A simple conversion of amines into monosubstituted ureas in organic and aqueous solvents

Qi Liu, Nathan W. Luedtke and Yitzhak Tor*

Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA 92093-0358, USA

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Abstract—A versatile and highly efficient synthesis of monosubstituted ureas is described. The reaction of an amine with 4-nitrophenyl-N-benzylcarbamate, followed by hydrogenolysis, provides the corresponding urea in high yield and purity. This carbamate can also be employed for the derivatization of water-soluble polyamines (e.g. aminoglycoside antibiotics), while other reagents (e.g. benzylisocyanate) fail to give the desired products in any significant yield. © 2001 Elsevier Science Ltd. All rights reserved.

Substituted ureas are found in natural products, pharmaceutical and agricultural preparations, as well as in numerous artificial receptors and self-assembled supramolecules. During our investigation of small organic molecules as RNA binders, we have become interested in monosubstituted urea functionalities as uncharged, isostructural analogs of guanidinium groups. A general approach for the synthesis of such derivatives that can tolerate amines of various structure and complexity, as well as reaction media (i.e. organic or water-containing), has become a necessity.

Most synthetic approaches to ureas utilize phosgene or its tamed analogs. Commercially available reagents, such as benzylisocyanate, also effectively convert amines into easily deprotected disubstituted ureas. We have suspected, however, that such reagents might not withstand aqueous conditions or react efficiently with complex starting materials. Indeed, reactions of aminoglycoside antibiotics with benzylisocyanate in dioxane/water mixtures failed to yield the desired products in any significant yield. We have therefore sought to develop a simple reagent that is electrophilic enough to effectively react with amines of various structures, yet reasonably stable in aqueous environments. Here we report on a highly versatile and efficient two-step synthesis of monosubstituted ureas using 4-nitrophenyl-N-benzylcarbamate 1 (Scheme 1). The reaction of amines with 1, followed by hydrogenolysis, provides the corresponding ureas in high yield and purity (Scheme 1).

4-Nitrophenyl-N-benzylcarbamate 1 was obtained in high yield by condensing benzylamine with 4-nitrophenyl chloroformate. The colorless, crystalline material 1 effectively reacts with various amines to give the corresponding N-benzyl ureas in excellent yields (Table 1). Thus, reaction of cyclohexanemethylamine with 1 in dichloromethane in the presence of triethylamine for 30 min, followed by a basic aqueous workup gives the disubstituted urea 2 in 92% yield and in pure form (Scheme 1). No additional chromatography or recrystallizations are needed. Medium pressure (30–50 psi) hydrogenolysis in acetic acid, in the presence of Pd black, yields the desired monosubstituted urea 3 in

\[
\text{O}_2\text{N} + \text{NH}_2 \rightarrow \text{Et}_3\text{N} \rightarrow \text{H}_2/\text{Pd} \rightarrow \text{NH}_2
\]

Scheme 1. The reaction of cyclohexanemethylamine with 1 provides urea 3 in 92% overall yield after hydrogenolysis.

* Corresponding author. Tel.: (858) 534-6401; fax: (858) 534-5383; e-mail: ytor@ucsd.edu

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quantitative yield after filtration and evaporation of the solvent (Scheme 1). NMR spectroscopy indicates >95% purity and the melting point of the ‘crude’ product (165–168°C) is very close to the literature value (170–172°C). A single recrystallization from 2-propanol furnishes the analytically-pure cyclohexanemethylurea 3 (entry 1, Table 1).13

Numerous other amines can be similarly converted into their corresponding urea derivatives utilizing this simple two-step procedure. Cyclohexylamine reacts with 1 to give the desired urea in 93% yield for the two steps (entry 2, Table 1). Secondary amines also react effectively. Piperidine, for example, gives the substituted urea in 96% overall yield (entry 3). Sterically hindered amines, such as t-butylamine, react well and yield the desired urea in higher than 90% yield (entry 4, Table 1). Less nucleophilic amines such as aniline require longer reaction time (ca. 6 h), but react well with 1 to give the desired product after hydrogenolysis (entry 5, Table 1). In all these cases, no purification steps are required to furnish reasonably pure products (>90% by NMR).

