Variations in Site of Lithiation of N-(2-(4-Methoxyphenyl)ethyl)pivalamide; Use in Ring Substitution

<table>
<thead>
<tr>
<th>Journal:</th>
<th>SYNLETT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID:</td>
<td>ST-2012-11-0962-L.R1</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Letter</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>15-Nov-2012</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Smith, Keith; Cardiff University, School of Chemistry El-Hiti, Gamal; Cardiff University, School of Chemistry; Tanta University, Chemistry Alshammari, Mohammed; Cardiff University, School of Chemistry; Salman bin Abdul-Aziz University, Chemistry</td>
</tr>
<tr>
<td>Keywords:</td>
<td>lithium, metatation, lithiation, electrophilic aromatic substitution, aldehydes</td>
</tr>
</tbody>
</table>

**Abstract:** Lithiation of N-(2-(4-methoxyphenyl)ethyl)pivalamide at -20 to 0 °C with three mole equivalents of n-BuLi in anhydrous THF, followed by reactions with various electrophiles, gives high yields of products involving ring substitution ortho- the pivaloylaminoethyl group, which was unexpected in view of earlier results reported with t-BuLi.
Variations in Site of Lithiation of \(N\)-(2-(4-Methoxyphenyl)ethyl)pivalamide; Use in Ring Substitution

Keith Smith,* Gamal A. El-Hiti,* Mohammed B. Alshammari

School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT, UK
Fax: +442920870600; E-mail: smithk13@cardiff.ac.uk; el-hitiga@cardiff.ac.uk

Abstract: Lithiation of \(N\)-(2-(4-methoxyphenyl)ethyl)pivalamide at \(-20\) to \(0\) °C with three mole equivalents of \(n\)-BuLi in anhydrous THF, followed by reactions with various electrophiles, gives high yields of products involving ring substitution ortho- to the pivaloylaminoethyl group, which was unexpected in view of earlier results reported with \(t\)-BuLi.

Key words: \(N\)-(2-(4-methoxyphenyl)ethyl)pivalamide, directed lithiation, synthesis, electrophile, dilithium intermediate

Phenylethylamine derivatives, especially ones containing oxygen substituents on the phenyl ring (which includes many biologically active compounds such as dopamine, adrenaline and mescaline), represent a hugely important class of chemicals of interest to both industry and academe, and selective methods for their synthesis are of considerable interest. Organolithium reagents play an important role in the development of clean and environmentally friendly processes for the regioselective production of specific products. For example, lithiation of aromatic compounds often takes place proximal to a directing metalating group (DMG), which typically possess an oxygen or nitrogen atom. Use of such
DMGs to facilitate lithiation, followed by reactions of the organolithium intermediates obtained \textit{in-situ} with electrophiles, has found wide application in a variety of synthetic transformations to produce substituted aromatics or heterocycles.\textsuperscript{5,6} This approach is one of the most efficient for synthesis of substituted and/or modified derivatives, which sometimes might be difficult to produce by other routes.\textsuperscript{5,6}

In connection with other work on the use of lithium reagents in organic synthesis,\textsuperscript{7} we have recently reported a detailed study for the regioslective lithiation and substitution of various substituted benzylamines.\textsuperscript{8,9} Sometimes different products were formed, depending on the nature of the lithiating agent or reaction conditions. We found, for example, that treatment of \(N\)-(2-methoxybenzyl)pivalamide with \(t\)-BuLi in THF at \(-78\) °C, followed by reaction with an electrophile, gave substitution \textit{ortho-} to the methoxy group selectively,\textsuperscript{8} in sharp contrast with results reported by Simig and Schlosser, who showed that lithiation of this substrate using \(n\)-BuLi at \(0\) °C, followed by treatment with carbon dioxide, resulted in carboxylation \textit{ortho-} to the pivaloylaminomethyl group in \(64\)% yield.\textsuperscript{10}

Recently, we have been interested in regioselective lithiation and substitution of phenethylamine derivatives and found that direct lithiation of ring-unsubstituted acyl derivatives occurred at the \(\alpha\)-position.\textsuperscript{11} Simig and Schlosser also reported that lithiation of \(N\)-2-((4-methoxyphenyl)ethyl)pivalamide (1) using \(t\)-BuLi at \(-75\) to \(-50\) °C, followed by treatment with carbon dioxide, resulted in carboxylation at the \(\text{CH}_2\) next to the 4-methoxyphenyl ring (\(\alpha\)-lithiation) to give 2 in \(79\)% yield (Scheme 1).\textsuperscript{12} We wished to investigate the possibility of ring lithiation of \(N\)-(2-(4-methoxyphenyl)ethyl)pivalamide (1), notwithstanding that lithiation at this site was not reported at all under the conditions used by Simig and Schlosser.\textsuperscript{12} We have therefore investigated lithiation under other conditions and
now report that we have been able to establish conditions for a high-yielding and general ring-substitution process.

\[
\begin{align*}
&\text{1) } t\text{-BuLi (3.0 equiv), THF} \\
&\quad \text{(-75 to -50 °C, 3 h)} \\
&\text{2) } \text{CO}_2 \\
&\text{3) dil. HCl}
\end{align*}
\]

