Electronic Supplementary Material (ESI) for Green Chemistry

Trifluoromethylation of Heterocycles in Water at Room Temperature

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Supporting Information

Experimental

I. General Information

The water used in this study was HPLC grade and was degassed prior to use by bubbling a flow of argon through the mixture for several hours. All commercially available reagents were used without further purification unless otherwise stated. The surfactant TPGS-750-M is commercially available from Sigma-Aldrich[1] but can be synthesized through a previously published procedure.[2] Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). The developed chromatogram was analyzed by UV lamp (254 nm) and/or aqueous potassium permanganate ($KMnO_4$), and developed by applying heat with a heat gun. Flash chromatography was performed in glass columns using Silica Flash® P60 (SiliCycle, 40-63 μm). ^1H and ^{13}C spectra were recorded at 23 °C on a Varian UNITY INOVA 500 MHz. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. GC/MS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). As capillary column a HP-5MS cross-linked 5% phenylmethyl- polysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min.

II. Standard Procedures

i. Procedure for surfactant screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1 x 5mm) with septum was added 2 wt % surfactant ([0.5], 0.2 mL, Table 1), 4-*t*-butylpyridine (0.10 mmol, 15 uL), and sodium trifluoromethanesulfinate (0.30 mmol, 47 mg) and the mixture was then cooled to ~ 5 °C. Then via syringe 70 wt % TBHP (0.50 mmol, 68 uL) was added. The mixture was allowed to stir at rt (~ 23 °C) for 24 h, quenched with saturated $NaHCO_3$ (1 mL), and then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Table 1: Impact of the surfactant for the conversion of **1** to **2**

entry	surfactant[a]	conversion (%)[b]
1	**TPGS-750-M**[1, 2]	**84**
2	PTS-600 [3-5]	54
3	Cremophor	36
4	Triton X 100	22
5	Brij-30	22
6	TPGS-1000	19
7	PQS[6]	18
8	none	17

[a] Conditions: substrate (0.1 mmol); $NaSO_2CF_3$ (3 equiv); TBHP (5 equiv); surfactant:water (2% w/w), [b] % conversion, by GC.

ii. Loading of surfactant screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1x5mm) with septum was added TPGS-750-M ([0.5], 0.2 mL, Table 2), 4-*t*-butylpyridine (0.10 mmol, 15 uL), and sodium trifluoromethanesulfinate (0.30 mmol, 47 mg), and the mixture was then cooled to ~ 5 °C. Then via syringe 70 wt % TBHP (0.50 mmol, 68 uL) was added. The mixture was allowed to stir at rt (~ 23 °C) for 24 h, quenched with saturated $NaHCO_3$ (1 mL), and then extracted with EtOAc (1 mL). The percent conversion was determined by GC.

Table 2: Impact of the weight percent of TPGS-750-M for the conversion of 1 to 2

entry	weight (%)	conversion (%)[b]
1	1	37
2	2	80
3	3	83
4	5	60

[a] Conditions: Substrate (0.1 mmol); $NaSO_2CF_3$ (3 equiv.); TBHP (5 equiv.); TPGS-750-M:Water (2% w/w), [b] % conversion, by GC.

iii. Peroxide screening

To a 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) and a septum was added 2 wt % TPGS-750-M ([0.5], 0.2 mL), 4-*t*-butylpyridine (0.10 mmol, 15 uL), and sodium trifluoromethanesulfinate (0.30 mmol, 47 mg), and the mixture was then cooled to ~ 5 °C. The peroxide (Table 3) was then added dropwise for liquid reagents, while for solids it was added slowly: 70 wt % TBHP (0.50 mmol, 68 uL), 80% CHP (0.5 mmol, 94 uL), benzoyl peroxide (0.5 mmol, 121 mg), and 30% hydrogen peroxide (0.5 mmol, 40 uL). The mixture was allowed to stir at rt (~ 23 °C) for 24 h, and then quenched with saturated $NaHCO_3$ (2 mL), extracted with EtOAc (3 mL), and concentrated under reduced pressure. The crude material was passed through a bed a silica gel with 20% EtOAc:hex.

Table 3. Peroxide screening for the conversion of 1 to 2[a]

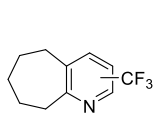
entry	peroxide	yield(%)
1	TBHP	88
2	CHP	72
3	Bz_2O_2	0
4	H_2O_2	0

[a] Conditions: Substrate (0.1 mmol); $NaSO_2CF_3$ (3 equiv); peroxide (5 equiv); TPGS-750-M:Water (2% w/w)

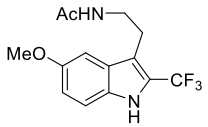
iv. Metal additives

To a 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) with a septum was added 2 wt % TPGS-750-M ([0.5], 0.3 mL), annulated pyridine **3** or substituted indole **4** (0.15 mmol), sodium trifluoromethanesulfinate (0.45 mmol, 70 mg), and one of various metal salts (10 mol %) and associated ligands (1 equiv; Table 4). The mixture was then cooled to ~ 5 °C. To this mixture was then added 70 wt % TBHP (0.75 mmol, 103 uL) dropwise. After stirring at rt (~ 23 °C) for 24 h, the mixture was then quenched with saturated $NaHCO_3$ (2 mL), extracted with EtOAc (3 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with 20% EtOAc:hex provided the trifluoromethylated product.

Table 4. Effects of metal salts of the annulated pyridine **3** and substituted indole **4**[a]



3



4

		yield(%)	
entry	metal	**3**	**4**
1	none	73	64
2	$ZnCl_2$ [b]	51	42
3	$ZnCl_2$ [c]	0	0
4	CuI	53	49
5	CuOAc	54	50
6	$CuBr{\cdot}SMe_2$	52	47
7	$NiCl_2$	42	Nd[d]
8	$NiI_2(PPh_3)_2$	47	Nd[d]
9	$Ni(COD)_2$	45	Nd[d]

[a] Conditions: substrate (0.15 mmol); metal salts (10 mol %) $NaSO_2CF_3$ (3 equiv); TBHP (5 equiv); TPGS-750-M:water (2% w/w), [b] TMEDA (1 equiv), [c] 1,10-Phen (1 equiv), [d] Not Determined.

v. Portionwise addition of TBHP

To a 5 mL microwave vial equipped with a PTFE stir bar (1 x 5 mm) with a septum was added 2 wt % TPGS-750-M ([0.5], 0.5 mL), and caffeine (0.25 mmol). The sodium trifluoro-methanesulfinate (0.75 mmol, 117 mg), and TBHP (70 wt % TBHP; 1.25 mmol, 171 uL) were then added in three equal portions each hour over three hours. The mixture was allowed to stir at rt (~ 23 °C) for 48 h, then quenched with saturated $NaHCO_3$ (2 mL), extracted with EtOAc (3 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with 20% EtOAc:hex provided the trifluoromethylated caffeine analog **6** in 81% yield as a white crystalline solid.

vi. Representative Procedure

To a 5 mL round bottom flask with a PTFE stir bar (1 x 5 mm) with a septum was added 2 wt % TPGS-750-M ([0.5], 2.0 mL), the heterocycle (1.00 mmol), and sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and the mixture was then cooled to ~ 5 °C and stirred for 2-3min. Then added 70 wt % TBHP (5.00 mmol, 690 uL) dropwise, and the mixture allowed to stir at rt (~ 23 °C) until complete as judged by TLC. It was then quenched with saturated $NaHCO_3$ (2 mL), extracted with EtOAc (3 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with 20% EtOAc:hex provided the desired trifluoromethylated analog.

