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A convenient method for the synthesis of *N*-hydroxyureas

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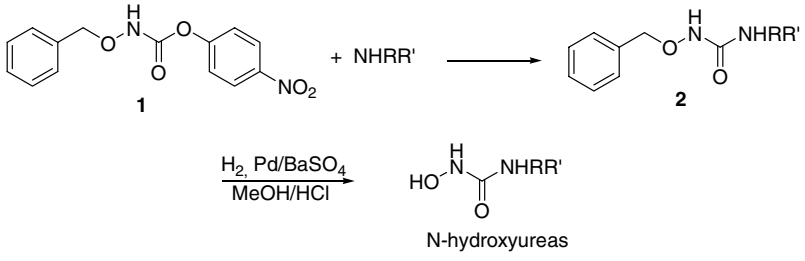
Abstract—Treatment of amines with 1-(4-nitrophenol)-*N*-(*O*-benzylhydroxy)carbamate yields the *O*-benzyl protected *N*-hydroxyureas. Hydrogenation of the *O*-benzyl protected *N*-hydroxyureas over 5% $Pd/BaSO_4$ cleanly gives the *N*-hydroxyureas in good yield. In addition to primary and secondary aliphatic and aromatic amines, this method converts amino sugars to the corresponding *N*-hydroxyureas without extensive protecting group chemistry.

The hydroxyurea functional group possesses metal-chelating and redox-properties allowing compounds containing this group to interact with a variety of metallo and redox-active proteins. *N*-Hydroxyureas act as inhibitors of various metal containing hydrolytic enzymes including carboxypeptidase A,[1] urease,[2] and ribonuclease[3] and redox enzymes including lipoxygenase and ribonucleotide reductase.[4,5] The simplest member of this class, *N*-hydroxyurea, currently finds clinical use as a treatment for a variety of cancers and sickle cell disease.[6,7] Oxidation of *N*-hydroxyurea, a non-substituted *N*-hydroxyurea containing the –NHOH group, leads to the formation of nitric oxide, (NO), an important biological second messenger that may play a role in the activity of *N*-hydroxyurea.[8] Our group initiated a project for the synthesis and evaluation of carbohydrate-derived *N*-hydroxyureas as potential site-specific NO donors. The preparation of such compounds by traditional condensation of hydroxylamine with amino sugar-derived isocyanates requires lengthy protection/deprotection sequences.[2,9] Using a previous method for the synthesis of ureas as inspiration,[10] we wish to report a convenient two-step procedure for the conversion of amines, including unprotected amino sugars, to the corresponding non-substituted *N*-hydroxyureas.

Scheme 1 depicts the general method for the conversion of amines to *N*-hydroxyureas. Condensation of an amine with 1-(4-nitrophenol)-*N*-(*O*-benzylhydroxy)carbamate, **1** in the presence of triethylamine yields the *O*-benzyl protected *N*-hydroxyureas (**2**) in 84–98% yield (Scheme 1).[11] Addition of *O*-benzyl hydroxylamine to 4-nitrophenyl chloroformate reproducibly forms **1** in 71% yield.[12] Hydrogenation (1 atm) of the *O*-benzyl protected hydroxyureas over 5% $Pd/BaSO_4$ in MeOH/HCl cleanly yields the desired *N*-hydroxyureas (Table 1). Using Pd/C as the hydrogenation catalyst results in the partial reduction of the N–O bond to give mixtures



Scheme 1.

Keywords: *N*-Hydroxyureas; Nitric oxide; Nitric oxide donors; Carbohydrates; Hydrogenation.
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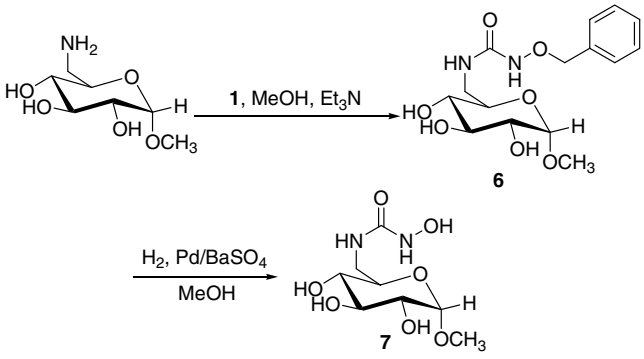
Table 1. Hydrogenation yields of *O*-benzyl protected *N*-hydroxyureas using 5% $Pd/BaSO_4$ in MeOH/HCl

