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Catalyst-Free Regio- and Stereospecific Synthesis of β-Sulfonamido Dithiocarbamates: Efficient Ring-Opening Reactions of *N*-Tosyl Aziridines by Dialkyldithiocarbamates

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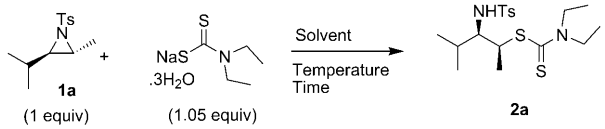
Functionalized dithiocarbamates are of great interest because of their potential applications in pharmaceuticals and agrochemicals.[1–4] Functionalization of the carbamate moiety offers an attractive method for the generation of compounds containing sulfur and nitrogen, which have wide applications and utility in solid-phase organic synthesis,[5] vulcanization,[6] and polymerization.[7] They are well exploited as protective groups in peptide synthesis,[8a] in addition to being used as ligands to stabilize transition metals in a wide range of oxidation states.[8b] Due to their strong metal binding capability, they also can act as inhibitors of enzymes and have a profound effect on biological systems. As a result, dithiocarbamate derivatives are used in medicinal chemistry for the treatment of cancer.[8c,d] Additionally, dithiocarbamates serve as the precursors for substituted thiazole derivatives, which are potential anti-HIV agents, antibacterial agents, and phosphodiesterase 10 inhibitors.[9,10] Interestingly, in most of the reactions that achieve such compounds, thiocarbamates are treated with halides in the presence of a metal catalyst to form C–S bonds.[10] Hence, the development of new synthetic routes to accomplish functionalized dithiocarbamates has been an attractive field of research for organic chemists for the past few decades.[11]

Interestingly, aziridines are versatile building blocks for the synthesis of biologically important compounds.[12] The ring-opening reaction of aziridines and their importance has been reviewed by Hu,[13] Lu,[14] and others.[14b] The ring-opening of *meso*-aziridines in an asymmetric fashion has been well exploited by Schnieder[15] and Kagan.[16] The reactivity of aziridines towards ring-opening reactions is attributed to their extremely strained ring structure, which enables them to act as carbon electrophiles.[17,18]The classical methods of synthesizing *N*-alkyl or *N*-aryl dithiocarbamate derivatives involves the reaction of amines with expensive and toxic reagents, such as thiophosgene and/or an isothiocyanate.[19] Recent examples of synthesizing *N*-alkyl- or *N*-aryl-dithiocarbamate derivatives have involved the following: a one-pot Michael addition of alkyl dithiocarbamates to chalcones,[20a] reaction of dithiocarbamate with alcohols under Mitsunobu conditions,[20b] coupling sodium dialkyldithiocarbamate with aryl iodide in the presence of copper iodide as the catalyst,[20c] and ring-opening of epoxides using alkyl dithiocarbamates in an ionic liquid medium.[20d] Although nucleophilic ring-opening of aziridines have been known for over three decades, there are only few reports on the nucleophilic ring-opening of aziridines by thiols and other thio-derivatives.[12a,13a,21] Therefore, we envisioned that ring-opening of aziridine using sodium dialkyl dithiocarbamate would be a useful addition for the synthesis of functionalized dithiocarbamates. In continuation of our research program to develop environmentally benign methods,[22] herein we report a novel, efficient, and catalyst-free synthesis of β-sulfonamido dithiocarbamates through ring-opening of various *N*-tosyl aziridines.

Preliminary experiments of the ring-opening reaction of *N*-tosylaziridine **1a** by sodium diethyldithiocarbamate (DEDTC) using toluene as the solvent at ambient temperature did not give the expected product, even after a prolonged reaction time (48 h; Table 1, entry 1). Nevertheless, the same reaction heated at reflux resulted in a ring-opening of the aziridine to give the (*S*)-alkylthiocarbamate **2a** in excellent yield (80%, 24 h; Table 1, entry 2). However, the same reaction in water did not give the expected product,

Table 1. Optimization of the reaction conditions.



Entry	Solvent	*T* [°C]	*t* [h]	Yield [%][a]
1	toluene	RT	48	–
2	toluene	110	24	80
3	H_2O	RT	120	–
4	H_2O	100	48	–
5	EtOH	RT	96	95
6	EtOH	78	24	95
7	EtOH	50	67	95
8	CH_3CN	RT	96	95
9	CH_3CN	80	12	97

[a] Yields of isolated products. Ts = tosyl.

