The application of vinamidinium salt to the synthesis of 3-chloro-α-carbolines

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General:

All chemicals (including 2-indolinones) and solvents were purchased from commercial sources and used as received. Thin layer chromatography (TLC) was performed on precoated silica gel plates with a fluorescent indicator and detection at 254 nm. NMR spectra were measured with Brüker 500 MHz NMR spectrometer operating at 500 MHz (1H NMR) and at 125MHz (13C NMR). Mass spectra were recorded on a thermofisher orbitrap UPLC-HRMS/MS.

Experimental Details and Characterization Data

Preparation of 2-chloro-3-(dimethylamino) prop-2-en-1-iminium chloride salt 3

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{Cl} \\
\text{N} & \quad \text{H} \\
\text{1. DMF, (COCl)}_2 & \quad 2. \text{NH}_3/\text{CH}_3\text{OH}
\end{align*}
\]

In a 1.0 L 3-neck round bottom flask with dropping addition funnel and thermometer placed in the cooling water bath, 246.0g (3.37mol) DMF was added and heated to 50 °C, then 71.2g (0.63 mol) chloroacetyl chloride was added slowly, once the addition was completed, the reaction mixture was maintained at 50 °C for about 2 h. Then oxalyl chloride (79.1g, 0.62 mol) was added slowly, during addition the reaction temperature was controlled by varing addtion time. After the addition was over, the reaction mixture was heated slowly to 65-70 °C and maintained for 4h. The reaction mass was cooled to -10 °C and 180 mL 25% methanolic ammonia solution was added to adjust the pH of the solution to 8-9 (Note: the temperature was kept under 10 °C). The separated solids was filtered then suspended in 150 mL isopropanol. The mixture was stirred for 1h and filtered. The filter cake was washed with 50 mL isopropanol. The dry product was purified by 500 mL acetone at reflux for 1hr and cooled to room temperature and maintained for 1hr and filtered and washed with 50 mL acetone, the wet cake was dried under vacuum to get the purified product, 91.05g (yield 86.4%), a yellow solid. 1H NMR (500 MHz, D2O): δ 7.92 (s, 1H), 7.78 (s, 1H), 3.63 (s, 3H), 3.42 (s, 3H); 13C NMR (125 MHz, D2O): δ 160.31, 158.67, 95.73, 49.10, 39.47.

Compounds 4b-4l were synthesized from the desired 2-indolinones with 3-chlorovinamidinium salt 3 according to the procedure described for the synthesis of 4a.

3-(3-amino-2-chloropropylidene)-5-chloro-2-indolinone (4b)
Yield 83%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 10.33 (s, 1H), 8.09 (s, 2H), 7.79 (t, $J = 11.0$ Hz, 1H), 7.56 (s, 1H), 7.47 (s, 1H), 7.04 (dd, $J_1 = 8.5$ Hz, $J_2 = 1.5$ Hz, 1H), 6.78 (d, $J = 8.0$ Hz, 1H); $^{13}$C NMR (125 MHz, DMSO): $\delta$ 170.34, 151.85, 139.17, 138.86, 125.081, 124.84, 124.52, 123.46, 110.39, 109.83, 101.22; HRMS (ESI): found 255.0080 ([M + H$^+$]+), calcd. for C$_{11}$H$_9$Cl$_2$N$_2$O$^+$ 255.0086.

3-(3-amino-2-chloropropylidene)-5-fluoro-2-indolinone (4c)

Yield 86%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 10.20 (s, 1H), 8.01 (s, 1H), 7.87-7.95 (m, 1H), 7.76 (t, $J = 11.0$ Hz, 1H), 7.46 (s, 2H), 6.79-6.85 (m, 1H), 6.70-6.78 (m, 1H); $^{13}$C NMR (125 MHz, DMSO): $\delta$ 170.68, 158.49, 156.65 ($J = 230.13$ Hz), 151.46, 138.64, 136.82, 124.25, 124.17 ($J = 9.63$ Hz), 111.84, 111.65 ($J = 23.63$ Hz), 111.07, 110.86 ($J = 5.23$ Hz), 110.75, 109.52, 109.45 ($J = 8.88$ Hz), 101.24; HRMS (ESI): found 239.0380 ([M + H$^+$]+), calcd. for C$_{11}$H$_9$ClFN$_2$O$^+$ 239.0382.