Note: An additional water wash may be necessary to remove oxidized surfactant (vitamin E and MPEG)

Note: Highly crystalline solids must be ground to a fine powder (mortar and pestle) thereby forming a uniform suspension in the aqueous medium prior to introduction of reagents. Slow addition of the TBHP is also necessary. Failure to do so causes clumping, and/or rapid release of sulfur dioxide and ultimately quenching of the CF_3 radical to form fluoroform (CHF_3) [7].

vii. Recycling study

To a 5 mL round bottom flask with a PTFE stir bar (1 x 5 mm) with a septum was added 2 wt % TPGS-750-M ([0.5], 2.0 mL), 4-*t*-butylpyridine (1.0 mmol, 148 uL), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg) then cooled to ~ 5 °C. Then added 70 wt % TBHP (5.00 mmol, 690 uL) dropwise (~100 uL/min) and the mixture was allowed to stir at rt (~ 23 °C for 24 h, and then extracted with EtOAc (1 mL), and concentrated under reduced pressure. Passage through a bed a silica gel with 20% EtOAc:hex provided the trifluoromethylated 4-*t*-butyl pyridine analog **2**. The aqueous reaction medium was then subjected to a subsequent identical reaction, and the cycle repeated four more times, as summarized in Table 5.

Table 5. Recycling of the aqueous reaction mixture for the conversion of 1 to 2.[a]

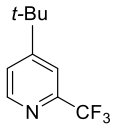
entry	cycle	yield(%)
1	1	78
2	2[b]	79
3	3[b]	73
4	4[b]	68
5	5[b]	62

[a] Conditions: substrate (1 mmol); $NaSO_2CF_3$ (3 equiv); TBHP (5 equiv); TPGS-750-M:water (2% w/w), [b] Extracted with EtOAc; aqueous medium used for next reaction.

viii. Surfactant solution preparation

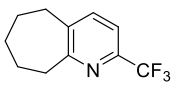
The water used in this study was HPLC grade and was degassed prior to use by bubbling a flow of argon through the mixture for several hours. Then each solution was prepared by weight percent for the desired surfactant concentration with degassed HPLC grade water and subjected to an additional sparging with argon for an hour. All surfactants were stored under an argon atmosphere prior to use. Surfactants PTS and TPGS-750-M are both commercially available from Sigma-Aldrich[1] but can be synthesized through a previously published procedure.[2]

III. Compound Data

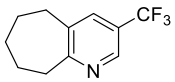


2

4-*t*-Butyl-2-trifluoromethylpyridine (2). The representative procedure was followed using 4-*t* butylpyridine (1.0 mmol, 148 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). Reaction was complete after 15 h by TLC. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex. (R_f = 0.55, 20% EtOAc:hex) to yield 161 mg, 79% of faint yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.19 Hz, 1H), 7.66 (s, 1H), 7.47 (d, J = 5.19 Hz, 1H), 1.35 (s, 9H). GC/MS m/z: 203.09. Compound data match that previously reported. [7]



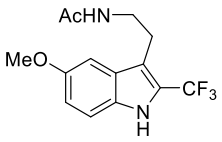
3-C2



3-C3

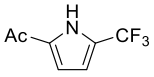
2-(Trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (3-C2) and **3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (3-C3).** The representative procedure was followed using 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (1.0 mmol, 156 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete after 43 h by TLC. Crude product by purified by passage through a bed a silica gel with 20% EtOAc:hex to yield 394 mg, 73%, (1:3.8 **3-C2:3-C3)** of faint yellow liquid. Data for **(3-C2)** (105 mg), (R_f = 0.60, 20% EtOAc:hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.68 Hz, 1H) 7.38 (d, *J* = 7.70 Hz, 1H), 3.14 – 3.08 (m, 2H), 2.88 – 2.81 (m, 2H), 1.95 – 1.86 (m, 2H), 1.79 – 1.64 (m, 4H), GC/MS m/z: 215.1. Data for **(3-C3)** (289 mg), (R_f = 0.55, 20% EtOAc:hex).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.20 Hz, 1H), 7.33 (d, *J* = 5.19 Hz, 1H), 3.21 – 3.11 (m, 2H), 2.98 – 2.90 (m, 2H), 1.92 – 1.83 (m, 2H), 1.74 – 1.62 (m,

4H). GC/MS m/z: 215.09. Compound data match that previously reported. [7] Note: Minor region-isomer impurities observed in ^{1}H NMR.



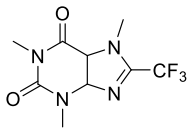
4

2-Trifluoromethyl melatonin (4). The representative procedure was followed using melatonin (1.0 mmol, 232 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). Reaction was complete as judged by TLC in 44 h. Crude product was purified by passage through a bed a silica gel with EtOAc (R_f = 0.70, 100% EtOAc) to yield 192 mg, 64% of off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.54 (d, *J* = 9.04 Hz, 1H), 7.06 (d, *J* = 9.06 Hz, 1H), 5.72 (t, J = 5.36 Hz, 1H), 3.89 (s, 3H), 3.47 (m, 2H), 3.10 (t, *J* = 6.93 Hz, 2H), 1.95 (s, 3H). GC/MS m/z: 300.11. Compound data match that previously reported. [7]



5

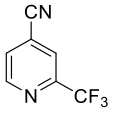
1-(5-(Trifluoromethyl)-1H-pyrrol-2-yl)ethan-1-one (5). The representative procedure was followed using 1-(1H-pyrrol-2-yl)ethan-1-one (1.0 mmol, 109 mg), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 28 h. Crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex (R_f = 0.45, 20% EtOAc:hex) to yield 110 mg, 62% of an off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (brs, 1H), 6.87 (s, 1H), 6.61 (s, 1H), 2.48, (s, 3H). GC/MS m/z: 177.04. Compound data match that previously reported. [7] Note: Minor regio-isomer impurities observed in ^{1}H NMR.



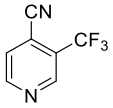
6

Trifluoromethylated caffeine (6). The representative procedure was followed using caffeine (1.0 mmol, 194 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 23 h. The crude product was purified by passed through a bed a silica gel with 20% EtOAc:hex (R_f = 0.25, 20% EtOAc:hex) to yield 222 mg, 84% of white crystalline solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16

(s, 3H), 3.58 (s, 3H), 3.40 (s, 3H). GC/MS m/z: 264.08. Compound data match that previously reported. [7]

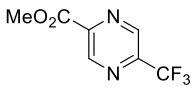


7-C2



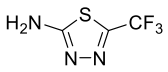
7-C3

2-Trifluoromethyl-4-cyano-pyridine (7-C2) and **3-trifluoromethyl-4-cyano-pyridine (7-C3).** The representative procedure was followed using 4-cyano-pyridine (1.0 mmol, 104 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 44 h. The crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex to yield 97 mg, 55% (1.6:1 **7-C2:7-C3**) of a colorless oil. **Data for 7-C2** (61 mg), (R_f = 0.50, 20% EtOAc:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (d, *J* = 4.93 Hz, 1H), 7.92 (s, 1H), 7.76 (d, *J* = 4.92 Hz, 1H). GC/MS m/z: 172.02; **Data for (7-C3)** (35 mg), (R_f = 0.30, 20% EtOAc:hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 9.03 (d, *J* = 4.93 Hz, 1H), 7.74 (d, *J* = 4.94 Hz, 1H). GC/MS m/z: 172.02. Compound data match that previously reported. [7] Note: Minor regio-isomer impurities observed in ^{1}H NMR.



