Electronic Supplementary Information for

Electro-induced carbamoylation of arenes optimized by a machine learning model.

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General Information

All solvents were dried and used as received from commercial suppliers (Sigma-Aldrich, Carlo Erba). Aromatic reagents were distilled before use via ball-tube distillation. Cyclohexyl and *tert*-butyl isocyanide were made following the carbylamine protocol [1] and distilled afterwards via a vacuum distillation apparatus. The other isocyanides were used as received or freshly made from commercially available amines, following the method developed by Domling *et coll* [2]. Milli-Q® water was used. Electrodes, ElectraSyn®, vial caps, and glass vials were bought from IKA, and used as received, except for the electrodes that were cleaned by polishing on a 1000 grit sandpaper sheet before every experiment. *n*-Bu_4NBF_4 was prepared and recrystallized before use, other supporting electrolytes were used as received from commercial suppliers (Sigma-Aldrich, TCI, BLDpharm). Silica gel chromatography was performed using silica (40–63 μm) from Fisher Scientific. Thin-layer chromatography (TLC) was conducted on silica plates purchased from Fisher Scientific, with visualization under UV light and/or with developing agents including ceric ammonium molybdate, basic potassium permanganate, or acidic *para*-anisaldehyde solutions, followed by heating. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer and are calibrated using residual non-deuterated solvent (for ^{1}H NMR: $CHCl_3$ at 7.26 ppm) and characteristic solvent peak (for ^{13}C NMR: $CDCl_3$ 77.23 ppm). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and combinations thereof.

X-Ray data were collected with a Bruker Kappa APEX II system using fine-focus sealed tube Mo-Kα radiation (Intensity Data). Unit-cell parameters determination, data collection strategy, integration and absorption correction were carried out with the Bruker APEX suite of programs. The structure was solved with SHELXT and refined anisotropically by full-matrix least-squares methods with SHELXL using WinGX.

General Method A:

To an oven-dried 5 mL glass vial charged with a stirring magnet, supporting electrolyte (0.5 equivalent) was added. Distilled solvent (0.2 M) and water (50 equivalents) were added, followed by the aromatic reagent (3 equivalents) and isocyanide (1 equivalent, 0.8 mmol). The electrodes were mounted on an IKA cap, and screwed on top of the glass vial for connection to the ElectraSyn. The desired current density (25 $mA.cm^{-2}$) and charge (2 F/mol) were programmed on the ElectraSyn, and the electrolysis started. After completion, solvent and water were removed *in vacuo*, and a flash column chromatography afforded the desired product.

General Method B (for optimization experiments):

To an oven-dried 5 mL glass vial charged with a stirring magnet, supporting electrolyte (X_1 equivalents) was added. Distilled solvent (X_2 M) and water (X_3 equivalents) were added, followed by the mesitylene (X_4 equivalents) and cyclohexyl isocyanide (X_5 equivalent). The electrodes were mounted on an IKA cap and screwed on top of the glass vial for connection to the ElectraSyn. The desired current density and charge were programmed on the ElectraSyn, and the electrolysis started. After completion, solvent and water were removed *in vacuo*. The dried crude was dissolved in $CDCl_3$, and a representative sample was taken to measure the yield through ^1H NMR. The yield of the desired product was measured via the ratio between a characteristic peak of the product against one of *n*-Bu_4NBF_4 (see figure below).

Stability of the supporting electrolyte as an internal standard was tested with external standard first (1,1,2,2-tetrachloroethane and 1,3,5-trimethoxybenzene), and found to be stable in the electrolysis' conditions.

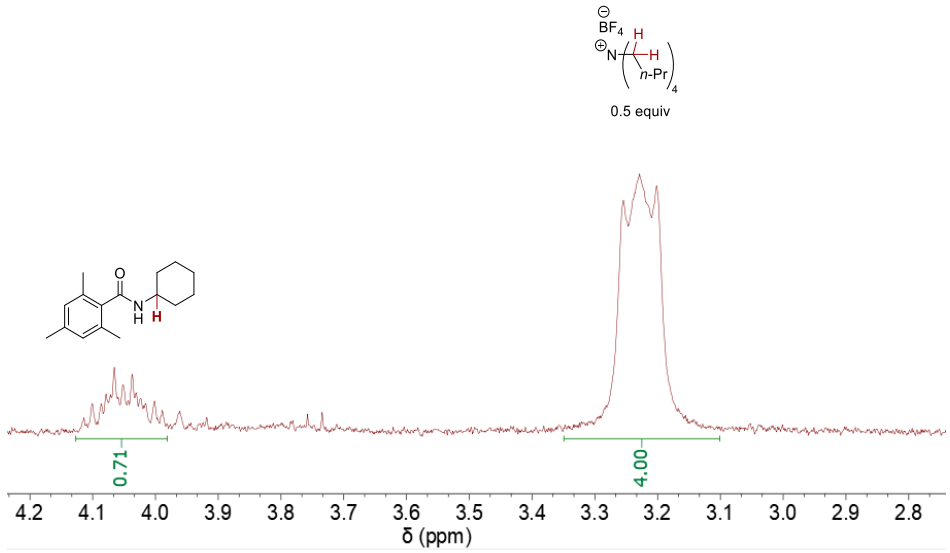
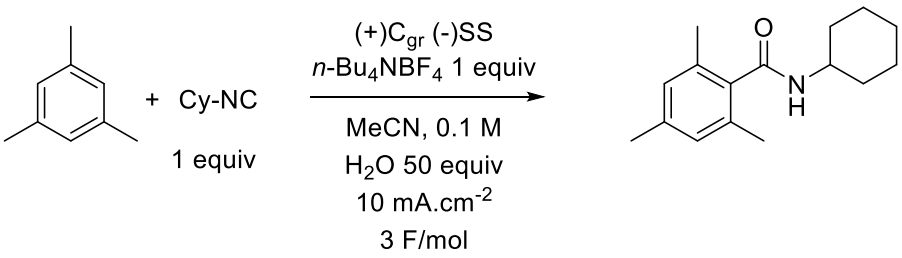


Figure S1: Yield measurement via ^{1}H NMR

Pre-optimization on mesitylene



Entry	Changes	Yield (NMR, %)
1	20 °C	38%
2	60 °C	41%
3	0 °C	n.d.
4	Stirring at 400 / 800 Rotation per minute	37% / 38 %

Table S1: Pre-optimization

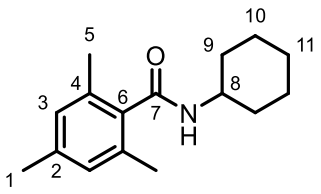
List of experiments proposed by EDBO+:

