Supporting Information
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Formation of imidazolones by ring-closure of \( \alpha \)-isocyanamides: exploring new reactivities

Supporting Information

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**General information**

All reagents were purchased from commercial suppliers and were used without further purification.

The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation ($\lambda = 254$ nm) and/or spraying TLC stain such as a KMnO$_4$ solution followed by heating at 200 °C. Flash chromatography columns were performed on silica gel 60 (230-400 mesh, 0.040-0.063 mm).

$^1$H and $^{13}$C NMR spectra were recorded at room temperature on a Brucker Advance spectrometer operating at 300 MHz and 75 MHz respectively. Chemical shifts are given in parts per million and $^1$H and $^{13}$C NMR spectra were referenced using the solvent signal as an internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, qt: quintet, m: multiplet, b: broad. Coupling constants ($J$) are reported in Hertz (Hz). When necessary, signals were assigned by means of two-dimensional NMR spectroscopy: $^1$H-$^{13}$C-COSY (HSQC: Heteronuclear Single Quantum Coherence) and $HMBC$ (Heteronuclear Multiple Bond Correlation).

HRMS were recorded on a LC Waters Acquity coupled to a Waters LCT Premier XE instrument. The infrared spectra of compounds were recorded on a Perkin Elmer Spectrum 100 FT IR spectrometers.

Melting points (mp [°C]) were measured in open capillary tubes and are uncorrected, performed on a Stuart SMP3.
Synthetic Procedures and Analytical Data

1. Synthetic Procedures for isocyanocyclopentane-1-carboxamide

1-formamidocyclopentane-1-carboxylic acid:

\[
\text{NH} \quad \text{H} \\
\text{O} \quad \text{OH}
\]

To a solution of 1-amino-1-cyclopentanecarboxylic acid (cycloleucine, 10.0 g, 0.08 mol) in formic acid (100 mL), acetic anhydride (3.5 equiv., 26 mL, 0.28 mol) was added dropwise. The reaction mixture was stirred 4 hours at 50°C. Then, water (50 mL) was introduced and the mixture was cooled to room temperature. The solvents were removed in vacuo and the product was obtained by trituration in diethyl ether, as a white solid in 98% yield. It was used without further purification.

\(^1H\) NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 12.30 (bs, 1H, COOH), 8.37 (bs, 1H, NH), 7.88 (d, 1H, J=3Hz, H\text{CHO}), 2.05-1.82 (m, 4H, H\text{Cy}), 1.68-1.61 (m, 4H, H\text{Cy})

\(^{13}C\) NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) 174.9, 160.8, 64.3, 36.4, 24.0

IR (ATR): 3295, 2979, 2875, 1699, 1621, 1536, 1263, 1199, 696, 419 cm\(^{-1}\)

m.p.: 185.8 – 186.7 °C

HRMS: Calcd for C\(_7\)H\(_{11}\)NO\(_3\): [M+H]+ 156.0661, found 156.0656

N-benzyl-1-formamidocyclopentane-1-carboxamide:

\[
\text{NH} \quad \text{H} \\
\text{O} \quad \text{NH}
\]

To 1-formamidocyclopentane-1-carboxylic acid (5.0 g, 0.032 mol) in dichloromethane (75 mL), N,N'-dicyclohexylcarbodiimide (1 equiv., 6.6 g, 0.032 mol) was introduced in one portion. The reaction mixture was stirred 1 hour at reflux. After cooling at rt, N,N'-dicyclohexylurea was removed by filtration. Benzylamine (1 equiv., 3.5 ml, 0.032 mol) was added to the filtrate and the reaction was stirred 1 hour at reflux. The reaction mixture was cooled to room temperature and the solid was filtrated. The desired compound was obtained by trituration in pentane as a white solid in 95% yield.

\(^1H\) NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 8.24 (s, 1H, H\text{CHO}), 8.18 (br t, 1H, NH), 7.96 (bs, 1H, NH), 7.30-7.19 (m, 5H, H\text{Aro}), 4.27 (d, 2H, J=6.13 Hz, H\text{Bn}), 2.11-1.88 (m, 4H, H\text{Cy}), 1.66-1.64 (m, 4H, H\text{Cy})

\(^{13}C\) NMR (75 MHz, DMSO-d\(_6\)) \(\delta\) 173.1, 161.1, 139.9, 128.0, 126.7, 126.4, 65.8, 42.3, 36.3, 23.9
IR (ATR): 3273, 3028, 2872, 1649, 1534, 1386, 754, 699 cm⁻¹
m.p.: 102.0 °C
HRMS: Calcd for: [M+H]+ 247.1441, found 247.1447

