Synthesis of cyanamides from cyanogen bromide under mild conditions through $N$-cyanation of allylic tertiary amines

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SUPPORTING INFORMATION

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1.1 General Information

All reactions of N-allylation were performed in the flask sealed with glass stoppers and stirred with IKA RCT basic magnetic stirrer bars. And all reactions of N-cyanation were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and stirred with IKA RCT basic magnetic stirrer bars. Dry chloroform (CHCl$_3$) was obtained by distilling in calcium chloride. All other solvents and reagents were used as supplied without further purification.

Room temperature (rt) refers to 20-30°C. Temperature of 0°C was obtained using ice/water.

Analytical thin layer chromatography (TLC) was carried out using glass plates coated with silica and visualization was achieved ultraviolet light (254nm) or iodine. Flash chromatography used silica with Biotage Isolera One.

Infra-red spectra were recorded on a Bruker Tensor 27 spectrometer. Characteristic peaks are quoted ($v_{\text{max}}$/cm$^{-1}$).

$^1$H, $^{13}$C NMR spectra were obtained on an Agilent DD2 ($^1$H 600MHz, $^{13}$C 150MHz) spectrometer at rt in the solvent stated at Beijing Physical and Chemical Analysis and Testing Center. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent signal. All coupling constants, J, are quoted in Hz. Multiplicities are reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, m
= multiplet and multiples thereof.

Mass spectrometry (MS, m/z) and high resolution mass spectrometry (HRMS, m/z) data was acquired at Institute of Chemistry Chinese Academy of Sciences on a Shimadzu LC-MS-2010 and a Bruker Solarix 9.4T spectrometer.
1.2 Experimental and Characterization data

1.21 N-allylation of secondary amines

General procedure A

Secondary amine (10.00 mmol) was mixed with K$_2$CO$_3$ (20.00 mmol) in H$_2$O (25 mL). The mixture was cooled to 0°C and allyl bromide (20.00 mmol) was added dropwise. The reaction mixture was left stirring at 0°C for 30 minutes and then at room temperature for 16 h. The crude product was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (anhydrous Na$_2$SO$_4$) and the solvent was evaporated under reduced pressure. The crude product was purified using flash column chromatography on silica gel to afford the desired product (as indicated).

General procedure B

A solution of the cinnamyl bromide (10.00 mmol) in THF (0.5 M) was added dropwise to a solution of the secondary amine (25.00 mmol) in THF (2.5 M) via a dropping funnel at rt. After addition was complete, the funnel was rinsed with a small portion of THF and the reaction stirred for 10 mins. 1 M aq NaOH (20.00 mmol) was then added in one portion, and the reaction stirred for a further 10 minutes. The reaction was diluted with Et$_2$O (equal volume), the layers separated and the aqueous layer extracted with Et$_2$O (2 equal volume). The combined organics were washed with brine (equal volume), dried over MgSO$_4$, filtered, and concentrated in
vacuo. The residue was triturated with Et₂O, any solids removed by filtration, and the solution concentrated in vacuo to afford the tertiary allylic amines that was purified further by flash chromatography on silica gel (as indicated).

**General procedure C**

A solution of the 1-bromo-3-methylbut-2-ene (10.00 mmol) in THF (0.5 M) was added dropwise to a solution of the secondary amine (25.00 mmol) in THF (2.5 M) via a dropping funnel at rt. After addition was complete, the funnel was rinsed with a small portion of THF and the reaction stirred for 10 mins. 1 M aq NaOH (20.00 mmol) was then added in one portion, and the reaction stirred for a further 10 minutes. The reaction was diluted with Et₂O (equal volume), the layers separated and the aqueous layer extracted with Et₂O (2 equal volume). The combined organics were washed with brine (equal volume), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was triturated with Et₂O, any solids removed by filtration, and the solution concentrated in vacuo to afford the tertiary allylic amines that was purified further by flash chromatography on silica gel (as indicated).
N-allyl-2-methylpiperidine

Following general procedure A. The reaction gave the title compound N-allyl-2-methylpiperidine (0.64 g, 4.60 mmol, 46%) as a colorless liquid after purification by flash chromatography on silica gel (eluent = 5% methanol in dichloromethane). \( \nu_{\text{max}}/(\text{cm}^{-1}) \) (film): 2933, 2783, 1642, 1441, 1375, 915; \(^1\text{H NMR (CDCl}_3, 600 MHz) \delta H: 1.08 (3H, s), 1.26 (2H, m), 1.59 (4H, m), 2.09-2.25 (2H, m), 2.84-2.95 (2H, m), 3.37-3.39 (1H, d, \( J = 10.2 \text{Hz} \)), 5.13 (2H, m), 5.89-5.90 (1H, m); \(^{13}\text{C NMR (CDCl}_3, 150 MHz) \delta C: 134.9, 117.5, 57.3, 56.0, 52.3, 34.6, 26.0, 24.0, 19.1; \) MS (ESI\(^+\)): 140.1 (M+H\(^+\)).
N-allyl-3-methylpiperidine

Following general procedure A. The reaction gave the title compound N-allyl-3-methylpiperidine (0.58 g, 4.17 mmol, 42%) as a colorless liquid after purification by flash chromatography on silica gel (eluent = 5% methanol in dichloromethane). ν\text{max}/(cm\textsuperscript{-1}) (film): 2927, 2853, 1679, 1609, 1464, 918; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 600MHz) δ\textsubscript{H}: 0.84-0.85 (3H, d, J=6.6Hz), 1.49-1.82 (7H, m), 2.82-2.88 (2H, dd, J=26.4, 10.2Hz), 2.96-2.70 (2H, d, J=3.6Hz) 5.11-5.17 (2H, dd, J=24.6, 16.8Hz), 5.88-5.89 (1H, m); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 150 MHz) δ\textsubscript{C}: 135.3, 117.7, 62.3, 61.2, 53.9, 32.9, 31.1, 25.5, 19.7; MS (ESI\textsuperscript{+}): 140.1 (M+H\textsuperscript{+}).
N-allyl-4-methylpiperidine

