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Protecting group migration in the chemistry of 1-*t*-butyldimethylsilyl-4-hydroxymethyl-2-azetidinone

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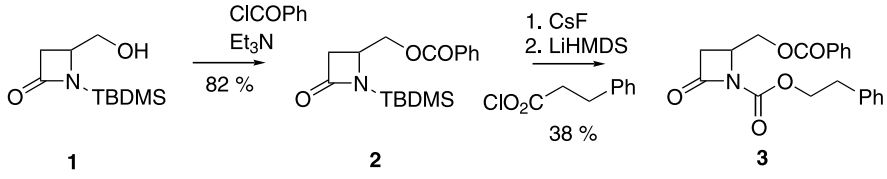
Abstract—The alkoxide anion derived from 1-*t*-butyldimethylsilyl-4-hydroxymethyl-2-azetidinone (**1**) rearranged at −78°C into amide anion by N–O migration of the silyl protecting group. The occurrence of this intermediate was proved by quenching with benzyl bromide and phenethyl chloroformate, giving respectively *N*-benzyl (**4**) and *N*-(phenethyloxycarbonyl) (**6**) derivatives of 4-(*t*-butyldimethylsilyloxy)methyl-2-azetidinone.

1-*t*-Butyldimethylsilyl-4-hydroxymethyl-2-azetidinone (**1**) has been used as key-intermediate for the synthesis of β-lactam antibiotics such as carbapenems, isoclavams and isocephems.[1,2] This compound (racemic or enantiomerically pure) was obtained by reduction of related 4-alkyloxycarbonyl-2-azetidinones,[3,4] or by oxidative cleavage of the corresponding *p*-methoxyphenyl ether.[2] Further transformations of the hydroxymethyl residue were described by mesylation followed by nucleophilic substitution,[1] reaction with vinyl alkyl ether under acidic catalysis,[3] and silylation.[5] The unstability of **1** under strongly basic conditions was evoked by Banfi et al.[3] and Cundi et al.,[4] and attributed to the possible N–O migration of the silyl group. Nevertheless, selective C3 methylation of **1** could be realized by treatment with two equivalents of *n*Buli or LDA at −78°C followed by addition of three equivalents of methyl iodide;[4] concomitant *O*-methylation was not reported (nor *N*-methylation, in the case of silyl group migration occurrence).

Our interest in 1-alkyloxycarbonyl-2-azetidinone derivatives as elastase inhibitors[6,7] led us to consider **1** as starting material for the synthesis of various C4 substituted compounds. During this work, we unambiguously identified rearrangement products arising from the silyl group migration.

4-Benzyloxycarbonyl-2-azetidinone[8] was first *N*-silylated[9] (diisopropylethylamine, *t*-butyldimethylsilyl chloride, CH_2Cl_2, 20°C, 24 h), then reduced with lithium borohydride (THF, 0°C to 20°C, 1h) to furnish 1-*t*-butyldimethylsilyl-4-hydroxymethyl-2-azetidinone (**1**) in about 95% overall yield. The alcohol function of **1** could be readily acylated, without trouble due to silyl group migration. For instance, reaction with benzoyl chloride, in the presence of triethylamine and dimethylaminopyridine (DMAP) as catalyst,[10] gave the ester **2** (Scheme 1) in 82% yield.[11] *N*-Deprotection of **2** with cesium fluoride followed by *N*-acylation with phenethyl chloroformate, according to a previously described pro-



1 2 3

Scheme 1.

Keywords: *N*-silylation; *O*-silylation; silyl migration; β-lactam.
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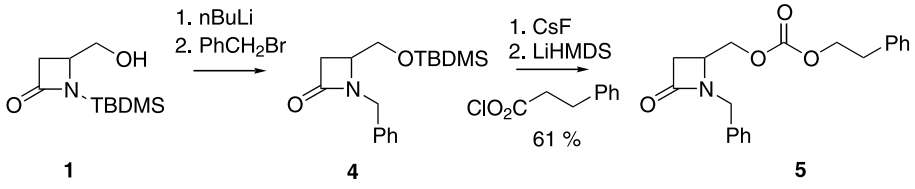
cedure,[6] afforded azetidinone **3** in 38% yield after chromatographic purification.[12] This compound was inactive against PPE (porcine pancreatic elastase).

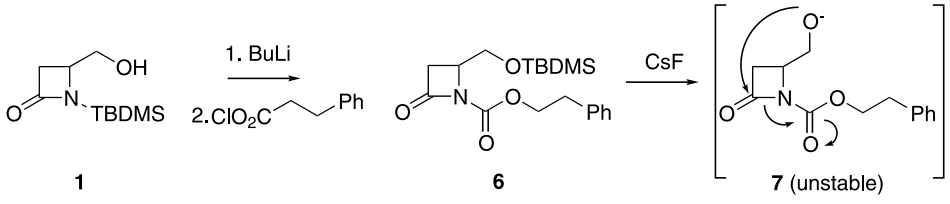
On the other hand, all attempts to alkylate the alcohol function of **1**, under Williamson-type conditions, failed. Treatment of **1** with one equivalent of a strong base at low temperature (NaH, LiHMDS, LDA or *n*Buli, THF, −78°C) followed by quenching with benzyl bromide gave 1-benzyl-2-(*t*-butyldimethylsilyloxy)methyl-2-azetidinone (**4**) as the unique product. Silyl deprotection and acylation as before finally furnished compound **5** (Scheme 2) in 61% overall yield.[13] The presence of a carbonate function (resulting from *O*-acylation) was inferred from the ^{13}C NMR signal at 154 ppm; the carbamate function of **3** (resulting from *N*-acylation) showed a characteristic signal at 148 ppm. We further unambiguously demonstrated the occurrence of the N–O migration of the silyl group by reacting **1** with one equivalent of BuLi and quenching the anion with phenethyl chloroformate (Scheme 3). After chromatography, 1-phenethyloxycarbonyl-4-(*t*-butyldimethylsilyloxy)methyl-2-azetidinone (**6**) was recovered in 52% yield;[14] the carbamate function of **6** was characterized by a typical signal at 149 ppm in the ^{13}C NMR spectrum. We were unable to deprotect the silyl ether function of **6** (CsF, Bu_4NF or $LiOH–H_2O$) without degradation of the four-membered ring most probably due to an intramolecular *O*-nucleophilic attack on the activated β-lactam carbonyl.

Thus, in our hands, the mono-anion **8** derived from **1** was unstable, even at −78°C, and rearranged rapidly into the amide anion **9** which could be trapped with electrophiles (RX = $PhCH_2Br$, $PhCH_2CH_2OCOCl$) to furnish *N*-derivatized β-lactams **10** with the alcohol function protected as silyl ether (Scheme 4). In the previous literature,[4] the precursor **1** was treated with an excess of base to furnish the bis-anion **11**; this intermediate is obviously less prone to silyl migration. Quenching with a soft electrophile (RX = CH_3I) gave thus C3-substituted β-lactam **12**, still *N*-protected with the silyl group. Accordingly, azetidinone **1** appears to be a good precursor for selective substitution of either position C3 or position N1, depending on the amount of base used for the initial deprotonation step. Thus, under strongly basic conditions the hydroxyl group of **1** could not be further functionalized. On the other hand, this OH group could selectively react, without migration of the *N*-silyl protecting group, under smoothly acidic and electrophilic conditions, such as in acylation reactions, or via nucleophilic substitutions of the corre-

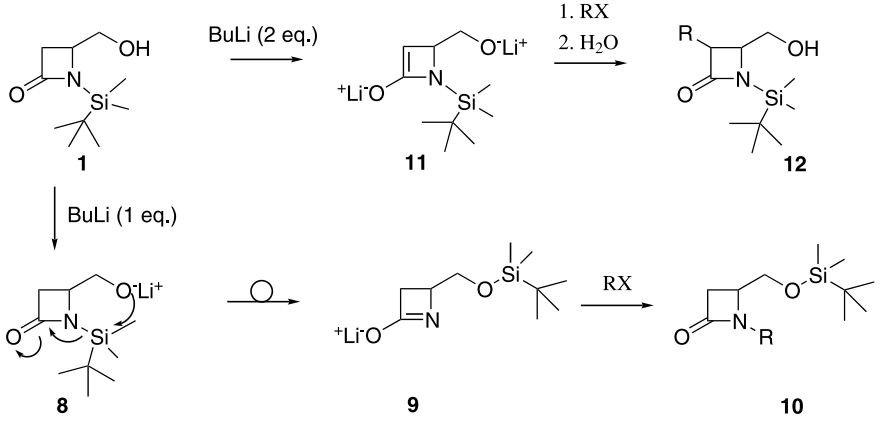


1 **4** **5**

Scheme 2.



Scheme 3.



1 **11** **12** **8** **9** **10**

Scheme 4.

sponding mesylate.[1] Our contribution has now defined better the scope and limitation of the reactivity of 1-*t*-butyldimethylsilyl-4-hydroxymethyl-2-azetidinone, a key intermediate for antibiotic synthesis.

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11. Synthesis and characterization of 4-benzoyloxymethyl-*N*-(*tert*-butyldimethylsilyl)-2-azetidinone (**2**). A solution of **1** (216 mg; 1 mmol) and DMAP (catalytic amount) in dry CH_2Cl_2 (10 mL) was stirred at room temperature. Triethylamine (140 μL; 1 mmol) and benzoyl chloride (120 μL; 1 mmol) were added and stirring was continued for 20 h. Then, excess of triethylamine (28 μL; 0.2 mmol) and benzoyl chloride (23 μL; 0.2 mmol) were added to the solution and the mixture was stirred for an additional 20 h. The solution was washed three times with water (10 mL) and dried over $MgSO_4$. After filtration and concentration under vacuum, the resulting β-lactam was purified by column chromatography on silica gel (CH_2Cl_2) to yield **2** (261 mg, 82%) as a colorless oil. (Found: C, 63.96; H, 7.87; N, 4.38%. $C_{17}H_{25}O_3NSi$ requires C, 63.91; H, 7.89; N, 4.38%); ν_{max}/cm^{-1} 1791, 1718 and 1180; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.27 (6H, s, 2×$SiCH_3$), 0.95 (9H, s, $C(CH_3)_3$), 2.98 (1H, dd, *J* 15.9 and 6.3, H-3), 3.25 (1H, dd, *J* 15.9 and 3.4, H-3′), 3.95 (1H, m, H-4), 4.38 (1H, dd, *J* 11.1 and 2.5, CH_2O), 4.52 (1H, dd, *J* 11.1 and 2.4, CH_2O), 7.45–7.54 (3H, m, Ar), 8.01–8.09 (2H, m, Ar); δ_C (75 MHz; $CDCl_3$; Me_4Si) −5.6 and −5.5 ($SiCH_3$), 18.0 ($C(CH_3)_3$), 26.1 ($C(CH_3)_3$), 41.7 (C-4), 47.3 (C-3), 65.9 (CH_2O), 128.4 129.5 and 129.6 (CH_{Ar}), 133.1 (C_{Ar}), 166.1 and 171.8 (2×C=O); *m*/*z* (EI) 319 (3), 121 (69), 105 (100) and 77 (66).
12. Synthesis and characterization of 1-phenethyloxycarbonyl-4-benzoyloxymethyl-2-azetidinone (**3**). A solution of **2** (169 mg; 0.5 mmol) and cesium fluoride (114 mg; 0.75 mmol) in dry DMF (3 mL) was stirred for 2 h at room temperature. The crude mixture was concentrated and after addition of EtOAc, the organic layer was washed twice with water, dried over $MgSO_4$, filtered and concentrated under vacuum. A solution of the deprotected β-lactam in THF (5 mL), cooled at −78°C under argon atmosphere, was dropwise added to a solution of LiHMDS (1 equiv.) in dry THF (3 mL). The mixture was stirred for 30 min at −78°C, then phenethyl chloroformate (46 mg; 0.25 mmol) was added with a syringe through a rubber stopper. Stirring was continued for 1 h at this temperature and the mixture was allowed to reach room temperature and stirred for 3 h at 20°C. After addition of 10% NH_4Cl (10 mL) and extraction with CH_2Cl_2, the organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting β-lactam was purified by column chromatography on silica gel (CH_2Cl_2:EtOAc, 90/10) to yield **3** (33 mg, 38%) as a colorless oil; (Found HRMS: 354.1341. $C_{20}H_{20}NO_5$ requires 354.1341); ν_{max}/cm^{-1} 1817 and 1726; δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.00 (2H, t, *J* 7.3, CH_2CH_2Ph), 3.05 (1H, dd, *J* 16.0 and 6.2, H-3), 3.19 (1H, dd, *J* 16.0 and 3.5, H-3′), 4.33 (1H, m, H-4), 4.43 (2H, t, *J* 7.3, CH_2CH_2Ph), 4.56 (1H, dd, *J* 12.1 and 3.8, CH_2O), 4.69 (1H, dd, *J* 12.1 and 3.1, CH_2O), 7.15–7.69 (8H, m, Ar), 8.01–8.05 (2H, m, Ar); δ_C (100 MHz; $CDCl_3$; Me_4Si) 34.9 (CH_2CH_2Ph), 39.6 (C-3), 49.4 (C-4), 61.2 (CH_2O), 67.0 (CH_2CH_2Ph), 126.7 128.4 129.2 129.5 and 129.6 (CH_{Ar}), 133.3 and 136.8 (C_{Ar}), 148.7 (CO carbamate), 163.1 and 165.9 (CO azetidinone and CO amide); *m*/*z* (CI) 354 (M+1, 4), 105 (100), 91 (12) and 77 (66).
13. Synthesis and characterization of 1-benzyl-4-(2′,4′-dioxa-3′-oxy-6′-phenylhexyl)-2-azetidinone (**5**). A solution of *n*BuLi (600 μL; 2M in hexane; 1.2 mmol) was added to a solution of **1** (216 mg; 1 mmol) in dry THF (10 mL), cooled at −78°C under argon atmosphere. Benzyl bromide (130 μL; 1.1 mmol) was added dropwise and the mixture was stirred for 3 h at −78°C. The solution was then washed with water (10 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. A solution of the resulting β-lactam **4** (169 mg; 0.5 mmol) and cesium fluoride (114 mg; 0.75 mmol) in dry DMF (3 mL) was stirred for 2 h at room temperature. The crude mixture was concentrated and after addition of EtOAc, the organic layer was washed twice with water, dried over $MgSO_4$, filtered and concentrated under vacuum. A solution of the deprotected β-lactam in THF (5 mL), cooled at −78°C under argon atmosphere, was added dropwise to a solution of LiHMDS (1 equiv.) in dry THF (5 mL). The mixture was stirred for 30 min at −78°C, then phenethyl chloroformate (46 mg; 0.25 mmol) was added with a syringe through a rubber stopper. Stirring was continued for 30 min at this temperature and the mixture was allowed to reach room temperature and stirred for 3 h at 20°C. After addition of 10% NH_4Cl (5 mL) and extraction with CH_2Cl_2, the organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The