**Scheme 1.** Lithiation of 1 followed by reaction with CO₂ as reported by Schlosser¹²

Initially, 1 was lithiated with \(t\)-BuLi (three molar equivalents) under conditions similar to those used by Schlosser,¹² followed by reaction with benzophenone (1.4 molar equivalents). The crude product was purified by column chromatography to give residual 1 (30%) and a new product, \(N\)-(3-hydroxy-2-(4-methoxyphenyl)-3,3-diphenylpropyl)pivalamide (3; Figure 1), obtained in 58% yield. Compound 3 was clearly obtained via the intermediacy of dilithium species 4 (Figure 1), which was in accord with the results reported by Schlosser.¹²

**Figure 1** Structures of compound 3 and dilithium intermediate 4

A reaction carried out with \(n\)-BuLi under the same conditions as were used with \(t\)-BuLi resulted in the starting material 1 being recovered quantitatively, indicating that no C-lithiation had taken place, but lithiation of 1 with \(n\)-BuLi (3.0 molar equivalents) at \(-20\) to 0
°C over 2 h, followed by treatment with benzophenone gave a new compound, shown by its spectral properties\textsuperscript{13,14} to be 7 (Scheme 2), isolated in 92% yield. This suggested that lithiation took place on the ring and that lithium reagents 5 and 6 were produced \textit{in-situ} (Scheme 2).

\textbf{Scheme 2} Lithiation of 1 with \textit{n}-BuLi followed by reactions with benzophenone

The latter reaction clearly had potential as a synthetic method and therefore the same lithiation procedure was used for reactions with a range of different electrophiles (Scheme 3). Following work-up of the reaction mixtures the crude products were purified by column chromatography (silica gel; Et\textsubscript{2}O–hexane, 1:1) to give the corresponding substituted products 7–13 in 80–98% yields (Table 1).

\textbf{Scheme 3} Lithiation of 1 with \textit{n}-BuLi followed by reactions with electrophiles
Lithiation of \(N\)-(4-Methoxyphenethyl)pivalamide

Table 1 Synthesis of Products 7–13 According to Scheme 3

<table>
<thead>
<tr>
<th>Product</th>
<th>Electrophile</th>
<th>E</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Ph(_2)CO</td>
<td>Ph(_2)C(OH)</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>(CH(_2))(_3)CO</td>
<td>(CH(_2))(_2)C(OH)</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>EtCOMe</td>
<td>EtC(OH)Me</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>4-MeOC(_6)H(_4)CHO</td>
<td>4-MeOC(_6)H(_4)CH(OH)</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>4-Me(_2)NC(_6)H(_4)CHO</td>
<td>4-Me(_2)NC(_6)H(_4)CH(OH)</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>Me(_2)NCHO</td>
<td>CHO</td>
<td>98</td>
</tr>
<tr>
<td>13</td>
<td>I(_2)</td>
<td>I</td>
<td>89</td>
</tr>
</tbody>
</table>

\(^a\) Yield of isolated product after purification by flash column chromatography.

Clearly, the procedure outlined in Scheme 3 represents a simple, efficient and high yielding route for substitution of \(N\)-(2-(4-methoxyphenyl)ethyl)pivalamide (1) ortho- to the pivaloylaminoethyl group. However, it was not clear why lithiation of 1 with \(t\)-BuLi at \(-75\) to \(-50\) °C gave side-chain substitution, while lithiation with \(n\)-BuLi at \(-20\) to \(0\) °C gave ring substitution. One possibility was that at low temperature the lithiation step was under kinetic control, leading to the intermediate 4, with only the \(t\)-BuLi sufficiently reactive to effect the lithiation under such conditions, but that at higher temperature the organolithium intermediate 4 was capable of isomerization to 6, so that reactions conducted at the higher temperature were under thermodynamic control. In order to test this possibility, the reaction of 1 was initially carried out at \(-75\) to \(-50\) °C with \(t\)-BuLi (3.0 molar equivalents) for 3 h (conditions previously shown to produce 4), and the mixture was then warmed to 0 °C and maintained for a further 2 h, after which benzophenone (1.4 molar equivalents) was added. The cooling bath was removed and the mixture was stirred for 2 h while warming to room temperature. Purification of the crude product by column chromatography gave 7 in 82% yield along with
residual 1 (14%). This finding clearly indicated that the dilithium reagent 6 (Scheme 2) is thermodynamically more stable than the dilithium reagent 4 (Figure 1) at higher temperature.

In conclusion, N-(2-(4-methoxyphenyl)ethyl)pivalamide (1) undergoes lithiation with n-BuLi at 0 ºC, followed by treatment with various electrophiles, to give high yields of the corresponding substituted products having the substituent ortho- to the pivaloylaminoethyl group. This contrasts sharply with earlier results using t-BuLi at lower temperature, which gave α-substitution. The variation arises because the dilithium reagent 4, formed at low temperature with t-BuLi, is less stable than dilithium reagent 6, to which it isomerises at 0 ºC.

Acknowledgments

We thank Cardiff University and the Saudi Government for financial support.

References and Notes

(1) Permanent address: G. A. El-Hiti, Department of Chemistry, Faculty of Science, Tanta University, Tanta 31527, Egypt.


K. Smith et al.


(13) Assignments of signals are based on integration values, coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged.

