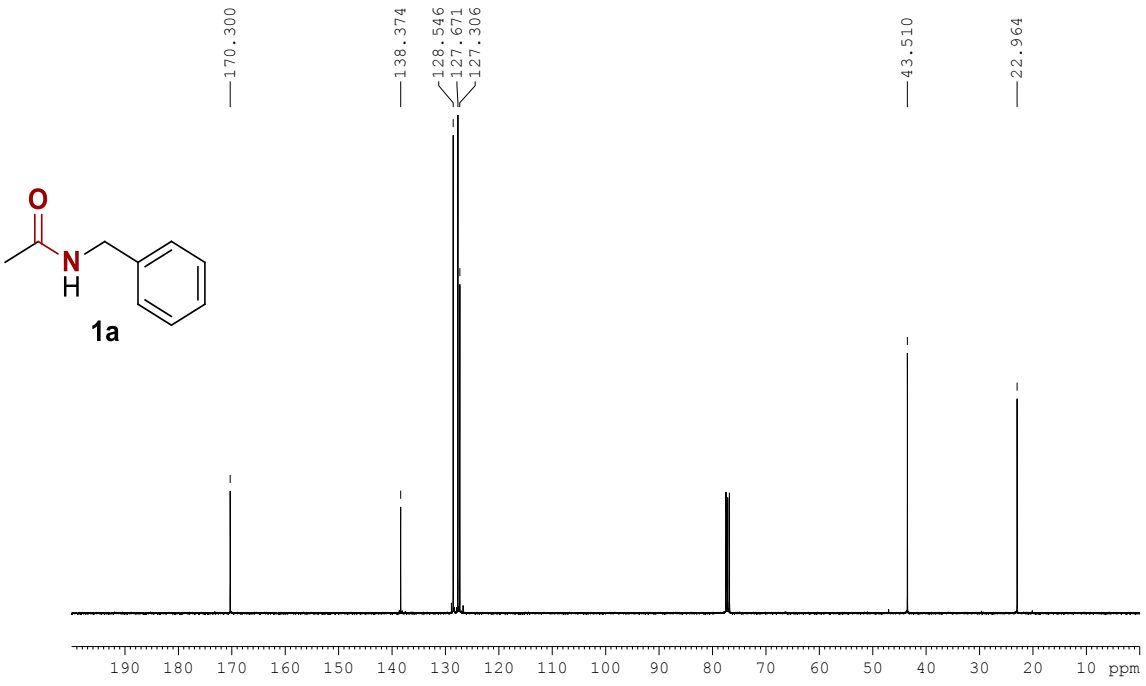
0.93
2.00
3.09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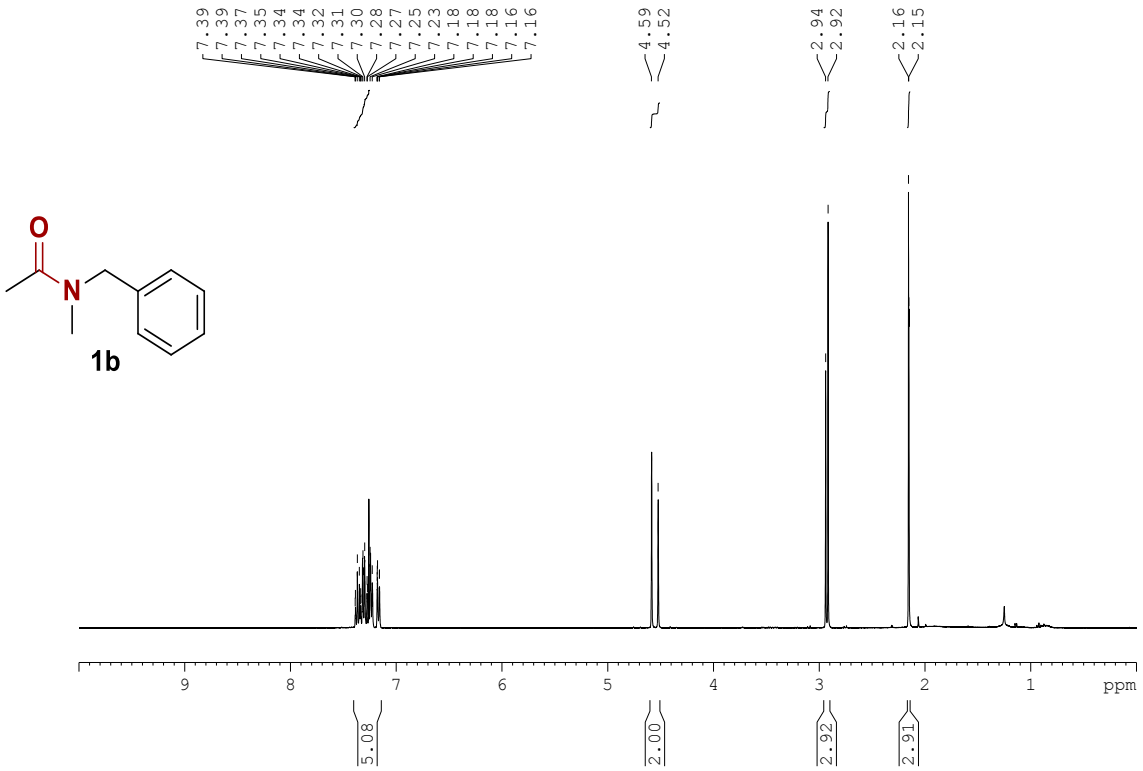
10
ppm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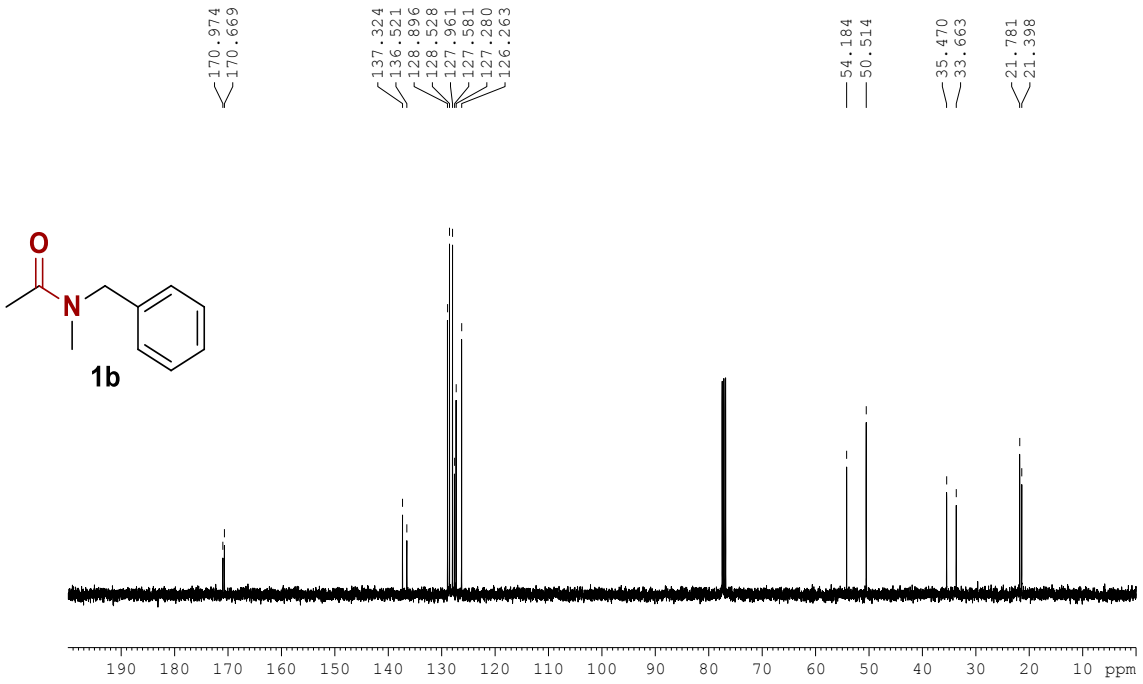
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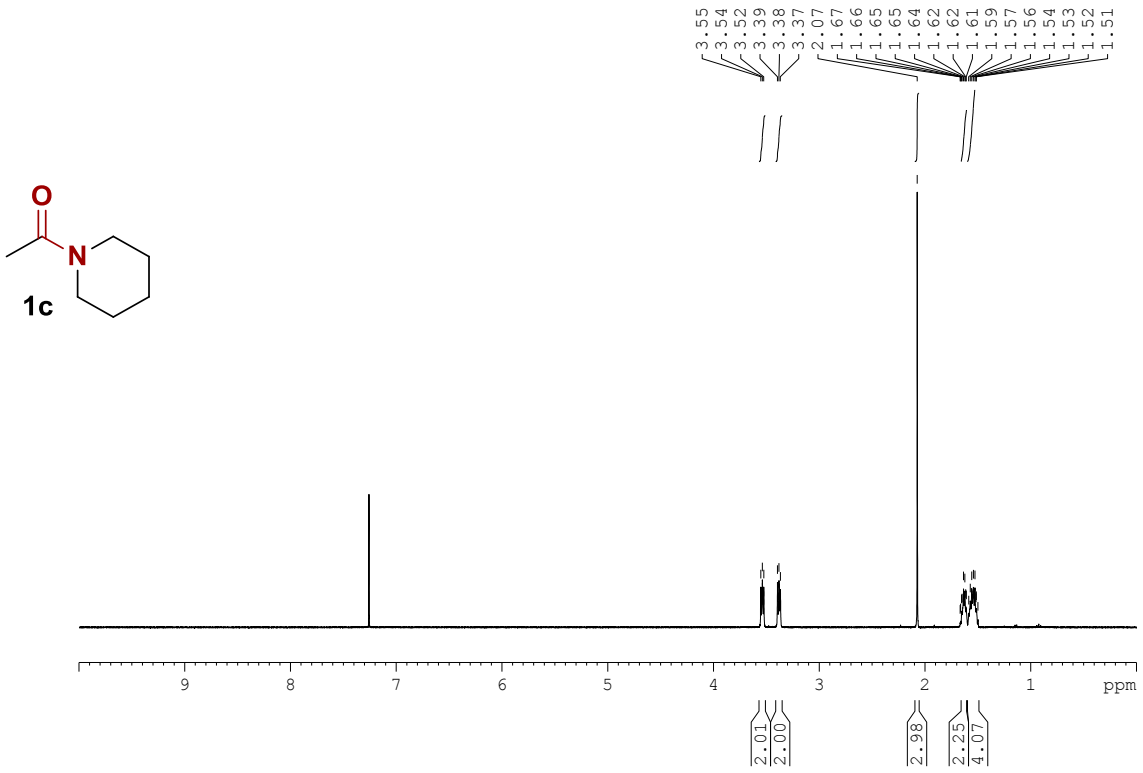
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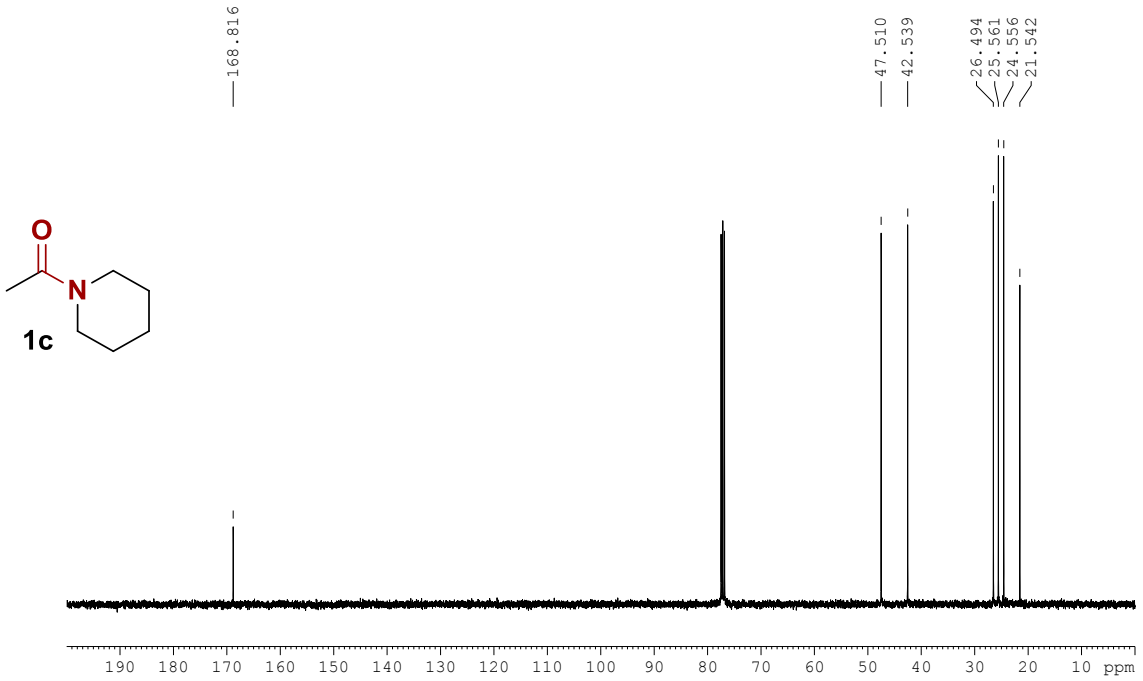
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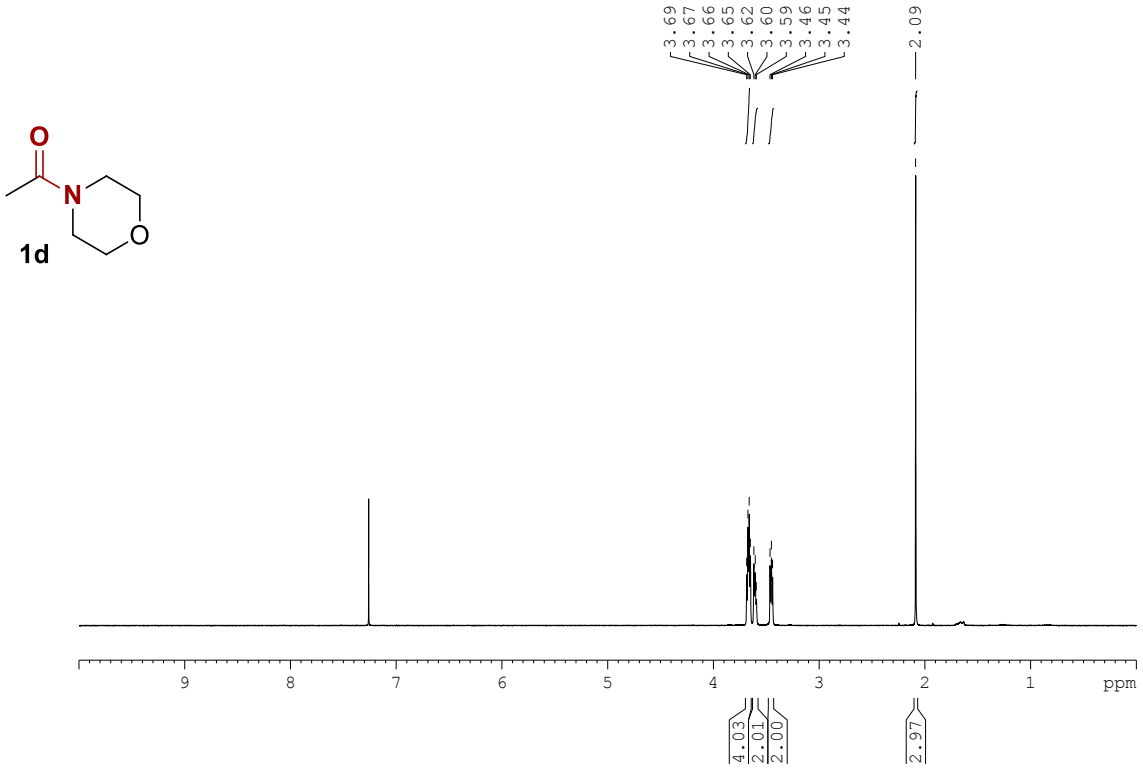
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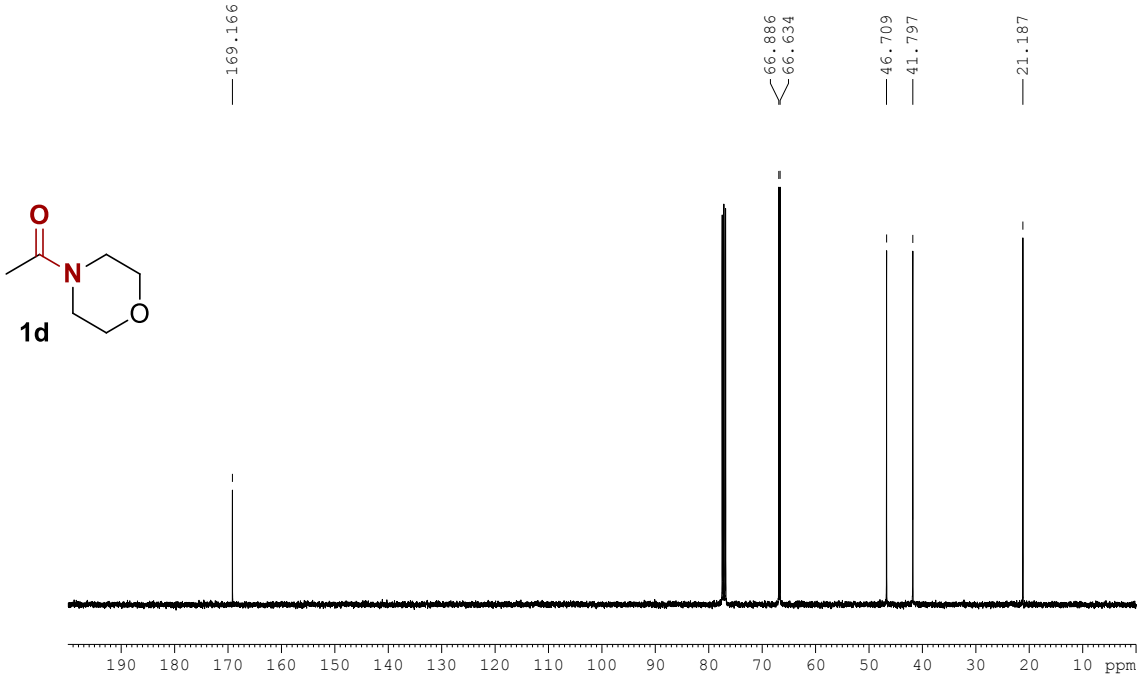
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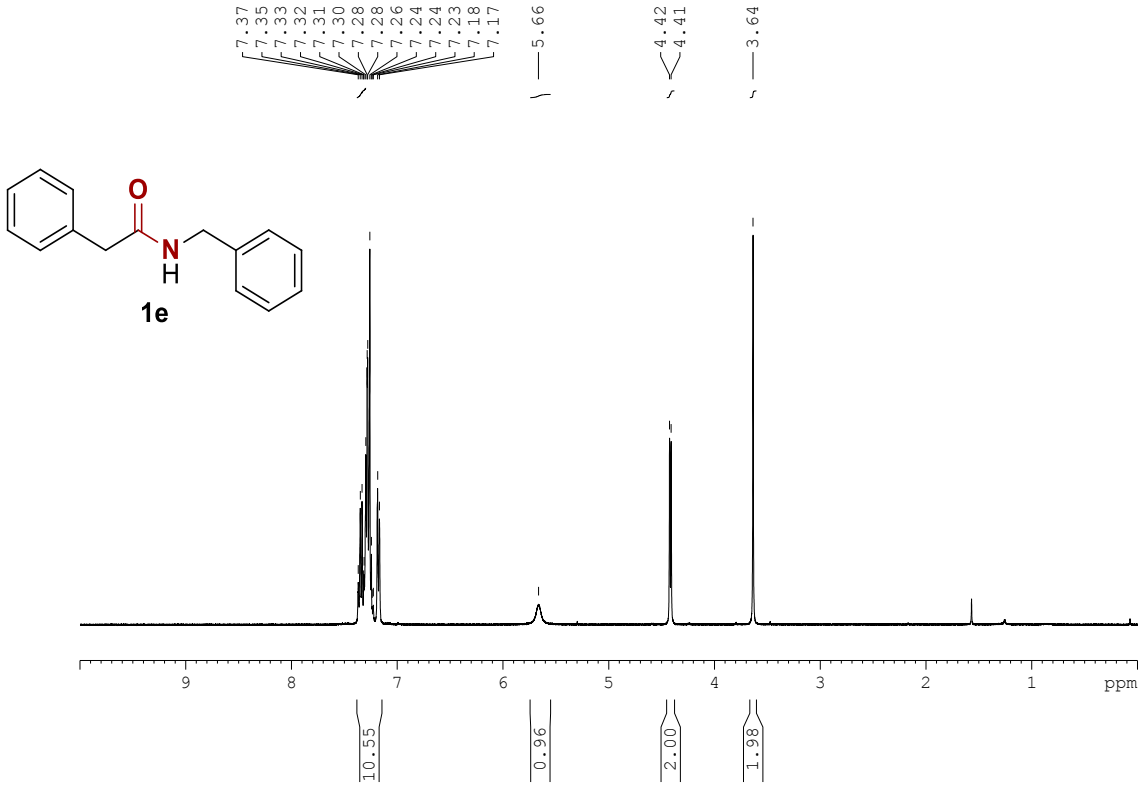
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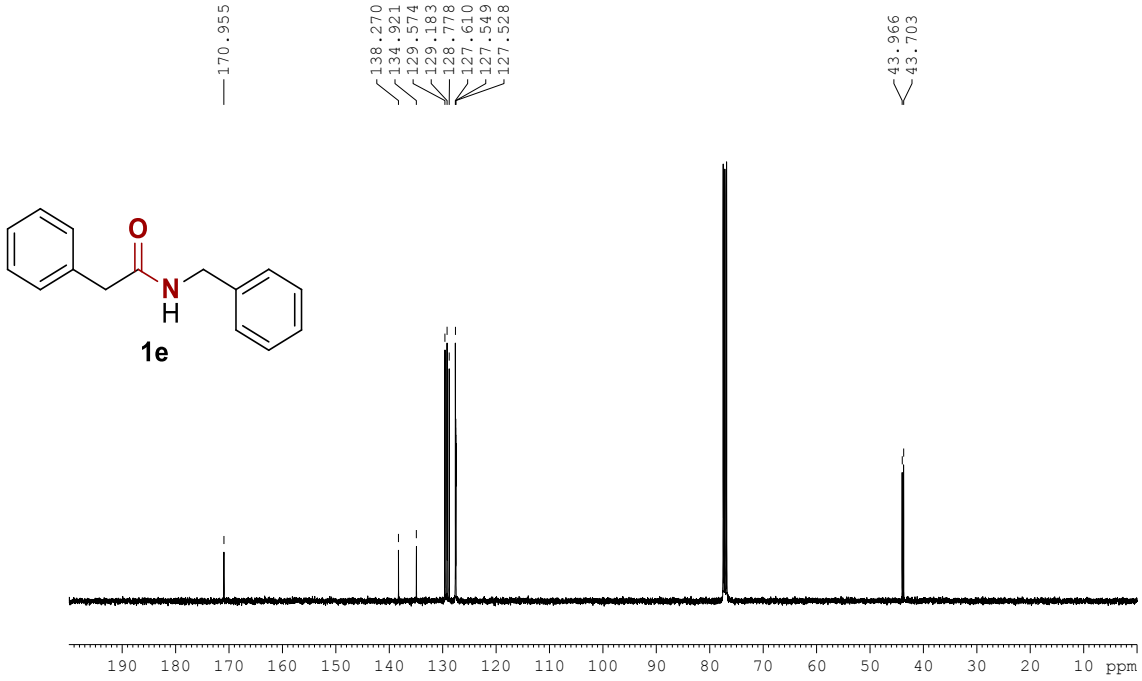
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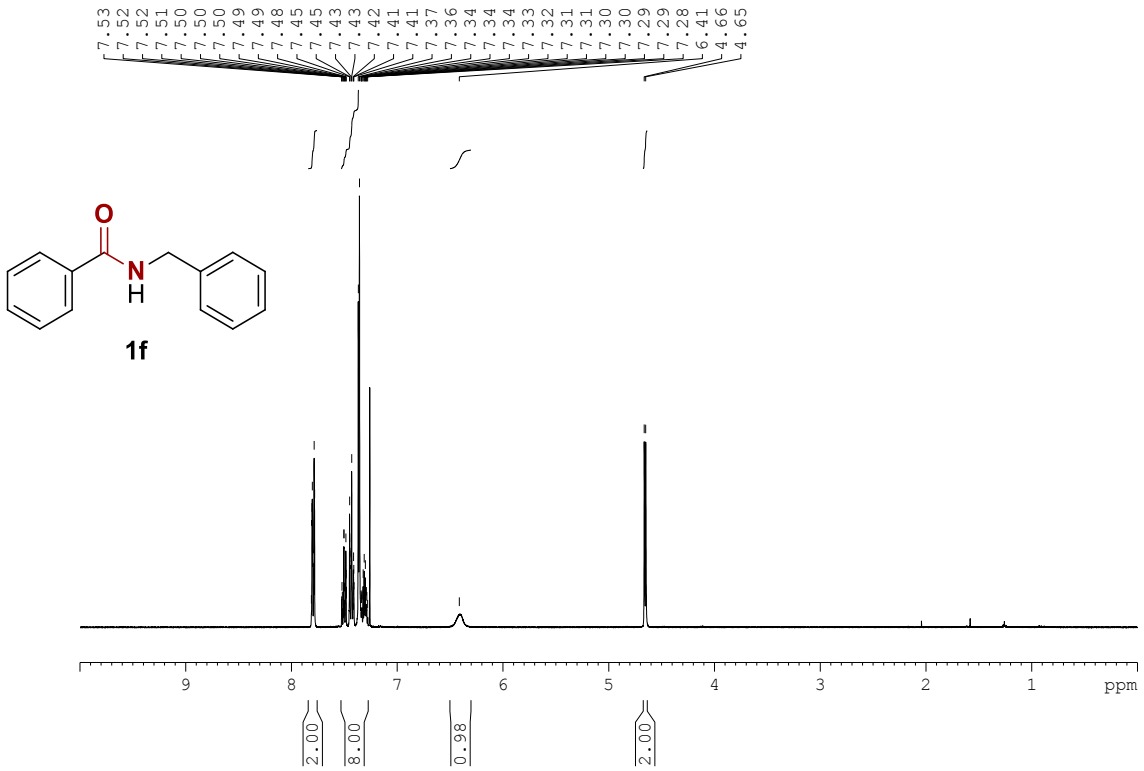
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4.65
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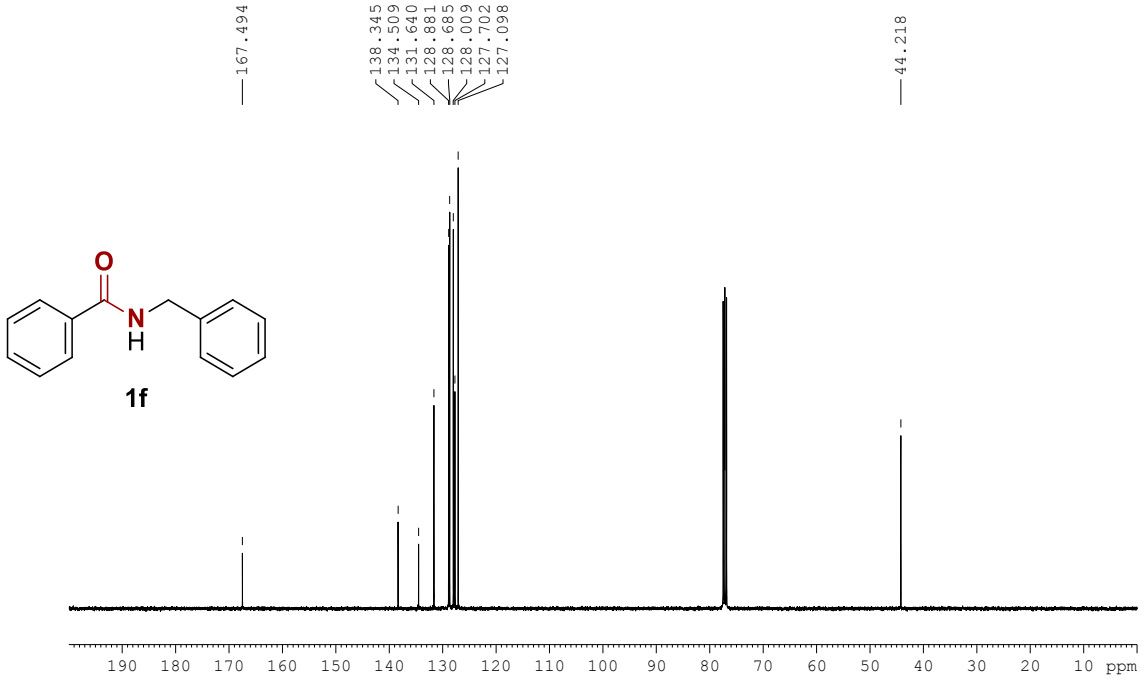
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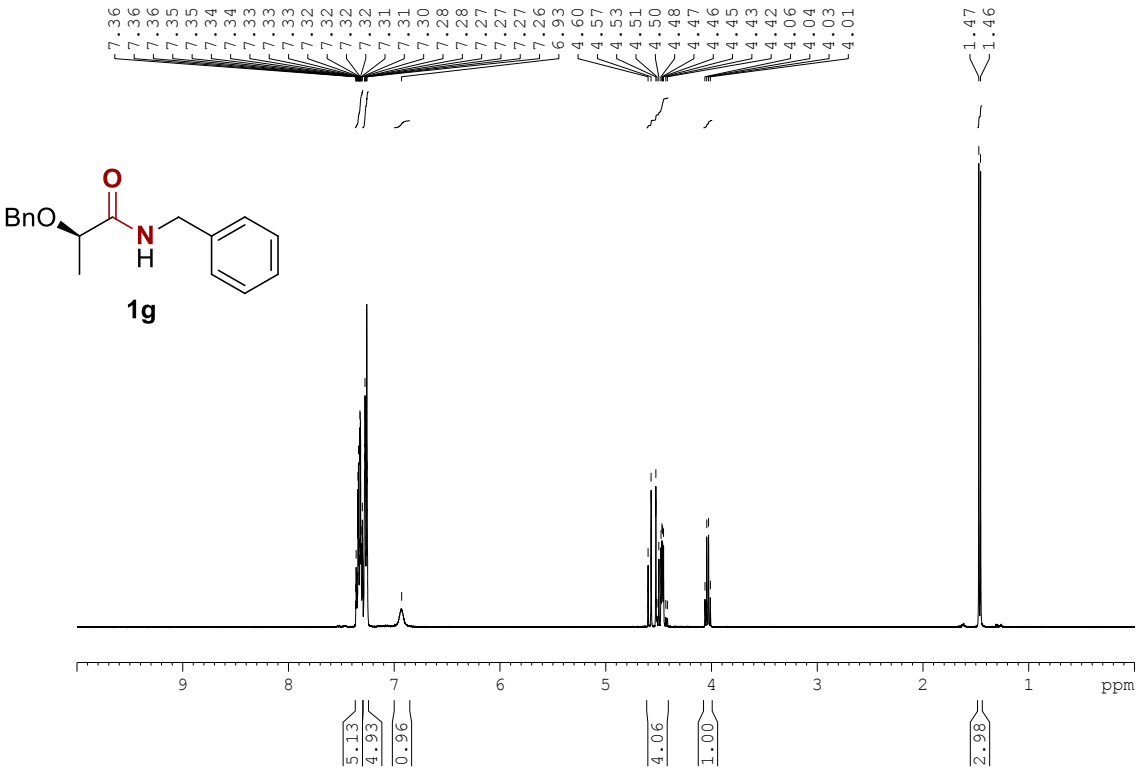
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4.46
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4.43
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4.04
4.03
4.01
1.47
1.46
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O
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H
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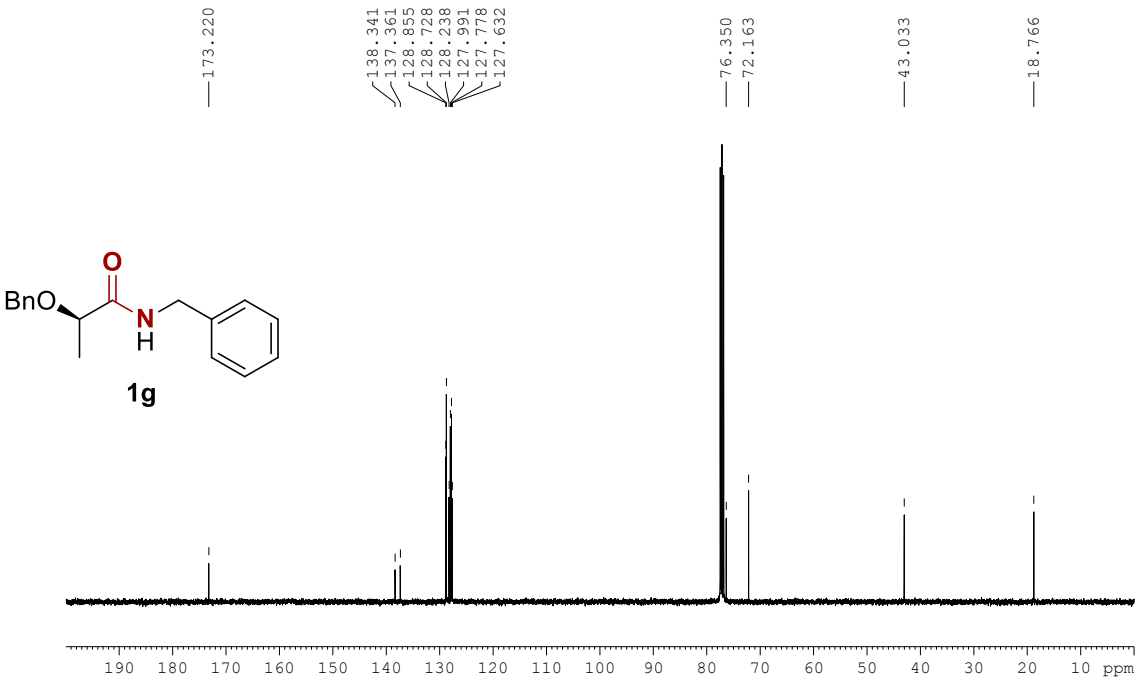
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O
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H
1g
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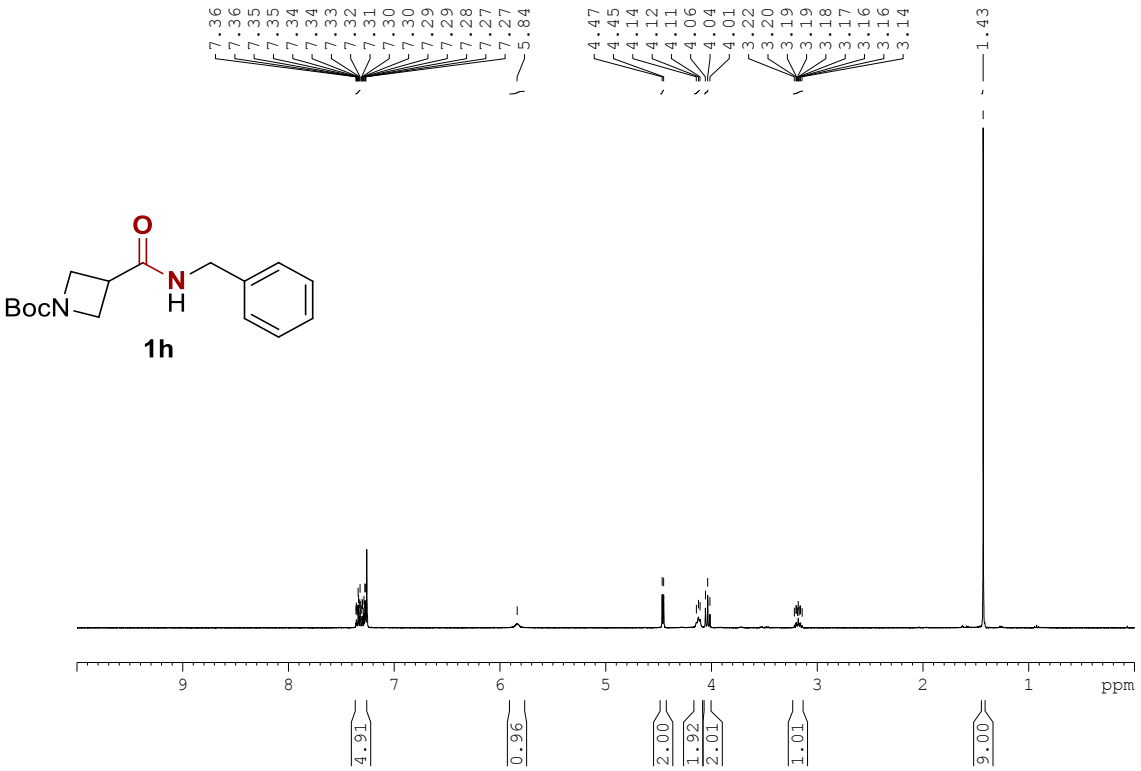
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7.27
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4.06
4.04
4.01
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3.20