_N-benzyl-1-isocyanocyclopentane-1-carboxamide 1:_

To _formamidocyclopentane-1-carboxamide_ (5.0 g, 0.02 mol) and triethylamine (14 mL, 0.1 mol, 5 equiv.) in dry dichloromethane (100 mL), phosphoryl chloride (2.3 mL, 0.025 mol, 1.25 equiv.) was added dropwise while maintaining the temperature between 0-5°C. The reaction mixture was warmed to room temperature and stirred 2 hours. Then, a saturated aqueous solution of NaHCO₃ (100 mL) was added slowly and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried on magnesium sulphate, filtered and evaporated _in vacuo_. The crude product was purified by silica gel column chromatography (Petroleum Ether 100% to Petroleum Ether-Ethyl Acetate 80-20) to afford the expected product, as a white solid (90% yield).

¹H NMR (300 MHz, CDCl₃) δ 7.34-7.21 (m, 5H, H_aromatic), 6.95 (bs, 1H, NH), 4.43 (d, 2H, J = 5.75 Hz, H_Bn), 2.34 -1.84 (m, 8H, H_cyclo)

¹³C NMR (75 MHz, CDCl₃) δ 168.6, 160.7 (bt, J= 4.3 Hz, C_isocyanate), 137.4, 128.9, 127.8, 127.7, 70.8 (bt, J= 4.3 Hz, C_quatcy), 44.2, 40.4, 23.3

IR (ATR): 3331, 2945, 2124, 1663, 1520, 1368, 1250, 1027, 696, 673 cm⁻¹
m.p.: 69.5 – 70.6 °C
HRMS: Calcd for C₁₄H₁₆N₂O: [M+H]+ 229.1341, found 229.1340

2. General Procedure for ring-closure reaction

To _N-benzyl-1-isocyanocyclopentane-1-carboxamide 1_ (200 mg, 0.88 mmol) in dry THF (35 mL) at -78°C, was added dropwise n-butyllithium (0.42mL, 2.5 M in hexanes, 1.056 mmol, 1.2 equiv.). The reaction mixture was stirred 1 hour at -78°C. The appropriate electrophile (1.056 mmol, 1.2 equiv.) was added to the solution and the reaction was left warming to room temperature. Then, a saturated aqueous solution of NH₄Cl (20 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried on magnesium sulphate, filtered and evaporated _in vacuo_. The crude product was purified by silica gel column chromatography (Petroleum Ether 100% to Petroleum Ether-Ethyl Acetate 50-50), to afford the expected product.
3-benzyl-1,3-diazaspiro[4.4]non-1-en-4-one 2:

2 was obtained according to the general procedure with acetic acid as electrophile. It was obtained with as a pale-yellow oil in 91% yield. Characterizations were in accordance with the literature.1

$^{1}$H NMR (300 MHz, CDCl$_3$) δ 7.50 (s, 1H, H$_{imid}$), 7.33-7.16 (m, 5H, H$_{Aro}$), 4.58 (s, 2H, H$_{Bn}$), 2.00-1.70 (m, 8H, H$_{Cy}$)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 184.9, 151.0, 135.6, 128.9, 128.0, 127.4, 77.7, 44.4, 37.1, 25.7

3-benzyl-2-(hydroxy(phenyl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one 2a:

2a was obtained according to the general procedure with benzaldehyde as electrophile. It was obtained as a white solid in 80% yield.

$^{1}$H NMR (300 MHz, CDCl$_3$) δ 7.40-7.25 (m, 8H, H$_{Aro}$), 7.00-6.97 (m, 2H, H$_{Aro}$), 5.15 (s, 1H, H$_{Bn}$), 4.80 (d, 1H, $J=16.10$ Hz, H$_{Bn}$), 4.61 (bs, 1H, OH), 3.82 (d, 1H, $J=16.10$ Hz, H$_{Bn}$), 2.10-1.85 (m, 8H, H$_{Cy}$)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 186.3, 163.0, 137.9, 135.8, 129.4, 129.4, 129.1, 128.0, 127.7, 126.7, 76.6, 69.9, 43.5, 37.7, 26.1

IR (ATR): 3678, 2971, 2903, 1737, 1621, 1394, 1252, 1072, 1051, 693, 466 cm$^{-1}$

m.p.: 138.4 - 139.2 °C

HRMS: Calcd for C$_{21}$H$_{22}$N$_2$O$_2$: [M+H]$^+$ 335.1760, found 335.1757

3-benzyl-2-(hydroxy(4-methoxyphenyl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one 2b:

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1 Muselli, M.; Colombeau, L.; Hédouin, J.; Hoarau, C.; Bischoff, L. Synlett 2016, 27, 2819
2b was obtained according to the general procedure with p-anisaldehyde as electrophile. It was obtained as a white solid in 66 % yield.