Following general procedure A. The reaction gave the title compound N-allyl-4-methylpiperidine (0.77 g, 5.53 mmol, 55%) as a colorless liquid after purification by flash chromatography on silica gel (eluent = 5% methanol in dichloromethane). $\nu_{\text{max}}$/(cm$^{-1}$) (film): 2951, 2924, 2789, 1644, 1421, 1367, 917; $^1$H NMR (CDCl$_3$, 600MHz) $\delta$ H: 0.84-0.85 (3H, d, J=6.6Hz), 1.16-1.19 (2H, m), 1.24-1.30 (1H, m), 1.53-1.55 (2H, d, J=13.8Hz), 1.79-1.84 (2H, m), 2.80-2.82 (2H, d, J=11.4Hz), 2.89-2.90 (2H, d, J=6.6Hz), 5.03-5.09 (2H, m), 5.79-5.83 (1H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ C: 135.5, 117.3, 62.2, 53.8, 34.2, 30.6, 21.8; MS (ESI+): 140.1 (M+H)$^+$. 
**N-allyl-3,5-dimethylpiperidine**

Following general procedure A. The reaction gave the title compound N-allyl-3,5-dimethylpiperidine (0.68 g, 4.89 mmol, 49%) as a colorless liquid after purification by flash chromatography on silica gel (eluent = 5% methanol in dichloromethane). $\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 2953, 2912, 2846, 1685, 1644, 1464, 1075, 917; $^1$H NMR (CDCl$_3$, 600MHz) $\delta$: 0.92-0.93 (6H, d, J=7.2Hz), 1.23-1.25 (2H, t, J=6.0Hz), 1.87-1.89 (2H, m), 2.03 (2H, m), 2.32-2.34 (2H, m), 2.80-2.83 (1H, q, J=6.6Hz), 2.96-2.99 (1H, dd, J=13.2, 5.4Hz), 5.06-5.14 (2H, m), 5.81-5.85 (1H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$: 135.8, 116.9, 62.2, 60.9, 39.0, 27.3, 19.2; MS (ESI+): 154.1 (M+H)$^+$. 

![N-allyl-3,5-dimethylpiperidine](image)
8-allyl-1,4-dioxa-8-azaspiro[4,5]decane

Following general procedure A. The reaction gave the title compound 8-allyl-1,4-dioxa-8-azaspiro[4,5]decane (1.15 g, 5.08 mmol, 51%) as a colorless liquid after purification by flash chromatography on silica gel (eluent = 3% methanol in dichloromethane). \( \nu_{\text{max}}/(\text{cm}^{-1}) \) (film): 3076, 2957, 2802, 1643, 1470, 1365, 1337, 1258, 1092; \(^1\)H NMR (CDCl\(_3\), 600MHz) \( \delta_{\text{H}} \): 1.74 (4H, s), 2.53 (4H, s), 3.02 (2H, s), 3.91 (4H, s), 5.14-5.17 (2H, d, \( J=18.0\text{Hz} \)), 5.86-5.87 (1H, s); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \( \delta_{\text{C}} \): 134.9, 118.1, 106.9, 64.2, 61.2, 51.1, 34.5; MS (ESI+): 184.2 (M+H\(^+\)).
ESI-MS Spectrum, A8

#1 Ret.Time:Averaged 1.227-1.440(Scan#:47-55)
Mass Peaks:101 Base Peak:184.20(2314423) Polarity:Pos Segment1 - Event1
Intensity

S15
1-allyl-4-ethylpiperazine

Following general procedure A. The reaction gave the title compound 1-allyl-4-ethylpiperazine (0.77 g, 5.00 mmol, 50%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent = 8% methanol in dichloromethane). $\nu_{\text{max}}$/(cm$^{-1}$) (film): 2971, 2935, 2808, 1643, 1450, 1339, 1164, 1016, 919; $^1$H NMR (CDCl$_3$, 600MHz) $\delta$H: 0.98-1.00 (3H, t, J=7.2Hz), 2.31-2.44 (10H, m), 2.91-2.92 (2H, d, J=6.6Hz), 5.04-5.11 (2H, dd, J=32.4, 17.4Hz), 5.74-5.81 (1H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$C: 134.9, 117.9, 61.7, 52.9, 52.6, 52.2, 11.8. Data consistent with literature.$^1$
Tert-butyl 4-allylpiperazine-1-carboxylate

Following general procedure A. The reaction gave the title compound tert-butyl 4-allylpiperazine-1-carboxylate (1.48 g, 6.54 mmol, 81%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent = 32% ethyl acetate in petroleum ether). $\nu_{\text{max}}/\text{(cm}^{-1}\text{)}$ (film): 2978, 2933, 2863, 2798, 1700, 1457, 1366, 1005; $^1$H NMR (CDCl$_3$, 600MHz) $\delta$H: 1.22 (9H, s), 2.14 (4H, s), 2.74-2.75 (2H, d, J=6.6Hz), 3.19 (4H, s), 4.90-4.96 (2H, dd, J=25.8, 17.4Hz), 5.57-5.62 (1H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$C: 154.3, 134.5, 117.8, 79.1, 61.5, 52.6, 28.2; MS (ESI+): 227.1 (M+H)$^+$. Data consistent with literature.$^2$
ESI-MS Spectrum, A5