Iteration	Changes	Yield (NMR, %)
0	No change	38%
1	2 equiv Cy-NC, 2 equiv *n*-Bu_4NBF_4,1 equiv H_2O, 25 mA/cm², 6 F/mol	26%
2	0.33 equiv Cy-NC, 0.5 equiv *n*-Bu_4NBF_4, 0.2 M, 5 mA/cm², 2 F/mol	32%
3	3 equiv Cy-NC, 0.5 equiv *n*-Bu_4NBF_4, 5mA/cm², 2 F/mol	41%
4	3 equiv Cy-NC, 2 equiv *n*-Bu_4NBF_4, 0.05 M, 5 mA/cm², 2 F/mol	42%
5	3 equiv Cy-NC, 2 equiv *n*-Bu_4NBF_4, 0.05 M, 25 mA/cm², 2 F/mol	56%
6	3 equiv Cy-NC, 2 equiv *n*-Bu_4NBF_4, 0.2 M, 25 mA/cm², 2 F/mol	45%
7	3 equiv Cy-NC, 2 equiv *n*-Bu_4NBF_4, 0.05 M, 25 mA/cm², 6 F/mol	33%
8	0.33 equiv Cy-NC, 2 equiv *n*-Bu_4NBF_4, 0.05 M, 25 mA/cm², 2 F/mol	63%
9	0.33 equiv Cy-NC, 0.5 equiv *n*-Bu_4NBF_4, 0.05 M, 25 mA/cm², 2 F/mol	70%
10	0.33 equiv Cy-NC, 1 equiv H2O, 2 equiv *n*-Bu_4NBF_4, 0.05 M, 25 mA/cm², 2 F/mol	54%
11	0.5 equiv Cy-NC, 2 equiv *n*-Bu_4NBF_4, 0.2 M, 25 mA/cm², 2 F/mol	62%
12	3 equiv Cy-NC, 2 equiv *n*-Bu_4NBF_4, 0.2 M, 25 mA/cm², 6 F/mol	49%
13	0.5 equiv Cy-NC, 0.5 equiv *n*-Bu_4NBF_4, 0.1 M, 25 mA/cm², 2 F/mol	65%
14	0.33 equiv Cy-NC, 0.5 equiv *n*-Bu_4NBF_4, 0.2 M, 25 mA/cm², 6 F/mol	71%
15	0.33 equiv Cy-NC, 0.5 equiv *n*-Bu_4NBF_4, 0.2 M, 25 mA/cm², 2 F/mol	74%

Table S2: $EDBO^+$- led optimization

Synthetic procedures

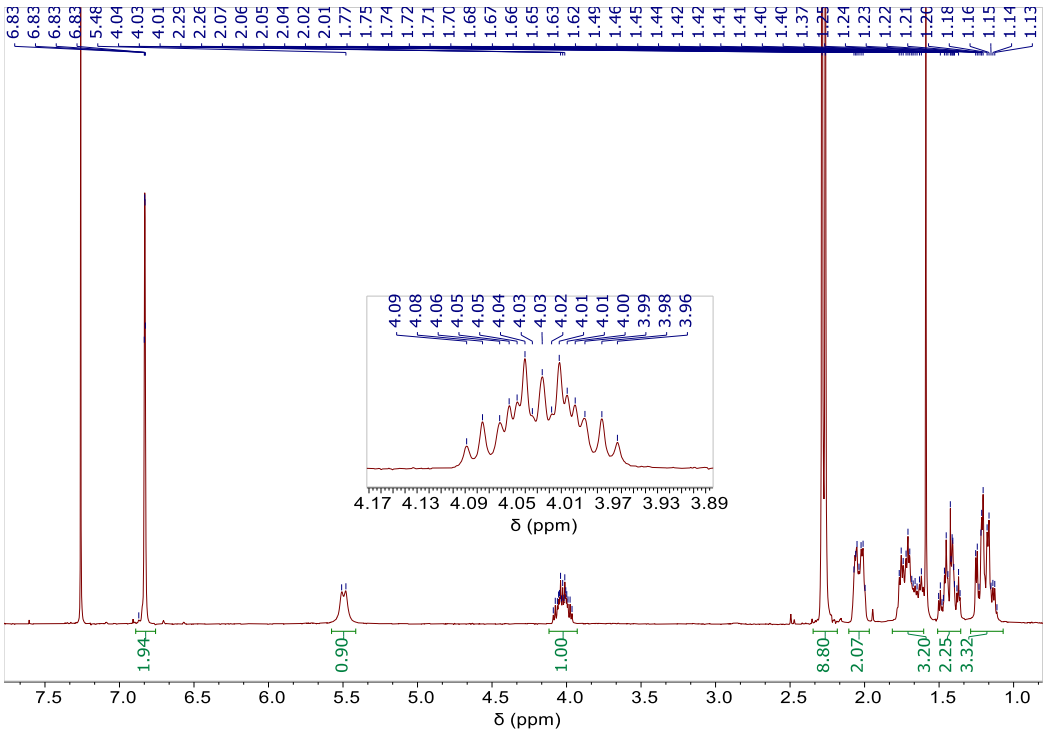
N-cyclohexyl-2,4,6-trimethylbenzamide, **3a**



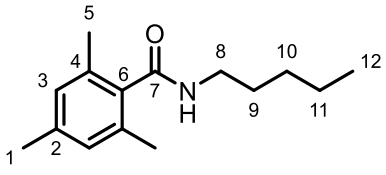
Compound **3a** was obtained following General Method A from mesitylene **1a** and cyclohexyl isocyanide **2a** in up to 74 % yield (145 mg, white solid, purified by Flash Colum Chromatography (FCC), gradient 100 % cyclohexane to 9/1 cyclohexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 – 6.80 (s, 2H, H3), 5.49 (br d, *J* = 8.5 Hz, 1H, N-H), 4.12 – 3.95 (m, 1H, H8), 2.29 (s, 6H, H5), 2.26 (s, 3H, H1), 2.01 – 1.97 (m, 2H, H9), 1.79 – 1.61 (m, 2H, H9), 1.52 – 1.33 (m, 2H, H10), 1.28 – 1.08 (m, 4H, H10, H11).

Data were consistent with the literature [3].