3-(3-amino-2-chloropropylidene)-2-indolinone (4d)

Yield 77%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 10.19 (s, 1H), 8.13 (d, $J = 8.0$ Hz, 1H), 7.66 (t, $J = 11.0$ Hz, 2H), 7.46 (s, 1H), 7.39 (s, 1H), 7.00-7.03 (m, 1H), 6.83-6.86 (m, 1H), 6.78 (d, $J = 7.5$ Hz, 1H); $^{13}$C NMR (125 MHz, DMSO): $\delta$ 170.57, 149.93, 140.72, 137.22, 126.09, 124.39, 123.03, 120.64, 111.69, 109.37, 101.09; HRMS (ESI): found 221.0471 ([M + H$^+$]+), calcd. for C$_{11}$H$_{10}$ClN$_2$O$^+$ 221.0476.

3-(3-amino-2-chloropropylidene)-5-trifluoromethyl-2-indolinone (4e)

Yield 86%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 10.45 (s, 1H), 8.28-8.29 (m, 1H), 7.88 (t, $J = 11.0$ Hz, 1H), 7.63-7.76 (m, 1H), 7.57 (s, 1H), 7.19 (d, $J = 8.0$ Hz,
1H), 6.99 (s, 1H); \(^{13}\)C NMR (125 MHz, DMSO): \(\delta\) 170.42, 152.93, 140.40, 140.35, 127.04, 126.28, 124.12 (d, \(J=269.88\) Hz), 125.37, 125.12 (d, \(J=31.25\) Hz), 123.98, 117.28, 109.04, 105.17, 105.14 (d, \(J=3.75\) Hz), 101.70; HRMS (ESI): found 289.0351 ([M + H]+), calcd. for \(\text{C}_{12}\text{H}_{9}\text{ClF}_{3}\text{N}_{2}\text{O}^+\) 289.0356.

3-(3-amino-2-chloropropylidene)-5,7-dichloro-2-indolinone (4f)

Yield 86%, yellow solid; \(^1\)H NMR (500 MHz, DMSO): \(\delta\) 10.60 (s, 1H), 8.40 (s, 1H), 8.22 (d, \(J=1.0\) Hz, 1H), 7.90 (d, \(J=8.0\) Hz, 2H), 7.56 (s, 1H), 7.39 (d, \(J=1.5\) Hz, 1H); \(^{13}\)C NMR (125 MHz, DMSO): \(\delta\) 169.99, 153.74, 140.70, 138.23, 129.04, 126.83, 124.90, 112.41, 108.55, 102.46, 101.54; HRMS (ESI): found 376.8679 ([M + H]+), calcd. for \(\text{C}_{11}\text{H}_{8}\text{BrCl}_{2}\text{N}_{2}\text{O}^+\) 376.8686.

3-(3-amino-2-chloropropylidene)-5-bromo-6-chloro-2-indolinone (4g)

Yield 86%, yellow solid; \(^1\)H NMR (500 MHz, DMSO): \(\delta\) 10.43 (s, 1H), 8.34 (s, 1H), 8.22 (s, 1H), 7.86 (s, 1H), 7.49 (s, 1H), 6.94 (s, 1H); \(^{13}\)C NMR (125 MHz, DMSO): \(\delta\) 170.21, 152.74, 140.76, 139.43, 129.01, 127.65, 124.33, 111.65, 110.48, 108.30, 101.43; HRMS (ESI): found 332.9188 ([M + H]+), calcd. for \(\text{C}_{11}\text{H}_{8}\text{BrCl}_{2}\text{N}_{2}\text{O}^+\) 332.9192.

3-(3-amino-2-chloropropylidene)-5-nitro-6-chloro-2-indolinone (4h)

Yield 87%, yellow solid; \(^1\)H NMR (500 MHz, DMSO): \(\delta\) 10.90 (s, 1H), 8.82 (s, 1H), 8.52 (s, 1H), 7.95-8.03 (m, 2H), 7.61 (s, 1H), 6.95 (s, 1H); \(^{13}\)C NMR (125 MHz, DMSO): \(\delta\) 170.61, 154.44, 144.47, 140.91, 140.17, 123.65, 122.72, 120.99, 110.83, 106.79, 101.97; HRMS (ESI): found 321.9754 ([M + H]+), calcd. for \(\text{C}_{11}\text{H}_{7}\text{Cl}_{2}\text{N}_{3}\text{O}_{3}\text{Na}^+\) 321.9757.

