Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

A Practical Two-Step Synthesis of Imidazo[1,2-*a*]pyridines from *N*-(prop-2-yn-1-yl)pyridin-2-amines

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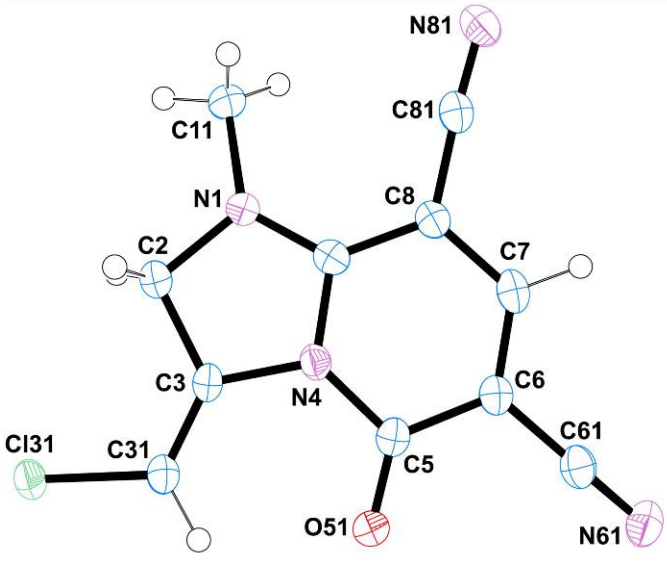
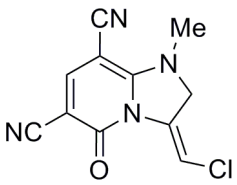
X-Ray analysis for compound 3a





3a

X-ray molecular structure of (*E*)-3-(chloromethylene)-1-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (**3a**) showing the atomic numbering scheme. Ellipsoids are drawn at the 50% probability level for non-H atoms, and the H atoms are denote.

Synthesis

Experimental Part

General Methods. Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during work-ups and the removal of solvents was carried out under *vacuum* with a rotary evaporator. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck). Melting points were determined on a Kofler block and are uncorrected. IR spectra were obtained on a Perkin-Elmer Spectrum One spectrophotometer. ^{1}H NMR spectra were recorded with a Varian VXR-200S spectrometer, using tetramethylsilane as internal standard and ^{13}C NMR spectra were recorded with a Bruker WP-200-SY. All the assignments for protons and carbons were in agreement with 2D COSY, HSQC, HMBC, and 1D NOESY spectra. Elemental analyses were conducted on a Carlo Erba EA 1108 apparatus.

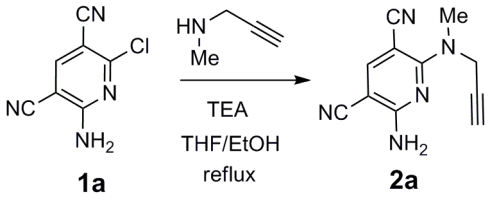
General procedure for the synthesis of 6-*N*-substituted 2-amino-3,5-dicyanopyridines (2a-c). The corresponding 6-amino-2-chloropyridine-3,5-dicarbonitrile (**1a** or **1b**) was suspended in a mixture of THF/EtOH (2:1, v:v). The corresponding amine, followed by triethylamine, were then added. The mixture was then heated under reflux. After cooling, the solvent was removed *in vacuum* and the resulting crude submitted to flash column chromatography, to give compounds **2a-c**.

General procedure for Sandmeyer reaction conditions (except for compound 3i). Isoamilnitrite (1.5 equiv) was added to a solution of $CuCl_2$ (1.5 equiv) in dry acetonitrile. The mixture was heated at 65 ºC. To this solution the corresponding 6-(prop-2-yn-1-ylamino)pyridine (1.0 equiv) in dry CH_3CN was added dropwise. The reaction mixture was heated at 65 ºC during the time indicated for each compound. The solution was cooled, acidified (HCl, 2N) to pH 2. The precipitate was collected, washed with water, dried and purified by flash chromatography to give pure compounds.

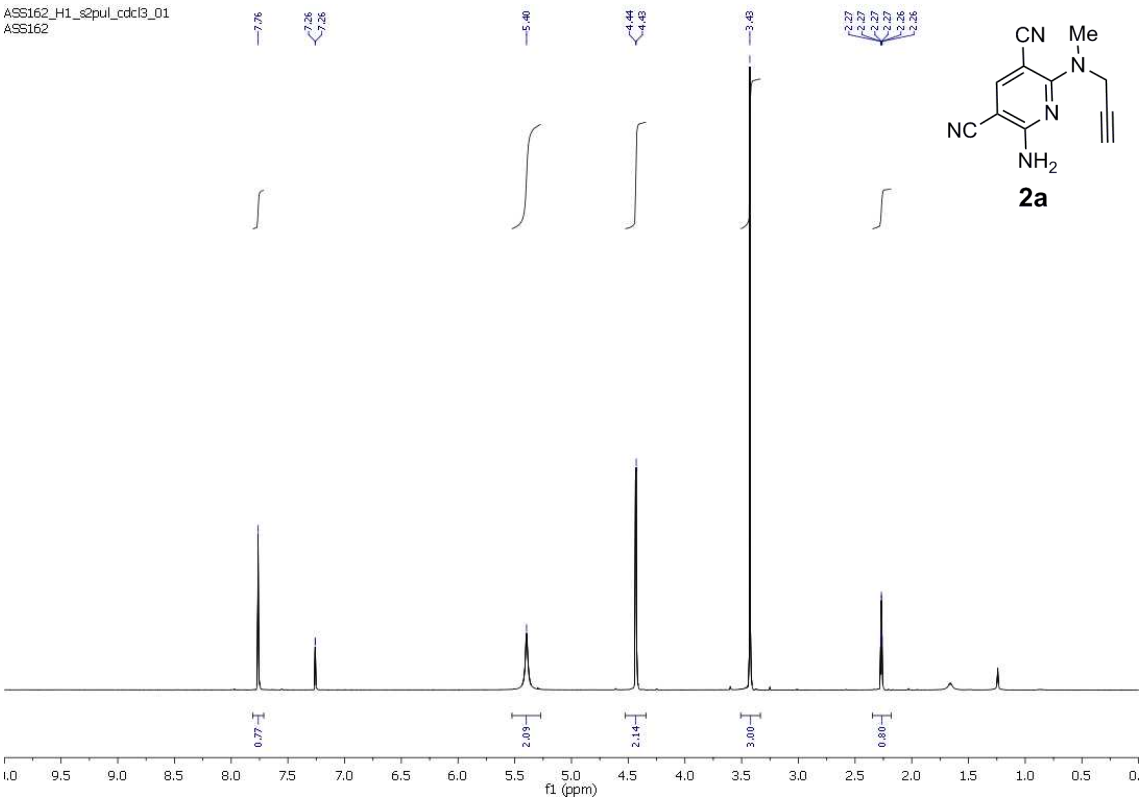
General procedure for transition metal promoted heterocyclization reaction. To a solution of the corresponding 6-(prop-2-yn-1-ylamino)pyridine (1.0 equiv) in dry acetonitrile was added a catalytic amount of the transition metal complex. The reaction mixture was heated at 65 ºC during the time indicated for each compound. When the reaction was complete (TLC analysis), the reaction mixture was diluted with water, extracted with EtOAc, dried over anhydrous sodium sulphate, filtered and the solvent

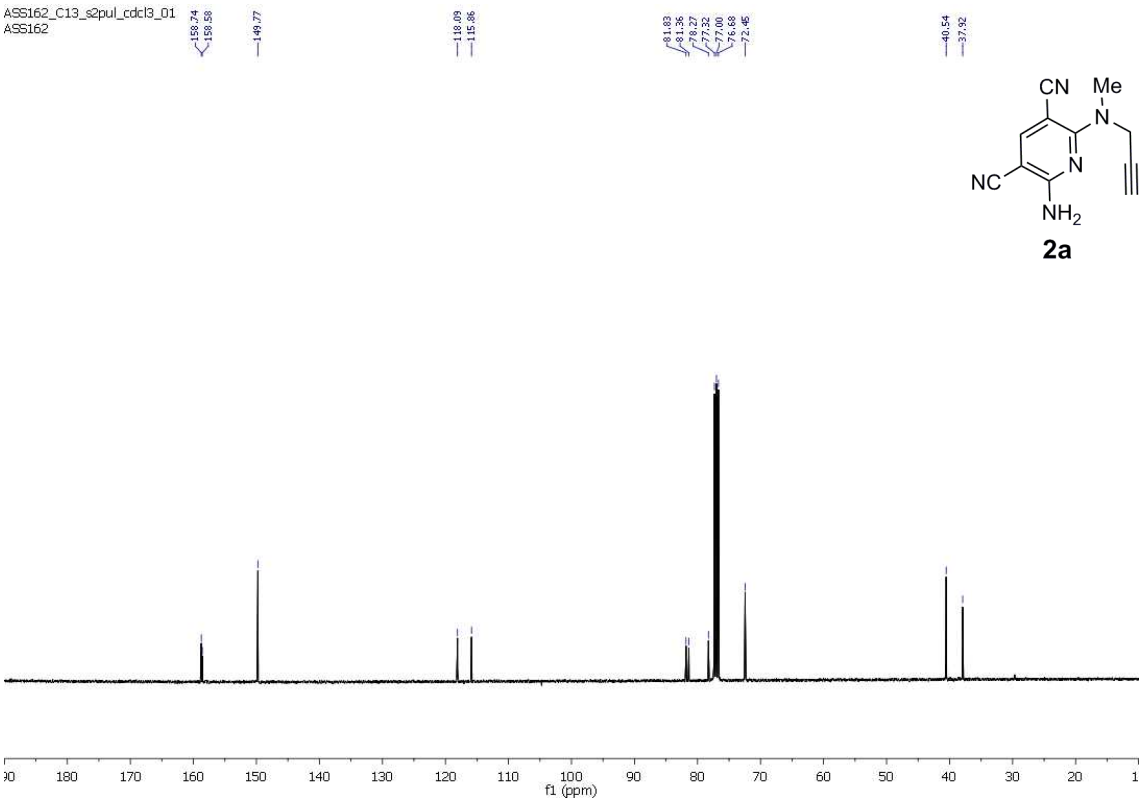
was evaporated. The resultant mixture was purified by flash chromatography to give pure compounds.

2-Amino-6-(methyl(prop-2-yn-1-yl)amino)pyridine-3,5-dicarbonitrile (2a).

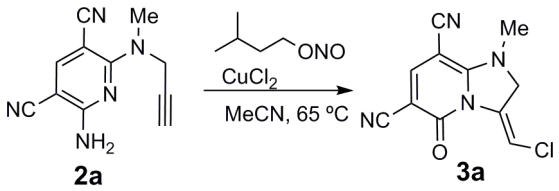


Following the general procedure, reaction of 6-amino-2-chloropyridine-3,5-dicarbonitrile **1a**[6a] (0.508 g, 2.85 mmol) with *N*-methylprop-2-yn-1-amine (0.285 mL, 3.42 mmol) and triethylamine (0.87 mL) in EtOH/THF (1/2, 15 mL), after 2 h, and column chromatography gave product **2a** (0.57 g, 95%) as a white solid: R*f*= 0.65 (CH_2C_2/EtOAc, 10/1, v/v): mp 169-171 ºC; IR (KBr) ν 3426, 3337, 3267, 3234, 2210, 1649, 1603, 1541, 1502, 1483, 1413, 1290 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H, CH4), 5.40 (br s, 1H, NH_2), 4.43 (d, J = 2.4 Hz, 2H, CH_2), 3.43 (s, 3H, CH_3), 2.27 (t, J = 2.4 Hz, 1H, C≡CH); ^{13}C NMR (100 MHz, DMO-d_6) δ 158.8 (C6), 158.6 (C2), 149.8 (C4), 118.1, 115.9 (2xCN), 81.8, 81.4 (C3, C5), 78.3 (*C*≡), 72.5 (*C*H≡), 40.5 (CH_2), 37.9 (CH_3); MS (EI) *m*/*z* (%): 196 (24) $[M\text{-}Me]^+$, 210 (100) $[M\text{-}H]^+$, 211 (38) $[M]^+$. Anal. Calcd. for $C_{11}H_9N_5$: C, 62.55; H, 4.29; N, 33.16. Found: C, 62.49; H, 4.42; N, 32.97.

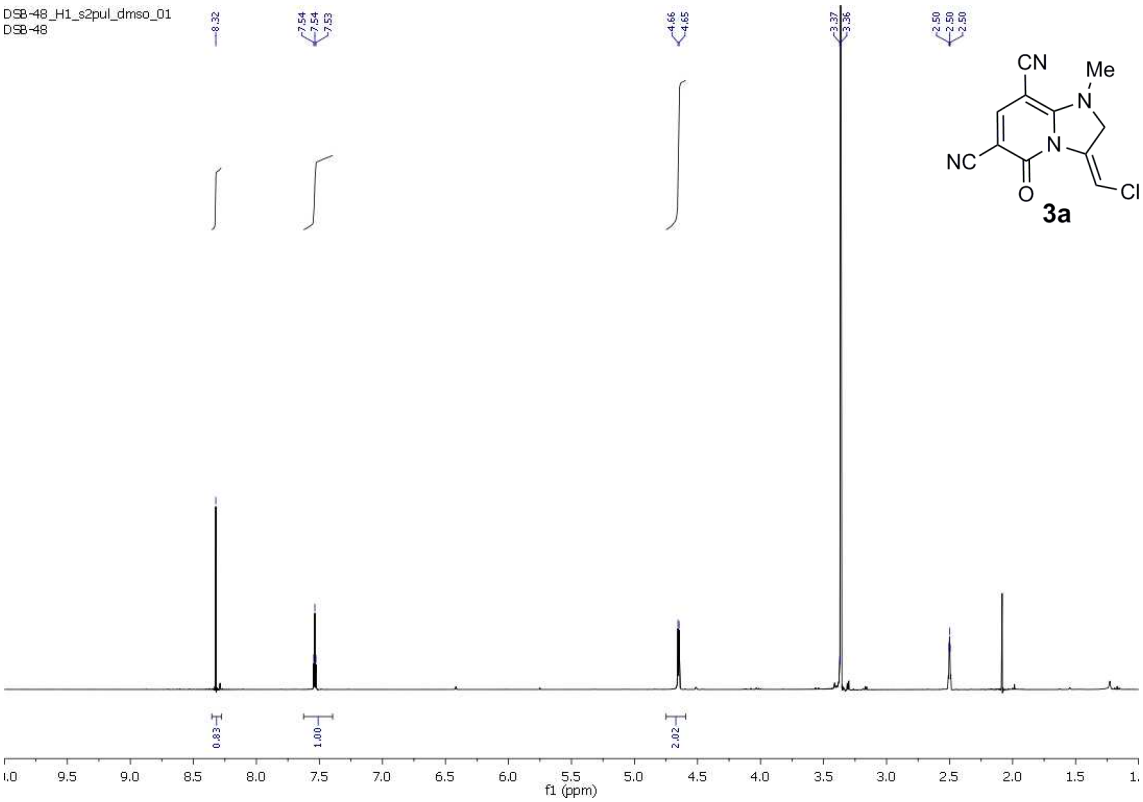




(*E*)-3-(Chloromethylene)-1-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (3a).