3.19
3.19
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3.17
3.16
3.16
3.14
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H
BocN
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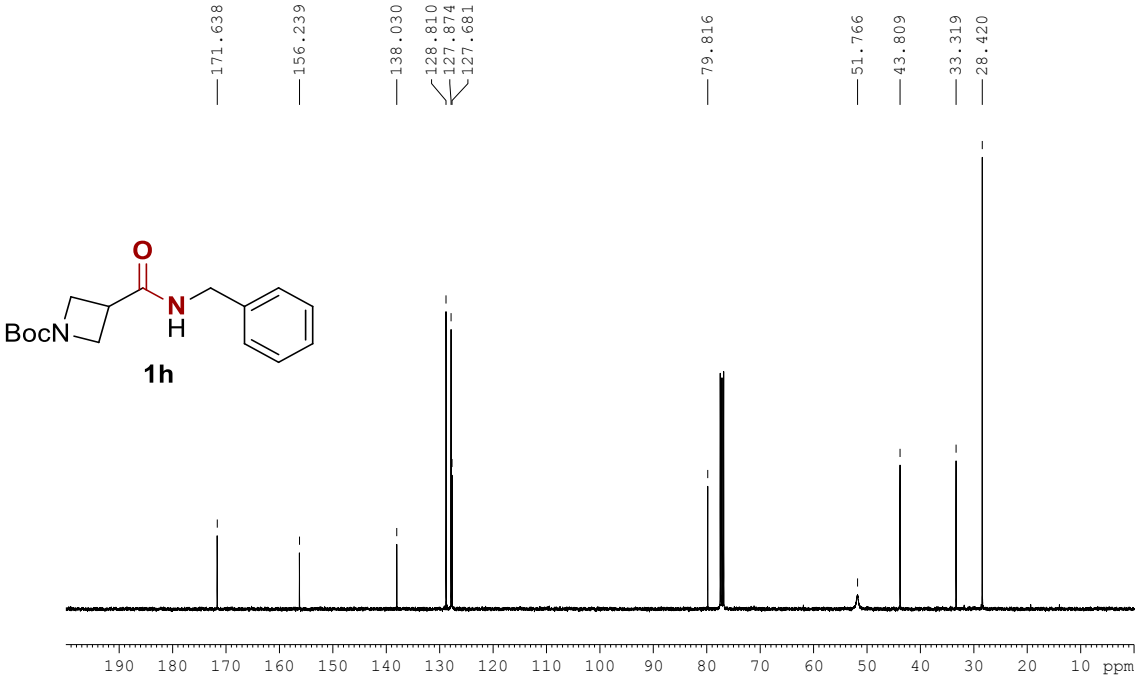
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O
N
H
BocN
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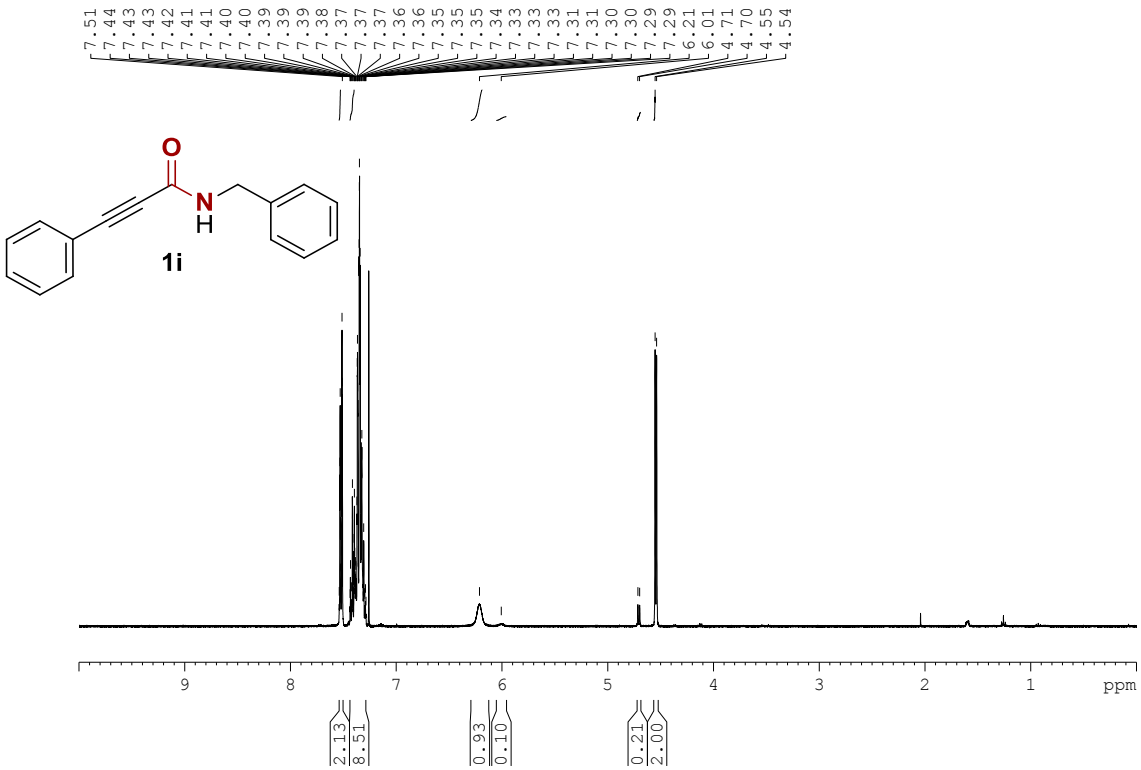
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N
H
1i
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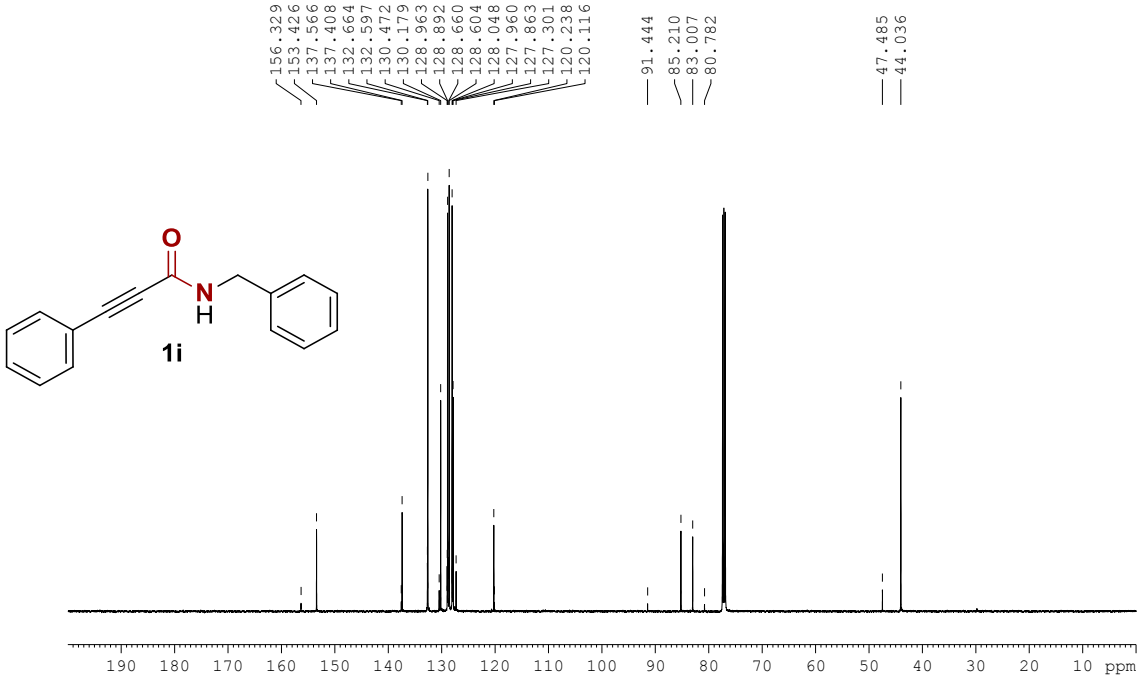
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85.210
83.007
80.782
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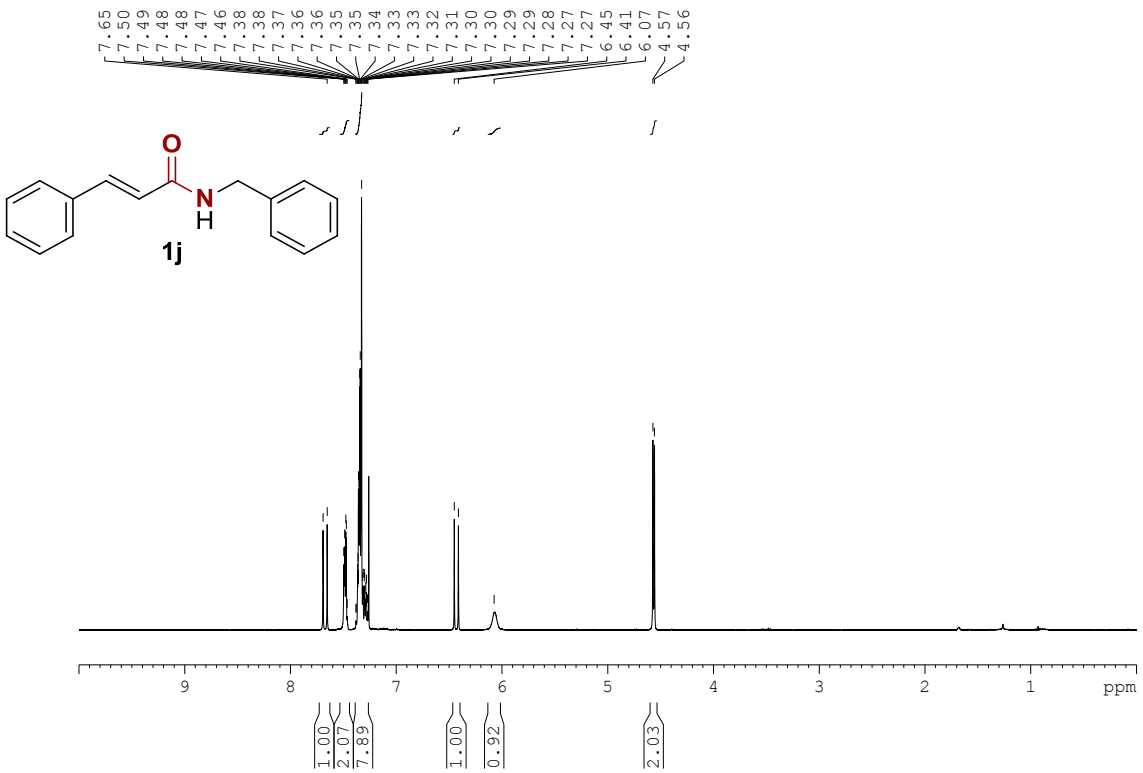
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7.28
7.27
7.27
6.45
6.41
6.07
4.57
4.56
O
N
H
1j
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4
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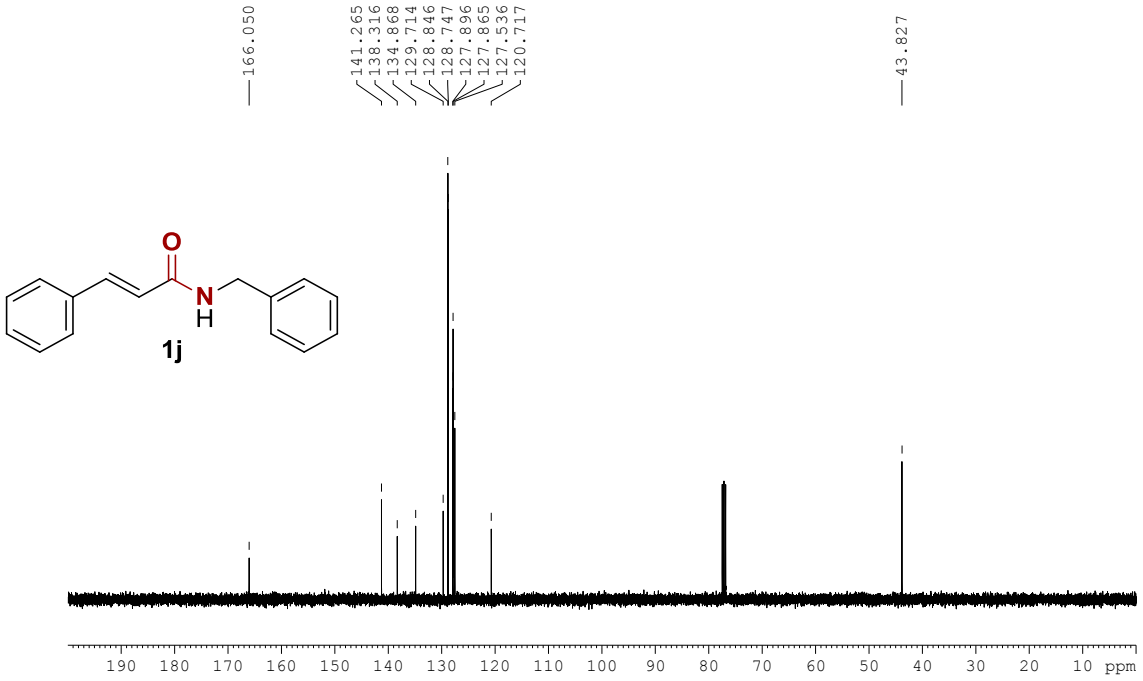
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N
H
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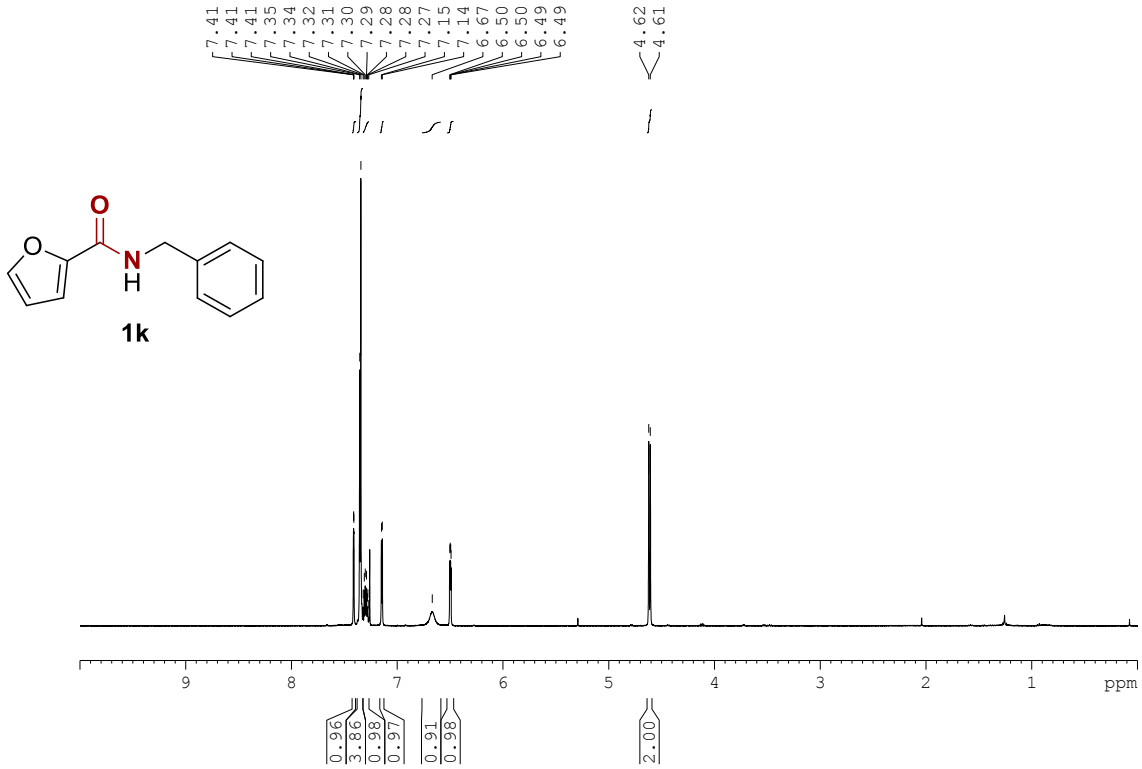
ppm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6.50
6.50
6.49
6.49
4.62
4.61
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O
N
H
1k
9
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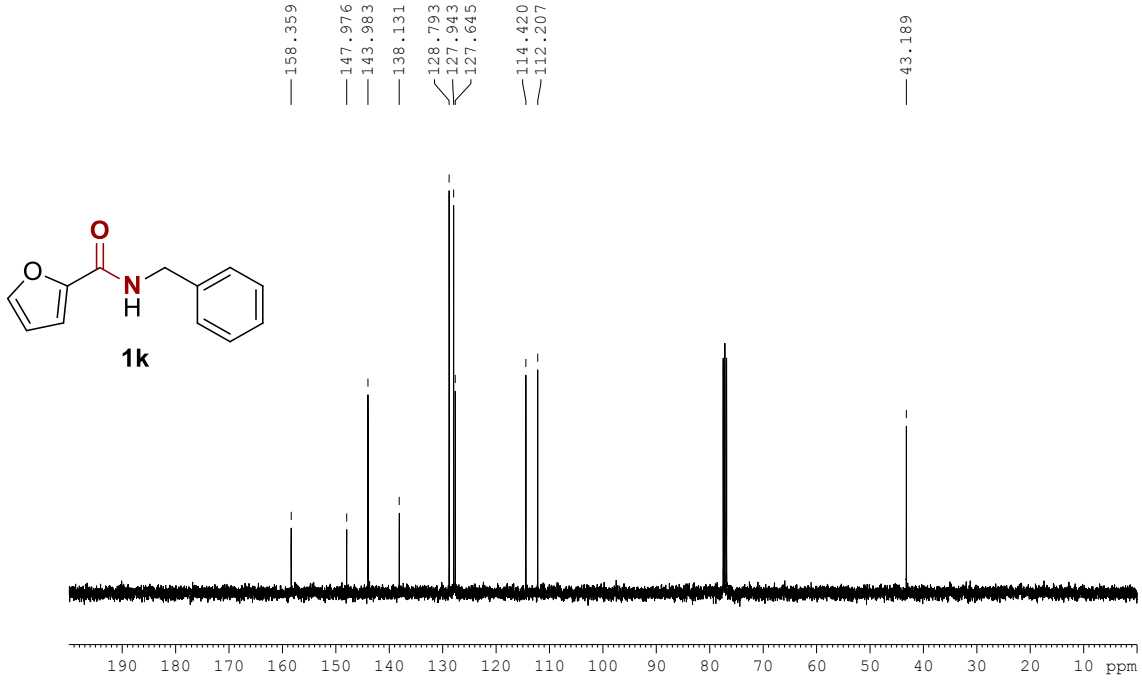
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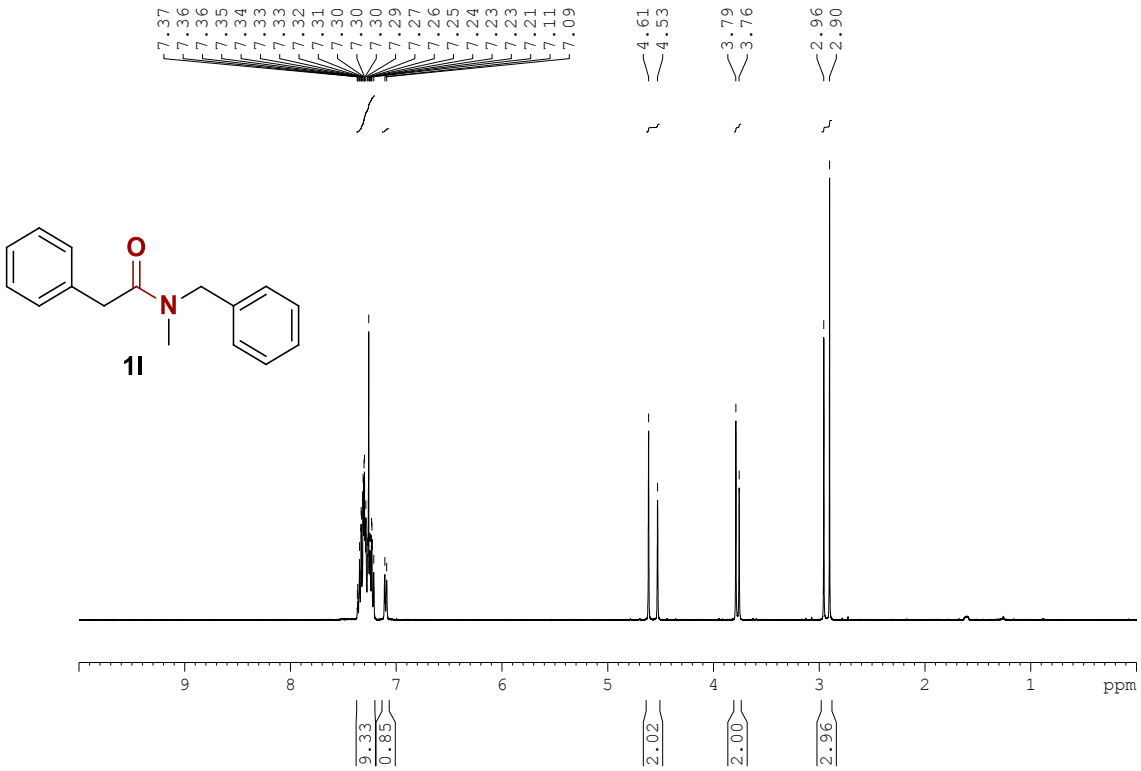
ppm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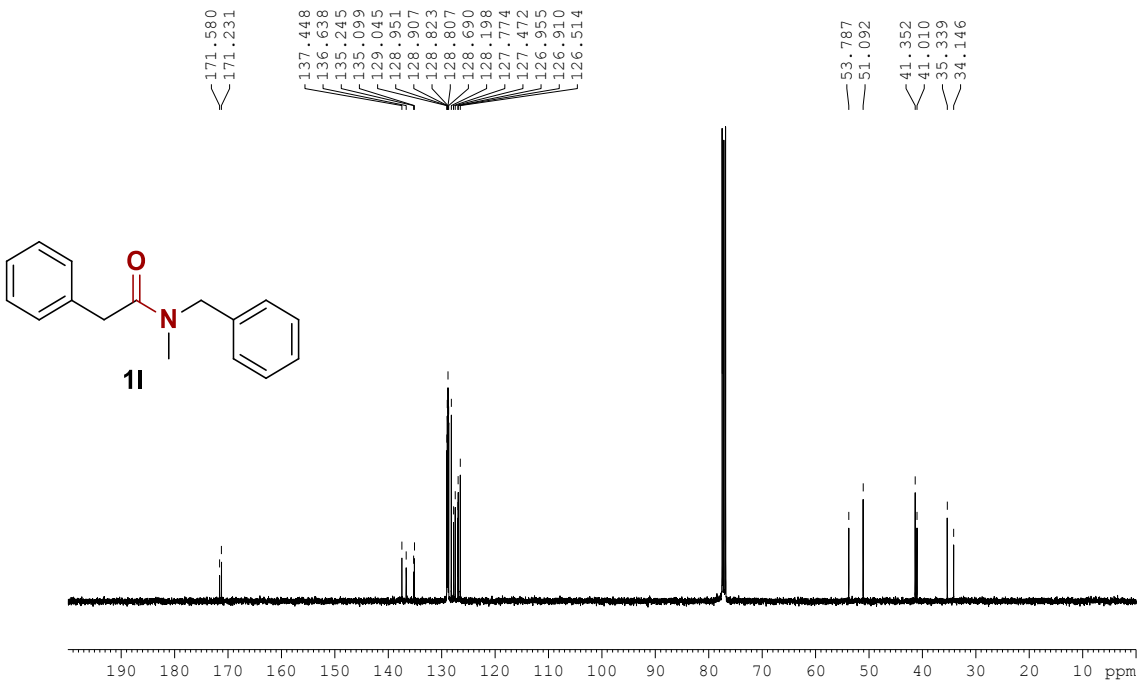
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127.472
126.955
126.910
126.514
53.787
51.092
41.352
41.010
35.339
34.146
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N
1l
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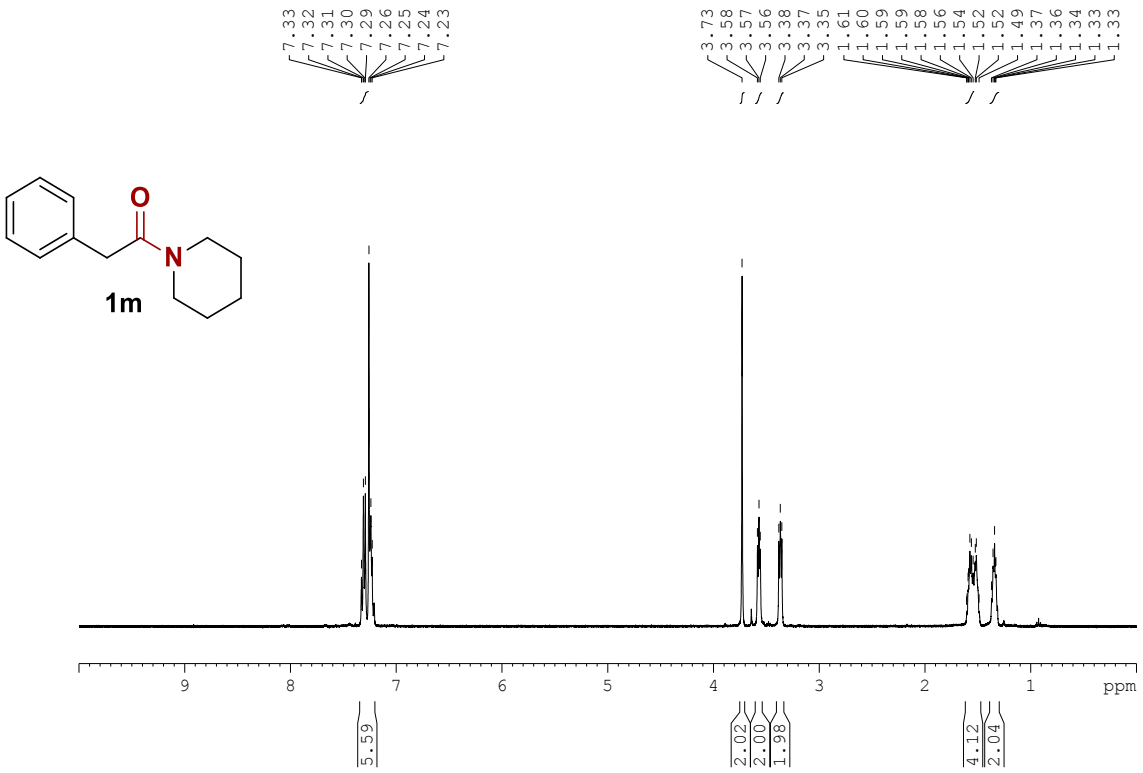
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1.58