3-(3-amino-2-chloropropylidene)-5-bromo-2-indolinone (4i)
Yield 84%, yellow solid; $^1$H NMR (500 MHz, DMSO): δ 10.93 (s, 1H), 9.02 (d, J = 1.0 Hz, 1H), 8.39 (s, 1H), 7.91-7.99 (m, 3H), 7.61 (s, 1H), 6.94 (d, J = 8.5 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO): δ 170.82, 153.69, 145.83, 141.48, 140.38, 123.59, 122.10, 118.82, 108.92, 108.01, 101.65; HRMS (ESI): found 298.9578 ([M + H]$^+$), calcd. for C$_{11}$H$_9$BrClN$_2$O 298.9581.

3-(3-amino-2-chloropropylidene)-5-chloro-7-bromo-2-indolinone (4j)

Yield 87%, yellow solid; $^1$H NMR (500 MHz, DMSO): δ 10.58 (s, 1H), 8.39 (s, 1H), 8.09 (s, 1H), 7.89-7.56 (m, 3H), 7.29 (s, 1H), 6.94 (d, J = 8.5 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO): δ 170.16, 153.72, 140.73, 137.91, 126.50, 126.29, 124.95, 122.22, 108.72, 101.99, 101.57; HRMS (ESI): found 332.9186 ([M + H]$^+$), calcd. for C$_{11}$H$_8$BrClN$_2$O 332.9192.

3-(3-amino-2-chloropropylidene)-5-methyl-2-indolinone (4k)

Yield 86%, yellow solid; $^1$H NMR (500 MHz, DMSO): δ 10.07 (s, 1H), 7.95 (s, 1H), 7.63 (t, J = 11.0 Hz, 1H), 7.35 (s, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 7.5 Hz), 2.25 (s, 3H); $^{13}$C NMR (125 MHz, DMSO): 170.66, 154.11, 150.10, 137.29, 134.71, 123.88, 112.05, 111.18, 109.30, 100.98, 21.66. HRMS (ESI): found 235.0631 ([M + H]$^+$), calcd. for C$_{12}$H$_{12}$ClN$_2$O 235.0638.

3-(3-amino-2-chloropropylidene)-5-methoxy-2-indolinone (4l)

Yield 82%, yellow solid; $^1$H NMR (500 MHz, DMSO): δ 9.98 (s, 1H), 7.63-7.75 (m, 3H), 7.22-7.36 (m, 2H), 6.62-6.67 (m, 2H), 3.69 (s, 3H); $^{13}$C NMR (125 MHz, DMSO): δ 170.66, 154.11, 150.10, 137.29, 134.71, 123.88, 112.05, 111.18, 109.30,
Compounds 1b-1l were synthesized from the desired 3-(3-amino-2-chloropropylidene)-2-indolinone 4 according to the procedure described for the synthesis of 1a.

3,6-dichloro-α-carboline (1b)

Yield 94%, yellow solid; \(^{1}H\) NMR (500 MHz, DMSO): \(\delta\) 12.16 (s, 1H), 8.70 (s, 1H), 8.44 (d, \(J = 2.0\) Hz, 1H), 8.21 (d, \(J = 8.0\) Hz, 1H), 7.52 (s, 1H), 7.28 (d, \(J = 8.0\) Hz, 1H); \(^{13}C\) NMR (125 MHz, DMSO): \(\delta\) 150.93, 145.47, 138.61, 129.20, 127.79, 124.60, 122.48, 121.84, 121.32, 116.04, 113.63; MS (ESI): m/z 237.1 ([M + H]\(^{+}\)), calcd. for C\(_{11}\)H\(_{7}\)Cl\(_2\)N\(_{2}\): 237.0.

3-chloro-6-fluoro-α-carboline (1c)

Yield 92%, yellow solid; \(^{1}H\) NMR (500 MHz, DMSO): \(\delta\) 12.13 (s, 1H), 8.71 (d, \(J = 1.5\) Hz, 1H), 8.45 (d, \(J = 2.0\) Hz, 1H), 8.06 (dd, \(J_1 = 9.0\) Hz, \(J_2 = 2.0\) Hz, 1H), 7.52 (dd, \(J_1 = 8.5\) Hz, \(J_2 = 4.5\) Hz, 1H), 7.37-7.35 (m, 1H); \(^{13}C\) NMR (125 MHz, DMSO): \(\delta\) 158.29, 156.43 (\(J = 232.88\) Hz), 151.00, 144.93, 136.75, 129.43, 122.05, 120.53, 120.45 (\(J = 10.13\) Hz), 116.90, 116.86 (\(J = 4.13\) Hz), 116.06, 115.86 (\(J = 25.25\) Hz), 113.38, 113.31 (\(J = 8.88\) Hz), 108.03, 107.83 (\(J = 24.13\) Hz); HRMS (ESI): found 221.0274 ([M + H]\(^{+}\)), calcd. for C\(_{11}\)H\(_{7}\)Cl\(_2\)N\(_{2}\) 221.0276.