Following the general procedure, reaction of 2-amino-6-(methyl(prop-2-yn-1-yl)amino)pyridine-3,5-dicarbonitrile **2a** (140.8 mg, 0.67 mmol), $CuCl_2$ (114.0 mg, 0.79 mmol) and isoamyl nitrite (0.14 mL, 1.01 mmol) in anhydrous acetonitrile (8 mL), after 15 min reaction time, and column chromatography (hexane/EtOAc, 1/1, v/v), gave compound **3a** (116.9 mg, 62%) as a green solid, which was recrystallized from acetone: mp dec >250 ºC; IR (KBr) ν_{max} 3152, 2852, 2227, 2212, 1674, 1607, 1577, 1479, 1417, 1361, 1302, 1276, 1258, 1209, 1096 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H, H-8) 7.54 (t, J = 3.6Hz, 1H, H-4); 4.65 (d, J = 3.6Hz, 2H, H-2); 3.36 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.6 (C-9a), 155.3 (C-6), 151.4 (C-8), 134.1 (C-3), 116.0 (CN C-9), 115.7 (CN C-7), 106.0 (C-4), 88.8 (C-7), 69.6 (C-9), 55.5 (C-2), 33.5 (NCH_3); MS (EI) *m/z*: 264 $(M)^+$, 211$(M\text{-}Cl)^+$, 163; MS (ESI)**:** 285 $(M+K)^+$, 247 $(M+H)^+$. Anal. Calcd. for $C_{11}H_7N_4OCl$: C, 53.56; H, 2.86; N, 22.71; Cl, 14.37. Found: C, 53.37; H, 3.04; N, 22.39; Cl, 14.00.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Me
N
N
NC
O
Cl
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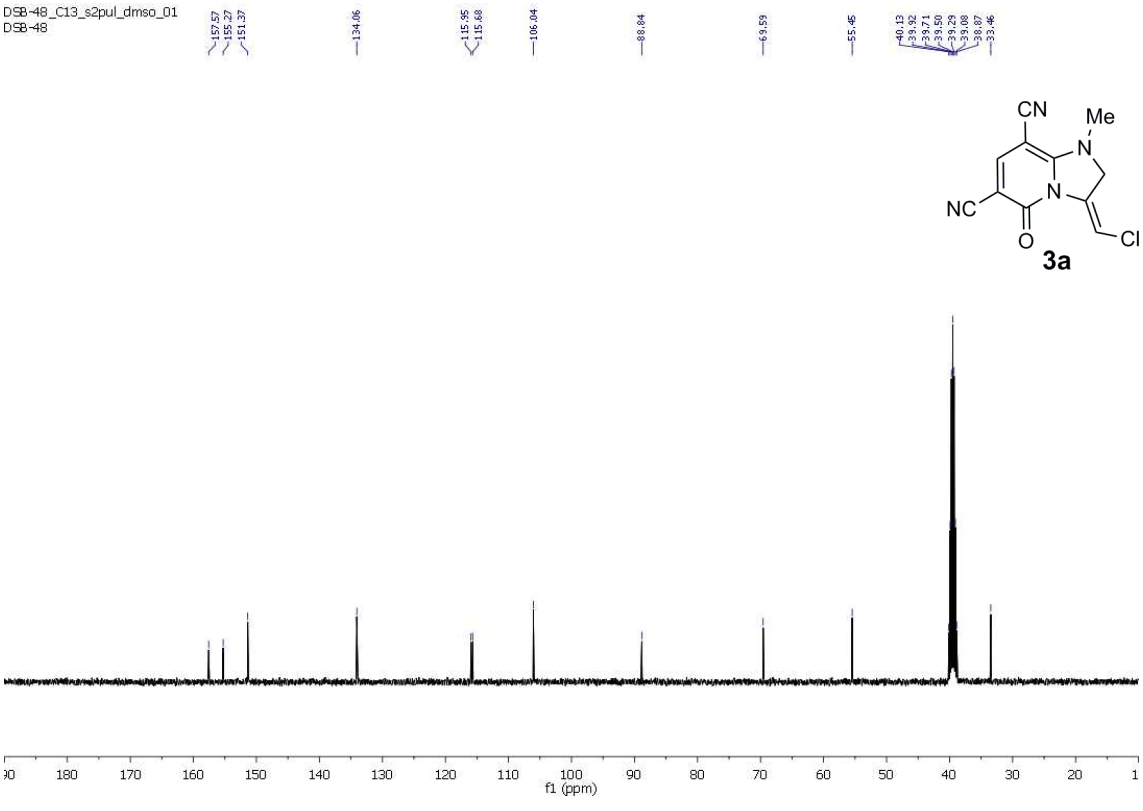
f1 (ppm)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55.45
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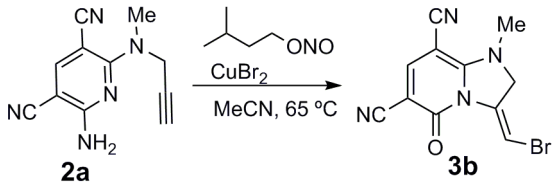
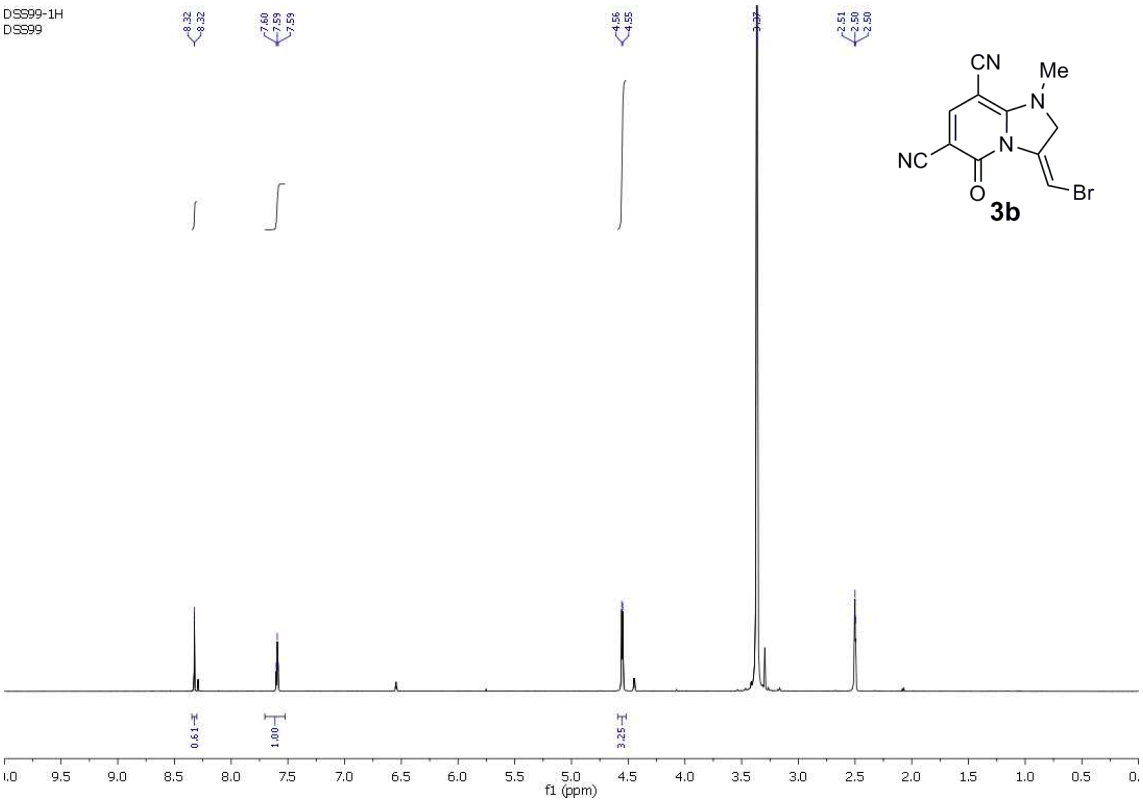
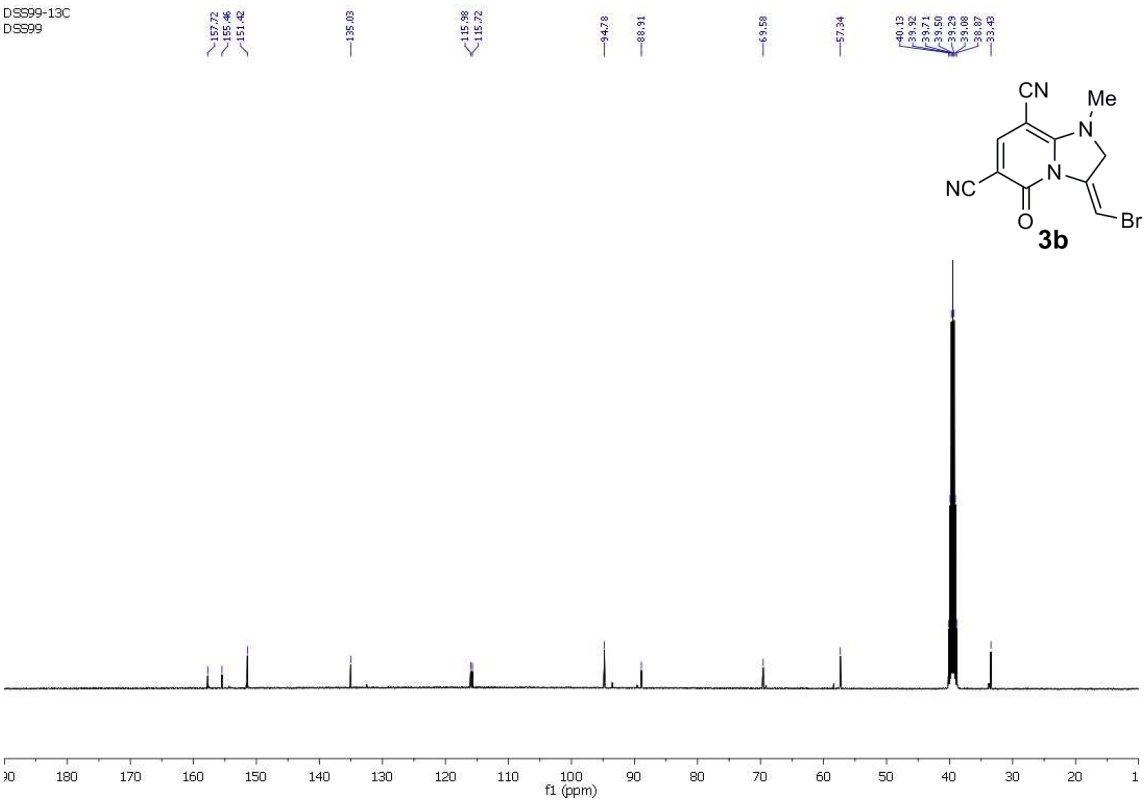
39.92
39.71
39.50
39.29
39.08
38.87
33.46
CN
Me
N
N
NC
O
Cl
3a
f1 (ppm)

(*E*)-3-(Bromomethylene)-1-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (3b).

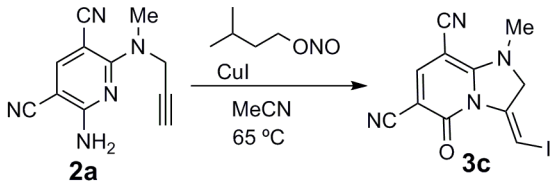


Following the general procedure, reaction of 2-amino-6-(methyl(prop-2-yn-1-yl)amino)pyridine-3,5-dicarbonitrile **2a** (75 mg, 0.36 mmol), $CuBr_2$ (95 mg, 0.43 mmol) and isoamyl nitrite (72 µL, 0.53 mmol) in anhydrous acetonitrile (5 mL), after 20 min. reaction time, and column chromatography (hexane/EtOAc, 1/1, v/v), gave compound **3b** (69 mg, 63%) as a solid: mp 230-2 ºC; IR (KBr) ν_{max} 3436, 3153, 2224, 2211, 1672, 1607, 1575, 1476, 1300, 1272, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H, CH=CCN), 7.59 (t, 1H, J = 3.5 Hz, CHBr), 4.55 (d, 2H, J = 3.5 Hz, CH_2), 3.36 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 155.5 (C=O, C=*C*NN), 151.4 (*C*H=CCN), 135.0 (*C*=CHI), 116.0, 115.7 (2CN), 94.8 (C=*C*HCl), 88.9, 69.6 (2*C*CN), 57.3 (CH_2), 33.4 (CH_3); MS (EI) *m/z*: 292, 290 $(M)^+$, 211, 168, 89; MS (ESI) *m/z*: 293.0, 291.0 $(M+H)^+$. Anal. Calcd. for $C_{11}H_7BrN_4O$: C, 45.39; H, 2.42; N, 19.25; Br, 27.45. Found: C, 45.18; H, 2.19; N, 19.06; Br, 27.12.



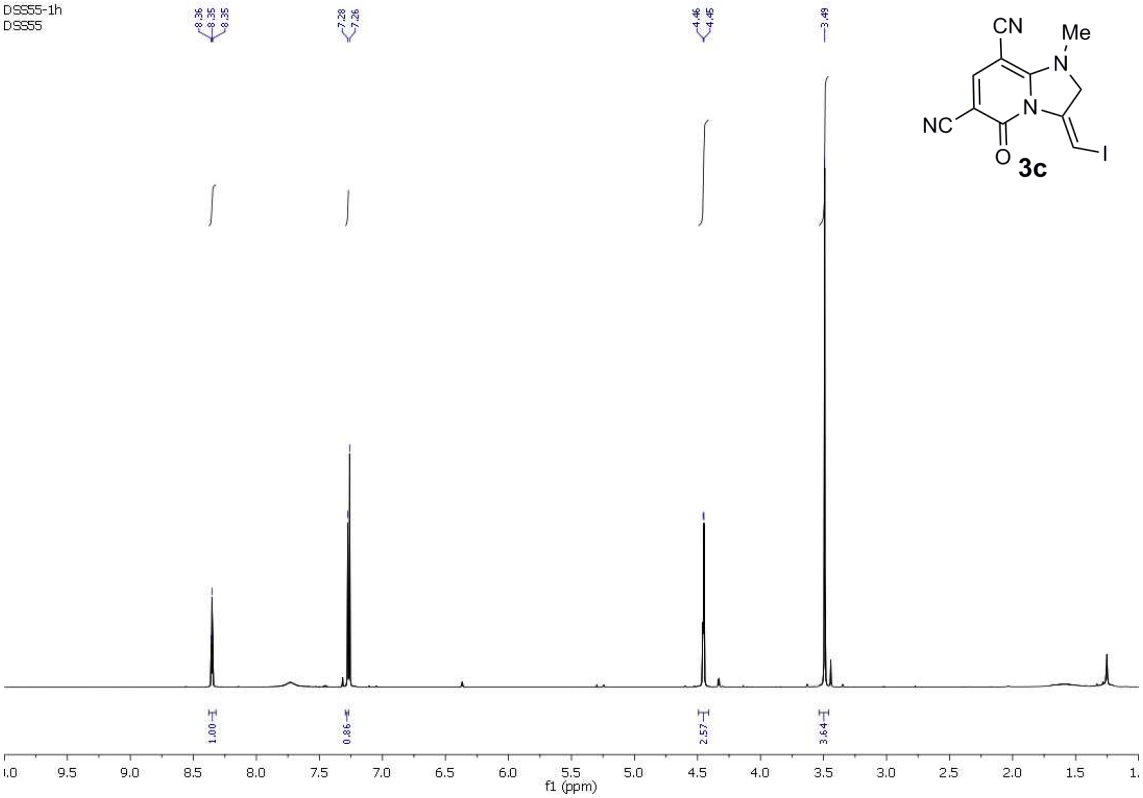


(*E*)-3-(Iodomethylene)-1-methyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (3c).



Sandmeyer reaction conditions. Following the general procedure, reaction of 2-amino-6-(methyl(prop-2-yn-1-yl)amino)pyridine-3,5-dicarbonitrile **2a** (75 mg, 0.36 mmol), CuI (81 mg, 0.43 mmol) and isoamyl nitrite (72 µL, 0.53 mmol) in anhydrous acetonitrile (5 mL), after 45 min, and column chromatography (hexane/EtOAc, 1/1, v/v), gave compound **3c** (49 mg, 41%) as a solid.

NIS. To a solution of 2-amino-6-(methyl(prop-2-ynyl)amino)pyridine-3,5-dicarbonitrile (**2a**) (50 mg, 0.24 mmol) in dry CH_2Cl_2 (3 mL) was added *N*-iodosuccinimide (64 mg, 0.28 mmol). The mixture was heated at 50ºC for 1 hour and a half. The solvent was removed by evaporation, and the crude was purified by flash chromatography (hexane/EtOAc, 7/3, v/v) to yield compound **3c** (54 mg, 68%) as a solid: mp decomp. 185 ºC; IR (KBr) ν_{max} 3436, 3282, 2202, 1639, 1585, 1471, 1313, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (t, 1H, *J* = 3.2 Hz, CHI), 7.28 (s, 1H, CH=CCN), 4.45 (d, 2H, *J* = 2.9 Hz, CH_2), 3.49 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 153.6 (C=O, C=*C*NN), 144.3 (*C*H=CCN), 135.3 (*C*=CHI), 116.2, 115.2 (2CN), 92.2 (*C*CN), 69.9 (C=*C*HI), 65.4 (*C*CN), 61.3 (CH_2), 34.2 (CH_3); MS (EI) *m/z*: 337 $(M)^+$, 210, 194; MS (ESI) *m/z*: 338.0 $(M+H)^+$. Anal. Calcd. for $C_{11}H_7IN_4O$: C, 39.08; H, 2.09; N, 16.57. Found: C, 39.31; H, 2.35; N, 16.73.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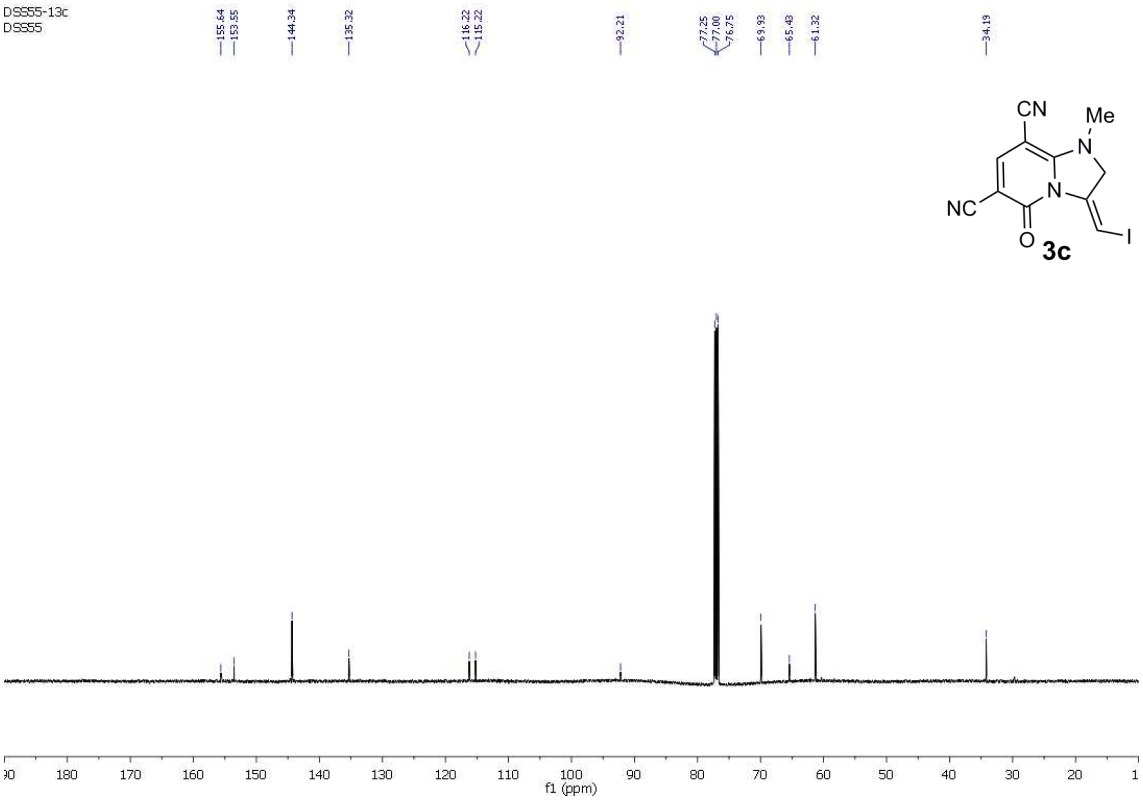
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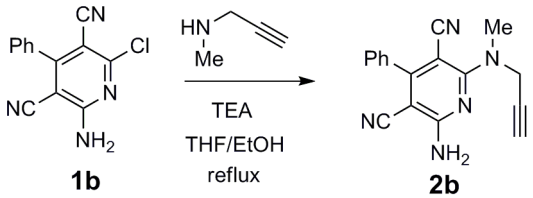
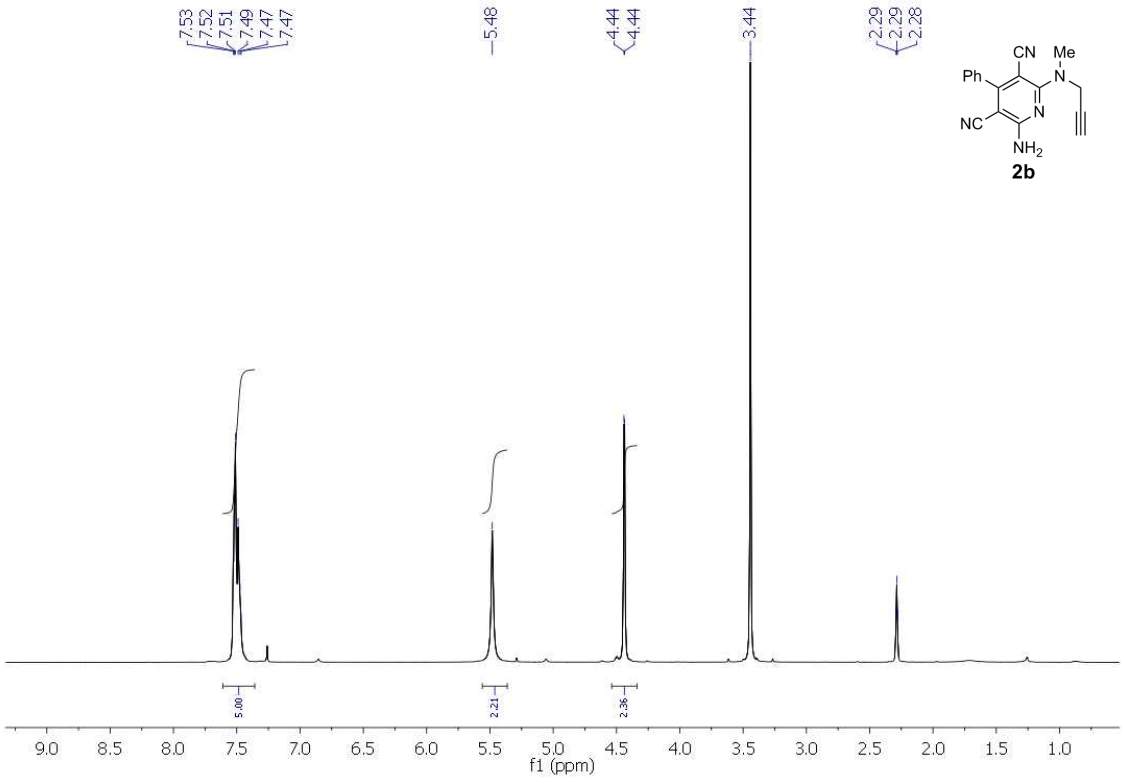
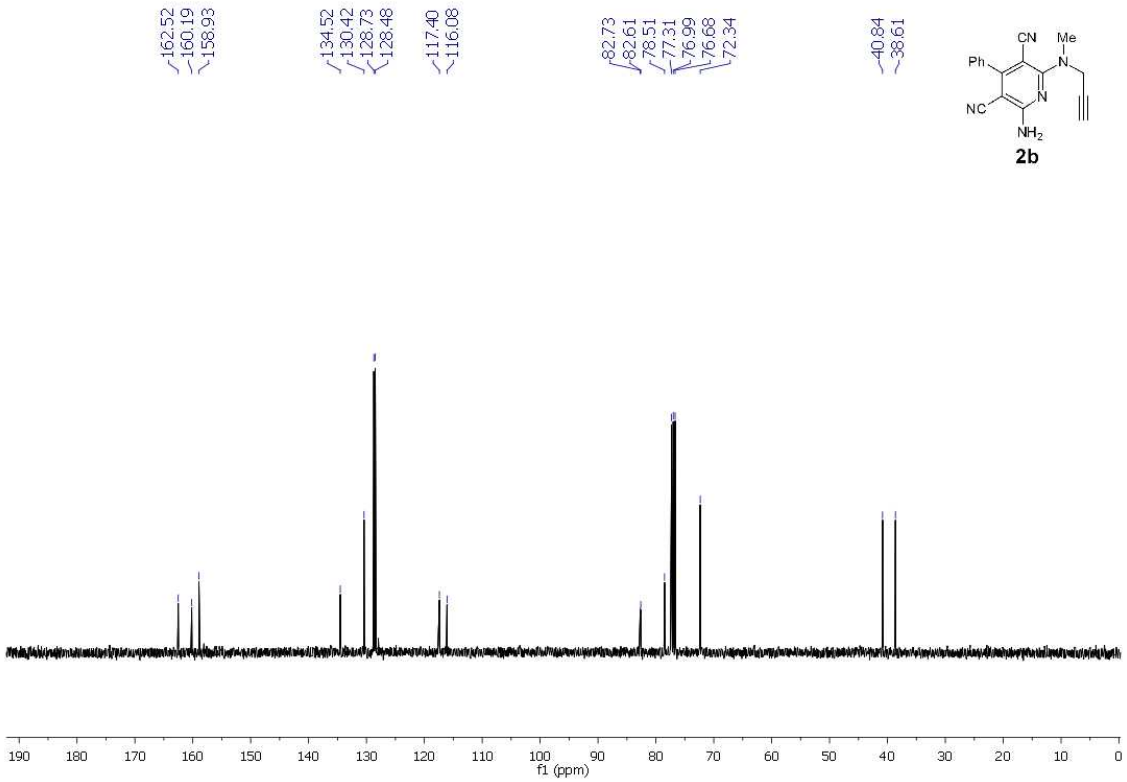
65.48
61.32
34.19
CN
Me
N
N
NC
O
I
3c
f1 (ppm)