^1H NMR (300 MHz, CDCl₃) δ 7.30-7.25 (m, 3H, HAro), 7.18 (d, 2H, J= 8.75 Hz, H_Aro), 7.00-6.97 (m, 2H, HAro), 6.89 (d, 2H, J= 8.75 Hz, H_Aro), 5.05 (s, 1H, HBn), 4.80 (d, 1H, J= 16.10 Hz, H_Bn), 4.31 (bs, 1H, OH), 3.81 (s, 3H, HMeO), 3.80 (d, 1H, J= 16.10 Hz, H_Bn), 2.11-1.86 (m, 8H, H_Cy).

^13C NMR (75 MHz, CDCl₃) δ 186.5, 162.9, 160.4, 136.0, 130.1, 129.2, 129.1, 128.0, 126.7, 114.8, 76.7, 69.4, 55.5, 43.4, 37.8, 37.7, 26.0.

IR (ATR): 3058, 2955, 2236, 1671, 1586, 1522, 1165, 909, 850, 624, 484 cm⁻¹

m.p.: 144.8 - 145.9 °C


methyl 4-((3-benzyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-2-yl)(hydroxy)methyl)benzoate 2c:

2c was obtained according to the general procedure with methyl 4-formylbenzoate as electrophile. It was obtained as a white solid in 71 % yield.

^1H NMR (300 MHz, CDCl₃) δ 8.16 (d, 2H, J= 8.40 Hz, H_Aro), 7.33 (d, 2H, J= 8.40 Hz, H_Aro), 7.28-7.25 (m, 3H, H_Aro), 6.96-6.93 (m, 2H, H_Aro), 5.20 (s, 1H, H_Bn), 4.80 (d, 1H, J= 16.15 Hz, H_Bn), 4.57 (bs, 1H, OH), 3.93 (s, 3H, HMeO), 3.88 (d, 1H, H_Bn), 2.10-1.86 (m, 8H, H_Cy)

^13C NMR (75 MHz, CDCl₃) δ 186.2, 166.5, 162.6, 142.6, 135.6, 131.1, 130.6, 129.1, 128.1, 127.7, 126.6, 69.6, 52.5, 43.6, 37.8, 26.1
3-benzyl-2-(9-hydroxy-9H-fluoren-9-yl)-1,3-diazaspiro[4.4]non-1-en-4-one 2d:

2d was obtained according to the general procedure with 9-fluorenone as electrophile. It was obtained as a pale-yellow solid in 73 % yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.55 (d, 2H, $J$= 7.50 Hz, HAro), 7.29 (dt, 2H, $J$= 7.50 Hz; 1.15 Hz, HAro), 7.22 (d, 2H, $J$= 7.45 Hz, HAro), 7.10 (dt, 2H, $J$= 7.45 Hz; 1.15 Hz, HAro), 7.00-6.89 (m, 3H, HAro), 7.30-7.27 (m, 2H, HAro), 5.80 (s, 1H, OH), 3.81 (s, 2H, HBn), 2.15-2.01 (m, 8H, HCy)

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 187.0, 163.4, 144.0, 141.0, 135.4, 130.5, 128.7, 127.9, 126.7, 125.4, 124.7, 120.7, 78.9, 76.1, 43.8, 38.1, 26.1

IR (ATR): 3296, 2954, 1722, 1600, 1452, 1338, 775, 716, 597 cm$^{-1}$

m.p.: 160.3 – 161.5 °C

HRMS: Calcd for C$_{27}$H$_{24}$N$_2$O$_2$: [M+H]$^+$ 409.1916, found 409.1907

3-benzyl-2-(hydroxydiphenylmethyl)-1,3-diazaspiro[4.4]non-1-en-4-one 2e:

