Electronic Supplementary Material (ESI) for RSC Advances

A convenient synthesis of the key intermediate of selective COX-2 inhibitor Etoricoxib

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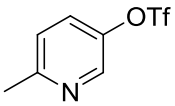
Content of Supporting Information
(12 pages)

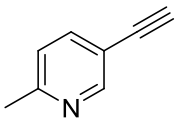
General. All reactions, if not stated otherwise, were performed in oven-dried glassware under an argon atmosphere containing a teflon-coated stirring bar and dry septum. Chemicals and solvents were either purchased (puriss. p.A.) from commercial suppliers or purified by standard techniques. All reactions were monitored by GC using tetradecane as an internal standard. Response factors of the products with regard to tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP-5 capillary column (Phenyl methyl siloxane, 30 m x 320 x 0.25, 100/2.3-30-300/3, 2 min at 50 °C, heating rate 25 °C/min, 3 min at 250 °C). Column chromatography was performed with 230-400 mesh silica-gel. NMR spectra were obtained on a Bruker AVANCE 300 spectrometer (300 MHz) using $CDCl_3$ as solvent, 300 MHz and 75 MHz, respectively. Mass spectral data were acquired on a Trace GC-MS 2000 ThermoQuest. Melting points were measured on a Büchi 535.

Trifluoromethanesulfonic acid 2-methylpyridin-5-yl ester (17) [CAS-No 111770-91-3][1]



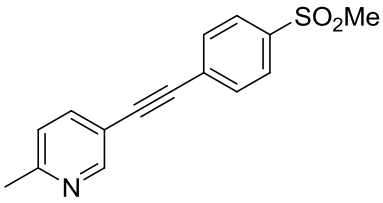
To a solution of 5-hydroxy-2-methylpyridine (10.0 g, 91.7 mmol) and pyridine (11.0 mL, 137.0 mmol) in DCM (100 mL), trifluoromethanesulfonic anhydride (18.5 mL, 110.0 mmol) was added dropwise at 0°C. After stirring for 1.5 h, MeOH (2 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added to the mixture. The organic layer was washed with brine (50 mL), and dried over $MgSO_4$. The solvent was removed in *vacuum*, and the residue was distilled at reduced pressure (85 °C, 0.1 torr) to obtain trifluoromethanesulforic acid 6-methyl-pyridin-3-yl ester as a colorless oil (20.3 g, 92% yield). ^{1}H-NMR (300 MHz, $CDC1_3$): δ = 8.44 (d, *J* = 2.8 Hz, 1 H), 7.49 (dd, *J* = 8.6, 2.9 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 1 H), 2.58 (s, 3 H) ppm; ^{13}C-NMR (75 MHz, $CDC1_3$): δ = 159.0, 144.9, 141.8, 129.0, 124.2, 118.6 (q, *J* = 320.4 Hz), 23.9 ppm; MS (70 eV), m/z (%): 241 (60) [M^+], 108 (58), 80 (100), 69 (29), 53 (62).

5-Ethynil-2-methylpyridine (12) [CAS-No 1945-85-3][2]



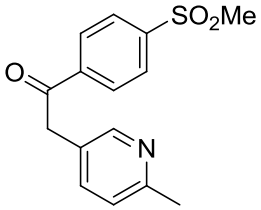
An oven-dried vessel equipped with a magnetic stirring bar was charged with tri(*p*-tolyl)phosphine (176 mg, 0.58 mmol), $Pd(OAc)_2$ (65.0 mg, 0.29 mmol) and 6-methylpyridin-3-yl trifluoromethanesulfonate (5.0 mL, 29.0 mmol). After purging the vessel with alternating *vacuum* and Argon cycles, a degassed solution of piperidine (11.0 mL, 117.4 mmol) in NMP/Toluene (1:1, 40 mL) was added. 2-Methyl-3-butyn-2-ol (4.2 mL) was added via syringe and the mixture was stirred at 40 °C overnight. After cooling to rt, the mixture was diluted with saturated aqueous $NaHCO_3$ (80 mL) and extracted with Et_2O (3×50 mL). Combined organic extracts were washed with H_2O (20 mL), saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The crude product was redissolved in dry toluene (100 mL) and finely crushed NaOH (11.0 g, 275 mmol) was added. The mixture was heated to reflux for few hours and monitored via TLC till the conversion of **18** was complete. After filtration, the solution was washed with saturated aqueous $NaHCO_3$ (50 mL) and dried over $MgSO_4$. The solvent was removed under *vacuum* and the crude product was purified by sublimation at reduced pressure to obtain a colorless solid (2.79 g, 82% yield), mp 50-51 °C. ^{1}H-NMR (300 MHz, $CDC1_3$): δ = 8.59 (d, *J* = 2.0 Hz, 1 H), 7.63 (dd, *J* = 8.1, 2.2 Hz, 1 H), 7.10 (d, *J* = 8.1 Hz, 1 H), 3.15 (s, 1 H), 2.54 (s, 3 H) ppm; ^{13}C-NMR (75 MHz, $CDC1_3$): δ = 158.3, 152.1, 132.2, 122.6, 116.1, 80.6, 79.8, 24.4 ppm; MS (70 eV), m/z (%) 117. (100) [M^+], 89 (44), 63 (12), 50 (8).

2-Methyl-5-((4-(methylsulfonyl)phenyl)ethynyl)pyridine (15)



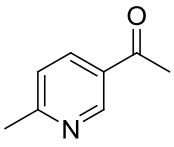
An oven-dried vessel equipped with a magnetic stirring bar was charged with triphenylphosphine (126 mg, 0.48 mmol), $Pd(OAc)_2$ (53.8 mg, 0.24 mmol), copper(I) iodide (60.8 mg, 0.32 mmol), 5-ethynil-2-methylpyridine (1.87 g, 16.0 mmol) and 4-bromophenyl methyl sulfone (5.64 g, 24.0 mmol). After purging the vessel with alternating vacuum and Argon cycles, a degassed solution of piperidine (6.3 mL, 64 mmol) in toluene (30 mL) was added and the mixture was stirred for 2 hrs at 60 °C. After cooling to rt, the mixture was diluted with water (50 mL) and extracted with AcOEt (3×50 mL). Combined organic extracts were washed with H_2O (20 mL), saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum*. The crude product was purified by silica gel chromatography (eluant hexane/AcOEt in gradient from 8:2 to 2:8) affording the product **15** (3.4 g, 78% yield) as a pale yellow solid, mp 154-155 °C; ^{1}H-NMR (300 MHz, $CDC1_3$): δ = 8.67 (d, *J* = 2.2, 1 H), 7.93 (d, *J* = 8.2, Hz, 2 H), 7.69-7.74 (m, 3 H), 7.18 (d, *J* = 8.3 Hz, 1 H), 3.07 (s, 3 H), 2.59 (s, 3 H) ppm; ^{13}C-NMR (75 MHz, $CDC1_3$): δ = 158.7, 151.7, 139.9, 138.9, 132.3, 128.6, 127.4, 122.8, 116.3, 90.2, 90.0, 44.4, 24.6 ppm; MS (70 eV), m/z (%) 271 (100) [M^+], 208 (48), 192 (48), 165 (26), 152 (11), 139 (9), 99 (7), 63 (9). Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.48; H, 4.77; N, 5.25.

