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Intramolecular epoxide ring opening cyclisation reactions involving guanidines

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ABSTRACT

The cyclisation of N-allyl- and N-homoallylguanidines using DMDO leading to the formation of novel 5- and 6-membered guanidine heterocycles is reported. Several of the products formed displayed weak inhibition of glycosidase enzymes.

1. Introduction

As part of a project directed towards the synthesis of marine natural products, we have previously reported the intramolecular cyclisation of guanidine epoxides[1] and the cyclisation of allyl and homoallyl substituted guanidines using DMDO,[1,2] I_2/K_2CO_3[1–3] and under palladium catalysed conditions.[4] We take this opportunity to report our findings on the oxidative cyclisation reactions in full.

2. Epoxide ring opening using guanidines

Very few examples of epoxide ring opening processes utilising guanidines[5] have been reported and our preliminary investigations focused on the addition of guanidine to the simple epoxide **1**. We treated **1** with guanidine in *t*-BuOH at room temperature for 24 h to effect *N*-alkylation of guanidine, which we presumed to be faster than the epoxide ring opening process. At this point, potassium *t*-butoxide was added to regenerate the free guanidine from its salt, following which the reaction was heated at 60 °C for a further 48 h to affect cyclisation to give the 5-membered guanidine **2** (Scheme 1). In our previous work,[1] we had reported efforts to purify **2** by column chromatography and had succeeded in obtaining product of relatively high purity (>95%) though it was apparent that it was contaminated with what appeared to be polymeric material. We also tried to purify **2** by derivatisation as its *t*-butyldimethylsilyl ether **3**. However this proved difficult as the compound was prone to hydrolysis on chromatography which was thought to be promoted by the anchimeric assistance or the guanidinium group.[6] We were however able to purify **2** by HPLC and on examination of higher field NMR data, it was apparent that significant quantities of a contaminant were present. Indeed re-examination of the crude reaction product indicated a ca 9:1 ratio of **2** and what was though to be the isomeric **4**. Compound **4** gave signals at δ 3.33 (2H, dd, *J* 3.1, 12.3, 2 × CH), 3.45, (2H, dd, *J* 2.7, 12.3 Hz, 2 × CH) and 4.38 (1H, tt, *J* 2.7, 3.1 Hz, CH) ppm and this 6-*endo-tet* isomer **4** could possibly be formed by the attack of the guanidine on the CH_2 of the epoxide

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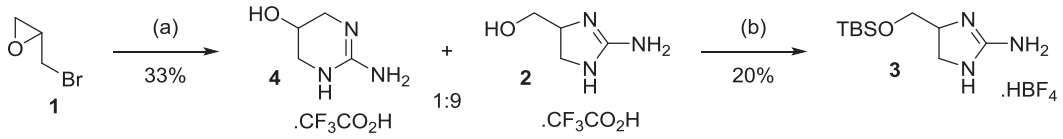


Scheme 1. (a) (i) Guanidine hydrochloride, *t*BuOK, *t*BuOH, then epoxide **1** 16 h, rt. (ii) *t*BuOK, 60 °C, 24 h (iii) CF_3CO_2H, MeOH. (c) (i) 3 equiv. TBSCl, Imid., DMF, 16–24 h (ii) $NaBF_4$ (sat., aq.).

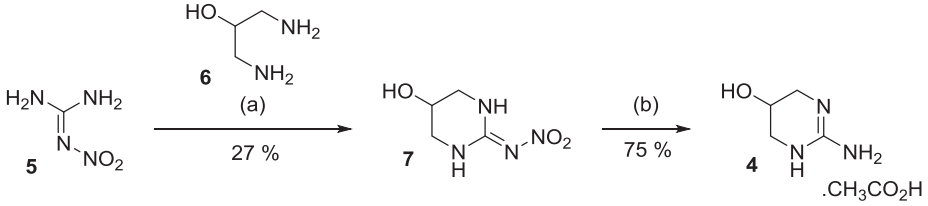
after alkylation or more likely by initial epoxide opening by guanidine followed by the 6-*exo-tet* displacement of bromine.

We wished to prepare **4** independently and thus reacted nitroguanidine **5** with 1,3-diaminopropan-2-ol **6** at 70 °C in water to give 5-hydroxy-2-nitrimino-1,3-diazacyclohexane **7** in 27% yield,[7] which on hydrogenation in aqueous acetic acid gave **4** as its acetate salt in 75% yield (Scheme 2). Spectroscopic data for the synthetic sample of **4** corresponded exactly to the impurity found in the previous reactions.

