The Influence of Substituents on the Hydroxyl-Bearing Carbon in the Aza-Payne Rearrangement of Aziridinemethanols

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Abstract: A new series of α,α-disubstituted aziridinemethanols have been synthesized and their aza-Payne rearrangement reactions were studied. The results show that α,α-disubstituted aziridinemethanols with electron-withdrawing groups accelerate the aza-Payne rearrangement than those with electron-donating groups. All of the rearrangements proceeded through an inversion of configuration at the C-2 carbon.

Keywords: Aziridinemethanols, aza-Payne rearrangement, inversion of configuration, electron-withdrawing groups, electron-donating groups.

The aza-Payne rearrangement of aziridinemethanols [1] has emerged as an important synthetic endeavor for the synthesis of bioactive compounds [2-4] owing, among other things, to the important role played by aziridinemethanols as chiral auxiliaries [5,6] and building blocks in the preparation of biologically active compounds [7-13] and their biological activities [14-20].

Aziridinemethanols having a primary or secondary hydroxymethyl group at the C-2 position afford high yields of rearranged products. On the other hand, aziridinemethanols possessing a tertiary hydroxyl group rearrange slowly in THF in the presence of KH to give solely the epoxy sulfonamide [21]. The mechanism of which is intramolecular SN2, with an inversion of configuration at the C-2 carbon [22]. Obviously the substituents on the hydroxy-bearing carbon have great influences on the aza-Payne rearrangement of aziridine methanols. Our previous studies [23, 24] have primarily reported such electronic effects. However, further studies are still necessary to validate the correlations between the efficiency of the rearrangement and the substituents effects of the aromatic groups. So we designed and synthesized a series of novel α,α-disubstituted aziridinemethanols to extend the expected influence of substituents on the hydroxyl-bearing carbon.

Compounds **3** and **4** were synthesized starting from the methyl N-tritylaziridinecarboxylic acid esters **1** and **2**, which were prepared from L-serine and L-threonine, respectively [25]. The N-Ts and N-Boc aziridinemethanols **5**, **6**, **9** and **10** were synthesized from **3** and **4** in high yields. The aza-Payne rearrangement reactions of **5**, **6**, **9** and **10** to epoxy amides **7**, **8**, **11**, **12** were shown in Scheme **1** and the results were summarized in Table **1**.

Compound **4a** substituted on the hydroxyl-bearing carbon by 4-methoxyphenyl groups did not provide N-Ts and N-Boc protected products, the N-tosylation was inhibited by an O-tosyl side reaction. A possible explanation may be that the electron density of the p-methoxy phenyl groups favored formation of the O-tosyl. However, compound **4b** substituted with 3-methoxyphenyl groups was successfully acylated. The other derivatives of compounds **3** and **4** reacted smoothly.

Except for compounds **10c** and **10d**, all aziridines protected by N-Ts and N-Boc afforded the corresponding rearranged products in reasonable isolated yields. N-Ts aziridinemethanols having inductive electron-withdrawing groups (3-methoxyphenyl group, 4-fluorophenyl group, 3-fluorophenyl group, 4-trifluoromethylphenyl group, 3-trifluoromethylphenyl group) substituted on methanol reacted equally well to yield epoxy sulfonamides in high isolated yields (>95%) within 1 h, whereas the electron-releasing group (4-methoxy phenyl group) substituted N-Ts aziridinemethanols **5a** rearranged to epoxy sulfonamide in a high yield (97%) in 24 h. The same behavior was observed in the N-Boc aziridinemethanol (**9a-h**, **10b**, **10e-h**) (**10c** and **10d** didn't afford the rearrangement products even with NaH in THF/HMPA (10:1) [24]), although they reacted distinctly more slowly compared with the N-Ts aziridinemethanols under the same conditions (0.28mol/L NaOH in *t*-BuOH/H_2O/THF (4:5:1) rt) [21, 23]. Compound **9a** afforded only a 30% yield. Compounds with 3-trifluoromethylphenyl group have the greatest tendency to rearrange than the others.

Compounds **5** rearranged faster than compounds **6**. The methyl group on the C-3 position of aziridine has a positive effect on the rearrangement. It can be concluded that the mechanism responsible for the methyl group increases the strain of the aziridine ring, therefore the ring is opened easily in the alkali condition. Disubstitution with electron-withdrawing groups on hydroxyl-bearing carbon is more favourable to the rate of aza-Payne rearrangement than those with electron-releasing groups. It is believed that the mechanism responsible for the stability of the oxa anion [22] is proposed for the conjugative effect of phenyl group and the electron-withdrawing effect of the substituents on the phenyl group. The activating groups contribute to the