2-Amino-6-(methyl(prop-2-yn-1-yl)amino)-4-phenylpyridine-3,5-dicarbonitrile (2b).

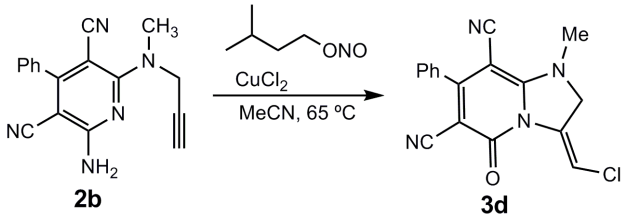


Following the general procedure, reaction of 6-amino-2-chloro-4-phynelpyridine-3,5-dicarbonitrile **1b**[6b] (0.77 g, 3.03 mmol) with *N*-methylprop-2-yn-1-amine (0.3 mL, 3.63 mmol) and triethylamine (1.4 mL, 9.09 mmol) in EtOH/THF (1/2, 30 mL), after 1 h, and column chromatography (CH_2Cl_2/hexane, 70:30) gave product **2b** (0.83 g, 95 %) as a white solid: R*f*= 0.38 (CH_2C_2, 100%); mp 143-5 ºC; IR (KBr) ν 3487, 3360, 3267, 2209, 1630, 1586, 1559, 1532, 1511, 1411, 1397 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.47 (m, 5H, CH-ar), 5.48 (br s, 2H, NH_2), 4.44 (d, *J* = 2.2 Hz, 2H, CH_2), 3.44 (s, 3H, CH_3), 2.29 (t, *J* = 2.2 Hz, 1H, C≡CH); ^{13}C NMR (100 MHz, DMO-d_6) δ 162.5 (C4), 160.2 (C6), 158.9 (C2), 134.5 (C1'), 130.4 (C4'), 128.7 (2 x CH, Ph), 128.4 (2 x CH, Ph), 117.4, 116.0 (2xCN), 82.7, 82.6 (C3, C5), 78.5 (*C*≡), 72.3 (*C*H≡), 40.8 (CH_2), 38.6 (CH_3); MS (EI) *m*/*z* (%): 261 (44) $[M\text{-}CN]^+$, 272 (11) $[M\text{-}Me]^+$, 286 (100) $[M\text{-}H]^+$, 287 (37) $[M]^+$. Anal. Calcd. for $C_{17}H_{13}N_5$: C, 71.06; H, 4.56; N, 24.37. Found: C, 70.95; H, 4.37; N, 25.23.

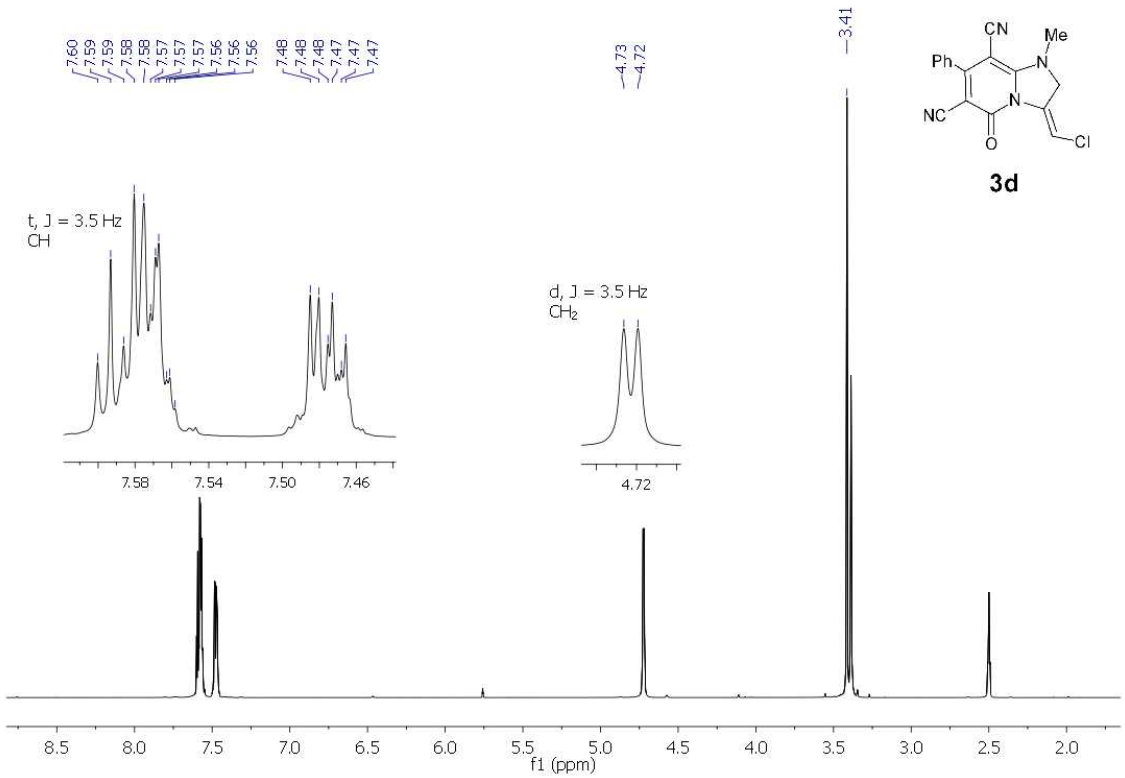




(*E*)-3-(Chloromethylene)-1-methyl-5-oxo-7-phenyl-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (3d).



Following the general procedure, reaction of 2-amino-6-(methyl(prop-2-yn-1-yl)amino)-4-phenylpyridine-3,5-dicarbonitrile **2b** (0.287 g, 1 mmol), $CuCl_2$ (0.16 g, 1.2 mmol) and isoamyl nitrite (0.2 mL, 1.5 mmol) in anhydrous acetonitrile (15 mL), after 15 min, and column chromatography (CH_2Cl_2/EtOAc, 40/1, v/v), gave compound **3d** (0.216 g, 67 %) as a solid: mp 277-280 ºC; IR (KBr) ν 3132, 2213, 1674, 1663, 1606, 1539, 1465, 1275 cm^{-1}; 1H NMR (400 MHz, DMSO-d_6) δ 7.59 (t, H, J = 3.5 Hz, CH), 7.55-7.58 (m, 3H), 7.45-7-50 (m, 2H), 4.72 (d, 2H, J = 3.5 Hz, CH_2), 3.41 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.19 (C), 157.75 (C), 155.34 (C), 134.60 (C), 134.19 (C), 131.06 (C4'), 129.24 (2 x CH), 128.38 (2 x CHar), 116.01 (C), 115.91 (C), 106.55 (CH), 90.39 (C), 72.02 (C), 56.27 (CH_2), 34.48 (N-CH_3); MS (EI) *m/z* (%): 287 (100) $[M-Cl]^+$, 322 (26) $[M]^+$.Anal. Calcd. for $C_{17}H_{11}ClN_4O$ (322.06): C, 63.26; H, 3.44; Cl, 10.98; N, 17.36. Found: 63.41; H, 3.65; Cl, 11.13; N, 17.89.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4.72
3.41
CN
Me
Ph
N
NC
N
O
Cl
3d
t, J = 3.5 Hz
CH
d, J = 3.5 Hz
CH2
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7.50
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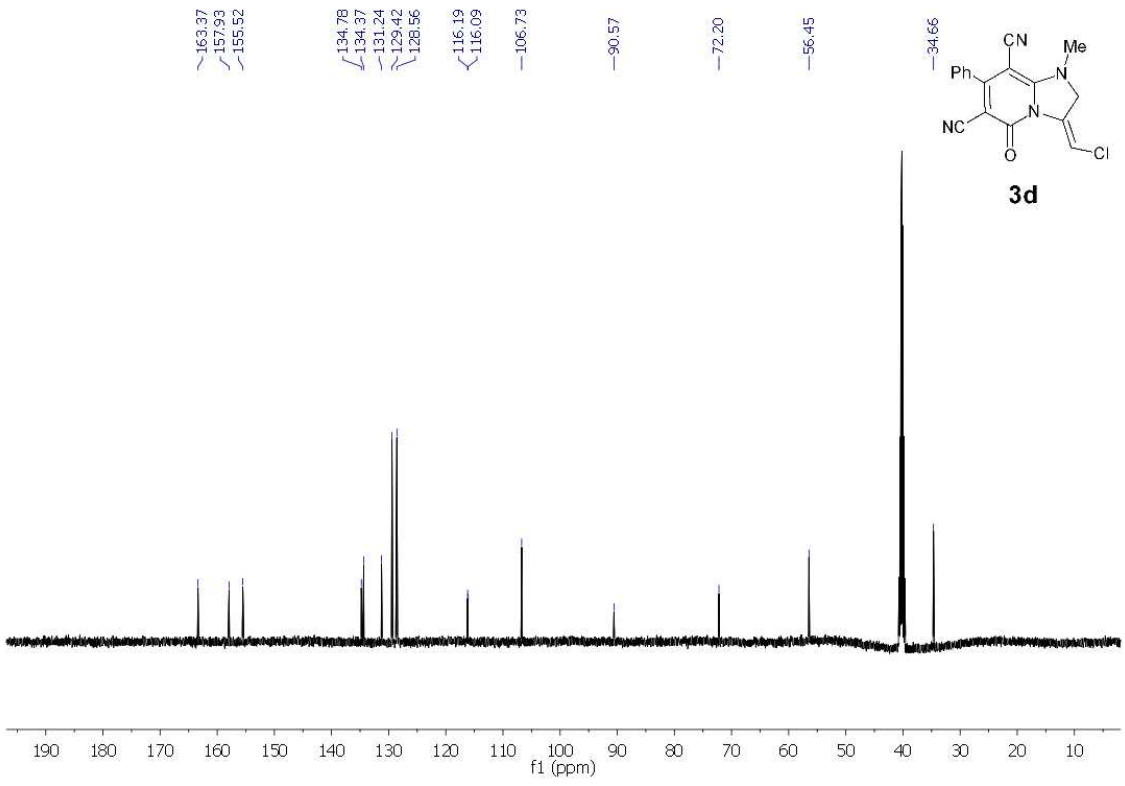
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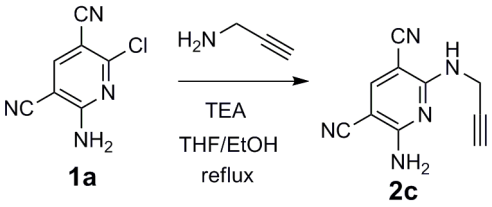
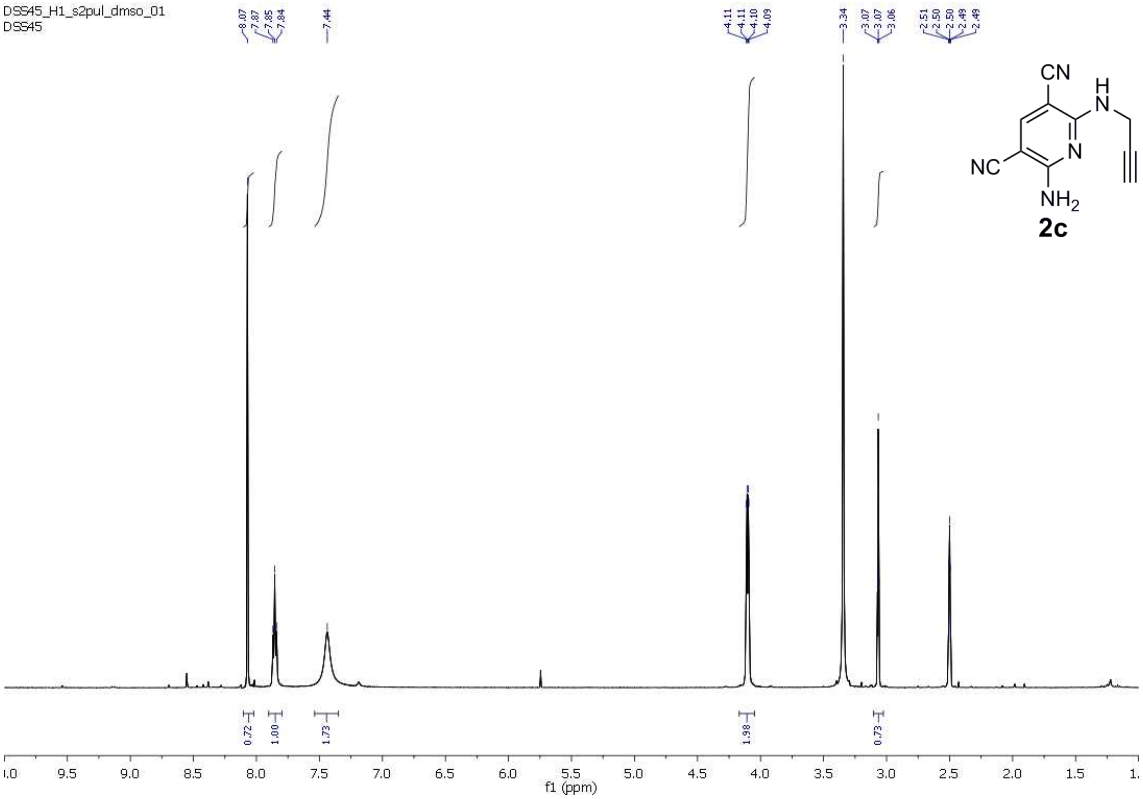
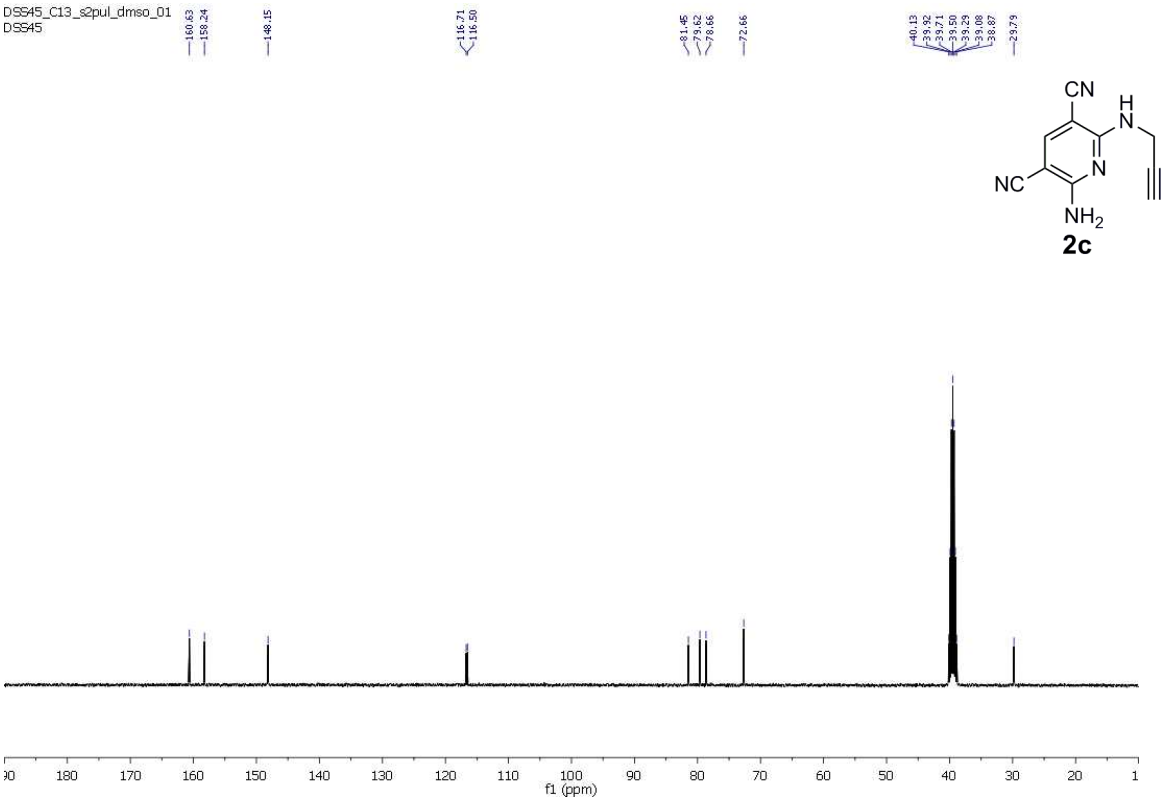
O
Cl
3d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

2-Amino-6-(prop-2-ynylamino)pyridine-3,5-dicarbonitrile (2c).