#1 Ret.Time:Averaged 1.200-1.760(Scan#:A6-67)
Mass Peaks:139  Base Peak:227.10(11695567)  Polarity:Pos  Segment1 - Event1
Intensity

S19
**Tert-butyl 4-allyl-1,4-diazepane-1-carboxylate**

Following general procedure A. The reaction gave the title compound tert-butyl 4-allyl-1,4-diazepane-1-carboxylate (2.04 g, 8.49 mmol, 85%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent = 24% ethyl acetate in petroleum ether). ν<sub>max</sub>/cm<sup>-1</sup> (film): 3005, 2977, 2935, 2803, 1696, 1643, 1412, 1392, 1173; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600MHz) δH: 1.29 (9H, s), 1.63-1.66 (2H, m), 2.41-2.47 (4H, m), 2.93-2.94 (2H, d, J=6.0Hz), 3.24-3.32 (4H, m), 4.94-5.01 (2H, m), 5.64-5.70 (1H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δC: 155.3, 135.6, 117.3, 78.9, 61.1, 55.9, 55.6, 54.5, 46.7, 45.7, 44.8, 28.3, 27.7; MS (ESI+): 241.2 (M+H).
ESI-MS Spectrum, A6

#1 Ret.Time:Averaged 1.387-1.947(Scan#:53-74)
Mass Peaks:65  Base Peak:241.15(9415886)  Polarity:Pos  Segment1 - Event1
Intensity

[Graph showing mass peaks and retention time distribution]
2-allyl-1-methyl-1,2,3,4-tetrahydroisoquinoline

Following general procedure A. The reaction gave the title compound 2-allyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (1.74 g, 9.30 mmol, 93%) as a brown liquid after purification by flash chromatography on silica gel (eluent = 2% methanol in dichloromethane). ν max/(cm⁻¹) (film): 3078, 2972, 2907, 2788, 1642, 1493, 1419, 1100, 972, 757; ¹H NMR (CDCl₃, 600MHz) δ H: 1.40-1.41 (3H, d, J=7.2Hz), 2.74-2.83 (2H, m), 2.93-3.13 (2H, m), 3.25-3.35 (2H, m), 3.94-3.95 (1H, q, J=6.6Hz), 5.21-5.30 (2H, dd, J=43.2, 17.4Hz), 6.00-6.01 (1H, m), 7.10-7.17 (4H, m); ¹³C NMR (CDCl₃, 150 MHz) δ C: 140.2, 136.2, 134.1, 128.9, 127.4, 125.9, 125.7, 117.3, 57.2, 56.2, 43.7, 27.3, 19.4; MS (ESI+): 188.1 (M+H)+.
**Tert-butyl 4-cinnamylpiperazine-1-carboxylate**

Following general procedure B. The reaction gave the title compound tert-butyl 4-cinnamylpiperazine-1-carboxylate (2.90 g, 9.60 mmol, 96%) as a white solid after purification by flash chromatography on silica gel (eluent = 30% ethyl acetate in petroleum ether). $\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 3022, 2998, 2971, 2860, 1684, 1453, 1420, 1247, 1167, 1128, 1001, 743; $^1$H NMR (CDCl$_3$, 600MHz) $\delta_H$: 1.45 (9H, s), 2.43 (4H, m), 3.14-3.16 (2H, d, $J=6.6\text{Hz}$), 3.45 (4H, s), 6.22-6.27 (1H, m), 6.49-6.52 (1H, d, $J=15.6\text{Hz}$), 7.21-7.36 (5H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta_C$: 154.7, 136.7, 133.4, 128.6, 127.6, 126.3, 79.6, 61.1, 52.9, 28.4; MS (ESI+): 303.2 (M+H)$^+$. Data consistent with literature.$^2$
**Tert-butyl 4-(3-methylbut-2-en-1-yl)piperazine-1-carboxylate**

Following general procedure C. The reaction gave the title compound tert-butyl 4-(3-methylbut-2-en-1-yl)piperazine-1-carboxylate (1.93 g, 7.59 mmol, 76%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent = 15% ethyl acetate in petroleum ether). $\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 2976, 2862, 2812, 2768, 1707, 1697, 1691, 1477, 1420, 1243, 1122, 1002; $^1$H NMR (CDCl$_3$, 600MHz) $\delta$: 1.24 (9H, s), 1.43 (3H, s), 1.52 (3H, s), 2.17 (4H, s), 2.73-2.74 (2H, d, J=7.2Hz), 3.22 (4H, s), 5.03 (1H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$: 154.4, 135.4, 120.4, 79.1, 55.9, 52.7, 28.2, 25.7, 17.8; MS (ESI+): 255.2 (M+H$^+$). Data consistent with literature.$^3$
1-benzyl-4-cinnamylpiperazine

Following general procedure B. The reaction gave the title compound 1-benzyl-4-cinnamylpiperazine (2.19 g, 7.50 mmol, 75%) as a brown liquid after purification by flash chromatography on silica gel (eluent = 18% methanol in dichloromethane). $\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 3057, 2943, 2806, 2762, 1598, 1494, 1452, 1390, 1152, 1008, 964, 738, 689; $^1$H NMR (CDCl$_3$, 600MHz) $\delta_H$: 2.56 (8H, s), 3.18-3.19 (2H, d, $J$=7.2Hz), 3.55 (2H, s), 6.31-6.35 (2H, m), 6.53-6.55 (1H, d, $J$=16.2Hz), 7.23-7.41 (10H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta_C$: 138.2, 137.0, 133.1, 129.2, 128.6, 128.2, 127.5, 127.1, 126.6, 126.4, 63.1, 61.1, 53.3, 53.1; MS (ESI+): 293.2 (M+H)$^+$. 
ESI-MS Spectrum, A11

