ORGANIC LETTERS

2001
Vol. 3, No. 3
433−435

Unprecedented Migration of *N*-Alkoxycarbonyl Groups in Protected Pyroglutaminol

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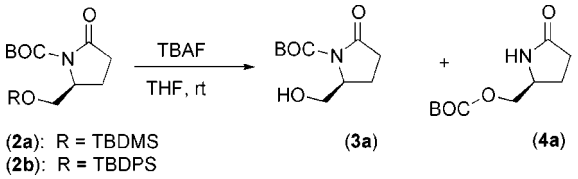
Received November 30, 2000

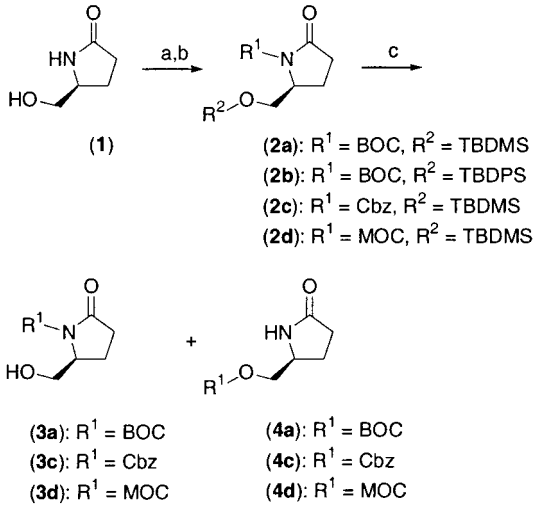
ABSTRACT



Cleavage of an *O*-silyl ether in an *N*-BOC-protected pyroglutaminol using TBAF led to an unprecedented migration of the BOC group. An investigation of the mechanism, based on experimental data and quantum mechanical calculations, is presented. Similar migration was observed for *N*-Cbz and *N*-methoxycarbonyl groups.

(*S*)-Pyroglutaminol (**1**), derived from (*S*)-glutamic acid in two steps, serves as an important building block in synthetic organic chemistry.[1] In an approach to synthesize a novel potentially CNS active glutamic acid analogue, selective cleavage of the TBDMS ether in **2a** with TBAF was expected to proceed in high yield on the basis of a previously reported synthesis.[2] However, instead of obtaining the expected free hydroxyl functionality in compound **3a**, migration of the BOC group led to the lactam-carbonate derivative **4a** as the only product observed (Scheme 1). An X-ray diffraction study of **4a** confirmed the structure (Figure 1). In general, migration of the oxycarbonyl moiety in *N*-carbamates is a known but rarely observed rearrangement reaction and only favorable if an additional anion stabilizing group is present

Scheme 1. Reaction Pathway to **3** and **4**



Reagents and conditions: (a) TBDMSCl or TBDPSCl, DMAP, Et_3N, CH_2Cl_2, rt, 99%; (b) for **2a**,**b**: BOC_2O, DMAP, Et_3N, CH_2Cl_2, rt, 86%; for **2c**,**d**: BuLi then CbzCl or MOCCl, THF, -78 °C, both 75%; (c) TBAF, THF, rt.

(1) For an extensive review, see: Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245−2303.
(2) Ikota, N. *Chem. Pharm. Bull.* **1992**, *40*, 1925−1927
(3) Valentekovich, R. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 9069−9070
(4) Johnson, C. K. ORTEPII. Report ORNL-5138; Oak Ridge Laboratory, Tennessee, 1976.
(5) **Experimental procedure:** To 0.30 mmol of **2a**−**d** in dry THF (0.5 mL) was added 0.9−1.6 equiv of a 1 M solution of TBAF·$3H_2O$ in THF (Aldrich). The reaction mixture was stirred for 5 or 30 min at rt and then diluted with EtOAc and quenched by addition of H_2O. The organic layer was separated and washed with brine, dried over Na_2SO_4, and evaporated. Ratios of products determined from ^1H NMR.

