Synthesis of 2-(Phenoxymethyl)Oxirane Derivatives through Unexpected Rearrangement of Oxiran-2-Ylmethyl Benzenesulfonates

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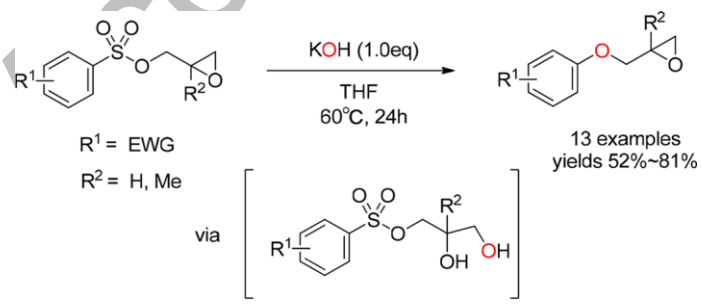
Abstract

The synthesis of 2-(phenoxymethyl)oxirane derivatives from oxiran-2-ylmethyl benzenesulfonates was developed through a base promoted rearrangement . A new C-O bond was formed along with the unexpected cleavage of C-S bond via this process. This unusual reaction was characterized with mild reaction conditions, high efficiency and excellent functional group tolerance. A plausible reaction mechanism was proposed on the basis of experimental results and control experiments.

Graphical Abstract



KEYWORDS: 2-(phenoxymethyl)oxirane; potassium hydroxide; rearrangement; C–S cleavage; oxiran-2-ylmethyl benzenesulfonate

INTRODUCTION

Epoxides serving as powerful intermediates in organic synthesis could be easily converted to various biologically active compounds through ring opening [1]. For example, β-amino alcohols including metoprolol[2], propranolol[3], atenolol[4] which are easily obtained through ring opening of 2-(phenoxymethyl)oxirane derivatives represent as a class of drugs used primarily in cardiovascular diseases. The recent medicinal chemistry applications include synthesis of delamanid [5], an anti-tuberculosis drug approved by EMA (European Medicines Agency) in 2014 (Figure 1). Furthermore, a simple and efficient method for the synthesis of cyclic carbonates from epoxides and CO_2 was reported recently [6].Thus, the development of effective methods for the synthesis of 2-(phenoxymethyl)oxirane derivatives remain as an important task in organic synthesis and medicinal chemistry.

The classical methods utilized for the synthesis of 2-(phenoxymethyl)oxirane derivatives involve the reaction between substituted phenols and oxiran-2-ylmethyl benzenesulfonates (eq 1, Scheme 1). Non-nucleophilic strong base was commonly employed to avoid the ring opening of epoxides, thus the reaction with substituted phenols occurs at the carbon atom connecting to the leaving group rather than ring

opening [7]. Although this protocol provided the corresponding epoxides in good to excellent yield, electron-withdrawing group substituted phenols often suffer from relatively low yield and harsh conditions [8]. Herein we report an effective method for the synthesis of electron-withdrawing groups substituted 2-(phenoxymethyl)oxirane derivatives through the base promoted rearrangement of oxiran-2-ylmethyl benzenesulfonates, which could be easily prepared from substituted benzene sulfonic chloride and glycidol [9].

RESULTS AND DISCUSSION

As part of our studies toward the process research of delamanid, (*R*)-(2-methyloxiran-2-yl)methyl 4-nitrobenzenesulfonate **1a** was treated with 4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)phenol for the preparation of 2-(phenoxymethyl)oxirane derivatives , while a side product **2a** was observed when sodium hydroxide was used as base. The byproduct **2a** turned out to be 2-methyl-2-((4-nitrophenoxy)methyl)oxirane which might be generated through the rearrangement of **1a**. This unexpected result provided a new approach for the synthesis of 2-(phenoxymethyl)oxirane derivatives. Therefore, further investigations were conducted to optimize the reaction conditions and explore the plausible mechanism.

To our delight, the product **2a** was isolated in 42% yield when NaOH (1.0 equiv) was added to the solution of **1a** in THF at room temperature (Table 1, entry 1). In order to

improve the conversion rate of raw materials, the reaction was conducted at elevated temperature and the desired product was isolated in 65% yield at 60 ^{o}C (entries 2−3). Further optimization work indicated that the KOH was more appropriate compared with NaOH and LiOH (entries 3−5). Interestingly, no reaction was observed when non-nucleophilic base was employed (Table 1, entry 6-8). Other solvents included 1, 4-dioxane, toluene and DMF were also tested, and THF proved to be the most effective medium (Table 1, entry 9-11). Besides, increasing or decreasing the equivalent of base both led to the decrease in yield (Table 1, entry 12-13). Thus, the optimum conditions for this base-promoted rearrangement are as follows: 1 equiv of KOH as base in THF at 60 ^{o}C for 24 h in the air.