3-chloro-α-carboline (1d)

Yield 80%, yellow solid; \(^{1}H\) NMR (500 MHz, DMSO): \(\delta\) 12.00 (s, 1H), 8.68 (d, \(J = 2.0\) Hz, 1H), 8.42 (d, \(J = 2.0\) Hz, 1H), 8.20 (d, \(J = 7.5\) Hz, 1H), 7.48-7.52 (m, 2H), 7.23-7.26 (m, 1H); \(^{13}C\) NMR (125 MHz, DMSO): \(\delta\) 150.89, 145.40, 139.11, 130.29, 129.18, 124.77, 122.39, 121.93, 115.88, 114.13 112.16; MS (ESI): 203.2 ([M + H]\(^{+}\)), calcd. for C\(_{11}\)H\(_{8}\)Cl\(_{2}\): 203.0.

3-chloro-6-trifluoromethyl-α-carboline (1e)
Yield 64%, off-white solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 12.40 (s, 1H), 8.87 (s, 1H), 8.55 (d, $J = 2.5$ Hz, 1H), 8.45 (d, $J = 8.0$ Hz, 1H), 7.80 (s, 1H), 7.59 (d, $J = 8.5$ Hz, 1H); $^{13}$C NMR (125 MHz, DMSO): $\delta$ 151.28, 146.31, 139.28, 129.82, 127.88, 127.62 (d, $J = 31.5$ Hz), 128.38, 126.21, 124.04, 121.89 (q, $J = 270.5$ Hz), 123.34, 123.07, 122.91, 116.55, 115.84, 108.95; HRMS (ESI): found 269.0099 ([M - H]$^+$), calcd. for C$_{12}$H$_5$ClF$_3$N$_2$ 269.0093.

3-chloro-6,8-dibromo-α-carboline (1f)

Yield 86%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 12.52 (s, 1H), 8.81 (s, 1H), 8.53-8.55 (m, 2H), 7.92 (s, 1H); $^{13}$C NMR (125 MHz, DMSO): $\delta$ 150.93, 146.41, 137.87, 131.90, 129.91, 124.21, 123.25, 123.08, 116.16, 112.22, 105.39; HRMS (ESI): found 358.8580 ([M + H]$^+$), calcd. for C$_{11}$H$_6$ClBr$_2$N$_2$ 358.8581.

6-bromo-3,7-dichloro-α-carboline (1g)

Yield 87%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 12.35 (s, 1H), 8.76 (d, $J = 2.0$ Hz, 1H), 8.68 (s, 1H), 8.48 (d, $J = 2.0$ Hz, 1H), 7.73 (s, 1H); $^{13}$C NMR (125 MHz, DMSO): $\delta$ 151.02, 145.80, 139.68, 131.59, 129.48, 127.05, 122.95, 120.72, 115.49, 113.47, 112.14; HRMS (ESI): found 314.9081 ([M + H]$^+$), calcd. for C$_{11}$H$_6$ClBr$_2$N$_2$ 314.9086.

3,7-dichloro-6-nitro-α-carboline (1h)

Yield 70%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 12.76 (s, 1H), 9.14 (s, 1H), 8.90 (s, 1H), 8.57 (s, 1H), 7.74 (s, 1H); $^{13}$C NMR (125 MHz, DMSO): $\delta$ 151.83, 146.76, 142.14, 140.78, 130.22, 124.83, 123.90, 121.64, 118.69, 116.43, 114.20; HRMS (ESI): found 281.9829 ([M + H]$^+$), calcd. for C$_{11}$H$_6$Cl$_2$N$_3$O$_2$ 281.9832.

3-chloro-6-bromo-α-carboline (1i)
Yield 90%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 12.21 (s, 1H), 8.75 (s, 1H), 8.47 (d, $J = 5.5$ Hz, 2H), 7.62 (d, $J = 7.0$ Hz, 1H), 7.49 (d, $J = 5.5$ Hz, 1H); $^{13}$C NMR (125 MHz, DMSO): $\delta$ 150.72, 145.47, 138.86, 130.36, 129.24, 124.82, 122.51, 121.92, 115.88, 114.05, 112.27; MS (ESI): 281.1 ([M + H$^+$]), calcd. for C$_{11}$H$_7$BrClN$_2$ 280.9.