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1.52
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O
N
1m
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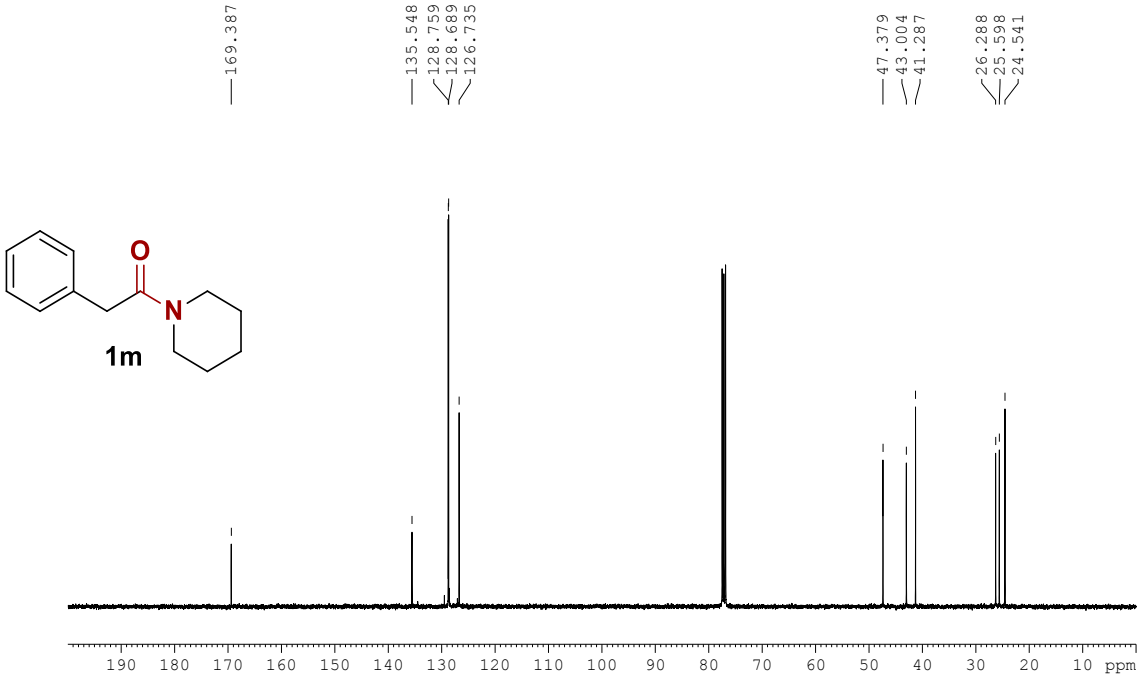
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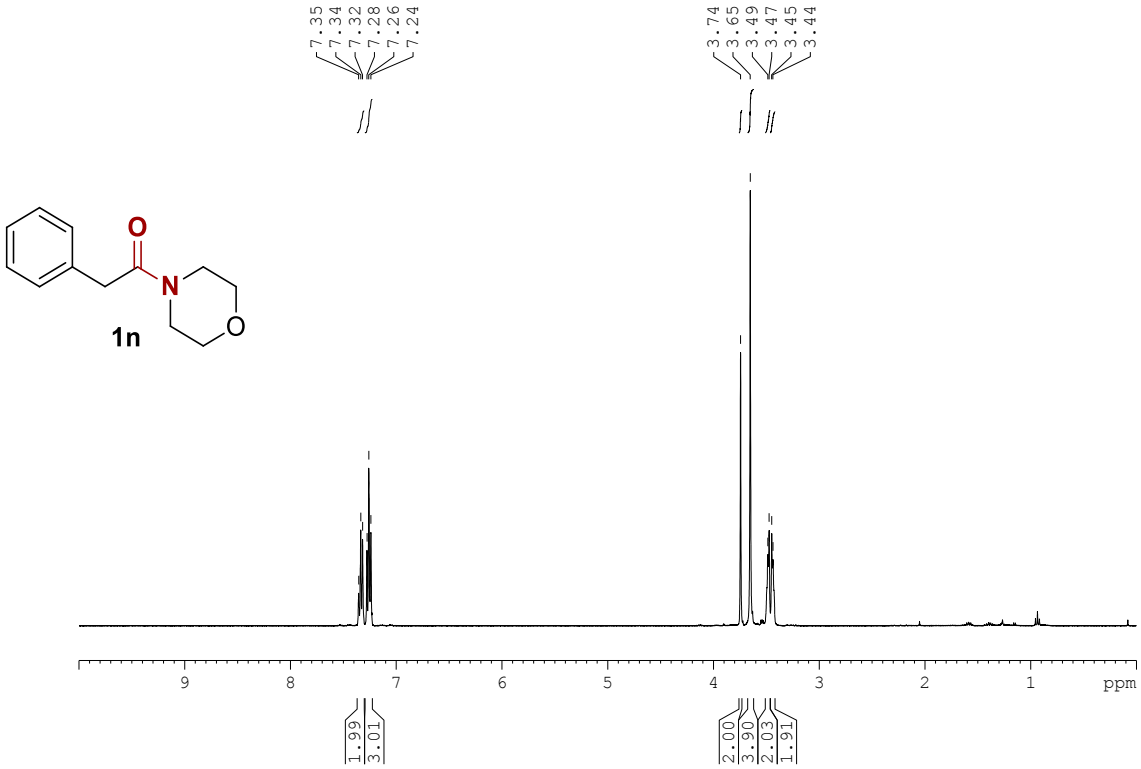
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O
1n
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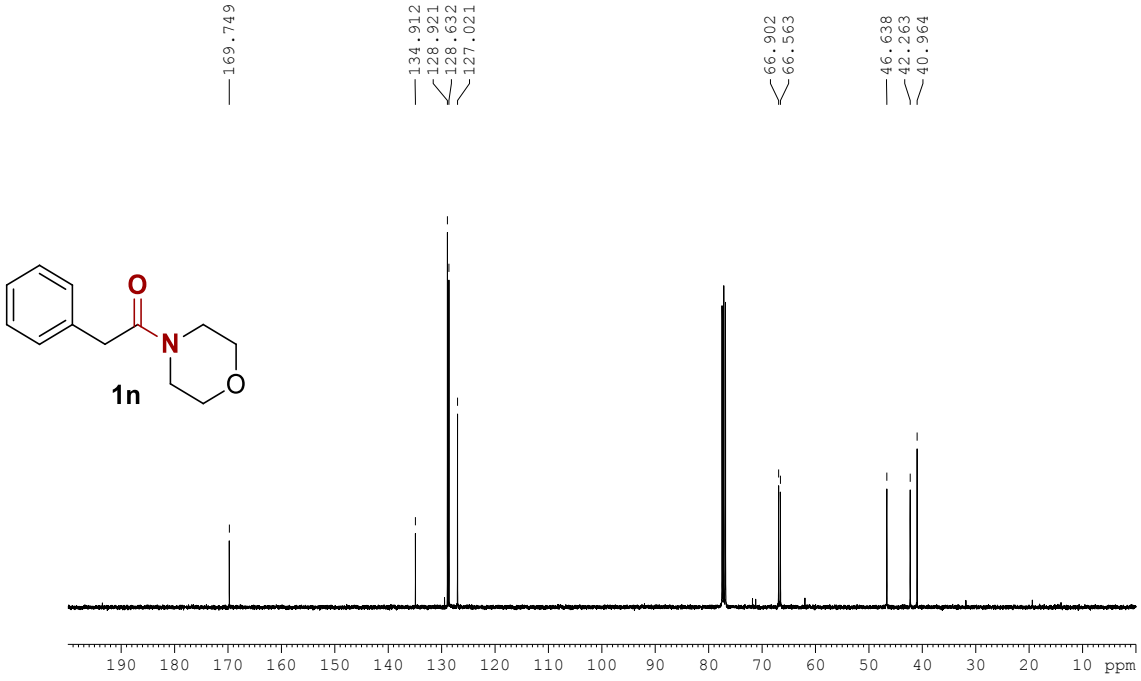
1.91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N
O
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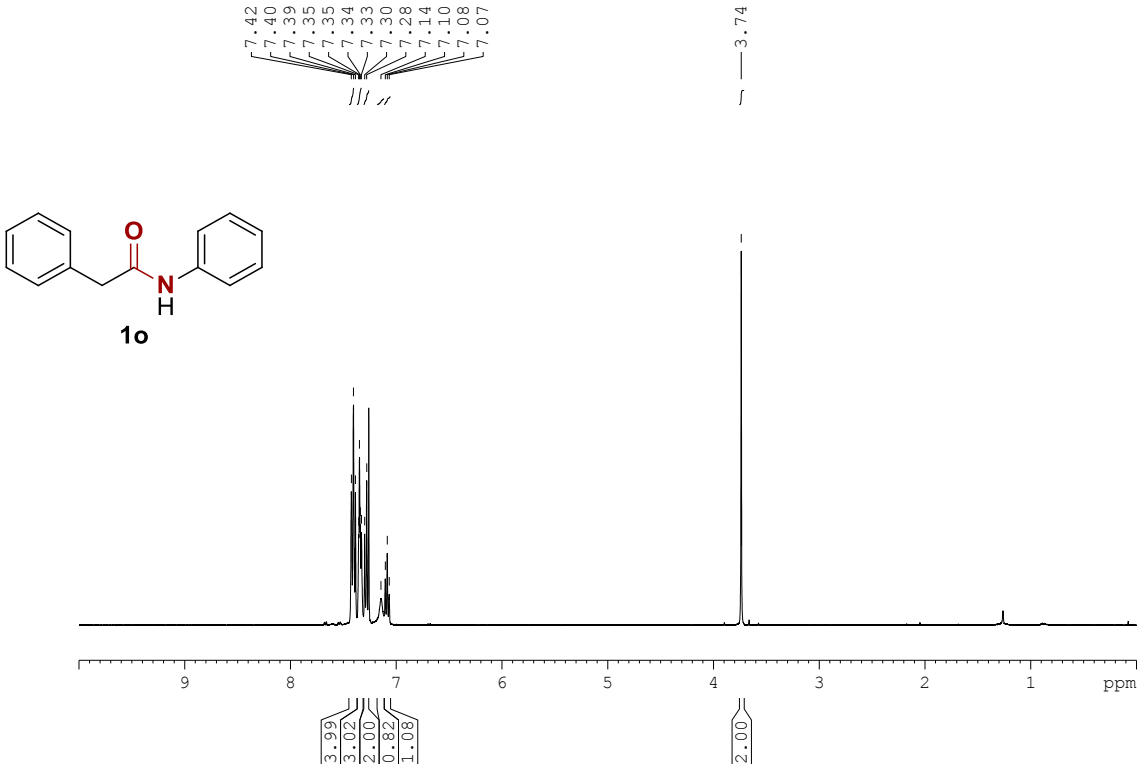
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7.10
7.08
7.07
3.74
1o
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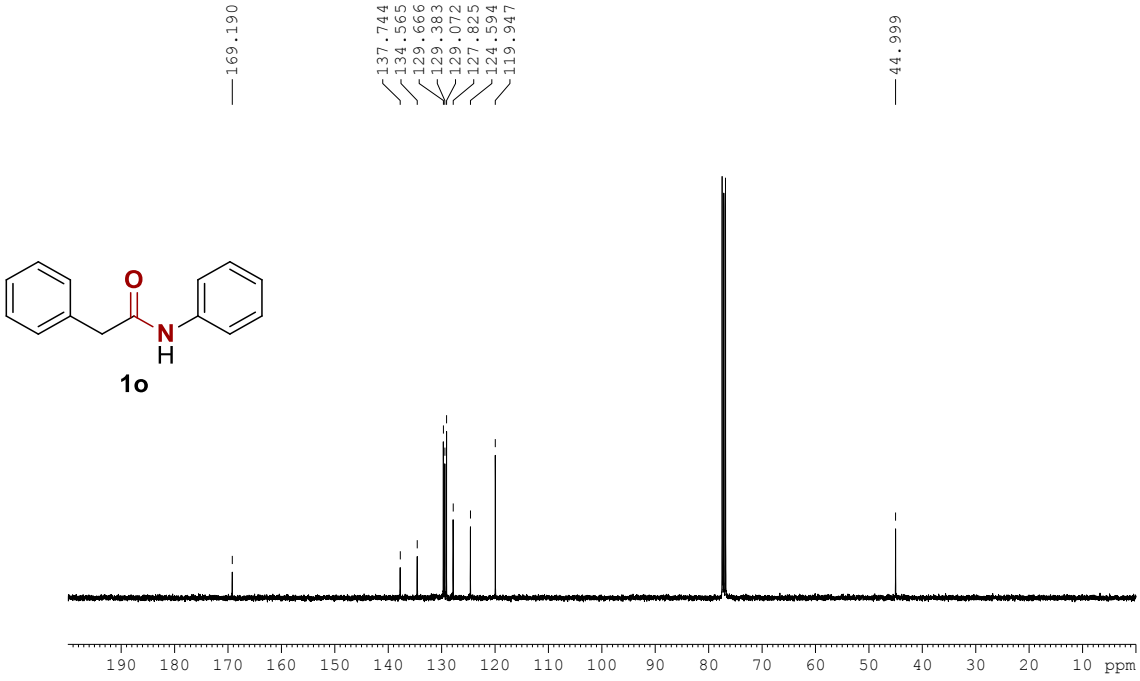
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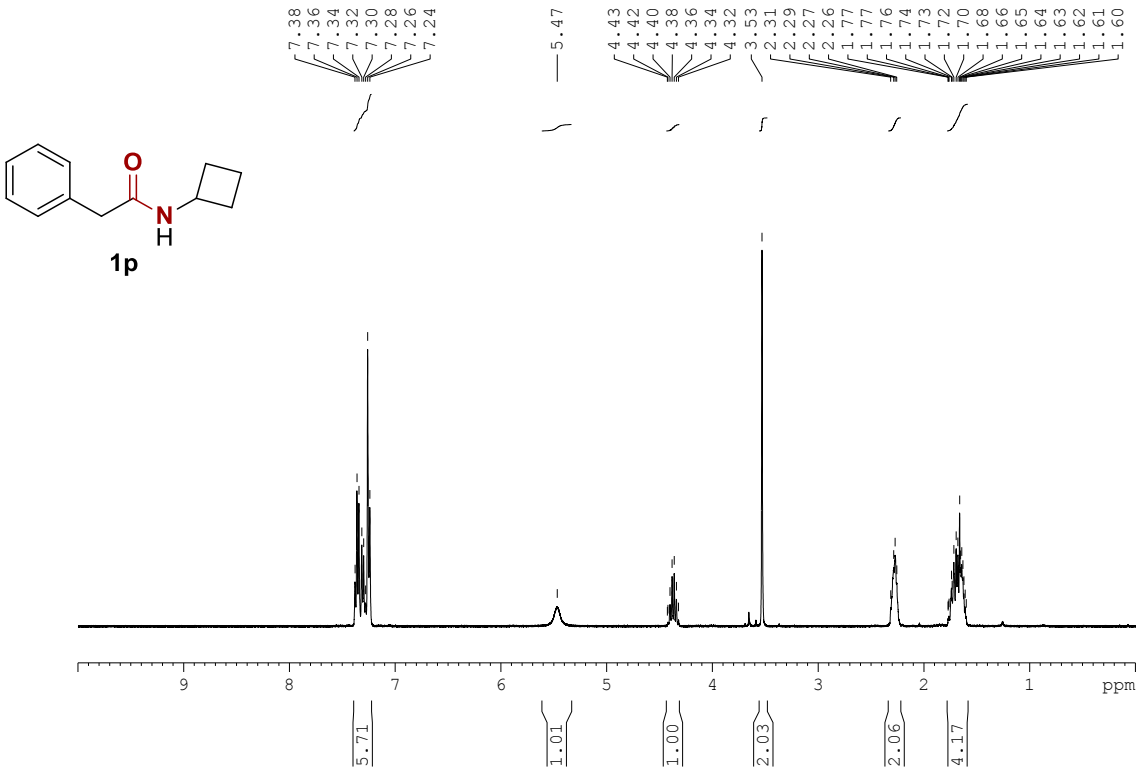
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4.36
4.34
4.32
3.53
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2.29
2.27
2.26
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1.74
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1.72
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1.65
1.64
1.63
1.62
1.61
1.60
O
N
H
1p
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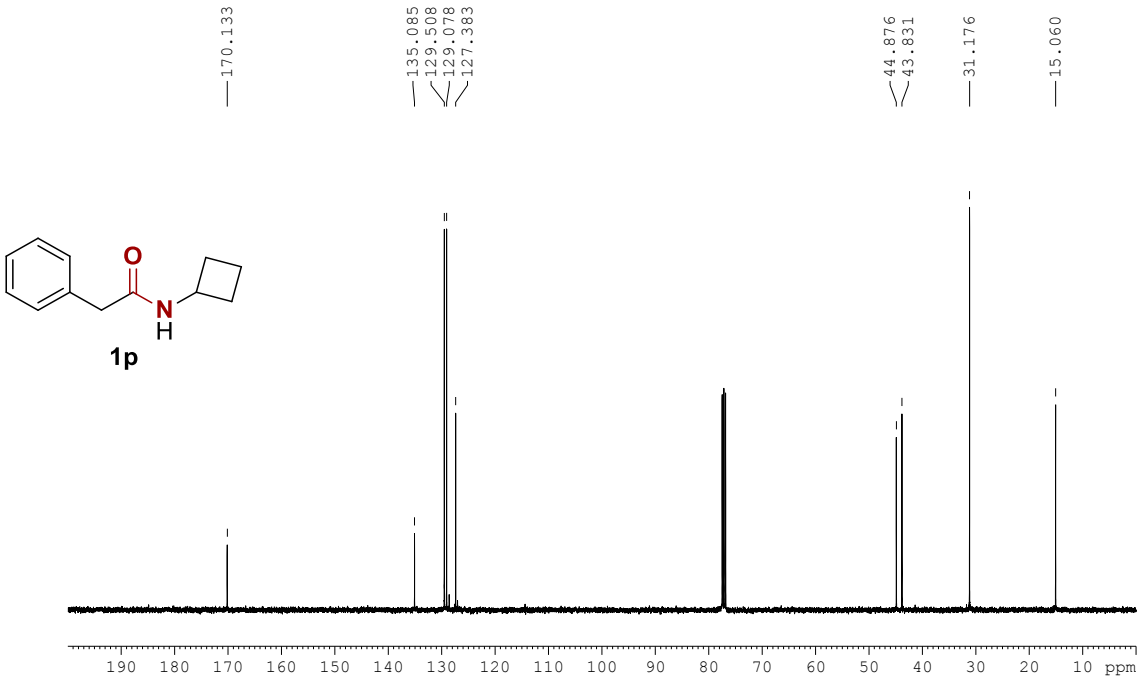
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O
N
H
1p
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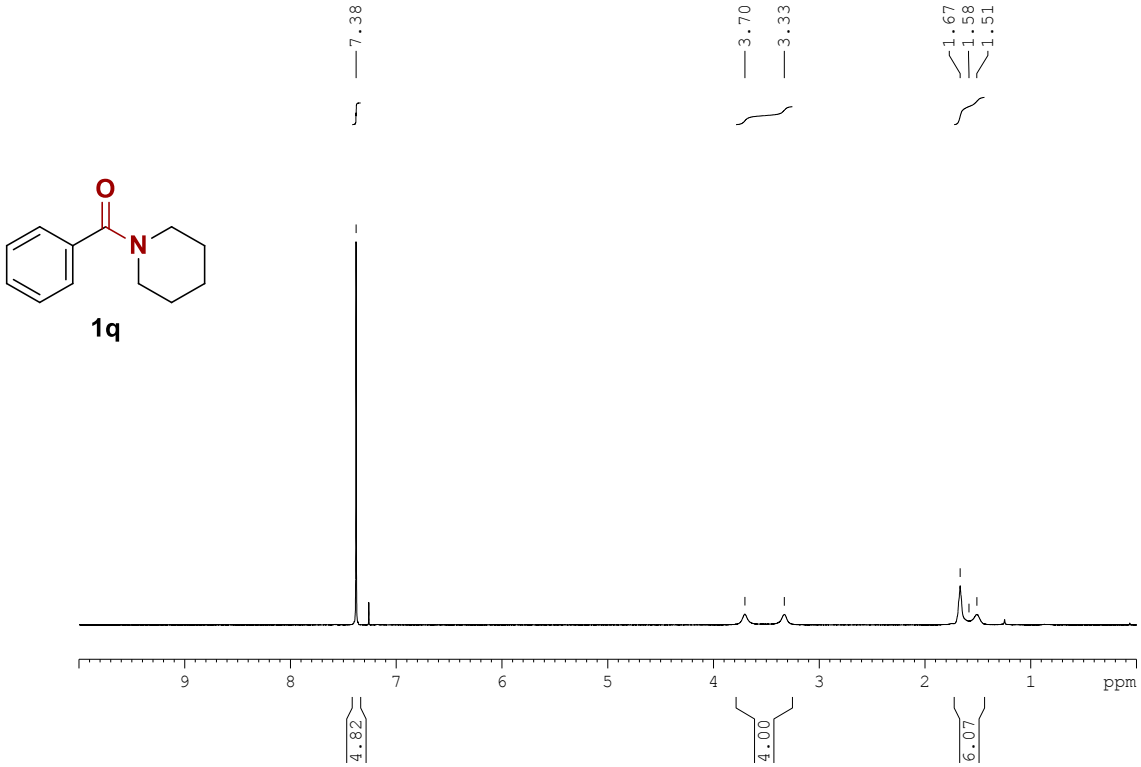
ppm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6
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4
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2
1
ppm
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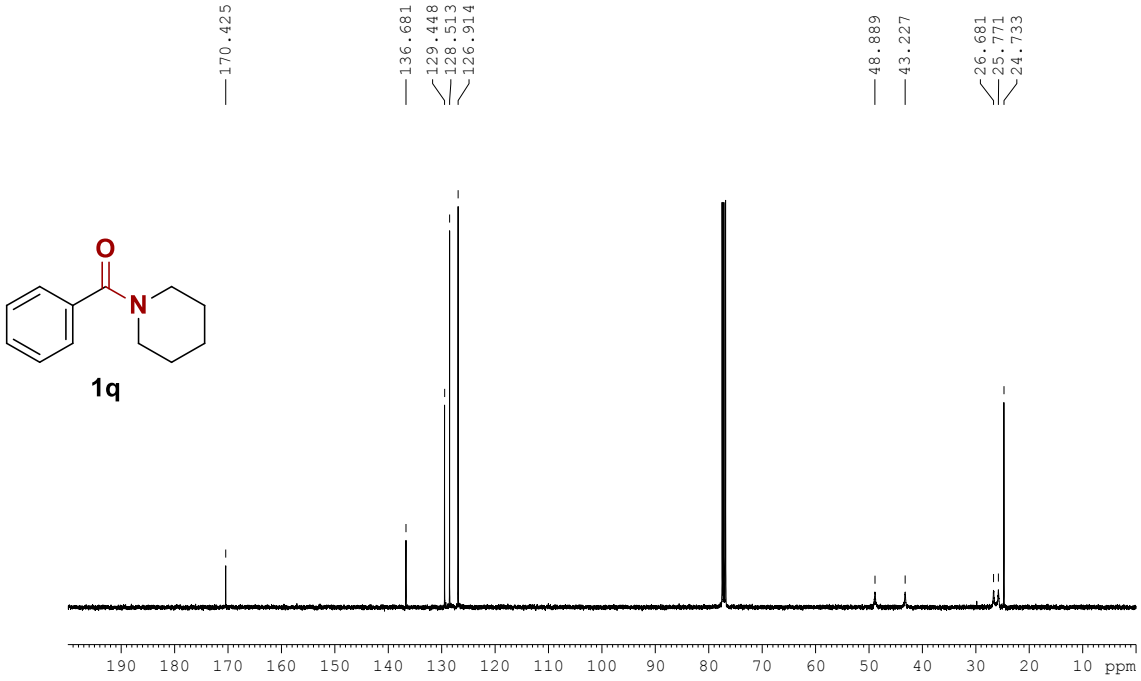
6.07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70
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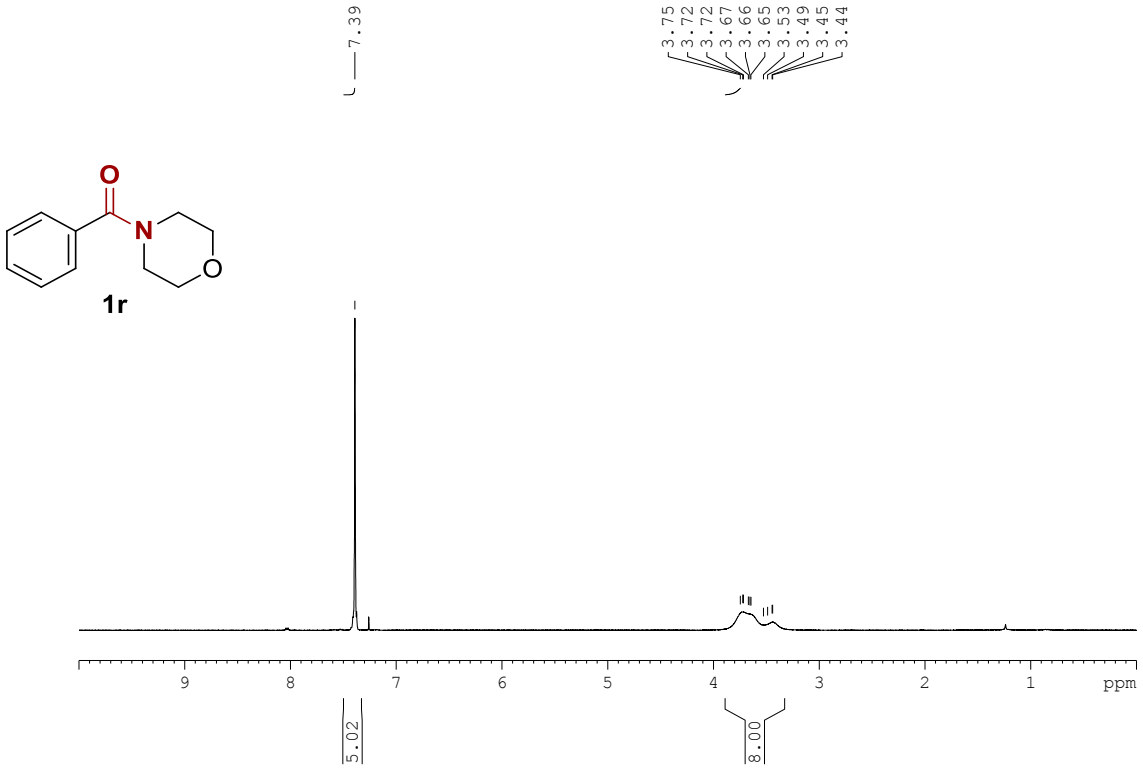
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3.65
