Supporting information:

CDI Mediated Monoacylation of Symmetrical Diamines and Selective Acylation of Primary Amines of Unsymmetrical Diamines

Sanjeev K. Verma*, Ramarao Ghorpade, Ajay Pratap and M. P. Kaushik
Process Technology Development Division, Defence R & D Establishment, Jhansi Road,
Gwalior-474002 (MP) India
Fax: +91(751)2340042,
Email Address: Skv002002@gmail.com

Contents

1.  Experimental Section:  2-6
2.  NMR spectra:          6-17
Experimental Section.

General information:

All the starting materials were obtained from commercial supplies and used as received. The dihydrochloride salts of all diamines were prepared according to literature method\(^1\). The reactions were performed in air atmosphere without any specific precautions. Column chromatography was performed with silica gel 200-400 mesh using ethyl acetate and ethanol as eluents under N\(_2\) Pressure.

General Procedure 1: monoacylation of symmetrical diamines

**Synthesis of Phenyl-piperazin-1-yl-methanone:** In a round bottom flask add 0.01 mole (1.36 g) phenyl acetic acid, and 0.012 moles (1.94 g) of CDI. Mix the reaction mixture with spatula to start the reaction. CO\(_2\) gas starts releasing with exothermic reaction. Left the reaction mixture at room temperature for 5 minutes till solid reaction mixture turned to pale yellow liquid. In a separate round bottom flask add 0.05 moles (0.43 g) of piperazine and 0.05 moles (0.80 g) of piperazine dihydrochloride in 20 ml of water. Stir the reaction mixture for 5 minutes and add 4 gm of NaCl. Add this brine solution to the round bottom flask containing acyl imidazole. Stir the reaction mixture for half hour. The aqueous layer was washed with 4 x 5 ml of ethyl acetate to remove diacylated product. 10 ml of saturated solution of NaOH was added to the aqueous layer and washed with ethyl acetate (4 x 10ml). The aqueous layer was discarded. The organic layer was washed with water (4 x 10ml), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated to give pale yellow coloured liquid. The pure product 2-phenyl-1-(piperazin-1-yl)ethanone was purified by flash chromatography as a colourless liquid.
General Procedure 2: Synthesis of N-BOC piperazine (monocarbamate of diamines).

The synthesis is mainly carried out in two steps.

First step:

**synthesis of tert-butyl 1H-imidazole-1-carboxylate:** In a round bottom flask add 0.01 mole (0.75 g) of t-butanol and 0.012 mole (1.94 g) of CDI. Stir the reaction mixture for 10 minutes at 40°C. Add 10 ml of ethyl acetate in it. Wash the organic layer with 2 x 5ml of 0.1 N HCl and 2 x 10 ml of water. Dry organic layer over anhydrous Na₂SO₄ and concentrated to give coloured liquid. The product formed is enough pure to be used for next step.

2nd step:

**Synthesis of N-BOC piperazine:**

In a separate round bottom flask add 0.05 moles (0.43 g) of piperazine and 0.005 moles (0.80 g) of piperazine dihydrochloride in 20 ml of water. Stir the reaction mixture for 5 minutes and add 4 gm of NaCl. Add tert-butyl 1H-imidazole-1-carboxylate from 1st step to the brine solution. Stir the reaction mixture for half hour. 10 ml of saturated solution of NaOH was added to the aqueous layer and washed with ethyl acetate (4 x 15ml). The aqueous layer was discarded. The organic layer was washed with water (4 x 5ml), dried over anhydrous Na₂SO₄ and concentrated to give pale yellow coloured liquid. The pure product N-BOC piperazine was purified by flash chromatography as a colourless liquid.

Reference data related to compounds (Table 3, entry 1-5, 11-20) is available in the supporting information of “S. K. Verma, B. N. Acharya and M. P. Kaushik, *Org. Lett.*, 2010, 12, 4232”.

3
2-phenyl-1-(piperazin-1-yl)ethanone.

\[
\text{\begin{center}
\begin{tikzpicture}
\node[rectangle,draw] (a) {O};
\node[rectangle,draw, below of=a] (b) {NH};
\end{tikzpicture}
\end{center}}
\]

\( ^1\text{H NMR (400MHz, CDCl}_3\): \delta 2.6 (t, 2H), 2.8 (t, 2H), 3.4 (t, 2H), 3.6 (t, 2H), 3.7 (s, 2H) 7.2 (m, 5H); \ ^{13}\text{C NMR (100 MHz, CDCl}_3\): \delta 40.6, 42.6, 45.4, 45.7, 47.0, 121.6, 126.6, 128.4, 134.8, 169.4 m/z = 204(M + 1)^+ .