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Intensity

m/z

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225 250 275 300 325 350 375

293.2

S29
4-cinnamylthiomorpholine

Following general procedure B. The reaction gave the title compound 4-cinnamylthiomorpholine (1.75 g, 7.99 mmol, 80%) as a brown liquid after purification by flash chromatography on silica gel (eluent = 12% ethyl acetate in petroleum ether). ν max/(cm⁻¹) (film): 3025, 2905, 2810, 2761, 1652, 1416, 1363, 1131, 740; ¹H NMR (CDCl₃, 600MHz) δH: 2.65-2.70 (8H, m), 3.11-3.12 (2H, d, J=7.2Hz), 6.19-6.22 (1H, m), 6.46-6.48 (1H, d, J=16.2Hz), 7.19-7.35 (5H, m); ¹³C NMR (CDCl₃, 150 MHz) δC: 136.8, 133.2, 128.6, 127.5, 126.3, 61.8, 55.0, 28.0; MS (ESI⁺): 220.1 (M+H)⁺.
N,N-dibenzylprop-2-en-1-amine

Following general procedure A. The reaction gave the title compound N,N-dibenzylprop-2-en-1-amine (1.90 g, 8.01 mmol, 80%) as a colorless liquid after purification by flash chromatography on silica gel (eluent = pure petroleum ether). ν_max/(cm⁻¹) (film): 3063, 2923, 2794, 2712, 1642, 1603, 1494, 1453, 1369, 1121, 918, 739, 698; ¹H NMR (CDCl₃, 600MHz) δ_H: 3.23-3.25 (2H, d, J=6.6Hz), 3.75 (4H, s), 5.31-5.40 (2H, m), 6.05-6.12 (1H, m), 7.37-7.56 (10H, m); ¹³C NMR (CDCl₃, 150 MHz) δ_C: 139.8, 136.1, 128.9, 128.4, 127.0, 117.5, 57.9, 56.5. Data consistent with literature.⁴
Following general procedure C. The reaction gave the title compound N,N-dibenzyl-3-methylbut-2-en-1-amine (1.78 g, 6.71 mmol, 67%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent = 10% ethyl acetate in petroleum ether). ν max/(cm⁻¹) (film): 3027, 2969, 2928, 2878, 1671, 1601, 1494, 1452, 698; ¹H NMR (CDCl₃, 600MHz) δH: 1.81 (3H, s), 1.97 (3H, s), 3.26-3.27 (2H, d, J=7.2Hz), 3.80 (4H, s), 5.59-5.61 (1H, t, J=6.6Hz), 7.43-7.64 (10H, m); ¹³C NMR (CDCl₃, 150 MHz) δC: 140.2, 135.0, 129.0, 128.4, 127.0, 122.3, 58.2, 51.3, 26.2, 18.3; MS (ESI+): 266.2 (M+H)⁺. Data consistent with literature.⁵
ESI-MS Spectrum, A12

#1 Ret.Time:Averaged 1.200-1.707(Scan#46-65)
Mass Peaks:70 Base Peak:266.15(12916540) Polarity:Pos Segment1 - Event1
Intensity

266.2

334.3

m/z
1.22 N-cyanation of allylic tertiary amines

A typical procedure for N-cyanation of allylic tertiary amines

To the allylic tertiary amines (4 mmol) in anhydrous chloroform (5 mL) at room temperature, BrCN (4.4 mmol) was slowly added under inert atmosphere (N₂). After addition was complete, the mixture was further stirred for 24 h at room temperature. The N-cyanation of allylic tertiary amines was monitored by TLC. The reaction mixture was purified by column chromatography on silica gel (as indicated).
1. Piperidine-1-carbonitrile

The reaction gave the title compound piperidine-1-carbonitrile (0.33 g, 3.00 mmol, 75%) as a colorless liquid after purification by flash chromatography on silica gel (eluent=10% ethyl acetate in Petroleum ether). $\nu_{\text{max}}$(cm$^{-1}$) (film): 2945, 2857, 2210(C≡N), 1451; $^1$H NMR (CDCl$_3$, 600MHz) $\delta_{H}$: 1.47 (2H, m), 1.53-1.54 (4H, m), 3.06-3.07 (4H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta_{C}$: 118.6, 50.1, 24.5, 23.0; HRMS (ESI+) calculated for $[C_6H_{10}N_2Na]^+$ (M+Na)$^+$: m/z 133.073677, found 133.073619.
2. Pyrrolidine-1-carbonitrile

The reaction gave the title compound pyrrolidine-1-carbonitrile (0.27 g, 2.81 mmol, 70%) as a colorless liquid after purification by flash chromatography on silica gel (eluent=12% ethyl acetate in Petroleum ether). ν max/(cm⁻¹) (film): 2985, 2885, 2220(C≡N), 1635, 1488, 1352, 1027, 909; ¹H NMR (CDCl₃, 600MHz) δH: 1.86-1.88 (4H, m), 3.34-3.37 (4H, m); ¹³C NMR (CDCl₃, 150 MHz) δC: 117.8, 50.5, 25.6; HRMS (ESI+) calculated for [C₅H₈N₂Na]⁺ (M+Na)⁺: m/z 119.058023, found 119.057969.
3. Morpholine-4-carbonitrile