With the optimized reaction conditions in hand, the scope and generality were explored. Various oxiran-2-ylmethyl benzenesulfonates that were synthesized from substituted benzene sulfonic chloride and glycidol were subjected to this reaction and the results were summarized in Table 2. (*R*)-(2-methyloxiran-2-yl)methyl 4-nitrobenzenesulfonate **1a** and its corresponding isomer **1b** worked efficiently to furnish the corresponding products in excellent yields with high enantioselectivity (Table 2, entries 1-2). Nitro–substituted oxiran-2-ylmethyl benzenesulfonates all underwent the rearrangement reaction smoothly with good to excellent yield (58%-74%), while *p*-substituted substrate afforded the product with a higher yield compared with ortho- or meta- analogues (Table 2, entries 3-5). Halo substituents including F, Cl and Br are compatible with the reaction

conditions, providing the target products with moderate yield (Table 2, entries 6-10). Other substrates bearing different electron-withdrawing groups (CN, CF_3) all efficiently delivered the products with a yield ranging from 56% to 81% (Table 2, entries 11-13). While oxiran-2-ylmethyl benzenesulfonate and Methyl substituted substrates gave the product with poor yield even under higher reaction temperature and pressure (Table 2, entries 14-15). Electronic effect of substituents on the aromatic ring was found to be significant; substrates with electron-withdrawing groups usually gave a better result. On the other hand, *p*-substituted substrate generally worked more efficiency as a result of less steric hindrance and stronger electron withdrawing ability.

On the basis of the above experimental results and recent work on C-S functionalization owing to the its relative weak bond energy[10], we assumed that the reaction might go through the epoxide ring opening of the substrate, intramolecular aromatic nucleophilic substitution, carbon-sulfur bond cleavage and formation of a new epoxide compound (Scheme 2). To test this hypothesis, compound **3** was subjected to the standard reaction conditions, the desired product **2c** could be obtained smoothly in 70% yield (Scheme 3).

In conclusion, an efficient novel approach to obtain 2-(phenoxymethyl)oxirane derivatives via the rearrangement of oxiran-2-ylmethyl benzenesulfonate has been developed. The highlights of this work include the mild reaction conditions, good

functional group tolerance and the metal-free feature. Further studies concerning its appliance in the field of drug synthesis are currently underway in our laboratory.

EXPERIMENTAL

General Infrared spectra were recorded with a FTIR spectrometer. NMR spectra were recorded for ^{1}H NMR at 400 MHz or 500 MHz, and ^{13}C NMR at 100 MHz or 125 MHz using TMS as internal standard. The following abbreviations were used to describe peak patterns where appropriate: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m), broad resonances (br). Mass spectroscopy data of the products were collected on an HRMS-EI-TOF instrument or a low-resolution MS instrument using EI or ESI ionization.

Preparation of 2-(phenoxymethyl)oxirane derivatives 2 : A mixture of oxiran-2-ylmethyl benzenesulfonate **1** (0.5 mmol), KOH(0.5mmol, powder) in THF (2 mL) was stirred at 60 ^{o}C under air for 24 h. Afterward, the mixture was cooled to room temperature, filtered through a pad of celite and the filtrate was concentrated. The crude product was dissolved in Et_2O (20 mL), washed with water (2×20 mL), brine (20 mL), then dried over Na_2SO_4. The solvent was evaporated with rotary evaporator, and the residue was subjected to flash column chromatography to obtain the desired product **2**.

SUPPORTING INFORMATION

Full experimental details, ^{1}H and ^{13}C NMR spectra, HPLC traces. This material can be found via the "Supplementary Content" section of this article's webpage.

ACKNOWLEDGMENT

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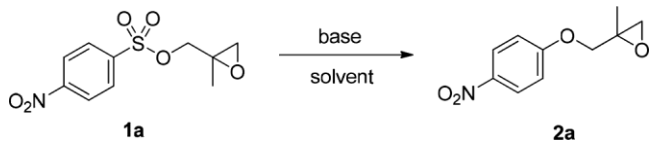
TABLE 1. Optimization of Reaction Conditions [a]



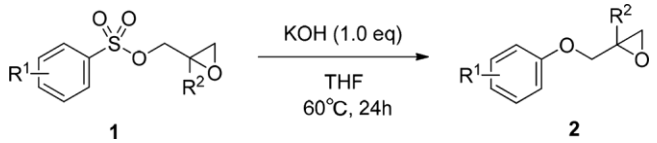
1a 2a

Entry	base(equiv)	solvent	T(^{o}C)	yield(%)[b]
1	NaOH(1.0)	THF	RT	42
2	NaOH(1.0)	THF	40	57
3	NaOH(1.0)	THF	60	65
4	KOH(1.0)	THF	60	73
5	LiOH(1.0)	THF	60	44
6	NaH(1.0)	THF	60	NR
7	K_2CO_3(1.0)	THF	60	NR
8	Cs_2CO_3(1.0)	THF	60	NR
9	KOH(1.0)	dioxane	60	61
10	KOH(1.0)	toluene	60	46
11	KOH(1.0)	DMF	60	18
12	KOH(0.5)	THF	60	55
13	KOH(1.5)	THF	60	62

[a] All reactions were carried out with (2-methyloxiran-2-yl)methyl 4-nitrobenzenesulfonate (0.3 mmol), solvent (2 mL), 24 h.