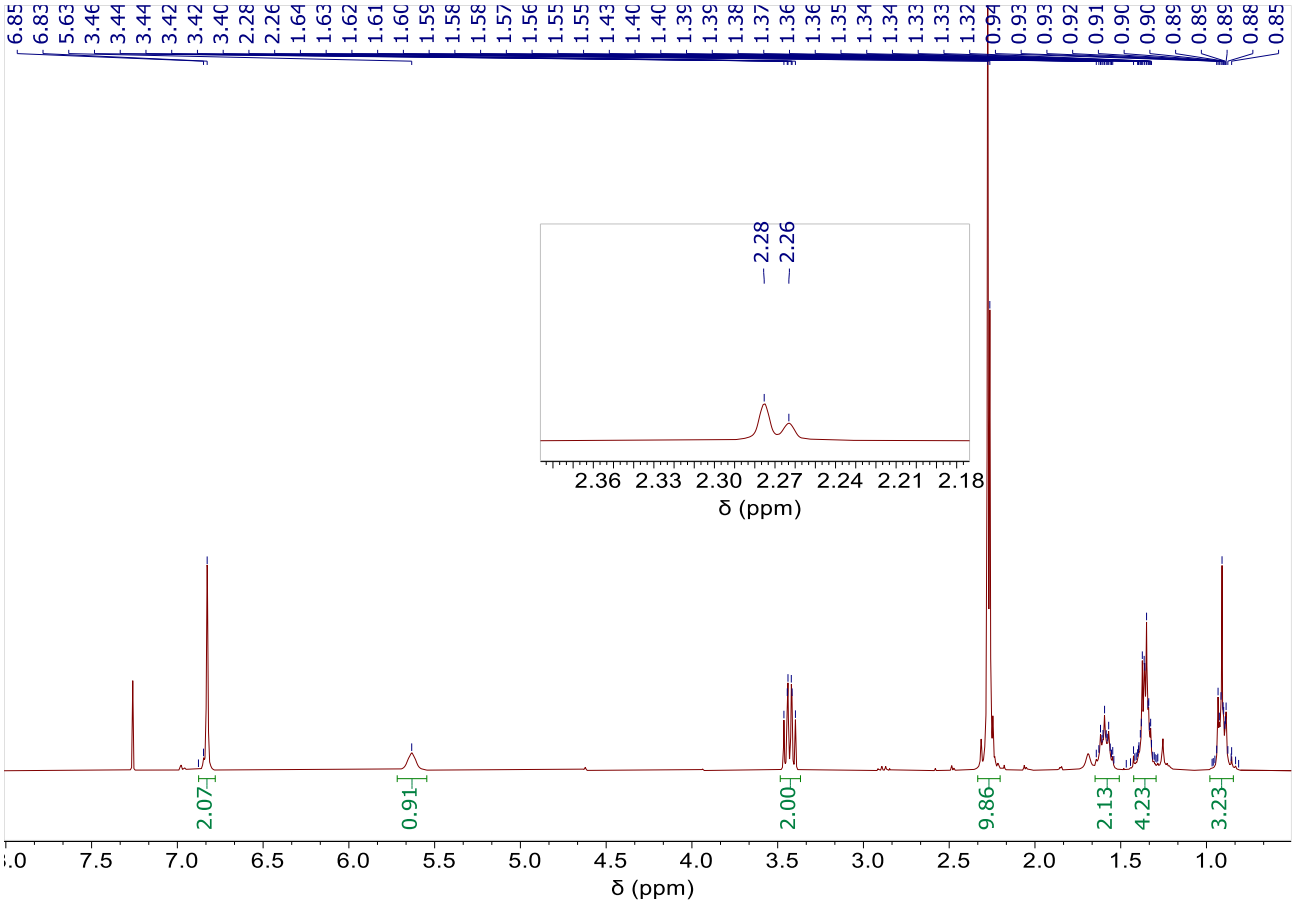
2,4,6-trimethyl-*N*-pentylbenzamide, **3b**



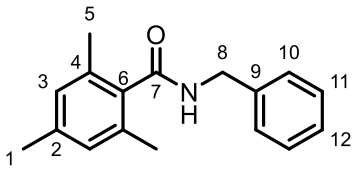
Compound **3e** was obtained following General Method A, from 1-isocyanopentane and mesitylene **1a** (97 mg, 52 %, white solid, purified by FCC, gradient 100 % cyclohexane to 9/1 cyclohexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 2H, H3), 5.63 (br s, 1H, N-H), 3.43 (td, *J* = 7.0, 6.0 Hz, 2H, H8), 2.28 (s, 6H, H5), 2.26 (s, 3H, H1), 1.66 – 1.52 (m, 2H, H9), 1.47 – 1.27 (m, 4H, H10, H11), 0.97 – 0.80 (m, 3H, H12).

Data were consistent with the literature [3].



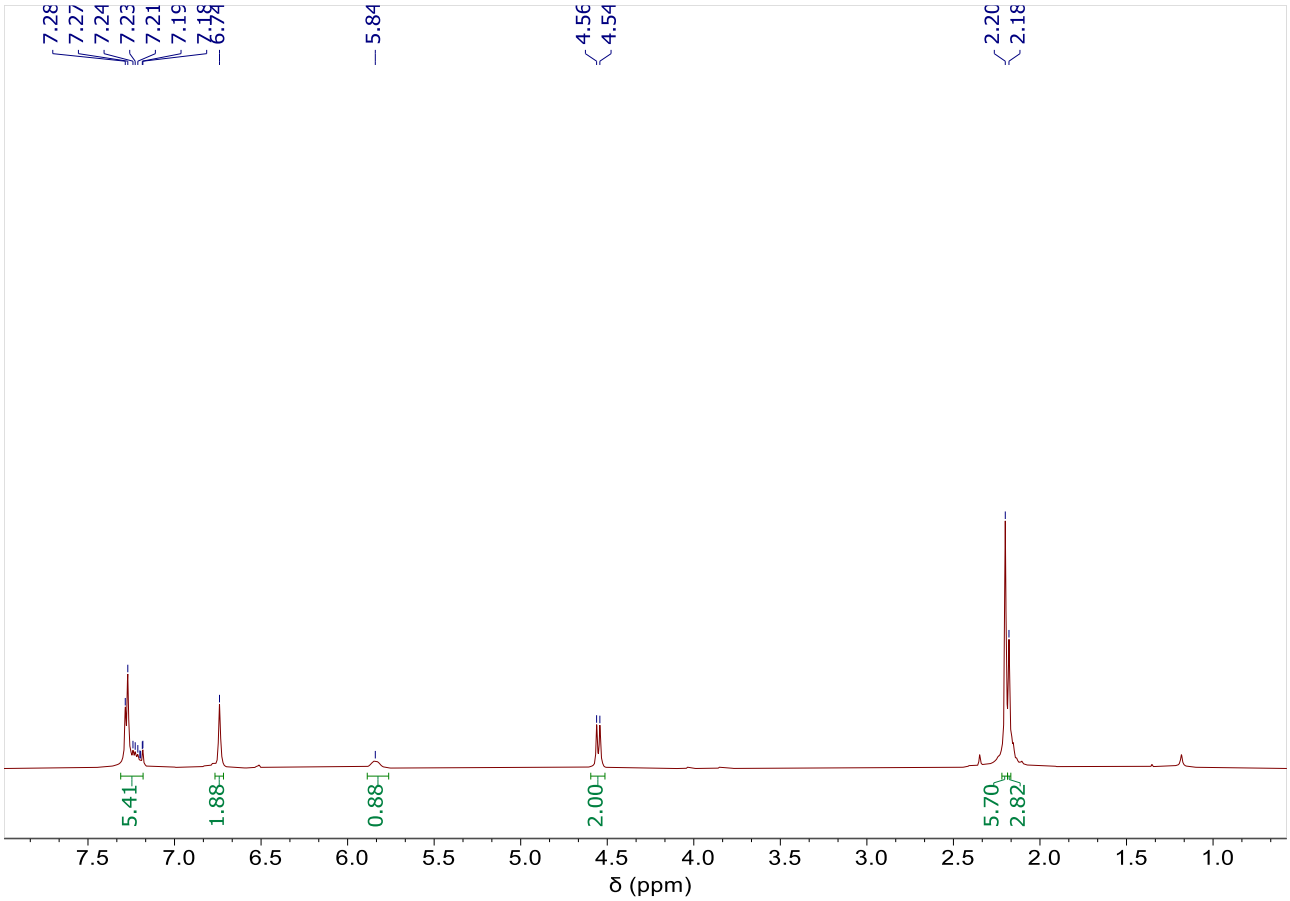
N-benzyl-2,4,6-trimethylbenzamide, **3c**



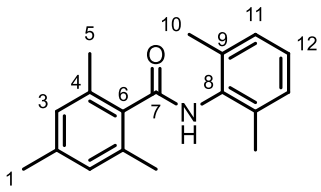
Compound **3f** was obtained following General Method A, from mesitylene **1a** and (isocyanomethyl)benzene (63 mg, 31 %, white solid, purified by FCC, gradient 100 % cyclohexane to 9/1 cyclohexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 5H, H10, H11, H12), 6.74 (s, 2H, H3), 5.84 (br s, 1H, N-H) 4.55 (d, *J* = 5.5 Hz, 1H, H8), 2.20 (s, 6H, H5), 2.18 (s, 3H, H1).