(14) Analytical data for 7: white solid (0.32 g, 92%); mp 179–181 °C. IR (FT): $\nu_{\text{max}}$ = 3321, 2958, 1627, 1575, 1292, 1243 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.35–7.26 (m, 11 H, OH and 2 C$_6$H$_3$), 7.16 (d, $J$ = 8.3 Hz, 1 H, H-6 of 4-MeOC$_6$H$_3$), 6.79 (dd, $J$ = 2.8, 8.3 Hz, 1 H, H-5 of 4-MeOC$_6$H$_3$), 6.24 (d, $J$ = 2.8 Hz, 1 H, H-3 of 4-MeOC$_6$H$_3$), 6.15 (br, exch., 1 H, NH), 3.63 (s, 3 H, OCH$_3$), 3.37 (app. q, $J$ = 7 Hz, 2 H, CH$_2$NH), 2.60 (t, $J$ = 7.2 Hz, 2 H, CH$_2$), 1.11 [s, 9 H, C(CH$_3$)$_3$] ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 178.8 (s, C=O), 156.9 (s, C-4 of 4-MeOC$_6$H$_3$), 147.1 (s, C-1 of 2 C$_6$H$_3$), 146.6 (s, C-2 of 4-MeOC$_6$H$_3$), 132.8 (d, C-6 of 4-MeOC$_6$H$_3$), 130.7 (s, C-1 of 4-MeOC$_6$H$_3$), 127.9 (d, C-3/C-5 of 2 C$_6$H$_3$), 127.7 (d, C-2/C-6 of 2 C$_6$H$_3$), 127.2 (d, C-4 of 2 C$_6$H$_3$), 117.1 (d, C-3 of 4-MeOC$_6$H$_3$), 111.9 (d, C-5 of 4-MeOC$_6$H$_3$), 83.0 (s, C–OH), 55.0 (q, OCH$_3$), 41.1 (t, CH$_2$NH), 38.4 [s, C(CH$_3$)$_3$], 32.5 (t,
K. Smith et al.

ArCH$_2$), 27.5 [q, C(CH$_3$)$_3$] ppm. MS (EI): $m/z$ (%) = 399 (77, [M – H$_2$O]$^-$), 298 (99), 285 (90), 261 (33), 239 (10), 222 (26), 209 (31), 193 (73), 165 (53), 152 (13), 105 (48), 83 (100).

HRMS (EI): $m/z$ calcd for C$_{27}$H$_{29}$NO$_2$ ([M – H$_2$O]$^-$): 399.2198; found: 399.2187.
Electronic Supplementary Information (ESI)

Variations in Site of Lithiation of
N-(2-(4-Methoxyphenyl)ethyl)pivalamide; Use in Ring Substitution

Keith Smith,* Gamal A. El-Hiti* and Mohammed B. Alshammari

School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK
E-mail: smithk13@cardiff.ac.uk and el-hitiga@cardiff.ac.uk
Fax: +44(2920)870600; Tel: +44(2920)870600

Table of Contents

Instrumentation and Chemicals S2
Synthesis of N-(2-(4-Methoxyphenyl)ethyl)pivalamide (1) and its Characterization Data S2
Synthesis of N-(3-Hydroxy-2-(4-methoxyphenyl)-3,3-diphenylpropyl)pivalamide (3) and its Characterization Data S3
General Procedure for Lithiation and Substitution of N-(2-(4-Methoxyphenyl)ethyl)pivalamide (1): Synthesis of 3-Substituted Derivatives 7-12 and Their Characterization Data S4
NMR Spectra of Compound 1 S11-S17
NMR Spectra of Compound 3 S18-S25
NMR Spectra of Compound 7 S26-S35
NMR Spectra of Compound 10 S36-S44
Instrumentation and Chemicals

**General.** Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AV500 spectrometer operating at 500 MHz for $^1$H and 125 MHz for $^{13}$C measurements. Chemical shifts $\delta$ are reported (for compounds 3 and 7 in the main manuscript) in parts per million (ppm) relative to TMS and coupling constants $J$ are in Hz, reported to the nearest 1 Hz. $^{13}$C multiplicities were revealed by DEPT signals. Assignments of signals are based on integration values, coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. The proton multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Low-resolution mass spectra were recorded on a Waters GCT Premier spectrometer and high-resolution mass spectra were recorded on a Waters LCT Premier XE instrument. IR spectra were recorded on a Jasco FT/IR-660 plus instrument by dissolving the product in chloroform, applying droplets on a NaCl plate and allowing evaporation of the solvent. Column chromatography was carried out using Fischer Scientific silica 60A (35-70 micron). Alkylolithiums were obtained from Aldrich Chemical Company and were estimated prior to use by the method of Watson and Eastham. Other chemicals were obtained from Aldrich Chemical Company and used without further purification.