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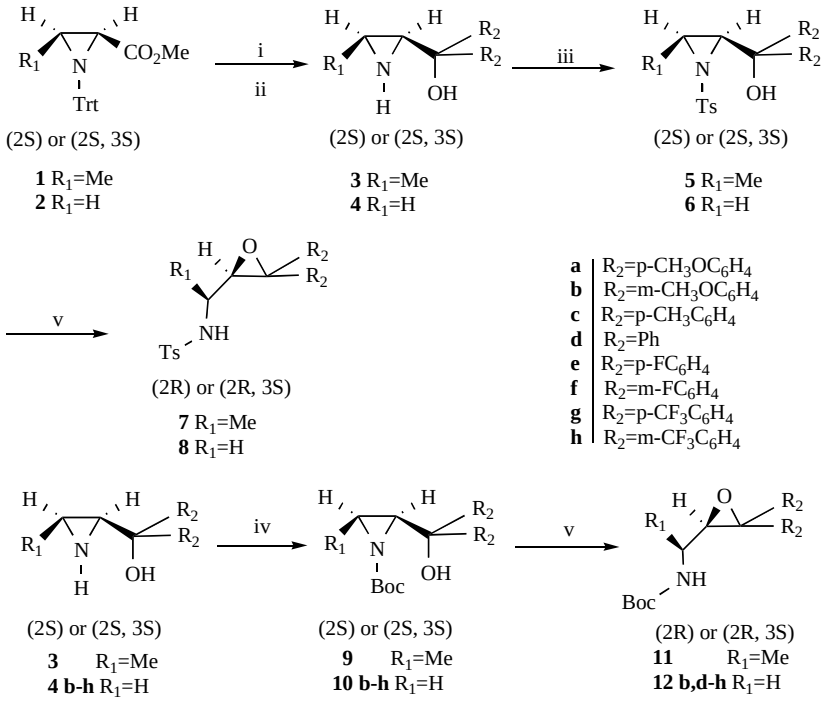

Reagents and conditions: i) R_2Br, Mg, THF; ii) $MeOH/H_2O/H_2SO4$(60:8:3); iii) TsCl (1eq.), Py; iv)$(Boc)_2O$ NEt_3, THF; v) 0.28mol/L NaOH in $tBuOH/H_2O$/THF(4:5:1) rt.

Scheme 1. The aza-Payne rearrangement of α,α-disubstituted aziridinemethanols.

Table 1. Aza-Payne Rearrangement of *α,α*-Disubstituted Aziridinemethanol to Epoxy Amide

Entry	Starting Material	NaOH[a]		Product
		Reaction Time	Yield(%)[b]	
1	**5a**	24h	97	**7a**
2	**5b**	1h	98	**7b**
3	**5c**	2h	98	**7c**
4	**5d**	1h	96	**7d**
5	**5e**	30min	98	**7e**
6	**5f**	30min	98	**7f**
7	**5g**	30min	97	**7g**
8	**5h**	5min	98	**7h**
9	**6b**	<1h	96	**8b**
10	**6c**	2h	97	**8c**
11	**6d**	1h	95	**8d**
12	**6e**	50min	98	**8e**
13	**6f**	50min	97	**8f**
14	**6g**	50min	99	**8g**
15	**6h**	20min	97	**8h**
16	**9a**	24h	30[c]	**11a**
17	**9b**	11h	98	**11b**
18	**9c**	24h	56[c]	**11c**
19	**9d**	24h	70[c]	**11d**
20	**9e**	8h	97	**11e**

(Table 1). Contd…..

Entry	Starting Material	NaOH[a]		Product
		Reaction Time	Yield(%)[b]	
21	**9f**	6h	98	**11f**
22	**9g**	2h	99	**11g**
23	**9h**	2h	97	**11h**
24	**10b**	24h	92	**12b**
25	**10c**	24h	—[d]	—[d]
26	**10d**	24h	—[d]	—[d]
27	**10e**	12h	93	**12e**
28	**10f**	12h	95	**12f**
29	**10g**	<3h	98	**12g**
30	**10h**	2h	97	**12h**

[a]solvent: *t*-BuOH/H_2O/THF (4:5:1), rt.; [b]isolated yield; [c]detected by HPLC; [d]no reaction.

generation of oxygen anion thereby the intramolecular attack on C-2 carbon is more effective.

The stereochemical purity of esters **1** and **2** was determined by HPLC analysis using Diacel Chiracel AD-H column (eluent: hexane/ethanol = 100:5), the ees were more than 99.6%. We obtained some aza-Payne rearrangement products prepared from D-serine and D-*allo*-threonine. Contrasted with them, the ees of all rearrangement products were determined, all were almost 100%.

In conclusion, aziridinemethanols α,α-disubstituted with electron-withdrawing groups accelerate the aza-Payne rearrangement than those α,α-disubstituted with electron-releasing groups under the same alkali and solvent conditions. The effective aza-Payne rearrangement of N-Ts and N-Boc aziridinemethanols introduces a potential synthesis method for functionalized amino alcohols. Moreover, we found that all of α,α-disubstituted aziridinemethanols rearranged to the stereochemically pure epoxyamides. It can be deduced that the mechanism is intramolecular S_N2, proceeding through an inversion of configuration at the C-2 carbon. Besides, their stereochemistry structures have also been confirmed [25].

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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