Data were consistent with the literature [3].



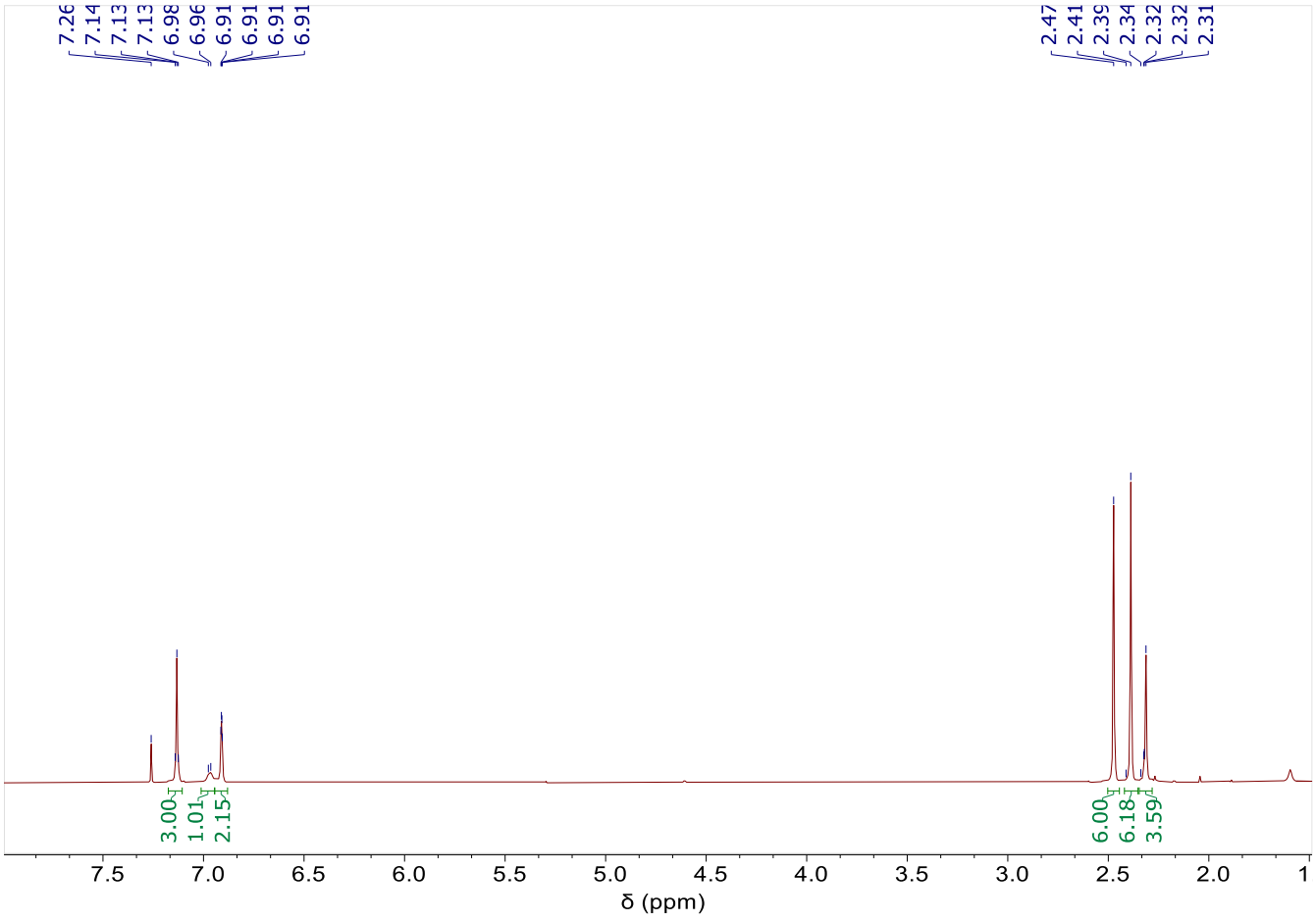
N-(2,6-dimethylphenyl)-2,4,6-trimethylbenzamide, **3d**



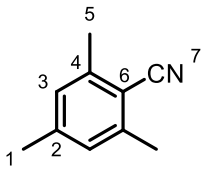
Compound **3g** was obtained following General Method A, from 2-isocyano-1,3-dimethylbenzene and mesitylene **1a** (5 mg, 5 %, off-white solid, purified by FCC, gradient 100 % cyclohexane to 9/1 cyclohexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 – 7.12 (m, 3H, H11, H12), 6.97 (br s, 1H, N-H), 6.90 (s, 2H, H3), 2.47 (s, 6H, H10 or H5), 2.39 (s, 6H, H5 or H10), 2.31 (s, 3H, H1).

Data were consistent with the literature [3].



2,4,6-trimethylbenzonitrile, **3e**

137 

138 Compound **3h** (white crystals) was obtained following General Method A, from various tertiary
139 isocyanides and mesitylene. Isolated yields are lower than the NMR yields due to sublimation of **3h**
140 under vacuum. Purified by FCC (Gradient 100 % cyclohexane /diethyl ether).

Entry	Starting isocyanide	NMR yield	Isolated yield
1	*tert*-butyl isocyanide	85 %	51 %
2	*tert*-octyl isocyanide	91 %	52 %
3	(2-isocyanopropan-2-yl)benzene	75 %	50 %

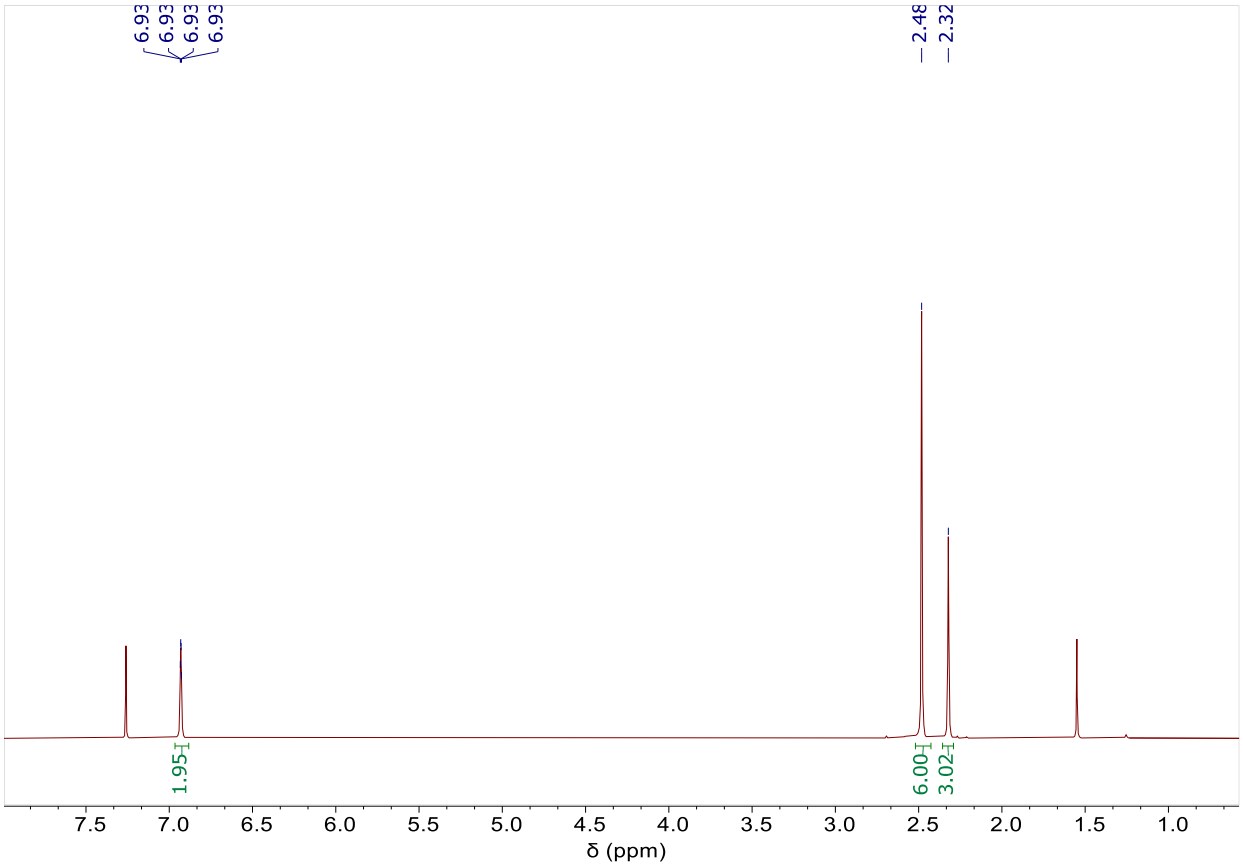
141 Table S3: Tertiary isocyanides results