3.53
3.49
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O
1r
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6
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4
3
2
1
ppm
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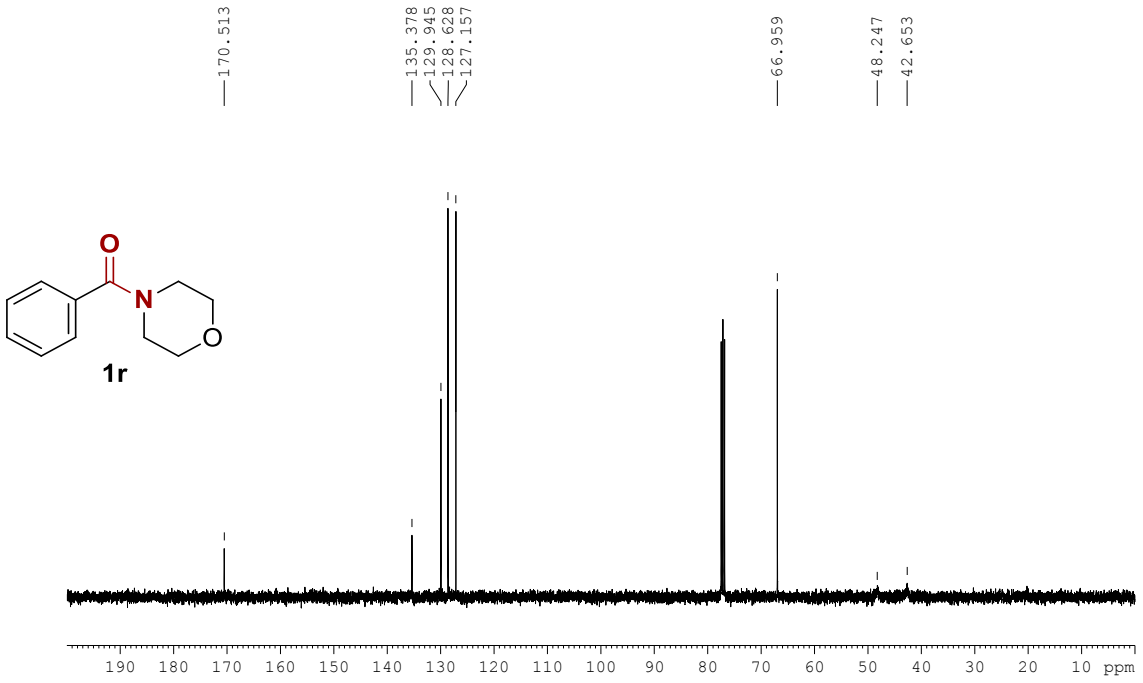
8.00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N
O
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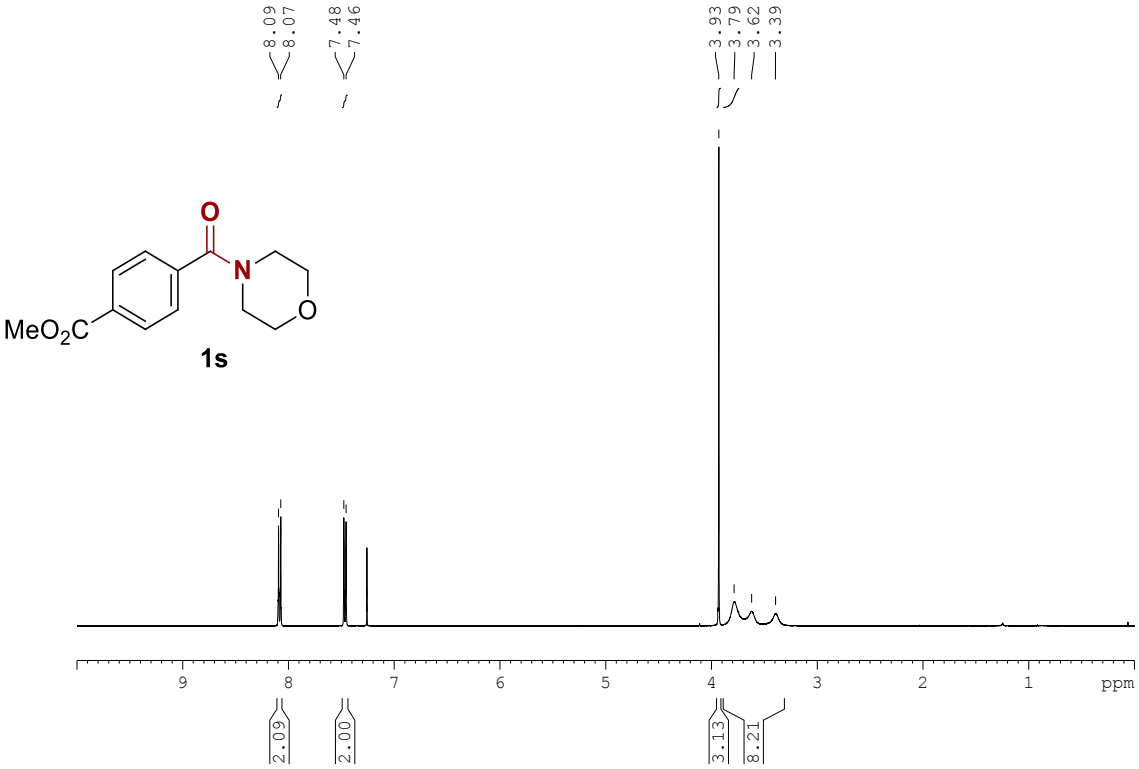
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3.62
3.39
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N
O
MeO2C
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8
7
6
5
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ppm
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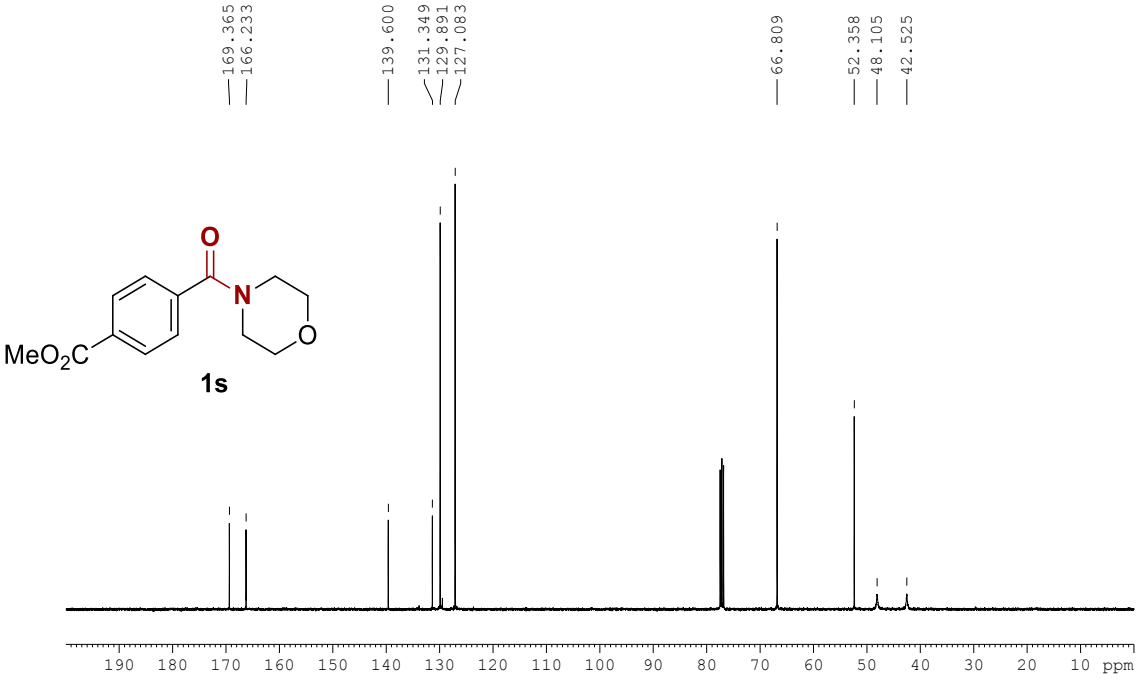
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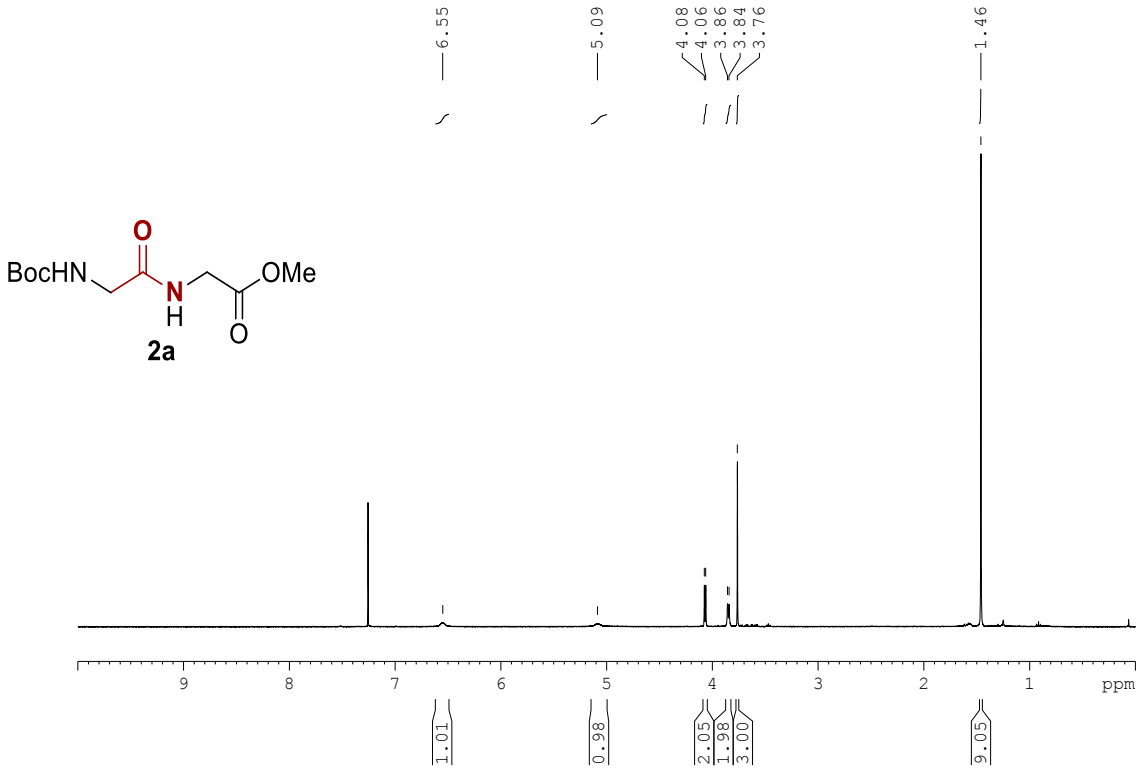
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3.76
1.46
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O
N
H
OMe
O
2a
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8
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5
4
3
2
1
ppm
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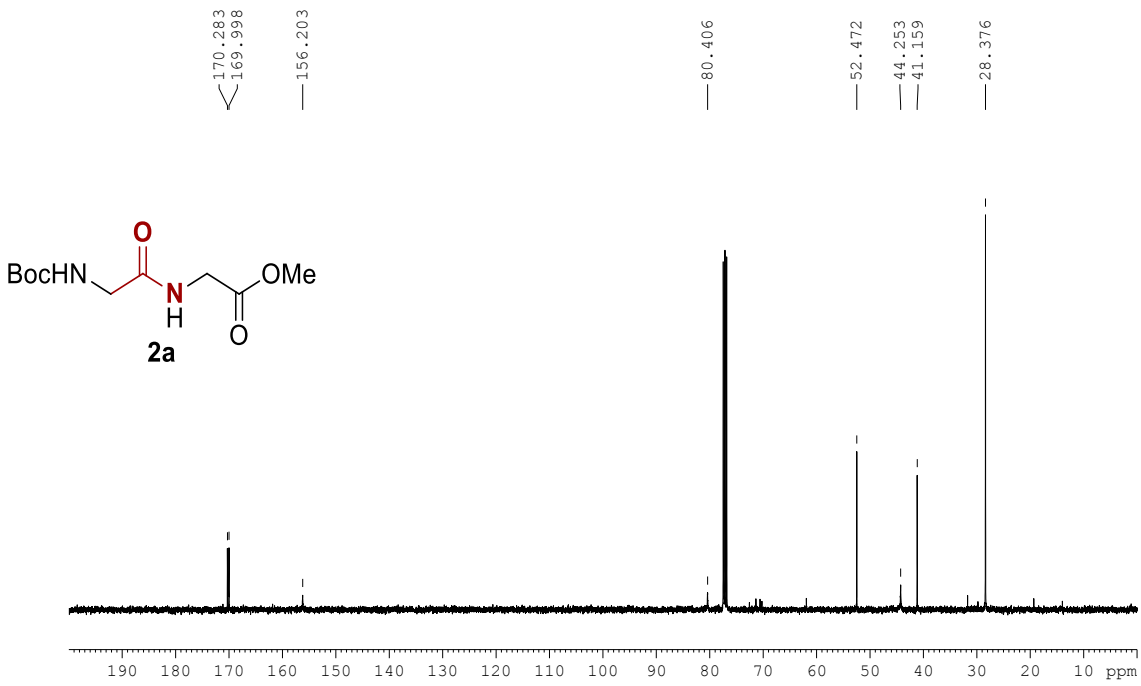
2.05
1.98
3.00
9.05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N
H
OMe
O
2a
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150
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120
110
100
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70
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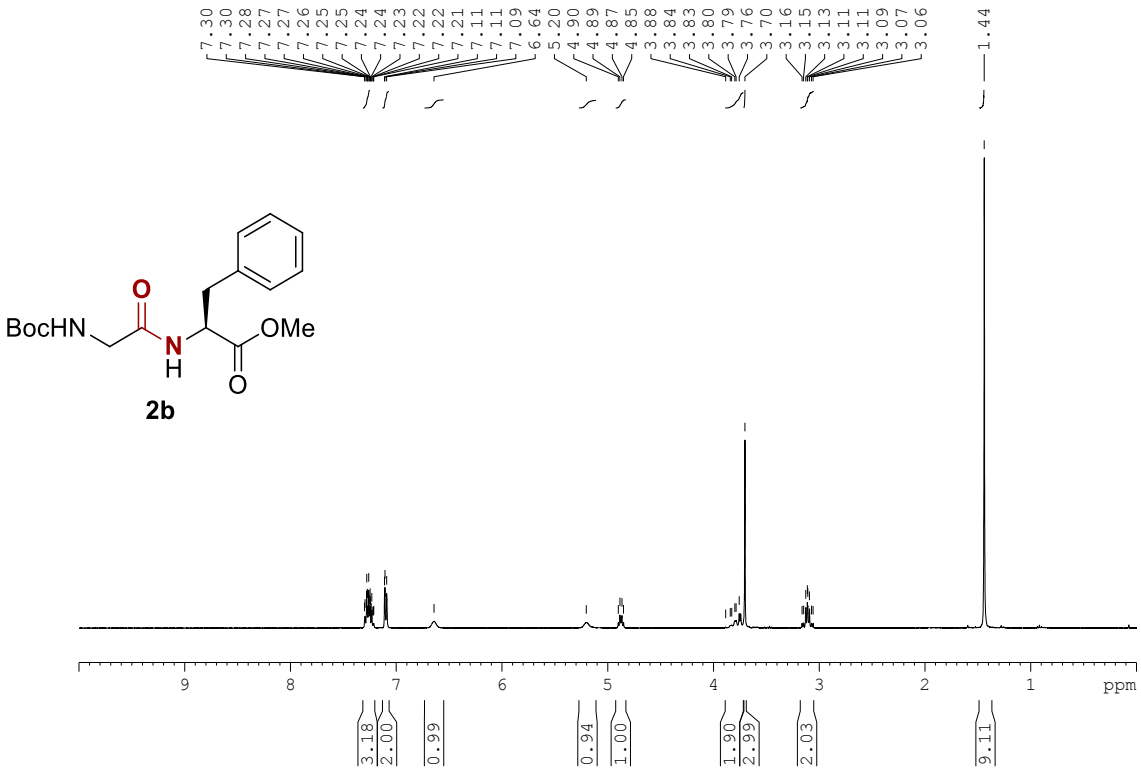
30
20
10
ppm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7.23
7.22
7.22
7.21
7.11
7.11
7.09
6.64
5.20
4.90
4.89
4.87
4.85
3.88
3.84
3.83
3.80
3.79
3.76
3.70
3.16
3.15
3.13
3.11
3.11
3.09
3.07
3.06
1.44
BocHN
O
N
H
OMe
O
2b
9
8
7
6
5
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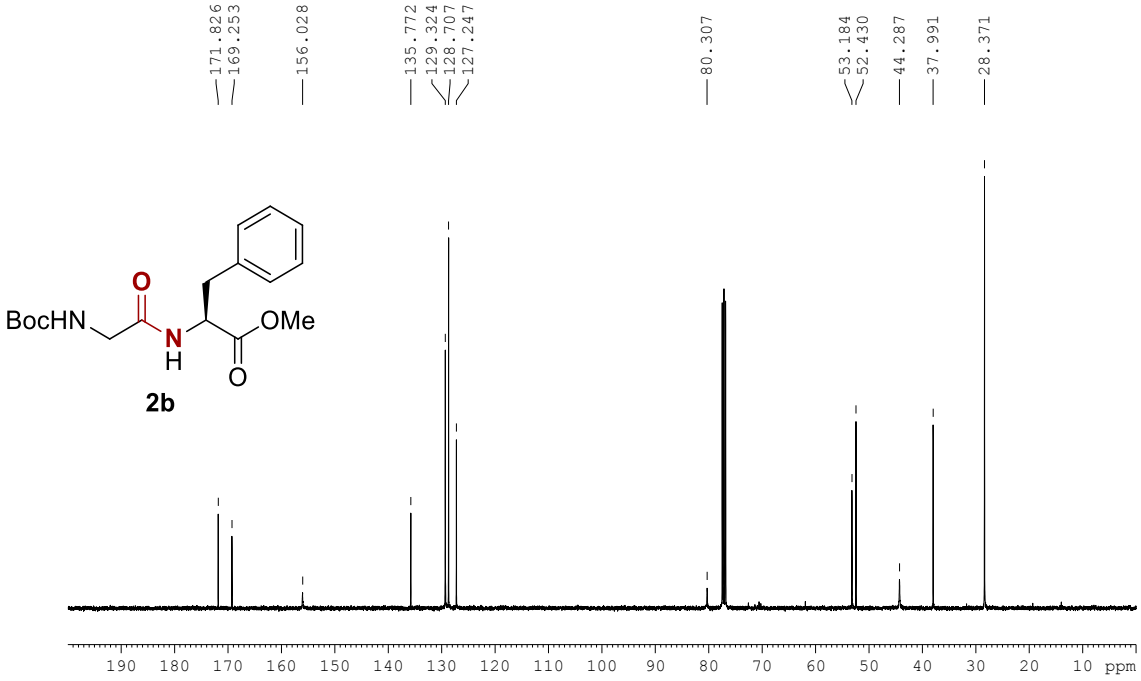