10.1021/ol0069397 CCC: $20.00
Published on Web 01/06/2001

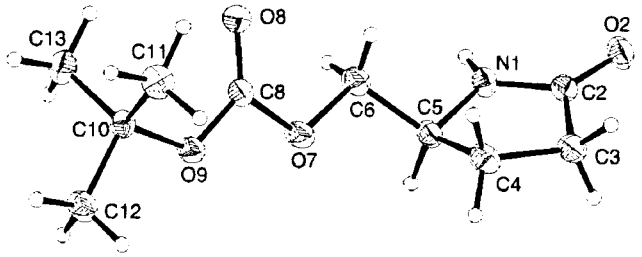


Figure 1. Molecular structure (ORTEPII)[4] of compound **4a** as determined from an X-ray diffraction analysis (see Supporting Information).

on the nitrogen.[3] Here we wish to report an investigation of this so far overlooked problem in pyroglutaminol chemistry.

In the area of pyroglutaminol chemistry, the most commonly used *O*-protective groups are the TBDMS and TBDPS ethers. Thus, **2a** and **2b** were included in this investigation. To investigate the structural generality of this *N*-oxycarbonyl group migration, the benzyloxycarbonyl **2c** and methoxycarbonyl (MOC) **2d** groups were also included in this study.

At first, the influence of the amount of TBAF and the reaction time on the percentage of migration were investigated, see Table 1.[5]

Table 1. Deprotection of **2a** and **2b** with TBAF

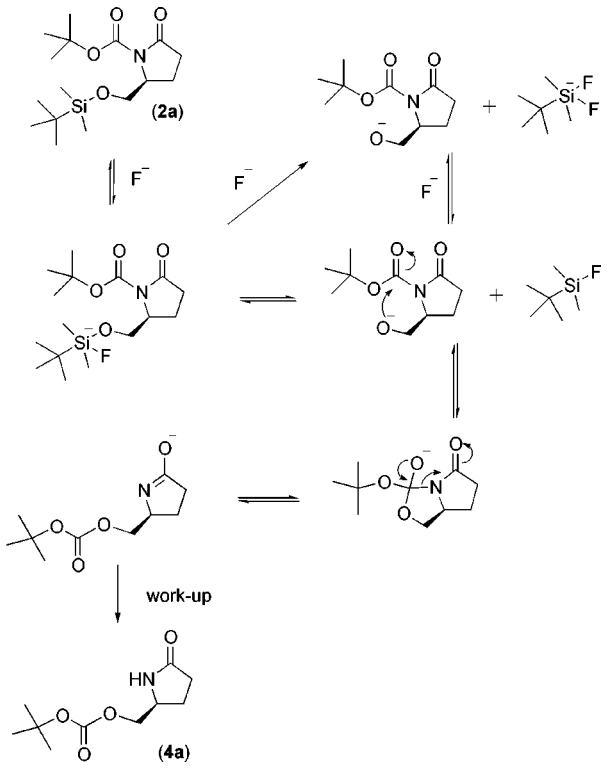
TBAF	*t*	**2a** (R = TBDMS)			**2b** (R = TBDPS)		
(equiv)	(min)	% **2a**	% **3a**	% **4a**	% **2b**	% **3a**	% **4a**
1.6	30	0	0	100	0	0	100
1.6	5	0	39	61	0	12	88
1.2	30	0	20	80	0	14	86
1.2	5	0	60	40	0	23	77
0.9	30	0	53	47	0	33	67
0.9	5	<5	75	20	<5	45	55

It is well established that the cleavage of an *O*-silyl ether with fluoride anions proceeds through an initially formed pentacoordinate silicate which then collapses either spontaneously or upon the following aqueous workup.

Addition of two fluoride anions to form a hexacoordinate silicate is also known and may facilitate the following collapse of the Si−O bond, setting free the alkoxide. It has also been shown that nucleophilic attack on a pentacoordinate silicate is a faster process than attack on the starting tetracoordinate silane.[6]

From Table 1 it is clear that the ratio of **3a** and **4a** is dependent on both time and the amount of TBAF added. It can be concluded that the stability of the pentacoordinate TBDMS ether compared to that of the TBDPS ether is higher, thus giving rise to the lower tendency of migration. This difference in stability of the pentacoordinate silane complexes is presumably due to the difference in steric bulk around the silane. According to experimental results, the rate of migration for the TBDMS ether shows a higher dependency on the TBAF concentration. This may be a result of the prolonged lifetime of the pentacoordinate TBDMS ether which is then susceptible to attack by a second fluoride anion, followed by a rapid release of the alkoxide.[6] The proposed general mechanism is illustrated for **2a** in Scheme 2.