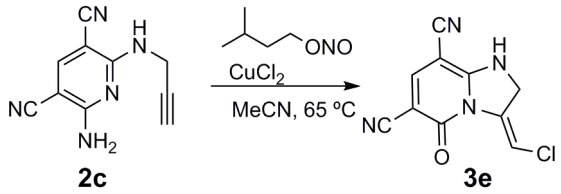


Following the general procedure, reaction of 6-amino-2-chloropyridine-3,5-dicarbonitrile **1a**[6a] (0.4 g, 2.25 mmol) with prop-2-yn-1-amine (0.17 mL, 2.70 mmol) and triethylamine (0.68 mL, 4.49 mmol) in EtOH/THF (1/2, 15 mL), after 3 h, and column chromatography (hexane/EtOAc, 7/3, v/v) gave product **2c** (402 mg, 91%) as a solid: mp 215-8 ºC; IR (KBr) ν_{max} 3449, 3340, 2212, 1632, 1605, 1567, 1512, 1484 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H, Ar), 7.84 (t, 1H, J = 5.6 Hz, NH), 7.42 (s, 2H, NH_2), 4.10-4.07 (m, 2H, CH_2N), 3.05 (t, 1H, J = 2.3, C≡CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 158.3, 148.2 (3Ar), 116.7, 116.5 (2CN), 81.5, 79.6, 78.7 (2Ar, *C*≡CH), 72.7 (C≡*C*H), 29.8 (CH_2N); MS (EI) *m/z*: 197 $(M)^+$, 196, 170, 169, 143, 89, 43, 31; MS (ESI) *m/z*: 198.0 $(M+H)^+$. Anal. Calcd. for $C_{10}H_7N_5$: C, 60.91; H, 3.58; N, 35.51. Found: C, 60.79; H, 3.80; N, 35.26.

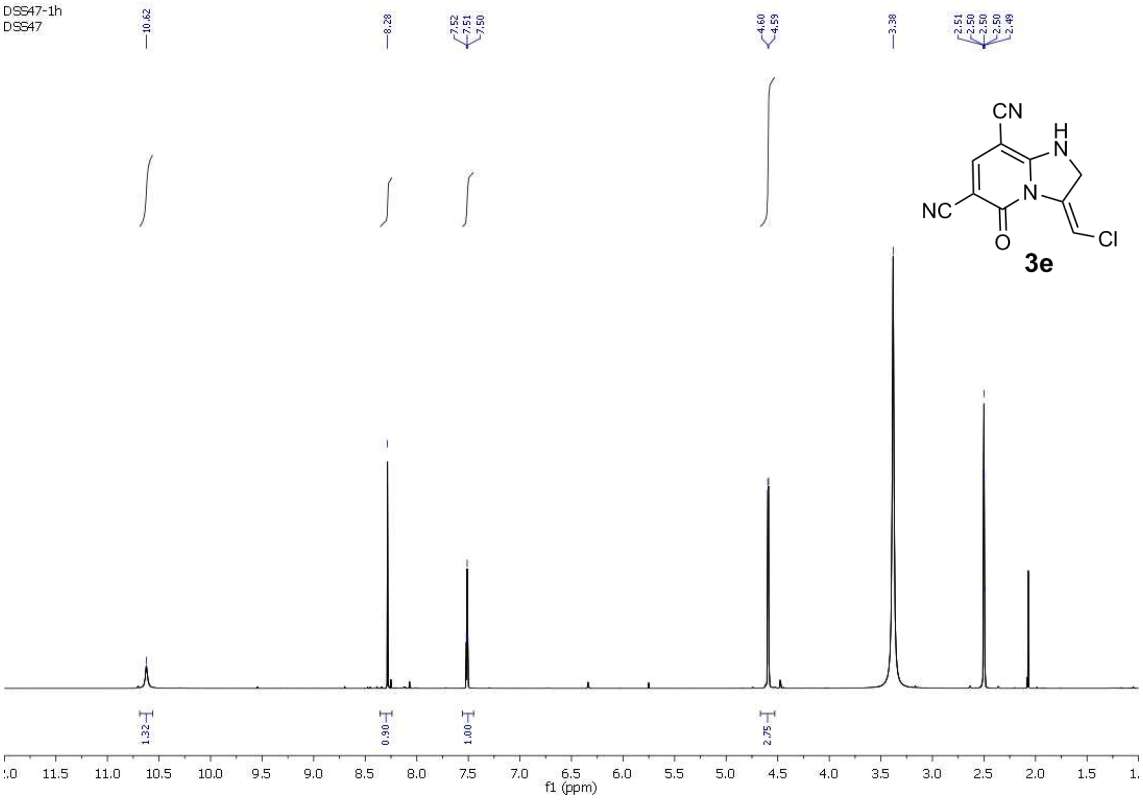




(*E*)-3-(Chloromethylene)-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (3e).



Following the general procedure, reaction of 2-amino-6-(prop-2-ynylamino)pyridine-3,5-dicarbonitrile **2c** (100 mg, 0.51 mmol), $CuCl_2$ (82 mg, 0.61 mmol) and isoamyl nitrite (0.1 mL, 0.76 mmol) in anhydrous acetonitrile (5 mL), after 30 min, and column chromatography (Hexane/AcOEt, 1/1, v/v), gave compound **3e** (65 mg, 55%) as a solid: mp >320 ºC; IR (KBr) ν_{max} 3202, 3136, 2232, 2219, 1665, 1644, 1615, 1575, 1467, 1275, 1267 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H, NH), 8.27 (s, 1H, CH=CCN), 7.50 (t, 1H, J = 3.4 Hz, CHCl), 4.58 (d, 2H, J= 3.9 Hz, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 157.7 (C=O, C=*C*NN), 150.2 (*C*H=CCN), 136.2 (*C*=CHCl), 116.0, 114.9 (2CN), 105.9 (C=*C*HCl), 88.3, 70.0 (2*C*CN), 48.3 (CH_2); MS (EI) *m/z*: 232 $(M)^+$, 197, 169, 142, 89, 66; MS (ESI) *m/z*: 255.0 $(M+Na)^+$. Anal. Calcd. for $C_{10}H_5ClN_4O$: C, 51.63; H, 2.17; N, 24.08; Cl, 15.24. Found: C, 51.44; H, 2.43; N, 23.81; Cl, 15.31.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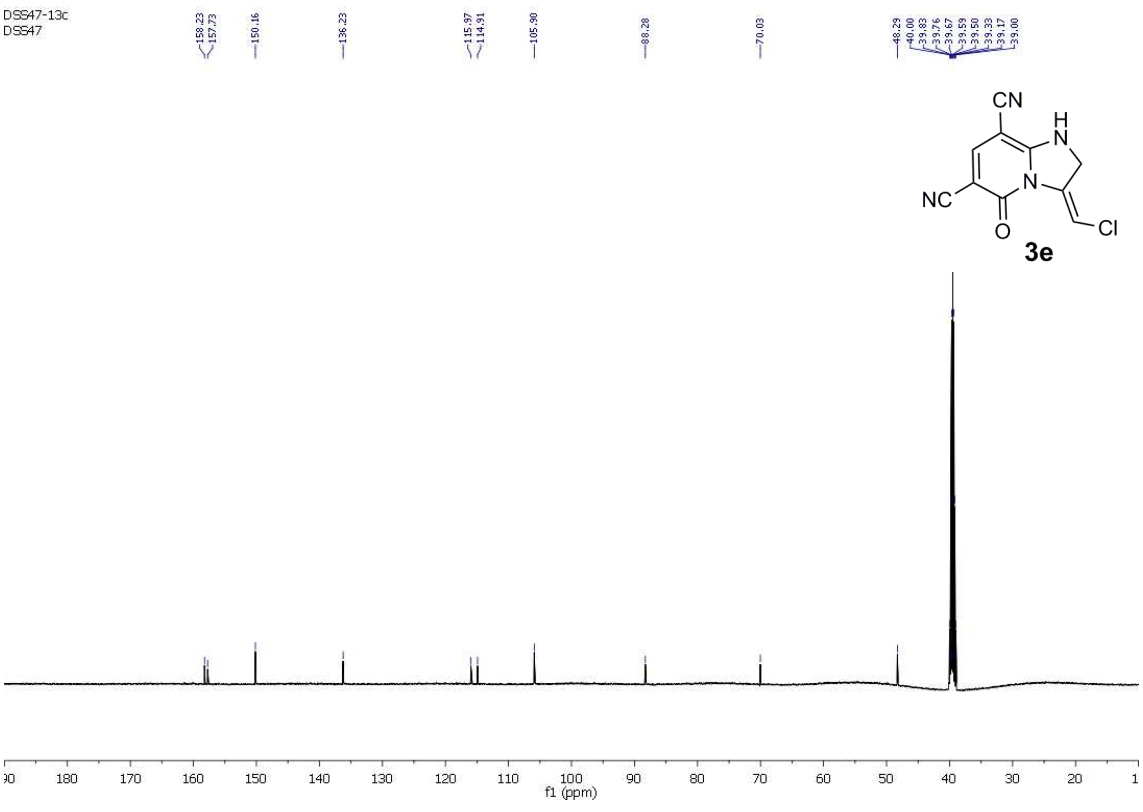
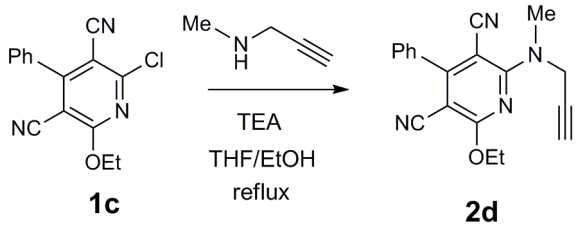
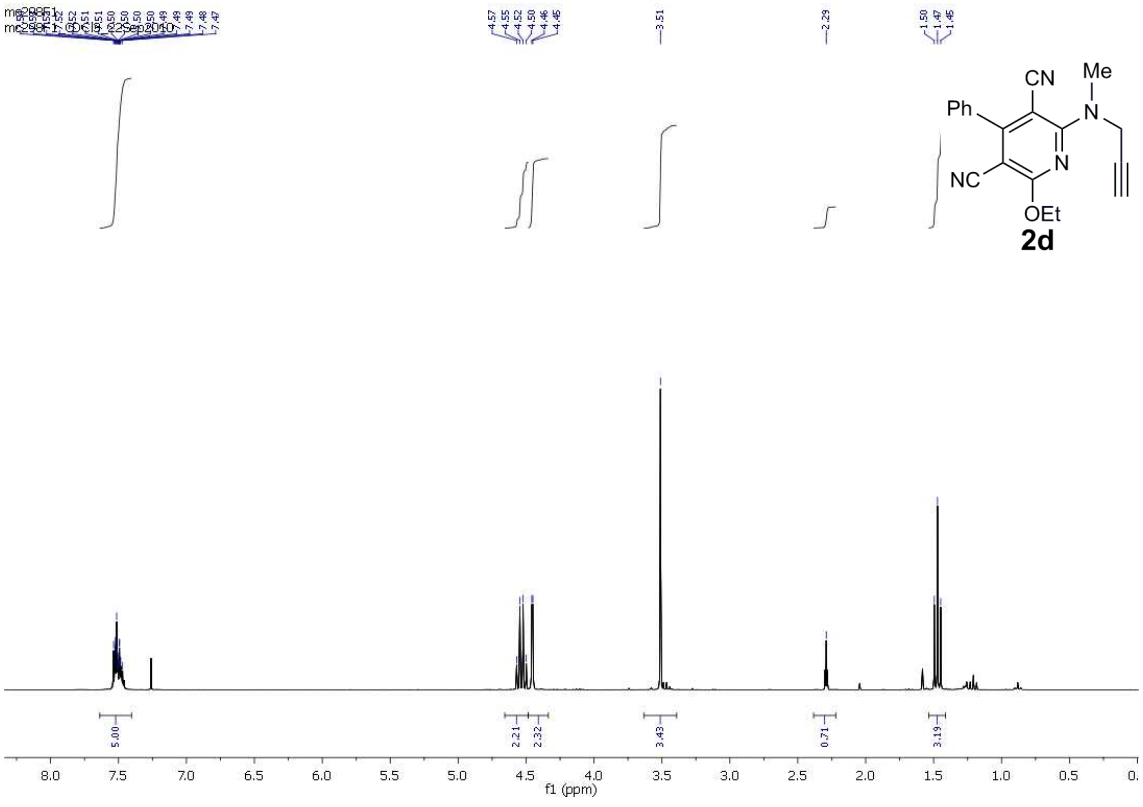
7.52
7.51
7.50
4.60
4.59
3.38
2.51
2.50
2.50
2.50
2.49
CN
H
N
N
NC
O
Cl
3e
1.32
0.90
1.00
2.75
f1 (ppm)

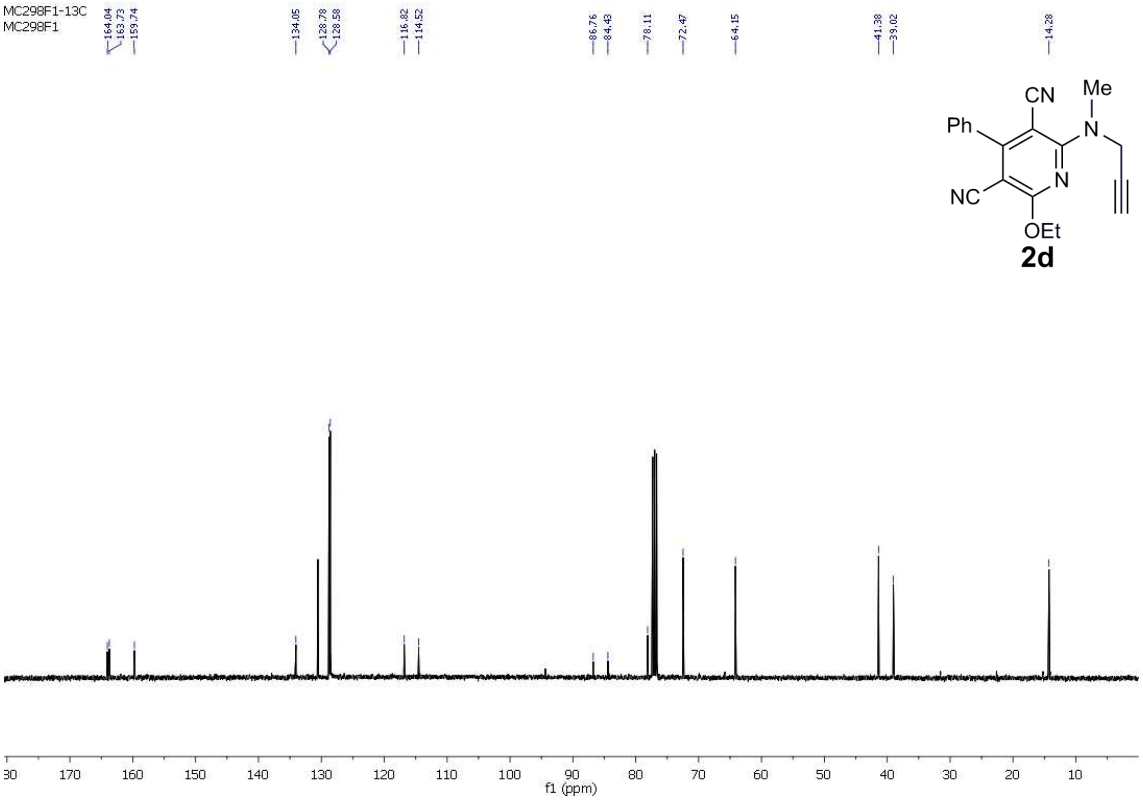

DSS47-13c
DSS47
159.23
157.73
150.16
136.23
115.97
114.91
105.90
88.28
70.03
48.29
40.00
39.83
39.76
39.67
39.59
39.50
39.33
39.17
39.00
CN
H
N
N
NC
O
Cl
3e
f1 (ppm)

2-Ethoxy-6-(methyl(prop-2-yn-1-yl)amino)-4-phenylpyridine-3,5-dicarbonitrile (2d)

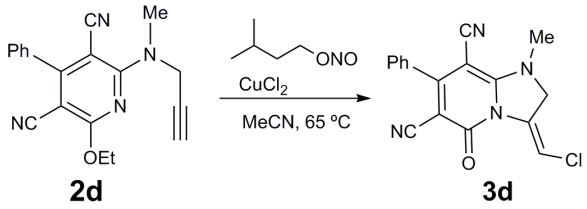


Following the general procedure, the reaction of 2-chloro-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **1c**[6c] (142 g, 0.5 mmol) with *N*-methylprop-2-yn-1-amine (63 µL, 0.75 mmol) and triethylamine (0.11 mL) in EtOH/THF (1/2, 10 mL), after 1 h, gave product **2d** (147 mg, 93 %) as white solid; mp 107-109 ºC; IR (KBr) ν_{max} 3283, 2984, 2220, 2210, 1583, 1567, 1544 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.51 (m, 5H, Ph), 4.53 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.45 (d, J = 2.4 Hz, 2H, CH_2), 3.51 (s, 3H, NCH_3), 2.29 (t, J = 2.4 Hz, 1H, C≡CH), 1.47 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0 (C2), 163.7 (C4), 159.7 (C6), 134.0 (C1'), 130.5 (C4'), 128.7 (2CH, Ph), 128.6 (2CH, Ph), 116.8 (CN), 114.5 (CN), 86.7 (C-CN), 84.4 (C-CN), 78.1 (C3''), 72.4 (C2''), 64.1 (OCH_2), 41.3 (CH_2), 39.0 (NCH_3), 14.2 (CH_3); MS (EI) *m/z*: 262 [M-C_4H_6, 57]$^+$, 273 [M- OC_2H_5, 57]$^+$, 273 [M-Et, 100]$^+$, 315 [M-H, 91]$^+$, 316 [M, 55]$^+$; MS (ESI) *m/z*: 317 [M+H]$^+$, 339 [M+Na]$^+$, 655 [2M+Na]$^+$; Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.34; H, 5.15; N, 17.75.