9.11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28.371
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O
N
H
OMe
O
2b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


6.57
5.10
4.58
4.56
4.55
4.54
3.89
3.88
3.85
3.83
3.80
3.80
3.79
3.74
2.22
2.20
2.19
2.18
2.17
2.17
2.15
2.15
2.14
2.12
1.46
0.95
0.93
0.91
0.89
BocHN
O
N
H
OMe
O
2c
9
8
7
6
5
4
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ppm
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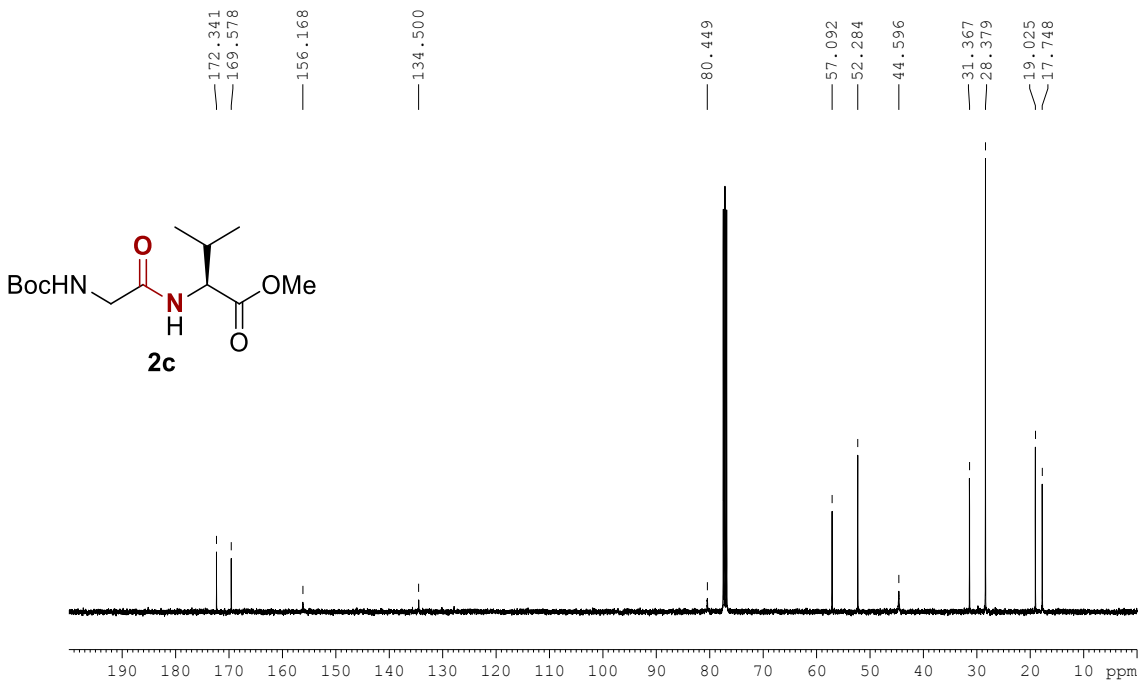
3.08
1.09
8.97
3.07
3.07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H
OMe
O
2c
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30
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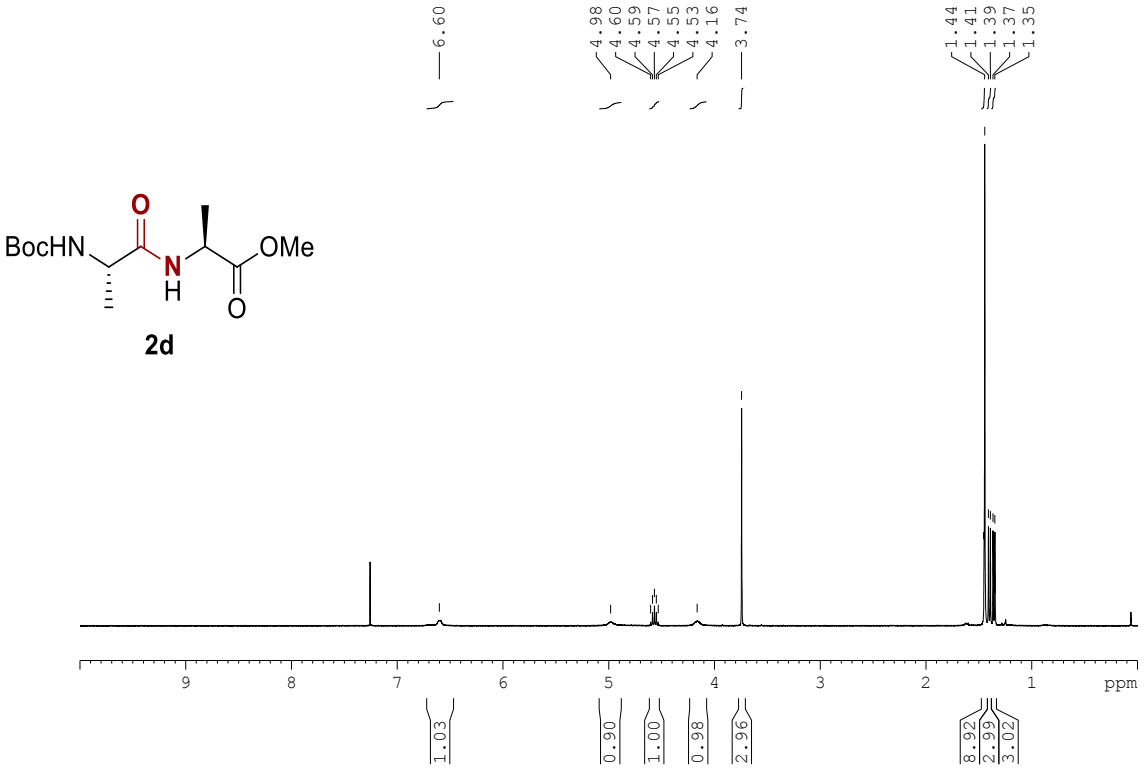
10
ppm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4.98
4.60
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4.57
4.55
4.53
4.16
3.74
1.44
1.41
1.39
1.37
1.35
BocHN
O
N
H
OMe
O
2d
9
8
7
6
5
4
3
2
1
ppm
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0.90
1.00
0.98
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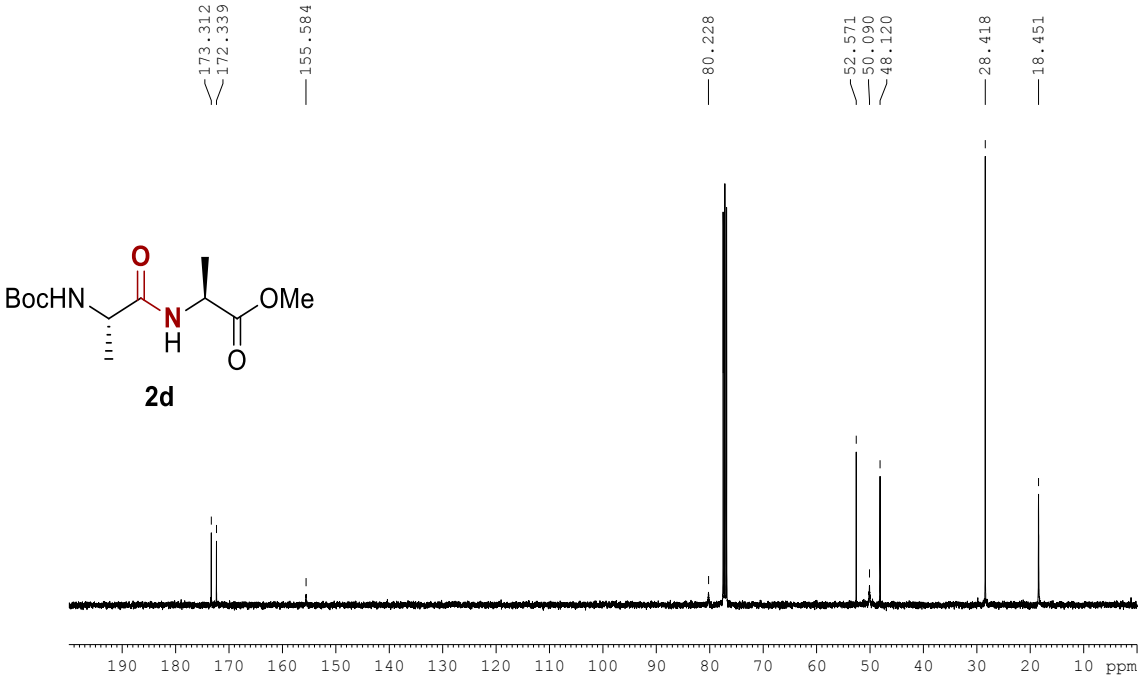
8.92
2.99
3.02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48.120
28.418
18.451
BocHN
O
N
H
OMe
O
2d
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150
140
130
120
110
100
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70
60
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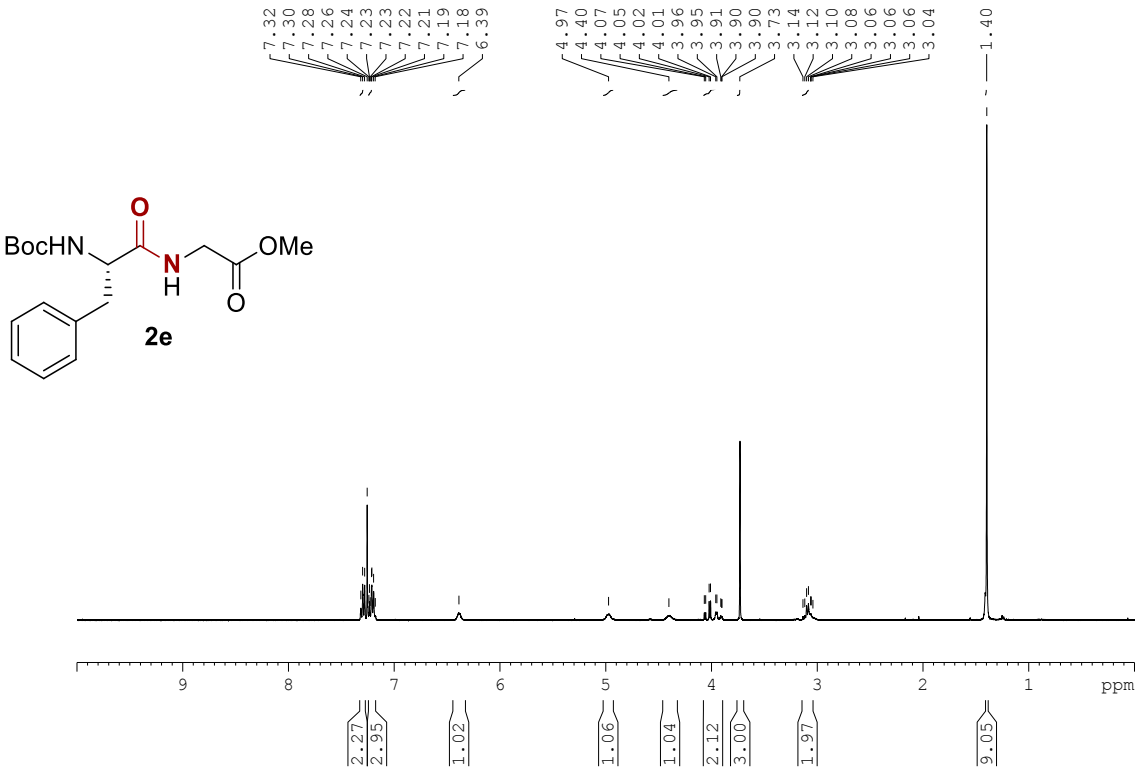
40
30
20
10
ppm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7.23
7.22
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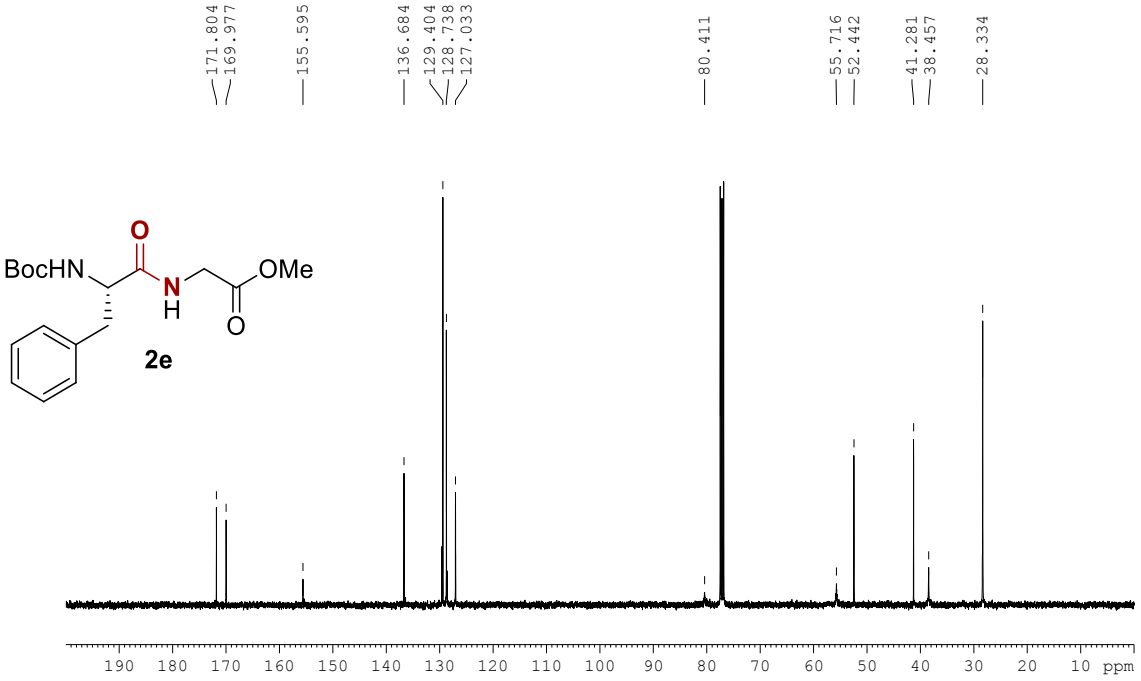
7.19
7.18
6.39
4.97
4.40
4.07
4.05
4.02
4.01
3.96
3.95
3.91
3.90
3.90
3.73
3.14
3.12
3.10
3.08
3.06
3.06
3.06
3.04
1.40
BocHN
O
N
H
OMe
O
2e
9
8
7
6
5
4
3
2
1
ppm
2.27
2.95
1.02
1.06
1.04
2.12
3.00
1.97
9.05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52.442
41.281
38.457