Entry	R, R′	Yield
1	*n*-Bu, H	100
2	Bn, H	50
3	Ph, H	81
4	*t*Bu, H	94
5	Et, Et	93

of *N*-hydroxyureas and ureas. This sequence converts primary and second aliphatic amines (Table 1, entries 1, 2, 4, 5) and aromatic amines (Table 1, entry 3) to the corresponding *N*-hydroxyureas. While the non-protected version of **1**, 4-nitrophenol *N*-hydroxycarbamate, provides direct access to a nucleotide-derived hydroxyurea following preparative HPLC,[3] this reagent did not yield reproducibly useful results in our experiments. Control reactions show that this compound decomposes in methylene chloride and triethylamine to carbon dioxide (as determined by headspace gas chromatography) and 4-nitrophenol. In our hands the two-step procedure using **1** appears more general for the preparation of *N*-hydroxyureas.

Condensation of a suspension of D-1-amino-1-deoxy fructose hydrochloride[13] in MeOH with **1** yields the *O*-benzyl protected *N*-hydroxyurea of 1-amino fructose (**3**, Scheme 2) in 76% yield. This result demonstrates the ability of **1** to selectively react with amines relative to alcohols, allowing the formation of carbohydrate-derived *N*-hydroxyureas without alcohol protection. Hydrogenation of **3** initially produces the hydroxyurea (**4**, Scheme 2) but NMR spectroscopy clearly shows this compound undergoes rearrangement to another species. X-ray crystallography identifies this new compound as the cyclic hydroxyurea (**5**, Scheme 2) that likely arises from a condensation of the *N*-hydroxyurea nitrogen atom on the keto form of the carbohydrate to give a five-membered ring that dehydrates to **5** (Scheme 2). Exposure of D-glucosamine to the same sequence similarly gives a stable *O*-benzyl protected *N*-hydroxyurea that rearranges to the corresponding cyclic hydroxyurea upon deprotection.



Scheme 3.

Treatment of methyl 6-amino-6-deoxy-α-D-glucopyranoside[14] in MeOH with **1** yields the *O*-benzyl protected *N*-hydroxyurea of methyl 6-amino-α-D-glucopyranoside (**6**, Scheme 3) in 65% yield.[15] Catalytic hydrogenation over 5% $Pd/BaSO_4$ of **6** yields the *N*-hydroxyurea derived from methyl 6-amino-6-deoxy-a-D-glucopyranoside in 97% yield (**7**, Scheme 3).[15] This sequence shows that protection of the anomeric position as the methyl glycoside prevents the observed cyclization/dehydration sequence and allows the preparation of stable, highly functionalized carbohydrate-derived *N*-hydroxyureas. In summary, this two-step procedure provides a direct, convenient, and alternative method for the preparation of non-substituted *N*-hydroxyureas from the condensations of hydroxylamines with isocyanates or other carbamates.[16] This preparation of carbohydrate-derived *N*-hydroxyureas indicates this method will be quite useful for the synthesis of highly functionalized *N*-hydroxyureas using minimal functional group protection.

Acknowledgments

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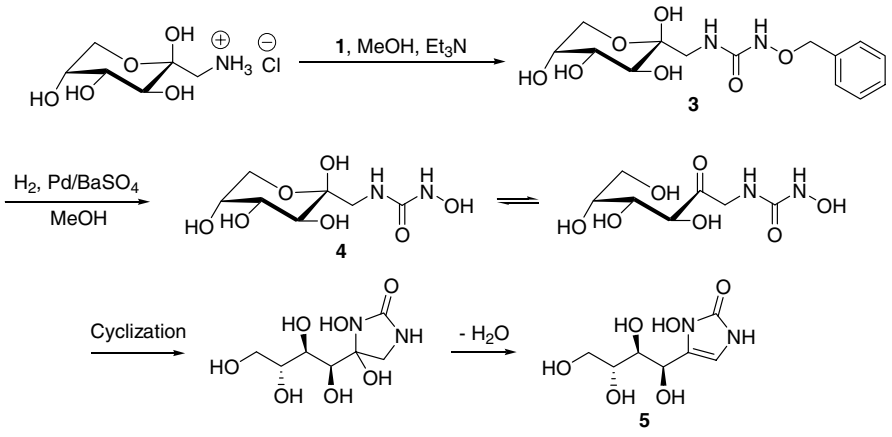

Scheme 2.

