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KOH-catalyzed regioselective ring openings of *N*-tosylaziridines with malonates in acetone

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ABSTRACT

A simple and efficient method has been developed which describes KOH-oriented catalytic regioselective ring-opening reactions of various *N*-tosylaziridines with malonates. In the presence of 20 mol% KOH, most *N*-tosylaziridines can smoothly react with malonates to give the corresponding products in good to excellent yields (up to 99%) and with good to excellent regioselectivity under mild experimental conditions.

1. Introduction

γ-Amino acids are key structural motifs and widespread subunits prevalent in many biologically active compounds, such as clinically used neurotransmission modulators [1–3]. Their synthetic utility as well as interesting biological activities has led many researchers to develop more interesting and efficient routes toward their transformation [4–11]. In recent years, some attractive strategies for the stereoselective synthesis of γ-amino acids have been gradually reported. Among these routes, the methods *via* stereoselective and enantioselective ring openings of *meso*-aziridines with enolates are known as one of the most efficient strategies and provide straightforward access to γ-amino acids [12–16]. Several reports and promoters such as inorganic base-directed ring-opening reactions of aziridines with enolates as a stoichiometric amount of promoter (See Scheme 1(a) and (b)) [11–14], have been observed for the ring openings of aziridines with malonate, in which a plenty of inorganic base and lower temperature was needed and necessary that restrict their development. Up to now, however, inorganic base-catalyzed ring-opening reactions of *N*-tosylaziridines under mild conditions are still not observed (See Scheme 1(c)). Herein, we wish to describe KOH-catalyzed regioselective ring-opening reactions of various *N*-tosylaziridines **1** with malonates **2** as an efficient catalyst in acetone for the preparation of γ-amino acids precursor and the corresponding compounds.

2. Experimental

^{1}H NMR spectra were taken with a Bruker AVANCE III 600 MHz NMR spectrometers. The chemical shifts are reported in ppm downfield to the $CDCl_3$ resonance (δ = 7.24). Spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration, and assignment. ^{13}C NMR data were collected at 150 MHz with complete proton decoupling. The chemical shifts are reported in ppm downfield to the central $CDCl_3$ resonance (δ = 77.23). Coupling constants in ^{1}H NMR spectra are given in Hz. High-resolution mass spectra were performed on a micrOTOF-Q II instrument with an ESI source. Melting points were measured with a RD-II melting point apparatus and are uncorrected. Unless otherwise noted, Reagents obtained from commercial sources were used without further purification. All solvents were purchased from commercial sources and used with further purification. Deuterated solvents were purchased from aladdin. Column chromatography was performed on silica gel (200–300 mesh). All yields were referred to isolated yields (average of two runs) of compounds.

Typical procedure for the ring-opening reactions. The mixture of diethyl malonate **2a** (304 μL, 2 mmol, 10 equiv.) and the powdered KOH (2.3 mg, 20 mol%) in acetone (1.0 mL) was stirred in a test tube under air atmosphere at 35 °C for 0.5 h. Subsequently, a solution of *N*-tosylaziridine **1** (0.2 mmol) in acetone (0.5 mL) was added, and the reaction mixture was stirred until *N*-tosylaziridine **1**

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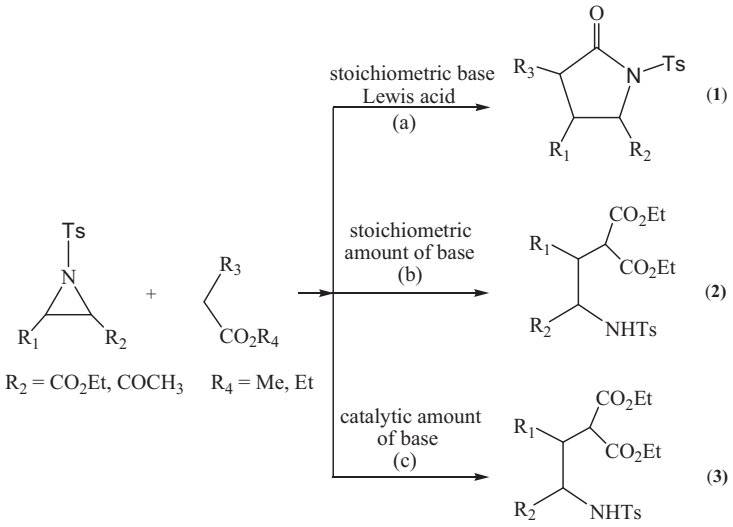