8

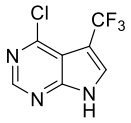
Methyl 5-(trifluoromethyl)pyrazine-2-carboxylate (8). The representative procedure was followed using methyl pyrazine-2-carboxylate (1.0 mmol, 138 uL), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete by TLC in 51 h. The crude product by passed through a bed a silica gel with 20% EtOAc:hex (R_f = 0.35, 20% EtOAc:hex) to yield 112 mg, 54%, as an off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 9.07 (s, 1H), 4.10 (s, 3H). GC/MS m/z: 206.03. Compound data match that previously reported. [7]



9

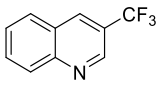
5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (9). The representative procedure was followed using 1,3,4-thiadiazol-2-amine (1.0 mmol, 101.mg), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete by TLC in 38 h. The crude product by passed through a bed a silica gel with 50% EtOAc:hex (R_f = 0.73,

75% EtOAc:hex) to yield 73 mg, 43%, as an off white solid; ^{1}H NMR (500 MHz, MeOD) δ 4.88 (s, 2H), GC/MS m/z: 169.12. Compound data match that previously reported. [7]



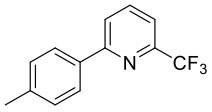
10

4-chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidine (10). The representative procedure was followed using 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (1.0 mmol, 154.mg), sodium trifluoro-methanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete by TLC in 52 h. The crude product by passed through a bed a silica gel with 40% EtOAc:hex (R_f = 0.70, 50% EtOAc:hex) to yield 73 mg, 47%, as an off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.67 (br s, 1H), 8.81 (s, 1H), 7.09 (s, 1H). GC/MS m/z: 221.54. Compound data match that previously reported. [7]



11

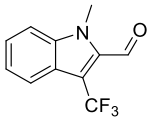
3-(Trifluoromethyl)quinolone (11). The representative procedure was followed using quinoline (1.0 mmol, 129 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was stopped after 36 h (no additional conversion passed this point). The crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex (R_f = 0.25, 20% EtOAc:hex) to yield 140 mg of product and starting material. The yield was determined by NMR to be 71%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, J = 4.15 Hz, 1H), 8.24 (d, J = 8.30 Hz, 1H), 8.10 (d, J = 7.27 Hz, 1H), 8.04 (d, J = 8.28 Hz, 1H), 7.61 (t, J = 7.32 Hz, 1H), 7.52 (m, 1H). GC/MS m/z: 197.16. Compound data match that previously reported.[8] Quinoline proton chemical shifts are dependent upon concentration.[9]



12

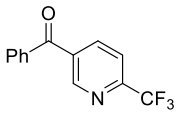
2-(*p*-Tolyl)-6-(trifluoromethyl)pyridine (12). The representative procedure was followed using 2-(*p*-tolyl)pyridine (1.0 mmol, 169 uL), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The reaction was complete as judged by TLC in 18 h. The crude product was purified by passage through a bed a silica gel with 20% EtOAc:hex (R_f = 0.35, 10% EtOAc:hex) to yield 161 mg, 68%, as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97

(d, J = 8.13 Hz, 2H), 7.89 (d, J = 4.61 Hz, 2H), 7.57 (t, J = 3.89 Hz, 1H), 7.30 (d, J = 8.05 Hz, 2H), 2.42 (s, 3H). GC/MS m/z: 237.08. Compound data match that previously reported.[10]



13

1-Methyl-3-(trifluoromethyl)-1H-indole-2-carbaldehyde (13). The representative procedure was followed using 1-methyl-1H-indole-2-carbaldehyde (1.0 mmol, 159 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The crude product was isolated by passage through a bed a silica gel with 20% EtOAc:hex (R_f = 0.55, 10% EtOAc:hex) to yield 96 mg, 42%, of an off white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.91 (d, J = 8.32 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.32 (ddd, J = 1.22, 6.66, 8.08 Hz, 1H), 4.15 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 182.62, 154.30, 131.87, 130.72, 127.49, 122.96, 121.88, 110.78, 96.12, 92.77, 32.49. HREIMS calcd for $C_{11}H_8F_3NO$: 227.0558. Found: 227.0560



14

phenyl(6-(trifluoromethyl)pyridin-3-yl)methanone (14). The representative procedure was followed using phenyl(pyridin-3-yl)methanone (1.0 mmol, 183 mg), sodium trifluoromethanesulfinate (3.0 mmol, 468 mg), and 70 wt % TBHP (5.00 mmol, 690 uL). The crude product was isolated by passage through a bed a silica gel with 15% EtOAc:hex (R_f = 0.35, 20% EtOAc:hex) to yield 166 mg, 66%, of a clear solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 1.97 Hz, 1H), 8.19 (d, J = 8.22 Hz, 2H), 8.13 (dd, J = 0.96, 7.85 Hz, 1H), 7.94 (m, 1H), 7.75 (d, J = 8.15 Hz, 2H), 7.53 (m, 1H). GC/MS m/z: 251.23. Compound data match that previously reported.[8]

IV. References

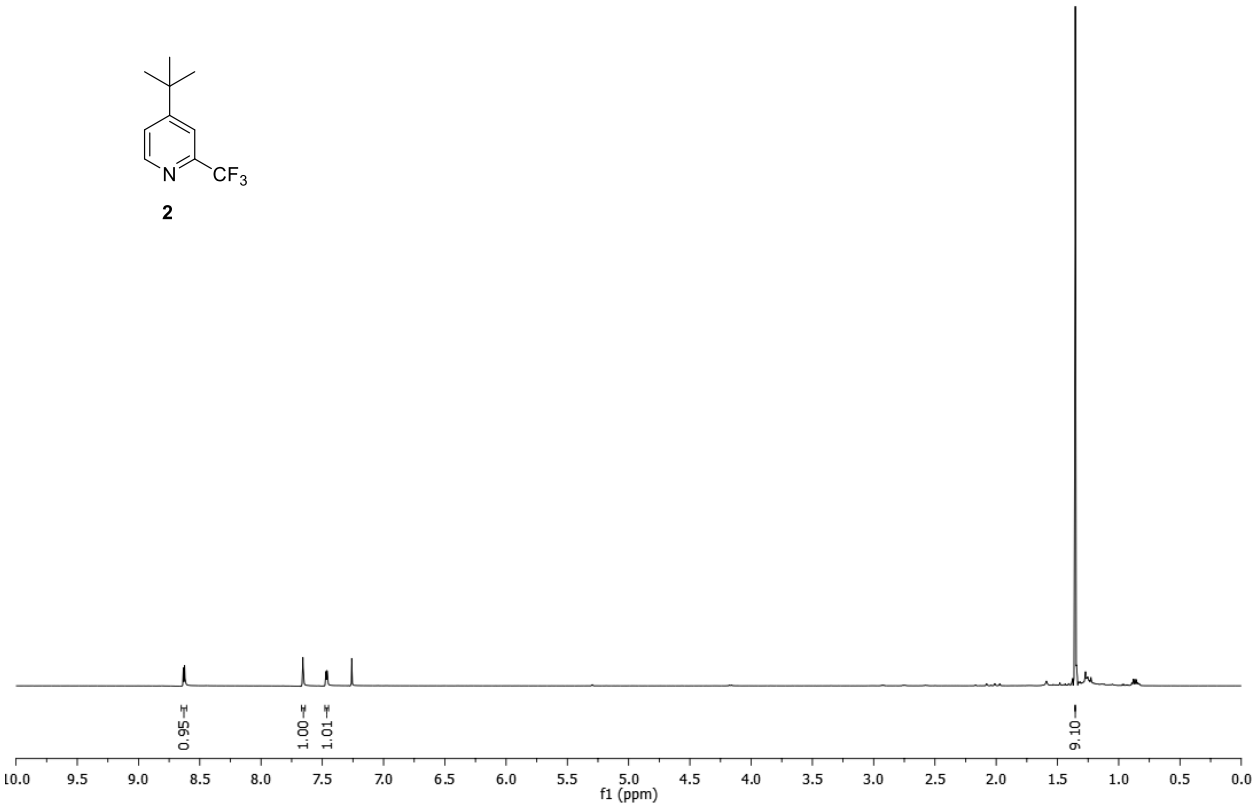
1. Aldrich catalog number. 763918.
2. B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston and R. C. Gadwood, *J. Org. Chem.*, 2011, **76**, 4379-4391.
3. B. H. Lipshutz, S. Ghorai, W. W. Y. Leong, B. R. Taft and D. V. Krogstad, *J. Org. Chem.*, 2011, **76**, 5061-5073.
4. B. H. Lipshutz and B. R. Taft, *Org. Lett.*, 2008, **10**, 1329-1332.
5. A. c. n. 698717.

6. B. H. Lipshutz and S. Ghorai, *Org. Lett.*, 2008, **11**, 705-708.
7. Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond and P. S. Baran, *Proc. Natl. Acad. Sci.,* 2011, **108**, 14411-14415.
8. T. D. Senecal, A. T. Parsons and S. L. Buchwald, *J. Org. Chem.*, 2011, **76**, 1174-1176.
9. A. Beck, University of North Carolina Wilmington, 2007.
10. D. X. Yang, S. L. Colletti, K. Wu, M. Song, G. Y. Li and H. C. Shen, *Org. Lett.*, 2008, **11**, 381-384.