2-(6-Methylpyridin-3-yl)-1-(4-(methylsulfonyl)phenyl)ethanone (19)[3]



2-Methyl-5-((4-(methylsulfonyl)phenyl)ethynyl)pyridine (54.3 mg, 0.20 mmol) was dissolved in a toluene/H_2SO_4 mixture (1:4, 2.5 mL) and stirred at 80 °C for 3 hours. After cooling to rt, the solution was neutralized with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3×20 mL). Combined organic extracts were washed with H_2O (20 mL), saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and concentrated in *vacuum* to afford the product **19** as a colourless solid (55.5 mg, 96% yield), mp 159-160 °C; ^{1}H-NMR (300 MHz, $CDC1_3$): δ = 8.39 (d, *J* = 1.8 Hz, 1 H), 8.17 (d, *J* = 8.8 Hz, 2 H), 8.05 (d, *J* = 8.8 Hz, 2 H), 7.48 (dd, *J* = 7.9, 2.2 Hz, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 4.29 (s, 2 H), 3.07 (s, 3 H), 2.54 (s, 3 H) ppm; ^{13}C-NMR (75 MHz, $CDC1_3$): δ = 195.5, 157.5, 149.7, 144.5 140.2, 137.4, 129.3, 127.9, 126.0, 123.2, 44.2, 42.5, 24.0 ppm; MS (70 eV), m/z (%) 289 (13) [M^+], 183 (100), 121 (35), 106 (18), 77 (17), 50 (4).

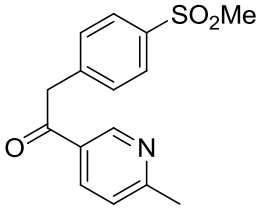
3-Acetyl-6-methylpyridine (14) [CAS-No 36357-38-7][4]



5-Ethynil-2-methylpyridine (1.0 g, 8.5 mmol) was dissolved in toluene and sulphuric acid (1:4, 10 mL) and heated at 80°C for 3 hours. the solution was neutralized with saturated aqueous $NaHCO_3$

(30 mL) and extracted with AcOEt (3×30 mL). Combined organic extracts were washed with H_2O (20 mL), saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and concentrated in vacuum to afford the product 14 as a pale yellow oil (1.06 g, 92% yield). ^{1}H-NMR (300 MHz, $CDC1_3$): δ = 8.96 (d, *J* = 1.8 Hz, 1 H), 8.04 (dd, *J* = 8.5, 2.4 Hz, 1 H), 7.18 (d, *J* = 7.9 Hz, 1 H), 2.55 (s, 1 H), 2.55 (s, 3 H) ppm; ^{13}C-NMR (75 MHz, $CDC1_3$): δ = 196.4, 163.2, 149.5, 135.6, 129.8, 123.1, 26.5, 24.6 ppm; MS (70 eV), m/z (%) 135. (47) [M^+], 120 (100), 92 (72), 65 (23), 43 (9).

1-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl] ethanone (1) [CAS-No 221615-75-4][5]



An oven-dried vessel equipped with a magnetic stirring bar and reflux condenser was charged with palladium(II) acetylacetonate (6.1 mg, 0.02 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (23.2 mg, 0.04 mmol), 4-bromophenyl methyl sulfone (1.17 g, 5.0 mmol), 1-(6-methyl pyridine-3-yl) ethanone (541 mg, 4.0 mmol) and K_3PO_4 (2.55 g, 12.0 mmol). After purging the vessel with alternating vacuum and argon cycles, dry and degassed NMP (15 mL) was added and the mixture was stirred at 100 °C for 16 h. After cooling to rt the mixture was diluted with water (50 mL) and extracted with AcOEt (4×50 mL). Combined organic extracts were washed with H_2O (50 mL), saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and concentrated in vacuum. The crude product was purified by silica gel chromatography (eluant hexane/AcOEt in gradient from 5:5 to 0:10) affording the product **1** as a colorless solid (1.05 g, 91% yield), mp 172-173 °C.

Alternatively, product 1 was prepared as follows: an oven-dried vessel equipped with a magnetic stirring bar and reflux condenser was charged with palladium(II) acetylacetonate (15.2 mg, 0.05 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (30.5 mg, 0.1 mmol), 4-chlorophenyl methyl sulfone (2.10 g, 11 mmol), 1-(6-methyl pyridine-3-yl) ethanone (1.35 g, 10.0 mmol) and K_3PO_4 (6.36 g, 30.0 mmol). After purging the vessel with alternating vacuum and argon cycles, dry and degassed DMSO (20 mL) was added and the mixture was stirred at 150 °C for 16 h. Work up and purification were carried out as described above. Product **1** was obtained as a colourless solid (1.98 g, 69% yield), mp 172-173 °C; ^{1}H-NMR (300 MHz, $CDC1_3$): δ = 9.13 (d, *J* = 2.2, 1 H), 8.17 (dd, *J* = 8.2, 2.4 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 7.9 Hz, 1 H), 4.39 (s, 2 H), 3.05 (s, 3 H), 2.65 (s, 3 H) ppm; ^{13}C-NMR (75 MHz, $CDC1_3$): δ = 194.8, 163.9, 149.4, 140.1 139.3, 136.1, 130.6, 129.1, 127.7, 123.6, 45.1, 44.5, 24.7 ppm; MS (70 eV), m/z (%) 289 (0.1) [M^+], 120 (100), 92 (28), 65 (13), 39 (3).

