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N-Heterocyclic Carbene: An Efficient Catalyst for the Ring-Opening Reaction of Aziridine with Acid Anhydride

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A N-heterocyclic carbene serves as an efficient catalyst for the regioselective ring-opening reactions of aziridines in the presence of acid anhydrides to afford the desired products in good to excellent yields.

N-Heterocyclic carbenes (NHCs) have received considerable attention in recent years. They have been successfully employed as ligands in a wide range of transition-metal catalyzed processes,[1] as well as substrates in multi-component reactions.[2] They have also served as versatile organocatalysts in various organic transformations,[3] such as nucleophilic substitutions,[4] umpolung reactions,[5] addition reaction,[6] transesterification reactions,[7] and polymerization.[8] In the course of our studies on novel methods for aziridine transformations, we were attracted to the use of readily available NHCs as catalysts for ring-opening reactions of aziridines.[9]

It is well-known that aziridine is a versatile building block for the syntheses of many nitrogen-containing biologically active molecules.[10] The reactivity of aziridines toward ring opening and expansion is dependent upon their extremely strained ring structure. Among the procedures available for the ring opening of aziridines, the nucleophilic ring-opening reaction is one of the major routes used to access highly functionalized compounds.[10] Ring-opening reactions of aziridines have been developed with the use of acid anhydrides as the nucleophiles.[11] In 2003, tributylphosphane[11b] was developed as a catalyst for the ring-opening reactions of aziridines with acetic anhydride in toluene heated at reflux. A high temperature (>110 °C) and a prolonged reaction time were necessary in the reaction process. Subsequently, $Sc(OTf)_3$[11a] was reported to be effective in the reactions of aziridines with acid anhydrides. However, poor regioselectivity was observed in the reactions. Inspired by the recent advances of N-heterocyclic carbene catalysts, we envisioned that we could exploit the strong σ-donating property of NHCs to effect reactions between aziridines and acid anhydrides. Herein, we would like to disclose our preliminary results for this transformation.

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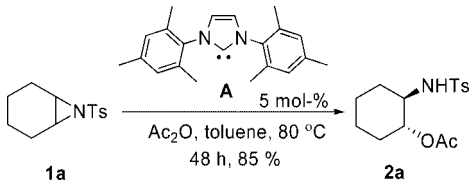
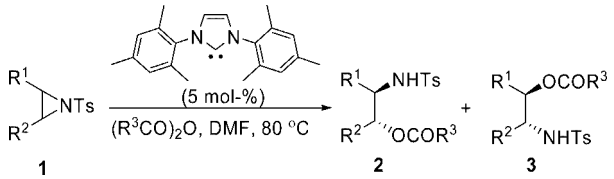
Our studies commenced with the ring-opening reaction of aziridine **1a** with acetic anhydride catalyzed by NHC **A** (5 mol-%) in toluene heated at 80 °C. (Scheme 1) To our delight, we observed the formation of desired product **2a**. An isolated yield of 85% was obtained after 48 h. The *anti* stereochemistry of product **2a** was confirmed by the coupling constant of the two cyclic methine hydrogens at the *trans* positions. Further studies showed DMF was the best choice of solvent among the solvents screened (DMF, 8 h, 96%; toluene, 48 h, 85%; MeCN, 12 h, trace; DMSO, 12 h, complicated). The reaction was retarded when the temperature was decreased. To demonstrate the generality of this method, we next investigated the scope of this reaction under the optimized reaction conditions (Scheme 2, NHC **A**: 5 mol-%, DMF, 80 °C) and the results are summarized in Table 1. These conditions have proven to be useful for the ring-opening reactions of a range of aziridines **1**. In all the cases, reactions were very clean and the desired products were afforded in good to excellent yields. In contrast to pre-



Scheme 1. Ring-opening reaction of aziridine **1a** with acetic anhydride catalyzed by N-heterocyclic carbene **A** (5 mol-%) in toluene.

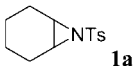
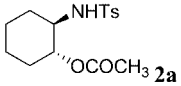
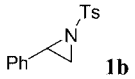
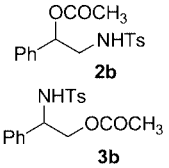
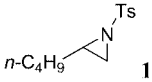
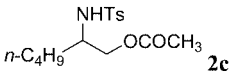
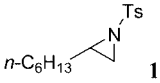
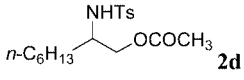
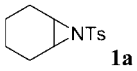
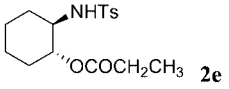
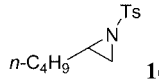
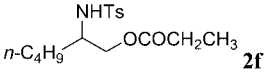
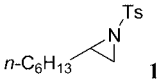
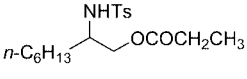
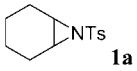
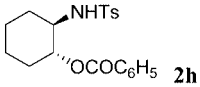
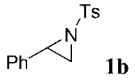
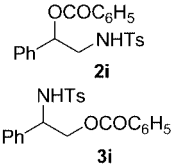
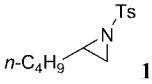
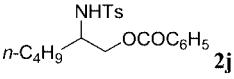
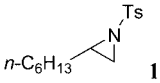
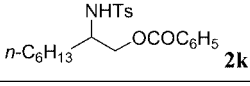


Scheme 2. Ring-opening reactions of aziridines with acid anhydrides catalyzed by N-heterocyclic carbene (5 mol-%).