V. ^{1}H and ^{13}C NMR Spectra

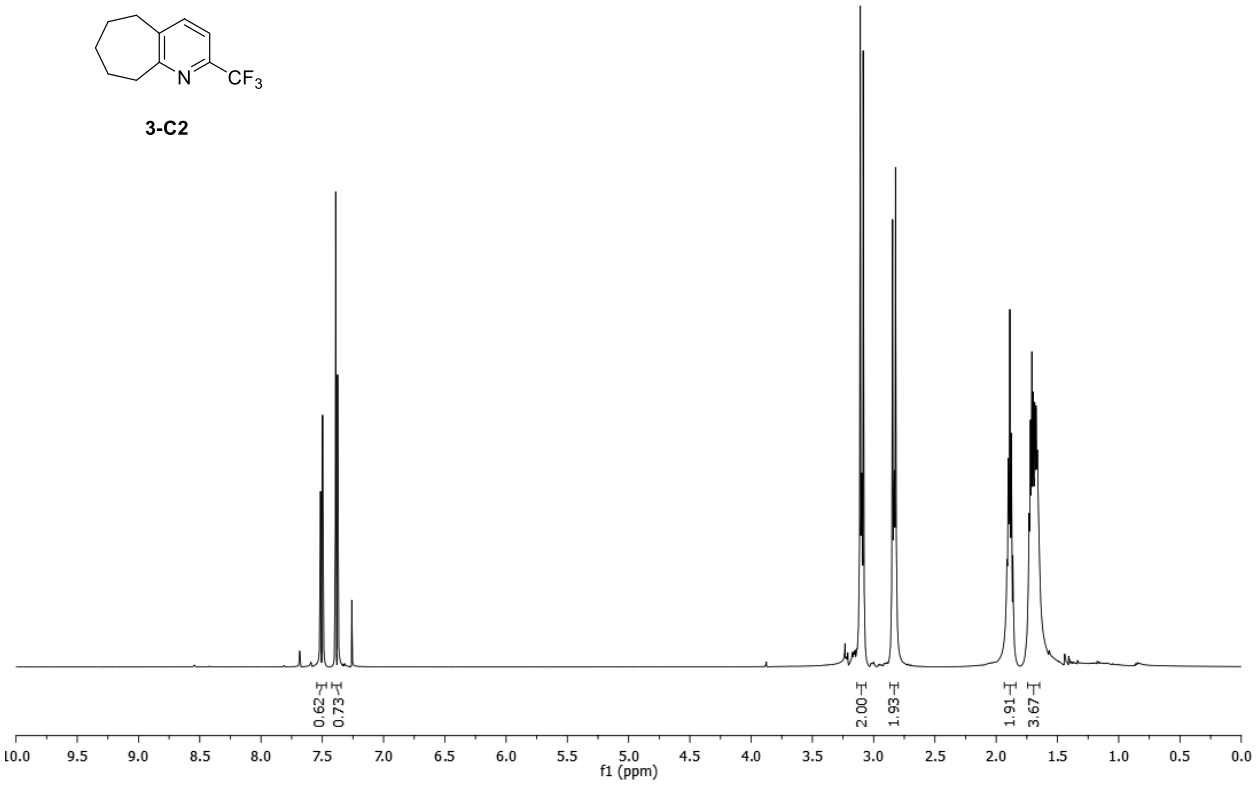
4-*tert* butyl-2-trifluoromethyl pyridine (2)

Proton NMR ($CDCl_3$)



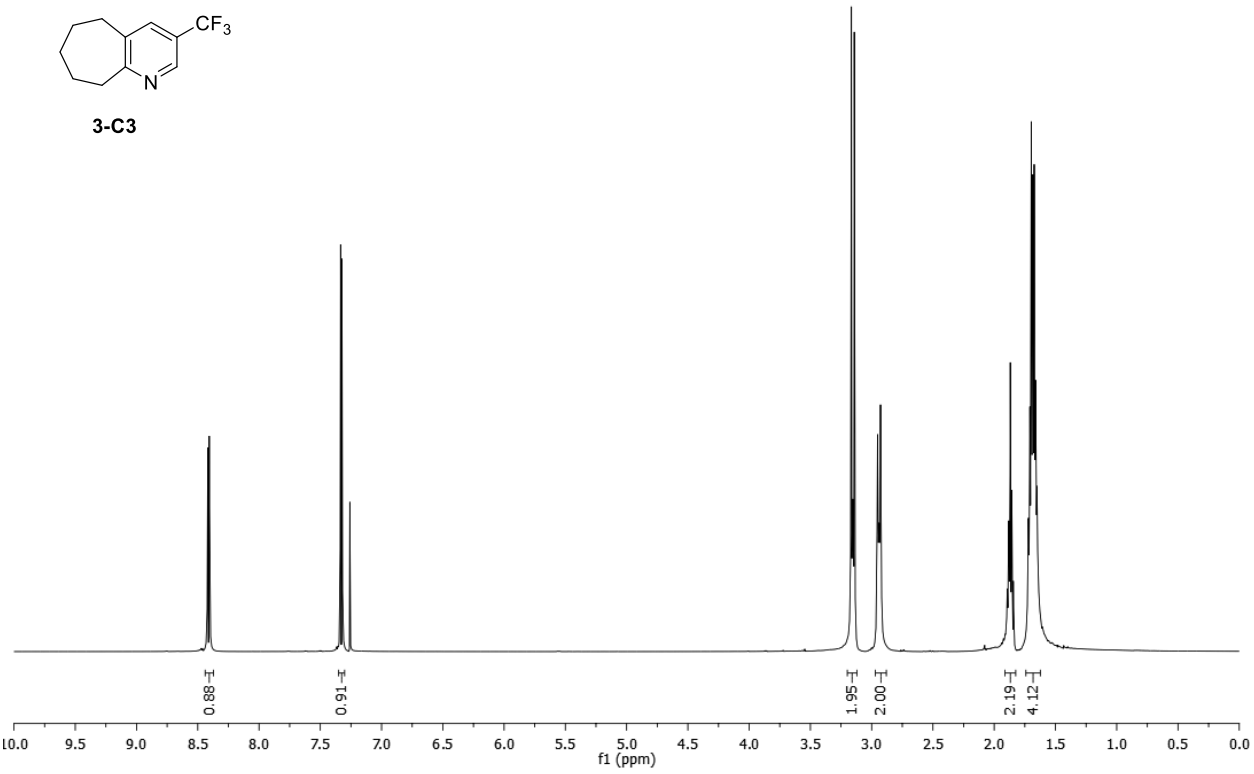
2-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (3-C2)

Proton NMR ($CDCl_3$)