**Synthesis of N-(2-(4-Methoxyphenyl)ethyl)pivalamide (1)**

The synthesis of 1 was not previously reported, although use of the compound has been reported. A mixture of 2-(4-methoxyphenyl)ethanamine (5.00 g, 33.1 mmol), pivaloyl chloride (4.40 g, 36.4 mmol) and triethylamine (4.60 g, 45.5 mmol) in DCM (50 mL) was stirred for 1 h at room temperature. The mixture was washed with H$_2$O (2 × 25 mL). The organic layer was dried (MgSO$_4$) and removed under reduced pressure. The solid obtained was purified by crystallization from hexane to give pure 1 (7.09 g, 30.1 mmol; 91%) as a white crystalline solid, mp: 71–73 °C.

```
\begin{center}
\begin{tikzpicture}
  \node (N) at (0,0) {N};
  \node (MeO) at (-1,0) {MeO};
  \node (Bu') at (1,0) {Bu'};
  \node (Bu) at (0.5,0) {Bu};
  \node (C=O) at (1,0) {C=O};
  \draw [->] (N) -- (MeO);
  \draw [->] (N) -- (Bu');
  \draw [->] (N) -- (Bu);
  \draw [->] (N) -- (C=O);
\end{tikzpicture}
\end{center}
```

IR (FT): $\nu_{max}$ 3350, 2959, 1655, 1534, 1365 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.03$ (d, $J = 9$ Hz, 2 H, H-2/H-6 of 4-CH$_3$OC$_6$H$_4$), 6.78 (d, $J = 9$ Hz, 2 H, H-3/H-5 of 4-CH$_3$OC$_6$H$_4$), 5.60 (br., exch., 1 H, NH), 3.72 (s, 3 H, OCH$_3$), 3.39 (app. q, $J = 7$ Hz, 2 H, CH$_2$NH), 2.68 (t, $J = 7$ Hz, 2 H, CH$_2$), 1.07 [s, 9 H, C(CH$_3$)$_3$].
13C NMR (125 MHz, CDCl3): δ = 178.3 (s, C=O), 158.3 (s, C-4 of 4-CH3OC6H4), 131.0 (s, C-1 of 4-CH3OC6H4), 129.7 (d, C-2/C-6 of 4-CH3OC6H4), 114.0 (d, C-3/C-5 of 4-CH3OC6H4), 55.3 (q, OCH3), 40.8 (t, CH2NH), 38.6 [s, C(CH3)3], 34.7 (t, CH2), 27.5 [q, C(CH3)3].

MS (EI): m/z (%) = 235 (8, [M]+), 220 (4), 192 (7), 134 (100), 121 (30), 105 (8), 91 (14), 77 (10), 65 (4), 57 (10).


**Synthesis of N-(3-Hydroxy-2-(4-methoxyphenyl)-3,3-diphenylpropyl)pivalamide (3)**

A solution of t-BuLi in pentane (1.45 mL, 1.9 M, 2.8 mmol) was added to a cold (−75 °C), stirred solution of N-(2-(4-methoxyphenyl)ethyl)pivalamide (1; 0.20 g, 0.85 mmol) in anhydrous THF (15 mL) under N2. The mixture was stirred for 3 h at −50 °C after which a solution of benzophenone (0.255 g, 1.40 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was stirred for 2 h. The reaction mixture was quenched with aqueous saturated NH4Cl (20 mL) and diluted with diethyl ether (20 mL). The organic layer was separated, washed with H2O (2 × 20 mL), dried (MgSO4) and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; hexane: Et2O, 1:1 by volume) to give pure 3 (0.20 g, 58%) as a white solid; mp 157–160 °C.

![Chemical Structure](https://via.placeholder.com/150)

**IR (FT):** νmax 3399, 2960, 1641, 1511, 1301, 1248 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 7.65 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-CH3OC6H4), 7.28 (app. t, J = 7 Hz, 2 H, H-3/H-5 of one C6H5), 7.22 (d, J = 7 Hz, 2 H, H-2/H-6 of one C6H5), 7.13 (t, J = 7 Hz, 1 H, H-4 of one C6H5), 7.06 (d, J = 7 Hz, 2 H, H-2/H-6 of other C6H5), 7.00 (app. t, J = 7 Hz, 2 H, H-3/H-5 of other C6H5), 6.90 (t, J = 7 Hz, 1 H, H-4 of other C6H5), 6.61 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-CH3OC6H4), 5.39 (br., exch., 1 H, NH), 4.08 (app. t, J = 7 Hz, 1 H, CH), 3.81 (app. dt, J = 14, 7 Hz, 1 H, CH2Hb), 3.64 (s, 3 H, OCH3), 3.34 (m, 1 H, CH2Hb), 0.85 [s, 9 H, C(CH3)3].

13C NMR (125 MHz, CDCl3): δ 179.1 (s, C=O), 158.3 (s, C-4 of 4-CH3OC6H4), 146.5, 146.1 (2 s, C-1 of 2 C6H5), 131.0 (d, C-3/C-5 of one C6H5), 130.8 (s, C-1 of 4-CH3OC6H4), 128.4 (d, C-3/C-5 of other C6H5), 127.6 (d, C-2/C-6 of 4-CH3OC6H4), 126.8, 126.0 (2 d, C-4 of 2 C6H5), 125.9, 125.7
General Procedure for Lithiation and Substitution of 1: Synthesis of 3-Substituted Derivatives 7–12

A solution of n-BuLi in hexane (1.75 mL, 1.60 M, 2.80 mmol) was added to a cold (−20 °C), stirred solution of 1 (0.20 g, 0.85 mmol) in anhydrous THF (15 mL) under N2. The mixture was stirred for 2 h while it was allowed to warm up to 0 °C, after which an electrophile (1.40 mmol), in anhydrous THF (5 mL) if solid, neat otherwise, was added. The cooling bath was removed and the reaction mixture was stirred for 2 h. The reaction mixture was quenched with aqueous saturated NH4Cl (20 mL) and diluted with diethyl ether (20 mL). The organic layer was separated, washed with H2O (2 × 20 mL), dried (MgSO4) and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; hexane: Et2O in 1:1 by volume) to give the pure products 7–12.