142 ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 – 6.90 (m, 2H, H3), 2.48 (s, 6H, H5), 2.32 (s, 3H, H1).

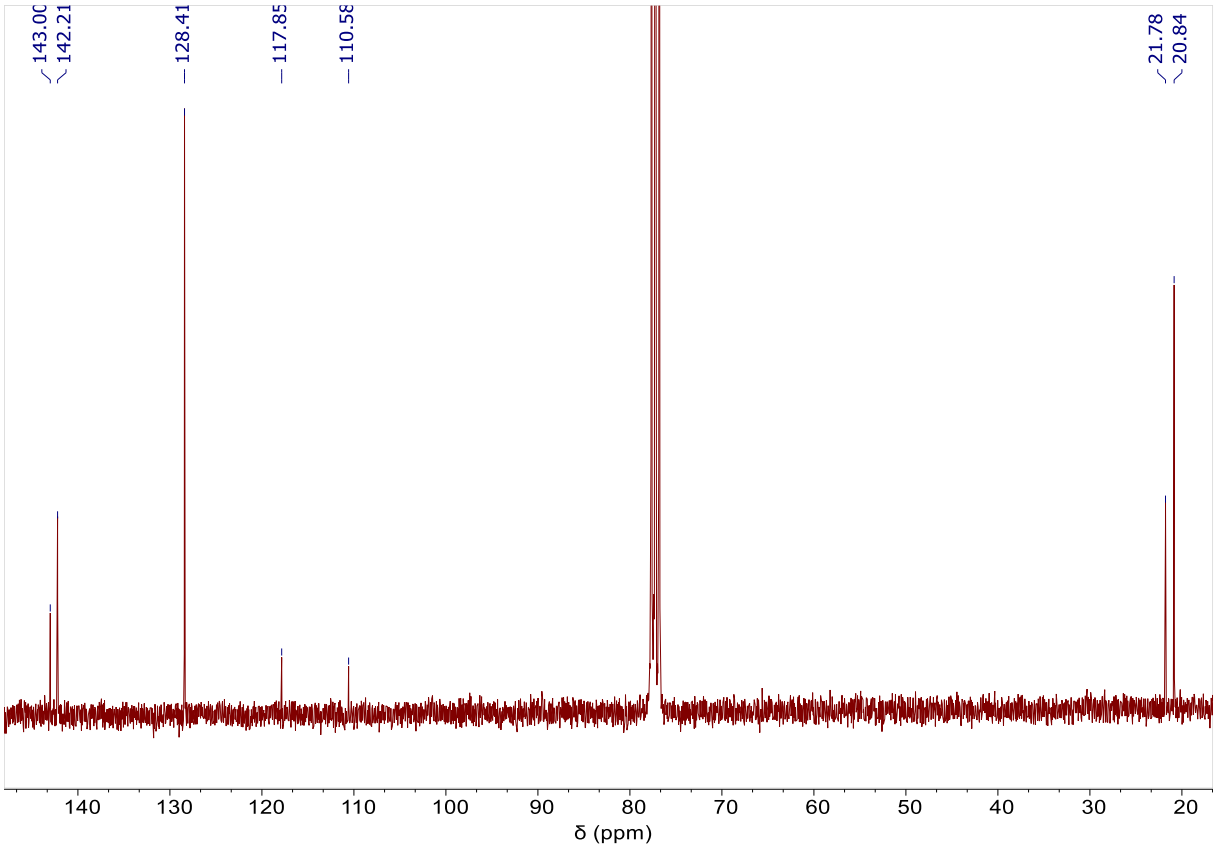
143 ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0 (C6), 142.2 (C4), 128.4 (C3), 117.9 (C2)), 110.6 (C7), 21.8 (C1), 20.8
144 (C5).

145 Data were consistent with the literature [4].

146


6.93
6.93
6.93
6.93
2.48
2.32
1.95
6.00
3.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
δ (ppm)

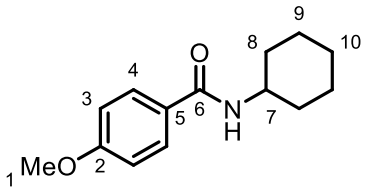
147


143.00
142.21
128.41
117.85
110.58
21.78
20.84
140
130
120
110
100
90
80
70
60
50
40
30
20
δ (ppm)