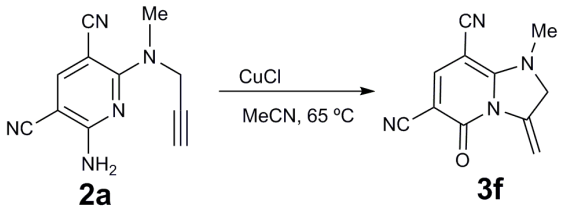


(*E*)-3-(Chloromethylene)-1-methyl-5-oxo-7-phenyl-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (3d)

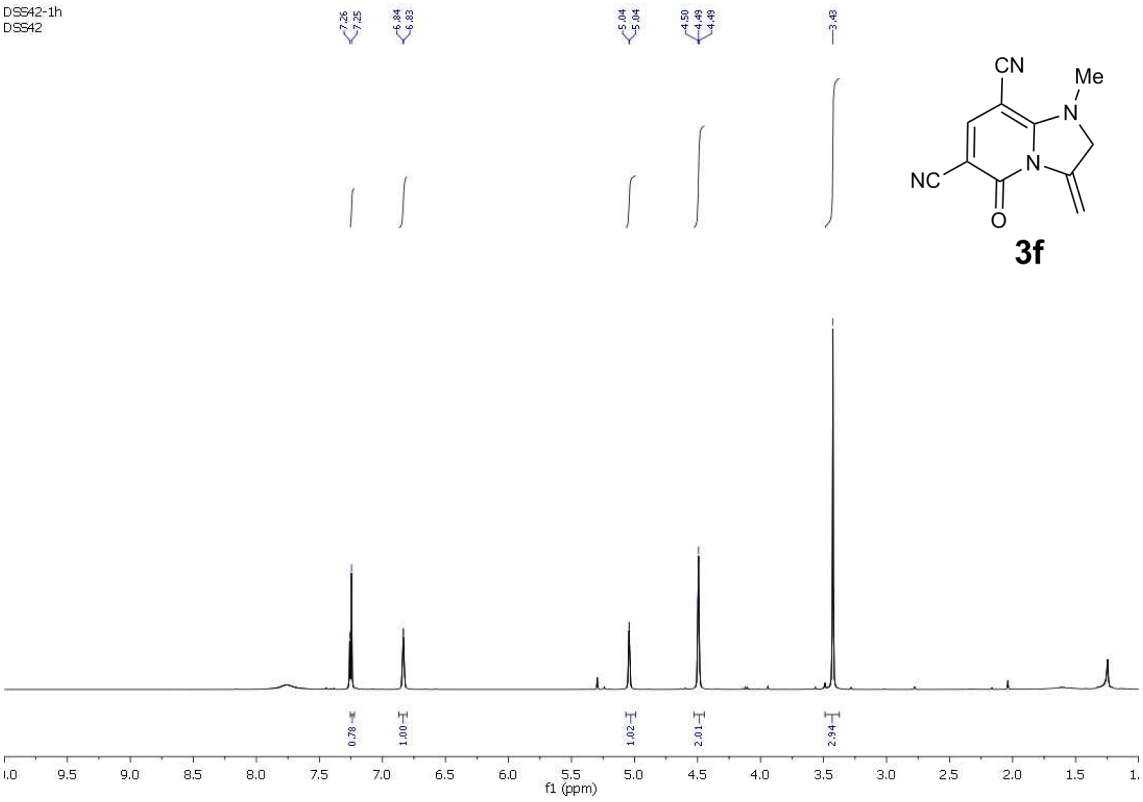


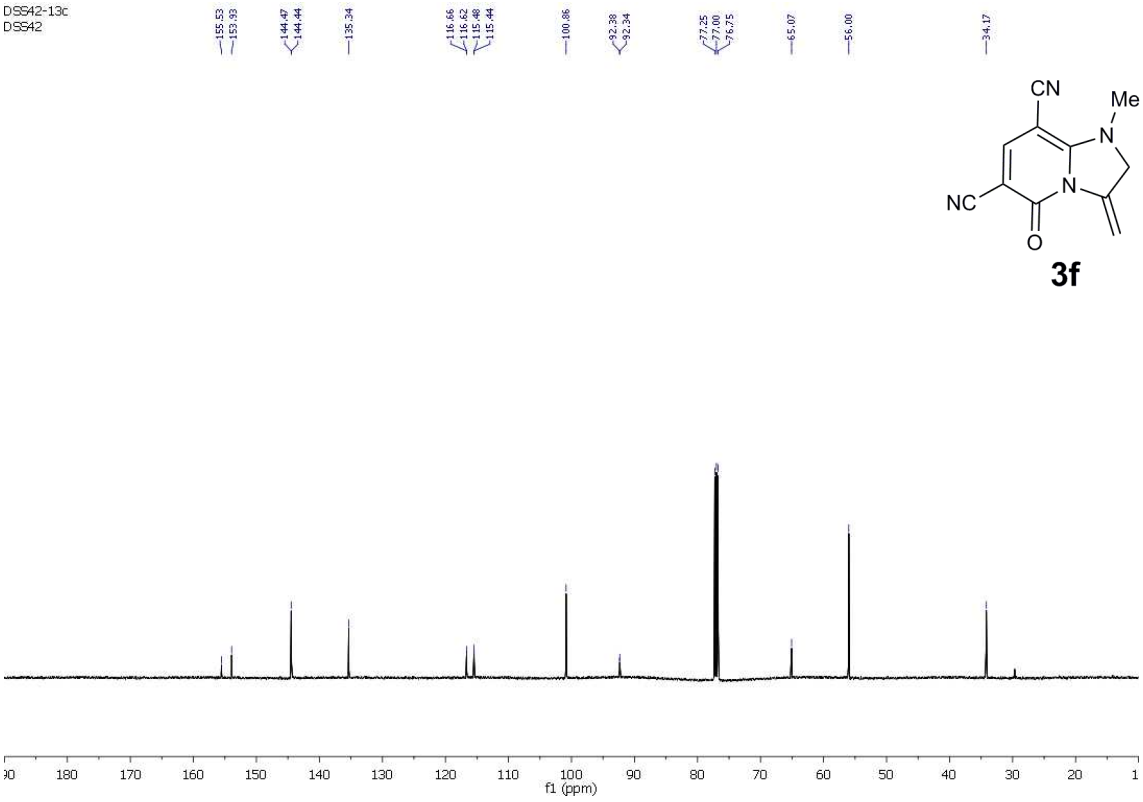
Following the general procedure, reaction of 2-ethoxy-6-(methyl(prop-2-yn-1-yl)amino)-4-phenylpyridine-3,5-dicarbonitrile **2d** (108 mg, 0.34 mmol), $CuCl_2$ (60 mg, 0.51 mmol) and isoamyl nitrite (0.10 mL, 0.51 mmol) in anhydrous acetonitrile (5 mL), after 18 h, and column chromatography (hexane/EtOAc, 1/1, v/v), gave compound **3d** (83 mg, 76 %) as white solid.

1-Methyl-3-methylene-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (3f)

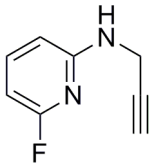


Following the general procedure, reaction of 2-amino-6-(methyl(prop-2-ynyl)amino)pyridine-3,5-dicarbonitrile **2a** (50 mg, 0.24 mmol) and CuCl (6 mg, 0.06 mmol) in anhydrous acetonitrile (5 mL), after 30 min. reaction time, and column chromatography (hexane/EtOAc, 1/1, v/v), gave compound **3f** (40 mg, 80%) as a solid: mp 183-5 ºC; IR (KBr) ν_{max} 3437, 3291, 2201, 1663, 1635, 1583, 1476, 1407, 1307, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 1H, CH=CCN), 6.83 (t, 1H, J = 3.0 Hz, C=CH_2), 5.04 (t, 1H, J = 2.7 Hz, C=CH_2), 4.49 (d, 2H, J = 3.0 Hz, CH_2N), 3.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 154.0 (C=O, C=*C*NN), 144.5 (*C*H=CCN), 135.3 (*C*=CH_2), 116.7, 115.5 (2CN), 100.9 (C=*C*H_2), 92.4, 65.1 (2*C*CN), 56.0 (CH_2), 34.2 (CH_3); MS (EI) *m/z*: 212 $(M)^+$, 211, 210, 196, 169; MS (ESI) *m/z*: 213.1 $(M+H)^+$. Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 62.08; H, 4.01; N, 26.52.

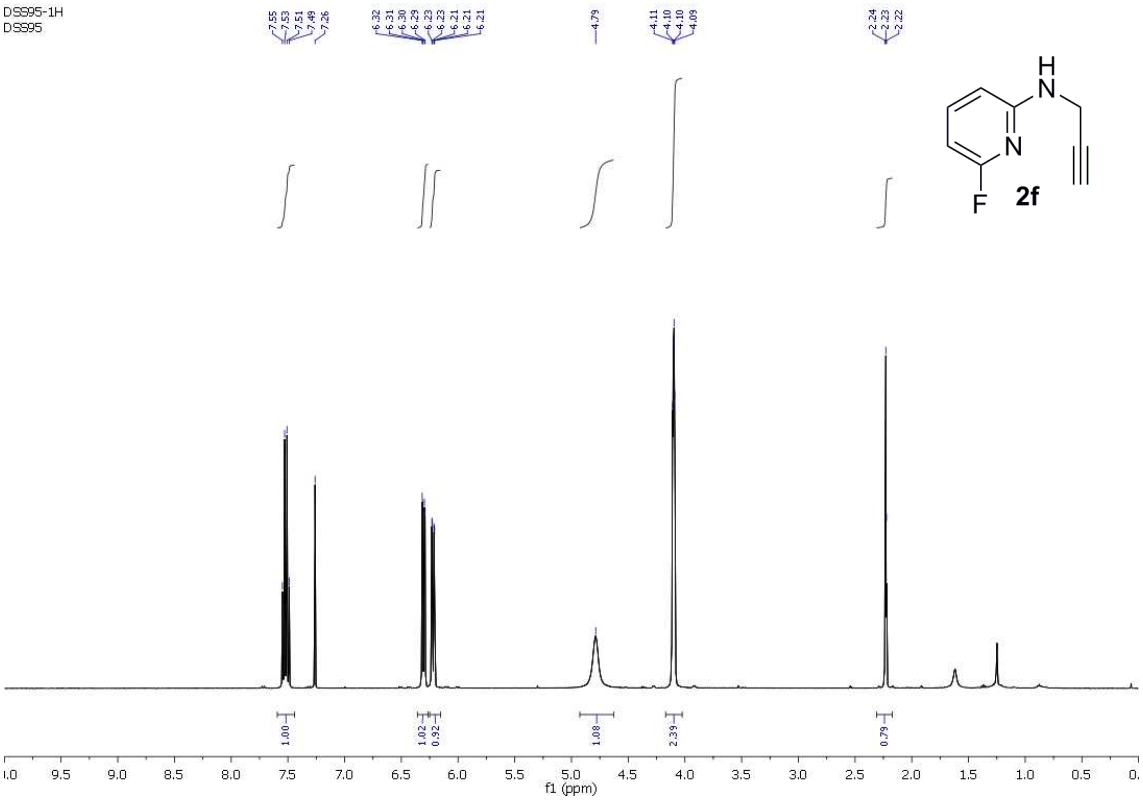




6-Fluoro-*N*-(prop-2-ynyl)pyridin-2-amine (2f).



In a 20 mL glass tube equipped with septa, 2,6-difluoropyridine (0.40 mL, 4.41 mmol), pyridine (1.10 mL,13.22 mmol) and prop-2-yn-1-amine (0.56 mL, 8.81 mmol) were added. The mixture was stirred for 30 seg, and then exposed to MW irradiation (250 W) at 125 ºC during 15 h. When the reaction was complete (TLC analysis), the reaction mixture was diluted in MeOH and evaporated. The resultant solid was purified by flash chromatography (Hexane/AcOEt, 9/1, v/v) to yield compound **2f** (605 mg, 92%) as a solid: mp 93-5 ºC; IR (KBr) ν_{max} 3293, 3265, 3089, 1622, 1609, 1584, 1542, 1458, 1437, 1335, 1226, 1129, 778, 664, 642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (q, 1H, J = 8.1 Hz, H-4), 6.30 (dd, 1H, J_1 = 8.1 Hz, J_2 = 2.3 Hz, H-3), 6.22 (dd, 1H, J_1 = 8.1 Hz, J_2 = 2.0 Hz, H-5), 4.79 (s, 1H, NH), 4.10 (d, 2H, J = 2.5 Hz, CH_2N), 2.23 (t, 1H, J = 2.5, C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J= 237.3 Hz, C-6), 156.9 (C-2), 141.8 (C-4), 103.4 (C-3), 96.8 (d, J= 35.9 Hz, C-5), 80.2 (*C*≡CH), 71.3 (C≡*C*H), 31.7 (CH_2N); MS (EI) *m/z*: 150 $(M)^+$, 149, 110, 97, 81, 43, 31; MS (ESI) *m/z*: 151.0 $(M+H)^+$. Anal. Calcd. for $C_8H_7FN_2$: C, 63.99; H, 4.70; N, 18.66. Found: C, 64.18; H, 4.99; N, 18.39.


DS995-1H
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7.53
7.51
7.49
7.26
6.32
6.31
6.30
6.29
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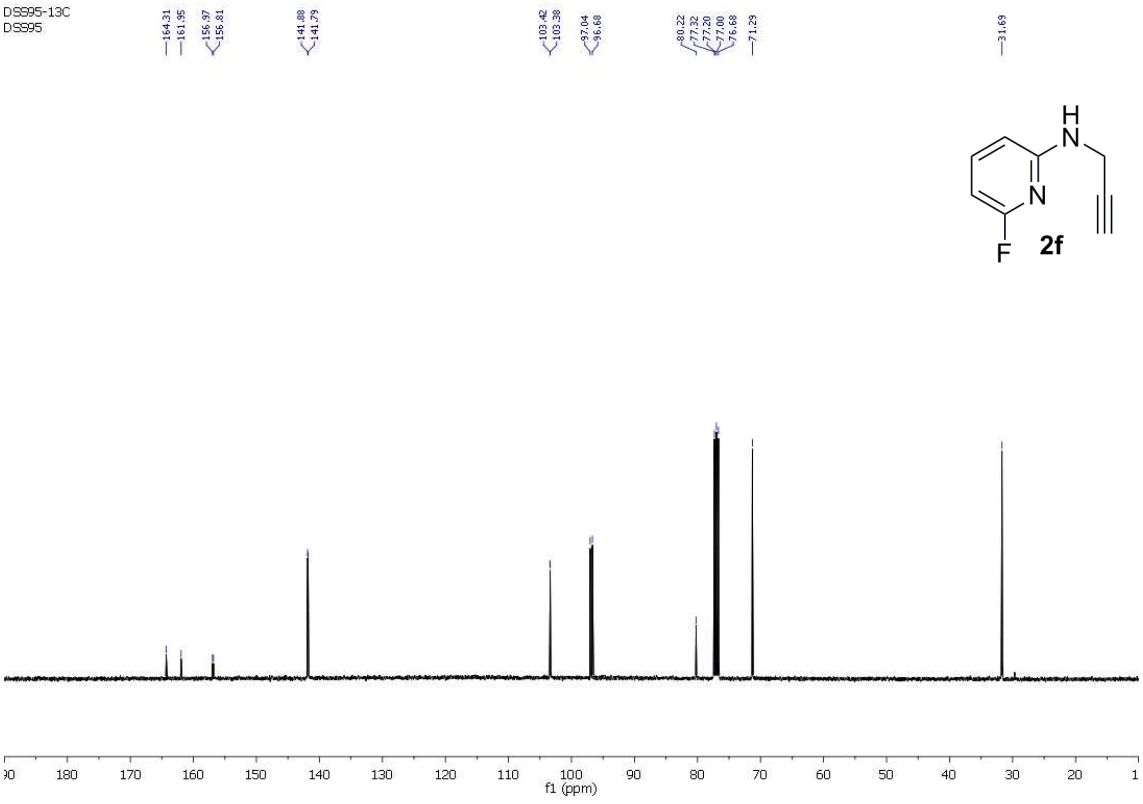
6.23
6.21
6.21
6.21
4.79
4.11
4.10
4.10
4.09
2.24
2.23
2.22
H
N
N
F
2f
1.00
1.02
0.32
1.08
2.39
0.79
f1 (ppm)