resulting β-lactam was purified by column chromatography on silica gel (CH_2Cl_2:EtOAc, 95/5) to yield **5** (142 mg, 61%) as a colorless oil; (Found HRMS: 340.1542. $C_{20}H_{22}NO_4$ requires 340.1549); ν_{max}/cm^{-1} 3031 and 1750; δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.76 (1H, dd, *J* 14.5 and 2.8, H-3), 2.97 (2H, t, *J* 6.8, CH_2CH_2Ph), 3.01 (1H, dd, *J* 14.5 and 5.2, H-3′), 3.69 (1H, m, H-4), 4.03 (1H, dd, *J* 15.1 and 6.4, CH_2O), 4.16 (1H, d, *J* 15.1, CH_2Ph), 4.28 (1H, dd, *J* 15.1 and 3.6, CH_2O), 4.31 (2H, t, *J* 6.8, CH_2CH_2Ph), 4.61 (1H, d, *J* 15.1, CH_2Ph), 7.15–7.35 (10H, m, Ar); δ_C (125 MHz; $CDCl_3$; Me_4Si) 34.9 (CH_2CH_2Ph), 39.3 (C-3), 45.1 (NCH_2Ph), 48.8 (C-4), 67.5 (CH_2O), 68.6 (CH_2CH_2Ph), 126.7 127.6 128.4 128.5 128.6 and 128.7 (CH_{Ar}), 135.6 and 136.9 (C_{Ar}), 154.4 (CO carbonate), 166.1 (CO azetidinone); *m*/*z* (CI) 340 (M+1, 12), 298 (51) and 105 (100).

14. Synthesis and characterization of 1-phenethyloxycarbonyl-4-(*t*-butyldimethylsilyloxy) methyl-2-azetidinone (**6**). A solution of *n*BuLi (2.1 M in hexane, 476 μL; 1 mmol) was dropwise added to a solution of **1** (215 mg; 1 mmol) in dry THF (5 mL), cooled at −78°C under argon atmosphere. The mixture was stirred for 1 h at −78°C, then phenethylchloroformate (184 mg; 1 mmol) was added with a syringe through a rubber stopper. Stirring was continued for 1 h at this temperature and the mixture was allowed to reach room temperature and stirred for 45 min at 20°C. After addition of water and extraction with CH_2Cl_2, the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting β-lactam was purified by column chromatography on silica gel (CH_2Cl_2) to yield **6** (189 mg, 52%) as a colorless oil; ν_{max}/cm^{-1} 1813 and 1750; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.15 (6H, s, $2\times SiCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 2.98–3.05 (4H, m, H-3 and CH_2Ph), 3.75 (1H, m, H-4), 4.05 (2H, m, CH_2O), 4.39 and 4.40 ($2\times$1H, 2×t, *J* 5.9, OCH_2CH_2), 7.21–7.38 (5H, m, Ar); δ_C (75 MHz; $CDCl_3$; Me_4Si) −5.6 and −5.5 ($SiCH_3$), 18.2 ($C(CH_3)_3$), 25.7 ($C(CH_3)_3$), 35.2 (CH_2Ph), 38.7 (C-4), 51.8 (C-3), 60.1 (CH_2O), 66.9 (CH_2CH_2O), 126.8 128.6 and 129.1 (CH_{Ar}), 137.2 (C_{Ar}), 149.1 (CO carbamate), 164.0 (CO azetidinone); *m*/*z* (CI) 364 (M+1, 12), 105 (83), 91 (100).