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11. General procedure illustrated with *n*-butylamine. Carbamate **1** (0.976 g, 3.39 mmol) was added to a solution of *n*-butylamine (0.335 mL, 3.39 mmol) and triethylamine (0.472 mL, 3.39 mmol) in methylene chloride (40 mL). The reaction mixture was stirred until starting material was consumed (as determined by TLC) and washed with 1 M NaOH (3×30 mL), 1 M HCl (30 mL), and water (30 mL). The organic fraction was dried with $MgSO_4$, filtered, and concentrated to give the *O*-benzyl protected *N*-hydroxyurea (0.737 g, 98%) as a white solid; R_f 0.40 (1:1 EtOAc/hexanes); mp 46–48 °C; ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 4.70 (s, 2H), 3.09 (t, 2H), 1.31 (m, 2H), 1.17 (m, 2H), 0.81 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 160.0, 135.5, 129.1, 128.7, 128.6, 78.5, 39.2, 31.8, 19.8, 13.6.
12. 4-Nitrophenyl-*N*-(*O*-benzylhydroxy)carbamate (**1**). *O*-Benzyl hydroxylamine (2.565 g, 20.82 mmol) was dissolved in methylene chloride (70 mL) followed by the addition of pyridine (2.00 mL, 24.99 mmol) under an argon atmosphere. The reaction flask was cooled to 0 °C and 4-nitrophenyl chloroformate (4.200 g, 20.82 mmol) was added. A reflux condenser was attached, and the reaction mixture was heated at reflux for 24 h. Upon cooling, the homogeneous organic solution was washed with 1 M $NaHCO_3$ (3×40 mL) and H_2O (40 mL). The organic fraction was dried with $MgSO_4$, filtered, and concentrated until solid material began to precipitate. A chloroform–hexane mixture (5:6, 22 mL) was added. The resulting solid was collected by vacuum filtration, washed with the chloroform–hexane mixture until all yellow discoloration was removed, and dried to give **1** (4.25 g, 71%) as a white solid; R_f 0.78 (1:1 EtOAc/hexanes); mp 131–133 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, 2H), 7.82 (s, 1H), 7.40–7.34 (m 5H), 7.26 (d, 2H), 4.92 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 155.0, 153.7, 145.1, 134.7, 129.2, 128.9, 128.7, 125.2, 121.9, 79.0.
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15. For **6**: R_f 0.25 (4:1 CH_2Cl_2/CH_3OH); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.39–7.28 (m, 5H), 4.75 (s, 2H), 4.61 (d, $J = 3.75$, 1H), 3.55–3.47 (m, 2H), 3.35–3.26 (m, 3H), 3.31 (s, 3H), 3.07 (t, $J = 9.3$Hz, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 163.2, 137.8, 130.6, 129.9, 101.7, 79.9, 75.1, 74.0, 73.6, 72.1, 56.0, 42.0; LRMS (FAB) *m/z* 365 $(M+Na)^+$; 377 $(M+Cl)^-$; Anal. Calcd for $C_{15}H_{22}N_2O_7 \cdot 0.5\ H_2O$: C, 51.28; H, 6.60; N, 7.97; Found: C, 51.22; H, 6.36; N, 7.72. For **7**: R_f 0.22 (2:1 CH_2Cl_2/CH_3OH); ^{1}H NMR (D_2O, 300 MHz) δ 4.61 (m, 1H), 3.58–3.42 (m, 3H), 3.39–3.10 (m, 3H), 3.31 (s, 3H); ^{13}C NMR (D_2O, 75 MHz) δ 163.8, 99.4, 73.3, 71.6, 71.5, 70.6, 55.2, 40.3; LRMS (FAB) *m/z* 275 $(M+Na)^+$, 287 $(M+Cl)^-$; Anal. Calcd for $C_8H_{16}N_2O_7 \cdot 0.5\ H_2O$: C, 36.78; H, 6.56; N, 10.72. Found: C, 36.76; H, 6.93; N, 10.20.
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