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# Alkylation of N-Benzyloxyureas and Carbamates

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**Summary:** ***N-Benzyloxyureas and orthogonally protected N-hydroxycarbamates can be alkylated in high yields and subsequently deprotected to provide N-alkyl hydroxyureas and hydroxylamines.***

Synthetic methods for the preparation of N-alkyl hydroxylamines from alkyl halides or sulfonates generally require harsh conditions, prolonged reaction times, involve not-readily-available intermediates or are not regiospecific.[1-6] Recently, we required hydroxylamine derivatives that could be mildly and specifically substituted on nitrogen. We have found that the orthogonally protected[7] synthon 1 reacts with a variety of alkylating agents to produce *t*-butyl N-benzyloxycarbamates 2 in high yields (Table I and Scheme 1). With the appropriate reagents, these carbamates can be specifically deprotected at nitrogen or at oxygen. Similarly, N-benzyloxyureas of general structure 5 can be alkylated and deprotected to give N-hydroxyureas 7 (Table II and Scheme 2).

Unsubstituted carbamate 1 was readily prepared in 98% yield from commercially available di-*t*-butyl dicarbonate and O-benzyl hydroxylamine in aqueous base. Treatment of 1 with sodium hydride (1.1 equivalents) in N,N-dimethylformamide at 25° C, followed by the addition of a primary halide or secondary mesylate or iodide (1.1 equivalents) at 25° to 100° C gave the *t*-butyl carbamates 2 in 60-90% yields. Similarly, treatment of N-benzyloxyureas 5 (R,R'=H, alkyl, aryl; readily available from O-benzylhydroxylamine and the corresponding isocyanate or carbamyl chloride) with sodium hydride in dimethylformamide followed by alkyl halide addition gave the substituted benzyloxyureas 6 in yields of 50-90%. Monoalkyl-substituted benzyloxyureas (5a-f) alkylated exclusively on the benzyloxy-substituted nitrogen.

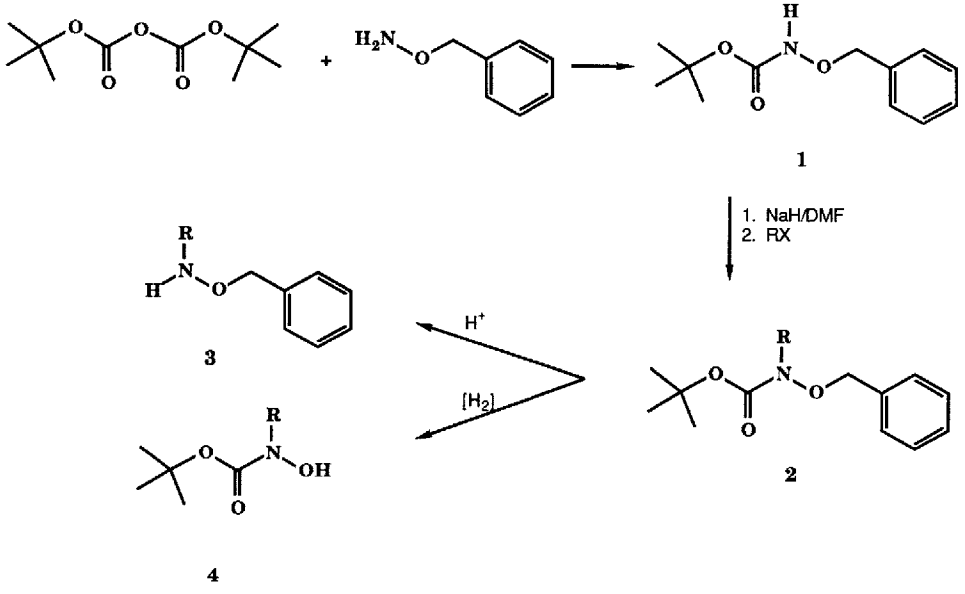
The *t*-butyl N-hydroxy carbamates 4 and N-hydroxyureas 7 were prepared by catalytic transfer hydrogenolysis[8] of the corresponding benzyloxy derivatives 2 and 6 using ammonium formate and 10% palladium on charcoal in ethanol in 67-93% yields. We have noted that hydrogenolysis under more severe conditions (palladium black catalyst, 50 psi hydrogen) resulted in complete N-O bond cleavage, leading to N-alkyl carbamates and ureas.

