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Flow microreactor synthesis of tricyclic sulfonamides via *N*-tosylaziridinyllithiums

Eiji Takizawa, Aiichiro Nagaki, Jun-ichi Yoshida *

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

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ABSTRACT

Tricyclic sulfonamides were synthesized by the generation of aziridinyllithiums from *N*-tosylaziridines followed by an intramolecular nucleophilic reaction and the subsequent reaction with electrophiles using a flow microreactor system. The reactions could be carried out at 0 °C, although much lower temperatures such as −78 °C are needed for batch macro reactors.

Cyclic sulfonamides have a vast array of biological activities such as pharmaceuticals,[1] agricultural chemicals,[2] and food additives (Fig. 1). Various methods including radical processes,[3] intramolecular Diels–Alder reactions,[4] ring-closing metathesis,[5] catalytic transition metal reactions[6] have been developed so far. Intramolecular aziridination method also serves as an efficient method for synthesizing polycyclic sulfonamides.[7]

In particular, tricyclic sulfonamides having a three-membered nitrogen-containing ring have received significant research interest because of their unique structure.[8] Such tricyclic sulfonamides are often prepared by intramolecular nucleophilic addition of aziridinyllithium to the aromatic ring (Scheme 1). Although this reaction serves as a powerful method for synthesizing a wide variety of tricyclic sulfonamides from aziridines, yields are usually very low because *N*-tosylaziridinyllithium and cyclized organolithium intermediates are highly unstable. For example, lithiation of 2-phenyl-*N*-tosylaziridine (**1**) using *sec*-BuLi to generate aziridinyllithium **2** followed by intramolecular addition to generate **3** and the subsequent reaction with iodomethane gave the desired tricyclic sulfonamide **4** in only 39% yield (Scheme 1).[8a]

Recently, flow microreactors have received significant research interest both from academia and industry, because they are expected to make a revolutionary change in chemical synthesis and production.[9,10] For example, highly exothermic reactions can be conducted in a controlled way by taking advantage of efficient heat transfer of a flow microreactor.[11] Flow microreactors are also quite effective for conducting reactions involving highly unstable short-lived intermediates such as organolithiums.[12,13] In particular, highly unstable oxiranyl and aziridinyl lithium species can be effectively generated and used for reactions with electrophiles in flow microreactor systems.[14] Herein we report that various tricyclic sulfonamides are effectively synthesized via *N*-tosylaziridinyllithium intermediates using flow microreactors.

We chose to use 2-phenyl-*N*-tosylaziridine (**1**) as a substrate, and PhLi was used as a base to generate *N*-tosylaziridinyllithium

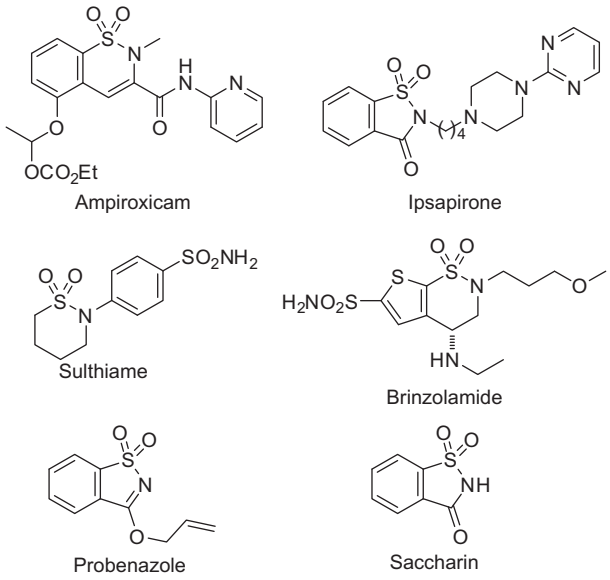

Figure 1. Biologically active compounds containing a cyclic sulfonamide structure.

* Corresponding author. Tel.: +81 75 383 2726; fax: +81 75 383 2725.
E-mail address: yoshida@sbchem.kyoto-u.ac.jp (J. Yoshida).

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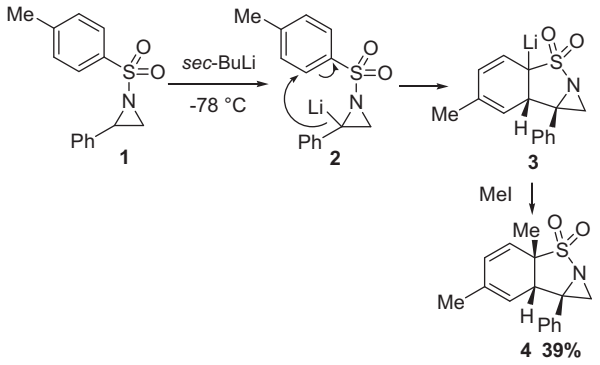


Scheme 1. Intramolecular nucleophilic addition of an aziridinyllithium to an aromatic ring.