N-(2-(2-(Hydroxydiphenylmethyl)-4-methoxyphenyl)ethyl)pivalamide (7)

White solid (0.32 g, 92%); mp 179–181 °C.

IR (FT): νmax 3321, 2958, 1627, 1575, 1292, 1243 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 7.35–7.26 (m, 11 H, OH and 2 C6H5), 7.16 (d, J = 8 Hz, 1 H, H-6 of 4-CH3OC6H3), 6.79 (dd, J = 3, 8 Hz, 1 H, H-5 of 4-CH3OC6H3), 6.24 (d, J = 3 Hz, 1 H, H-3 of 4-CH3OC6H3), 6.15 (br., exch., 1 H, NH), 3.63 (s, 3 H, OCH3), 3.37 (app. q, J = 7 Hz, 2 H, CH2NH), 2.60 (t, J = 7 Hz, 2 H, CH2), 1.11 [s, 9 H, C(CH3)3].

13C NMR (125 MHz, CDCl3): δ = 178.8 (s, C=O), 156.9 (s, C-4 of 4-CH3OC6H3), 147.1 (s, C-1 of 2 C6H5), 146.6 (s, C-2 of 4-CH3OC6H3), 132.8 (d, C-6 of 4-CH3OC6H3), 130.7 (s, C-1 of 4-CH3OC6H3), 127.9 (d, C-3/C-5 of 2 C6H5), 127.7 (d, C-2/C-6 of 2 C6H5), 127.2 (d, C-4 of 2
C₆H₅), 117.1 (d, C-3 of 4-CH₃OC₆H₅), 111.9 (d, C-5 of 4-CH₃OC₆H₅), 83.0 (s, C-OH), 55.0 (q, OCH₃), 41.1 (t, CH₂NH), 38.4 [s, C(CH₃)₃], 32.5 (t, CH₂), 27.5 [q, C(CH₃)₃].

MS (EI): m/z (%) 399 (77, [M – H₂O]⁺), 298 (99), 285 (90), 261 (33), 239 (10), 222 (26), 209 (31), 193 (73), 165 (53), 152 (13), 105 (48), 83 (100).

HRMS (EI): m/z ([M – H₂O]⁺) calcd for C₂₇H₂₉NO₂: 399.2198; found: 399.2187.

N-(2-(2-(1-Hydroxycyclohexyl)-4-methoxyphenyl)ethyl)pivalamide (8)

Oil (0.24 g, 88%).

IR (FT): ν_max 3369, 2931, 1645, 1529, 1365, 1238 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.07 (d, J = 2 Hz, 1 H, H-3 of 4-CH₃OC₆H₅), 6.97 (dd, J = 2, 8 Hz, 1 H, H-5 of 4-CH₃OC₆H₅), 6.80 (d, J = 8 Hz, 1 H, H-6 of 4-CH₃OC₆H₅), 6.69 (br. s, exch., 1 H, OH), 5.54 (br., exch., 1 H, NH), 3.81 (s, 3 H, OCH₃), 3.38 (app. q, J = 7 Hz, 2 H, CH₂NH), 2.68 (t, J = 7 Hz, 2 H, CH₂), 1.95–1.50 (m, 10 H, c-Hex), 1.08 [s, 9 H, C(CH₃)₃].

¹³C NMR (125 MHz, CDCl₃): δ = 178.5 (s, C=O), 156.0 (s, C-4 of 4-CH₃OC₆H₅), 140.0 (s, C-2 of 4-CH₃OC₆H₅), 126.3 (d, C-6 of 4-CH₃OC₆H₅), 126.0 (s, C-1), 111.5 (d, C-3 of 4-CH₃OC₆H₅), 111.0 (d, C-5 of 4-CH₃OC₆H₅), 73.0 (s, C- OH), 55.4 (q, OCH₃), 40.9 (t, CH₂NH), 38.6 [s, C(CH₃)₃], 36.7 (d, C-2/C-6 of c-Hex), 35.1 (t, CH₂), 27.5 [q, C(CH₃)₃], 25.9 (d, C-4 of c-Hex), 21.9 (d, C-3/C-5 of c-Hex).

MS (ES⁺): m/z (%) = 356 (100, [M + Na]⁺), 316 (5), 299 (10), 158 (3).