Acidolysis (trifluoroacetic acid in dichloromethane or hydrogen chloride in ethyl acetate) at room temperature gave the alkyl benzyloxyamines 3 in 90-100% yields. Hydrogenolysis of 2 (R= n-octyl), followed by acidolysis afforded N-octylhydroxylamine hydrochloride in 80% overall yield from 1.

Table I: Alkylation (products 2a-g) and acidolysis (products 3a-f) of *t*-butyl N-benzyloxycarbamate.

| RX | time(h) | temperature (°C) | Product | Yield, % | b p (°C/mmHg) | Product | Yield, % |
|---|---|---|---|---|---|---|---|
| $CH_2$=$CHCH_2Br$ | 1 | 50 | 2a | 99 | 95-100/0.1 | 3a | 95 |
| $EtOCO(CH_2)_3Br$ | 1 | 70 | 2b | 94 | *a* | 3b | 93 |
| $CH_3(CH_2)_9Br$ | 16 | 60 | 2c | 88 | *a* | 3c | 100 |
| $CH_3I$ | 1 | 25 | 2d | 95 | 90-95/0.1 | 3d | 93 |
| $CH_3(CH_2)_7Br$ | 1 | 70 | 2e | 99 | *a* | 3e | 93 |
| $(CH_3)_2CH(CH_2)_3CH(CH_3)OMs$ | 16 | 40 | 2f | 83 | 125-30/0.1 | 3f | 88 |
| $Br(CH_2)_2Br$ (10 eq.) | 1 | 25 | 2g | 61 | 110-15/0.1 | -- | -- |

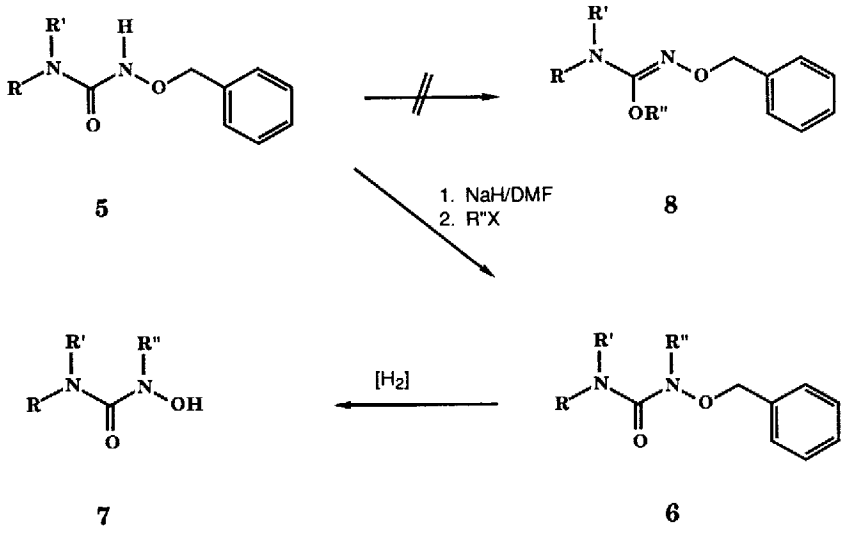
*a*--compounds purified by chromatography




**Scheme 1**

Table II: Alkylation (products 6a-h) and hydrogenolysis (products 7a-h) of N-benzyloxyureas

| R | R' | R"X | Product, Yield,% | Product | Yield,% | mp (°C) |
|---|---|---|---|---|---|---|
| 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$ | H | $CH_3I$ | 6a, 88 | 7a, | 90 | 98-99.5 |
| $CH_2$=$CH(CH_2)_8$ | H | $CH_3I$ | 6b, 90 | 7b, | 91 | 45-46 |
| $CH_3(CH_2)_9$ | H | $CH_3I$ | 6c, 73 | 7c, | 91 | 74-76 |
| $CH_3$ | H | $(C_2H_5O)_2CHCH_2Br$ | 6d, 73 | 7d, | 93 | 38-39 |
| 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$ | H | $(CH_3)_2CHI$ | 6e, 61 | 7e, | 83 | 113-114 |
| $CH_3OCO(CH_2)_6$ | H | $CH_3(CH_2)_9Br$ | 6f, 61 | 7f, | 80 | 81-82 |
| $CH_3$ | $CH_3$ | $(C_2H_5O)_2CHCH_2Br$ | 6g, 50 | -- | -- | -- |
| $CH_3$ | $CH_3$ | $CH_3(CH_2)_7Br$ | 6h, 81 | 7h, | 67 | 29-30 |




**Scheme 2**

## Experimental

*t*-Butyl N-benzyloxycarbamate (1)

To a stirred solution of di-*t*-butyl dicarbonate (36.28 g, 0.166 mol) in dioxane (170 ml) at room temperature was added O-benzylhydroxylamine hydrochloride (26.53 g, 0.166 mol) and then 1 M sodium bicarbonate solution (166 ml).

The resulting milky solution was stirred 2 h at room temperature and then partially evaporated in vacuo to remove dioxane. The residue was cooled and adjusted with citric acid to pH 4. The mixture was extracted twice with dichloromethane, the extracts combined, dried over $MgSO_4$, filtered and evaporated. Re-evaporation from hexanes gave *t*-butyl N-benzyloxycarbamate as a white solid, mp 45-46 °C, 36.35 g, 98%.

*t*-Butyl N-decyl-N-benzyloxycarbamate (2c)

To a solution of 1 (13.06 g, 58.4 mmol) in dimethylformamide (90 ml) at room temperature was added sodium hydride (60% mineral oil dispersion, 2.58 g, 64.5 mmol). Gas evolved and the resulting clear solution was stirred 30 min. 1-Bromodecane (13.4 ml, 64.6 mmol) was then added and the reaction mixture heated to 60 °C for 16 h. The reaction mixture was cooled, poured into water (500 ml) and extracted thrice with hexanes. The extracts were combined, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (2:3 dichloromethane:hexane) to give 2b as a colorless oil, 18.74 g, 88%.

1-Benzyloxy-1-(2,2-diethoxyethyl)-3-methylurea (6d)

To a stirred solution of 1-benzyloxy-3-methylurea (3.60 g, 20.0 mmol) in dimethylformamide (50 ml) at room temperature under $N_2$ was added sodium hydride (60% mineral oil dispersion, 420 mg, 23.8 mmol). The resulting thick precipitate was heated to 100 °C for 15 min. 2-Bromo-1,1-diethoxyethane (3.2 ml, 21 mmol) was then added and the reaction mixture stirred at 100-110° for 18 h. The resulting solution was cooled, diluted with water, adjusted to pH 8 with 10% citric acid and extracted thrice with ether. The extracts were combined, washed with water, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (55:45 hexanes:ethyl acetate) to give 6d as a colorless oil, 4.34 g, 73%.

1-(2,2-Diethoxyethyl)-3-hydroxy-3-methylurea (7d)

To a solution of 6d (2.08 g, 7.02 mmol) in ethanol (25 ml) at room temperature under $N_2$, was added ammonium formate (2 g, *ca.* 6 equivalents) and 10% palladium on carbon (0.5 g). After 2 h, the reaction mixture was filtered through Celite, rinsing with ethyl acetate. The filtrate was evaporated, the residue dissolved in dichloromethane, dried over $MgSO_4$, filtered and evaporated. Recrystallization from cold pentane gave 7d as a white solid, mp 38-39 °C, 1.34 g, 93%.

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