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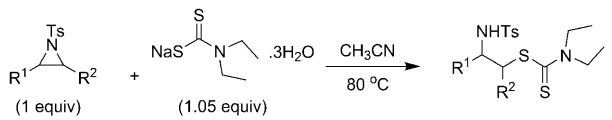
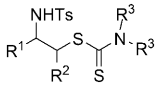
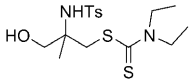
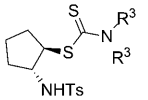
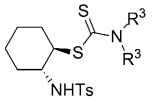
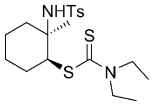
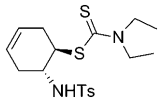
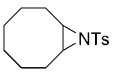
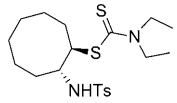
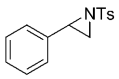
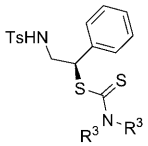
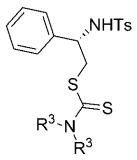
either at room temperature or at reflux conditions (Table 1, entries 3 and 4). Furthermore, ring-opening reactions of *N*-tosyl aziridine proceeded well in solvents such as EtOH or CH_3CN and afforded the corresponding ring-opened product in excellent yields (Table 1, entries 5–9). As shown in Table 1, the reactions at ambient temperature required a longer time (Table 1, entries 5 and 8), whereas the reactions at elevated temperature were faster (Table 1, entries 6, 7, and 9). Finally, we found that treatment of **1a** (1 equiv) with sodium DEDTC (1.05 equiv) in CH_3CN heated to reflux are the ideal conditions for this reaction, which gave the product **2a** in excellent yield (97%, 12 h; Table 1, entry 9).

After optimizing the conditions, we examined the generality of the reaction by using a variety of *N*-tosylaziridines and dialkyldithiocarbamates (Table 2). The reactions of different cyclic and open-chain *N*-tosyl aziridines proceeded smoothly under the optimized conditions with high regio- and stereoselectivity. We believe that the attack of the dialkyldithiocarbamate ion at the less hindered side of the aziridine ring is responsible for the formation of the product in a stereospecific fashion. To generalize the application of the ring-opening reaction by dialkylthiocarbamate we used sodium salts of DEDTC and sodium dimethyldithiocarbamate (DMDTC). As shown in Table 2, 2-isopropyl-3-methyl-1-tosylaziridine (**1a**) reacted well with DEDTC or DMDTC to produce the corresponding ring-opened products **2a** and **3a** in excellent yields (Table 2, entries 1 and 2). The reaction of (2-methyl-1-tosylaziridin-2-yl)-methanol **1b** with DEDTC also proceeded well to give the corresponding ring-opened product **2b** in excellent yield. Similarly, aziridines that are part of cyclic structures such as cyclopentyl- and cyclohexyl *N*-tosyl aziridines (**1c** and **1d**, respectively) underwent smooth ring-opening reaction with DEDTC or DMDTC to afford the corresponding *trans*-β-sulfonamido dithiocarbamates in excellent yields (Table 2, entries 4–7). Aziridines **1e** and **1f** reacted well with DEDTC to give the corresponding products **2e** and **2f** in almost quantitative yields (Table 2, entries 8 and 9). However, aziridine derived from cyclooctene **1g** required a longer time to give the product **2g** in moderate yield (3 days, 65%; Table 2, entry 5). Although, most of the reactions of aziridines with DEDTC and DMDTC were regiospecific (Table 2, entries 1–10), the reactions of 2-phenyl-1-tosylaziridine (**1h**) with DEDTC or DMDTC was different and gave a mixture of regioisomers (Table 2, entries 11 and 12).

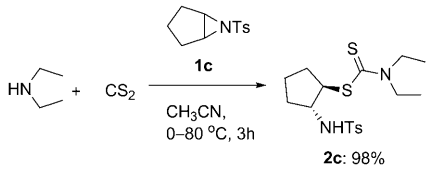
Table 2. Ring-opening of tosyl aziridine by sodium DEDTC[a] and DMDTC.[b]



Entry	Substrate		t	Product		Yield [%][c]
1		**1a**	12 h		**2a**: R^3 = Et	97
2		**1a**	1 h		**3a**: R^3 = Me	97
3		**1b**	0.5 h		**2b**	88
4		**1c**	1 h		**2c**: R^3 = Et	97
5		**1c**	30 min		**3c**: R^3 = Me	99
6		**1d**	10 min		**2d**: R^3 = Et	97
7		**1d**	10 min		**3d**: R^3 = Me	98
8		**1e**	12 h		**2e**	99
9		**1f**	0.5 h		**2f**	99
10		**1g**	3 days		**2g**	65
11		**1h**	1 h		**2h**: R^3 = Et	99[d]
					**3h**: R^3 = Et	
12		**1h**	10 min		**4h**, **5h**: R^3 = Me	99[e]

[a] DEDTC = Diethyldithiocarbamate. [b] DMDTC = Dimethyldithiocarbamate. [c] Yields of isolated products. [d] Isolated as a mixture of regioisomers: **2h**/**3h**; 2:1. [e] Isolated as a mixture of regioisomers: **4h**/**5h**; 3:1.