DS995-13C
DS995
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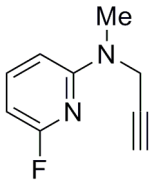
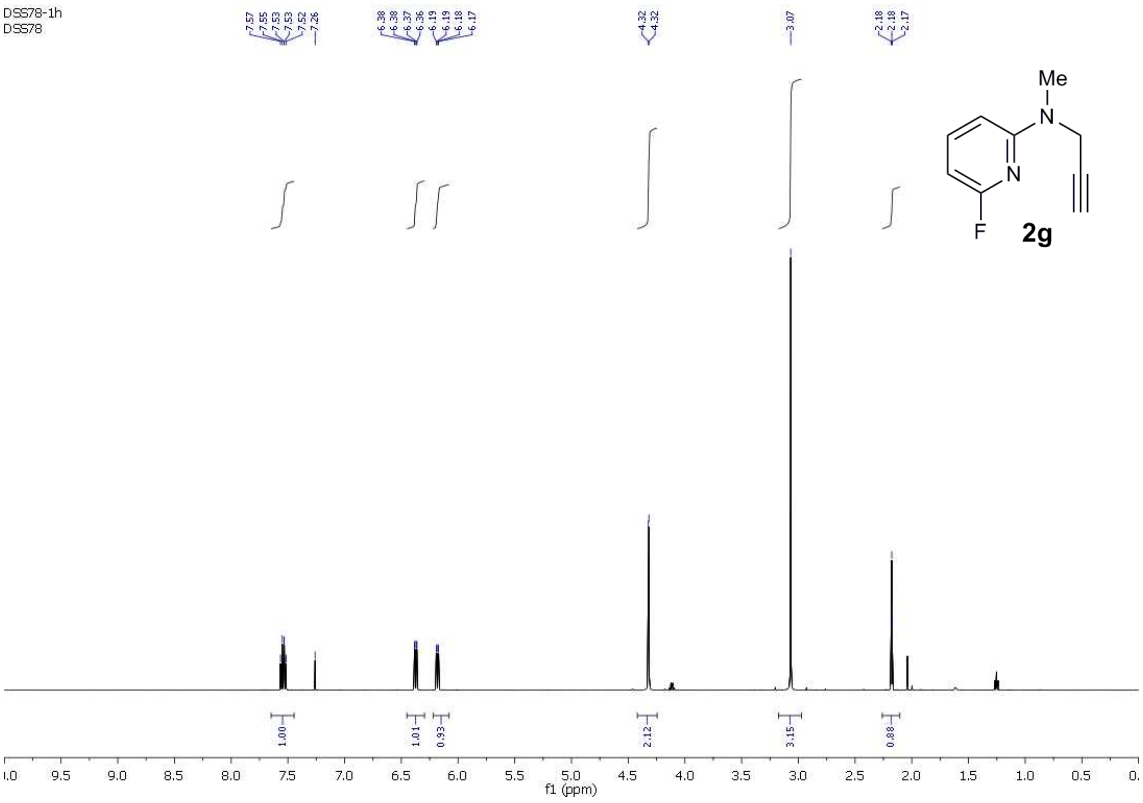
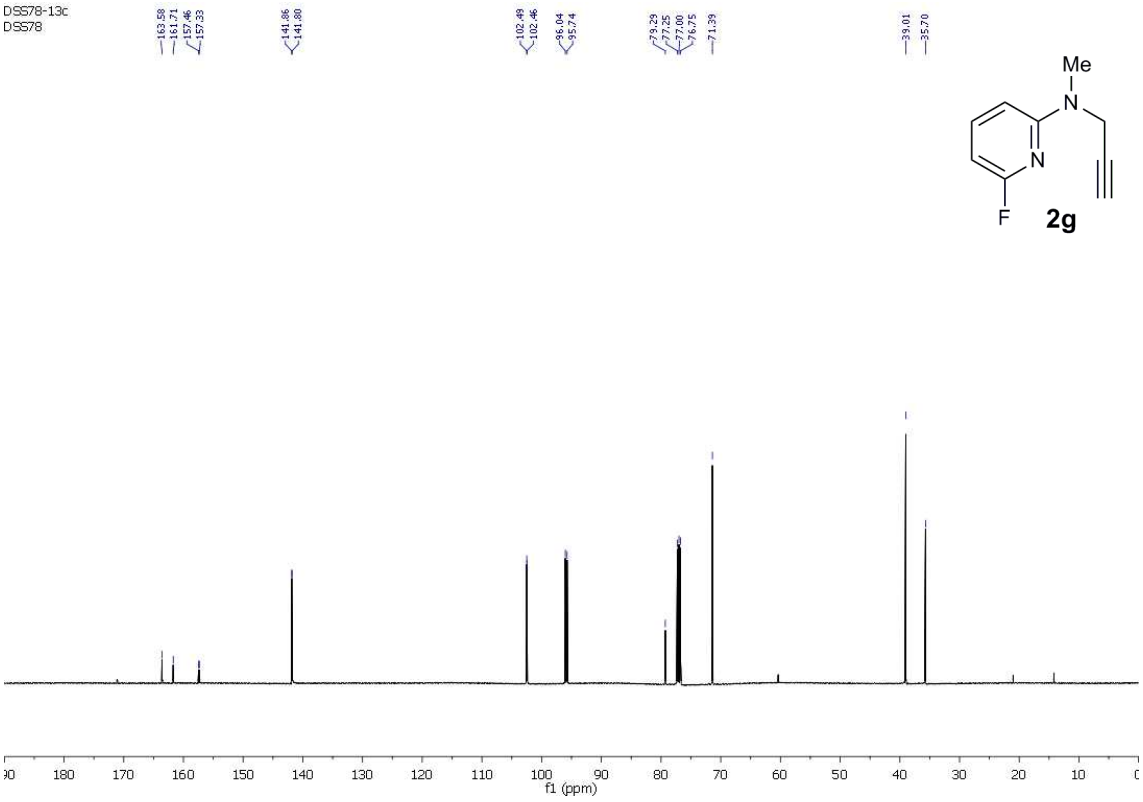
161.95
156.97
156.81
141.88
141.79
103.42
103.38
97.04
96.68
80.22
77.32
77.20
77.00
76.68
71.29
31.69
H
N
N
F
2f
f1 (ppm)

6-Fluoro-*N*-methyl-*N*-(prop-2-ynyl)pyridin-2-amine (2g).

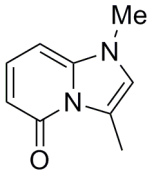


To a solution of 2,6-difluoropyridine (0.25 mL, 2.75 mmol) in EtOH (4 mL) was added *N*-methylprop-2-yn-1-amine (0.90 mL,11.02 mmol). The mixture was heated at 90 ºC for 16 h. The solvent was removed by evaporation, and the crude was purified by flash chromatography (hexane/EtOAc, 95/5, v/v) to yield compound **2g** (430 mg, 96%) as an oil: IR (KBr) ν_{max} 3299, 2928, 1615, 1567, 1498, 1427, 1202, 1025, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (q, 1H, J = 7.8 Hz, H-4), 6.37 (dd, 1H, J_1 = 7.8 Hz, J_2 = 2.6 Hz, H-3), 6.18 (dd, 1H, J_1 = 7.8 Hz, J_2 = 2.9 Hz, H-5), 4.32 (d, 2H, J= 2.4 Hz, CH_2N), 3.07 (s, 3H, CH_3), 2.18 (t, 1H, J = 2.5, C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J= 235.7 Hz, C-6), 157.4 (C-2), 141.8 (C-4), 102.5 (C-3), 95.9 (d, J= 38.1 Hz, C-5), 79.3 (*C*≡CH), 71.4 (C≡*C*H), 39.0 (CH_2N), 35.7 (CH_3); MS (EI) *m/z*: 164 $(M)^+$, 163, 149, 125, 96, 84; MS (ESI) *m/z*: 165.0 $(M+H)^+$. Exact. Mass Calcd for $C_9H_{10}FN_2$ $(M+H)^+$: 165.0828. Found *m/z* 165.0829.

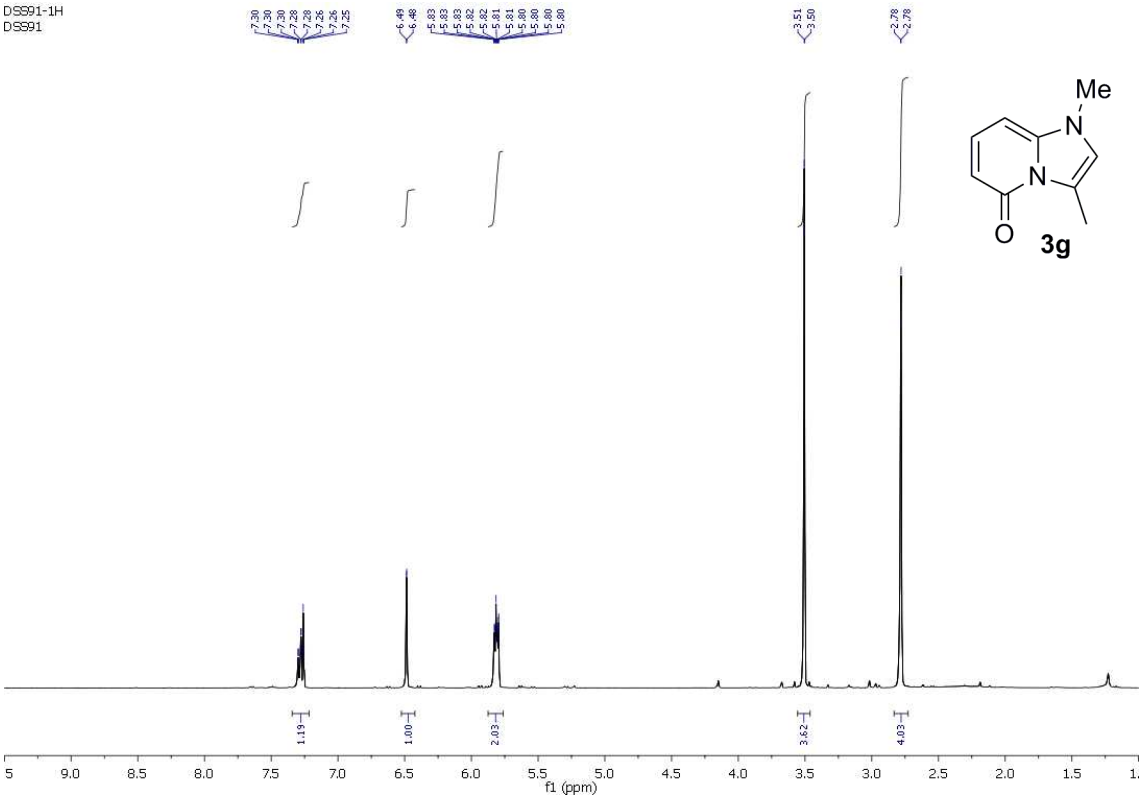


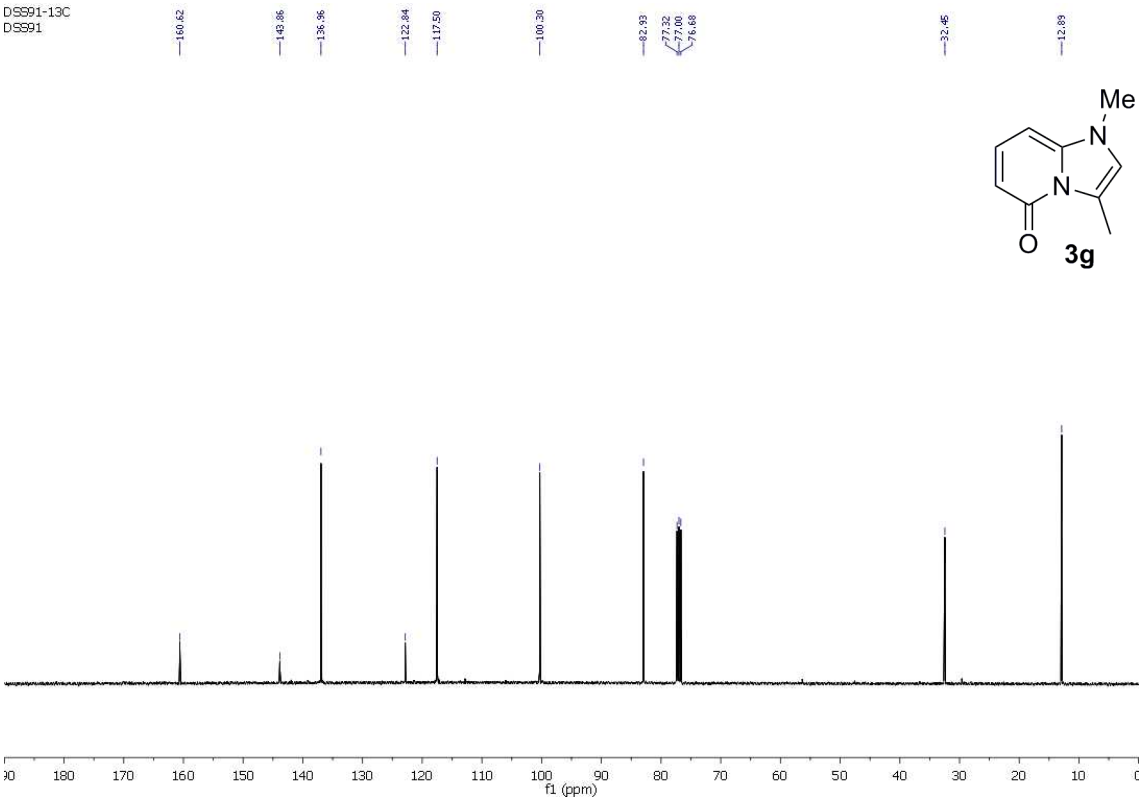


1,3-Dimethylimidazo[1,2-*a*]pyridin-5(1*H*)-one (3g).

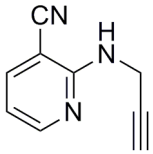


In a 20 mL glass tube equipped with septa, 6-fluoro-*N*-methyl-N-(prop-2-ynyl)pyridin-2-amine **2g** (60 mg, 0.37 mmol) was solved in 1 mL of 1,4-dioxane and treated with a mixture of concentrated hydrochloric acid (0.25 mL) and water (1.75 mL). The mixture was stirred for 30 seg, and then exposed to MW irradiation (250 W) at 140 ºC during 5 min. When the reaction was over (TLC analysis), the reaction mixture was diluted with aq. saturated solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (2 x 15 mL) and CH_2Cl_2/iPrOH (3:1) (2 x 15 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and the solvent was evaporated. The resultant mixture was purified by flash chromatography (CH_2Cl_2/MeOH, 95/5, v/v) to yield compound **3g** (30 mg, 51%) as a solid: mp 115-7 ºC; IR (KBr) ν_{max} 3400, 3110, 2926, 1656, 1609, 1530, 1557, 1152, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 1H, COCHC*H*), 6.49 (s, 1H, CHN), 5.83-5.79 (m, 2H, COCH, CHCNN), 3.50 (s, 3H, CH_3N), 2.78 (s, 3H, CH_3C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (CO), 143.9 (CNN), 137.0 (COCH*C*H), 122.8 (CH_3*C*), 117.5 (CHN), 100.3 (CO*C*H), 82.9 (*C*HCNN), 32.5 (*C*H_3N), 12.9 (*C*H_3C); MS (EI) *m/z*: 162 $(M)^+$, 147, 134, 133, 119; MS (ESI) *m/z*: 163.0 $(M+H)^+$. Exact mass. Calcd for $C_9H_{11}N_2O$ $(M+H)^+$: 163.0866. Found *m/z* 163.0869.

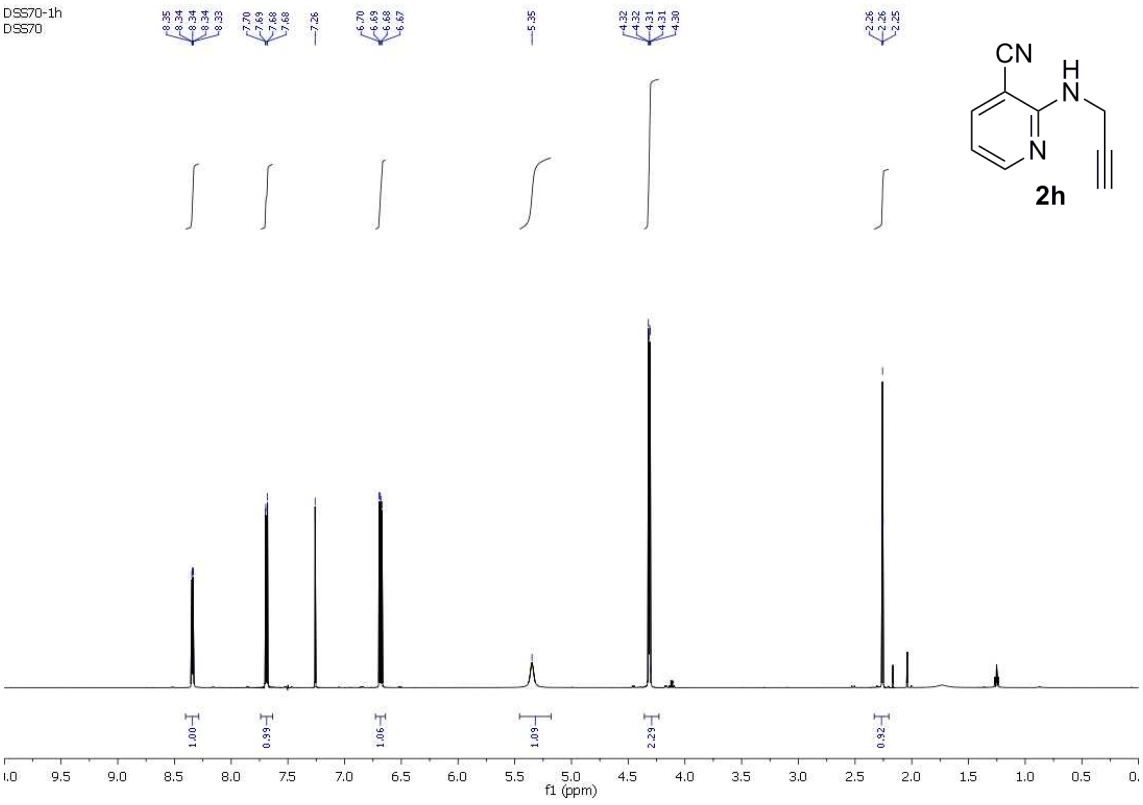

DSS91-1H
DSS91
Me
N
N
O
3g
f1 (ppm)

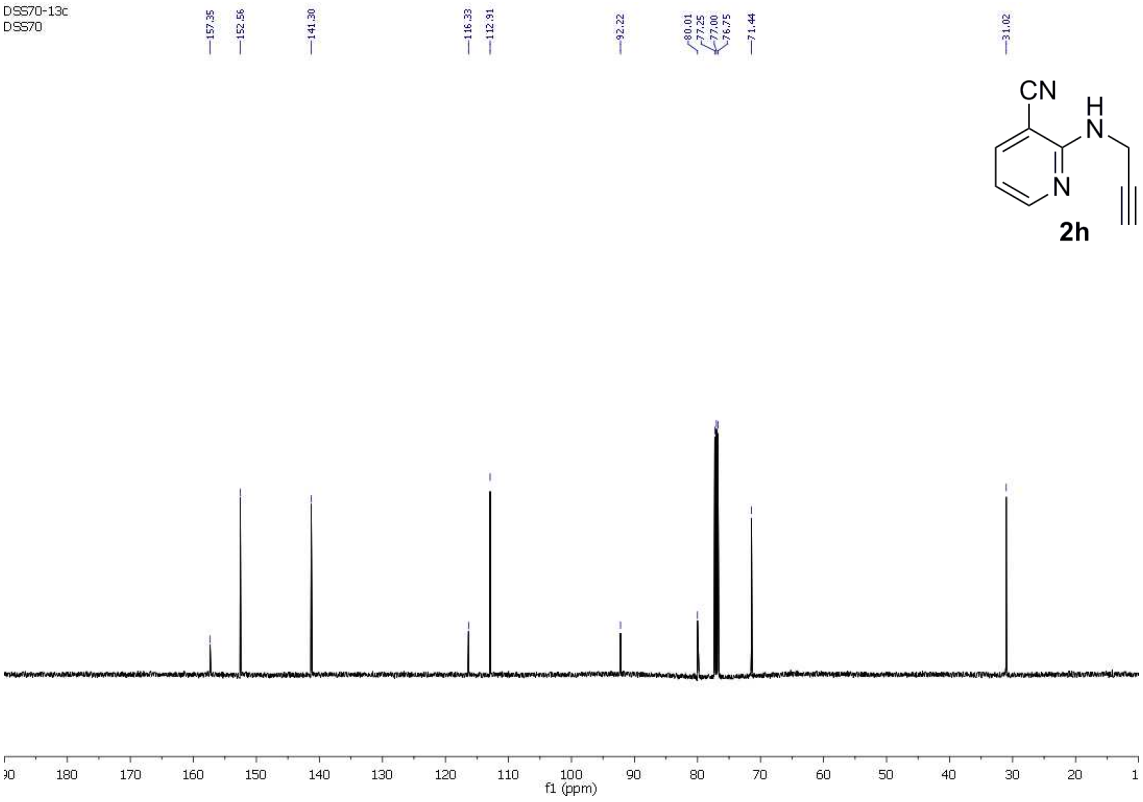

DSS91-13C
DSS91
Me
N
N
O
3g
f1 (ppm)

2-(Prop-2-ynylamino)nicotinonitrile (2h).