The reaction gave the title compound morpholine-4-carbonitrile (0.33 g, 2.94 mmol, 73%) as a colorless liquid after purification by flash chromatography on silica gel (eluent=37% ethyl acetate in Petroleum ether). $\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 2973, 2926, 2862, 2219(C≡N), 1454, 1377, 1114, 1002, 850; $^1$H NMR (CDCl$_3$, 600MHz) $\delta_H$: 3.15 (4H, m), 3.64 (4H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta_C$: 117.2, 65.5, 48.7; HRMS (ESI+) calculated for [C$_5$H$_9$N$_2$O]$^+$ (M+H)$^+$: m/z 113.070997, found 113.070939.
### ESI(P), LHG-05, 20160905

**Analysis Info**
- **Analysis Name**: D:\Data\ESI\2016\2016-09\0905\LHG-05_000001.d
- **Acquisition Date**: 9/5/2016 1:19:07 PM
- **Sample Name**: LHG-05
- **Instrument**: solarIX

**Acquisition Parameter**
- **Polarity**: Positive
- **Broadband Low Mass**: 57.7 m/z
- **Acquired Scans**: 10
- **Broadband High Mass**: 275.0 m/z

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4. Thiomorpholine-4-carbonitrile

The reaction gave the title compound thiomorpholine-4-carbonitrile (0.35 g, 2.73 mmol, 68%) as a white solid after purification by flash chromatography on silica gel (eluent=25% ethyl acetate in Petroleum ether). \( \nu_{\text{max}}/(\text{cm}^{-1}) \) (film): 2960, 2862, 2215(C≡N), 1451, 1413, 1390, 1285, 1201, 971; \(^1\)H NMR (CDCl\(_3\), 600MHz) \( \delta_H \): 2.66-2.68 (4H, t, J=5.4Hz), 3.42-3.43 (4H, t, J=5.4Hz); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \( \delta_C \): 117.3, 50.9, 26.1; HRMS (ESI+) calculated for \([\text{C}_5\text{H}_9\text{N}_2\text{S}]^+\) (M+H): m/z 129.048115, found 129.048096.
**ESI(P), N9, 20161227**

**Analysis Info**
- **Analysis Name**: D:\Data\ESI2016\2016-12\1227\N9_000001.d
- **Acquisition Date**: 12/27/2016 1:22:08 PM
- **Sample Name**: N9
- **Instrument**: solarIX

**Acquisition Parameter**
- **Acquisition Mode**: Single MS
- **Polarity**: Positive
- **Broadband Low Mass**: 57.7 m/z
- **Broadband High Mass**: 280.0 m/z
- **Acquired Scan**: 3
- **No. of Cell Pairs**: 1
- **Source Accumulation**: 0.001 sec
- **Ion Accumulation Time**: 0.050 sec

**Calibration Date**: Fri Dec 16 09:17:07 2016
- **Data Acquisition Size**: 1045579
- **Data Processing Size**: 2997152
- **Sine-Bell Multiplication**

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5. 4-methylpiperidine-1-carbonitrile

The reaction gave the title compound 4-methylpiperidine-1-carbonitrile (0.41 g, 3.30 mmol, 82%) as a colorless liquid after purification by flash chromatography on silica gel (eluent=10% ethyl acetate in Petroleum ether). $\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 2955, 2853, 2211(C≡N), 1456, 1385, 1085, 966; $^1$H NMR (CDCl$_3$, 600MHz) $\delta_H$: 0.71-0.72 (3H, d, J=6.6Hz), 1.01-1.08 (2H, m), 1.23-1.27 (1H, m), 1.40-1.43 (2H, d, J=14.4Hz), 2.73-2.78 (2H, m), 3.10-3.12 (2H, d, J=12.6Hz); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta_C$: 118.2, 49.5, 32.6, 29.4, 21.6; HRMS (ESI+) calculated for [C$_7$H$_{13}$N$_2$]$^+$ (M+H)$^+$: m/z 125.107361, found 125.107325.
6. 3-methylpiperidine-1-carbonitrile

The reaction gave the title compound 3-methylpiperidine-1-carbonitrile (0.38 g, 3.06 mmol, 76%) as a colorless liquid after purification by flash chromatography on silica gel (eluent=10% ethyl acetate in Petroleum ether). $\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 2932, 2855, 2209(C≡N), 1462, 1387, 1112, 1036, 889; $^1$H NMR (CDCl$_3$, 600MHz) $\delta_H$: 0.69-0.70 (3H, d, J=6.6Hz), 0.82-0.87 (1H, m), 1.42-1.60 (4H, m), 2.39-2.43 (1H, dd, J=12.0, 10.2Hz), 2.71-2.76 (1H, m), 3.06-3.12 (2H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta_C$: 118.3, 56.1, 49.5, 31.4, 29.9, 23.9, 18.4; HRMS (ESI+) calculated for [C$_7$H$_{13}$N$_2$]$^+$ (M+H)$^+$: m/z 125.10732, found 125.107325.
ESI(P), N2, 20161227

Analysis Info
Analysis Name: D:\Data\ESI2016\2016-121227\N2_000001.d
Sample Name: N2

Acquisition Parameter
Acquisition Mode: Single MS
Polarity: Positive
Broadband Low Mass: 57.7 m/z
Broadband High Mass: 200.0 m/z

Acquired Scans: 10
Source Accumulation Time: 0.001 sec
Ion Accumulation Time: 0.080 sec

