Unexpected Ring-opening Reaction of Aziridine with Acetic Anhydride in DMF

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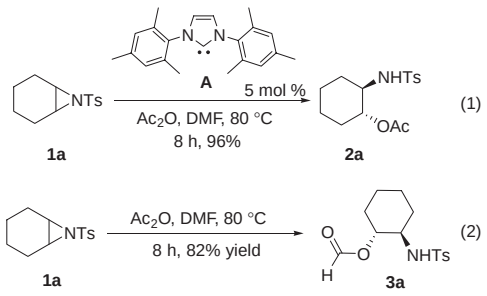
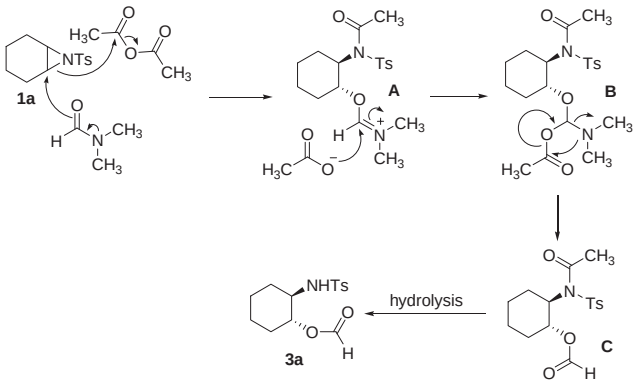
Ring-opening reactions of aziridines with acetic anhydride in DMF afforded the unexpected β-amino formate in moderate to good yields. The possible mechanism is also proposed.

Ring-opening reactions of aziridines with nucleophiles provide a useful protocol in organic synthesis, and many reagents have recently been developed to realize the opening of the aziridine ring.[1] Among these, acid anhydrides as nucleophiles are also applied in the ring-opening reactions of aziridines.[2] Recently, in the course of our ongoing studies on novel methods for the aziridine transformations,[2c,3] we found that the readily available *N*-heterocyclic carbene (NHC) could be served as catalyst for ring-opening reactions of aziridines with acid anhydrides (for example, eq 1 in Scheme 1).[2c] To our surprise, the further studies showed that reaction of aziridine **1a** with acetic anhydride also occurred without *N*-heterocyclic carbene catalyst in DMF. However, from spectral characterization, the product found was not the expected one **2a**. Structure elucidation by ^{1}H, ^{13}C NMR, and mass spectroscopy revealed this compound to be *trans*-2-(4-methylphenylsulfonamido)cyclohexyl formate (**3a**) (eq 2 in Scheme 1). The anti-stereochemistry of the product **3a** was confirmed by the coupling constant for two cyclic methine protons at the trans positions.

This interesting observation prompted us to investigate the reaction process. When other solvents (toluene, THF, MeCN, and CH_2Cl_2) were applied in the reaction of aziridine **1a** with acetic anhydride instead of DMF, no reaction was taken place and only starting material was recovered. And trace amount of product **3a** was detected after addition of 2 equiv. of DMF in the above reactions. It seemed that DMF was crucial in this reaction. As regards the role of acetic anhydride and DMF in the ring-opening reaction of aziridine **1a**, although the mechanism is not clear since there is no supporting evidence at present. We reasoned that DMF may act as a nucleophile to attack the aziridine ring firstly. The resulted nitrogen anion reacted with acetic anhydride to generate an iminium ion **A**. After intramolecular rearrangement and hydrolysis of the amide acetal **B**, the final compound **3a** could be produced. (Scheme 2)



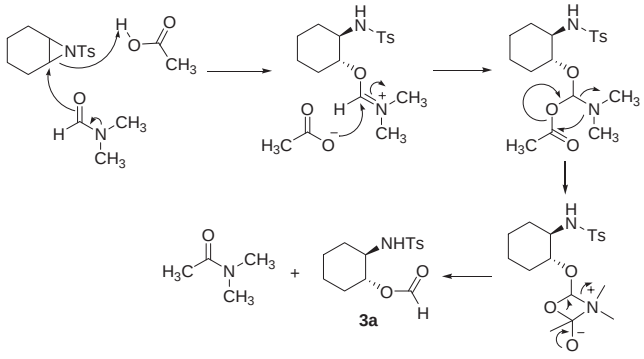
Scheme 1.



Scheme 2.

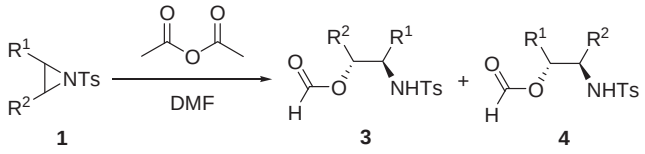
On the other hand, other pathways could not be excluded. For example, the acetic acid, which may be generated from the adventitious water with acetic anhydride in the reaction system, would also promote this unexpected transformation (Scheme 3). To test this idea, acetic acid was employed instead of acetic anhydride in the reaction of aziridine **1a** in DMF. However, no desired product **3a** was generated and only compound **2a** was isolated. In this reaction, as previous report,[3c,4] DMF may act as a Lewis base to activate nucleophile, thus promote the acetic acid to attack the aziridine ring. From this observation, it looks not like the acid-promoted reaction to afford compound **3a**, since the acid was a good nucleophile under this reaction conditions.