To investigate the reaction of 1 with water-soluble amines, 3-amino-1-propanol was allowed to react with 1 in a 3:1 dioxane/water mixture in the presence of Et3N at room temperature for 45 min. In this particular case, removal of the 4-nitrophenol from the crude reaction mixture by extraction is ineffective. Column chromatography, however, gives the desired protected urea in 92% yield. Hydrogenolysis quantitatively affords the desired product (entry 6, Table 1).

Carbamate 1 can also be employed for the derivatization of more sophisticated amines. Reaction of the aminoglycoside antibiotic kanamycin A 4 with 1 in dioxane/water proceeds to completion within 3 h at room temperature to give the desired tetra-N-benzylurea derivative in 93% yield (Step 1, Scheme 2).14 The reaction appears to be driven by the precipitation of the fully derivatized product and no purification is necessary. Hydrogenolysis of the benzyl protected tetraurea for 30 h at 55 psi H2 gives the desired fully urea-modified kanamycin A 5 in 98% yield (Step 2, Scheme 2).15 It is worth noting that similar reactions with benzylisocyanate results in extremely low yields of the benzyl-protected ureas,9,16 and reactions with aqueous potassium cyanate fail to yield the desired product.17

In summary, a simple and highly effective procedure for the conversion of amines into their corresponding ureas has been described. An easily accessible carbamate 1 reacts rapidly with various amines in apolar as well as highly polar media to provide the desired N-benzyl protected urea. Hydrogenolysis quantitatively converts the disubstituted ureas into the corresponding mono-substituted ureas.

### Table 1. Two-step conversion of amines into ureas

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conditions (step 1)a</th>
<th>Yield Ab</th>
<th>Mp A (°C)c</th>
<th>Yield B</th>
<th>Mp B (°C)d</th>
<th>Mp B (°C)e</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C2H5CH2</td>
<td>CH2Cl2, 20 min</td>
<td>92%</td>
<td>166–168</td>
<td>100%</td>
<td>165–168</td>
<td>169–172</td>
</tr>
<tr>
<td>2</td>
<td>C4H11</td>
<td>CH2Cl2, 30 min</td>
<td>93%</td>
<td>173–175</td>
<td>100%</td>
<td>177–180</td>
<td>186–188</td>
</tr>
<tr>
<td>3</td>
<td>t-C6H10</td>
<td>CH2Cl2, 50 min</td>
<td>96%</td>
<td>99–101</td>
<td>100%</td>
<td>96–98</td>
<td>97–99</td>
</tr>
<tr>
<td>4</td>
<td>i-Bu</td>
<td>CH2Cl2, 30 min</td>
<td>91%</td>
<td>109–111</td>
<td>100%</td>
<td>165–169</td>
<td>173–175</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>CH2Cl2, 6 h</td>
<td>83%</td>
<td>175–176</td>
<td>100%</td>
<td>134–136</td>
<td>143–145</td>
</tr>
<tr>
<td>6</td>
<td>HO(CH2)4</td>
<td>H2O–dioxane, 45 min</td>
<td>92%</td>
<td>95–97 (94)</td>
<td>100%</td>
<td>58–60</td>
<td>58–60</td>
</tr>
</tbody>
</table>

a All reactions have been carried out at room temperature.
b Yields of isolated ‘crude’ products are given.
c Melting points of the isolated ‘crude’ products are given and compared to the literature reported values (in parenthesis).
d Melting points of the isolated ‘crude’ monosubstituted ureas are given and compared to the literature reported values (in parenthesis).
e Melting points after single recrystallization.
f Piperidine.
g Product was purified by chromatography.
Acknowledgements