Scheme 1. Inorganic base-promoted ring openings of *N*-tosylaziridines.

was consumed fully as identified by TLC. The residue was then purified by column chromatography on silica gel with the mixture solvent of petroleum ether and ethyl acetate to afford the desired product.

3. Results and discussion

Our investigation began with the ring-opening reaction of *N*-tosylcyclohexylaziridine **1a** with diethyl malonate **2a** in the presence of 10 mol% Cs_2CO_3 as the catalyst. The initial studies were focused on finding the optimal solvent and catalyst. A series of solvents were tested under air atmosphere at 35 °C and the results are listed in Table 1. The reactivity was deeply dependent on the solvent type. When this reaction was performed in CH_2Cl_2 and DMSO, no corresponding product was attained (Table 1, entries 1 and 2). THF and dioxane afforded the product with the lower yields (Table 1, entries 3 and 4). CH_3CN and DMF gave the same yield of 44% (Table 1, entries 5 and 6). However, it was noteworthy that the screening of solvents showed that acetone exhibited the best performance and a 46% yield was obtained (Table 1, entry 7).

The catalyst was also revealed to be an important parameter for obtaining higher yield. Subsequently, a series of bases were explored as catalysts. When Cs_2CO_3 was used, 46% yield was obtained (Table 1, entry 7). In the case of other weak bases such as $NaHCO_3$ and CsF, worse results were observed (Table 1, entries 8 and 9). Although some strong bases such as NaH, LiOH and NaOH provided lower yields (Table 1, entries 10–12), *t*-BuOK and CsOH could give moderate yields (Table 1, entries 13 and 14). Noted that KOH was found to be the most promising catalyst with 66% isolated yield (Table 1, entry 15).

To further improve the yield, the effects of catalyst loading, solvent dosage, reaction temperature and the amount of diethyl malonate were examined. Unlike the solvent and catalyst which exhibited a dramatic effect in this reaction, the use of different catalyst loading, different solvent dosage, and different reaction temperature indicated no or little effects on the reaction yield and the results are listed in Table 2. Considering operational stability and the yield comprehensively, 20 mol% KOH was used (Table 2, entry 3 *vs.* 1 and 2) and the solvent dosage was chosen as 1.5 mL (Table 2, entry 5 *vs.* 3 and 6). At last, 35 °C was utilized as reaction temperature (Table 2, entry 5 *vs.* 7 and 8).

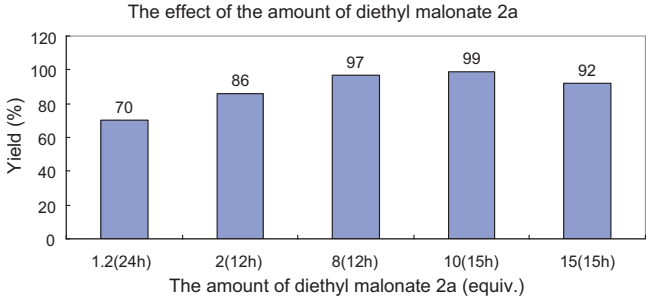
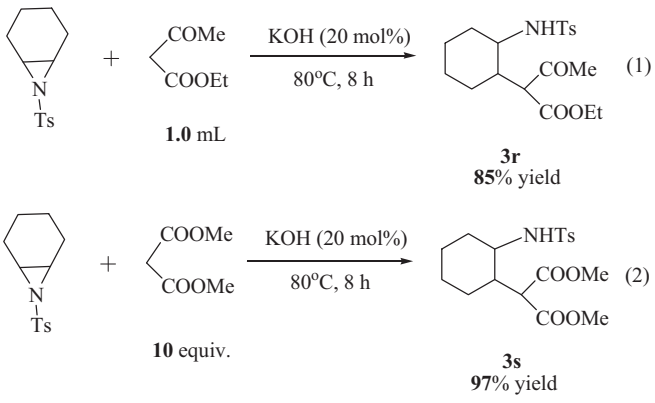