To demonstrate the generality of this method, a variety of aziridines have thus been examined for the ring-opening reactions, and the results are summarized in Table 1. As shown in Table 1, this condition has proved to be general and useful for ring openings of a range of aziridines **1**. High regioselectivity was obtained for this transformation. In the case of unsymmetrically substituted aziridines **1e**, **1f**, and **1g**, completely regioselectivity with the attack of nucleophile on the less substituted

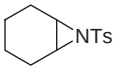
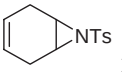
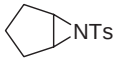
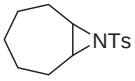
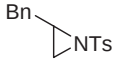
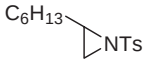
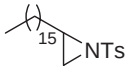
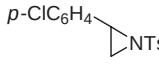


Scheme 3.

Table 1. Ring-opening reactions of aziridines **1** with acetic anhydride in DMF[5]

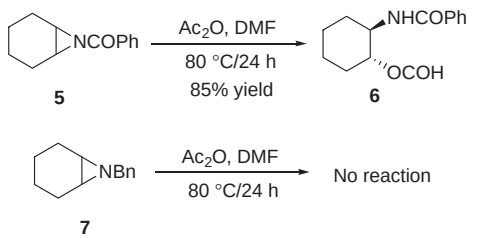


1 **3** **4**

Entry	Aziridine	Temp/°C, Time/h	Yield/%[a]
1	 **1a**	80, 8	92 (**3a**)
2	 **1b**	110, 12	82 (**3b**)
3	 **1c**	80, 24	54 (**3c**)
4	 **1d**	110, 48	60 (**3d**)
5	 **1e**	110, 24	86 (**3e**)
6	 **1f**	110, 10	90 (**3f**)
7	 **1g**	110, 16	85 (**3g**)
8	 **1h**	110, 10	61 (**3h**:**4h** = 5:2)[b]
9	 **1i**	80, 24	87 (**3i**:**4i** = 2:3)[b]

[a]Isolated yield based on aziridine **1**. [b]Ratio was determined by ^{1}H NMR.

aziridine carbon was observed. For the substrates **1h** and **1i**, it is reasonable that the regioselectivity is not as specific as that of other substrates due to electronic effects. The products resulting from the regioselective attack of the nucleophile at the benzylic position of aziridines **1h** and **1i**, were also generated. Moreover, we found that electron-withdrawing group attached on the nitrogen of aziridine was crucial in this reaction. No reaction occurred when non-activated aziridine was employed as substrate. For example, reaction of *N*-benzoylcyclohexanoaziridine (**5**) with acetic anhydride also proceeded smoothly in DMF to afford the desired product **6** in 85% yield. However, when *N*-benzylcyclohexanoaziridine (**7**) was employed as substrate in the reaction, no product was detected. (Scheme 4) This observation is similar to others as previous reports,[1] since the reactivity is different between activated aziridines and non-activated aziridines.



Scheme 4.

In conclusion, we have described an unexpected ring-opening reaction of aziridine with acetic anhydride in DMF, which provides an efficient route for the synthesis of β-amino formate. Efforts to understand the reaction mechanism and explore synthetic utilities of the reaction reported here are in progress in our laboratory.

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5 General procedure for the reaction of aziridine with acetic anhydride in DMF: acetic anhydride (1.0 equiv.) was added to a solution of aziridine **1** (0.25 mmol) in DMF (2.0 mL). The reaction mixture was stirred at 80 or 110 °C for a period of time indicated in Table 1. After the reaction was completed monitored by TLC, the mixture was cooled and washed with water and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by chromatography column on silica gel afforded the corresponding product. Data of selected example: *trans*-2-(4-methylphenylsulfonamido)cyclohexyl formate (**3a**), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15–1.45 (m, 4H), 1.60–1.75 (m, 2H), 1.90–2.05 (m, 2H), 2.42 (s, 3H), 3.20–3.30 (m, 1H), 4.65–4.75 (m, 1H), 5.22 (d, $J = 8.3$ Hz, 1H), 7.29 (d, $J = 8.3$ Hz, 2H), 7.58 (s, 1H), 7.75 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 23.5, 24.1, 30.8, 33.3, 56.5, 74.0, 127.0, 129.5, 138.6, 143.2, 160.8. MS (m/z): 297 (M^+). HRMS: Anal. Calcd for $C_{14}H_{19}NO_4S$, 297.1035. Found, 297.1031.

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