2e was obtained according to the general procedure with benzophenone as electrophile. It was obtained as a white solid in 83 % yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.34-7.26 (m, 10H, HAro), 7.11-7.09 (m, 3H, HAro), 6.70-6.65 (m, 2H, HAro), 4.68 (s, 1H, HBn), 4.52 (s, 2H, HBn), 2.10-1.94 (m, 8H, HCy)
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 187.7, 164.1, 141.4, 136.1, 128.5, 128.2, 128.0, 126.8, 126.0, 78.6, 76.4, 45.7, 37.6, 26.1

IR (ATR): 3423, 2938, 2830, 1704, 1513, 1354, 1248, 1173, 1030, 698 cm$^{-1}$

m.p.: 152.7 – 153.5 °C

HRMS: Calcd for C$_{27}$H$_{26}$N$_2$O$_2$: [M+H]$^+$ 411.2073, found 411.2071

3-benzyl-2-(4-methoxybenzoyl)-1,3-diazaspiro$[4.4]$non-1-en-4-one 2f:

\[ \text{O} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{O} \]
\[ \text{MeO} \]

2f was obtained according to the general procedure with 4-methoxy-N-methoxy,N-methylbenzamide (a) or $p$-anisoyl chloride (b) as electrophile. It was obtained as a white solid in 69 % (a) and 66 % (b) yield, respectively.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.95 (d, 2H, $J=9.00$ Hz, H$_{\text{Aro}}$), 7.19-7.09 (m, 5H, H$_{\text{Aro}}$), 6.86 (d, 2H, $J=9.00$ Hz, H$_{\text{Aro}}$), 4.90 (s, 2H, H$_{\text{Bn}}$), 3.84 (s, 3H, H$_{\text{MeO}}$), 2.15-1.94 (m, 8H, H$_{\text{Cy}}$)

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 185.6, 184.7, 165.0, 156.0, 136.7, 133.2, 128.8, 127.9, 127.8, 127.4, 114.0, 78.3, 55.7, 44.4, 37.7, 26.3

IR (ATR): 2954, 1719, 1585, 1261, 1151, 810, 694, 621 cm$^{-1}$

m.p.: 78.1 – 78.9 °C

HRMS: Calcd for C$_{22}$H$_{22}$N$_2$O$_3$: [M+H]$^+$ 363.1709, found 363.1700

3-benzyl-2-(phenylthio)-1,3-diazaspiro$[4.4]$non-1-en-4-one 2g:

\[ \text{O} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{S} \]

2g was obtained according to the general procedure with diphenyl disulfide as electrophile. It was obtained as a white solid in 81 % yield.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.53-7.50 (m, 2H, H$_{Ar}$), 7.38-7.27 (m, 8H, H$_{Ar}$), 4.70 (s, 2H, H$_{N}$), 2.01-1.78 (m, 8H, H$_{Cy}$)

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 185.4, 158.0, 136.3, 133.6, 129.4, 129.2, 128.9, 127.9, 127.6, 127.4, 78.5, 44.3, 37.5, 26.1

IR (ATR): 2958, 1717, 1563, 1432, 1331, 1148, 939, 751, 688, 476 cm$^{-1}$

m.p.: 104.8 - 105.6 °C

HRMS: Calcd for C$_{20}$H$_{20}$N$_2$OS: [M+H]$^+$ 337.1375, found 337.1368

3-benzyl-2-(benzylthio)-1,3-diazaspiro[4.4]non-1-en-4-one 2h:

2h was obtained according to the general procedure with dibenzyl disulfide as electrophile. It was obtained as a white solid in 73 % yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.27-7.11 (m, 10H, H$_{Ar}$), 4.52 (s, 2H, H$_{SBn}$), 4.23 (s, 2H, H$_{Bn}$), 1.95-1.68 (m, 8H, H$_{Cy}$)

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 185.2, 158.7, 136.4, 136.1, 129.3, 128.7, 128.6, 127.8, 127.7, 127.6, 78.1, 44.0, 37.6, 34.6, 26.0

IR (ATR): 3063, 3030, 3956, 1724, 1563, 1335, 1160, 950, 694 cm$^{-1}$

HRMS: Calcd for C$_{21}$H$_{22}$N$_2$OS: [M+H]$^+$ 351.1531, found 351.1535

3-benzyl-2-bromo-1,3-diazaspiro[4.4]non-1-en-4-one 2i:

2i was obtained according to the general procedure with N-bromosuccinimide as electrophile. The compound was obtained as a brown sticky oil in 80 % yield. It is preferable to use it quickly for further reactions, since it cannot be stored for a prolonged period of time.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36-7.23 (m, 5H, H$_{Ar}$), 4.72 (s, 2H, H$_{Bn}$), 2.01-1.84 (m, 8H, H$_{Cy}$)

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 183.0, 139.2, 135.8, 128.9, 128.1, 127.6, 80.8, 45.5, 37.3, 25.8.
HRMS: Calcd for C$_{14}$H$_{15}$N$_2$O$_7$Br: [M+H]$^+$ 307.0446, found 307.0451 and calcd for C$_{14}$H$_{15}$N$_2$O$_8$Br: [M+H]$^+$ 309.0426, found 309.0420

$3$-benzyl-$2$-iodo-$1,3$-diazaspiro[4.4]non-$1$-en-$4$-one $2j$:

$2j$ was obtained according to the general procedure with $N$-iodosuccinimide as electrophile. The compound was obtained as a brown sticky oil in 88 % yield. (Unstable product)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35-7.23 (m, 5H, HAro), 4.69 (s, 2H, HBn), 2.02-1.85 (m, 8H, HCy)

$^13$C NMR (75 MHz, CDCl$_3$) $\delta$ 182.4, 135.9, 128.9, 128.0, 127.6, 115.3, 81.9, 46.8, 37.5, 25.9

HRMS: Calcd for C$_{14}$H$_{15}$IN$_2$O: [M+H]$^+$ 355.0307, found 355.0314

3. General Procedures for organometallics coupling

a) General procedure for the synthesis of TMEDA-Pd(aryl)(I)$_2$

Pd(db$_2$(500 mg, 0.87 mmol) and the appropriate aryl iodide (1.218 mmol, 1.4 equiv.) were mixed in THF (50 mL). TMEDA (0.160 mL, 1.044 mmol, 1.2 equiv.) was added, and the resulting mixture was stirred at 50 ºC for 15 min. The reaction mixture was filtered through a plug of Celite (no protection from air was required), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography through silica gel (Petroleum Ether 100% to Ethyl Acetate 100%).

$TMEDA$-$Pd(phenyl)(I)$

The expected compound was obtained according to the general procedure with iodobenzene as aryl iodide. It was obtained as an orange solid in 74 % yield.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.25-7.21 (m, 2H, HAro), 6.93-6.87 (m, 2H, HAro), 6.81-6.75 (m, 1H, HAro), 2.73-2.69 (m, 2H, H$_{CH2}$), 2.67 (s, 6H, HMe), 2.56-2.52 (m, 2H, H$_{CH2}$), 2.31 (s, 6H, HMe)

$^13$C NMR (75 MHz, CDCl$_3$) $\delta$ 144.7, 136.5, 126.6, 122.7, 62.2, 58.3, 50.0, 49.8

The expected compound was obtained according to the general procedure with 4-iodotoluene as aryl iodide. It was obtained as an orange solid in 59% yield.

\[
\text{^{1}H NMR (300 MHz, CDCl}_3) \delta 7.10 (d, 2H, J= 8.00 Hz, H_{aro}), 6.76 (d, 2H, J= 8.00 Hz, H_{aro}), 2.73-2.70 (m, 2H, H_{CH2}), 2.67 (s, 6H, H_{Me}), 2.57-2.53 (m, 2H, H_{CH2}), 2.33 (s, 6H, H_{Me}), 2.21 (s, 3H, H_{Tol})
\]

\[
\text{^{13}C NMR (75 MHz, CDCl}_3) \delta 139.5, 136.1, 131.8, 127.7, 62.2, 58.3, 50.0, 49.8, 20.7
\]

The expected compound was obtained according to the general procedure with 4-iodoanisole as aryl iodide. It was obtained as an orange solid in 66% yield.

\[
\text{^{1}H NMR (300 MHz, CDCl}_3) \delta 7.08 (d, 2H, J= 8.60 Hz, H_{aro}), 6.61 (d, 2H, J= 8.60 Hz, H_{aro}), 3.70 (s, 3H, H_{MeO}), 2.73-2.69 (m, 2H, H_{CH2}), 2.67 (s, 6H, H_{Me}), 2.57-2.53 (m, 2H, H_{CH2}), 2.31 (s, 6H, H_{Me})
\]

\[
\text{^{13}C NMR (75 MHz, CDCl}_3) \delta 156.6, 136.2, 131.7, 113.0, 62.2, 58.4, 55.2, 50.0, 49.8
\]

The expected compound was obtained according to the general procedure with 4-iodobenzonitrile as aryl iodide. It was obtained as an orange solid in 77% yield.

\[
\text{^{1}H NMR (300 MHz, CDCl}_3) \delta 7.46 (d, 2H, J= 7.35 Hz, H_{aro}), 7.16 (d, 2H, J= 7.35 Hz, H_{aro}), 2.77-2.73 (m, 2H, H_{CH2}), 2.70 (s, 6H, H_{Me}), 2.61-2.57 (m, 2H, H_{CH2}), 2.33 (s, 6H, H_{Me})
\]

\[
\text{^{13}C NMR (75 MHz, CDCl}_3) \delta 156.9, 137.6, 128.7, 120.2, 106.2, 62.3, 58.5, 60.2, 50.1
\]

b) General procedure for organometallics coupling
**Suzuki coupling procedure A**

3-benzyl-2-bromo-1,3-diazaspiro[4.4]non-1-en-4-one 2i (0.32 mmol), the appropriate boronic acid (0.49 mmol, 1.5 equiv.), K$_2$CO$_3$ (4 equiv., 1.3 mmol) and PdCl$_2$dppf (0.1 equiv., 0.032 mmol) were placed in a sealed tube containing a magnetic stir bar. 1,4-dioxane (1 mL) and water (0.5 mL) were added into the tube and the solution was degassed with N$_2$. The tube was sealed and heated at 80 °C for 18 hours. The reaction was filtered over a Celite® pad (washed with DCM). The solvents were removed under reduced pressure and the crude product was then purified by column chromatography (Petroleum Ether 100% to Petroleum Ether-Ethyl Acetate 80-20).

**Suzuki coupling procedure B (one-pot from isonitrile)**

To N-benzyl-1-isocyanocyclopentane-1-carboxamide 1 (200 mg, 0.88 mmol) in dry THF (35 mL) at -78°C, was added dropwise n-butyllithium (0.42mL, 2.5 M in hexanes, 1.056 mmol, 1.2 equiv.). The reaction mixture was stirred 1 hour at -78°C. N-bromosuccinimide (188 mg, 1.056 mmol, 1.2 equiv.) was introduced in the solution and the reaction was left warming to room temperature. Then the reaction mixture was concentrated to approx. 1 mL and introduced in a sealed tube containing a magnetic stir bar. The appropriate boronic acid (1.32 mmol, 1.5 equiv.), K$_2$CO$_3$ (4.24 mmol, 4 equiv.) and PdCl$_2$dppf (0.1 equiv., 0.088 mmol) were placed in a sealed tube containing a magnetic stir bar. 1,4-dioxane (4 mL) and water (2 mL) were added into the tube and the solution was degassed with N$_2$. The tube was sealed and heated at 80 °C for 18 hours. The reaction was filtered through a Celite® pad (washed with DCM). The solvents were removed under reduced pressure and the crude product was then purified by column chromatography (Petroleum Ether 100% to Petroleum Ether-Ethyl Acetate 80-20).

**Zhu coupling procedure**

To a solution of N-benzyl-1-isocyanocyclopentane-1-carboxamide 1 (100 mg, 0.44 mmol), aryl iodide (0.66 mmol, 1.5 equiv) and PPh$_3$ (12 mg, 0.044 mmol, 0.1 equiv) in DMF (2 mL) were added Pd(OAc)$_2$ (5 mg, 0.022 mmol, 0.05 equiv,) and Cu$_2$O (63 mg, 0.44 mmol, 1 equiv). The reaction was performed in a sealed tube under inert atmosphere. The reaction mixture was stirred at 130 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with AcOEt (10 mL), washed with a 1:1 mixture of aqueous ammonia and brine. The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (Petroleum Ether 100% to Petroleum Ether-Ethyl Acetate 80-20).

**(tmeda)Pd(Aryl)(I) coupling procedure**

To isocyanocyclopentane-1-carboxamide 1 (150 mg, 0.66 mmol) in DCM (10 mL), was added the required palladium complex (tmeda)Pd(Aryl)(I) (0.66 mmol, 1 equiv.). The reaction mixture was stirred 15 minutes at 50 °C. The appropriate electrophile (1.056 mmol, 1.2 equiv.) was added to the solution and the reaction was warmed to room temperature. The reaction was filtered over a Celite® pad (washed with DCM). The solvents were evaporated under reduced pressure and the crude product was purified by column chromatography (Petroleum Ether 100% to Petroleum Ether-Ethyl Acetate 80-20).

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3-benzyl-2-phenyl-1,3-diazaspiro[4.4]non-1-en-4-one 3a:

3a was obtained according to “Suzuki coupling A” procedure with phenylboronic acid (a) as electrophile or “Palladium complex coupling” procedure with phenyl iodide (b) as electrophile. The compound was obtained as a white solid in 68 % (a) or 79 % (b) yield. Characterizations were in accordance with the literature4.

1H NMR (300 MHz, DMSO-d6) δ 7.51-7.48 (m, 5H, HAro), 7.28-7.19 (m, 3H, HAro), 6.96-6.93 (m, 2H, HAr), 7.75 (s, 2H, HBn), 1.95-1.82 (m, 8H, HCy)

13C NMR (75 MHz, DMSO-d6) δ 186.1, 159.9, 136.8, 130.7, 129.7, 128.6, 128.5, 127.9, 127.3, 126.1, 76.5, 44.0, 37.1, 25.5

3-benzyl-2-(p-tolyl)-1,3-diazaspiro[4.4]non-1-en-4-one 3b:

3b was obtained according to “Zhu coupling” procedure with 4-bromotoluene (a) as electrophile, “Suzuki coupling A” procedure with 4-tolyllboronic acid (b) as electrophile or “Palladium complex coupling” procedure with 4-iodotoluene (c) as electrophile. The compound was obtained as a white solid in 51 % (a), 76 % (b) or 86 % (c) yield. Characterizations were in accordance with the literature4.

1H NMR (300 MHz, DMSO-d6) δ 7.40 (d, 2H, J= 8.19 Hz, H_Aro), 7.29-7.19 (m, 5H, H_Aro), 6.99-6.96 (m, 2H, H_Aro), 4.75 (s, 2H, H_Bn), 2.30 (s, 3H, H_Tol), 1.97-1.80 (m, 8H, H_Cy)

13C NMR (75 MHz, DMSO-d6) δ 186.2, 159.9, 140.5, 136.9, 129.1, 128.7; 127.9, 127.2, 126.9, 126.0, 76.4, 44.0, 37.1, 25.5, 20.9

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3-benzyl-2-(4-methoxyphenyl)-1,3-diazaspiro[4.4]non-1-en-4-one 3c:

3c was obtained according to “Suzuki coupling A” or “B” procedure with 4-methoxyphenylboronic acid (a or b) as electrophile or “Palladium complex coupling” procedure with 4-iodoanisole (c) as electrophile. The compound was obtained as a pale-yellow oil in 91 % (a), 68 % (b) or 87 % (c) yield, respectively. Characterizations were in accordance with the literature4.

\[ \text{\textsuperscript{1}H NMR (300 MHz, DMSO-}\text{d}_6\text{)} \delta 7.47 \text{ (d, 2H, } J = 8.79 \text{ Hz, } H_{\text{Aro}}), 7.31-7.21 \text{ (m, 3H, } H_{\text{Aro}}), 7.00-6.97 \text{ (m, 2H, } H_{\text{Aro}}), 6.95 \text{ (d, 2H, } J = 8.79 \text{ Hz, } H_{\text{Aro}}), 4.76 \text{ (s, 2H, } H_{\text{Bn}}), 3.77 \text{ (s, 3H, } H_{\text{MeO}}), 1.95-1.80 \text{ (m, 8H, } H_{\text{Cy}}) \]

\[ \text{\textsuperscript{13}C NMR (75 MHz, DMSO-}\text{d}_6\text{)} \delta 186.3, 161.0, 159.5, 137.0, 129.6, 128.7, 127.2, 126.0, 121.9, 113.9, 76.3, 55.3, 44.1, 37.2, 25.5 \]

4-(3-benzyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-2-yl)benzonitrile 3d:

3d was obtained according to “Suzuki coupling A” procedure with 4-cyanophenylboronic acid (a) as electrophile or “Palladium complex coupling” procedure with 4-iodobenzonitrile (b) as electrophile. The compound was obtained as a white solid in 76 % (a) or 79 % (b) yield. Characterizations were in accordance with the literature4.