Calibration Date: Fri Dec 10 09:17:07 2016
Data Acquisition Size: 1540576
Data Processing Size: 2097152
Apodization: Sine-Weighted Multiplication

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Intensity x10^5

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Intensity x10^3

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err [ppm]: 0.3
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even: 2.6
N.Rule: ok
7. 2-methylpiperidine-1-carbonitrile

The reaction gave the title compound 2-methylpiperidine-1-carbonitrile (0.39 g, 3.14 mmol 78%) as a colorless liquid after purification by flash chromatography on silica gel (eluent=10% ethyl acetate in Petroleum ether). \( \nu_{\text{max}}/(\text{cm}^{-1}) \) (film): 2938, 2855, 2206(C≡N), 1451, 1387, 1100, 1002, 902; \(^1\text{H NMR (CDCl}_3, 600\text{MHz}) \) \( \delta_{\text{H}} \): 1.08-1.13 (4H, m), 1.20-1.22 (1H, m), 1.37-1.51 (3H, m), 1.60-1.63 (1H, m), 2.83-2.84 (2H, m), 3.20-3.23 (1H, d, \( J=13.2\text{Hz} \)); \(^{13}\text{C NMR (CDCl}_3, 150\text{MHz}) \) \( \delta_{\text{C}} \): 116.8, 53.9, 50.6, 32.3, 24.1, 23.1, 19.3; HRMS (ESI+) calculated for \([\text{C}_7\text{H}_{13}\text{N}_2]^+\) (M+H): m/z 125.107348, found 125.107325.

S49
8. 3,5-dimethylpiperidine-1-carbonitrile

The reaction gave the title compound 3,5-dimethylpiperidine-1-carbonitrile (0.41 g, 2.97 mmol, 75%) as a colorless liquid after purification by flash chromatography on silica gel (eluent=10% ethyl acetate in Petroleum ether). $\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 2958, 2875, 2208(C≡N), 1459, 1386, 1174,1085, 853; $^1$H NMR (CDCl$_3$, 600MHz) $\delta_{\text{H}}$: 0.76-0.77 (6H, d, J=6.6Hz), 0.88-0.89 (1H, d, J=7.2Hz), 1.66-1.70 (3H, m), 2.35-2.39 (2H, t, J=12.6Hz), 3.16-3.19 (2H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta_{\text{C}}$: 118.3, 55.8, 40.8, 30.3, 18.5; HRMS (ESI+) calculated for [C$_8$H$_{15}$N$_2$]$^+$(M+H)$^+$: m/z 139.123043, found 139.122975.
9. 1,4-dioxa-8-azaspiro[4,5]decane-8-carbonitrile

The reaction gave the title compound 1,4-dioxa-8-azaspiro[4,5]decane-8-carbonitrile (0.46 g, 2.74 mmol, 68%) as a white solid after purification by flash chromatography on silica gel (eluent=20% ethyl acetate in Petroleum ether). $\nu_{\text{max}}$(cm$^{-1}$) (film): 2987, 2931, 2883, 2207(C≡N), 1492, 1431, 1335, 1277, 1165, 1120, 1070, 1035, 944, 909; $^1$H NMR (CDCl$_3$, 600MHz) $\delta$: 1.73-1.75 (4H, t, J=6.0Hz), 3.27-3.29 (4H, t, J=6.0Hz), 3.92 (4H, s); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$: 117.9, 105.3, 64.5, 47.9, 34.0; HRMS (ESI+) calculated for [C$_8$H$_{13}$N$_2$O$_2$]$^+$ (M+H)$^+$: m/z 169.097207, found 169.097154.
ESI(P), N8, 20161227

Analysis Info
Analysis Name: D:\Data\ESI2016\2016-12\1227\N8_000001.d
Sample Name: N8
Instrument: solariX

Acquisition Parameter
Acquisition Mode: Single MS
Polarity: Positive
Broadband Low Mass: 57.7 m/z
Broadband High Mass: 200.0 m/z

Acquired Scans: 3
No of Cell Fills: 1
Source Accumulation: 0.01 sec
Ion Accumulation Time: 0.050 sec

Calibration Date: Fri Dec 16 09:17:07 2016
Data Acquisition Size: 1048576
Data Processing Size: 2097152
Sine-Flat Multiplication

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S54
10. 4-methylpiperazine-1-carbonitrile

The reaction gave the title compound 4-methylpiperazine-1-carbonitrile (0.26 g, 2.08 mmol, 52%) as a colorless liquid after purification by flash chromatography on silica gel (eluent = 2% methanol in dichloromethane). ν max/(cm⁻¹) (film): 2943, 2798, 2211(C≡N), 1452, 1375, 1002, 787; ¹H NMR (CDCl₃, 600MHz) δ H: 2.19 (3H, s), 2.35-2.37 (4H, t, J=5.4, 4.8Hz), 3.13-3.15 (4H, t, J=5.4Hz); ¹³C NMR (CDCl₃, 150 MHz) δ C: 117.6, 53.3, 48.9, 46.1; HRMS (ESI+) calculated for [C₆H₁₂N₃]+ (M+H)+: m/z 126.102620, found 126.102574.
ESI(P), LHG-09, 20160926

Analysis Info
Analysis Name: D:\Data\ESI20160926\LHG-09_000001.d
Sample Name: LHG-09
Acquisition Date: 9/26/2016 10:31:30 AM
Instrument: solarIX

Acquisition Parameter
Polarity: Positive
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Acquired Scans: 10
Broadband High Mass: 250.0 m/z

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11. 4-ethylpiperazine-1-carbonitrile

The reaction gave the title compound 4-ethylpiperazine-1-carbonitrile (0.33 g, 2.37 mmol, 60%) as a colorless liquid after purification by flash chromatography on silica gel (eluent = 2% methanol in dichloromethane).