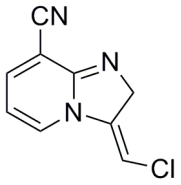


In a 20 mL glass tube equipped with septa, 2-chloronicotinonitrile (300 mg, 2.16 mmol) and prop-2-yn-1-amine (0.42 mL, 6.54 mmol) were added. The mixture was stirred for 30 seg, and then exposed to MW irradiation (250 W) at 100 ºC for 16 h. When the reaction was complete (TLC analysis), the reaction mixture was diluted in MeOH and evaporated. The resultant solid was purified by flash chromatography (hexane/EtOAc, 8/2, v/v) to yield compound **2h** (205 mg, 60%) as a solid: mp 104-6 ºC; IR (KBr) ν_{max} 3350, 3185, 2225, 2108, 1594, 1579, 1514, 1413, 1257 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, 1H, J_1= 5.2 Hz, J_2 = 1.8 Hz, H-6), 7.69 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.8 Hz, H-4), 6.68 (dd, 1H, J_1 = 7.6 Hz, J_2 = 5.2 Hz, H-5), 5.35 (s, 1H, NH), 4.31 (dd, 2H, J_1 = 5.5 Hz, J_2 = 2.6 Hz, CH_2N), 2.26 (t, 1H, J= 2.6 Hz, C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (C-2), 152.6 (C-6), 141.3 (C-4), 116.3 (CN), 112.9 (C-5), 92.2 (C-3), 80.0 (*C*≡CH), 71.4 (C≡*C*H), 31.0 (CH_2N); MS (EI) *m/z*: 157 $(M)^+$, 156, 130, 97, 83, 77, 69, 57; MS (ESI) *m/z*: 158.0 $(M+H)^+$. Anal. Calcd. for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.74. Found: C, 69.01; H, 4.33; N, 26.62.

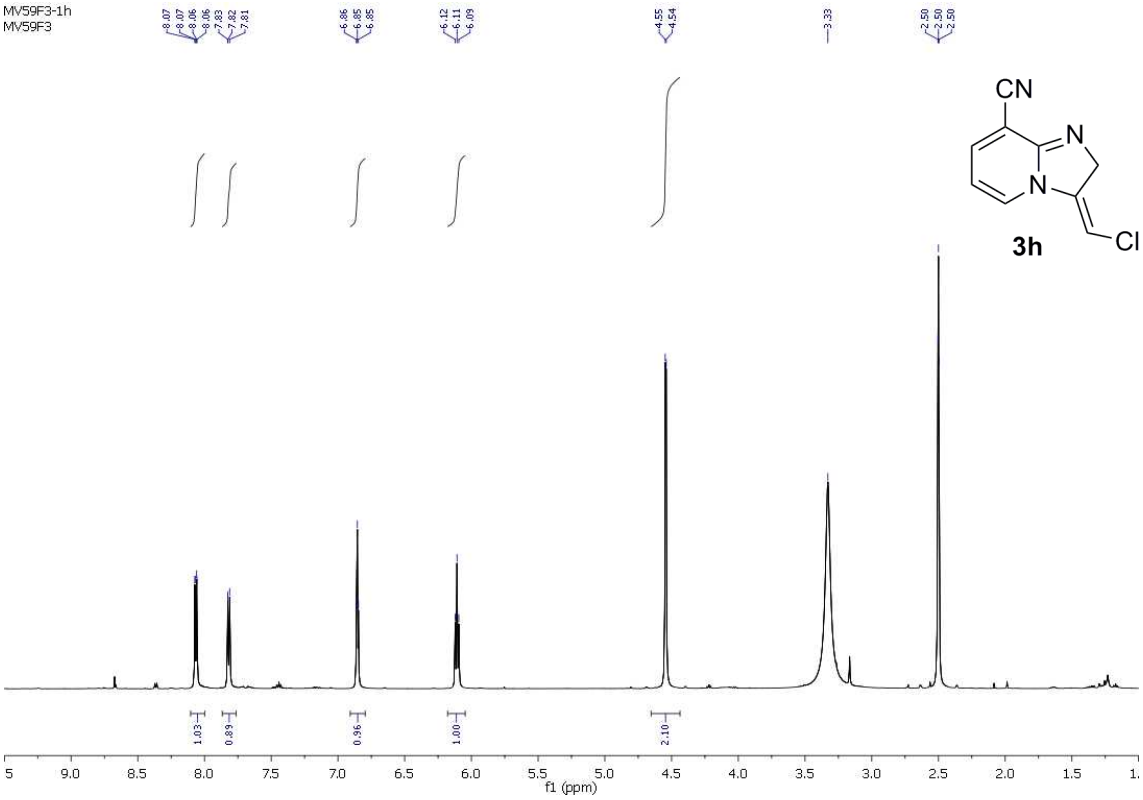




(*E*)-3-(Chloromethylene)-2,3-dihydroimidazo[1,2-*a*]pyridine-8-carbonitrile (3h).



Isoamilnitrite (0.13 mL, 0.95 mmol) was added to a solution of $CuCl_2$ (100 mg, 0.76 mmol) in dry acetonitrile (3 mL). The mixture was heated at 65ºC. To these solution was added 2-(prop-2-ynylamino)nicotinonitrile **2h** (100 mg, 0.64 mmol) in dry CH_3CN (2 mL) dropwise. The reaction mixture was heated at 65 ºC for 30 min. The solution was cooled, acidified (HCl, 2N) to pH 2. The mixture was diluted with aq. saturated solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and the solvent was evaporated. The resultant mixture was purified by flash chromatography (CH_2Cl_2/MeOH, 95/5, v/v) to yield compound **3h** (94 mg, 77%) as a solid: mp 190-3 ºC; IR (KBr) ν_{max} 3335, 2923, 2236, 2108, 1646, 1562, 1530, 1351, 1296, 787 m^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, 1H, J = 6.9 Hz, CHCCN), 7.81 (d, 1H, J = 6.9 Hz, CHN), 6.85 (t, 1H, J = 3.9 Hz, CHCl), 6.11 (t, 1H, J = 6.9 Hz, C*H*CHCCN), 4.54 (d, 2H, J = 3.9 Hz, CH_2N); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.5 (CNN), 147.0 (CHN), 141.8 (*C*CHCl), 134.5 (*C*HCCN), 115.1 (CN), 104.7 (*C*HCHCCN), 98.7 (CHCl), 98.4 (*C*CN), 56.9 (CH_2N); MS (EI) *m/z*: 191 $(M)^+$, 156, 129, 103, 76, 41; MS (ESI) *m/z*: 192.0 $(M+H)^+$. Anal. Calcd. for $C_9H_6ClN_3$: C, 56.41; H, 3.16; N, 21.93. Found: C, 55.85; H, 3.43; N, 21.62.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MV59F3
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8.07
8.06
8.06
7.83
7.82
7.81
6.86
6.85
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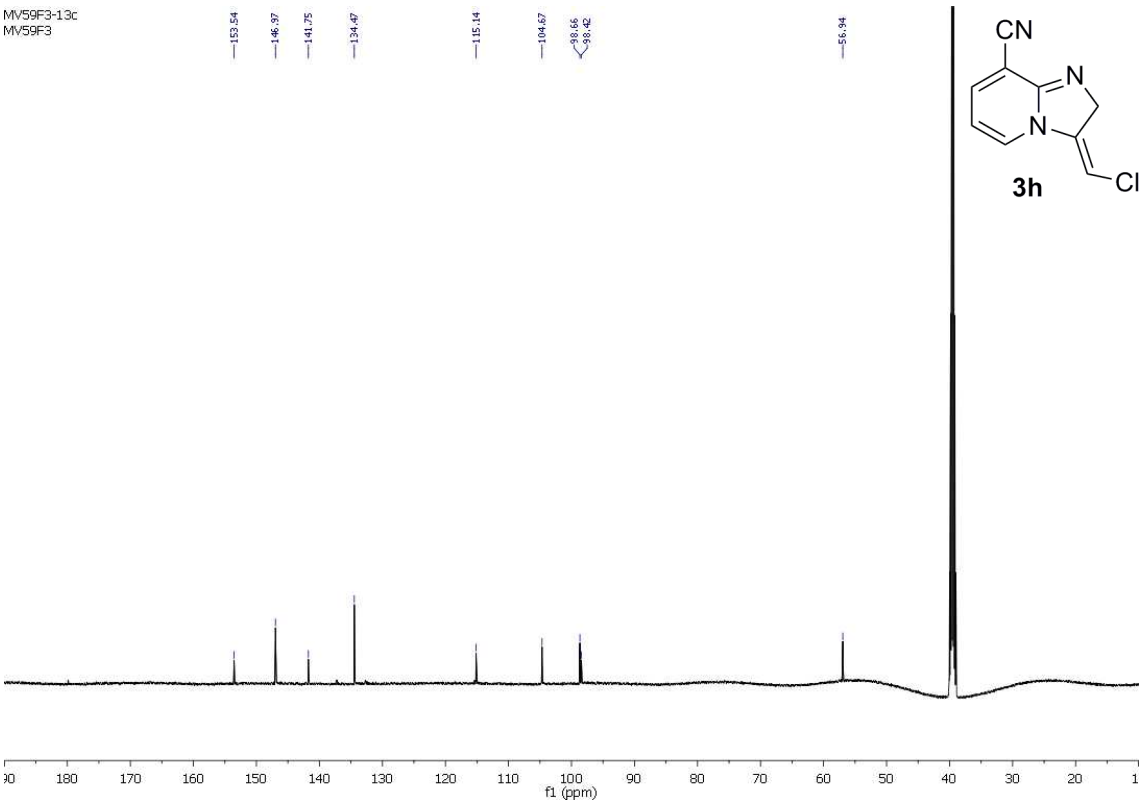
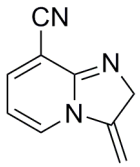
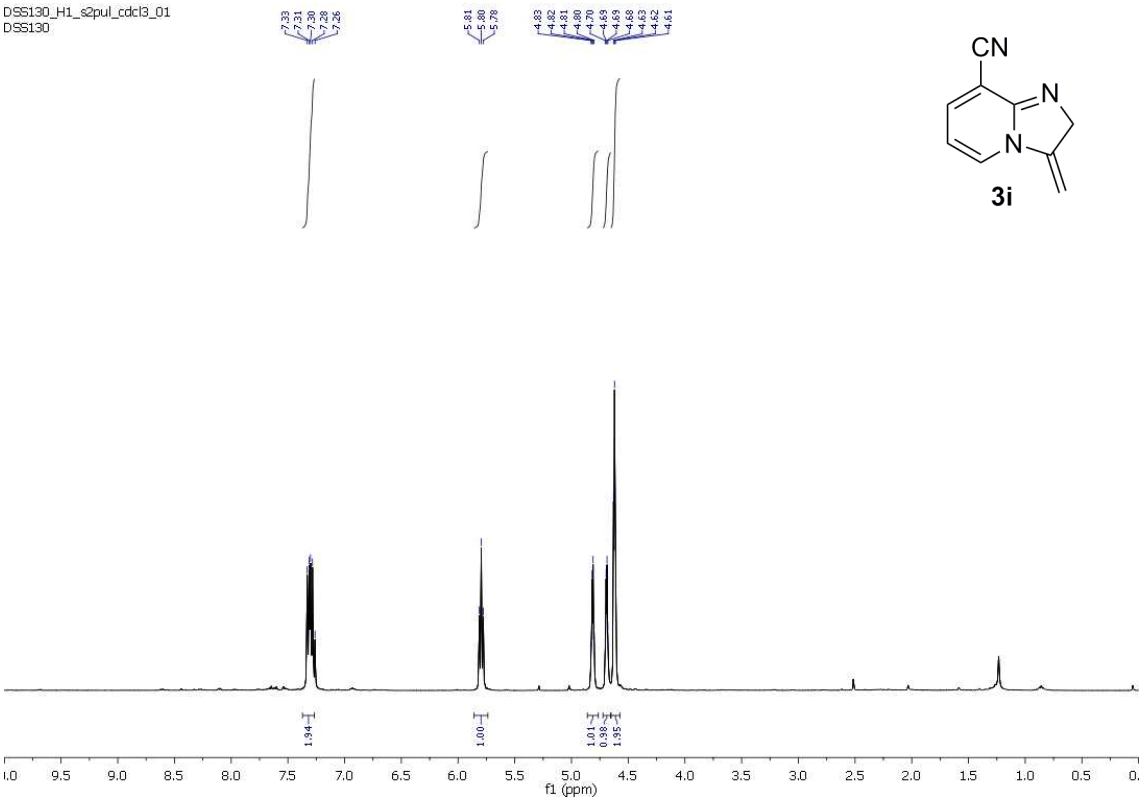
6.12
6.11
6.09
4.55
4.54
3.33
2.50
2.50
2.50
CN
N
N
Cl
3h
1.03
0.89
0.96
1.00
2.10
f1 (ppm)

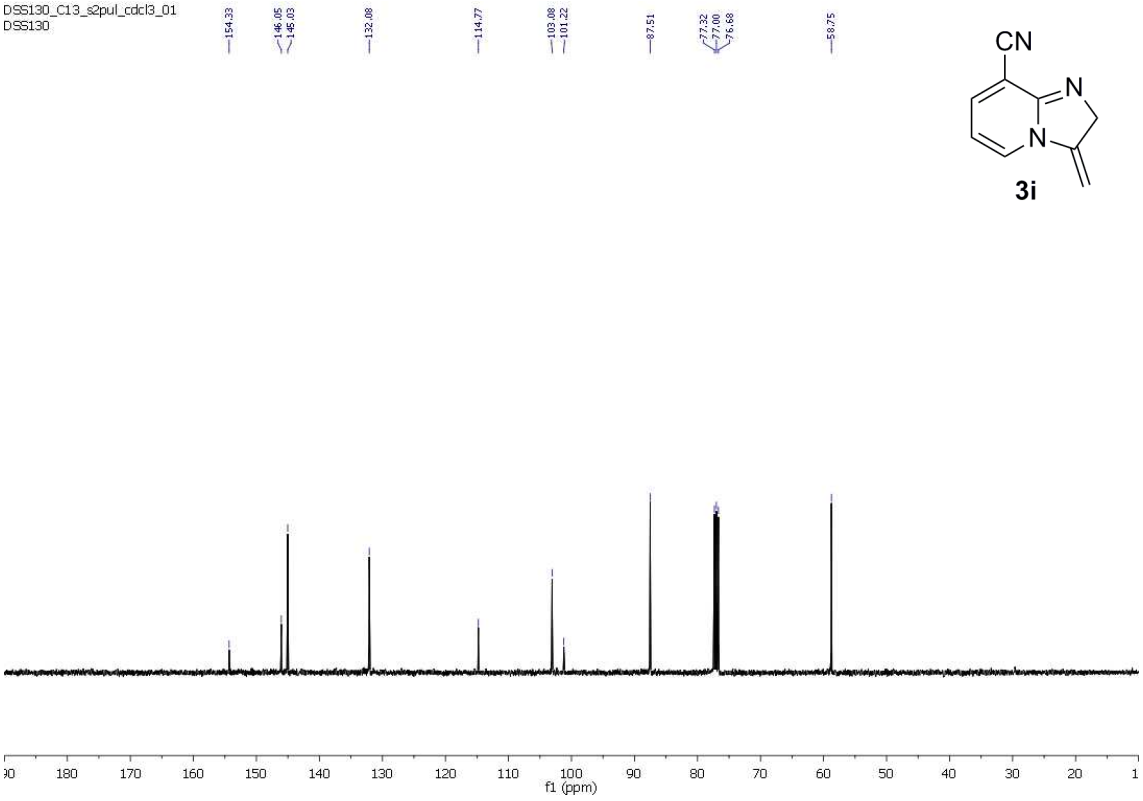

MV59F3-13c
MV59F3
153.54
146.97
141.75
134.47
115.14
104.67
98.66
98.42
56.94
CN
N
N
Cl
3h
f1 (ppm)

3-Methylene-2,3-dihydroimidazo[1,2-*a*]pyridine-8-carbonitrile (3i).

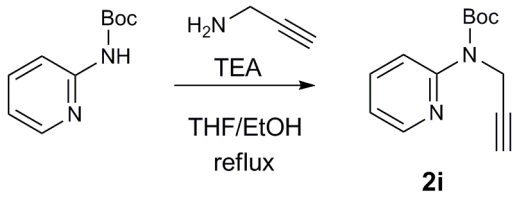


Following the general procedure, reaction of 2-(prop-2-ynylamino)nicotinonitrile **2h** (80 mg, 0.51 mmol) and CuCl (12.6 mg, 0.13 mmol) in anhydrous acetonitrile (5 mL), after 4 h and 30 min. reaction time, and column chromatography (CH_2Cl_2/MeOH, 95/5, v/v), gave compound **3i** (30 mg, 38%) as a solid: mp 130-3 ºC; IR (KBr) ν_{max} 2231, 1653, 1640, 1577, 1531, 1453, 1317, 1250, 836, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ [7.33-7.28 (m, 2H), 5.80 (t, 1H, J = 7.0 Hz)] (CHN, C*H*CHN, CHCCN), 4.83-4.80 (m, 1H, C=CH_2), 4.70-4.68 (m, 1H, C=CH_2), 4.63-4.61 (m, 2H, NCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3 (CNN), 146.1 (quaternary C), 145.0 (CH), 132.1 (CH), 114.8 (CN), 103.1 (CH), 101.2 (quaternary C), 87.5 (C=*C*H_2), 58.8 (CH_2N); MS (EI) *m/z*: 157 $(M)^+$, 156, 130, 104, 103, 76; MS (ESI) *m/z*: 158.0 $(M+H)^+$. Anal. Calcd. for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.74. Found: C, 68.59; H, 4.75; N, 26.52.