148

149

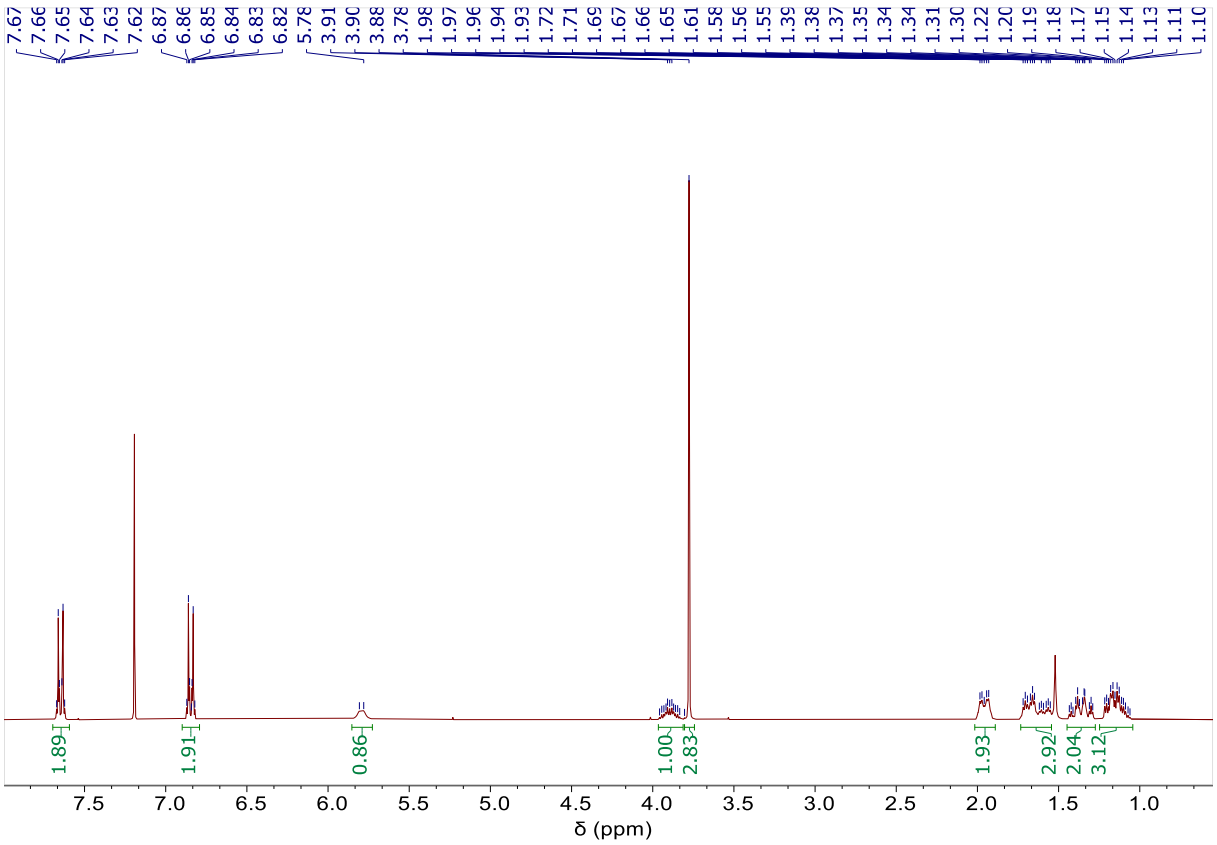
N-cyclohexyl-4-methoxybenzamide, **3f**



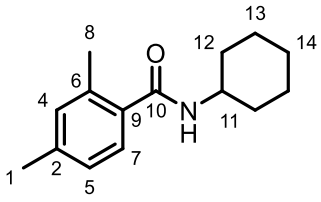
Compound **3b** was obtained following General Method A from anisole and cyclohexyl isocyanide **2a** in 17 % yield (17 mg, white solid, purified by FCC, gradient 100 % cyclohexane to 9/1 cyclohexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.59 (m, 2H, H4), 6.90 – 6.79 (m, 2H, H3), 5.79 (br d, *J* = 8.0 Hz, 1H, N-H), 3.96 – 3.83 (m, 1H, H7), 3.78 (s, 3H, H1), 2.01 – 1.90 (m, 2H, H8), 1.75 – 1.54 (m, 3H, H8, H10), 1.46 – 1.26 (m, 2H, H9), 1.15 (m, 3H, H9,H10).

Data were consitent with the literature [3].



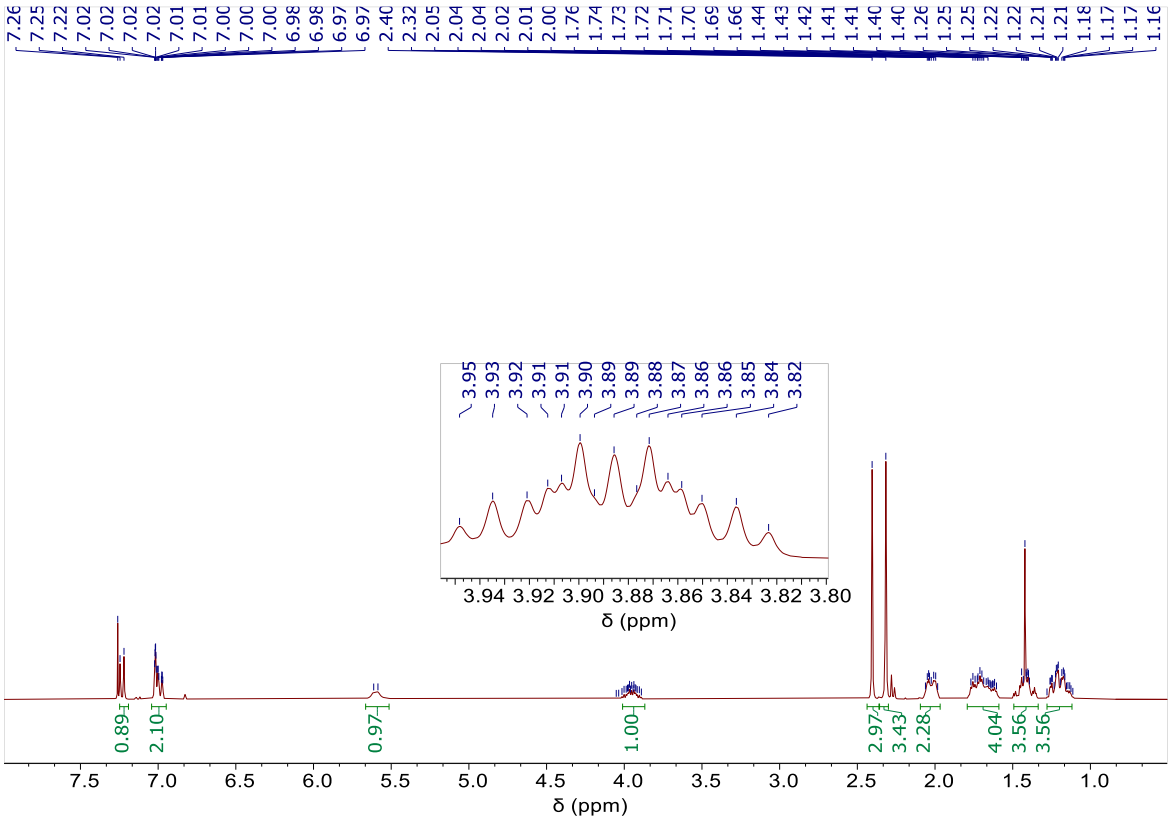
N-cyclohexyl-2,4-dimethylbenzamide, compound **3g**



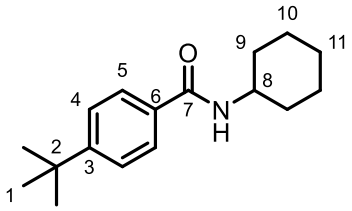
Compound **3c** was obtained following General Method A, from *m*-xylene and cyclohexyl isocyanide **2a** (67 mg, 36 %, white solid, purified by FCC, gradient 100 % cyclohexane to 9/1 cyclohexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 7.12 (m, 1H, H7), 6.99 – 6.87 (m, 2H, H4, H5), 5.53 (br d, *J* = 8.0 Hz, 1H, N-H), 3.95 – 3.80 (m, 1H, H11), 2.34 (s, 3H, H1), 2.25 (s, 3H, H3), 2.03 – 1.89 (m, 2H, H12), 1.77 – 1.52 (m, 2H, H12), 1.38 – 1.32 (m, 3H, H13, H14), 1.24 – 1.02 (m, 3H, H13, H14).

Data were consistent with the literature [5].