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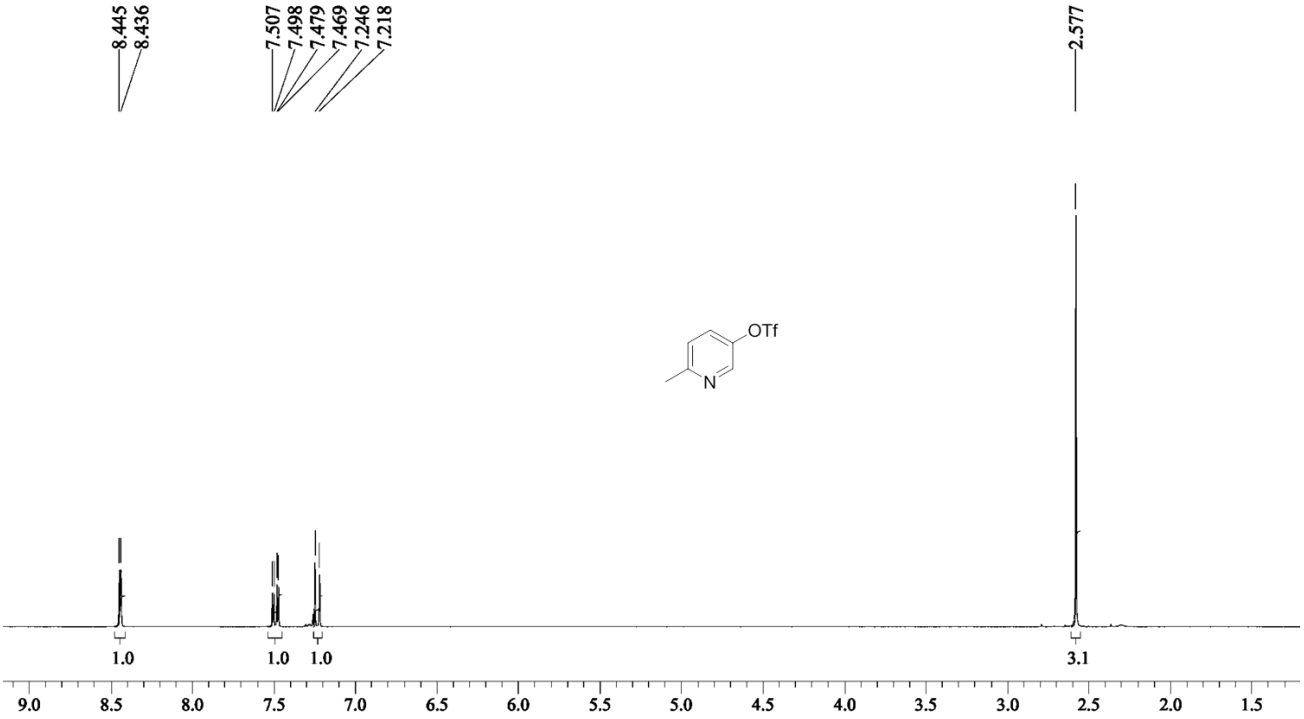
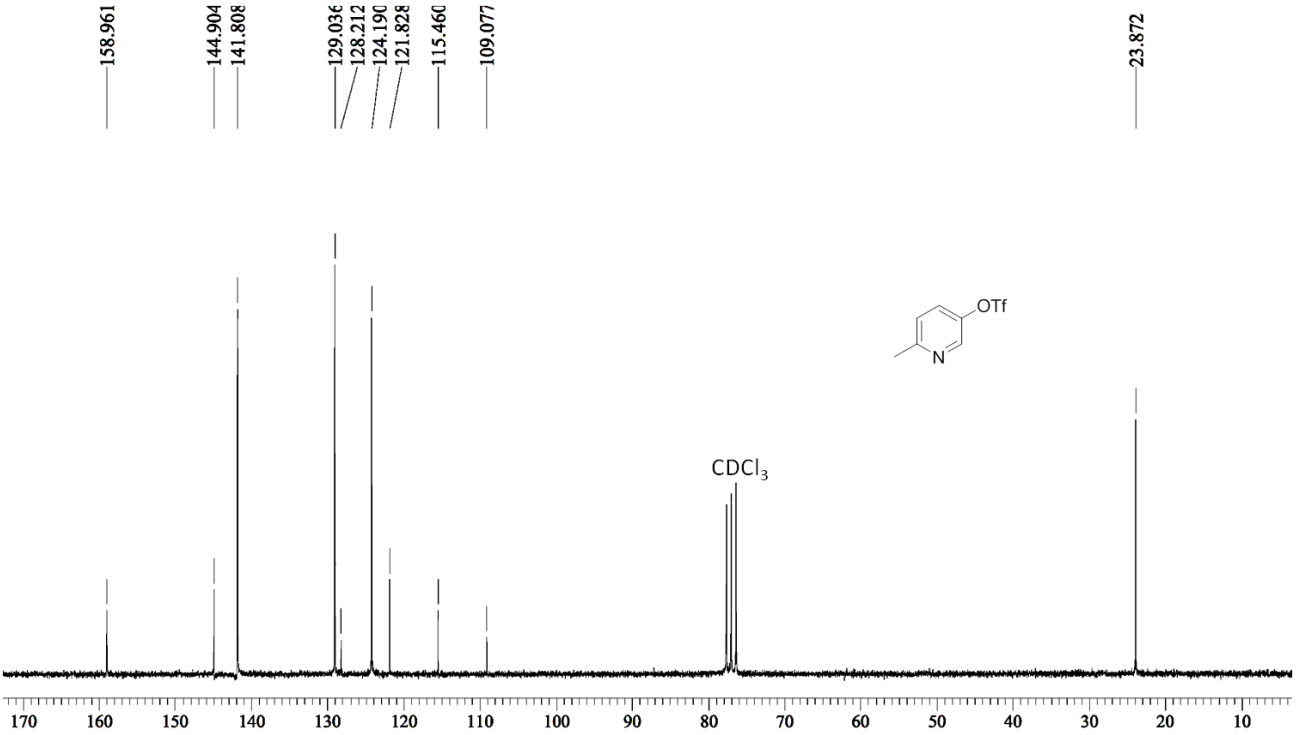
Trifluoromethanesulfonic acid 2-methylpyridin-5-yl ester (17)

^{1}H NMR ($CDCl_3$, 300 MHz)

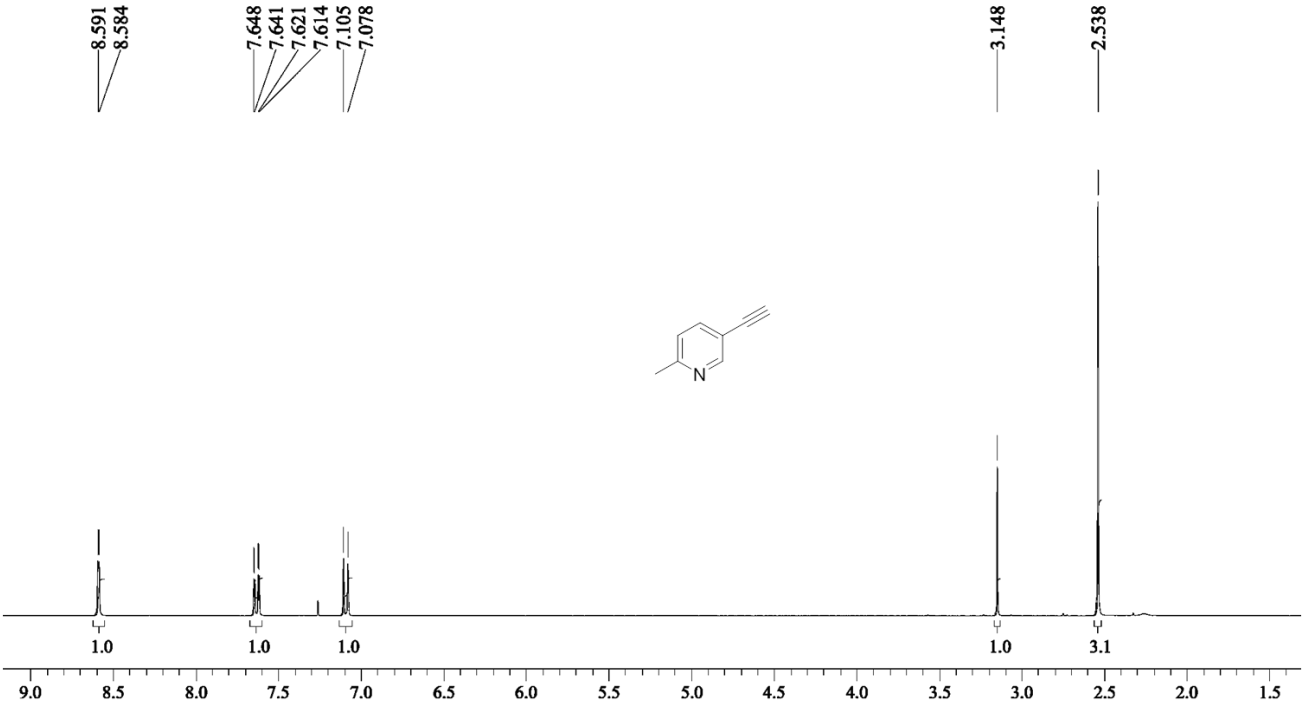


^{13}C NMR ($CDCl_3$, 75 MHz)