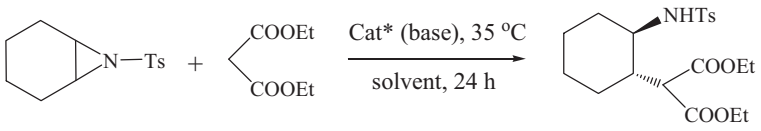
Fig. 1. The effect of the amount of diethyl malonate **2a** on the ring-opening reaction (reaction conditions: *N*-tosylcyclohexylaziridine **1a** (50 mg, 0.2 mmol), KOH (2.3 mg, 0.04 mmol, 20 mol%) and acetone (1.0 mL) with specified conditions under air atmosphere at 35 °C).

However, the amount of diethyl malonate evidently affected the yield. There was a tendency that higher amount resulted in higher yield (see Fig. 1). The yield reached to the highest value (99%) when 10 equiv. of diethyl malonate was adopted. Unfortunately, 15 equiv. of diethyl malonate resulted in somewhat lower yield. In summary, extensive screening showed that the optimized reaction conditions were 0.2 mmol *N*-tosylaziridine and 10 equiv. of diethyl malonate in the presence of 20 mol% KOH under air atmosphere in 1.5 mL acetone at 35 °C.



Scheme 2. Application of the ring opening.

Table 1
Screening of solvents and catalysts for the ring-opening reaction of *N*-tosylcyclohexylaziridine **1a** with diethyl malonate **2a**.[a]



1a **2a** **3a**

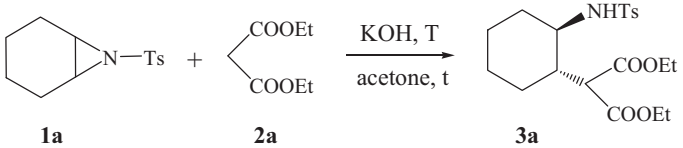
Entry	Solvent	Catalyst	Yield[b] [%]
1	CH_2Cl_2	Cs_2CO_3	Trace
2	DMSO	Cs_2CO_3	N.D.
3	THF	Cs_2CO_3	16
4	Dioxane	Cs_2CO_3	22
5	CH_3CN	Cs_2CO_3	44
6	DMF	Cs_2CO_3	44
7	Acetone	Cs_2CO_3	46
8	Acetone	$NaHCO_3$	N.D.
9	Acetone	CsF	9
10	Acetone	NaH	29
11	Acetone	LiOH	31
12	Acetone	NaOH	28
13	Acetone	*t*-BuOK	51
14	Acetone	CsOH	57
15	Acetone	KOH	66

N.D., not detected.
[a] Unless otherwise noted, all reactions were carried out with *N*-tosylcyclohexylaziridine **1a** (50 mg, 0.2 mmol), diethyl malonate **2a** (36 μL, 0.24 mmol, 1.2 equiv.), catalyst (base, 0.02 mmol, 10 mol%) and solvent (1.0 mL) under air atmosphere at 35 °C for 24 h.
[b] Isolated yield.