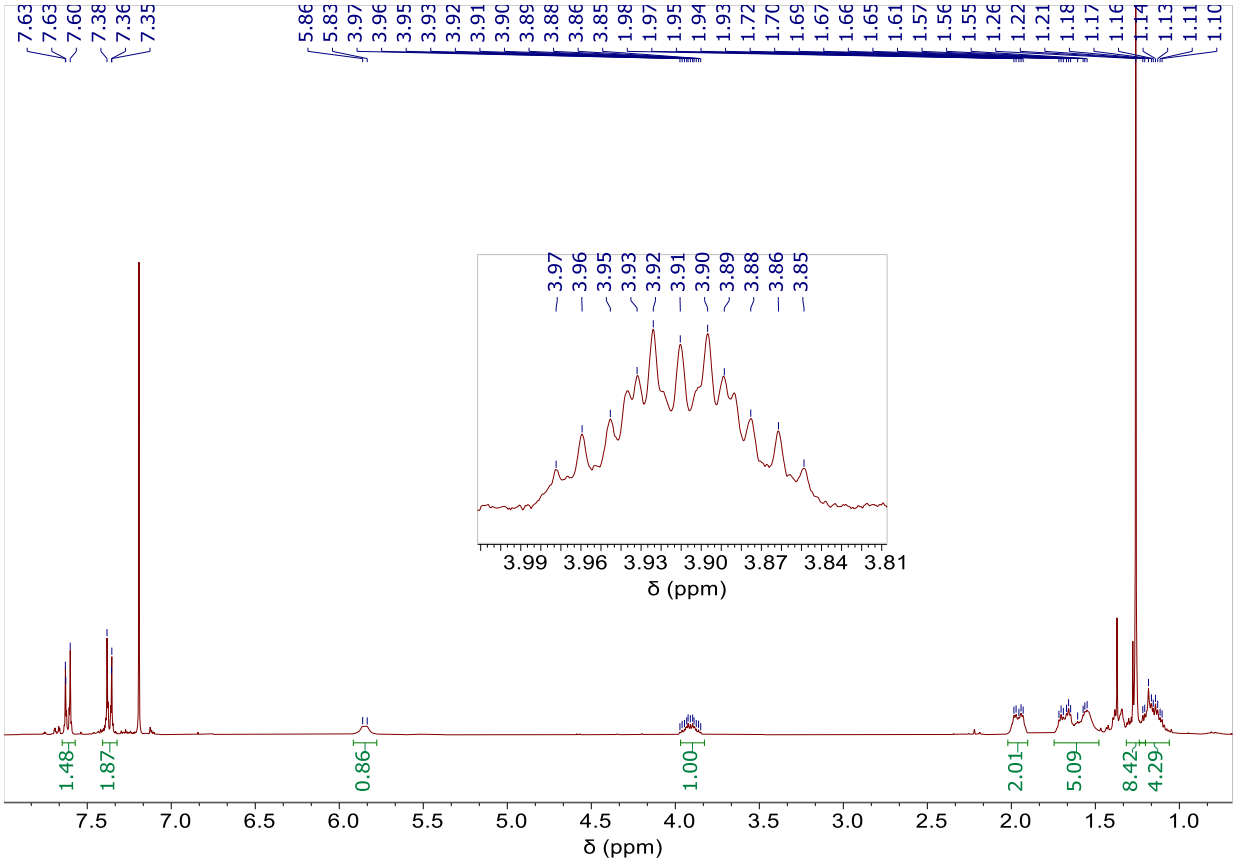
4-(*tert*-butyl)-N-cyclohexylbenzamide compound **3h**



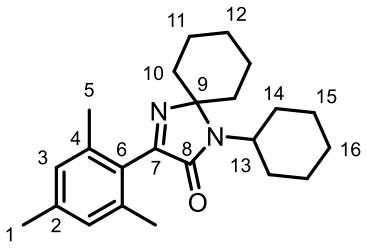
Compound **3d** was obtained following General Method A, from tert-butylbenzene and cyclohexyl isocyanide **2a** (14 mg, 7 %, white solid, purified by FCC gradient 100 % cyclohexane to 9/1 cyclohexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.51 (m, 2H, H5), 7.44 – 7.30 (m, 2H, H4), 5.85 (br d, *J* = 8.0 Hz, 1H, N-H), 3.98 – 3.85 (m, 1H, H8), 2.01 – 1.90 (m, 2H, H9), 1.75 – 1.52 (m, 4H, H9,H10), 1.26 (s, 9H, H1), 1.23 – 1.07 (m, 4H, H10,H11).

Data were consistent with the literature [6].



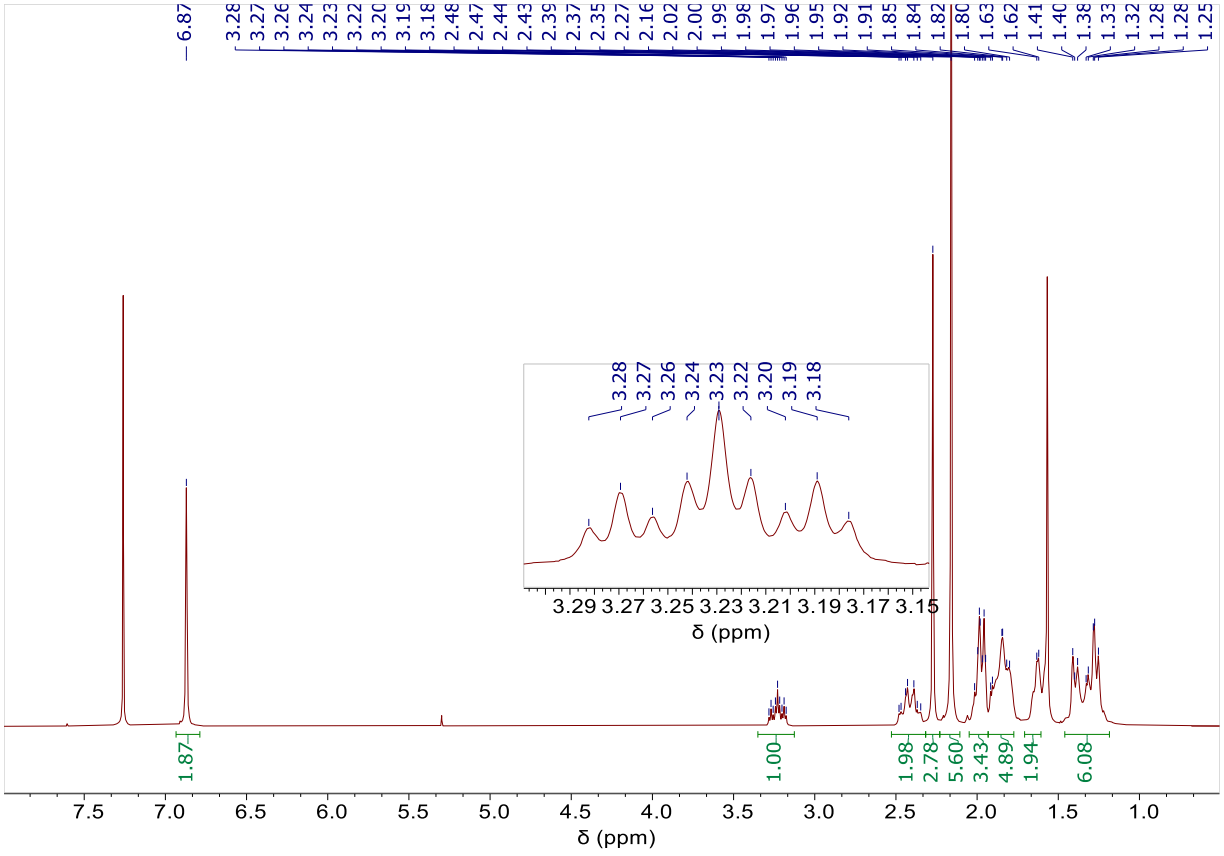
4a 1-cyclohexyl-3-mesityl-1,4-diazaspiro[4.5]dec-3-en-2-one,