28.334
BocHN
O
N
H
OMe
O
2e
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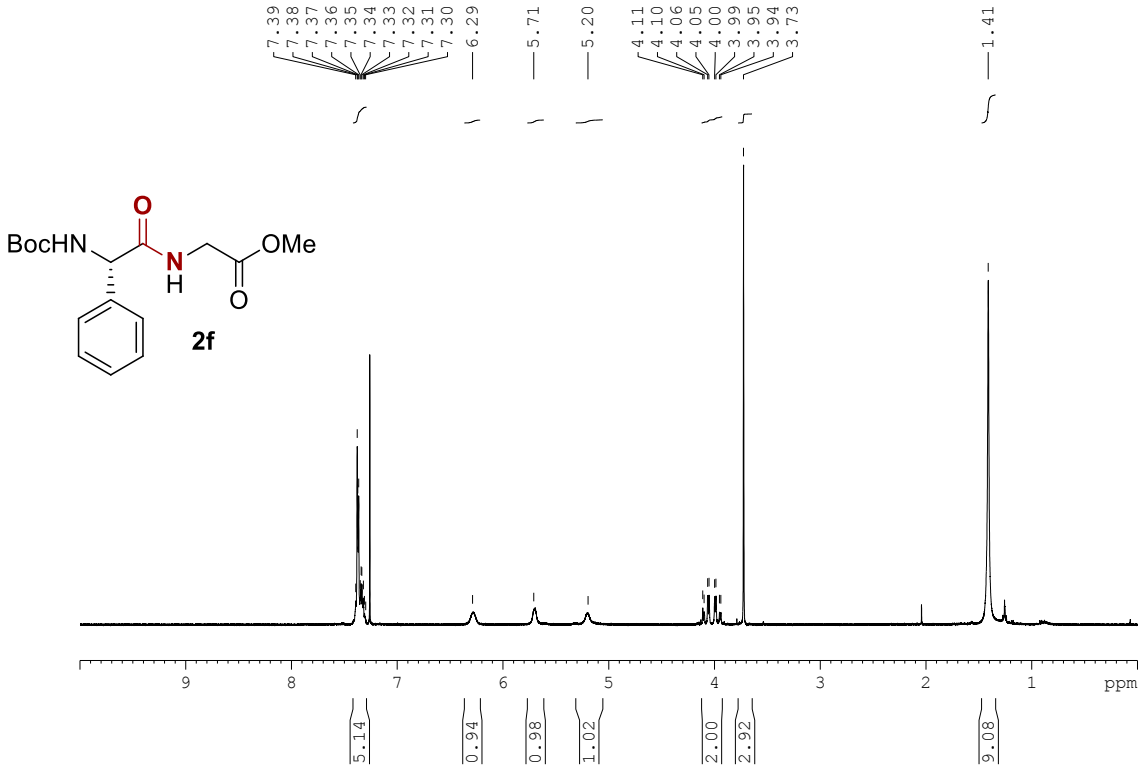
ppm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7.37
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7.34
7.33
7.32
7.31
7.30
6.29
5.71
5.20
4.11
4.10
4.06
4.05
4.00
3.99
3.95
3.94
3.73
1.41
BocHN
O
N
H
OMe
O
2f
9
8
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6
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4
3
2
1
ppm
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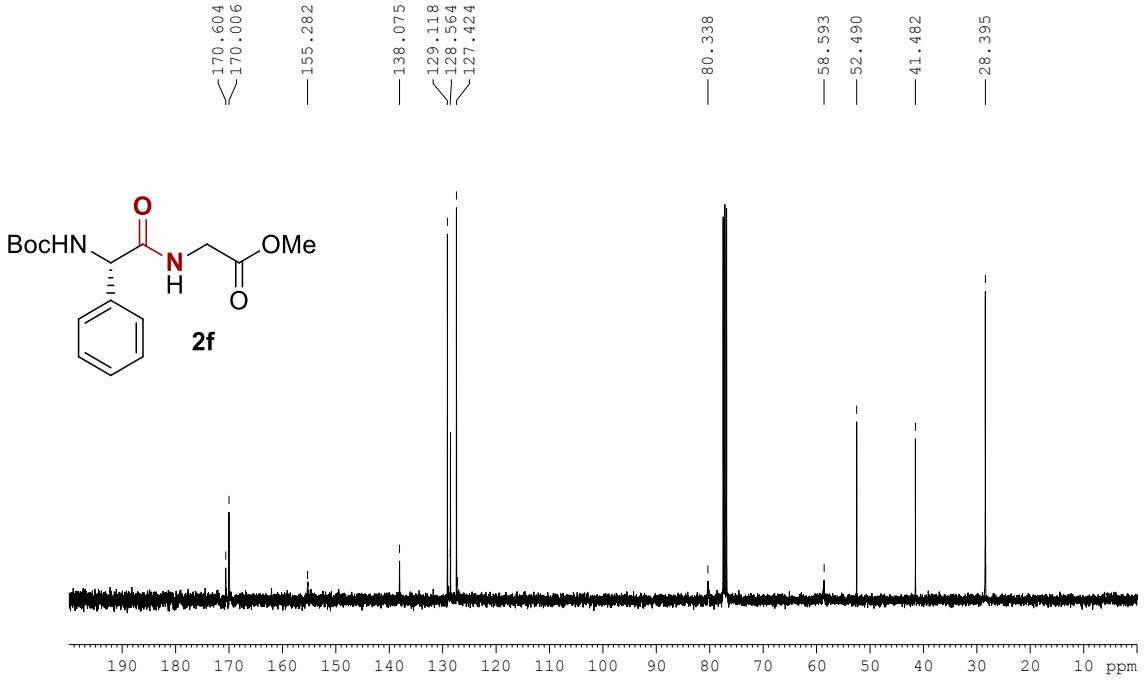
0.98
1.02
2.00
2.92
9.08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41.482
28.395
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O
N
H
OMe
O
2f
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150
140
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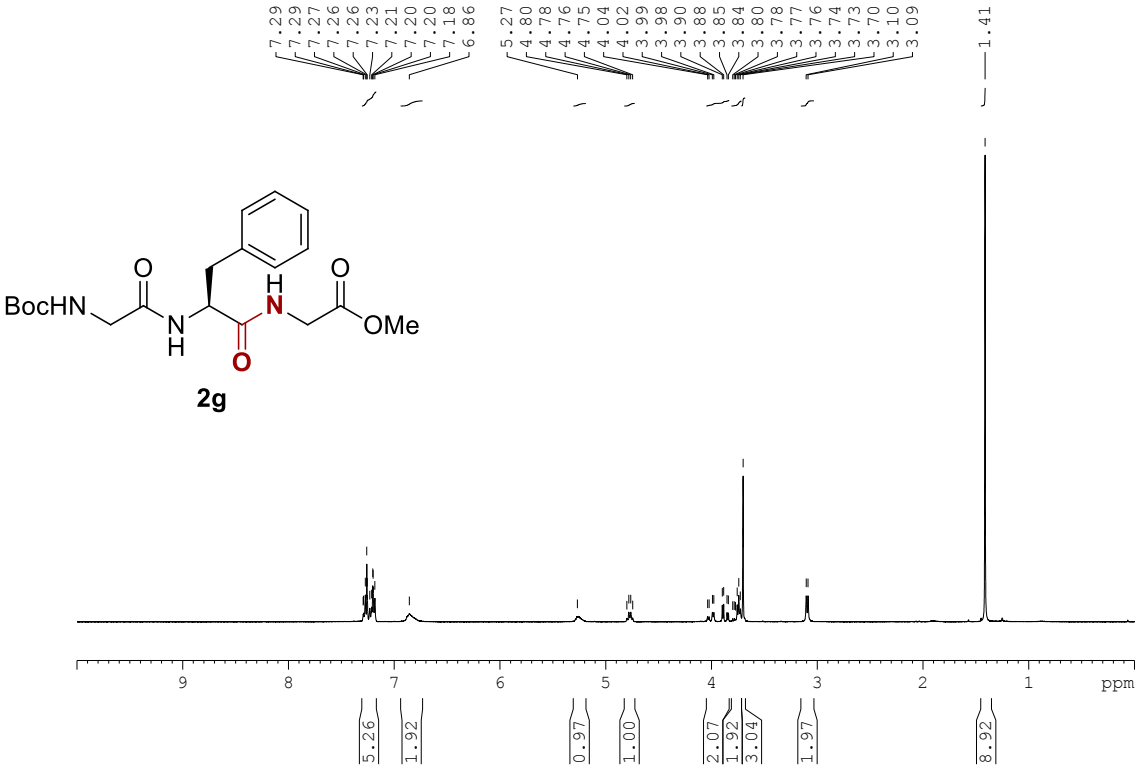
10
ppm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7.21
7.20
7.20
7.18
6.86
5.27
4.80
4.78
4.76
4.75
4.04
4.02
3.99
3.98
3.90
3.88
3.85
3.84
3.80
3.78
3.77
3.76
3.74
3.73
3.70
3.10
3.09
1.41
BocHN
O
N
H
O
H
N
O
OMe
2g
9
8
7
6
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ppm
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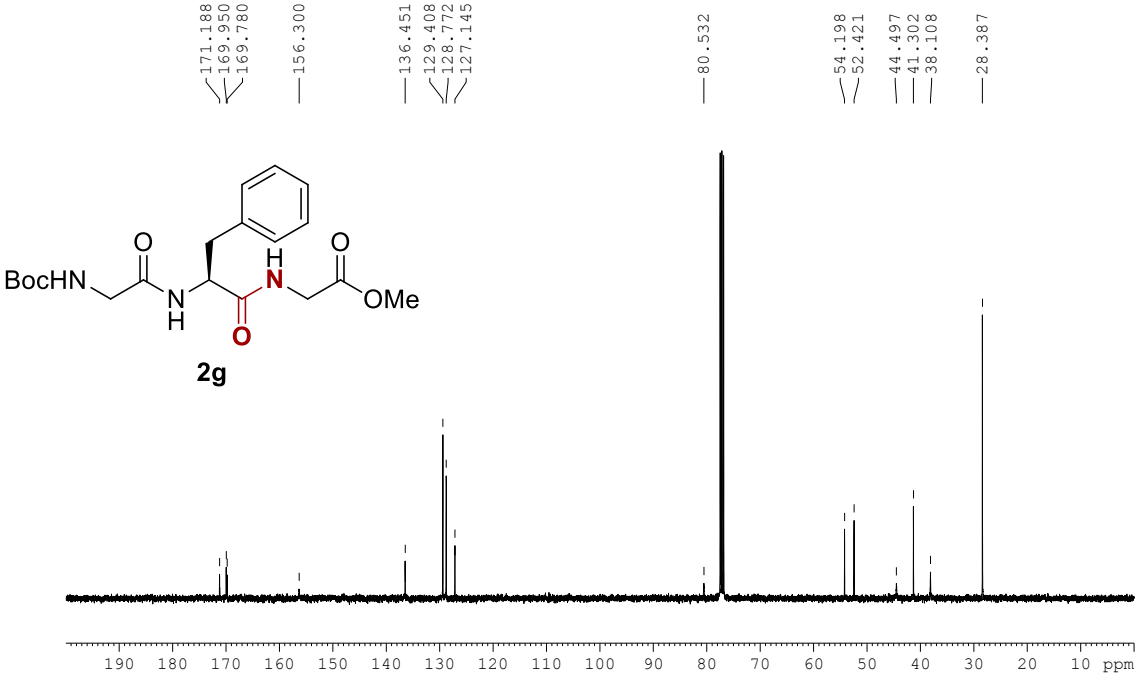
1.97
8.92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52.421
44.497
41.302
38.108
28.387
BocHN
O
N
H
O
H
N
O
OMe
2g
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150
140
130
120
110
100
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80
70
60
50
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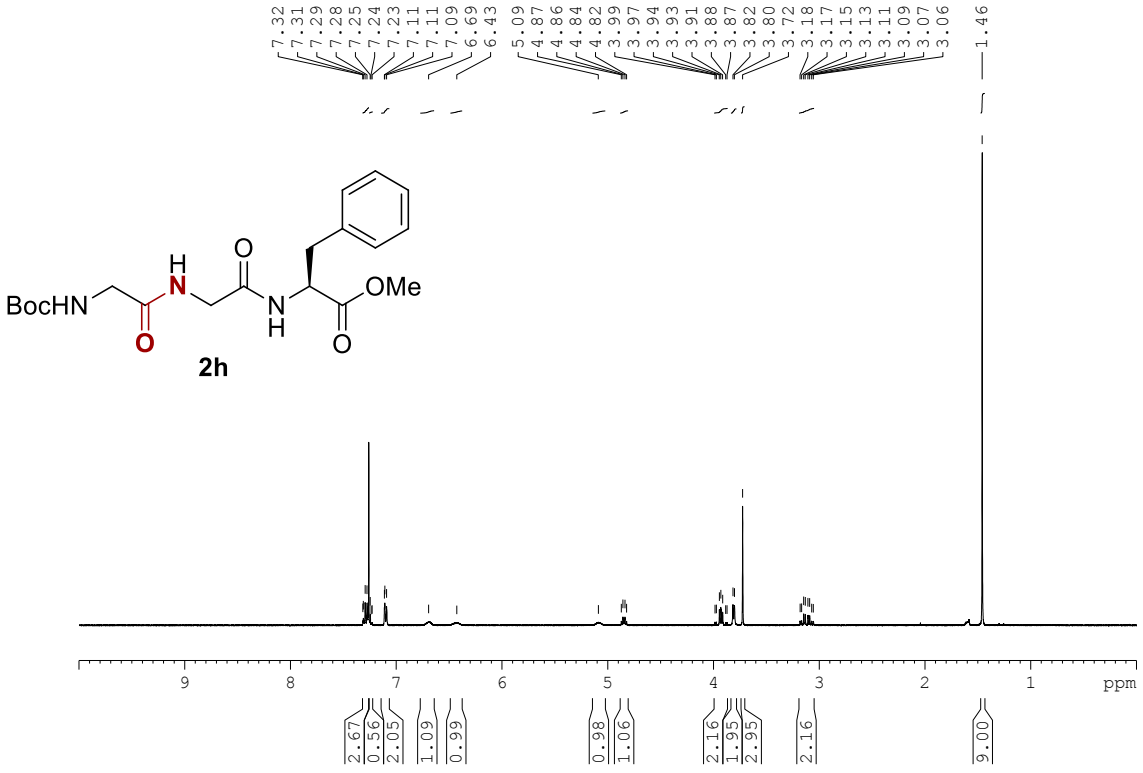
30
20
10
ppm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7.23
7.11
7.11
7.09
6.69
6.43
5.09
4.87
4.86
4.84
4.82
3.99
3.97
3.94
3.93
3.91
3.88
3.87
3.82
3.80
3.72
3.18
3.17
3.15
3.13
3.11
3.09
3.07
3.06
1.46
BocHN
H
N
O
O
N
H
O
OMe
O
2h
9
8
7
6
5
4
3
2
1
ppm