2-(4-methoxyphenyl)-1-(piperazin-1-yl)ethanone

\[
\text{\begin{center}
\begin{tikzpicture}
\node[rectangle,draw] (a) {O};
\node[rectangle,draw, below of=a] (b) {NH};
\end{tikzpicture}
\end{center}}
\]

\( ^1\text{H NMR (400MHz, CDCl}_3\): \delta 2.56 (t, 2H), 2.70 (t, 2H), 3.32 (t, 2H), 3.4 (t, 2H), 3.51 (s, 2H), 3.57 (s, 2H), 3.69 (s, 3H), 6.76 (m, 2H), 7.0 (d, 2H); \ ^{13}\text{C NMR (100 MHz, CDCl}_3\): \delta 39.1, 44.9, 45.3, 46.5, 54.5, 113.5, 125.9, 126.4, 128.9, 157.7, 157.8, 160.1 m/z = 234(M + 1)^+ .

2-(3-methoxyphenyl)-1-(piperazin-1-yl)ethanone

\[
\text{\begin{center}
\begin{tikzpicture}
\node[rectangle,draw] (a) {O};
\node[rectangle,draw, below of=a] (b) {NH};
\end{tikzpicture}
\end{center}}
\]

\( ^1\text{H NMR (400MHz, CDCl}_3\): \delta 2.66 (t, 2H), 2.80 (t, 2H), 3.40 (t, 2H), 3.60 (t, 2H), 3.77 (s, 2H), 3.79 (s, 3H), 6.79 (m, 3H), 7.24 (m, 1H); \ ^{13}\text{C NMR (100 MHz, CDCl}_3\): \delta 40.2, 42.2, 45.0, 45.3, 46.7, 54.6, 111.6, 113.6, 120.3, 129.0, 136.02, 159.2, 168.7 m/z = 234(M + 1)^+ .

2-(4-methylphenyl)-1-(piperazin-1-yl)ethanone

\[
\text{\begin{center}
\begin{tikzpicture}
\node[rectangle,draw] (a) {O};
\node[rectangle,draw, below of=a] (b) {NH};
\end{tikzpicture}
\end{center}}
\]

\( ^1\text{H NMR (400MHz, CDCl}_3\): \delta 2.32 (s, 3H), 2.65 (t, 2H), 2.80 (t, 2H), 3.40 (t, 2H), 3.60 (t, 2H), 3.69 (s, 2H), 7.12 (s, 5H); \ ^{13}\text{C NMR (100 MHz, CDCl}_3\): \delta 20.3, 39.6, 42.0, 44.8, 45.2, 46.4, 127.7, 128.56, 131.3, 135.4, 163.9 m/z = 218(M + 1)^+ .

2-(2-florophenyl)-1-(piperazin-1-yl)ethanone (CDCl\(_3\))
1H NMR (400MHz, CDCl₃): δ 2.75 (t, 2H), 2.82 (t, 2H), 3.45(t, 2H), 3.70 (s, 2H), 7.2-7.5 (m, 4H); 13C NMR (100 MHz, CDCl₃): δ 32.7, 42.4, 45.0, 45.4, 46.5, 114.5, 114.8, 121.8, 121.9, 123.7, 128.1, 128.2, 130.4, 158.7, 161.2, 168.1 m/z = 222(M + 1)⁺.

1H NMR of N-(2-(methylamino)ethyl)benzamide (CDCl₃)

1H NMR (400MHz, CDCl₃): δ 2.4 (s, 3H), 2.79 (t, 2H), 3.5 (t, 2H), 7.43 (m, 3H), 7.80(t, 2H); 13C NMR (100 MHz, CDCl₃): δ 34.5, 38.1, 49.7, 126.4, 126.9, 128.0, 131.1, 133.9, 167.9 m/z = 178(M + 1)⁺.

1H NMR of N-(2-(ethylamino)ethyl)benzamide (CDCl₃)

1H NMR (400MHz, CDCl₃): δ 1.10 (t, 3H), 2.64 (q, 2H), 2.83 (t, 2H), 3.53(q, 2H), 7.36-7.44(m, 3H), 7.81 (d, 2H); 13C NMR (100 MHz, CDCl₃): δ 14.6, 39.3, 43.3, 48.1, 126.8, 128.1, 131.0, 134.2, 167.6 m/z = 192(M + 1)⁺.