Under the optimized experimental conditions, the results of an examination of the scope of the ring-opening reactions of a series of *N*-tosylaziridines with diethyl malonate are presented in Table 3. With regard to most aliphatic *N*-tosylaziridines, good to excellent yields and high regioselectivity could be obtained (Table 3, entries 1–4). In terms of aromatic *N*-tosylaziridines, the electronic properties of the substituents on the aromatic ring of *N*-tosylaziridines had an obvious influence on the yield. *N*-tosylaziridines bearing electron-donating groups supplied better results than those with electron-withdrawing groups (Table 3, entry 6 *vs.* 8 and entry 7 *vs.* 9). It was noteworthy that steric hindrance played an important role on the yield which *para*-substituted *N*-tosylaziridines afforded the corresponding products with higher yields than *ortho*- and *meta*-substituted *N*-tosylaziridines (Table 3, entries 10, 12 and 13 *vs.* 6–9 and 11). At the same time, good to high regioselectivity were attained about them. Unfortunately, the *meta*-substituted *N*-tosylaziridine with nitro group (—NO_2) gave bad yield (Table 3, entry 16). In addition, aromatic *N*-tosylaziridines with condensed-ring were also found to be suitable substrates (Table 3, entries 14 and 15). Heteroaliphatic *N*-tosylazirdines also provided good yield and regioselectivity (Table 3, entry 17).

Furthermore, we explored the ring openings of *N*-tosylcyclohexylaziridine **1a** with ethyl acetoacetate and dimethyl malonate for better understanding the generality of this method in the presence of KOH under the optimum reaction conditions (see Scheme 2). As for ethyl acetoacetate, 85% yield was obtained in 1.0 mL of ethyl acetoacetate at 80 °C for 8 h (Scheme 2(1)). About dimethyl malonate, the corresponding desired ring-opening product **3s** could be provided in 97% yield (Scheme 2(2)).

Table 2
Optimization of the other reaction conditions for the ring-opening reaction of *N*-tosylcyclohexylaziridine **1a** with diethyl malonate **2a**.[a]

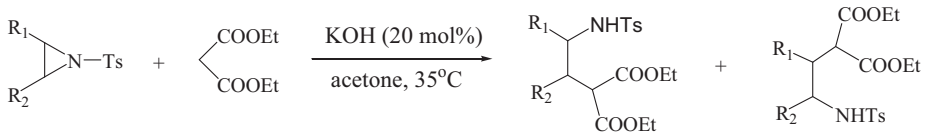


1a **2a** **3a**

Entry	Catalyst loading [mol%]	Solvent dosage[mL]	*T* [°C]	Yield[b] [%]
1	5	1.0	35	52
2	10	1.0	35	66
3	20	1.0	35	67
4	30	1.0	35	35
5	20	1.5	35	70
6	20	2.0	35	68
7	20	1.5	25	66
8	20	1.5	45	67

[a] Unless otherwise noted, all reactions were carried out with *N*-tosylcyclohexylaziridine **1a** (50 mg, 0.2 mmol) and diethyl malonate **2a** (36 μL, 0.24 mmol, 1.2 equiv.) under specified conditions for 24 h.
[b] Isolated yield.

Table 3
Substrate scope of the ring-opening reactions of *N*-tosylaziridine **1** with diethyl malonate **2a**.[a]