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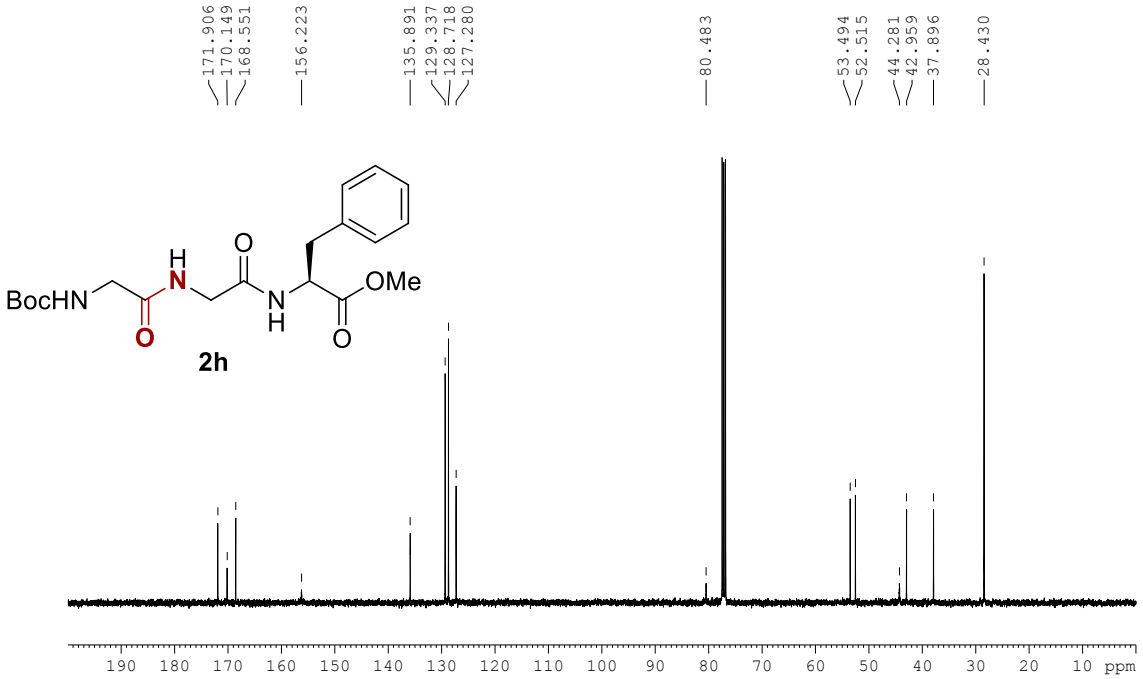
9.00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52.515
44.281
42.959
37.896
28.430
BocHN
H
N
O
O
N
H
O
OMe
O
2h
190
180
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150
140
130
120
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70
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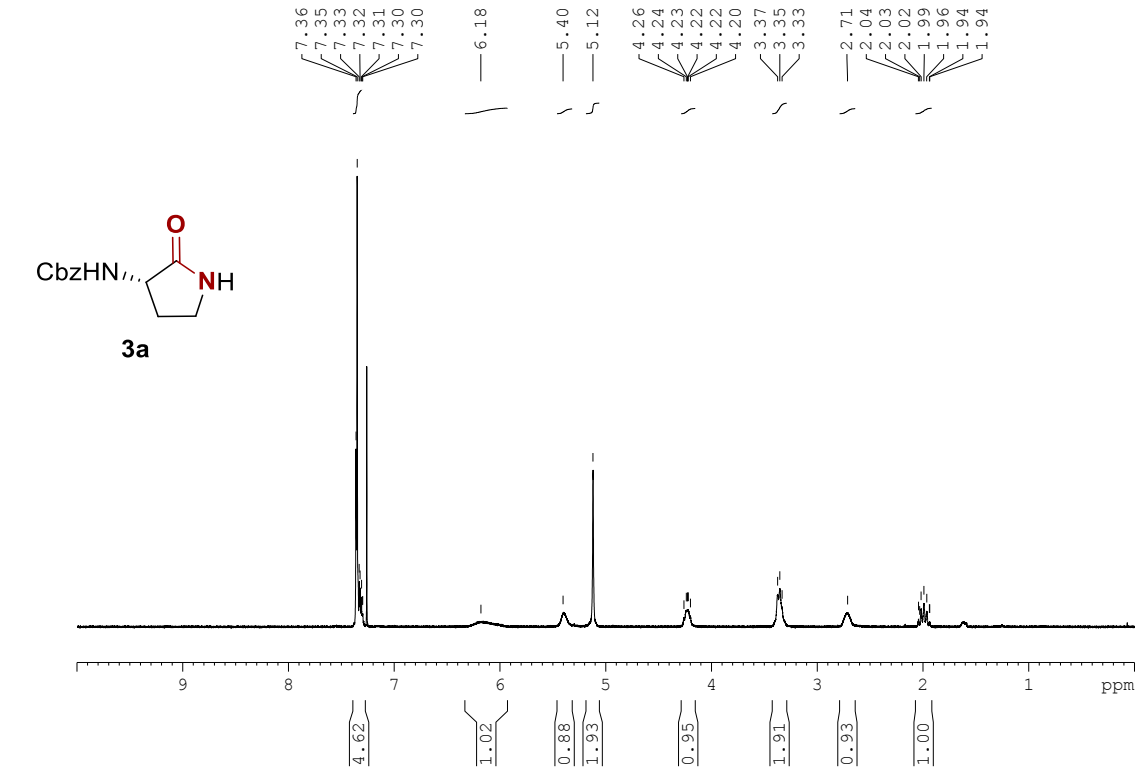
10
ppm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7.31
7.30
7.30
6.18
5.40
5.12
4.26
4.24
4.23
4.22
4.22
4.20
3.37
3.35
3.33
2.71
2.04
2.03
2.02
1.99
1.96
1.94
1.94
CbzHN
O
NH
3a
9
8
7
6
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4
3
2
1
ppm
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1.93
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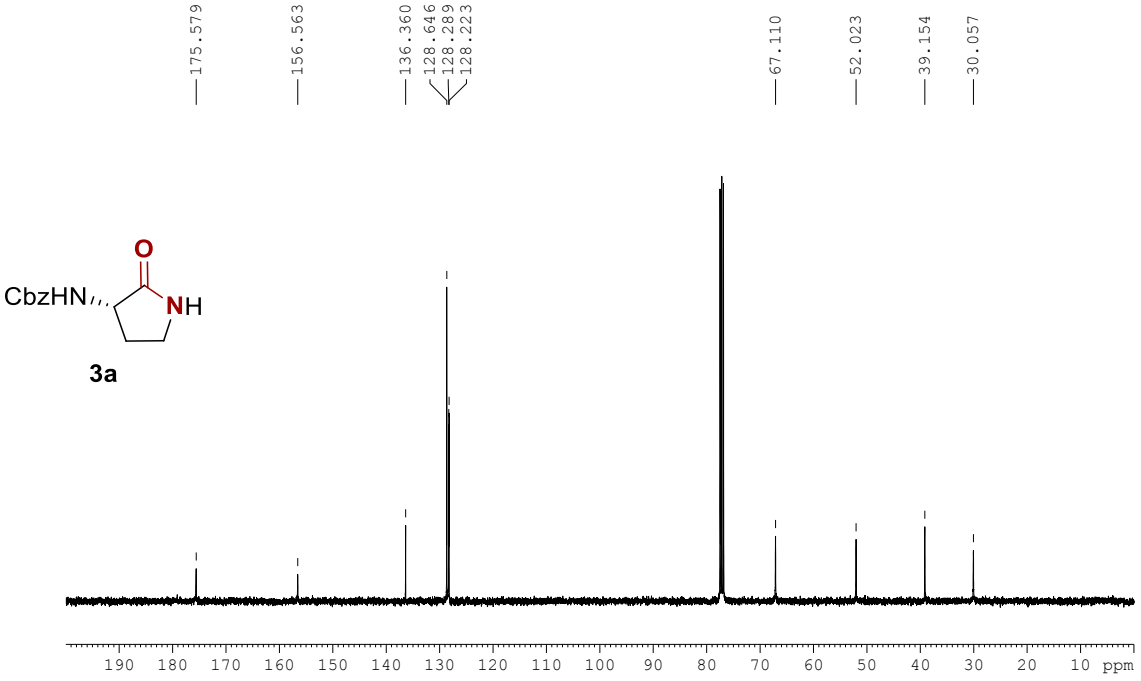
1.00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128.223
67.110
52.023
39.154
30.057
CbzHN
O
NH
3a
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150
140
130
120
110
100
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70
60
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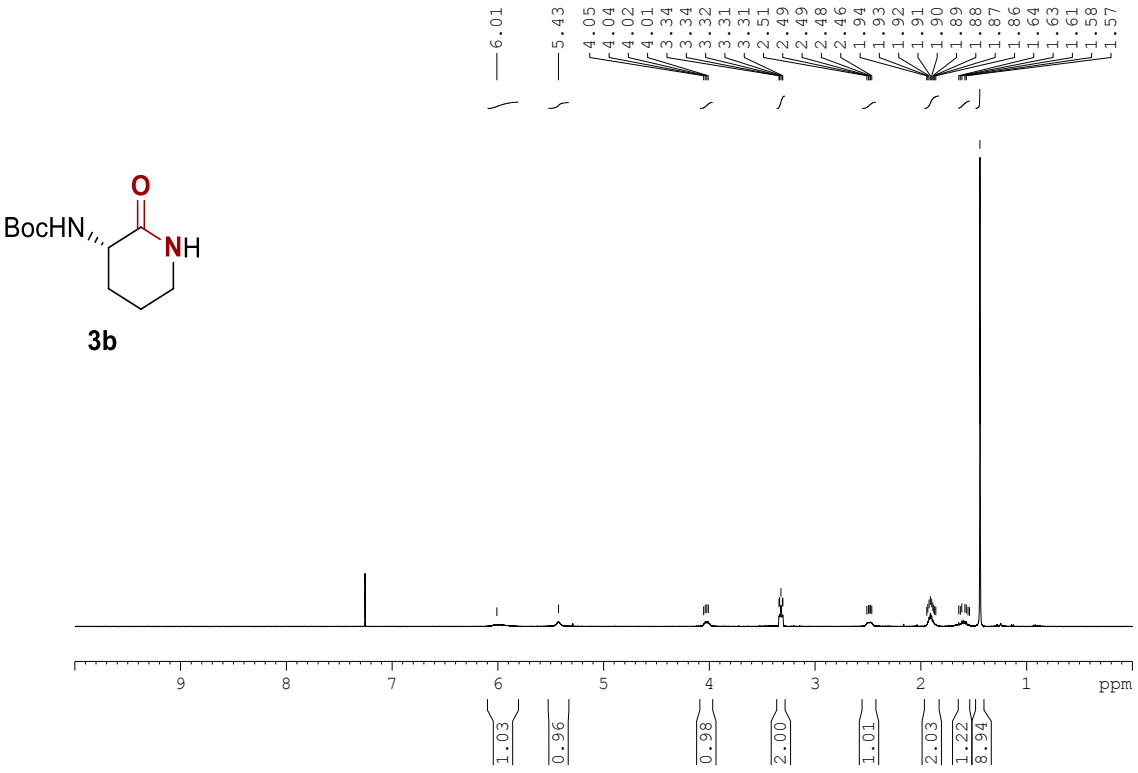
40
30
20
10
ppm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4.04
4.02
4.01
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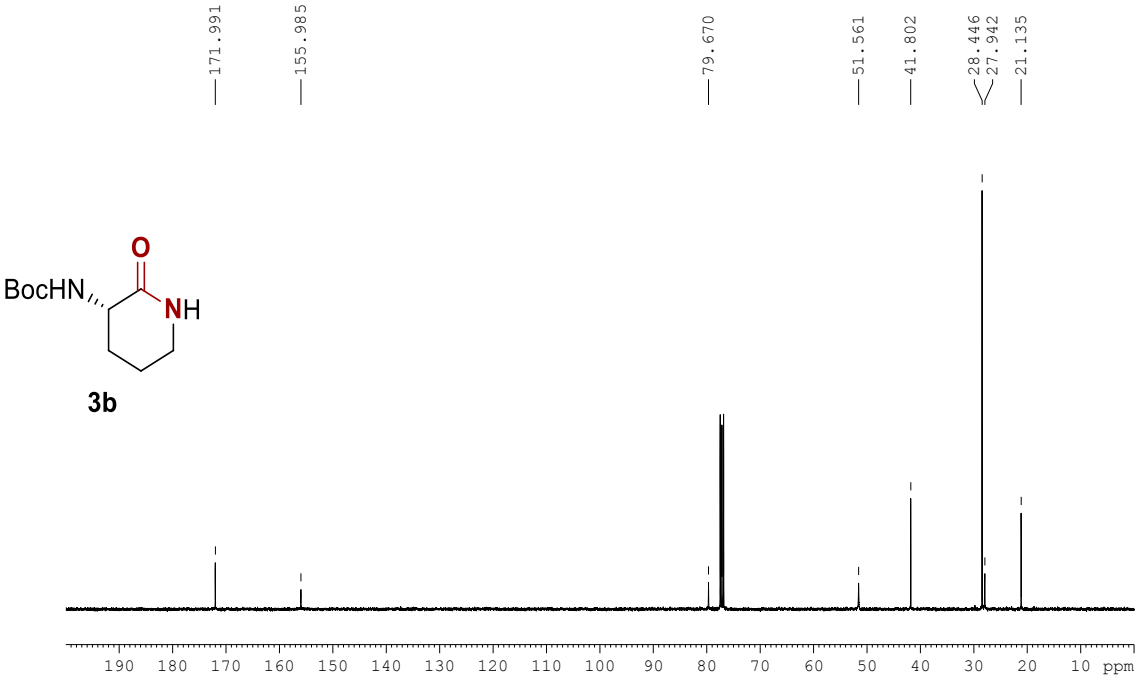
3.32
3.31
3.31
2.51
2.49
2.49
2.48
2.46
1.94
1.93
1.92
1.91
1.90
1.89
1.88
1.87
1.86
1.64
1.63
1.61
1.58
1.57
BocHN
O
NH
3b
9
8
7
6
5
4
3
2
1
ppm
1.03
0.96
0.98
2.00
1.01
2.03
1.22
8.94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21.135
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O
NH
3b
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180
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150
140
130
120
110
100
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70
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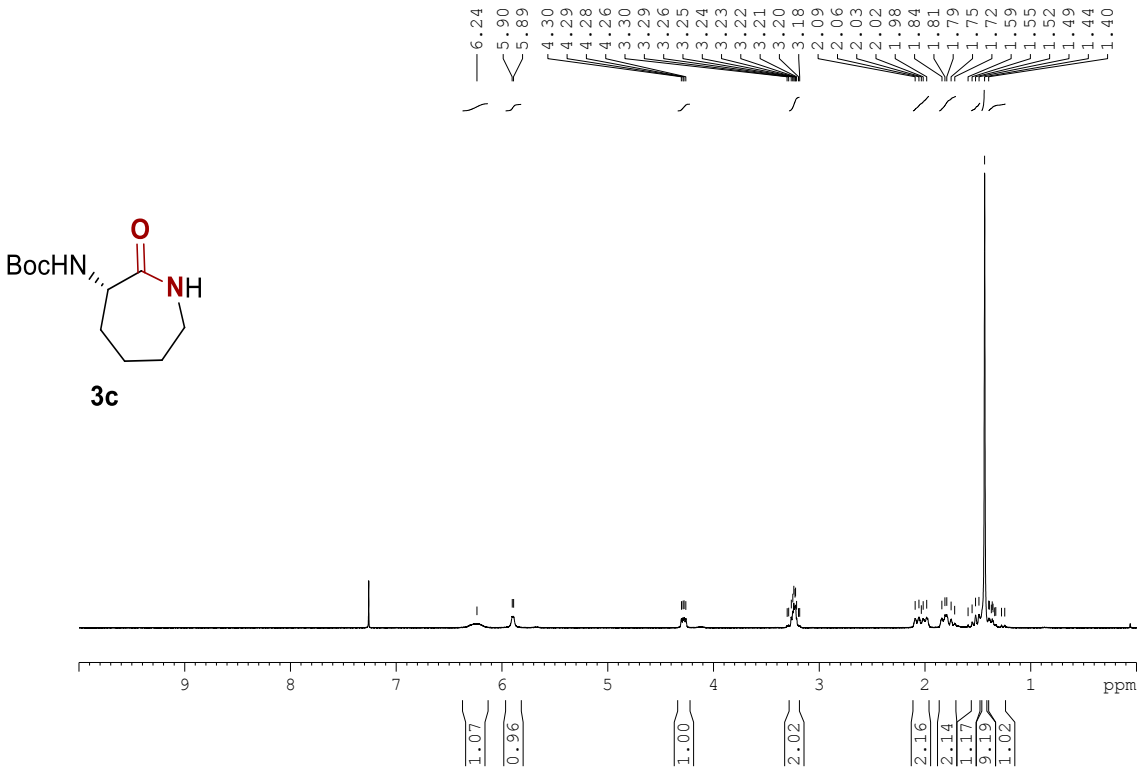
50