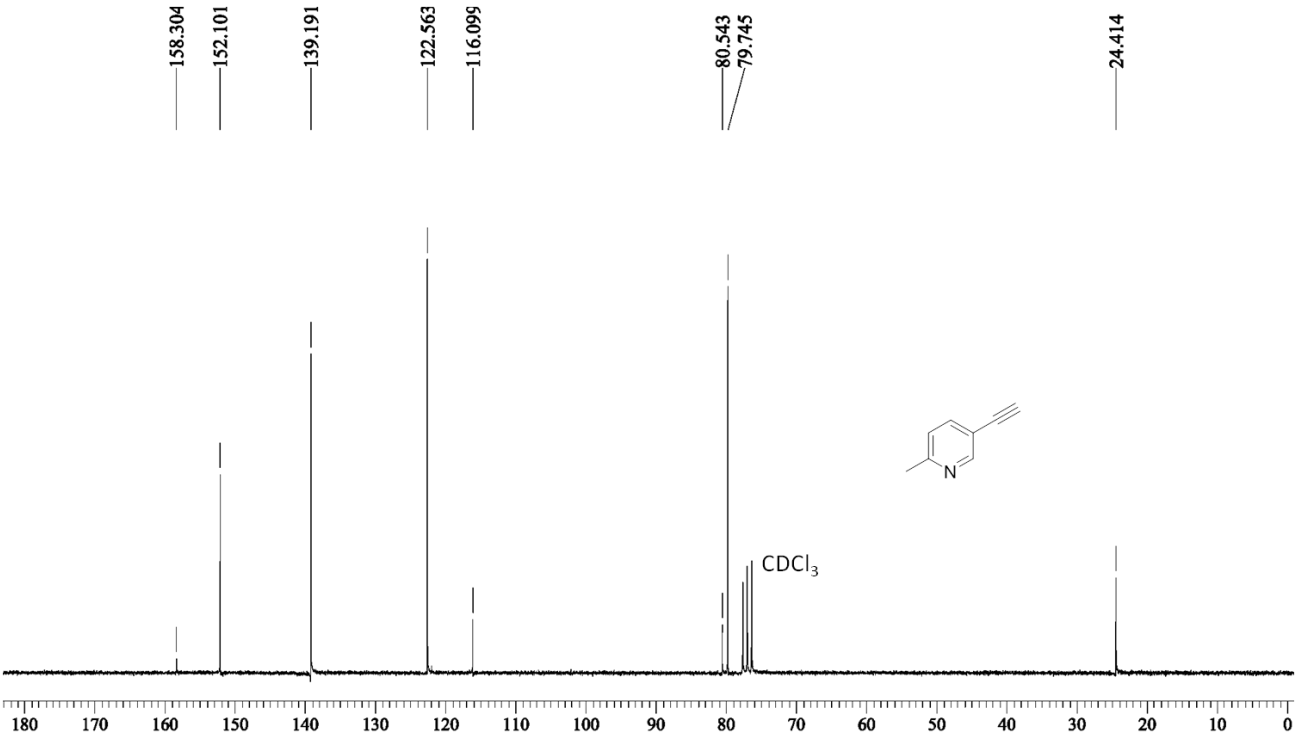


5-Ethynil-2-methylpyridine (12)

^{1}H NMR ($CDCl_3$, 300 MHz)

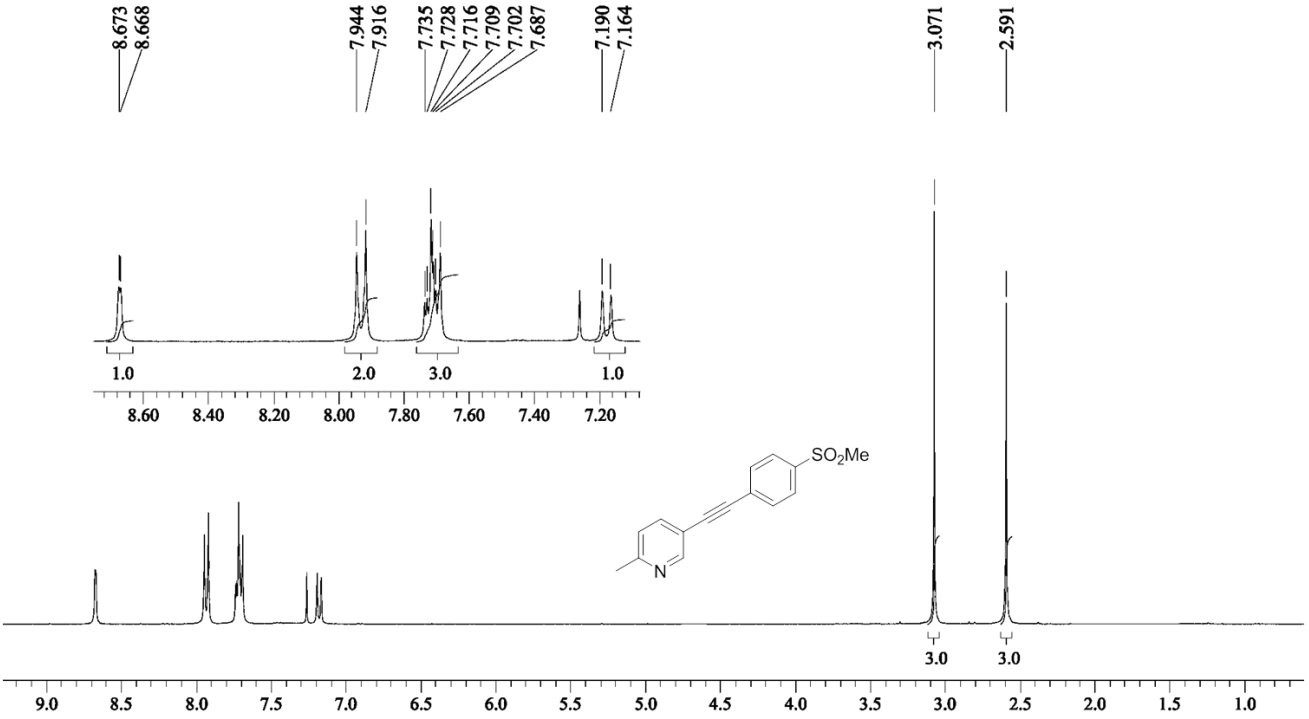


^{13}C NMR ($CDCl_3$, 75 MHz)

