One-Pot Synthesis of α-Halo β-Amino Acid Derivatives via the Difunctional Coupling of Ethyl α-Diazoacetate with Silyl Halides and N,O-Acetals or Aromatic Tertiary Amines

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General procedure for the preparation of \(N,O\)-acetals\(^{[1]}\)

General procedure for the synthesis of \(N,O\)-acetals. To a reaction vessel was successively added a secondary amine (10 mmol), methanol (0.60 mL, 13 mmol), paraformaldehyde (303 mg, 10.0 mmol), \(K_2CO_3\) (2.76 g, 20.0 mmol) and \(Na_2SO_4\) (2.84 g, 20.0 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for overnight. The resulting mixture was filtered, the filtrate was purified by a bulb-to-bulb distillation under reduced pressure to give the corresponding \(N,O\)-acetal.

\(N\)-(Methoxymethyl)-\(N\)-methylaniline.\(^{[1]}\)

\[\begin{align*}
\text{OMe} & \quad \text{N} \quad \text{Me}
\end{align*}\]

The general procedure was followed with \(N\)-methylaniline (10.4 g, 97.2 mmol). Distillation afforded 1a (6.94 g, 47%) as a colorless oil: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta = 7.24-7.27\) (m, 2 H, ArH), 6.88 (d, \(J = 8.0\) Hz, 2 H, ArH), 6.80 (t, \(J = 7.5\) Hz, 1 H, ArH), 4.75 (s, 2 H, \(CH_2\)), 3.30 (s, 3 H, \(CH_3\)), 3.10 (s, 3 H, \(CH_3\)); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz); \(\delta = 148.2, 129.1, 118.2, 113.3, 85.3, 55.0, 38.6;\) MS (FAB) \(m/z\) 151 (M\(^+\)).

2-Methyl-\(N\)-(methoxymethyl)-\(N\)-methylaniline.\(^{[1]}\)

\[\begin{align*}
\text{Me} & \quad \text{OMe} & \quad \text{N} \quad \text{Me}
\end{align*}\]

The general procedure was followed with 2-methyl-\(N\)-methylaniline (1.29 g, 10.6 mmol). Distillation afforded 1b (623 mg, 59%) as a pale yellow liquid: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta = 7.19-7.14\) (m, 3 H, ArH), 6.99 (t, \(J = 7.5\) Hz, 1 H, ArH), 4.41 (s, 2 H, \(CH_2\)), 3.30 (s, 3 H, \(CH_3\)), 2.87 (s, 3 H, \(CH_3\)), 2.31 (s, 3 H, \(CH_3\)); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz); \(\delta = 149.6, 131.1, 126.4, 123.5, 122.2, 109.1, 88.0, 55.8, 39.1, 18.4\).

3-Methyl-\(N\)-(methoxymethyl)-\(N\)-methylaniline.\(^{[1]}\)

\[\begin{align*}
\text{Me} & \quad \text{OMe} & \quad \text{N} \quad \text{Me}
\end{align*}\]

The general procedure was followed with 3-methyl-\(N\)-methylaniline (1.16 g, 9.58 mmol). Distillation afforded 1c (658 mg, 42%) as a colorless oil: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta = 7.14\) (t, \(J = 7.5\) Hz, 1 H, ArH), 6.70-6.68 (m, 2 H, ArH), 6.62 (d, \(J = 8.0\) Hz, 1 H, ArH), 4.73 (s, 2 H, \(CH_2\)), 3.30 (s, 3 H, \(CH_3\)), 3.08 (s, 3 H, \(CH_3\)), 2.32 (s, 3 H, \(CH_3\)); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz); \(\delta = 148.3, 138.8, 128.9, 119.1, 114.0, 110.5, 85.3, 55.0, 38.6, 21.9\).

4-Methyl-\(N\)-(methoxymethyl)-\(N\)-methylaniline.\(^{[1]}\)
The general procedure was followed with 4-methyl-N-methylaniline (1.29 g, 10.7 mmol). Distillation afforded 1d (608 mg, 34%) as a yellow oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta =$ 7.07 (d, $J =$ 8.5 Hz, 2 H, ArH), 6.78 (d, $J =$ 8.0 Hz, 2 H, ArH), 4.72 (s, 2 H, CH$_2$), 3.29 (s, 3 H, CH$_3$), 3.06 (s, 3 H, CH$_3$), 2.26 (s, 3 H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz); $\delta =$ 146.1, 129.6, 127.4, 113.5, 85.5, 55.0, 38.6, 20.3.

2-Methoxy-N-(methoxymethyl)-N-methylaniline.$^{[1]}$

The general procedure was followed with 2-methoxy-N-methylaniline (1.03 g, 7.51 mmol). Distillation afforded 1e (189 mg, 14%) as a colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta =$ 7.14 (dd, $J =$ 8.0 Hz, 2.0 Hz, 1 H, ArH), 7.02-7.00 (m, 1 H, ArH), 6.99-6.86 (m, 2 H, ArH), 4.62 (s, 2 H, CH$_2$), 3.87 (s, 3 H, CH$_3$), 3.28 (s, 3 H, CH$_3$), 2.97 (s, 3 H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz); $\delta =$ 139.2, 123.0, 121.0, 120.9, 111.3, 87.0, 56.1, 55.4, 38.4; MS (FAB) m/z 181 (M$^+$).

3-Methoxy-N-(methoxymethyl)-N-methylaniline.