$\nu_{\text{max}}$/(cm$^{-1}$) (film): 2973, 2875, 2816, 2211(C≡N), 1471, 1380, 1281, 1003;

$^1$H NMR (CDCl$_3$, 600MHz) $\delta$ H: 0.97-0.99 (3H, t, J=7.2Hz), 2.34-2.42 (6H, m), 3.16-3.18 (4H, t, J=5.4Hz); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ C: 117.7, 52.2, 51.2, 49.0, 11.6; HRMS (ESI+) calculated for [C$_7$H$_{14}$N$_3$]+ (M+H)$^+$: m/z 140.118237, found 140.118224.
12. 4-benzylpiperazine-1-carbonitrile

The reaction gave the title compound 4-benzylpiperazine-1-carbonitrile (0.52 g, 2.59 mmol, 65%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent=35% ethyl acetate in Petroleum ether). \( \nu_{\text{max}}/(\text{cm}^{-1}) \) (film): 2945, 2816, 2217(C≡N), 1494, 1452, 1352, 1132, 1001, 701; \(^1\)H NMR (CDCl\(_3\), 600MHz) \( \delta_H \): 2.47 (4H, s), 3.19 (4H, s), 3.49 (2H, s), 7.23-7.29 (5H, m); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \( \delta_C \): 137.2, 129.0, 128.4, 127.4, 117.8, 62.8, 51.5, 49.1; HRMS (ESI+) calculated for [C\(_{12}\)H\(_{16}\)N\(_3\)]\(^+\) (M+H\(^+\)): m/z 202.133794, found 202.133874.
13. **Tert-butyl 4-cyanopiperazine-1-carboxylate**

![Chemical structure of tert-butyl 4-cyanopiperazine-1-carboxylate](image)

The reaction gave the title compound *tert*-butyl 4-cyanopiperazine-1-carboxylate (0.47 g, 2.23 mmol, 56%) as a white solid after purification by flash chromatography on silica gel (eluent=25% ethyl acetate in Petroleum ether). $\nu_{\text{max}}$(cm$^{-1}$) (film): 2998, 2973, 2859, 2220(C=N), 1686, 1426, 1395, 1286, 1267, 1178, 1128, 1006, 868; $^1$H NMR (CDCl$_3$, 600MHz) $\delta_{\text{H}}$: 1.42 (9H, s), 3.16 (4H, s), 3.47-3.49 (4H, t, J=5.4Hz); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta_{\text{C}}$: 154.1, 117.2, 80.7, 48.8, 28.3; HRMS (ESI+) calculated for [C$_{10}$H$_{18}$N$_3$O$_2$]$^+$(M+H)$^+$: m/z 212.139422, found 212.139353.
### Analysis Info

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**Acquisition Date:** 12/27/2016 12:54:48 PM  
**Sample Name:** N5  
**Instrument:** solarIX

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### Mass Spectrogram

#### ESI(P),N5,20161227

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14. *Tert*-butyl 4-cyano-1,4-diazepane-1-carboxylate

The reaction gave the title compound *tert*-butyl 4-cyano-1,4-diazepane-1-carboxylate (0.52 g, 2.31 mmol, 58%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent=25% ethyl acetate in Petroleum ether). \( \nu_{\text{max}}/(\text{cm}^{-1}) \) (film): 2984, 2224(C≡N), 1713, 1670, 1485, 1194, 1069, 979, 860; \(^1\)H NMR (CDCl\(_3\), 600MHz) \( \delta_{\text{H}} \): 1.24 (9H, s), 1.71 (2H, m), 3.03-3.11 (4H, m), 3.24-3.33 (4H, m); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \( \delta_{\text{C}} \): 154.6, 117.7, 79.8, 51.8, 50.1, 47.3, 46.2, 45.6, 28.2; HRMS (ESI+) calculated for [C\(_{11}\)H\(_{20}\)N\(_3\)O\(_2\)]\(^+\) (M+H\(^+\)): m/z 226.155094, found 226.155003.
15. 1-methyl-3,4-dihydroisoquinoline-2(1H)-carbonitrile

The reaction gave the title compound 1-methyl-3,4-dihydroisoquinoline-2(1H)-carbonitrile (0.59 g, 3.43 mmol, 86%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent=15% ethyl acetate in Petroleum ether). \( \nu_{\text{max}}/(\text{cm}^{-1}) \) (film): 2975, 2841, 2219(C≡N), 1710, 1605, 1277, 1205, 1039, 730; \(^1\)H NMR (CDCl\(_3\), 600MHz) \( \delta_H \): 1.46-1.47 (3H, d, J=6.6Hz), 2.76-2.78 (2H, t, J=6.0Hz), 3.23-3.27 (1H, m), 3.35-3.39 (1H, m), 4.33-4.37 (1H, q, J=7.2Hz), 6.96-7.10 (4H, m); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \( \delta_C \): 136.0, 132.3, 129.1, 127.0, 126.6, 126.2, 117.3, 54.2, 44.5, 28.0, 21.3; HRMS (ESI+) calculated for [C\(_{11}\)H\(_{13}\)N\(_3\)]\(^+\) (M+H): m/z 173.107360, found 173.107325.
17. N, N-dimethylcyanamide

![Structure of N, N-dimethylcyanamide](image)