[b] Isolated yields.

Table 2. Synthesis of Various 2-(phenoxymethyl)oxirane [a]



1 2

Entry	substrate			product	Yield (%)[b]
		R^1=	R^2=		
1	**1a(*S*)**[c]	4-NO_2	CH_3	**2a(*R*)**	73[c]
2	**1b(*R*)** [c]	4-NO_2	CH_3	**2b(*S*)**	71[c]
3	**1c**	4-NO_2	H	**2c**	74
4	**1d**	2-NO_2	H	**2d**	66
5	**1e**	3-NO_2	H	**2e**	58
6	**1f**	4-F	H	**2f**	66
7	**1g**	2-F	H	**2g**	54
8	**1h**	4-Cl	H	**2h**	63
9	**1i**	4-Br	H	**2i**	61
10	**1j**	2-Br	H	**2j**	52
11	**1k**	4-CN	H	**2k**	70
12	**1l**	2-CN	H	**2l**	56
13	**1m**	4-CF_3	H	**2m**	81
14[d]	**1n**	H	H	**2n**	36
15[d]	**1o**	4-CH_3	H	**2o**	21

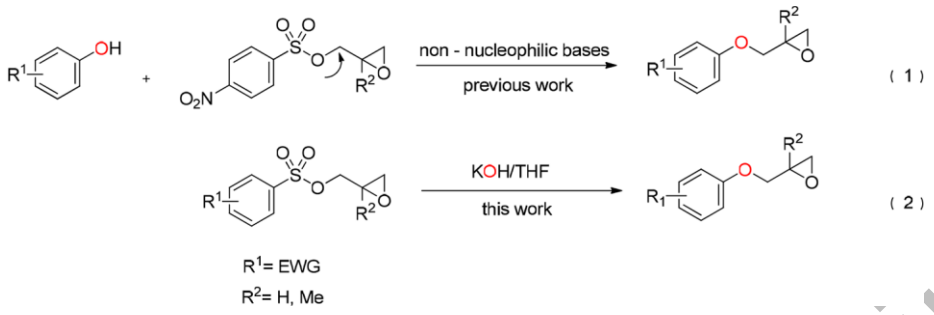
[a] Reaction conditions: **1** (0.5 mmol), KOH (0.5mmol), THF (2 ml), 60 ^{o}C, 24 h

[b] Isolated yields.

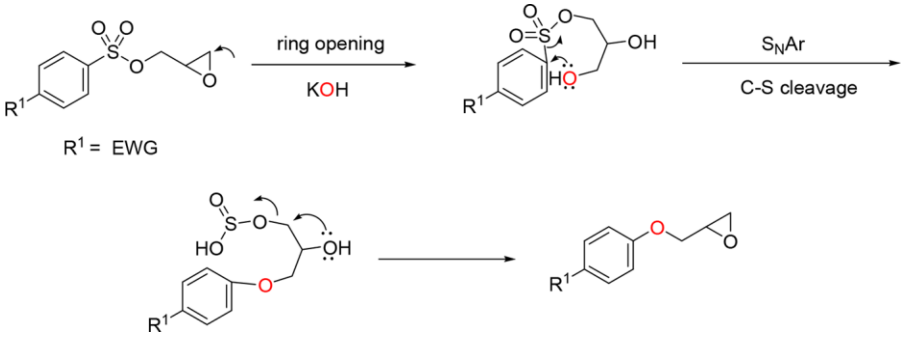
[c] *ee*=98%

[d] 80 ^{o}C, sealed tube

Scheme 1. Comparison of previous work with this work



Scheme 2. Possible reaction mechanism



Scheme 3. Control experiment

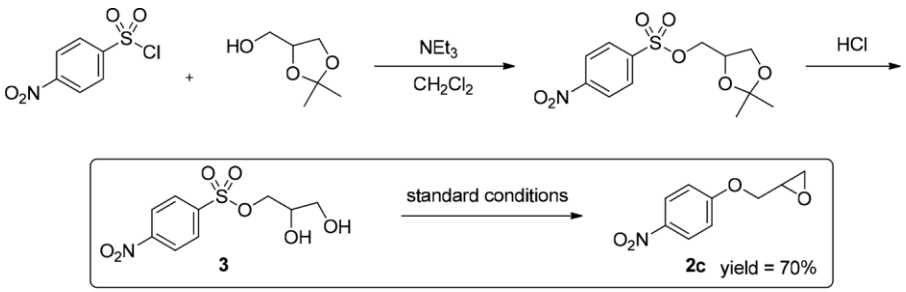


Figure 1. Examples of biologically compounds synthesized from epoxides.