N-(2-(2-(2-Hydroxybutan-2-yl)-4-methoxyphenyl)ethyl)pivalamide (9)

Oil (0.24 g, 95%).
IR (FT): \( \nu_{\text{max}} \) 3348, 2964, 1639, 1531, 1355, 1240 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.03 \) (d, \( J = 2 \) Hz, 1 H, H-3 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 6.98 (dd, \( J = 2 \), 8 Hz, 1 H, H-5 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 6.79 (d, \( J = 8 \) Hz, 1 H, H-6 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 5.56 (br., exch., 1 H, NH), 3.88 (br. s, exch., 1 H, OH), 3.80 (s, 3 H, OCH\(_3\)), 3.40 (app. q, \( J = 7 \) Hz, 2 H, CH\(_2\)NH), 2.68 (t, \( J = 7 \) Hz, 2 H, CH\(_2\)), 1.92–1.75 (m, 2 H, CH\(_2\)CH\(_2\)), 1.47 (s, 3 H, CH\(_3\)C–OH), 1.07 [s, 9 H, C(CH\(_3\))\(_3\)], 0.73 (t, \( J = 7 \) Hz, 3H, CH\(_2\)CH\(_2\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 178.3 \) (s, C=O), 155.6 (s, C-4 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 135.0 (s, C-2 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 131.1 (s, C-1 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 127.4 (d, C-6 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 113.8 (d, C-3 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 111.6 (d, C-5 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 75.3 (s, C–OH), 55.4 (q, OCH\(_3\)), 40.8 (t, CH\(_2\)NH), 38.6 [s, C(CH\(_3\))\(_3\)], 35.0 (t, CH\(_3\)CH\(_2\)), 34.7 (t, CH\(_2\)), 27.5 [q, C(CH\(_3\))\(_3\)], 26.7 (q, CH\(_3\)C–OH), 8.8 (q, CH\(_3\)CH\(_2\)).

MS (AP\(^+\)): \( m/z \) (%) = 290 (100, [M – H\(_2\)O]\(^+\)), 222 (3), 189 (2), 153 (3), 124 (3).

HRMS (AP\(^+\)): \( m/z \) [M – H\(_2\)O]\(^+\) calcd for C\(_{18}\)H\(_{28}\)NO\(_2\): 290.2120; found: 290.2119.

\( N\)-(2-(2-(Hydroxy(4-methoxyphenyl)methyl)-4-methoxyphenyl)ethyl)pivalamide (10)\)

Oil (0.25 g, 81\%).

IR (FT): \( \nu_{\text{max}} \) 3349, 2927, 1610, 1511, 1368, 1246 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 7.14 \) (d, \( J = 9 \) Hz, 2 H, H-2/H-6 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 7.05 (d, \( J = 8 \) Hz, 1 H, H-6 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 6.78 (dd, \( J = 3 \), 8 Hz, 1 H, H-5 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 6.76 (d, \( J = 9 \) Hz, 2 H, H-3/H-5 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 6.73 (d, \( J = 3 \) Hz, 1 H, H-3 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 5.63 (d, \( J = 1 \) Hz, 1 H, CH), 5.36 (br., exch., 1 H, NH), 5.05 (d, exch., \( J = 1 \) Hz, 1 H, OH), 3.74 (s, 3 H, OCH\(_3\)), 3.73 (s, 3 H, OCH\(_3\)), 3.40 (app. q, \( J = 7 \) Hz, 2 H, CH\(_2\)NH), 2.44 (t, \( J = 7 \) Hz, 2 H, CH\(_2\)), 1.03 [s, 9 H, C(CH\(_3\))\(_3\)].

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 178.2 \) (s, C=O), 159.4 (s, C-4 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 158.0 (s, C-4 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 142.9 (s, C-1 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 132.9 (s, C-2 of 4-CH\(_3\)OC\(_6\)H\(_4\)), 130.7 (d, C-6 of
4-CH₃OC₆H₅, 128.8 (s, C-1 of 4-CH₃OC₆H₅), 127.6 (d, C-2/C-6 of 4-CH₃OC₆H₅), 115.9 (d, C-3 of 4-CH₃OC₆H₅), 113.8 (d, C-3/C-5 of 4-CH₃OC₆H₅), 113.0 (d, C-5 of 4-CH₃OC₆H₅), 72.2 (d, CH), 55.33 (q, OCH₃), 55.31 (q, OCH₃), 40.1 (t, CH₂NH), 38.6 [s, C(CH₃)₃], 32.3 (t, CH₂), 27.6 [q, C(CH₃)₃].

MS (EI): m/z (%) = 353 (30, [M – H₂O]+), 308 (32), 281 (40), 264 (25), 165 (100), 134 (92), 120 (54), 105 (81), 84 (99).


\[N-(2-(2-((4-(Dimethylamino)phenyl)(hydroxy)methyl)-4-methoxyphenyl)ethyl)-pivalamide (11)\]

Oil (0.29 g, 90%).

IR (FT): ν_max 3343, 2956, 1612, 1520, 1350, 1249 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.12 (d, J = 9 Hz, 2 H, H-2/H-6 of 4-Me₂NC₆H₄), 7.02 (d, J = 3 Hz, 1 H, H-3 of 4-CH₃OC₆H₅), 6.96 (d, J = 8 Hz, 1 H, H-6 of 4-CH₃OC₆H₅), 6.69 (dd, J = 3, 8 Hz, 1 H, H-5 of 4-CH₃OC₆H₅), 6.61 (d, J = 9 Hz, 2 H, H-3/H-5 of 4-Me₂NC₆H₄), 5.91 (s, exch., 1 H, OH), 5.65 (br., exch., 1 H, NH), 3.71 (s, 3 H, OCH₃), 3.30 (m, 1 H, HₐHₕ of CH₂NH), 3.22 (m, 1 H, HₐHₕ of CH₂NH), 2.86 [s, 6 H, N(CH₃)₂], 2.78 (m, 1 H, HₐHₕ of CH₂), 2.57 (m, 1 H, HₐHₕ of CH₂), 1.03 [s, 9 H, C(CH₃)₃].