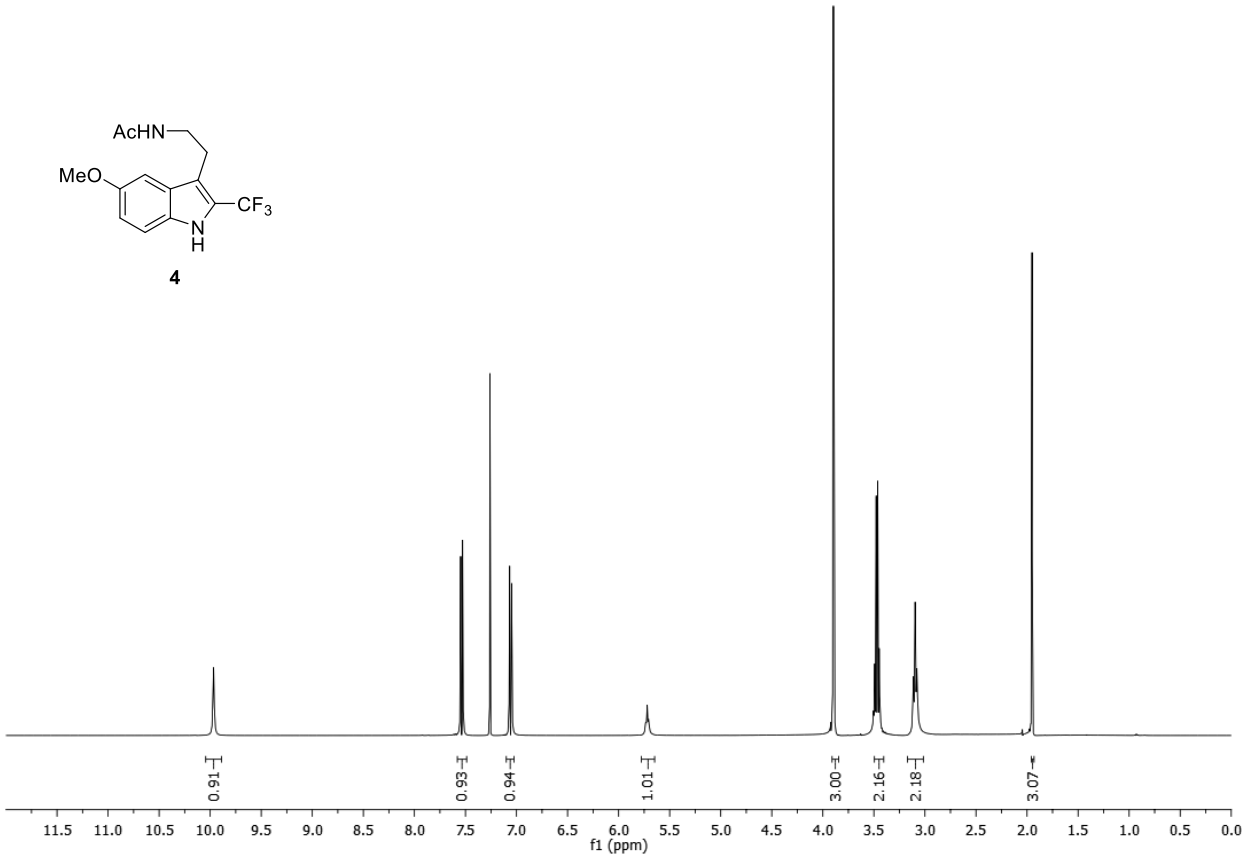
3-(trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine (3-C3)

Proton NMR ($CDCl_3$)



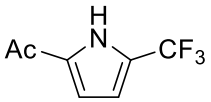
2-trifluoromethyl melatonin (4)

Proton NMR ($CDCl_3$)

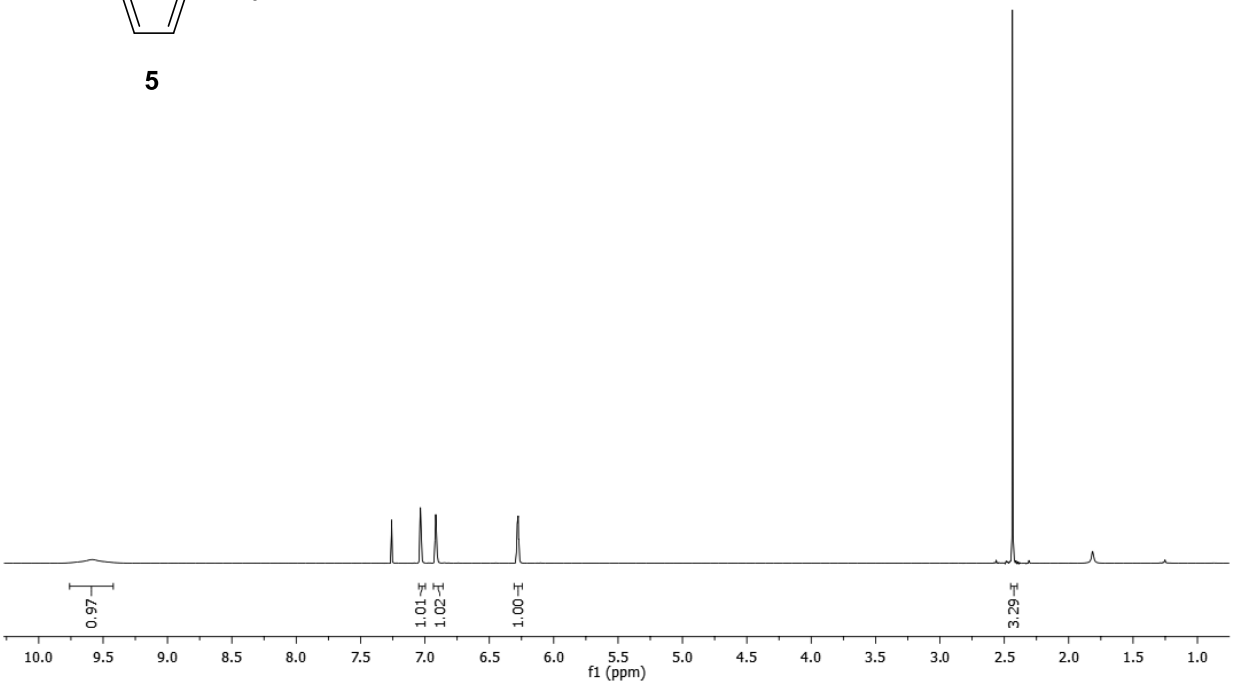


1-(5-(trifluoromethyl)-1H-pyrrol-2-yl)ethan-1-one (5)

Proton NMR ($CDCl_3$)

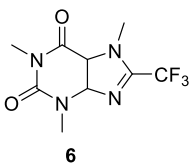


5



Trifluoromethylated caffeine (6)

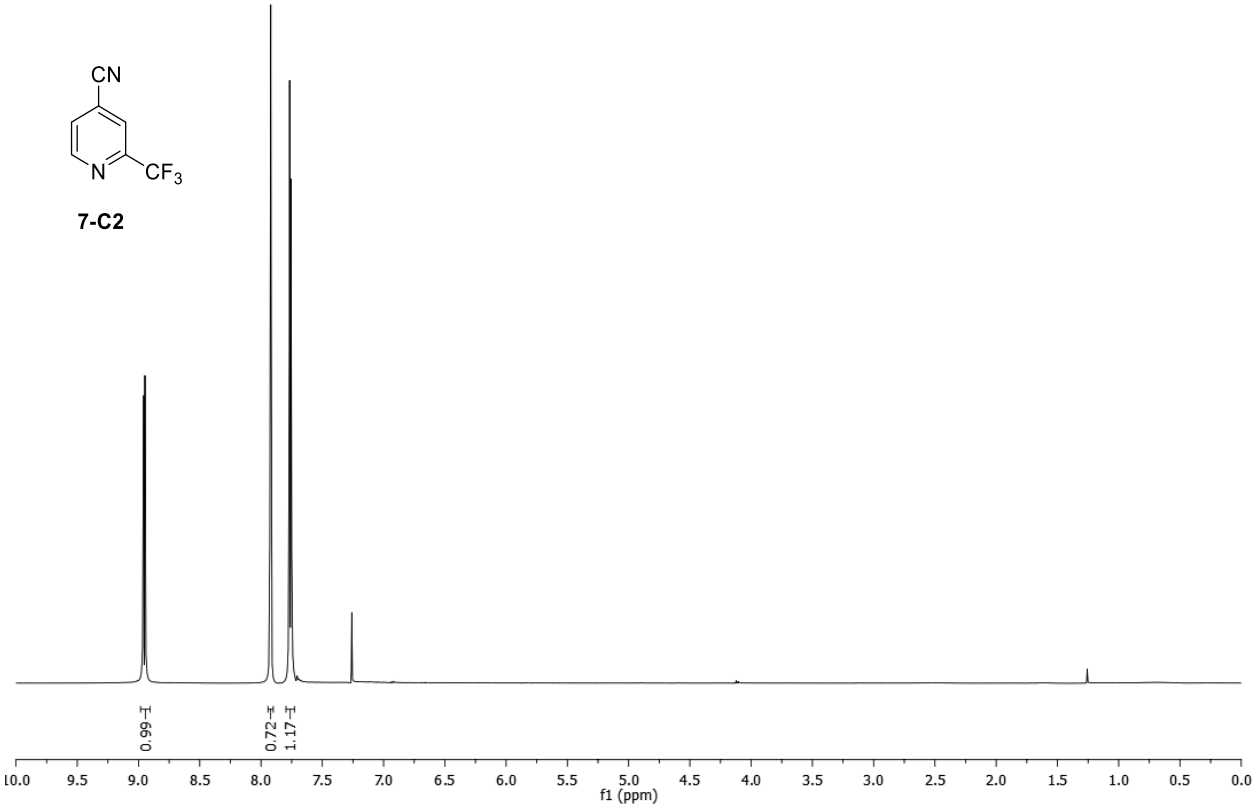
Proton NMR ($CDCl_3$)