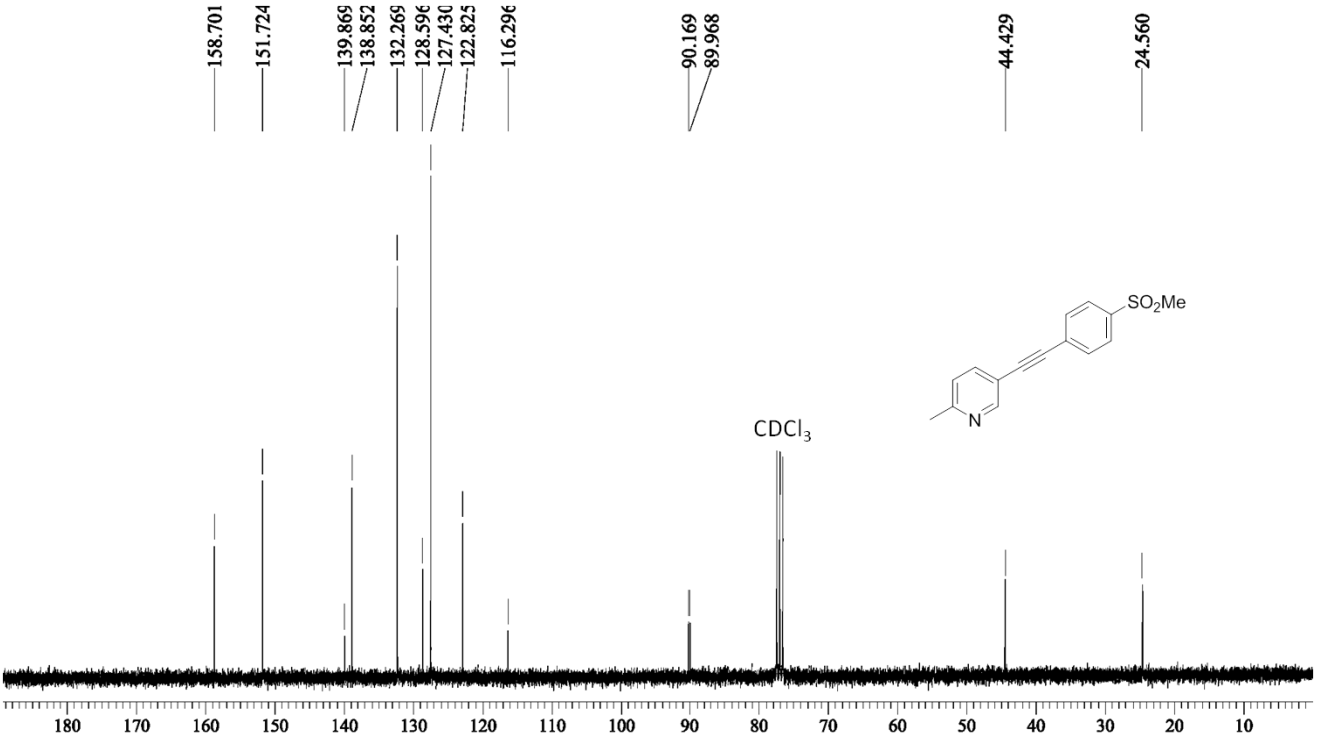


2-Methyl-5-((4-(methylsulfonyl)phenyl)ethynyl)pyridine (15)

^{1}H NMR ($CDCl_3$, 300 MHz)

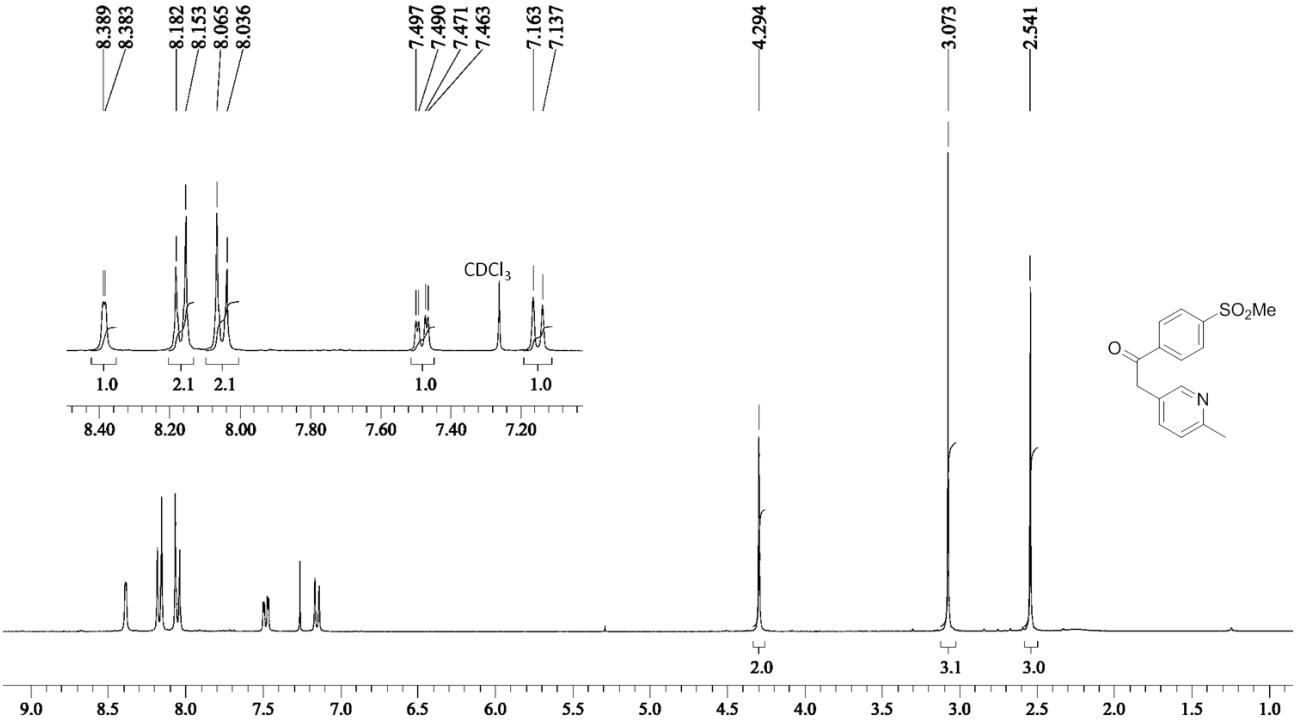


^{13}C NMR ($CDCl_3$, 75 MHz)



2-(6-Methylpyridin-3-yl)-1-(4-(methylsulfonyl)phenyl)ethanone (19)

^{1}H NMR ($CDCl_3$, 300 MHz)