40
30
20
10
ppm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4.28
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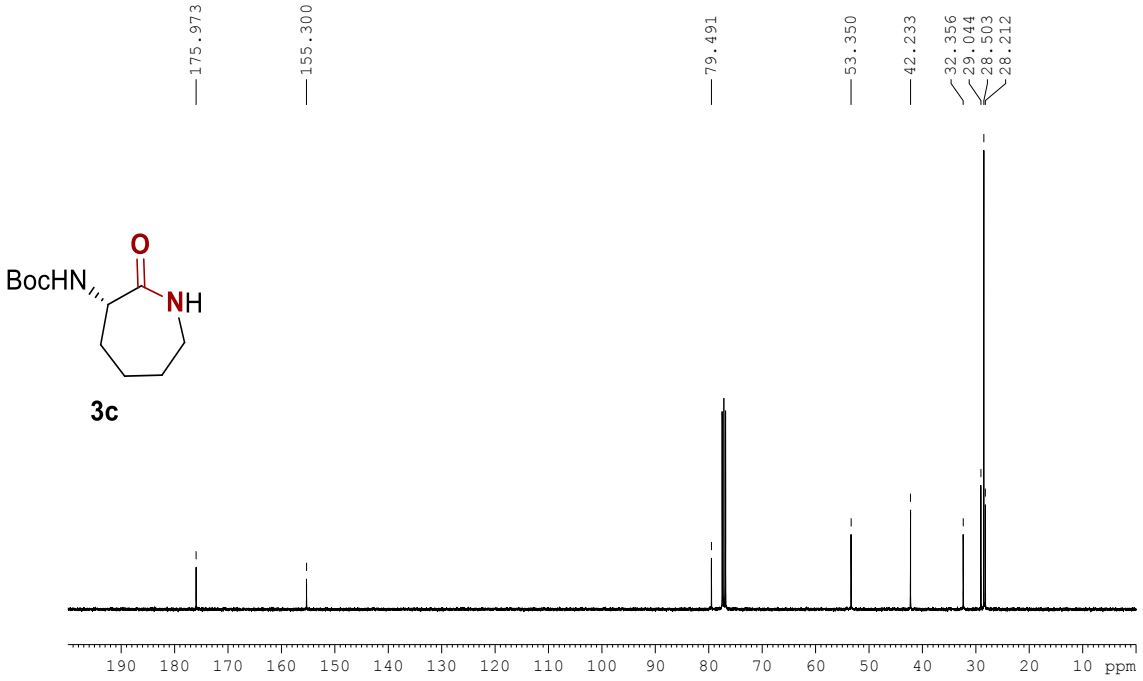
3.30
3.29
3.26
3.25
3.24
3.23
3.22
3.21
3.20
3.18
2.09
2.06
2.03
2.02
1.98
1.84
1.81
1.79
1.75
1.72
1.59
1.55
1.52
1.49
1.44
1.40
BocHN
O
NH
3c
9
8
7
6
5
4
3
2
1
ppm
1.07
0.96
1.00
2.02
2.16
2.14
1.17
9.19
1.02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O
NH
3c
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180
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150
140
130
120
110
100
90
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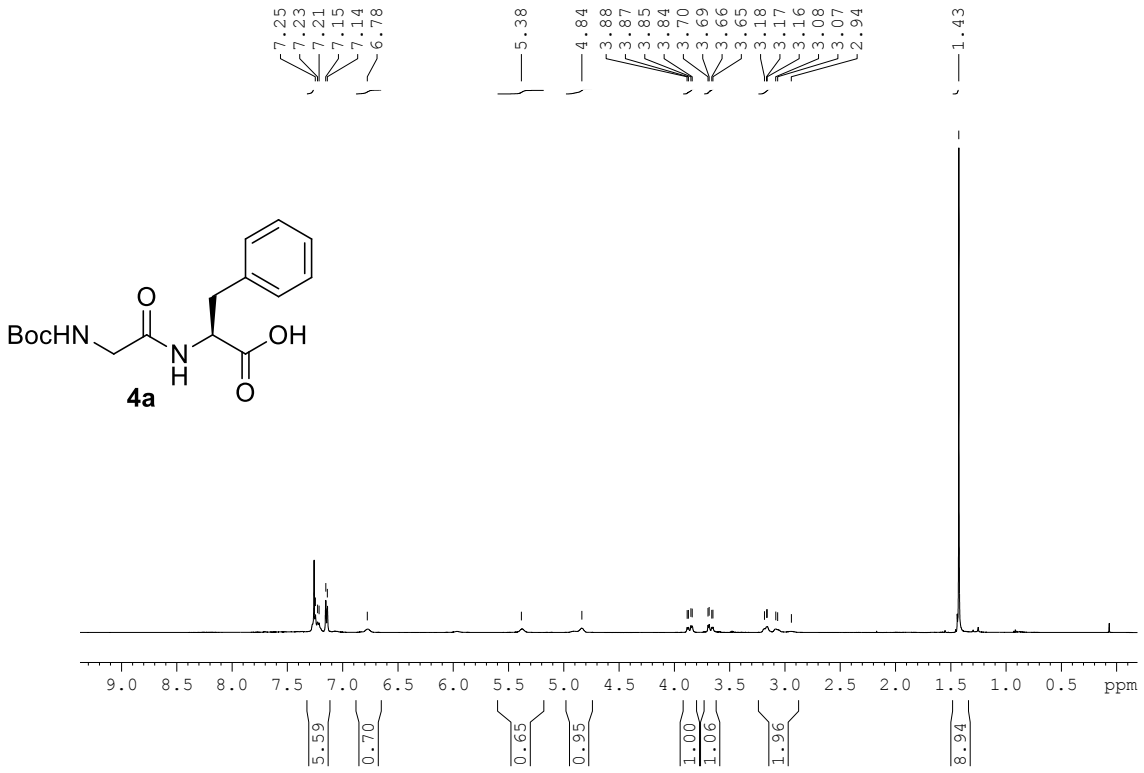
70
60
50
40
30
20
10
ppm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7.23
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7.15
7.14
6.78
5.38
4.84
3.88
3.87
3.85
3.84
3.70
3.69
3.66
3.65
3.18
3.17
3.16
3.08
3.07
2.94
1.43
BocHN
O
N
H
OH
O
4a
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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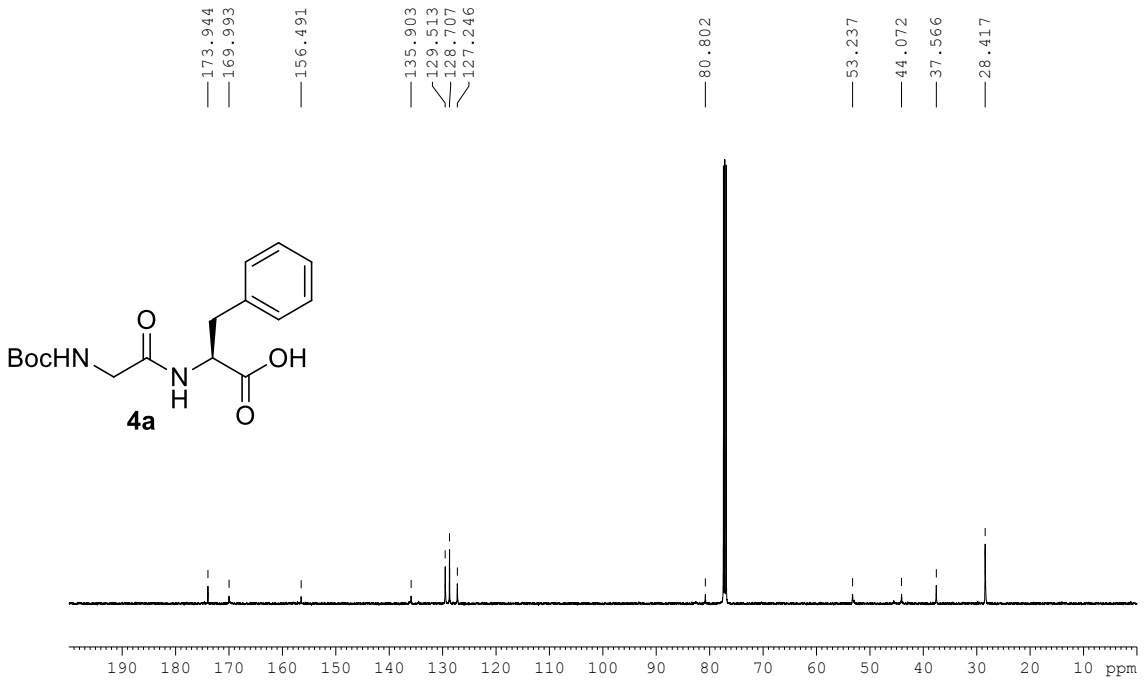
0.70
0.65
0.95
1.00
1.06
1.96
8.94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128.707
127.246
80.802
53.237
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37.566
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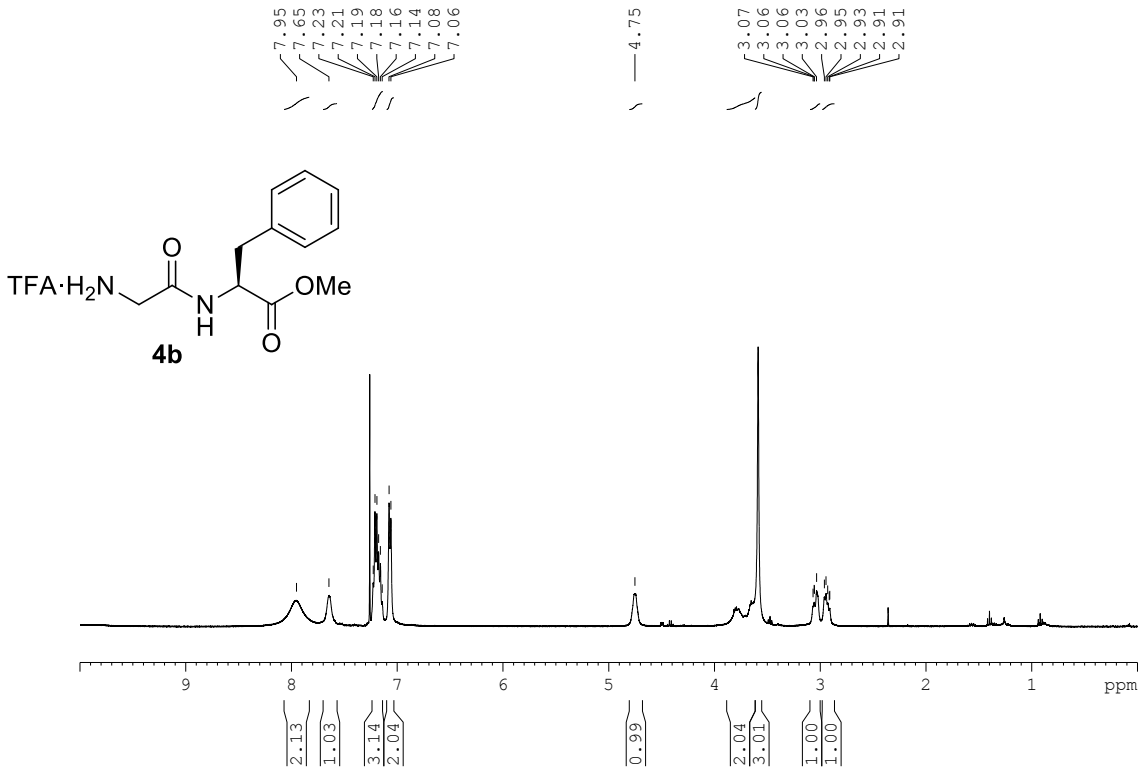
H
OH
O
4a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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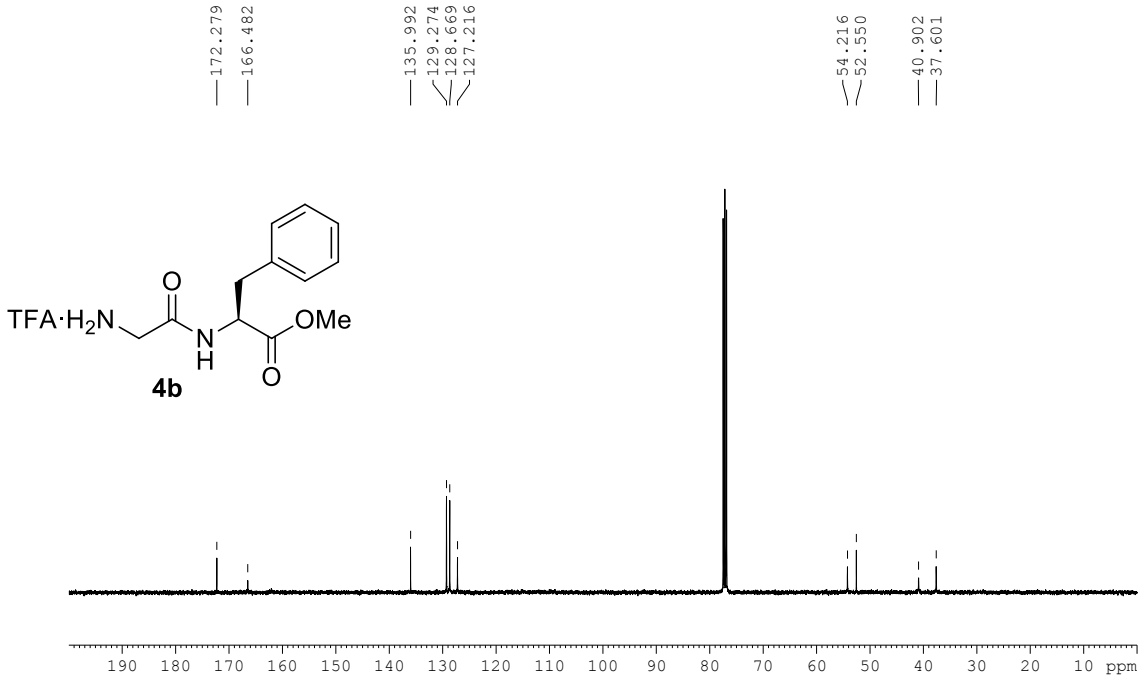
7.19
7.18
7.16
7.14
7.08
7.06
4.75
3.07
3.06
3.06
3.03
2.96
2.95
2.93
2.91
2.91
TFA·H2N
O
N
H
OMe
O
4b
9
8
7
6
5
4
3
2
1
ppm
2.13
1.03
3.14
2.04
0.99
2.04
3.01
1.00
1.00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127.216
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52.550
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37.601
TFA·H2N
O
N
H
OMe
O
4b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm