Supporting Information

Addition of Lithium Carbenoids to Isocyanates: a Direct Access to Synthetically Useful N-substituted 2-Haloacetamides

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Materials and methods.

All $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker Avance spectrometers operating at 200, 300, 400 or 500 MHz and at 50, 75, 100, or 125 MHz, respectively, from CDCl$_3$ solutions. The (residual) solvent signal was used as an internal standard which was related to TMS with $\delta$ 7.26 ppm ($^1$H) and $\delta$ 77.0 ppm ($^{13}$C). The $^{15}$N and $^{19}$F NMR experiments were conducted on a Bruker Avance 400 spectrometer (40 MHz and 377 MHz, respectively). The $^{15}$N NMR spectra were referenced against external nitromethane, for the $^{19}$F NMR spectra absolute referencing via the $\varepsilon$ ratio was used. Spin-spin coupling constants ($J$) are given in Hz. Full and unambiguous assignment of $^1$H, $^{13}$C, $^{15}$N and $^{19}$F-NMR resonances was achieved by combining standard NMR techniques, such as fully $^1$H-coupled $^{13}$C-NMR spectra, APT, DEPT, HSQC, HMBC and NOESY experiments.

All melting points are uncorrected. Column chromatography purifications were conducted on silica gel 60 (40-63 $\mu$m). TLC was carried out on aluminum sheets precoated with silica gel 60F254; the spots were visualized under UV light ($\lambda$ = 254 nm) and/or KMnO$_4$ (aq.) was used as revealing system. Elementary microanalyses were carried out using a Leco® CHNS 932 equipment. IR absorption spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrophotometer.
**General Procedure for the Chemoselective Addition of Li Carbenoids to Isocyanates.**

To a cooled (-78 °C) solution of the isocyanate (1.0 equiv.) in dry diethyl ether (1 M concentration) was added the dihalomethane derivative (1.5 equiv.) and, after 2 min, an ethereal solution of MeLi-LiBr (1.5 M, 1.2 equiv.) was added dropwise during 5 min. The resulting solution was stirred for the appropriate time (see Tables 1 and 2) at that temperature, before a saturated aqueous solution of NH₄Cl was added (2 mL / mmol substrate). After removal of the cooling bath, the mixture was stirred till it reached rt and then, extracted with additional diethyl ether and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and, after removal of the solvent under reduced pressure pure samples of haloacetamides were obtained.
**N-Chloroacetyl-1-aminoadamantane (2a)**

By following the general procedure, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol), ICH\(_2\)Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et\(_2\)O, α-chloroacetamide 2a was obtained in 97% yield (839 mg) as a white solid.

^1^H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 6.22 (bs, 1H), 3.90 (s, 2H), 2.12-2.03 (m, 3H), 2.03-1.95 (m, 6H), 1.66 (t, \(J = 2.8\) Hz, 6H).

^1^3^C NMR (126 MHz, CDCl\(_3\)) \(\delta\): 164.5, 52.3, 42.8, 41.1, 36.1, 29.3.

IR (NaCl, \(\nu_{max}\), cm\(^{-1}\)): 3239, 3080, 2108, 1662, 1569, 1234.

Mp: 119 °C (lit.\(^1\) 119-120 °C)

**Elemental Analysis (%)** for C\(_{12}\)H\(_{18}\)ClNO. Calcd: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.42; H, 8.09; N, 6.27.

**N-Bromoacetyl-1-aminoadamantane (2b)**

By following the general procedure, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol), ICH\(_2\)Br (1.26 g, 0.43 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et\(_2\)O, α-bromoacetamide 2b was obtained in 93% yield (962 mg) as a white solid.

^1^H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 6.12 (bs, 1H), 3.77 (s, 2H), 2.10 (s, 3H), 2.01 (d, \(J = 3.0\) Hz, 6H), 1.69 (t, \(J = 6.3\) Hz, 6H).

^1^3^C NMR (50 MHz, CDCl\(_3\)) \(\delta\): 164.1, 52.5, 41.1, 36.2, 29.9, 29.3.

IR (NaCl, \(\nu_{max}\), cm\(^{-1}\)): 3243, 2105, 1661, 1572, 1232.

Mp: 124 °C (lit.\(^2\) 123-125 °C).

**Elemental Analysis (%)** for C\(_{12}\)H\(_{18}\)BrNO. Calcd: C, 52.95; H, 6.67; N, 5.15. Found: C, 53.09; H, 6.82; N, 5.30.

**N-Iodoacetyl-1-aminoadamantane (2c)**

By following the general procedure, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol), I\(_2\)CH\(_2\) (1.53 g, 0.46 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et\(_2\)O, α-iodoacetamide 2c was obtained in 94% yield (1140 mg) as a yellow solid.
1H NMR (200 MHz, CDCl3) δ: 6.17 (s, 1H), 3.60 (s, 2H), 2.22 – 1.81 (m, 9H), 1.77 – 1.57 (m, 6H).

13C NMR (50 MHz, CDCl3) δ: 165.86, 52.70, 41.18, 36.39, 29.44, 1.60.

IR (NaCl, νmax, cm⁻¹): 3250, 1664, 1570, 1230, 996.

Elemental Analysis (%) for C12H16INO. Calcd: C, 45.16; H, 5.68; N, 4.39. Found: C, 45.31; H, 5.75; N, 4.52.

2-Chloro-N-cyclohexylacetamide (4a)³

By following the general procedure, starting from cyclohexyl isocyanate (0.47 g, 3.8 mmol), ICH2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et2O, α-chloroacetamide 4a was obtained in 97% yield (647 mg) as a white solid.

1H NMR (500 MHz, CDCl3) δ: 6.40 (bs, 1H), 3.96 (s, 2H), 3.73-3.69 (m, 1H), 1.87-1.84 (m, 2H), 1.65-1.63 (m, 2H), 1.5-1.33 (m, 1H), 1.33-1.29 (m, 2H), 1.16-1.13 (m, 3H).

13C NMR (126 MHz, CDCl3) δ: 164.8, 48.6, 42.7, 32.8, 25.4, 24.7.

IR (NaCl, νmax, cm⁻¹): 3241, 1651, 1567, 1223.

Mp: 113 °C (lit.³ 113-115 °C).

Elemental Analysis (%) for C8H14ClNO. Calcd: C, 54.70; H, 8.03; N, 7.97. Found: C, 54.83; H, 8.14; N, 8.12.

2-Chloro-N-cyclopropylacetamide (4b)

By following the general procedure, starting from isocyanatocyclopropane (0.32 g, 3.8 mmol), ICH2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et2O, α-chloroacetamide 4b was obtained in 95% yield (480 mg) as a white solid.

1H NMR (400 MHz, CDCl3) δ: 6.64 (bs, 1H, NH), 4.01 (s, 2H, CH2Cl), 2.74 (m, 1H, NCH), 0.82 (m, 2H, CHCH₂CH₂), 0.57 (m, 2H, CHCH₂CH₂).

13C NMR (100 MHz, CDCl3) δ: 167.2 (C=O), 42.5 (CH₂Cl), 22.8 (NCH), 6.4 (CHCH₂), 6.4 (CHCH₂).

15N NMR (40 MHz, CDCl3) δ: -262.5 (amide)

IR (NaCl, νmax, cm⁻¹): 3246, 1648, 1230, 990.

Elemental Analysis (%) for C₅H₈ClNO. Calcd: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.15 ; H, 6.23; N, 10.24.

2-chloro-N-(2,4,4-trimethylpentan-2-yl)acetamide (4c)
By following the general procedure, starting from 2-isocyanato-2,4,4-trimethylpentane (0.59 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4c was obtained in 95% yield (740 mg) as a white solid.

**¹H NMR** (200 MHz, CDCl₃) δ: 6.43 (s, 1H), 3.90 (s, 2H), 1.50 – 1.29 (m, 7H), 1.06 – 0.92 (m, 10H).

**¹³C NMR** (50 MHz, CDCl₃) δ: 164.6, 55.8, 51.9, 43.1, 32.9, 31.8, 31.5, 31.2, 29.4, 28.8.

**IR** (NaCl, νₘₐₓ, cm⁻¹): 3251, 1656, 1236, 907.

**Elemental Analysis (%)** for C₁₀H₂₀ClNO. Calcd: C, 58.38; H, 9.80; N, 6.81. Found: C, 58.19; H, 9.95; N, 6.68

(S)-2-Chloro-N-(1-phenylethyl)acetamide (4d)

![structure](image)

By following the general procedure, starting from (S)-methylbenzyl isocyanate (96 % ee purity) (0.56 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4d was obtained in 96% yield (721 mg) as a white solid.

**¹H NMR** (500 MHz, CDCl₃) δ: 7.30-7.18 (m, 5H), 6.74 (s, 1H), 5.05 (quint., J = 7.0 Hz, 1H), 3.98 (m, 2H), 1.46 (d, J = 6.9 Hz, 3H).

**¹³C NMR** (126 MHz, CDCl₃) δ: 165.0, 144.2, 128.8, 127.3, 125.8, 49.3, 42.7, 21.7.

**IR** (NaCl, νₘₐₓ, cm⁻¹): 3260, 2974, 1652, 1542, 1230, 907.

**Mp**: 100 °C (lit.¹ 101-102 °C).

**Elemental Analysis (%)** for C₁₀H₁₂ClNO. Calcd: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.89; H, 6.29; N, 7.24.

**HPLC analysis**: Column Chiralpak IA; eluent: hexane – i-propanol 95:5; 1 mL/min, 28 °C.

Racemic sample: tᵣ = 9.173 s (R)-enantiomer, tᵣmaj = 11.219 s. (S)-enantiomer. 96% ee purity.

Analytical data for rac-(4d) match perfectly with those ones reported for the enantiopure compound.

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Enantiopure

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(R)-2-Chloro-N-(1-(naphthalen-1-yl)ethyl)acetamide (4e)

By following the general procedure, starting from (R)-(−)-1-(1-naphthyl)ethyl isocyanate (> 99 % ee purity) (0.75 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4e was obtained in 97% yield (913 mg) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ: 8.11 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H₂), 7.86 (d, J = 7.6 Hz, 1H), 7.56 (m, 4H), 6.81 (s, 1H), 4.15 (s, 2H), 1.74 (d, J = 7.0 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ: 164.4, 137.0, 133.5, 130.5, 128.5, 128.2, 126.2, 125.5, 124.8, 122.6, 122.1, 44.8, 42.2, 20.4.

IR (NaCl, νmax, cm⁻¹): 3284, 1649, 1537, 1231.

Mp: 140 °C (lit.⁴ 140 °C).

Elemental Analysis (%) for C₁₄H₁₄ClNO. Calcd: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.99; H, 5.87; N, 5.82.

HPLC analysis: Column Chiralcel OD-H; eluent: hexane – i-propanol 80:20; 1 mL/min, 28 °C. 

Analytical data for rac-(4e) match perfectly with those ones reported for the enantiopure compound.
Racemic

By following the general procedure, starting from allyl isocyanate (0.32 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4f was obtained in 98% yield (508 mg) as a light orange oil.

**¹H NMR** (500 MHz, CDCl₃) δ: 6.69 (bs, 1H), 5.82-5.74 (m, 1H), 5.18-5.10 (m, 2H), 4.00 (s, 2H), 3.88-3.86 (m, 2H).

**¹³C NMR** (126 MHz, CDCl₃) δ: 164.8, 133.2, 115.7, 42.0, 41.1.

**IR** (NaCl, νmax, cm⁻¹): 3294, 1662, 1542, 1419, 1261, 992.

**Elemental Analysis (%)** for C₅H₈ClNO. Calcd: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.11; H, 6.21; N, 10.68.

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Enantiopure

By following the general procedure, starting from allyl isocyanate (0.32 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4f was obtained in 98% yield (508 mg) as a light orange oil.

**¹H NMR** (500 MHz, CDCl₃) δ: 6.69 (bs, 1H), 5.82-5.74 (m, 1H), 5.18-5.10 (m, 2H), 4.00 (s, 2H), 3.88-3.86 (m, 2H).

**¹³C NMR** (126 MHz, CDCl₃) δ: 164.8, 133.2, 115.7, 42.0, 41.1.

**IR** (NaCl, νmax, cm⁻¹): 3294, 1662, 1542, 1419, 1261, 992.

**Elemental Analysis (%)** for C₅H₈ClNO. Calcd: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.11; H, 6.21; N, 10.68.

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N-Allyl-2-chloroacetamide (4f)

\[
\text{CH}_2=\text{CH}-\text{N}^+\text{Cl}^{-}\]

By following the general procedure, starting from allyl isocyanate (0.32 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4f was obtained in 98% yield (508 mg) as a light orange oil.

**¹H NMR** (500 MHz, CDCl₃) δ: 6.69 (bs, 1H), 5.82-5.74 (m, 1H), 5.18-5.10 (m, 2H), 4.00 (s, 2H), 3.88-3.86 (m, 2H).

**¹³C NMR** (126 MHz, CDCl₃) δ: 164.8, 133.2, 115.7, 42.0, 41.1.

**IR** (NaCl, νmax, cm⁻¹): 3294, 1662, 1542, 1419, 1261, 992.

**Elemental Analysis (%)** for C₅H₈ClNO. Calcd: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.11; H, 6.21; N, 10.68.
**N-Benzyl-2-chloroacetamide (4g)**

By following the general procedure, starting from benzyl isocyanate (0.50 g, 3.8 mmol), ICH\(_2\)Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et\(_2\)O, α-chloroacetamide 4g was obtained in 95% yield (663 mg) as a white solid.

**\(^1\)H NMR** (300 MHz, CDCl\(_3\)) \(\delta\): 7.31-7.16 (m, 5H), 6.81 (bs, 1H), 4.42 (d, \(J = 6.1\) Hz, 2H), 4.02 (s, 2H).

**\(^{13}\)C NMR** (75 MHz, CDCl\(_3\)) \(\delta\): 165.9, 137.3, 128.8, 127.9, 127.8, 43.9, 42.6.

**IR** (NaCl, \(v_{\text{max}},\ \text{cm}^{-1}\)): 3286, 1658, 1535, 994.

**Mp**: 95 °C (lit.\(^6\) 95-96 °C)

**Elemental Analysis (%)** for C\(_9\)H\(_{10}\)ClNO. Calcd: C, 58.86; H, 5.49; N, 7.63. Found: C, 59.11; H, 5.65; N, 7.84.

**2-iodo-N-(1-phenylethyl)acetamide (4h)**

By following the general procedure, starting from methylbenzyl isocyanate (0.56 g, 3.8 mmol), I\(_2\)CH\(_2\) (1.53 g, 0.46 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et\(_2\)O, α-iodoacetamide 4h was obtained in 98% yield (1099 mg) as a light yellow solid.

**\(^1\)H NMR** (300 MHz, acetone-\(d_6\)) \(\delta\): 7.93 (bs, 1H), 7.33-7.13 (m, 5H), 4.99-4.93 (m, 1H), 3.71 (m, 2H), 1.37 (m, 3H).

**\(^{13}\)C NMR** (75 MHz, acetone-\(d_6\)) \(\delta\): 167.0, 144.6, 128.8, 127.3, 126.6, 49.5, 22.0, 0.0.

**IR** (NaCl, \(v_{\text{max}},\ \text{cm}^{-1}\)): 3298, 1655, 1551, 994.

**Elemental Analysis (%)** for C\(_{10}\)H\(_{12}\)INO. Calcd: C, 41.54; H, 4.18; N, 4.84. Found: C, 41.63; H, 4.32; N, 5.01.

**2-Chloro-N-phenylacetamide (4i)**

By following the general procedure, starting from isocyanatobenzene (0.45 g, 3.8 mmol), ICH\(_2\)Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et\(_2\)O, α-chloroacetamide 4i was obtained in 98% yield (632 mg) as a white solid.

**\(^1\)H NMR** (200 MHz, CDCl\(_3\)) \(\delta\): 8.27 (bs, 1H), 7.63 – 7.49 (m, 2H), 7.47 – 7.30 (m, 2H), 7.24 – 7.02 (m, 1H), 4.18 (s, 2H).

**\(^{13}\)C NMR** (50 MHz, CDCl\(_3\)) \(\delta\): 164.0, 136.8, 129.2, 125.4, 120.3, 43.0.

**IR** (NaCl, \(v_{\text{max}},\ \text{cm}^{-1}\)): 3262, 1651, 1546, 1235, 990, 907.

**Mp**: 134 °C (lit.\(^7\) 134-135 °C).
Elemental Analysis (%) for $C_8H_8ClNO$. Calcd: C, 56.65; H, 4.75; N, 8.26. Found: C, 56.81; H, 4.93; N, 8.12.

2-Iodo-N-phenylacetamide (4j)$^8$

![Structure of 2-Iodo-N-phenylacetamide (4j)](Attachment)

By following the general procedure, starting from isocyanatobenzene (0.45 g, 3.8 mmol), I$_2$CH$_2$ (1.53 g, 0.46 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et$_2$O, $\alpha$-iodoacetamide 4j was obtained in 96% yield (952 mg) as a white solid.

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 7.86 (bs, 1H), 7.62 – 7.43 (m, 2H), 7.43 – 7.28 (m, 2H), 7.21 – 7.05 (m, 1H), 3.86 (s, 2H).

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 165.3, 129.2, 125.2, 120.1, 0.1.

IR (NaCl, $\nu_{max}$, cm$^{-1}$): 3271, 1647, 1241, 992.

Mp: 145 °C (lit.$^8$ 143-146 °C).


2-Chloro-N-(3-methoxyphenyl)acetamide (4k)$^9$

By following the general procedure, starting from 3-methoxyphenyl isocyanate (0.57 g, 3.8 mmol), ICH$_2$Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et$_2$O, $\alpha$-chloroacetamide 4k was obtained in 94% yield (713 mg) as a white solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.14 (bs, 1H), 7.21-7.15 (m, 2H), 6.94 (m, 1H), 6.67-6.64 (m, 1H), 4.11 (s, 2H), 3.74 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 163.7, 160.3, 137.8, 129.9, 112.2, 111.0, 105.9, 55.4, 42.9.

IR (NaCl, $\nu_{max}$, cm$^{-1}$): 3291, 1661, 1543, 1376, 1254.

Mp: 93 °C (lit.$^9$ 92-94 °C).

Elemental Analysis (%) for $C_9H_{10}ClNO_2$. Calcd: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.33; H, 5.23; N, 7.27.
2-chloro-N-(3-chlorophenyl)acetamide (4l)

By following the general procedure, starting from 1-chloro-3-isocyanatobenzene (0.58 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4l was obtained in 96% yield (744 mg) as a white solid.

¹H NMR (200 MHz, CDCl₃) δ: 8.29 (bs, 1H), 7.69 (t, J = 2.0 Hz, 1H), 7.51 – 7.28 (m, 2H), 7.25 – 7.10 (m, 1H), 4.21 (s, 2H).

¹³C NMR (50 MHz, CDCl₃) δ: 164.34, 138.19, 135.25, 130.55, 125.75, 120.63, 118.48, 43.24.

IR (NaCl, νmax, cm⁻¹): 3278, 1661, 1267, 990.

Mp: 100 °C (lit. 98-100 °C).

Elemental Analysis (%) for C₈H₇Cl₂NO. Calcd: C, 47.09; H, 3.46; Cl, 34.75; N, 6.86; O, 7.84

N-(3-Chlorophenyl)-2-iodoacetamide (4m)

By following the general procedure, starting from 1-chloro-3-isocyanatobenzene (0.58 g, 3.8 mmol), I₂CH₂ (1.53 g, 0.46 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-iodoacetamide 4m was obtained in 93% yield (1.044 g) as a white solid.

¹H NMR (200 MHz, CDCl₃) δ: 7.99 (bs, 1H), 7.66 (t, J = 1.9 Hz, 1H), 7.46 – 7.28 (m, 2H), 7.16 (dt, J = 7.8, 1.6 Hz, 1H), 3.90 (s, 2H).

¹³C NMR (50 MHz, CDCl₃) δ: 165.89, 138.81, 135.18, 130.50, 125.52, 120.51, 118.38, -0.00.

IR (NaCl, νmax, cm⁻¹): 3289, 1659, 909.

Mp: 84-85°C.

Elemental Analysis (%) for C₈H₇ClINO. Calcd: C, 32.52; H, 2.39; N, 4.74. Found: C, 32.39; H, 2.21; N, 4.88.

2-Chloro-N-(2-chloro-5-(trifluoromethyl)phenyl)acetamide (4n)

By following the general procedure, starting from 1-chloro-2-isocyanato-4-(trifluoromethyl)benzene (0.80 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4n was obtained in 98% yield (1.013 g) as a white solid.
$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$: 9.01 (bs, 1H, NH), 8.73 (d, $J = 2.0$ Hz, 1H, Ph H-6), 7.51 (m, 1H, Ph H-3), 7.34 (m, 1H, Ph H-4), 4.25 (s, 2H, CH$_2$Cl).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 164.1 (C=O), 134.2 (Ph C-1), 130.3 (q, $J = 33.2$ Hz, Ph C-5), 129.6 (Ph C-3), 123.4 (q, $J = 272.6$ Hz, CF$_3$), 121.9 (q, $J = 3.8$ Hz, Ph C-4), 117.9 (q, $J = 4.0$ Hz, Ph C-6), 44.0 (CH$_2$Cl).

$^{15}$N NMR (40 MHz, CDCl$_3$) $\delta$: -259.3 (amide)

$^{19}$F NMR (235 MHz, CDCl$_3$) $\delta$: -62.4 (q, $J = 0.7$ Hz, CF$_3$)

IR (NaCl, $\nu_{max}$, cm$^{-1}$): 3293, 1664, 1242, 990.

Elemental Analysis (%) for C$_9$H$_6$Cl$_2$F$_3$NO. Calcd: C, 39.73; H, 2.22; N, 5.15. Found: C, 39.56; H, 2.07; N, 5.29.

$N$-(2-chloro-5-(trifluoromethyl)phenyl)-2-iodoacetamide (4o)

![Chemical structure](image)

By following the general procedure, starting from 1-chloro-2-isocyanato-4-(trifluoromethyl)benzene (0.80 g, 3.8 mmol), ICH$_2$Br (1.26 g, 0.43 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et$_2$O, $\alpha$-bromoacetamide 4o was obtained in 88% yield (1.21 g) as a white solid.

$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.89 (bs, 1H, NH), 8.71 (d, $J = 1.8$ Hz, 1H, Ph H-6), 7.52 (d, $J = 8.4$ Hz, 1H, Ph H-3), 7.35 (dd, $J = 8.4$, 2.0 Hz, 1H, Ph H-4), 4.09 (s, 2H, CH$_2$Br).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 163.6 (C=O), 134.5 (Ph C-1), 130.3 (q, $J = 33.2$ Hz, Ph C-5), 129.6 (Ph C-3), 123.4 (q, $J = 272.5$ Hz, CF$_3$), 121.9 (q, $J = 3.8$ Hz, Ph C-4), 117.9 (q, $J = 4.0$ Hz, Ph C-6), 29.4 (CH$_2$Br).

$^{15}$N NMR (40 MHz, CDCl$_3$) $\delta$: -257.3 (amide)

$^{19}$F NMR (235 MHz, CDCl$_3$) $\delta$: -62.7 (s, CF$_3$)

IR (NaCl, $\nu_{max}$, cm$^{-1}$): 3288, 1662, 1246, 996, 910.

Mp: 87-88 °C.

Elemental Analysis (%) for C$_9$H$_6$Cl$_2$F$_3$NO. Calcd: C, 29.74; H, 1.66; N, 3.85. Found: C, 29.56; H, 1.50; N, 3.69.

2-Chloro-$N$-(2,4,6-tribromophenyl)acetamide (4p)

![Chemical structure](image)

By following the general procedure, starting from 1,3,5-tribromo-2-isocyanatobenzene (1.46 g, 3.8 mmol), ICH$_2$Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et$_2$O, $\alpha$-chloroacetamide 4p was obtained in 82% yield (1.27 g) as a white solid.
**1H NMR** (200 MHz, CDCl$_3$) δ: 7.50 (s, 2H), 4.57 (s, 2H).

**13C NMR** (50 MHz, CDCl$_3$) δ: 141.46, 133.93, 108.94 43.6.

**IR** (NaCl, $\nu_{\text{max}}$, cm$^{-1}$): 3287, 1660, 998.

**Elemental Analysis (%)** for C$_9$H$_6$ClIF$_3$NO. Calcd: C, 23.65; H, 1.24; N, 3.45. Found: C, 23.79; H, 1.36; N, 3.62.

2-chloro-N-(naphthalen-1-yl)acetamide (4q)$^{10}$

By following the general procedure, starting from 1-naphthyl isocyanate (0.64 g, 3.8 mmol), ICH$_2$Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et$_2$O, α-chloroacetamide 4q was obtained in 92% yield (768 mg) as a white solid.

**1H NMR** (500 MHz, CDCl$_3$) δ: 8.78 (bs, 1H), 7.98 (d, $J = 7.5$ Hz, 1H), 7.88 (m, 2H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.58-7.51 (m, 3H), 4.36 (s, 2H).

**13C NMR** (125 MHz, CDCl$_3$) δ: 164.3, 134.1, 131.2, 128.9, 127.0, 126.9, 126.7, 126.5, 126.2, 125.7, 120.6, 120.2, 43.3.

**IR** (NaCl, $\nu_{\text{max}}$, cm$^{-1}$): 3273, 2963, 1663, 1552, 1509, 1399, 1270, 1251.

**Mp**: 154 °C (lit.$^{11}$ 153-159 °C).

**Elemental Analysis (%)** for C$_{12}$H$_{10}$ClNO. Calcd: C, 65.61; H, 4.59; N, 6.38. Found: C, 65.80; H, 4.77; N, 6.59.

2-Chloro-N-(2,6-dimethylphenyl)acetamide (4r)$^{12}$

By following the general procedure, starting from 2,6-dimethylphenyl isocyanate (0.56 g, 3.8 mmol), ICH$_2$Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et$_2$O, α-chloroacetamide 4r was obtained in 97% yield (729 mg) as a white solid.

**1H NMR** (300 MHz, CDCl$_3$) δ: 7.87 (bs, 1H), 7.15-7.10 (m, 3H), 4.26 (s, 2H), 2.25 (s, 6H).

**13C NMR** (75 MHz, CDCl$_3$) δ: 164.3, 135.4, 132.7, 128.4, 127.9, 42.8, 18.3.

**IR** (NaCl, $\nu_{\text{max}}$, cm$^{-1}$): 3266, 2975, 1655, 1588, 1331, 1251, 997.

**Mp**: 140 °C (lit.$^{13}$ 138-140 °C).

**Elemental Analysis (%)** for C$_{10}$H$_{12}$ClNO. Calcd: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.91; H, 6.31; N, 7.22.
2-chloro-N-(2,6-diethylphenyl)acetamide (4s)

By following the general procedure, starting from 2,6-diethylphenyl isocyanate (0.66 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4s was obtained in 95% yield (815 mg) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ: 7.82 (bs, 1H), 7.19-7.04 (m, 3H), 4.13 (s, 2H), 2.49 (q, J = 6.4 Hz, 4H), 1.11 (t, J = 6.4 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃) δ: 165.0, 141.4, 131.6, 128.5, 126.5, 42.8, 24.8, 14.4.

IR (NaCl, ν_max, cm⁻¹): 3259, 2970, 2873, 1657, 1592, 1470, 1330, 1247.

Mp: 201 °C (lit.¹⁴ 199-204 °C).

Elemental Analysis (%) for C₁₂H₁₆ClNO. Calcd: C, 63.85; H, 7.14; N, 6.21. Found: C, 64.00; H, 7.22; N, 6.35.

2-chloro-N-(2,6-diisopropylphenyl)acetamide (4t)

By following the general procedure, starting from 2-isocyanato-1,3-diisopropylbenzene (0.77 g, 3.8 mmol), ICH₂Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et₂O, α-chloroacetamide 4t was obtained in 97% yield (935 mg) as a white solid.

¹H NMR (200 MHz, CDCl₃) δ: 7.87 (s, 1H), 7.46 – 7.20 (m, 3H), 4.30 (s, 2H), 3.07 (p, J = 6.9 Hz, 2H), 1.26 (d, J = 6.9 Hz, 12H).

¹³C NMR (50 MHz, CDCl₃) δ: 165.5, 146.1, 130.1, 129.0, 123.8, 42.9, 28.9, 23.7.

IR (NaCl, ν_max, cm⁻¹): 3248, 1678, 1660, 1533, 998.

Mp: 149 °C (lit.¹ 148-149 °C).

Elemental Analysis (%) for C₁₄H₂₀ClNO. Calcd: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.09; H, 8.10; N, 5.69.
Preparation of 1-chloro-3-phenylacetone (6) via Charette’s chemistry.\textsuperscript{15}

To a solution of chloroacetamide 4a (200 mg, 1.04 mmol, 1.0 equiv.) in dry dichloromethane (26 mL, concentration 0.044 M), was added 2-fluoropyridine (62 mg, 1.26 mmol, 0.11 mL, 1.1 equiv.) and the resulting solution was cooled at -78 °C and stirred for 2 min. Triflic anhydride (354 mg, 1.26 mmol, 0.21 mL, 1.1 equiv.) was added dropwise at that temperature and the mixture was then stirred for 10 min. The solution was warmed at 0 °C and the reaction was stirred for 20 min. The reaction was then cooled at -78 °C and a solution of benzyl magnesium chloride 2.0 M in THF (2.08 mmol, 1.04 mL, 2.0 equiv.) was added dropwise during 10 min and stirred for further 50 min. The reaction was quenched with 8 mL of HCl 0.5 M and 8 mL of THF. The biphasic system was warmed at 65 °C leaving the flask open for 2 h. After extraction of the organic phase with additional DCM (10 mL), drying it over sodium sulphate, filtering and removal of the solvent under reduced pressure crude 6 was obtained. After chromatography on silica gel (eluent: petroleum ether ethyl acetate 9.5:0.5 v/v), pure chloroketone 6 (152 mg, 87% yield) was obtained as a yellow oil.

\begin{itemize}
\item \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\): 7.38 – 7.23 (m, 5H), 4.13 (s, 2H), 3.91 (s, 2H).
\item \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\): 199.1, 132.8, 129.4, 128.9, 127.5, 47.7, 46.8.
\item IR (NaCl, \(\nu\)max, cm\textsuperscript{-1}): 3082, 1737, 992, 897.
\end{itemize}

Elemental Analysis (%) for C\textsubscript{9}H\textsubscript{9}ClO. Calcd: C, 64.11; H, 5.38. Found: C, 64.29; H, 5.53.
References

COPIES OF $^1$H and $^{13}$C-NMR SPECTRA FOR ALL THE COMPOUNDS

(2a)
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