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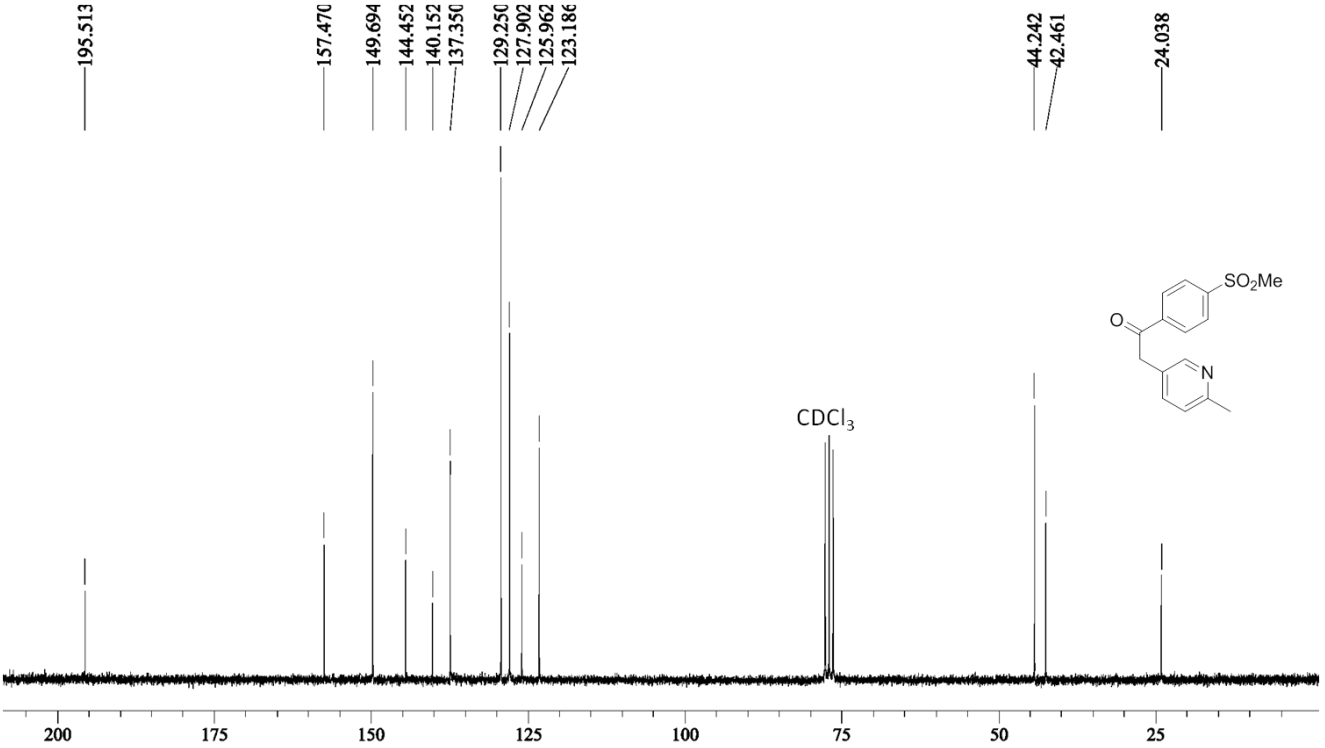
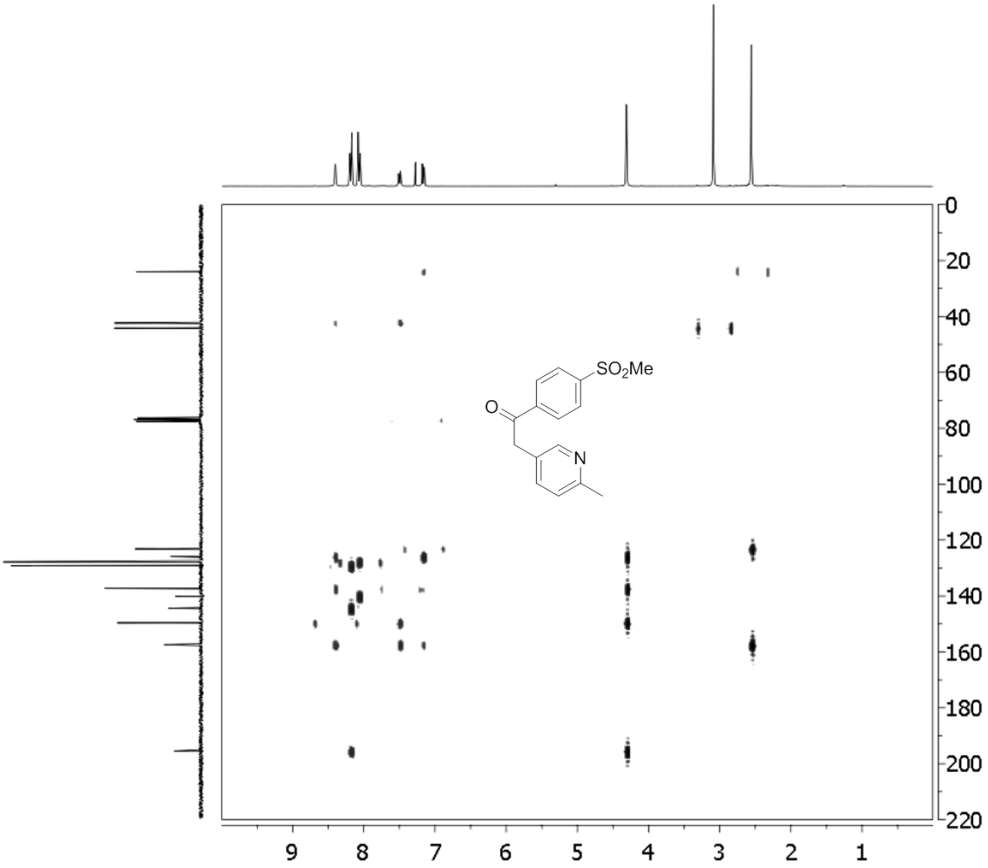
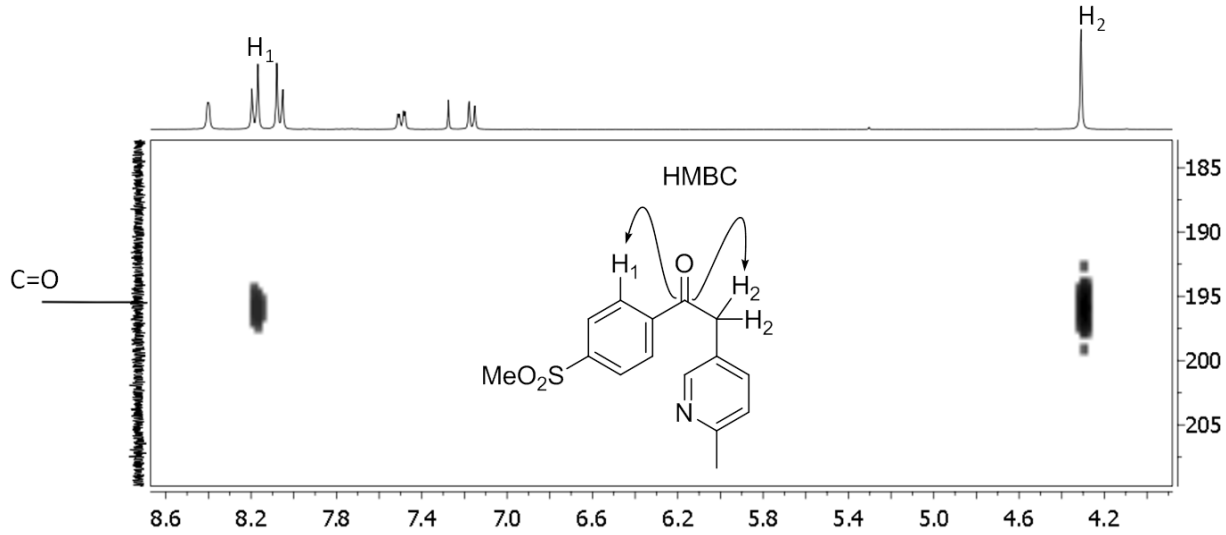


2-(6-Methylpyridin-3-yl)-1-(4-(methylsulfonyl)phenyl)ethanone (19)

HMBC ($CDCl_3$)

