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

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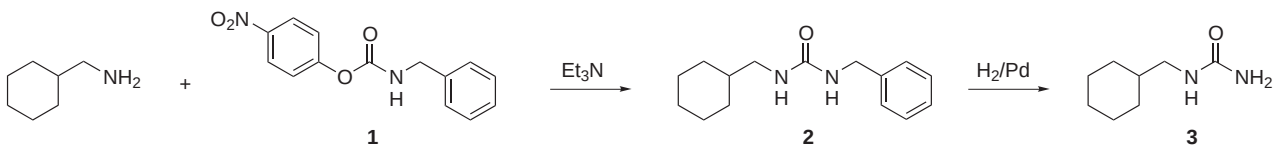
Abstract—A versatile and highly efficient synthesis of monosubstituted ureas is described. The reaction of an amine with 4-nitrophenyl-*N*-benzylcarbamate, followed by hydrogenolysis, provides the corresponding urea in high yield and purity. This carbamate can also be employed for the derivatization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

Substituted ureas are found in natural products,[1] pharmaceutical and agricultural preparations,[2] as well as in numerous artificial receptors and self-assembled supramolecules.[3] During our investigation of small organic molecules as RNA binders,[4] 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.[5,6] Commercially available reagents, such as benzylisocyanate,[7] also effectively convert amines into easily deprotected disubstituted ureas.[8] 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.[9] 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). Importantly, excellent transformations are obtained when **1** reacts with more sophisticated amines (such as aminoglycoside antibiotics) in aqueous solvents (Scheme 2).

4-Nitrophenyl-*N*-benzylcarbamate **1** was obtained in high yield by condensing benzylamine with 4-nitrophenyl-chloroformate.[10] The colorless, crystalline material **1** effectively reacts with various amines to give the corresponding *N*-benzyl ureas in excellent yields (Table 1).[11] 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).[12] 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



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

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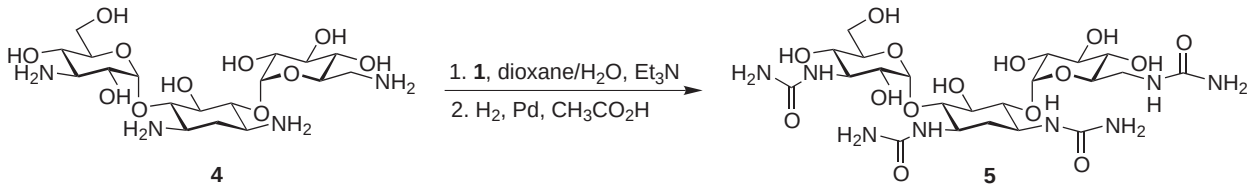


Scheme 2. Derivatization of kanamycin A, an aminoglycoside antibiotic, to the fully urea-modified analog.

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]

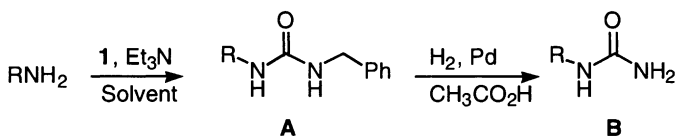
Numerous other amines can be similarly converted into their corresponding urea derivatives utilizing this simple two-step procedure. Cyclohexylamine reacts with **1** to give the desired urea in 93% yield for the two steps (entry 2, Table 1). Secondary amines also react effectively. Piperidine, for example, 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 Et_3N 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 H_2 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 monosubstituted ureas.

Table 1. Two-step conversion of amines into ureas



Entry	R	Conditions (step 1)[a]	Yield **A**[b]	Mp **A** (°C)[c]	Yield **B**	Mp **B** (°C)[d]	Mp **B** (°C)[e]
1	$C_6H_{11}CH_2$	CH_2Cl_2, 20 min	92%	166–168	100%	165–168 (170–172)	169–172
2	C_6H_{11}	CH_2Cl_2, 30 min	93%	173–175 (165–6)	100%	177–180 (188)	186–188
3	*c*-C_5H_{10}[f]	CH_2Cl_2, 50 min	96%	99–101 (98–102)	100%	96–98 (97–98)	97–99
4	*t*-Bu	CH_2Cl_2, 30 min	91%	109–111 (110–12)	100%	165–169 (173–175)	173–175
5	Ph	CH_2Cl_2, 6 h	83%	175–176 (169–172)	100%	134–136 (147)	143–145
6	$HO(CH_2)_3$	H_2O–dioxane, 45 min	92%[g]	95–97 (94)	100%	58–60 (60–61)	58–60

[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.

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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 (Na_2SO_4) and removed under reduced pressure to yield the colorless product (3.35 g, 86%). ^{1}H NMR indicates >95% purity. If desired, **1** can be further purified by flash chromatography (20% hexane/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): 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 (Na_2SO_4) and filtering, the solvent is removed under reduced pressure. ^{1}H 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. ^{1}H NMR indicates >90% purity. If desired, the crude product can be purified by recrystallization or flash chromatography.
12. Spectral data for **2**: ^{1}H NMR (400 MHz, DMSO-d_6): 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**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.92 (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%). ^{1}H 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 H_2 pressure (55 psi) and longer reaction time (30 h) are employed.
15. Spectral data for kanamycin A derivative **5**: MALDI MS calcd for $C_{22}H_{40}N_8NaO_{15}$ $[M-Na]^+$ 679.2505. Found: 679.2495. ^{1}H NMR (400 MHz, DMSO-d_6): 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 benzylisocyanate are used.
17. Multiple products are formed, none of which correspond to **5**.