1H NMR of N-(2-(propylamino)ethyl)benzamide (CDCl₃)

1H NMR (400MHz, CDCl₃): δ 0.90 (t, 3H), 1.51 (q, 2H), 2.5(s, NH) 2.61 (t, 2H), 2.87 (t, 2H), 3.55 (t, 2H), 3.69(s, 2H), 7.2 (s, NH) 7.2-7.4 (m, 3H), 7.80 (d, 2H); 13C NMR (100
MHz, CDCl₃): δ 11.5, 22.6, 39.1, 48.3, 51.0, 126.9, 128.3, 131.2, 134.4 167.6 20.3, m/z = 206(M + 1)⁺.

¹H NMR of N-(2-(isopropylamino)ethyl)benzamide (CDCl₃)

¹H NMR (400MHz, CDCl₃): δ 1.1 (D, 6H), 1.98(s, NH), 2.87(t, 2H), 3.53 (t, 2H), 7.2(s, NH), 7.4(m, 3H), 7.8(t, 2H) ¹³C NMR (100 MHz, CDCl₃): δ 22.7, 39.8, 45.9, 48.5, 126.9, 128.3, 131.2, 134.4, 167.5 m/z = 206(M + 1)⁺.

¹H NMR of N-(piperidin-4-yl)benzamide(CDCl₃)

¹H NMR (400MHz, CDCl₃): δ 1.2 (t, 2H), 1.9 (br, 5H), 2.95 (m, 3H), 2.6-4.5(br, 2H), 7.39 (s, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 34.8, 35.4, 46.0, 48.1, 126.4, 128.1, 129.2, 135.8, 169.9 m/z = 204(M + 1)⁺.
NMR study for the synthesis and stability of acyl imidazole without solvent.
\[^1^H\text{ NMR of 2-phenyl-1-(piperazin-1-yl)ethanone (CDCl}_3\text{)}\]

\[^{13}\text{C NMR of 2-phenyl-1-(piperazin-1-yl)ethanone (CDCl}_3\text{)}\]
$^1$H NMR of 2-(4-methoxyphenyl)-1-(piperazin-1-yl)ethanone (CDCl$_3$)

$^{13}$C NMR of 2-(4-methoxyphenyl)-1-(piperazin-1-yl)ethanone (CDCl$_3$)
\(^1\)H NMR of 2-(3-methoxyphenyl)-1-(piperazin-1-yl)ethanone (CDCl\(_3\))

\(^1\)C NMR of 2-(4-methoxyphenyl)-1-(piperazin-1-yl)ethanone (CDCl\(_3\))
$^1$H NMR of 2-(4-methylphenyl)-1-(piperazin-1-yl)ethanone (CDCl$_3$)

$^{13}$C NMR of 2-(4-methylphenyl)-1-(piperazin-1-yl)ethanone (CDCl$_3$)
$^1$H NMR of 2-(2-florophenyl)-1-(piperazin-1-yl)ethanone (CDCl₃)

$^{13}$C NMR of 2-(2-florophenyl)-1-(piperazin-1-yl)ethanone (CDCl₃)
$^1$H NMR of N-(2-(methylamino)ethyl)benzamide (CDCl$_3$)

$^{13}$C NMR of N-(2-(methylamino)ethyl)benzamide (CDCl$_3$)
$^1$H NMR of N-(2-(ethylamino)ethyl)benzamide (CDCl$_3$)

$^1$H NMR of N-(2-(ethylamino)ethyl)benzamide (CDCl$_3$)
$^1$H NMR of N-(2-(propylamino)ethyl)benzamide (CDCl$_3$)

![N-(2-(propylamino)ethyl)benzamide (CDCl$_3$) NMR](image)

$^{13}$C NMR of N-(2-(propylamino)ethyl)benzamide (CDCl$_3$)

![N-(2-(propylamino)ethyl)benzamide (CDCl$_3$) NMR](image)
$^1$H NMR of N-(2-(isopropylamino)ethyl)benzamide (CDCl$_3$)

$^{13}$C NMR of N-(2-(isopropylamino)ethyl)benzamide (CDCl$_3$)
$^1$H NMR of N-(piperidin-4-yl)benzamide (CDCl$_3$)

$^{13}$C NMR of N-(piperidin-4-yl)benzamide (CDCl$_3$)