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References

9. Hydrolysis of the isocyanate to benzylamine, followed by condensation of the latter with excess isocyanate gives N,N′-dibenzylurea as the major product.
10. Benzylamine (1.59 g, 14.9 mmol) is dissolved in a mixture of dry dichloromethane (80 ml) and pyridine (1.17 g, 14.9 mmol). 4-Nitrophenylchloroformate (2.98 g, 14.9 mmol) is added and the solution is refluxed for 6 h. The reaction mixture is then diluted with dichloromethane (200 ml) and washed with 1 M sodium bicarbonate solution, water and brine. The solvent is dried (Na2SO4) and removed under reduced pressure to yield the colorless product (3.35 g, 86%). 1H NMR indicates >95% purity. If desired, 1 can be further purified by flash chromatography (20% hexane/dichloromethane). 1H NMR (400 MHz, CDCl3): δ 8.22 (d, J = 9.2 Hz, 2H), 7.37–7.29 (m, 7H), 5.46 (t, J = 6 Hz, 1H), 4.45 (d, J = 6 Hz, 2H); IR (KBr pellet) 3317, 1708, 1525, 1348, 1253, 1211, 1036, 1011 cm−1.
11. General procedure for the synthesis of N-benzyl ureas: In a typical reaction, 4-nitrophenyl-N-benzylcarbamate 1 (1 mmol) is added to a solution of an amine (1 mmol) and triethylamine (1 mmol) in dichloromethane (8 ml). The mixture is stirred at room temperature until 1 is consumed (as evidenced by TLC). The reaction mixture is then diluted with dichloromethane (100 ml) and washed with dilute aq. NaOH, water and brine. After drying (Na2SO4) and filtering, the solvent is removed under reduced pressure. 1H NMR indicates >95% purity. If desired, the crude product can be purified by recrystallization or flash chromatography. General procedure for hydrogenolysis to a monosubstituted urea: In a typical reaction, the N-benzylurea (0.5 mmol) is dissolved in acetic acid (6 ml). An equal weight of Pd black is added and the reaction vessel is connected to a Parr medium pressure hydrogenation apparatus (30–50 psi). After completion of the reaction, the catalyst is filtered and washed with methanol. The solvent is removed under reduced pressure. 1H NMR indicates >90% purity. If desired, the crude product can be purified by recrystallization or flash chromatography.
12. Spectral data for 2: 1H NMR (400 MHz, DMSO-d6): δ 7.31–7.20 (m, 5H), 6.21 (t, J = 5.6 Hz, 1H), 5.92 (t, J = 5.6 Hz, 1H), 4.18 (d, J = 5.6 Hz, 2H), 2.84 (t, J = 6 Hz, 2H), 1.63 (m, 4H), 1.20 (m, 1H), 1.14 (m, 4H), 0.84 (m, 2H). IR (KBr pellet) 3329, 1627, 1591, 1581 cm−1.
13. Spectral data for 3: 1H NMR (400 MHz, DMSO-d6): δ 5.59 (t, J = 6 Hz, 1H), 5.32 (s, 2H), 2.77 (t, J = 6 Hz, 2H), 1.62 (m, 4H), 1.27 (m, 1H), 1.13 (m, 4H), 0.82 (m, 2H). IR (KBr pellet) 3392, 3213, 1654, 1609, 1551 cm−1.
14. A solution of kanamycin A (100 mg, 0.21 mmol) and triethylamine (84 mg, 0.83 mmol) in 1,4-dioxane/water (3:1, 2.5 ml) is treated with 1 (225 mg, 0.83 mmol). The reaction mixture is stirred at rt until 1 is consumed (ca. 3 h). The reaction mixture is then evaporated to dryness and the residue is washed with 1 mM NaOH and water and dried under reduced pressure to give a white powder (98 mg, 93%). 1H NMR indicates >95% purity. The product can be further purified by flash chromatography (5% methanol/dichloromethane). Hydrogenolysis is performed as described above with one weight-equivalent of Pd black per benzyl group. A higher H2 pressure (55 psi) and longer reaction time (30 h) are employed.
15. Spectral data for kanamycin A derivative 5: MALDI MS caleed for C32H49N8NaO15 [M+Na]+: 679.2505. Found: 679.2495. 1H NMR (400 MHz, DMSO-d6): δ 6.20 (d, J = 6 Hz, 1H), 6.12 (d, J = 6.4 Hz, 1H), 6.03 (t, J = 5.6 Hz, 1H), 5.84–5.82 (m, 3H), 5.72–5.65 (m, 5H), 5.58–5.55 (m, 3H), 5.41 (d, J = 5.2 Hz, 1H), 5.12–5.07 (m, 3H), 5.23 (d, J = 4.4 Hz, 1H), 4.95 (d, J = 3.6 Hz, 1H), 4.47 (t, J = 6 Hz, 1H), 3.82 (m, 1H), 3.67–3.17 (m, 15H), 2.99 (m, 1H), 2.07 (m, 1H), 1.31 (q, 1H).
16. The desired fully derivatized kanamycin A is obtained in less than 18% yield based on NMR analysis of the crude mixture when 4 equivalents of benzisocyanate are used.
17. Multiple products are formed, none of which correspond to 5.