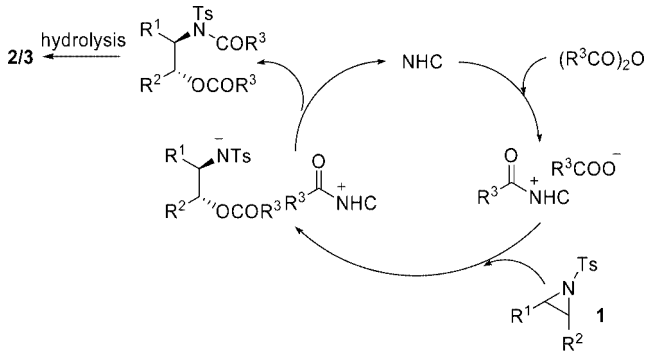
vious reports,[11] high regioselectivity was obtained for this transformation. In the case of unsymmetrically substituted aziridines **1c** and **1d**, complete regioselective attack of the nucleophile on the less substituted aziridine carbon was observed. For substrate **1b**, it is reasonable that the regioselectivity is not as specific as that of other substrates due to electronic effects. The product resulting from the regioselective attack of the nucleophile at the benzylic position of aziridine **1b**, was obtained as the major product. We also found that an electron-withdrawing group attached to the nitrogen atom of the aziridine was crucial for this reaction. No reaction occurred when nonactivated *N*-benzylcyclohexylaziridine was employed as the substrate (result not shown in Table 1).

What is the role of the N-heterocyclic carbene in this reaction? No change in the starting materials was observed when aziridine **1a** and the N-heterocyclic carbene were combined under the standard conditions for 10 h. According to this experimental fact, we could exclude the possibility that the N-heterocyclic carbene served as a trigger for this reaction.[9d] According to literature precedent,[11b] a possible mechanism could be proposed where the N-heterocyclic carbene acts as a nucleophilic catalyst to initiate the reaction (Scheme 3).

Table 1. Ring-opening reactions of aziridines with acid anhydrides catalyzed by N-heterocyclic carbene (5 mol-%).

Entry	Aziridine **1**	$(R^3CO)_2O$	Product	Time [h]	Yield [%][a]
1	 **1a**	$(CH_3CO)_2O$	 **2a**	8	96
2	 **1b**	$(CH_3CO)_2O$	 **2b** / **3b** **2b/3b** (9:1)[b]	8	70
3	 **1c**	$(CH_3CO)_2O$	 **2c**	12	94
4	 **1d**	$(CH_3CO)_2O$	 **2d**	8	80
5	 **1a**	$(CH_3CH_2CO)_2O$	 **2e**	12	96
6	 **1c**	$(CH_3CH_2CO)_2O$	 **2f**	6	81
7	 **1d**	$(CH_3CH_2CO)_2O$	 **2g**	12	80
8	 **1a**	$(C_6H_5CO)_2O$	 **2h**	1.5	91
9	 **1b**	$(C_6H_5CO)_2O$	 **2i** / **3i** **2i/3i** (10:1)[b]	3	70
10	 **1c**	$(C_6H_5CO)_2O$	 **2j**	3	99
11	 **1d**	$(C_6H_5CO)_2O$	 **2k**	3	98

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



Scheme 3. Possible mechanism for the ring-opening reactions of aziridines with acid anhydrides catalyzed by N-heterocyclic carbene.

In conclusion, we have developed an efficient and convenient method for the ring-opening reactions of aziridines with acid anhydrides that are catalyzed by N-heterocyclic carbene. The nucleophilic N-heterocyclic carbene shows high efficiency in this reaction, which broadens its utility in organic synthesis. Efforts to extend NHC catalysis to other organic transformations, including chiral N-heterocyclic carbene-catalyzed desymmetrization of *meso*-aziridines with acid anhydrides, are ongoing.

Experimental Section

General Procedure for the Reactions of Aziridines 1 with Acid Anhydride: Acid anhydride (1.2 equiv.) was added to a solution of aziridine **1** (0.25 mmol) and NHC **A** (5 mol-%) in DMF (2.0 mL). The reaction mixture was stirred at 80 °C for a period of time indicated in Table 1. After the reaction was complete as monitored by TLC, the mixture was washed with saturated NH_4Cl and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the corresponding product. Selected example: *trans*-2-(4-methylphenylsulfonamido)cyclohexyl acetate (**2a**).[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.40 (m, 4 H), 1.61–1.71 (m, 2 H), 1.76 (s, 3 H), 1.86–1.98 (m, 1 H), 1.99–2.15 (m, 1 H), 2.42 (s, 3 H), 3.15–3.29 (m, 1 H), 4.51–4.61 (dt, J = 12.0, 4.0 Hz, 1 H), 4.86 (d, J = 8.0 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.74 (d, J = 8.0 Hz, 2 H) ppm.

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