Since dialkyldithiocarbamates are obtained by the reaction of *N,N*-dialkylamine with CS_2 in the presence of a base, we thought that it would be ideal to generate the dialkyldithiocarbamate in situ by reacting CS_2 and the corresponding *N,N*-dialkylamine, then further treat the reaction mixture (without isolation) with aziridine. Therefore, we generated dithiocarbamate anion in situ by reacting CS_2 with *N,N*-diethylamine at 0°C for 2 h and the reaction mixture was then treated with aziridine **1c** and refluxed until completion of the reaction (1 h). As expected, the ring-opened product **2c** was isolated in almost quantitative yield (Scheme 1).



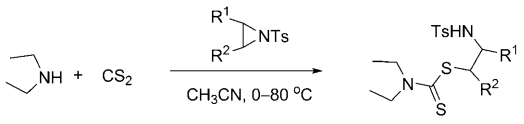
Scheme 1. One-pot reaction.

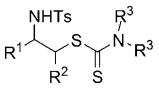
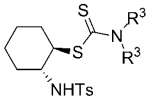
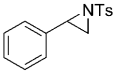
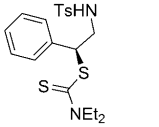
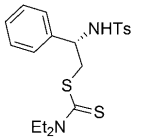
The one-pot reaction of dialkyldithiocarbamate (generated in situ) with aziridine to produce β-sulfonamido dithiocarbamates is further illustrated in Table 3 with several examples. This approach appears to be general, because the in situ generated DEDTC or DMDTC reacted with aziridines **1a** and **1d** to afford corresponding ring-opened products in excellent yields (Table 3, entries 1–4) As expected, the reaction of 2-phenyl-1-tosylaziridine (**1h**) resulted in the formation of mixture of regioisomers; isomers **2h** and **3h** were isolated in 2:1 ratios (99%; Table 3, entry 5).

However, the mechanism of this reaction is still not clear. Based on the literature precedence, we believe that the thiocarbamate anion is attacking aziridine at the less hindered side to generate the *trans* isomer.[12a] We speculate that both the nucleophilicity of sulfur and activation by the tosyl group on the aziridine ring facilitates the ring-opening.

In conclusion, we have developed an efficient protocol for the synthesis of β-sulfonamido dithiocarbamates by using a ring-opening strategy of aziridnes by thiocarbamates. This strategy provides an elegant method for synthesizing a wide range of β-sulfonamido dithiocarbamates by using inexpensive and readily available starting materials. In addition, a one-pot method has been developed for a facile ring-opening of aziridines by using in situ generated dialkyldithiocarbamate. These methods avoid toxic catalysts and, in most cases, give nearly quantitative yields without any byproducts. This methodology could potentially prove useful for the synthesis of medicinally active and other commercial dithiocarbamate derivatives. Further exploitation of this methodology and mechanism are currently underway in our laboratories.

Table 3. Ring-opening of tosyl aziridine by in situ generated DEDTC and DMDTC.



Entry	Substrate		t [h]	Product		Yield [%][a]
1		**1a**	15		**2a**: R^3 = Et	98
2		**1a**	3		**3a**: R^3 = Me	97
3		**1d**	2.5		**2d**: R^3 = Et	98
4		**1d**	2.5		**3d**: R^3 = Me	98
5		**1h**	3		**2h**	99[b]
					**3h**	

[a] Yields of isolated products. [b] Isolated as a mixture of regioisomers: **2h**/**3h**; 2:1.

Experimental Section

Typical experimental procedure: A mixture of well-stirred aziridine derived from cyclopentene (**1c**, 119 mg, 0.5 mmol) and sodium diethyldithiocarbamate (119 mg, 0.527 mmol) in CH_3CN (1 mL) was heated at reflux until the completion of reaction (1 h, monitored by TLC). The reaction mixture was concentrated under vacuum and the resultant crude mixture was purified by column chromatography on silica gel (EtOAc/Hexane; 1:10) to give the corresponding β-sulfonamido dithiocarbamate **2c** as a white solid in 97% yield.

Typical experimental procedure (in situ method): Carbon disulfide (0.06 mL, 1 mmol) was added to a well-stirred mixture of aziridine derived from cyclohexene (**1d**, 125 mg, 0.5 mmol) and diethyl amine (0.067 mL, 0.65 mmol) in CH_3CN (1 mL) at 0°C and the mixture was stirred at same temperature for 2 h and then heated at 80°C for 1 h. The reaction mixture was concentrated under vacuum and the resultant crude mixture was purified by column chromatography on silica gel (EtOAc/Hexane; 1:5) to give the corresponding β-sulfonamido dithiocarbamate **2d** as yellow-white solid in 98% yield.

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Keywords: aziridines · dithiocarbamates · regioselectivity · ring-opening · synthetic methods

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