The general procedure was followed with 3-methoxy-N-methylaniline (1.38 g, 10.1 mmol). Distillation afforded 1f (478 mg, 26%) as a yellow oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta =$ 7.16 (t, $J =$ 8.0 Hz, 1 H, ArH), 6.50 (dd, $J =$ 8.0 Hz, 2.0 Hz, 1 H, ArH), 6.42 (t, $J =$ 2.0 Hz, 1 H, ArH), 6.39-6.35 (m, 1 H, ArH), 4.73 (s, 2 H, CH$_2$), 3.80 (s, 3 H, CH$_3$), 3.30 (s, 3 H, CH$_3$), 3.08 (s, 3 H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz); $\delta =$ 160.6, 149.7, 129.8, 106.3, 102.9, 99.9, 85.1, 55.1, 55.0, 38.7; MS (FAB) m/z 181 (M$^+$); HRMS (FAB): Calcd for [M$^+$] (C$_{10}$H$_{15}$NO$_2$) m/z 181.1103, found 181.1103.

4-Methoxy-N-(methoxymethyl)-N-methylaniline.

The general procedure was followed with 4-methoxy-N-methylaniline (1.49 g, 10.5 mmol). Distillation afforded 1g (1.23 g, 65%) as a dark brown oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta =$ 6.84 (m, 4 H, ArH), 4.68 (s, 2 H, CH$_2$), 3.76 (s, 3 H, CH$_3$), 3.29 (s, 3 H, CH$_3$), 3.05 (s, 3 H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz); $\delta =$ 152.6, 116.2, 115.0, 114.6, 86.1, 55.7, 55.1, 38.8; MS (FAB) m/z 181 (M$^+$); HRMS (FAB): Calcd for [M$^+$] (C$_{10}$H$_{15}$NO$_2$) m/z 181.1103, found 181.1101.

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4-Fluoro-N-(methoxymethyl)-N-methylaniline.

The general procedure was followed with 4-fluoro-N-methylaniline (1.33 g, 10.6 mmol). Distillation afforded 1h (529 mg, 29%) as a pale yellow oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 6.95 (t, $J$ = 8.5 Hz, 2 H, ArH), 6.82-6.79 (m, 2 H, ArH), 4.69 (s, 2 H, CH$_2$), 3.30 (s, 3 H, CH$_3$), 3.07 (s, 3 H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ = 157.3 (d, $J$ = 236 Hz), 144.8 (d, $J$ = 1.3 Hz), 115.5 (d, $J$ = 21.3 Hz), 114.5 (d, $J$ = 7.5 Hz), 85.8, 55.0, 39.0; MS (FAB) m/z 169 (M$^+$); HRMS (FAB): Calcd for [M]$^+$ (C$_9$H$_{12}$FNO) m/z 169.0903, found 169.0902.

N-(methoxymethyl)-N-ethylaniline. [2]

The general procedure was followed with N-ethylaniline (1.34 g, 11.1 mmol). Distillation afforded 1i (131 mg, 7%) as a colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 7.23 (t, $J$ = 8.5 Hz, 2 H, ArH), 6.88 (d, $J$ = 8.0 Hz, 2 H, ArH), 6.77 (t, $J$ = 7.5 Hz, 1 H, ArH), 4.71 (s, 2 H, CH$_2$), 3.52 (q, $J$ = 7.0 Hz, 2 H, CH$_2$), 3.32 (s, 3 H, CH$_3$), 1.22 (t, $J$ = 7.0 Hz, 3 H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ = 147.3, 129.1, 113.9, 83.9, 54.6, 45.3, 13.4.

3-Methyl-N-(methoxymethyl)-N-ethylaniline. [1]

The general procedure was followed with N-ethyl-3-methylaniline (1.32 g, 9.76 mmol). Distillation afforded 1i (390 mg, 22%) as a colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 7.14-7.11 (m, 1 H, ArH), 6.69-6.67 (m, 2 H, ArH), 6.60 (d, $J$ = 7.0 Hz, 1 H, ArH), 4.70 (s, 2 H, CH$_2$), 3.51 (q, $J$ = 7.0 Hz, 2 H, CH$_2$), 3.31 (s, 3 H, CH$_3$), 2.31 (s, 3 H, CH$_3$), 1.21 (t, $J$ = 7.5 Hz, 3 H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ = 147.3, 138.8, 129.0, 118.9, 114.2, 110.7, 83.9, 54.6, 45.3, 21.9, 13.5.

N-(Methoxymethyl)-N-methylbenzylamine. [1]

The general procedure was followed with N-methyl-1-phenylmethanamine (1.30 g, 10.7 mmol). Distillation afforded 1k (293 mg, 20%) as a colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 7.33-7.30 (m, 5 H, ArH), 4.08 (s, 2 H, CH$_2$), 3.75 (s, 2 H, CH$_2$), 3.32 (s, 3 H, CH$_3$), 2.40 (s, 3 H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ = 139.0, 128.8, 128.2, 127.0, 89.1, 58.0, 56.0, 39.4.
References

\(^1\text{H NMR}\)

\[^{13}\text{C NMR}\]
$^1$H NMR

$^{13}$C NMR
NMR spectra for 

$^1$H NMR

$^{13}$C NMR
\[ ^1H \text{ NMR} \]

\[ ^{13}C \text{ NMR} \]

\[ \text{Ph} - \text{N} - \text{O} \text{Me} \]
$^1$H NMR

$^{13}$C NMR
$^{1}H$ NMR

$^{13}C$ NMR

S21
$^{13}$C NMR

$^1$H NMR
$^1$H NMR

$^{13}$C NMR
$^1$H NMR

$^{13}$C NMR
$^{1}$H NMR

$^{13}$C NMR
$^{1}$$H$ NMR

$^{13}C$ NMR
$^1$H NMR

$^{13}$C NMR

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