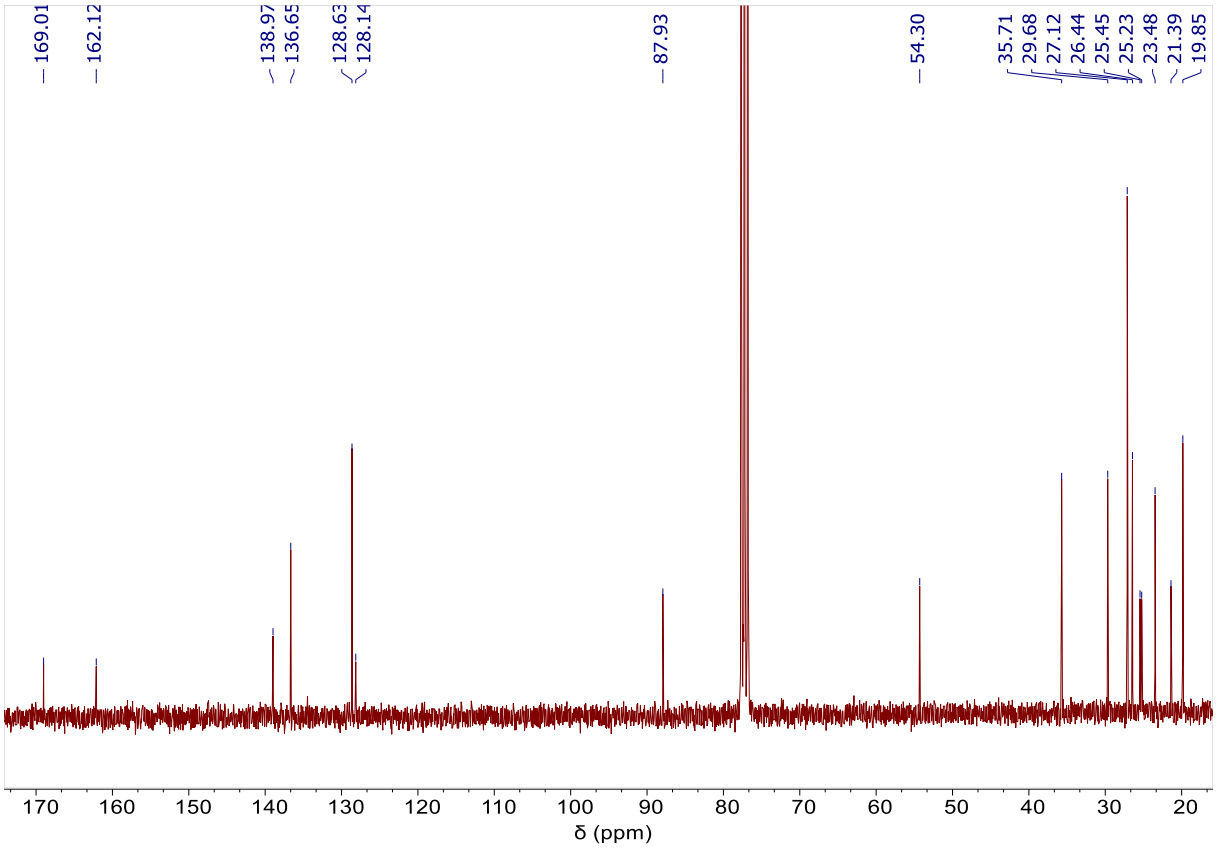


Compound **4a** was obtained along with **3a** in 13 % yield (21 mg, off-white crystals, purification by FCC, gradient 100 % cyclohexane to 9/1 cyclohexane/ethyl acetate). **4a** was recrystallized from *n*-heptane for X-Ray analyses.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 2H, H3), 3.23 (tt, *J* = 12.0, 4.0 Hz, 1H, H13), 2.43 (m, 2H, H10), 2.27 (s, 3H, H1), 2.16 (s, 6H, H5), 2.04 – 1.88 (m, 4H, H10, H14), 1.88 – 1.78 (m, 6H, H14, H11), 1.63 (d, *J* = 3.6 Hz, 2H, H15), 1.48 – 1.18 (m, 6H, H12, H15, H16).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C8), 162.1 (C7), 139.0 (C6), 136.7 (C3), 128.6 (C4), 128.1 (C2), 87.9 (C9), 54.3 (C13), 35.7 (C10), 29.7 (C14), 26.4 (C11), 25.5 (C15), 25.2 (C12), 23.5 (C16), 21.4 (C1), 19.9 (C5).





X-Ray crystal structure determination. A single crystal was selected, mounted and transferred into a cold nitrogen gas stream. Intensity data was collected with a Bruker Kappa APEX II system using fine-focus sealed tube Mo-Kα radiation. Unit-cell parameters determination, data collection strategy, integration and absorption correction were carried out with the Bruker APEX suite of programs. The structure was solved with SHELXT and refined anisotropically by full-matrix least-squares methods with SHELXL using WinGX. The structure was deposited at the Cambridge Crystallographic Data Centre with number CCDC 2492104 and can be obtained free of charge via www.ccdc.cam.ac.uk.

Crystal data for P9. $C_{23}H_{32}N_2O$, monoclinic P $2_1/c$, a = 17.2371(18) Å, b = 13.5548(13) Å, c = 8.8187(9) Å, α = γ = 90°, β = 102.058(3)°, V = 2015.0(4) $Å^3$, Z = 4, colorless prism 0.55 × 0.4 × 0.05 mm^3, μ = 0.071 mm^{-1}, min / max transmission = 0.97 / 1.00, T= 200(1) K, λ = 0.71073 Å, θ range = 25.24° to 30.56°, 8275 reflections measured, R_{int} = 0.0348, completeness = 0.975, 239 parameters, 0 restraints, final R indices R1 [I>2σ(I)] = 0.0461 and wR2 (all data) = 0.1189, GOF on F^2 = 1.033, largest difference peak / hole = 0.25 / -0.25 e·$Å^{-3}$.

References

213 [1] Gokel,G. W.; Widera,R. P.; Weber,W. P. *Organic Syntheses.* **1976**, *55*, 96.

214 [2] Patil, P.; Ahmadian-Moghaddama, M.; Dömling, A. *Green Chem*. **2020**, *22*, 6902-6911

215 [3] Zhu, YP; Sergeyev, S.; Franck, P.; Orru, R. V. A.; Maes, B. U. W. *Org. Lett.* **2016**, *18*, 4602–4605.

216 [4] Ushijima, S.; Moriyama, K.; Togo, H. *Tetrahedron*. **2011**, *67*, 958-964.

217 [5] Herbert, J. M.; Hewson, A. T.; Peace, J. E. *Synthetic Communications*, **1998**, *28*, 823-832.

218 [6] Jo, Y.; Ju, J.; Choe, J.; Ho Song, K.; Lee, S. *J. Org. Chem.* **2009**, *74*, 6358–6361.