\[ \text{\textsuperscript{1}H NMR (300 MHz, DMSO-}\text{d}_6\text{)} \delta 7.89 \text{ (d, 2H, } J = 8.57 \text{ Hz, } H_{\text{Aro}}), 7.68 \text{ (d, 2H, } J = 8.57 \text{ Hz, } H_{\text{Aro}}), 7.27-7.16 \text{ (m, 3H, } H_{\text{Aro}}), 6.94-6.91 \text{ (m, 2H, } H_{\text{Aro}}), 4.75 \text{ (s, 2H, } H_{\text{Bn}}), 1.98-1.83 \text{ (m, 8H, } H_{\text{Cy}}) \]

\[ \text{\textsuperscript{13}C NMR (75 MHz, DMSO-}\text{d}_6\text{)} \delta 185.8, 158.9, 136.5, 134.1, 132.5, 128.9, 128.7, 127.4, 126.3, 118.2, 113.3, 77.0, 43.9, 37.1, 25.5 \]

Sonogashira coupling procedure:

3-benzyl-2-bromo-1,3-diazaspiro[4.4]non-1-en-4-one (0.32 mmol), the appropriate boronic acid (0.49 mmol, 1.5 equiv.), CuI (0.0128 mmol, 0.04 equiv.) and PdCl\textsubscript{2}dppf (0.016 mmol, 0.05
equiv.) were placed in a sealed tube containing a magnetic stir bar. 1,4-dioxane (3 mL) and triethylamine (1.8 mL) were added in the tube and the solution was degassed with N₂. The tube was sealed and heated to 100 °C for 18 hours. The reaction was filtered over a Celite® pad (washed with DCM). The solvents were removed under reduced pressure and the crude product was then purified by column chromatography (Petroleum Ether 100% to Petroleum Ether-Ethyl Acetate 80-20).

3-benzyl-2-(phenylethynyl)-1,3-diazaspiro[4.4]non-1-ene-4-one 5a:

![Chemical Structure of 5a](image)

5a was obtained according to “Sonogashira coupling” procedure with ethynylbenzene as electrophile. It was obtained as a colourless liquid in 82 % yield.

¹H NMR (300 MHz, DMSO-d₆) δ 7.59-7.26 (m, 10H, H_Aro), 4.81 (s, 2H, H_Bn), 1.93-1.75 (m, 8H, H_Cy)

¹³C NMR (75 MHz, DMSO-d₆) δ 145.2, 136.9, 132.2, 130.9, 129.1, 128.8, 127.6, 127.0, 119.1, 94.4, 78.2, 77.6, 43.7, 37.0, 25.3

HRMS: Calcd for C₂₂H₂₀N₂O: [M+H]⁺ 329.1654, found 329.1657

3-benzyl-2-((trimethylsilyl)ethynyl)-1,3-diazaspiro[4.4]non-1-ene-4-one 5f:

![Chemical Structure of 5f](image)

5f was obtained according to “Sonogashira coupling” procedure with ethynylbenzene as electrophile. The compound was obtained as a colourless liquid in 79 % yield.

¹H NMR (300 MHz, DMSO-d₆) δ 7.38-7.19 (m, 5H, H_Aro), 4.68 (s, 2H, H_Bn), 1.85-1.67 (m, 8H, H_Cy), 0.19 (s, 9H, H_SiMe)

¹³C NMR (75 MHz, DMSO-d₆) δ 183.6, 144.7, 136.6, 128.7, 128.6, 127.6, 127.2, 126.8, 102.7, 92.7, 77.4, 73.7, 36.9, 25.2, -1.1

HRMS: Calcd for C₁₉H₂₄N₂O₅Si: [M+H]⁺ 325.1736, found 325.1730

3-benzyl-1,3-diazaspiro[4.4]nonane-2,4-dione 4:
4 was obtained as by-product in some palladium coupling reactions.

**$^1$H NMR (300 MHz, DMSO-d6)** δ 8.60 (s, 1H, NH), 7.36-7.20 (m, 5H, H_Aro), 4.53 (s, 2H, H_Bn), 1.97-1.69 (m, 8H, H_Cy)

**$^{13}$C NMR (75 MHz, DMSO-d6)** δ 177.5, 155.5, 136.9, 128.6, 127.4, 127.1, 67.3, 41.0, 37.2, 24.7

**IR (ATR):** 3217, 3107, 2971, 1769, 1703, 1441, 1135, 954, 736, 694 cm$^{-1}$

**m.p.:** 152.7 - 153.4 °C

**HRMS:** Calcd for C$_{14}$H$_{16}$N$_2$O$_2$: [M+H]$^+$ 245.1290, found 245.1284

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4. NMR Spectra
ON OH

2e
\[ \text{Diagram of molecular structure} \]