6

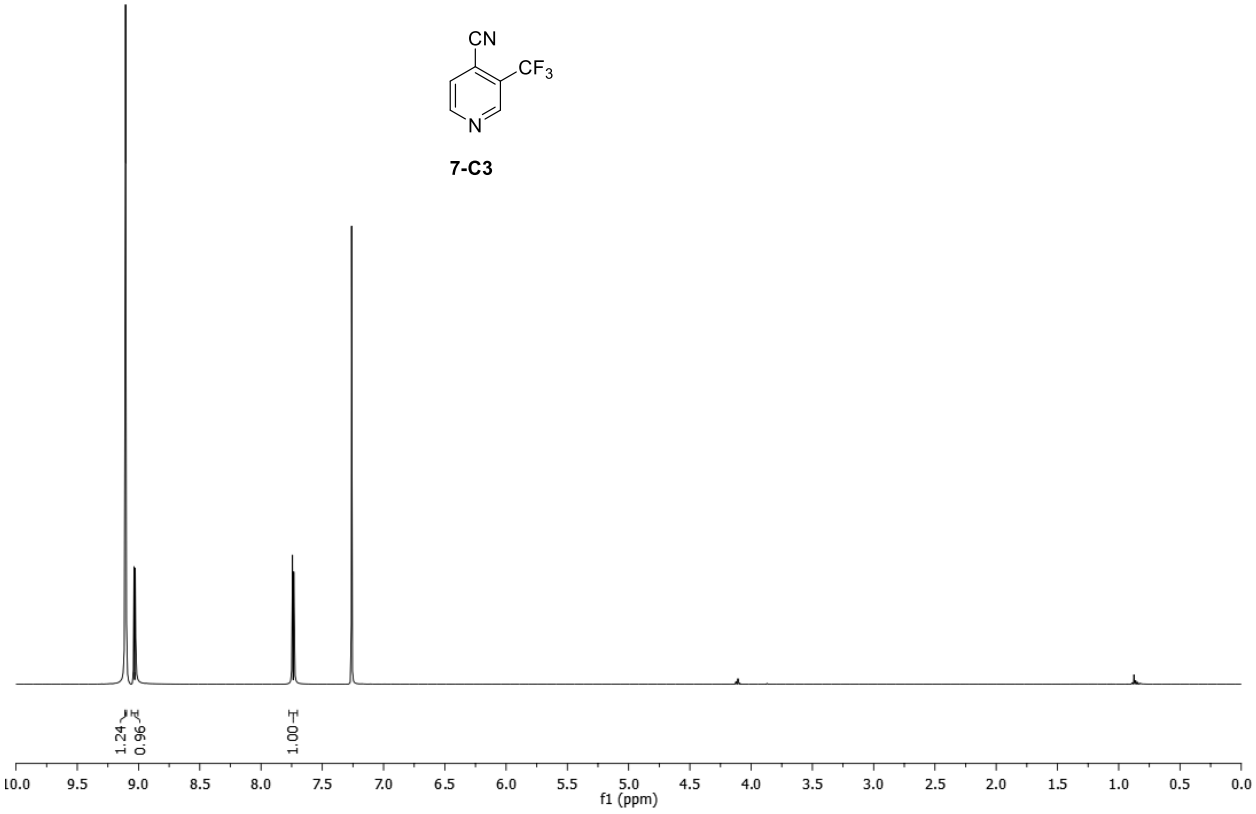
2-trifluoromethyl-4-cyano-pyridine (7-C2)

Proton NMR ($CDCl_3$)



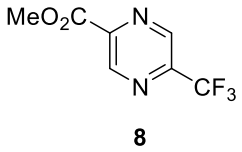
3-trifluoromethyl-4-cyano-pyridine (7-C3)

Proton NMR ($CDCl_3$)



methyl 5-(trifluoromethyl)pyrazine-2-carboxylate (8)

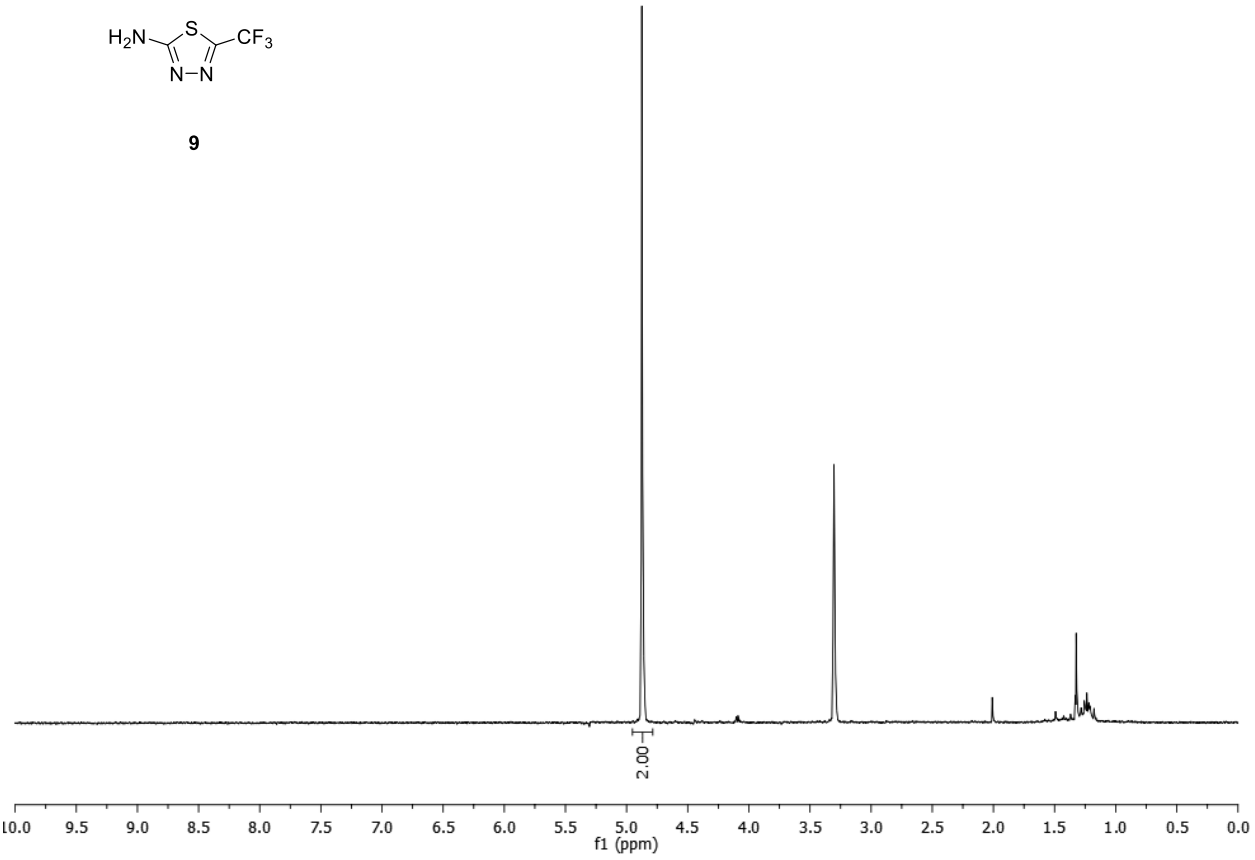
Proton NMR ($CDCl_3$)



8

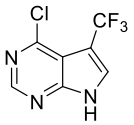
5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (9)

Proton NMR (MeOD)