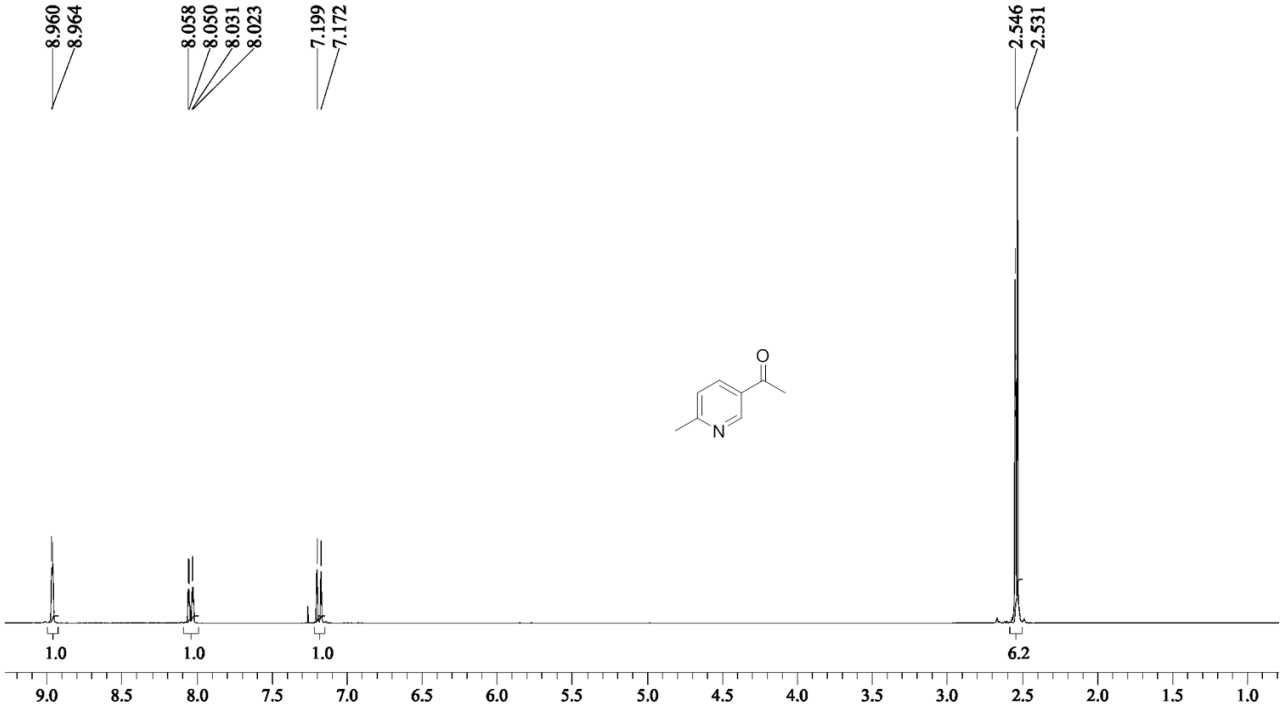


Significative portion of the HMBC spectra of compound **19**

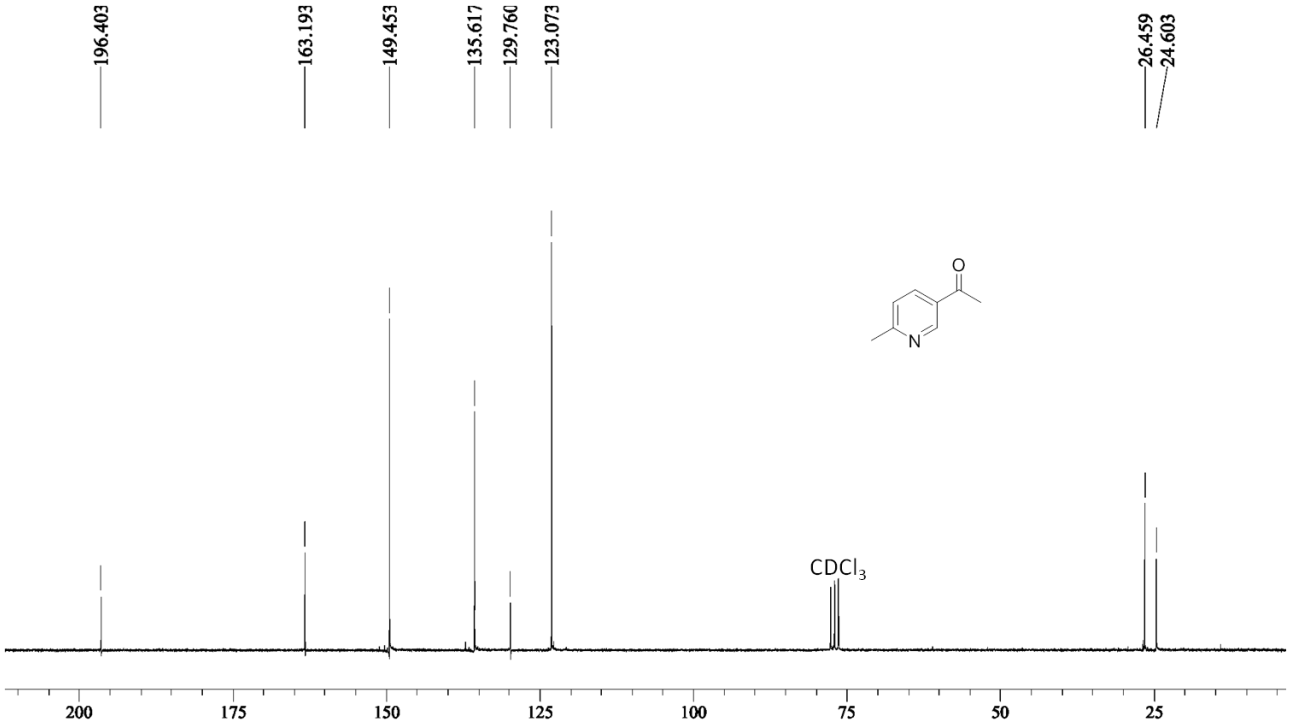


3-Acetyl-6-methylpyridine (14)

^{1}H NMR ($CDCl_3$, 300 MHz)