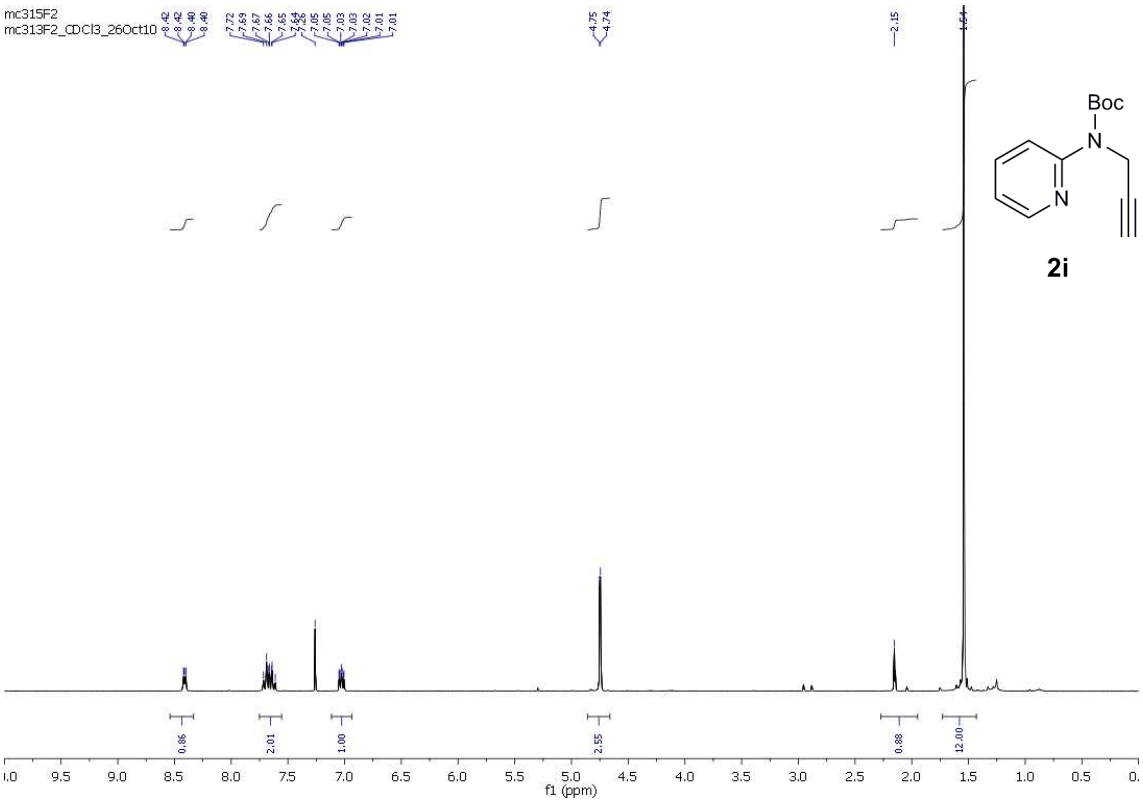


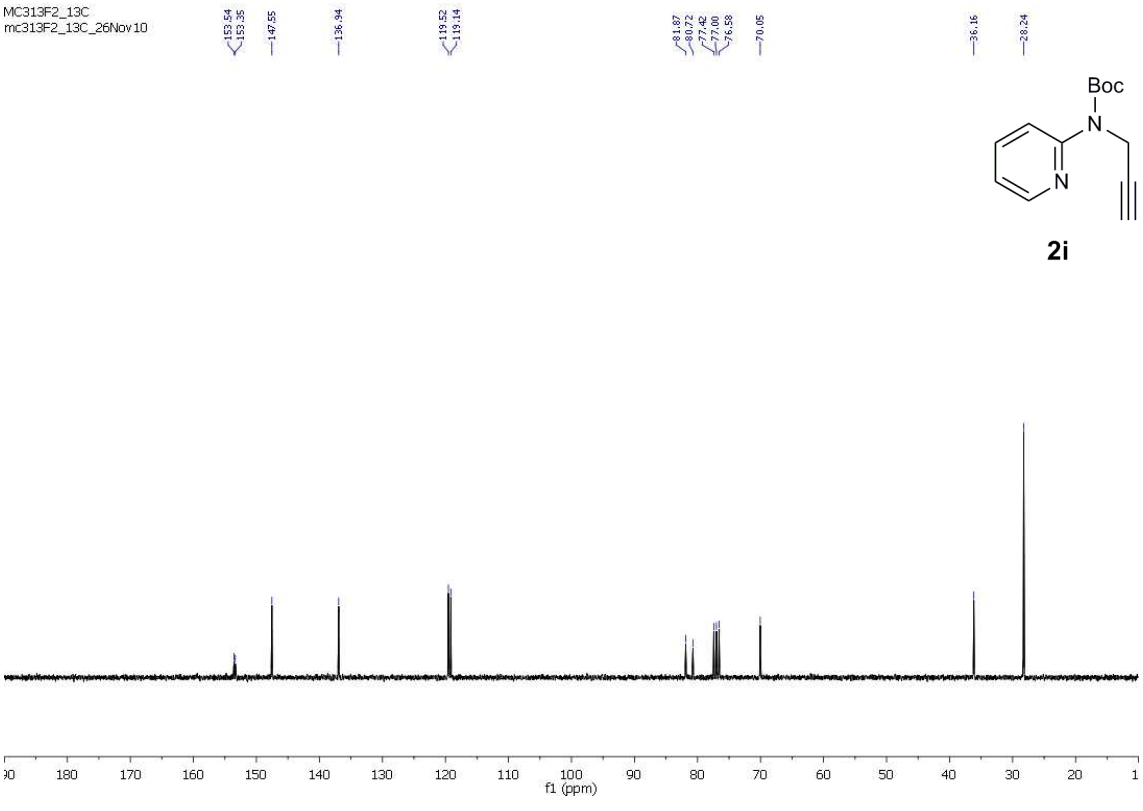


tert-Butyl prop-2-yn-1-yl(pyridin-2-yl)carbamate (2i)

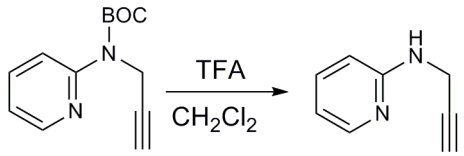


To a solution of *tert*-butyl pyridin-2-ylcarbamate[11c] (97 mg, 0.5 mmol) in dry DMF (2 mL), cooled to 0 °C in an ice/water bath, sodium hydride (24 mg, 60% suspension in oil, 0.6 mmol, 1.2 equiv) was added. The suspension was stirred vigorously for 20 min, maintaining the temperature below 5 °C; then, propargylbromid (80% solution in toluene, 67 µL, 0.6 mmol) was added dropwise. After stirring for 30 min, the reaction mixture was brought to rt over a 1 h, water (5 mL) was added, and acidified (HCl, 10%) to pH 6. The mixture was diluted with aq. saturated solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and the solvent was evaporated. The resultant mixture was purified by flash chromatography (hexane/EtOAc, 9/1, v/v) to yield compound **2i** (110 mg, 95%) as oil. IR (KBr) ν_{max} 3219, 2229, 1607, 1598, 1479, 1245, 1108, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, J = 5.1, 0.8 Hz, 1H, Ar), 7.75-7.56 (m, 2H, Ar), 7.12-6.94 (m, 1H, Ar), 4.75 (d, J = 2.4 Hz, 2H, CH_2), 2.15 (t, J = 2.4 Hz, 1H, C≡CH), 1.54 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5 (CO), 153.4 (C2), 147.6 (C6), 136.9 (C3), 119.5 (C5), 119.1 (C4), 81.9 ($C(CH_3)_3$), 80.7 (CCH), 70.1 (CH), 36.2 (CH_2), 28.2 ($3CH_3$).; MS (EI) *m/z*: 232 $(M)^+$, 176 $[M\text{-tertButil}]^+$, 159 $[M\text{-}OC(CH_3)_3]$, 131 [M-Boc], MS (ESI) *m/z*: 233.0 $(M+H)^+$. Anal. Calcd. For $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.03; H, 6.68; N, 12.33.


mc315F2
mc313F2_CDCl3_26Oct10
Boc
N
N
2i
f1 (ppm)

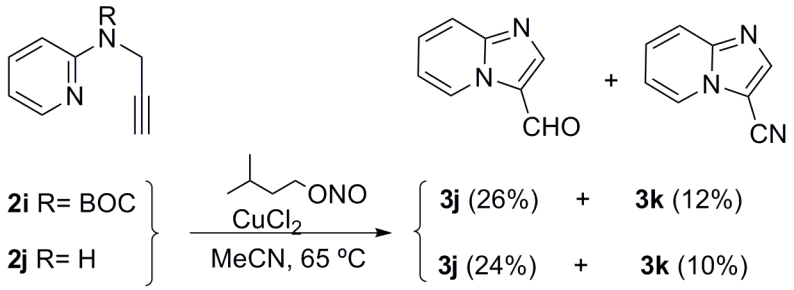

MC313F2_13C
mc313F2_13C_26Nov10
Boc
N
N
2i
f1 (ppm)

***N*-(prop-2-yn-1-yl)pyridin-2-amine (2j)**[11c]



2i **2j**

tert-Butyl prop-2-yn-1-yl(pyridin-2-yl)carbamate (**2i)** (870 mg, 3.75 mmol) was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 ºC in an ice/water bath. Then, TFA (99%, 4 mL) was added. The reaction mixture was stirred overnight. After complete reaction, the mixture was neutralized with 3 M NaOH to pH 12, and then, diluted with Et_2O (10 mL). The organic layer was separated and extracted with water and brine and then dried and concentrated. The product was purified by flash chromatography (hexane/EtOAc, 8/2, v/v) to yield compound **2j**[11c] (490 mg, 99%) as yellow oil.

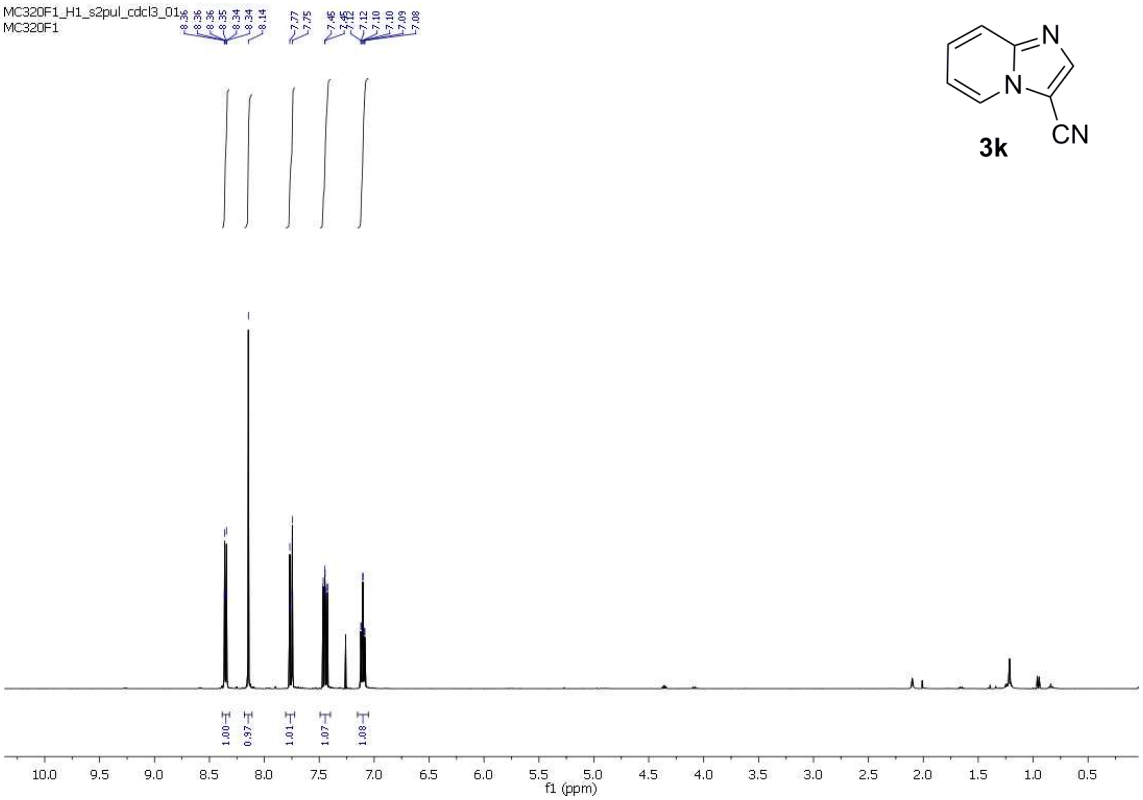


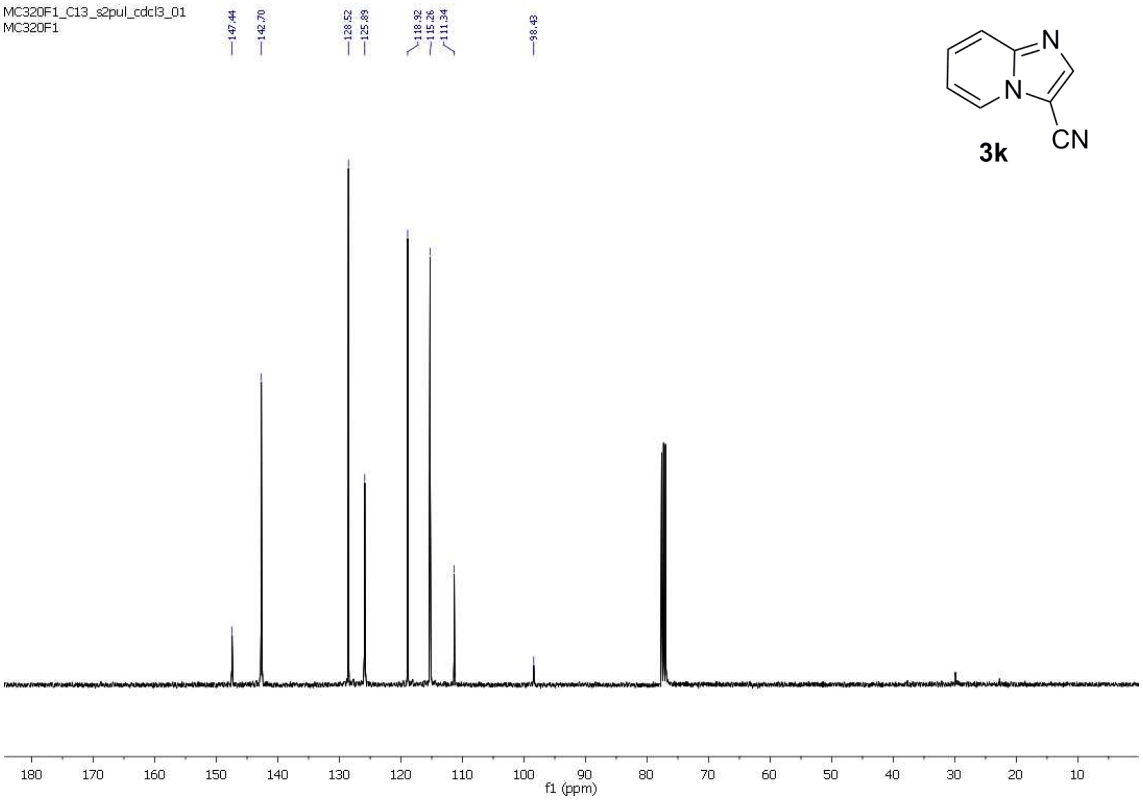
Sandmeyer reaction of *tert*-butyl prop-2-yn-1-yl(pyridin-2-yl)carbamate (2i).

Following the general procedure, reaction of *tert*-butyl prop-2-yn-1-yl(pyridin-2-yl)carbamate **2j** (100 mg, 0.43 mmol), $CuCl_2$ (86 mg, 0.65 mmol) and isoamyl nitrite (65 µL, 0.47 mmol) in anhydrous acetonitrile (5 mL), after 5 min, and column chromatography (CH_2Cl_2/EtOAc, 8/2, v/v), gave compound **3i**[16a] (18 mg, 26%) and **3j**[16b] (8 mg, 12%). Imidazo[1,2-*a*]pyridine-3-carbaldehyde (**3j**): White solid, mp 117-119 ºC, IR (KBr) ν_{max} 3097, 2814, 1664, 1491, 1309 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 9.46 (d, J = 6.7 Hz, 1H), 8.32 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.59–7.45 (m, 1H), 7.09 (t, J = 6.9 Hz, 1H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8 (CHO), 149.6 (C8a), 146.7 (C2), 130.0 (C7), 128.5 (C5), 125.2 (C3), 117.7 (C8), 115.3 (C6); MS (EI) *m/z*: 146 [M, 66]$^+$, 117 [M-CHO, 12]$^+$; MS (ESI) *m/z*: 147 [M+H]$^+$. Anal. Calcd. for $C_8H_6N_2O$: C, 65.75 H, 4.14; N, 19.17. Found $C_8H_6N_2O.3/4H_2O$: C,60.21; H,5.10; N,17.00.

Imidazo[1,2-*a*]pyridine-3-carbonitrile (**3k**): White solid, mp 148-150 ºC, IR (KBr) ν_{max} 3034, 2217, 1635, 1484, 1256, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (dt, J = 6.8, 1.2 Hz, 1H), 8.14 (s, 1H), 7.76 (dt, J = 9.1, 1.1 Hz, 1H), 7.50 – 7.37 (m, 1H), 7.10 (td, J = 6.9, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4 (C8a), 142.7 (C2), 128.5 (C7), 125.8 (C3), 118.9 (C8), 115.2 (C6), 111.3 (CN), 98.4 (C-CN); MS (EI) *m/z*: 143

[M, 87]+, 117 [M-CN, 10]+; MS (ESI) m/z: 144 [M+H]+. Anal. Calcd. for $C_8H_6N_2O$: C, 65.75 H, 4.14; N, 19.17. Found: C,67.31; H,3.58; N,29.31.

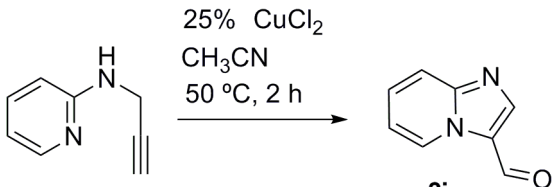




Sandmeyer reaction of *N*-(prop-2-yn-1-yl)pyridin-2-amine (2j).

Following the general procedure, reaction of *N*-(prop-2-yn-1-yl)pyridin-2-amine **2j** (490 mg, 3.7 mmol), $CuCl_2$ (81 mg, 4.45 mmol) and isoamyl nitrite (0.75 mL, 5.57 mmol) in anhydrous acetonitrile (10 mL), after 30 min, and column chromatography (CH_2Cl_2/EtOAc, 8/2, v/v), gave compound **3j** (130 mg, 24%) and **3k** (50 mg, 10%).

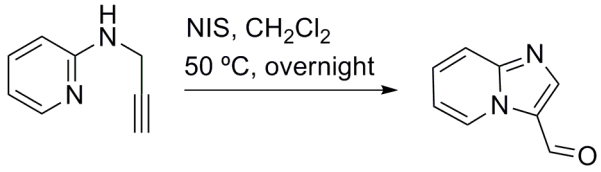
Imidazo[1,2-a]pyridine-3-carbaldehyde (3j).



2j **3j**

Following the general procedure, reaction of *N*-(prop-2-yn-1-yl)pyridin-2-amine **2j** (132 mg, 1 mmol), $CuCl_2$ (33 mg, 0.25 mmol, 0.25 equiv.) in anhydrous acetonitrile (2 mL), the reaction mixture was heated at 65 ºC during 2 h. Column chromatography (hexane/EtOAc, 1/1, v/v), gave only compound **3j** (12 mg, 8%) .

Imidazo[1,2-a]pyridine-3-carbaldehyde (3j).



2j **3j**

To a solution of *N*-(prop-2-yn-1-yl)pyridin-2-amine **2j** (132 mg, 1 mmol), in dry CH_2Cl_2 (9 mL) was added NIS (270 mg, 1.2 mmol). The mixture was heated overnight at 50 ºC. The solvent was removed by evaporation, and the crude was purified by flash chromatography (hexane/EtOAc, 1/1, v/v) to yield compound **3i** (15 mg, 10%).

References

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