Scheme 2. Proposed Mechanism for the Formation of **4a**



To investigate the generality of this migration, **2c**,**d** were threated with 1.2 or 1.6 equiv of TBAF for 5 or 30 min, respectively (Table 2). In both cases the migration proved to be a much faster process compared to that of **2a**. This may be attributed to the lower steric bulk of the benzyl and methyl group compared to the *tert*-butyl group.

Table 2. Deprotection of **2c** and **2d** with TBAF[5]

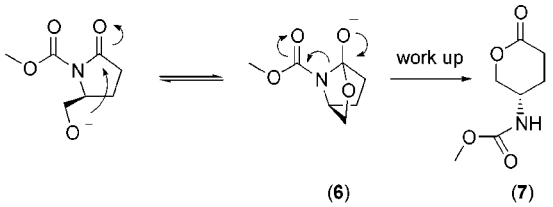
TBAF	*t*	**2c** (R = Cbz)			**2d** (R = MOC)		
(equiv)	(min)	% **2c**	% **3c**	% **4c**	% **2d**	% **3d**	% **4d**
1.6	30	0	0	100	0	0	100
1.2	5	0	0	100	0	0	100

To address the question of why oxycarbonyl migration is favored over rearrangement to the *N*-protected γ-amino lactone **7** (see Scheme 3), a quantum mechanical investigation was carried out.

Applying a THF-solvation model at the B3LYP/6-31+G*

(6) Chult, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371−1448.

Scheme 3. Mechanism Leading to **7**



level to the two tetrahedral intermediates **5** and **6**,[7] an energy difference of 9.4 kJ/mol was obtained in favor of **5** which leads to the observed product **4d** (see Figure 2).

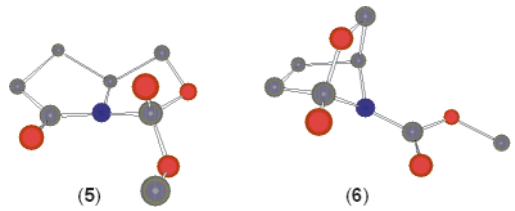


Figure 2. Application of a THF-solvation model at the B3LYP/6-31+G* level to the two intermediates **5** and **6**.[7] An energy difference of 9.4 kJ/mol was obtained in favor of **5**, which leads to the observed product **4d**.

In comparison, when the carbamate group is exchanged for an *N*-sulfonyl group, rearrangement to the γ-lactone is favored.[8] This can be explained on the basis of the low tendency of sulfones to undergo nucleophilic attack.

To circumvent the problem of migration of the oxycarbonyl moiety, the fluoride source must be applied in the presence of a proton source. This would lead to a rapid protonation of the released alkoxide preventing migration. The use of TBAF/AcOH,[9] TBAF/HF,[10] triethylammonium fluoride,[11] and triethylamine trihydrofluoride are all known reagents of which the latter was investigated in our laboratory. Starting from **2a**−**d**, full conversion into **3a**,**c**,**d** was accomplished without any detectable formation of **4a**,**c**,**d**.

In conclusion, we have demonstrated that desilylation of pyroglutaminol **2a**,**b** using TBAF not only provides the expected free hydroxyl functionality (compound **3a**) but also promotes migration of the BOC group giving **4a**. Our findings were confirmed by an X-ray diffraction study, and quantum chemical calculations provided support for mechanistic interpretation of the results. In addition, we have proven that this phenomenon can be extended to the Cbz and MOC groups. We propose that this novel observation could explain why TBAF, in some cases, has been reported not to be a feasible reagent.[2,11,12] For a 4-substituted pyroglutaminol derivative, one group has suggested a rearrangement to give the γ-lactone,[9] but at least in the unsubstituted case investigated here, it is clear that migration of the oxycarbonyl moiety is the favored process. However, in the case of *N*-sulfonyl-protected pyroglutaminols the rearrangement to the γ-lactone **7** is the favored process. As the general method for desilylation of *N*-carbamate pyroglutaminols, we recommend the use of an acidic fluoride source.

Supporting Information Available: X-ray structure determination for compound **4a** and ^{1}H and ^{13}C NMR data for compounds **3a**,**c**,**d** and **4a**,**c**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Calculations were performed in Jaguar 4.0, Schrodinger, Inc., Portland, OR, 2000. Following the Hammond postulate the activation energy of the rate-determining step is expected to correlate well with the energy of the high energy intermediates **5** and **6**. For reference, see: Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334−338.

(8) Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron Lett.* **1996**, *37*, 8173−8174.

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