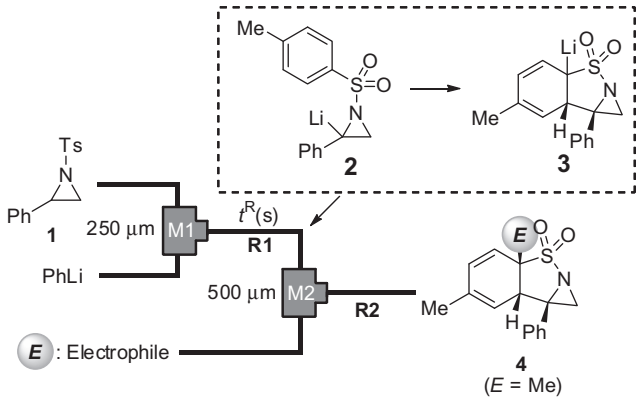


Figure 2. A flow microreactor system for the deprotonation of 2-phenyl-*N*-tosylaziridine (**1**) with PhLi followed by reaction with iodomethane. Flow rate of a solution of **1** (0.05 M in THF): 6.00 mL/min, flow rate of a solution of PhLi (0.60 M in hexane, cyclohexane, diethyl ether): 1.50 mL/min, flow rate of a solution of iodomethane (0.36 M in THF): 3.00 mL/min, **M1**, **M2**: micromixer, **R1**, **R2**: microtube reactor.

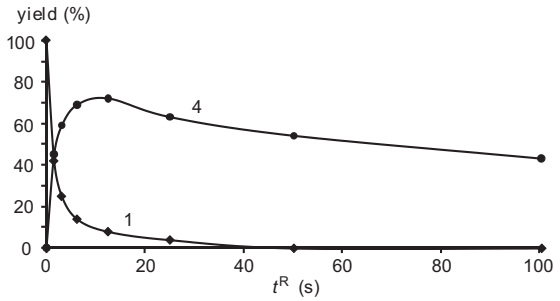
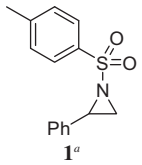
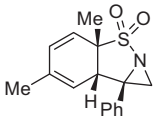
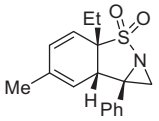
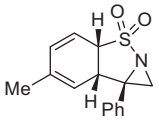
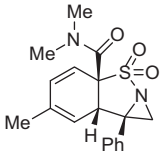


Figure 3. Effect of residence time in **R1** (t^R) on the yield of 1 and 4 in the deprotonation of 2-phenyl-*N*-tosylaziridine (**1**) with PhLi followed by reaction with iodomethane. Yields were determined by ^{1}H NMR.

intermediate **2**, which undergoes intramolecular addition to give **3** (Scheme 1). In conventional batch macro reactors, the reaction should be conducted at low temperatures such as −78 °C to avoid decomposition of **2** or/and **3**. However, as mentioned above, the yield of **4** was low even at such a low temperature.[8a] In contrast, we found that the reaction using a flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) (Fig. 2) gave the desired tricyclic sulfonamide **4** at 0 °C.[15] To get a deeper insight into the feature of the reaction and to optimize the reaction conditions, the reactions were carried out with varying the residence time in **R1** (t^R). As profiled in Figure 3, the amount of unchanged **1** and the yield of **4** significantly depend on t^R. The yield increased with an increase in t^R, and the maximum yield (72%) was obtained at 12.6 s. Further increase in t^R caused a decrease in the yield of **4**, presumably because of decomposition of **3**. Because the product derived from the trapping of **2** by iodomethane was not obtained, the cyclization of **2** to give **3** seems to be very fast.

Using the optimized conditions (t^R = 12.6 s), the reactions of **3** with various electrophiles were examined. As summarized in Table 1, reactions with iodomethane, iodoethane, methanol, *N*,*N*-dimethylcarbamoyl chloride, acetyl chlorides, benzoyl chloride, and

Table 1
Deprotonation of aziridines followed by reactions with electrophiles using a flow microreactor system

Aziridines	Electrophiles		Yield[d] (%)
 **1**[a]	MeI	 **4**	72
	EtI		63
	MeOH		62
	Me_2NCOCl		52