The reaction gave the title compound N, N-dimethylcyanamide (0.20 g, 2.86 mmol, 72%) as a colorless liquid after purification by flash chromatography on silica gel (eluent=10% ethyl acetate in Petroleum ether). $\nu_{\text{max}}$ (cm$^{-1}$) (film): 2971, 2823, 2217(C≡N), 1455, 1339, 1058, 762; $^1$H NMR (CDCl$_3$, 600MHz): $\delta$H: 2.75 (6H, s); $^{13}$C NMR (CDCl$_3$,150 MHz): $\delta$C: 119.3, 40.4; HRMS (ESI+) calculated for [C$_3$H$_6$N$_2$Na]$^+$ (M+Na)$^+$: m/z 93.042365, found 93.042319.
18. N, N-diethylcyanamide

The reaction gave the title compound N, N-diethylcyanamide (0.31 g, 3.16 mmol, 78%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent=10% ethyl acetate in Petroleum ether). $\nu_{\text{max}}$ (cm$^{-1}$) (film): 2982, 2879, 2211(C≡N), 1453, 1384, 1180, 978; $^1$H NMR (CDCl$_3$, 600MHz): $\delta$ H : 1.17-1.21 (6H, m), 2.94-2.99 (4H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ C: 117.2, 45.8, 12.8; HRMS (ESI+) calculated for [C$_5$H$_{11}$N$_2$]$^+$ (M+H)$^+$: m/z 99.091728, found 99.091675.
19. N, N-diisopropylcyanamide

The reaction gave the title compound N, N-diisopropylcyanamide (0.28 g, 2.22 mmol, 55%) as a colorless liquid after purification by flash chromatography on silica gel (eluent=10% ethyl acetate in Petroleum ether). \( \nu_{\text{max}}/(\text{cm}^{-1}) \) (film): 2978, 2879, 2200(C≡N), 1465, 1244, 1053; \(^1\text{H} \) NMR (CDCl\(_3, 600\text{MHz}\)): \( \delta_H \): 1.24 (12H, d, J=6.6Hz), 3.14-3.21 (2H, m); \(^{13}\text{C} \) NMR (CDCl\(_3, 150 \text{ MHz}\)): \( \delta_C \): 114.8, 50.9, 21.4; HRMS (ESI+) calculated for \([\text{C}_7\text{H}_{15}\text{N}_2]^+\) (M+H\(^+\)): m/z 127.123039, found 127.122975.
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Instrument: solariX

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Acquired Scans: 10
Broadband High Mass: 278.0 m/z

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data

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144.140624 1 C7H13N3 100.00 144.140624 -0.6 -0.7 7.1 0.5 even ok
149.104919 1 C7H14N2N8 100.00 149.104919 0.4 -0.8 18.0 1.5 even ok
165.078667 1 C7H14N2 100.00 165.078667 0.6 -0.6 6.4 1.5 even ok

S72
20. N-benzyl-N-methylcyanamide

The reaction gave the title compound N-benzyl-N-methylcyanamide (0.35 g, 2.40 mmol, 60%) as a yellowish liquid after purification by flash chromatography on silica gel (eluent = 5% methanol in dichloromethane).

$\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 3065, 3032, 2914, 2220$(\text{C}=\text{N})$, 1495, 1370, 1027, 968;

$^1$H NMR (CDCl$_3$, 600MHz): $\delta_H$: 2.76 (3H, s), 4.14 (2H, s), 7.26-7.39 (5H, m);

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta_C$: 134.4, 128.9, 128.6, 128.4, 118.8, 57.1, 37.8; HRMS (ESI+) calculated for $[\text{C}_9\text{H}_{11}\text{N}_2]^+ (\text{M}+\text{H})^+$: m/z 147.091738, found 147.091675.
21. N, N-diethylcyanamide

The reaction gave the title compound N, N-diethylcyanamide (0.56 g, 2.52 mmol, 63%) as a white solid after purification by flash chromatography on silica gel (eluent=18% ethyl acetate in Petroleum ether). $\nu_{\text{max}}/(\text{cm}^{-1})$ (film): 3062, 3030, 2200(C≡N), 1471, 1070, 730, 897; $^1$H NMR (CDCl$_3$, 600MHz): $\delta_H$: 4.11 (4H, s), 7.25-7.40 (10H, m); $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta_C$: 134.4, 128.9, 128.7, 128.6, 118.3, 54.3; HRMS (ESI+) calculated for [C$_{15}$H$_{15}$N$_2$]$^+$(M+H)$^+$: m/z 223.122878, found 223.122975.
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1.3 Detection of allyl bromide

We chose N-allylpiperidine as the model substrate to detect allyl bromide from the reaction mixture by LC-MS (Agilent Technologies 6120 Quadrupole LC/MS). In Figure 1, we could observe that there are two components, and identified as piperidine-1-carbonitrile (Figure 2) and allyl bromide (Figure 3) by MS.

Figure 1. LC of reaction mixture

Figure 2. MS of piperidine-1-carbonitrile
For quantitative testing, we analyzed the peak area of the two components, the area ratio of piperidine-1-carbonitrile to allyl bromide was 2.45:1 (Figure 1). We think that the main reason for this situation is that piperidine-1-carbonitrile and allyl bromide have different absorbancy index. We prepared a solution of 1:1 mole ratio of piperidine-1-carbonitrile to allyl bromide with methanol as solvent, and the area ratio of piperidine-1-carbonitrile to allyl bromide was 2.49:1 after LC/MS. So we think that the mole ratio of piperidine-1-carbonitrile to allyl bromide is 1:1.
1.4 References