¹³C NMR (125 MHz, CDCl₃): δ = 178.5 (s, C=O), 159.1 (s, C-4 of 4-CH₃OC₆H₅), 150.1 (s, C-4 of 4-Me₂NC₆H₄), 143.5 (s, C-2 of 4-CH₃OC₆H₅), 141.2 (s, C-1 of 4-Me₂NC₆H₄), 128.3 (s, C-1 of 4-CH₃OC₆H₅), 127.9 (d, C-2/C-6 of 4-Me₂NC₆H₄), 126.7 (d, C-6 of 4-CH₃OC₆H₅), 113.0 (d, C-3 of 4-CH₃OC₆H₅), 112.6 (d, C-5 of 4-CH₃OC₆H₅), 112.4 (d, C-3/C-5 of 4-Me₂NC₆H₄), 72.8 (s, C–OH), 55.3 (q, OCH₃), 40.6 [q, N(CH₃)₂], 40.1 (t, CH₂NH), 38.5 [s, C(CH₃)₃], 31.5 (t, CH₂), 27.5 [q, C(CH₃)₃].

MS (ES⁺): m/z (%) = 419 (100, [M + Cl]⁺), 383 (15), 374 (20), 327 (34), 292 (35), 291 (98), 283 (14), 220 (5).
HRMS (EI): \textit{m/z} [M + Cl]\textsuperscript{-} calcd for C\textsubscript{23}H\textsubscript{32}N\textsubscript{2}O\textsubscript{3}\textsuperscript{35}Cl: 419.2101; found: 419.2093.

\textit{N-}(2-(2-Formyl-4-methoxyphenyl)ethyl)pivalamide (12)

![Chemical structure of N-(2-(2-Formyl-4-methoxyphenyl)ethyl)pivalamide (12)]

Oil (0.22 g, 98%).

IR (FT): \textit{v}\textsubscript{max} 3380, 2928, 1662, 1639, 1528, 1360, 1246 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textit{\delta} = 10.38 (s, 1 H, CHO), 7.57 (d, \textit{J} = 2 Hz, 1 H, H-3 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 7.33 (dd, \textit{J} = 2, 8 Hz, 1 H, H-5 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 6.89 (d, \textit{J} = 8 Hz, 1 H, H-6 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 5.59 (br., exch., 1 H, NH), 3.85 (s, 3 H, OCH\textsubscript{3}), 3.40 (app. q, \textit{J} = 7 Hz, 2 H, CH\textsubscript{2}NH), 2.72 (t, \textit{J} = 7 Hz, 2 H, CH\textsubscript{2}), 1.07 [s, 9 H, C(CH\textsubscript{3})\textsubscript{3}].

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \textit{\delta} = 189.6 (d, CHO), 178.4 (s, C=O), 160.6 (s, C-4 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 141.0 (s, C-2 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 138.5 (s, C-1 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 136.3 (d, C-6 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 128.4 (d, C-5 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 112.0 (d, C-3 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 55.8 (q, OCH\textsubscript{3}), 40.9 (t, CH\textsubscript{2}NH), 38.6 [s, C(CH\textsubscript{3})\textsubscript{3}], 34.6 (t, CH\textsubscript{2}), 27.4 [q, C(CH\textsubscript{3})\textsubscript{3}].

MS (EI): \textit{m/z} (\%) = 263 (54, [M]\textsuperscript{+}), 231 (15), 162 (100), 144 (90), 135 (83), 116 (28), 105 (31), 83 (99).

HRMS (EI): \textit{m/z} [M]\textsuperscript{+} calcd for C\textsubscript{15}H\textsubscript{21}NO\textsubscript{3}: 263.1521; found: 263.1524.

\textit{N-}(2-(2-Iodo-4-methoxyphenyl)ethyl) pivalamide (13)

![Chemical structure of N-(2-(2-Iodo-4-methoxyphenyl)ethyl) pivalamide (13)]

Oil (0.27 g, 89%).

IR (FT): \textit{v}\textsubscript{max} 3351, 2957, 1641, 1511, 1365, 1246 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textit{\delta} = 7.29 (d, \textit{J} = 3 Hz, 1 H, H-3 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 7.02 (d, \textit{J} = 8 Hz, 1 H, H-6 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 6.78 (dd, \textit{J} = 3, 8 Hz, 1 H, H-5 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 5.62 (br., exch., 1 H, NH), 3.69 (s, 3 H, OCH\textsubscript{3}), 3.40 (app. q, \textit{J} = 7 Hz, 2H, CH\textsubscript{2}NH), 2.83 (t, \textit{J} = 7 Hz, 2 H, CH\textsubscript{2}), 1.09 [s, 9 H, C(CH\textsubscript{3})\textsubscript{3}].

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \textit{\delta} = 178.4 (s, C=O), 158.5 (s, C-4 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 133.7 (s, C-1 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 130.2 (d, C-6 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 124.6 (d, C-3 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}), 114.5 (d, C-5 of 4-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{3}).
4-CH$_3$OC$_6$H$_3$), 100.3 (s, C-2 of 4-CH$_3$OC$_6$H$_3$), 55.5 (q, OCH$_3$), 39.7 (t, CH$_2$NH), 39.0 (t, CH$_2$), 38.7 [s, C(CH$_3$)$_3$], 27.6 [q, C(CH$_3$)$_3$].