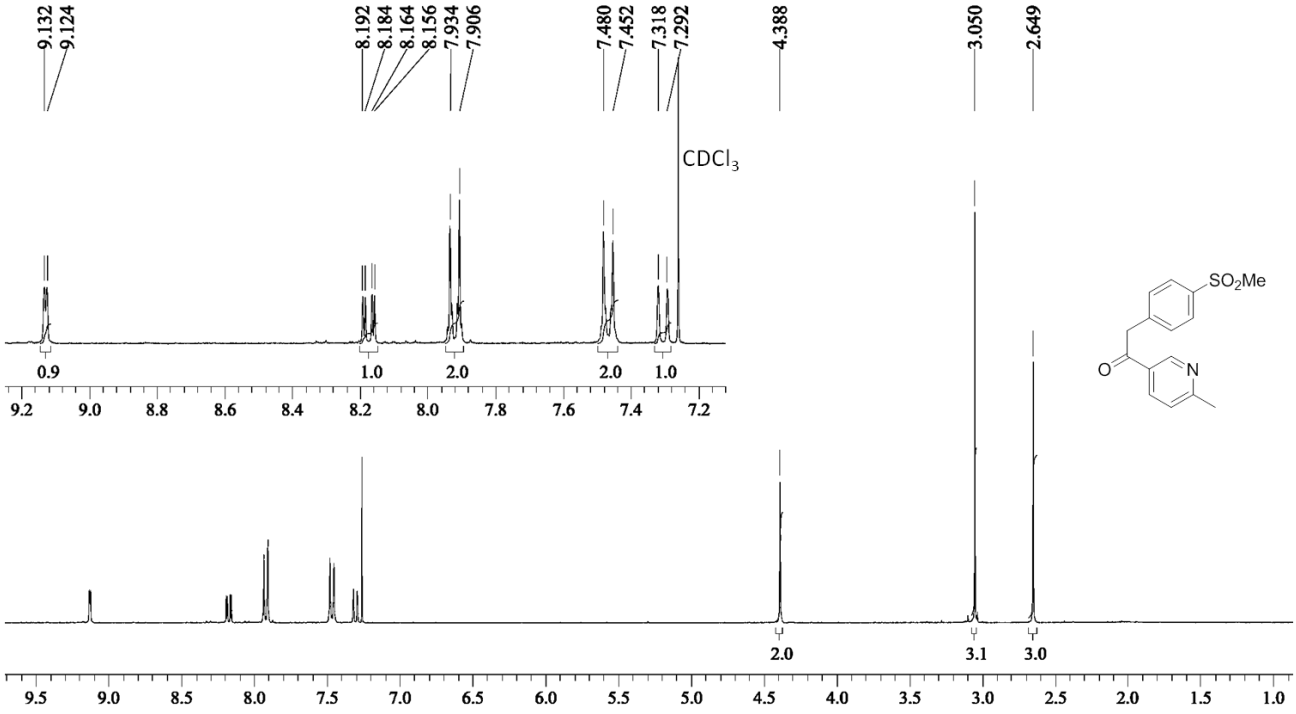


^{13}C NMR ($CDCl_3$, 75 MHz)

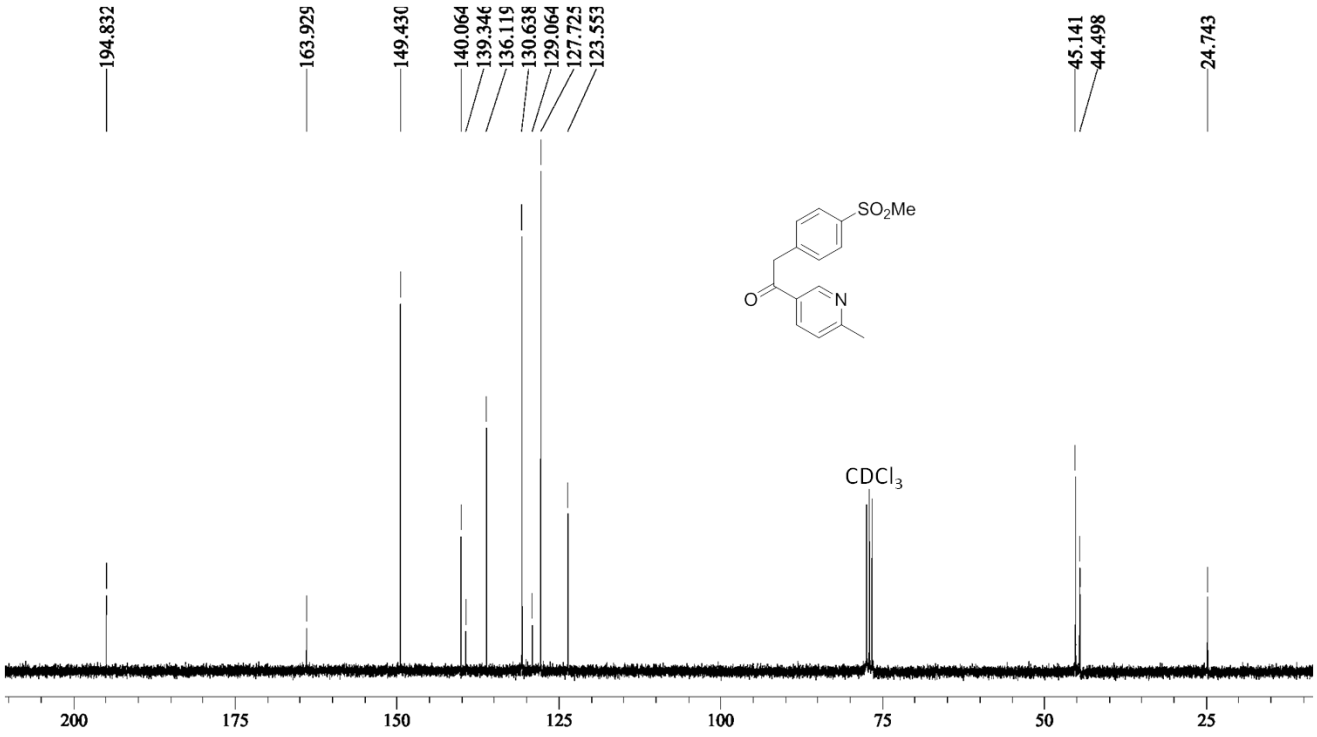


1-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl] ethanone (1)

^{1}H NMR ($CDCl_3$, 300 MHz)

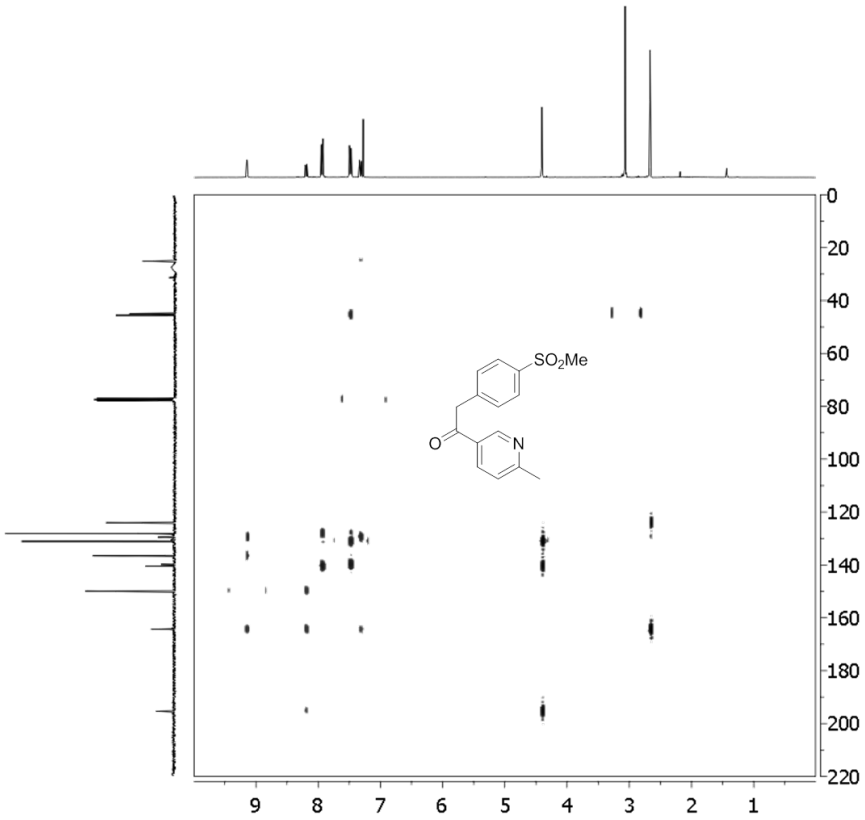


^{13}C NMR ($CDCl_3$, 75 MHz)



1-(6-methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl] ethanone (1)

HMBC ($CDCl_3$)



Significative portion of the HMBC spectra of compound **1**