1 **2a** **3** **4**

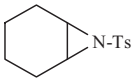
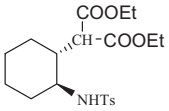
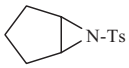
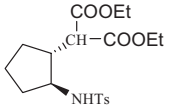
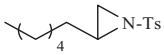
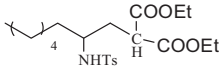
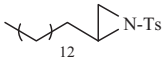
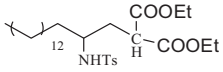
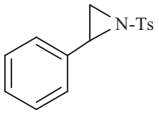
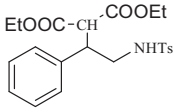
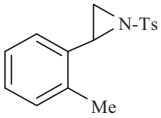
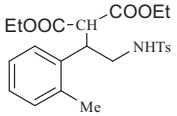
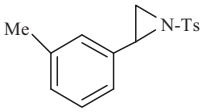
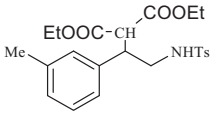
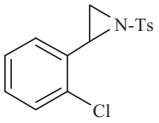
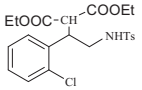
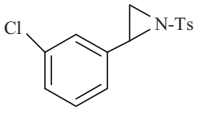
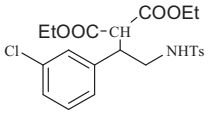
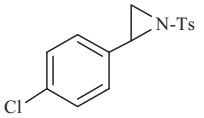
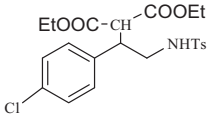
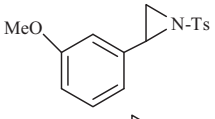
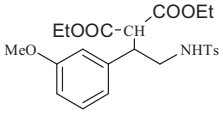
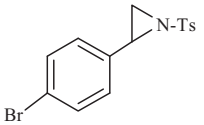
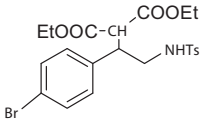
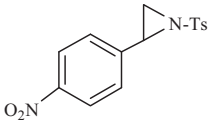
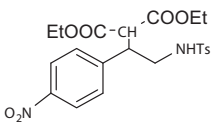
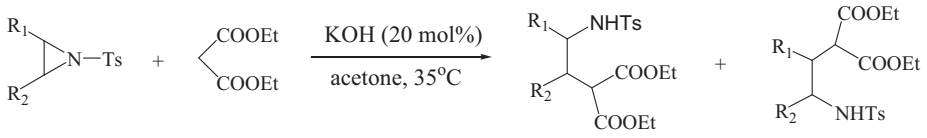
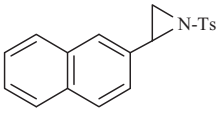
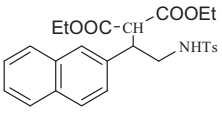
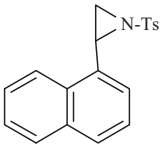
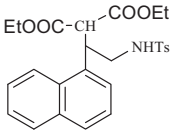
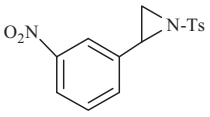
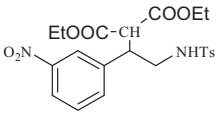
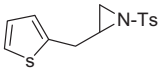
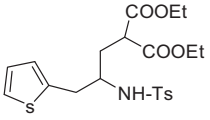
Entry	*N*-tosylaziridine	Product		*t* [h]	Yield[b] [%]	[c]Ratio **3**:**4**
1			**3a**	16	99	–
2			**3b**	56	94	–
3			**3c**	24	85	–
4			**3d**	53	82	–
5[d]			**4e**	37	92	11:89
6			**4f**	37	80	–
7			**4g**	37	84	–
8[d]			**4h**	20	73	19:81
9			**4i**	20	77	–
10[d]			**4j**	21	89	14:86
11[d]			**4k**	47	65	7:93
12[d]			**4l**	27	91	17:83
13			**4m**	20	96	–

Table 3 (*Continued*)



1 **2a** **3** **4**

Entry	*N*-tosylaziridine	Product		*t* [h]	Yield[b] [%]	[c]Ratio **3**:**4**
14			**4n**	21	73	–
15			**4o**	36	72	–
16			**4p**	20	Trace	
17			**3q**	21	83	95:5

[a] Unless otherwise specified, all reactions were carried out with *N*-tosylaziridine **1** (0.2 mmol), diethyl malonate **2a** (304 μL, 2 mmol, 10 equiv.), catalyst (KOH, 2.3 mg, 20 mol%) and acetone (1.5 mL) under air atmosphere at 35 °C for the identified time.
[b] Isolated yield.
[c] Combined yield of isolated **3** and **4**.
[d] These compounds gave two isomer products that could not be separated by column chromatography and HPLC, and their ratios were determined by ^{1}H NMR.

4. Conclusions

In conclusion, KOH, which is a low-cost and environmentally friendly reagent, is found to be an excellent base catalyst for the ring-opening reactions of *N*-tosylaziridines with diethyl malonate under mild conditions in acetone. Wide substrate scope, mild conditions, and simple handling are advantages of this procedure. More importantly, it provides a feasible direction of the ring-opening reaction for *N*-tosylaziridines with active methylene nucleophiles.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2012.07.023.

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