MS (EI): $m/z$ (%) = 361 (15, [M]$^+$), 259 (100), 246 (98), 234 (69), 148 (48), 134 (99), 121 (74), 83 (92).

HRMS (EI): $m/z$ [M]$^+$ calcd for C$_{14}$H$_{20}$NO$_2$I: 361.0539; found: 361.0533.

References


NMR Spectra for Some of the Synthesised Compounds
1H NMR Spectrum of compound 1
Expansion - 1H NMR Spectrum of compound 1
Expansion - 1H NMR Spectrum of compound 1

N
H
C
O
B
u
MeO

ppm (t1)
3.40 3.39 3.38 3.37

0 5000000 10000000 15000000 20000000 25000000

3.40
3.39
3.38
3.37
Expansion - 1H NMR Spectrum of compound 1

MeO

NHCOBu^t

ppm (t1)
13C NMR Spectrum of compound 1
13C NMR DEPT-90 Spectrum of compound 1

DEPT-90 Spectrum shows only CH carbons. Suppression of CH2 and CH3 is not complete.
13C NMR DEPT-135 Spectrum of compound 1

DEPT-135 Spectrum shows CH and CH₃ positive and CH₂ negative.

NHCOBu⁺
MeO
1H NMR Spectrum of compound 3

NHCOBu'
MeO
Expansion - 1H NMR Spectrum of compound 3
Expansion - 1H NMR Spectrum of compound 3

= C =

MeO

NHCOBu°

ppm (t1)
3.750 3.800 3.850 3.900 3.950 4.000 4.050 4.100 4.150
Expansion - 1H NMR Spectrum of compound 3

ppm (t1)
3.37 3.35 3.34 3.33 3.32 3.31 3.30 3.35 3.30 3.34 3.33 3.32 3.31

Expansion - 1H NMR Spectrum of compound 3

NHCOBu′
MeO
OH

Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany
13C NMR Spectrum of compound 3
Expansion - 13C NMR Spectrum of compound 3
DEPT-90 Spectrum shows only CH carbons. Suppression of CH2 and CH3 is not complete.
13C NMR DEPT-135 Spectrum of compound 3

DEPT-135 Spectrum shows CH and CH3 positive and CH2 negative.

\[
\text{MeO} \quad \text{NHCOBu}^t
\]
Expansion - 1H NMR Spectrum of compound 7

NHCOBu

MeO

OH

ppm (t1)

7.15 7.20 7.25 7.30 7.35

0 50000000 100000000

7.35 7.34 7.33 7.32 7.31 7.30 7.29 7.28 7.27 7.26

7.17 7.15
Expansion - 1H NMR Spectrum of compound 7

ppm (t1)
Expansion - 1H NMR Spectrum of compound 7

MeO
\[\text{N}\]
\[\text{H}\]
\[\text{C}\]
\[\text{O}\]
\[\text{B}\]
\[\text{u}\]
\[\text{t}\]

OH

ppm (t1)
0
5000000
10000000
15000000
20000000
25000000
30000000
6.25
6.24

For Peer Review
Expansion - 1H NMR Spectrum of compound 7
Expansion - 1H NMR Spectrum of compound 7
13C NMR Spectrum of compound 7

NHCOBu
MeO
OH
Expansion - 13C NMR Spectrum of compound 7

- NHCOBu<sup>t</sup>
- MeO
- OH

ppm (f1)

- 147.2
- 146.6
- 132.8
- 130.7
- 127.9
- 127.7
- 127.2
- 117.2
- 112.0
13C NMR DEPT-90 Spectrum shows only CH carbons. Suppression of CH2 and CH3 is not complete.
13C NMR DEPT-135 Spectrum of compound 7

13C NMR DEPT-135 Spectrum shows CH3 and CH positive and CH2 negative.
$^{1}H$ NMR Spectrum of compound 10
Expansion - 1H NMR Spectrum of compound 10
Expansion - 1H NMR Spectrum of compound 10

\[
\text{NHCOBu}^t
\]

\[
\text{MeO}
\]

\[
\text{OH}
\]

\[
\text{OMe}
\]
Expansion - 1H NMR Spectrum of compound 10

\[
\text{NHCOBu}^t
\]

\[
\text{MeO}
\]

\[
\text{OH}
\]

\[
\text{OMe}
\]
Expansion - 1H NMR Spectrum of compound 10

\[
\text{N} \quad \text{H} \quad \text{C} \quad \text{O} \\
\text{Bu} \\
\text{Me} \quad \text{O} \quad \text{OH} \\
\text{OH} \quad \text{Me} \quad \text{O} \\
\text{OMe}
\]
13C NMR Spectrum of compound 10

NHCOBu
MeO
OH
OMe
Expansion – 13C NMR Spectrum of compound 10

![13C NMR Spectrum of compound 10](image-url)
13C NMR DEPT-90 Spectrum of compound 10

13C NMR DEPT-90 spectrum shows only CH carbons. Suppression of CH2 and CH3 is not complete.
13C NMR DEPT-135 Spectrum of compound 10

13C NMR DEPT-135 Spectrum shows CH and CH3 positive and CH2 negative.