Because of the problems with this impurity and problems associated with purification of the guanidine salts in these reaction we turned our attention to the reaction of the protected guanidines **8a**[3] and **8b**[3] and their reaction with the epoxidising agent DMDO.[8] We had previously shown[1] that the *N*-allyl-*bis*-Boc-guanidine **8a** reacts with DMDO in acetone at −20 °C to give an intermediate epoxide **9a** as evidenced by signals at δ_H 2.62 (1H, dd, *J* 2.4, 4.2 Hz, CH), 2.80 (1H, dd, *J* 4.2, 4.4 Hz, CH) and 3.14–3.22 (1H, m, CH) ppm. On continued stirring this intermediate was consumed to give, on careful work up and chromatography, a 62% yield of the cyclic product **10a** the structure of which was confirmed by X-ray analysis.[1] On attempted repeat of this reaction it was observed that a second isomeric product was always formed in the reaction and, on isolation of this, X-ray crystallography[2] confirmed the structure of the product as the rearranged product **11a** isolated in 63% yield. A similar migration of a Boc-group was reported in an *N*-Boc-protected 5-membered amide so this result is not suprising.[9] More conveniently, a complete conversion of **10a** into **11a** could be effected if a solution of the crude reaction mixture in dichloromethane was stirred with silica gel overnight or by stirring in methanol containing a small amount (ca. 5%) of water. A similar result was observed with the Z-protected guanidine **8b** which was again treated with an excess of DMDO in acetone at −20 °C and the reaction monitored by proton NMR. Epoxidation was found to occur rapidly as evidenced by signals at δ_H 2.61 (1H, dd, *J* 2.8, 4.5 Hz, CH), 2.80 (1H, dd, *J* 4.4, 4.5 Hz, CH) and 3.16–3.22 (1H, m, CH) ppm for epoxide **9b**, but on continued stirring signals at δ_H 3.45 (1H, t, *J* 5.8 Hz, CH), 3.51 (1H, dd, *J* 5.1, 5.7 Hz, CH), 3.87 (1H, dd, *J* 3.0, 5.5 Hz, CH), 3.92 (1H, dd, *J* 2.8, 5.8 Hz, CH), and 4.03–4.11 (1H, m, CH) ppm appeared which are evident of the structure **10b**. However, after purification on silica gel, a new product was formed in 64% yield, which had a considerably simpler spectrum with signals at δ_H 3.20 (1H, dd, *J* 10.2, 4.0 Hz, CH), 3.45–3.51 (1H, m, CH) and 3.87–3.95 (3H, m, CH, CH_2) ppm and the two guanidine protons at δ_H (7.50–9.60 (2H, br s, 2 × NH) which assigned the structure as **11b**. Again it was possible to effect this rearrangement by stirring the crude reaction product with silica gel in dichloromethane or by stirring in methanol containing a small amount (ca. 5%) of water. Finally, deprotection of **1a** was accomplished by treatment with excess trifluoroacetic acid in dichloromethane for 4 h to give guanidine **2** in 98% yield (Scheme 3).

We were interested in the mechanism of the Boc- and Cbz-group migration and in order to investigate this a 1:1 mixture of **8a** and **8b** was treated with DMDO at −20 °C and stirred at rt for 5 days at which point the formation of a mixture of **10a** and **10b** was formed as indicated by ^{1}H NMR. This mixture was then dissolved in a mixture of methanol and water and stirred overnight at room temperature. Analysis of the product from this reaction by mass spectrometry confirmed the presence of three different ions with *m*/*z* peaks at 316.1867 and 350.1710 Daltons corresponding to the $[M+H]^+$ ions for **11a** and **11b** as well as a mass at 384.1552 which correspond closely to the $[M+H]^+$ ion for **11c**/**11d**. This observation suggest that the migration of the protecting groups is not exclusively intramolecular and some evidence of intermolecular rearrangement is apparent. However, this may be happening in the initial DMDO stage of the process (Scheme 4).

Following this work, we investigated the epoxidation of the dimethylallyl guanidine **8c**[3] and found that on treatment with DMDO an epoxide **12a** was formed after 16 h which gave distinctive signals at δ_H 2.95 (1H, dd, *J* 4.2, 7.4 Hz, CH), 3.24 (1H, ddd, *J* 4.4, 7.4, 14.3 Hz, CH), 3.98 (1H, ddd, *J* 4.2, 6.6, 14.3 Hz CH) ppm for the three methine protons. This epoxide slowly underwent ring opening to give some evidence for the formation of the 5-membered guanidine **13a** but this was transient and the rearranged **14a** was formed after stirring for 7 days. Attempted purification of this material was difficult as the product obtained was a gum which could not be recrystallised and was also prone to decomposition on silica gel. A similar reaction of *bis*-Z protected **8d**[3] gave as a stable product the epoxide **12b** (δ_H 2.87 (1H, dd, *J* 4.1, 7.4 Hz, CH), 3.13 (1H, ddd, *J* 4.7, 7.4, 14.3 Hz, CH) and 3.88 (1H, ddd, *J* 4.1, 6.5, 14.3 Hz, CH) ppm) which on attempted recrystallisation from dichloromethane/petrol deposited a precipitate of the cyclised and rearranged 5-membered guanidine **14b**. Distinctive signals were observed at δ_H 3.30 (1H, dd, *J* 10.3, 6.4 Hz, CH), 3.51 (1H, app t, *J* 10.3 Hz, CH) and 4.12 (1H, dd, *J* 10.3, 6.4 Hz, CH) ppm for the three methyne protons with 2 guanidine NH signals at δ_H 8.19 (1H, br s, NH) and 8.93 (1H, br s, NH) ppm. Conclusive proof of the 5-membered system was give in the carbon spectrum with the CH-N signal at δ_C 61.3 ppm, whilst the quaternary C-O appeared at δ_C 84.3 ppm.¶ The slow rearrangement



Scheme 2. (a) Water, 70 °C, 2 h (b) (a) H_2, 5% Pd/C, 15% aqueous acetic acid 72 h.