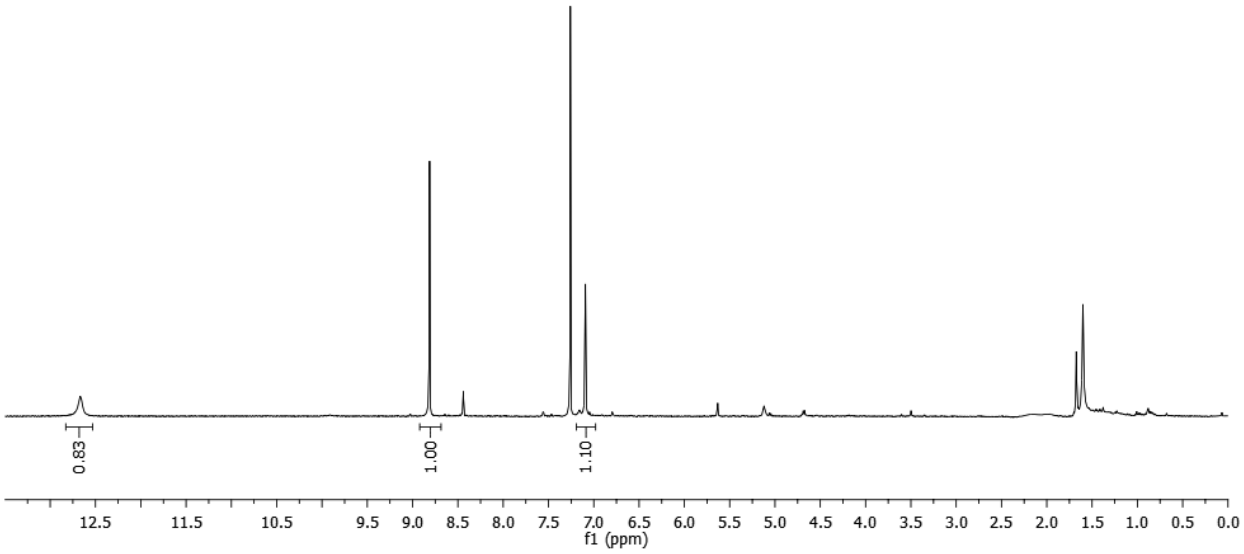


4-chloro-5-(trifluoromethyl)-7H-pyrrolo[2,3-d]pyrimidine (10)

Proton NMR ($CDCl_3$)

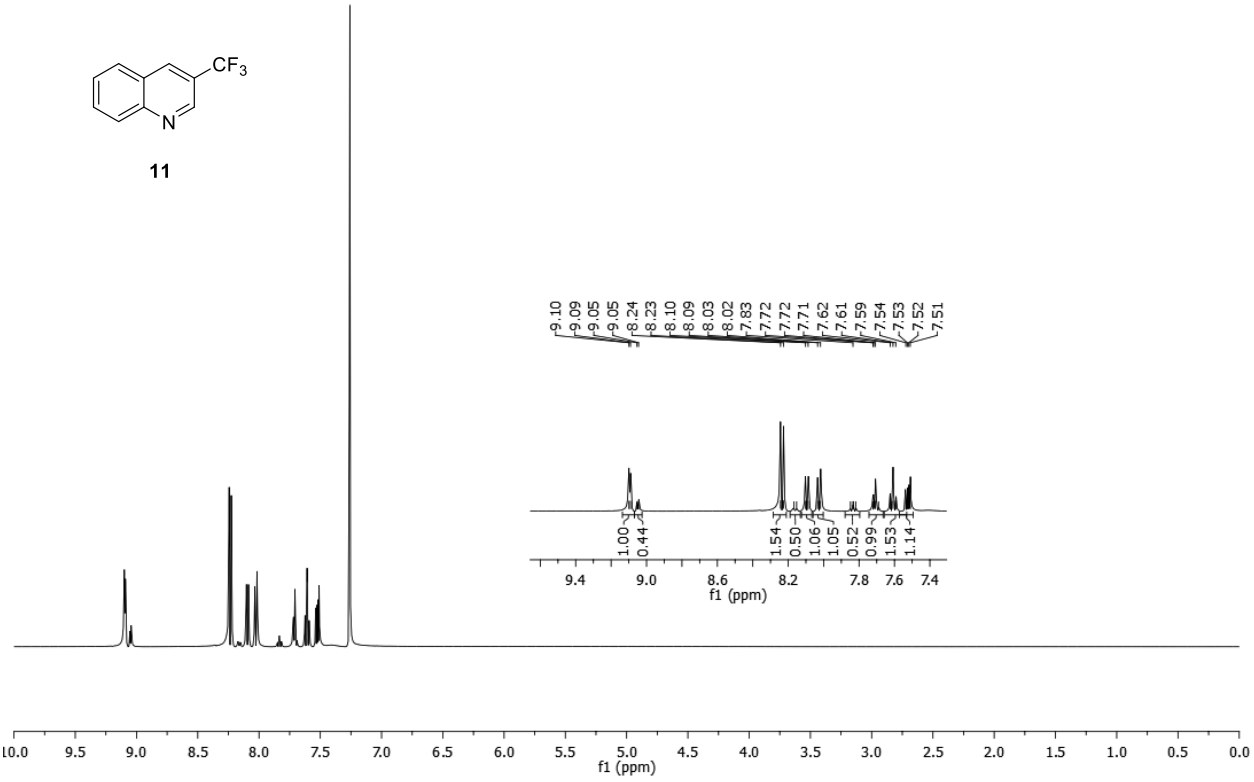


10



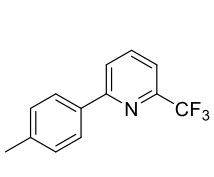
3-(trifluoromethyl)quinolone (11)

Proton NMR ($CDCl_3$)



2-(p-tolyl)-6-(trifluoromethyl)pyridine (12)

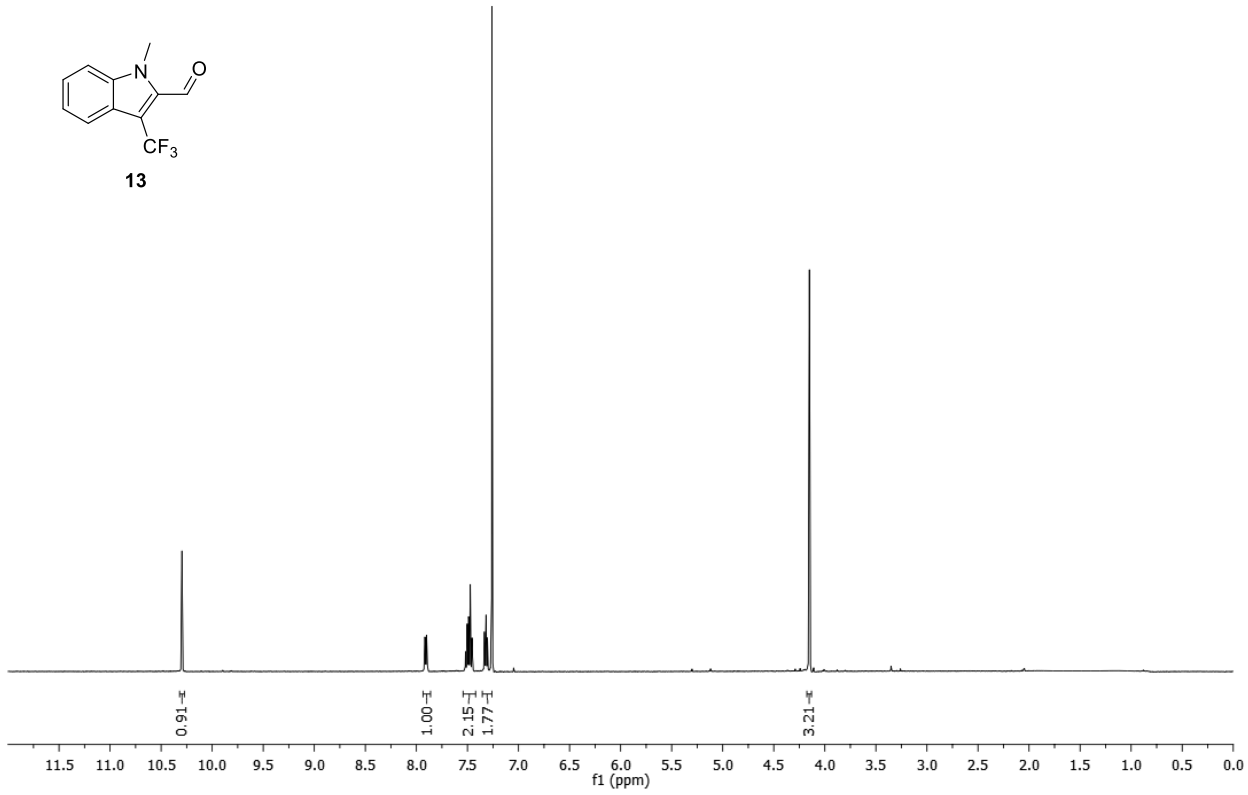
Proton NMR ($CDCl_3$)