3,7-dichloro-8-bromo-$\alpha$-carboline (Ij)

Yield 85%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 12.50 (s, 1H), 8.78 (s, 1H), 8.54 (s, 1H), 8.38 (s, 1H), 7.81 (s, 1H); $^{13}$C NMR (125 MHz, DMSO): $\delta$ 151.11, 146.42, 137.60, 129.88, 129.58, 124.93, 123.20, 122.43, 121.28, 116.33, 105.04; HRMS (ESI): found 314.9085 ([M + H$^+$]), calcd. for C$_{11}$H$_6$Cl$_2$BrN$_2^+$ 314.9086.

3-chloro-6-methyl-$\alpha$-carboline (Ik)

Yield 80%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 11.85 (s, 1H), 8.60 (d, $J = 2.5$ Hz, 1H), 8.38 (d, $J = 2.5$ Hz, 1H), 8.0 (s, 1H), 7.40 (d, $J = 8.5$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 1H), 2.45 (s, 3H); $^{13}$C NMR (125 MHz, DMSO): 150.78, 144.26, 138.27, 129.27, 129.10, 128.26, 121.90, 121.84, 120.14, 116.69, 111.72, 21.53; HRMS (ESI): found 217.0524 ([M + H$^+$]), calcd. for C$_{12}$H$_{10}$ClN$_2^+$ 217.0533.

3-chloro-6-methoxy-$\alpha$-carboline (Il)

Yield 81%, yellow solid; $^1$H NMR (500 MHz, DMSO): $\delta$ 11.81 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.81 (s, 1H), 7.43 (s, 1H), 7.14 (s, 1H), 3.86 (s, 3H); $^{13}$C NMR (125 MHz, DMSO): 154.15, 150.96, 144.35, 134.85, 128.46, 121.57, 120.42, 117.29, 116.90, 112.79, 104.79, 56.06; HRMS (ESI): found 233.0477 ([M + H$^+$]), calcd. for C$_{12}$H$_{10}$ClN$_2$O$^+$ 233.0482.
Proton NMR spectrum of compound 3

Carbon NMR spectrum of compound 3
Proton NMR spectrum of compound 4a

Carbon NMR spectrum of compound 4a
Proton NMR spectrum of compound 4b

Carbon NMR spectrum of compound 4b
Proton NMR spectrum of compound 4c

Carbon NMR spectrum of compound 4c
Proton NMR spectrum of compound 4d

Carbon NMR spectrum of compound 4d
Proton NMR spectrum of compound 4e

Carbon NMR spectrum of compound 4e
Proton NMR spectrum of compound 4f

Carbon NMR spectrum of compound 4f
Proton NMR spectrum of compound 4g

Carbon NMR spectrum of compound 4g
Proton NMR spectrum of compound 4h

Carbon NMR spectrum of compound 4h
Proton NMR spectrum of compound 4i

Carbon NMR spectrum of compound 4i
Proton NMR spectrum of compound 4j

Carbon NMR spectrum of compound 4j
Proton NMR spectrum of compound 4k

Carbon NMR spectrum of compound 4k
Proton NMR spectrum of compound 4l

Carbon NMR spectrum of compound 4l
Proton NMR spectrum of compound 1a

Carbon NMR spectrum of compound 1a
Proton NMR spectrum of compound 1b

Carbon NMR spectrum of compound 1b
Proton NMR spectrum of compound 1c

Carbon NMR spectrum of compound 1c
Proton NMR spectrum of compound 1d

Carbon NMR spectrum of compound 1d
Proton NMR spectrum of compound 1e

Carbon NMR spectrum of compound 1e
Proton NMR spectrum of compound 1f

Carbon NMR spectrum of compound 1f
Proton NMR spectrum of compound 1g

Carbon NMR spectrum of compound 1g
Proton NMR spectrum of compound 1h

Carbon NMR spectrum of compound 1h
Proton NMR spectrum of compound 1i

Carbon NMR spectrum of compound 1i
Proton NMR spectrum of compound 1j

Carbon NMR spectrum of compound 1j
Proton NMR spectrum of compound 1k

Carbon NMR spectrum of compound 1k
Proton NMR spectrum of compound II

Carbon NMR spectrum of compound II