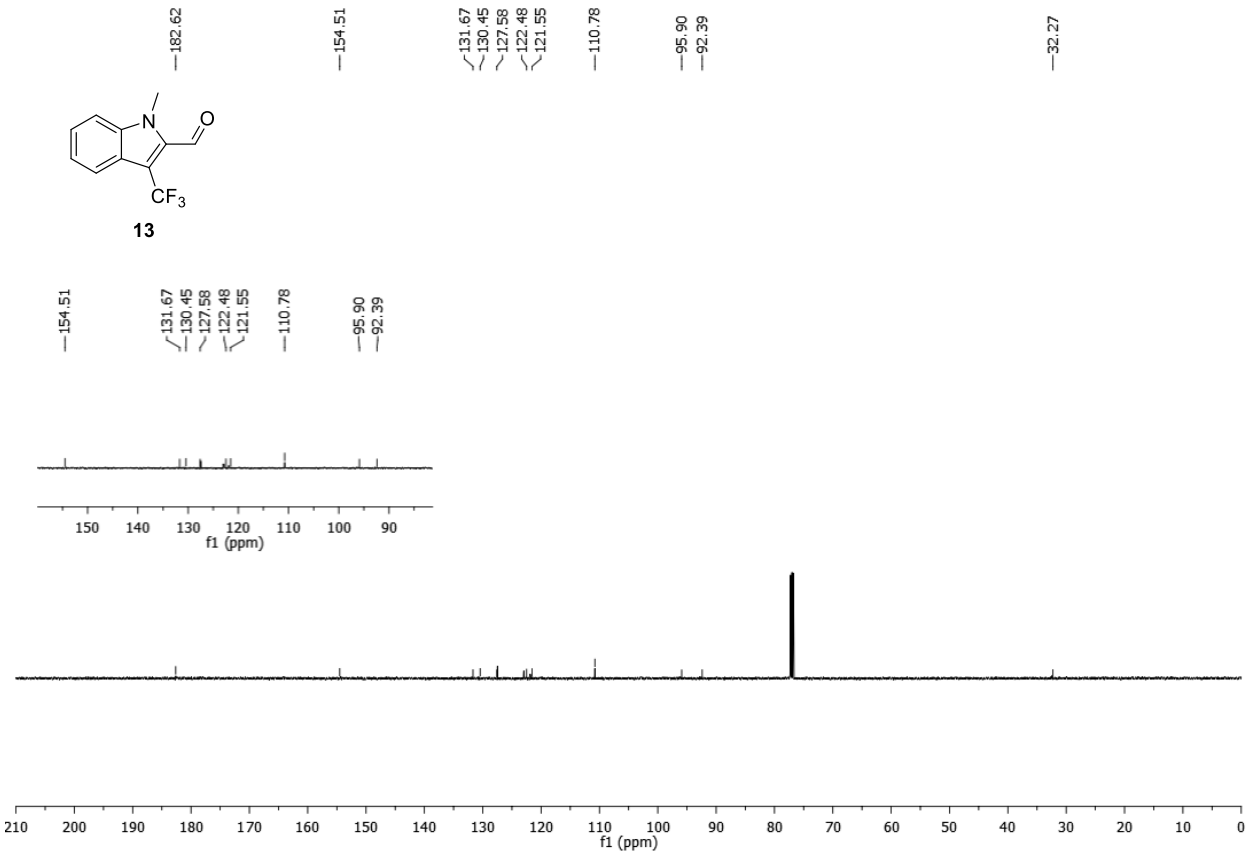
12

1-methyl-3-(trifluoromethyl)-1H-indole-2-carbaldehyde (13)

Proton NMR ($CDCl_3$)



Carbon NMR ($CDCl_3$)



HREIMS

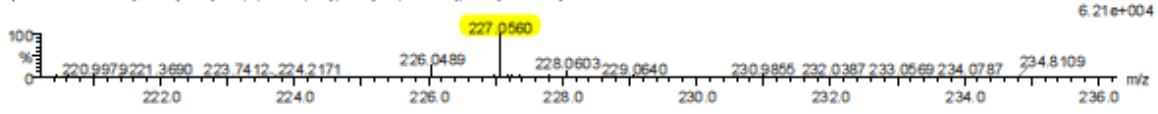
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 mDa / DBE: min = -1.5, max = 200.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
941 formula(e) evaluated with 27 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-200 N: 0-10 O: 0-10 F: 0-5

Fennewald\Joshutz JF-002-248, mw 227, EI+
lip040813PA 141 (2.350) Cn (Cen,3, 50.00, Ar); Sm (SG, 4x3.00); Cm (141:163)

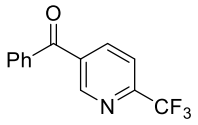
UCSB Chem-Biochem GCT Premier
TOF MS EI+
6.21e+004



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
Minimum:				-1.5		
Maximum:		3.0	10.0	200.0		
227.0560	227.0558	0.2	0.9	7.0	26.5	C11 H8 N O F3
	227.0556	0.4	1.8	11.0	32.3	C9 H5 N7 O
	227.0556	0.4	1.8	3.5	728.0	C6 H7 N4 O F4
	227.0556	0.4	1.8	5.5	215.4	C10 H11 O6
	227.0565	-0.5	-2.2	3.5	1805.9	C H5 N10 O2 F2
	227.0554	0.6	2.6	7.5	750.5	C4 H4 N10 O F
	227.0554	0.6	2.6	0.0	2395.3	C H6 N7 O F5
	227.0554	0.6	2.6	2.0	981.6	C5 H10 N3 O6 F
	227.0567	-0.7	-3.1	1.5	726.3	C7 H12 O7 F
	227.0567	-0.7	-3.1	7.0	411.4	C6 H6 N7 O2 F
	227.0567	-0.7	-3.1	-0.5	1772.2	C3 H8 N4 O2 F5
	227.0552	0.8	3.5	-1.5	2797.3	H9 N6 O6 F2
	227.0569	-0.9	-4.0	3.0	399.0	C8 H9 N O2 F4
	227.0569	-0.9	-4.0	10.5	9.7	C11 H7 N4 O2
	227.0547	1.3	5.7	11.0	121.6	C14 H7 N F2
	227.0545	1.5	6.6	7.5	176.2	C9 H6 N4 F3
	227.0543	1.7	7.5	-1.5	1331.6	C5 H11 O5 F4
	227.0543	1.7	7.5	4.0	1187.0	C4 H5 N7 F4
	227.0542	1.8	7.9	11.5	191.1	C7 H3 N10
	227.0542	1.8	7.9	6.0	281.7	C8 H9 N3 O5
	227.0578	-1.8	-7.9	3.0	1291.6	C3 H7 N7 O3 F2
	227.0580	-2.0	-8.8	6.5	205.2	C8 H8 N4 O3 F
	227.0540	2.0	8.8	2.5	1368.3	C3 H8 N6 O5 F
	227.0581	-2.1	-9.2	-1.0	1273.0	C5 H10 N O3 F5
	227.0582	-2.2	-9.7	10.0	119.5	C13 H9 N O3
	227.0531	2.9	12.8	2.5	455.5	C8 H10 O4 F3
	227.0590	-3.0	-13.2	-1.0	2689.1	H8 N7 O4 F3

phenyl(6-(trifluoromethyl)pyridin-3-yl)methanone (14)

Proton NMR ($CDCl_3$)



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