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Skeletal Reorganization Divergence of *N*-Sulfonyl Ynamides

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Abstract: Skeletal reorganization is a type of intriguing processes for their interesting mechanism, high atom-economy and synthetic versatility. Herein, we describe an unusual skeletal reorganization divergence of *N*-sulfonyl ynamides. Upon treatment with lithium diisopropylamine (LDA), the *N*-sulfonyl ynamides could undergo a skeletal reorganization to deliver thiete sulfones, while the additional use of DMPU would shift the process to furnish propargyl sulfonamides. Mechanistically, these processes are proposed to initiate from a lithiation/cyclization cascade, and the following ligand-dependent 1,3-sulfonyl migration or β -elimination would constitute the divergence. Therefore, this protocol not only represents a new skeletal reorganization mode, but also provides a facile access to privileged molecules from the easily accessible ynamides.

Skeletal reorganization is a type of process involving multiple bonds cleavage and formation for molecule framework reassembly (Fig. 1a)¹⁻². Owing to the intriguing reaction mechanism, high atom-economy property and capability of accessing complex and synthetically challenging molecules, the skeletal reorganization process has attracted considerable attention and also been widely applied in organic synthesis toward diverse carbocyclic and heterocyclic compounds³⁻⁵. For example, a variety of transition-metal-catalyzed skeletal reorganizations of enynes have been explored for efficient synthesis of polycyclic compounds⁶⁻¹⁰. Recently, Sun and coworkers discovered an unusual skeletal reorganization of oxetane for the synthesis of 1,2-dihydroquinolines (Fig. 1b)¹¹. Meanwhile, Liu and coworkers

established a skeletal reorganization protocol of olefine via a radical-initiated cyclization/1,n ($n = 3, 4, 5$) vinyl migration cascade for accessing medium- and large-sized cycles which are ubiquitous structural motifs in natural products and pharmaceutical agents (Fig. 1c)¹². Very recently, Zhu and coworkers reported a novel skeletal reorganization of kojic acid or maltol-derived alkynes under Indium-catalysis, which provided an expeditious access to valuable hydroxylated benzofurans (Fig. 1d)¹³. Despite these advances, the investigation of skeletal reorganizations toward synthetically challenging and biologically interesting molecules remains continuous interesting and important.

a) Skeletal reorganization

b) Sun's work

c) Liu's work

d) Zhu's work

Fig. 1 Skeletal reorganization. **a** Skeletal reorganization. **b** In-catalyzed skeletal reorganization of oxetanes. **c** Radical-initiated skeletal reorganization of olefines. **d** In-catalyzed skeletal reorganization of kojic acid- or maltol-derived alkynes.

The four-membered sulfur-containing heterocycles, such as thiete sulfones, thietane sulfone and thietanes, are type of strained small ring compounds which have found wide applications in the discovery of dye, drug and pesticide (Fig. 2)¹⁴⁻¹⁹. In typical, the unsaturated thiete sulfones showed valuable synthetic utility in organic synthesis. For example, thiete sulfones could be used as dienophiles in the Diels-Alder reaction with tetraphenyl cyclopentadienones or isobenzofurans for accessing bridged and fused-ring compounds²⁰⁻²². Moreover, they could participate [3+2] cycloadditions with diazo compounds or nitrile oxides for synthesis of heterocycles²³⁻²⁴. Recently, thiete sulfones have been investigated in C–H functionalization to establish axially chiral molecules and macrocyclic compounds²⁵⁻²⁶. However, the conventional synthesis of thiete sulfones relies on multi-step routes and also suffers from narrow scope²⁷⁻³². Therefore, it would be interesting to explore a distinct and efficient approach to functionalized thiete sulfones.

Fig. 2 Representative molecules containing the structures of sulfur-containing four-membered ring.

Ynamides are type of *N*-substituted electron rich alkynes which exhibit unique chemical properties and serve as versatile synthons in organic synthesis³³⁻⁴². For example, ynamides could act as flexible cyclization partners in heterocycle synthesis⁴³⁻⁴⁵, carbene precursors⁴⁶⁻⁴⁹ and enamides precursors⁵⁰⁻⁵¹, racemization-free coupling reagents for peptide and macrolide synthesis⁵²⁻⁵⁴, C2 building blocks of

multicomponent reactions (MCRs)⁵⁵⁻⁵⁷. In recent years, the intramolecular cyclizations of ynamides including transition-metal-catalyzed and Brønsted acid-catalyzed nucleophilic cyclizations, anionic cyclizations and radical cyclizations, have been extensively investigated for synthesis of *N*-heterocycles (Fig. 3a)⁵⁸⁻⁶¹. However, the skeletal reorganization of ynamides is rarely reported. In 2012, Evano and coworkers reported a *s*-BuLi mediated skeletal reorganization of *N*-Boc ynamides for *de novo* synthesis of 1,4-dihydropyridines and pyridines, which invoked a process of carbonyl-directed deprotonation and anionic *6-endo-dig* cyclization (Fig. 3b)⁶². Encouraged by these, we hypothesized that the deprotonation at the α -position of sulfonyl moiety of *N*-sulfonyl ynamides might initiate an anionic *4-exo-dig* or *5-endo-dig* cyclization to deliver cyclic sulfonamides which are privileged structures in medicinal chemistry (Fig. 3c)⁶³⁻⁶⁴. In continuation of our interests in ynamide chemistry^{55-57, 65}, herein we would like to report an unprecedented skeletal reorganization divergence of *N*-sulfonyl ynamides for selective entry to thiete sulfones and propargyl sulfonamides (Fig. 3d).

a) Intramolecular cyclizations of ynamides

b) Evans' work: skeletal reorganization of *N*-Boc ynamides

c) Our initial hypothesis

d) This work: skeletal reorganization divergence of *N*-sulfonyl ynamides

Fig. 3 Skeletal reorganization of ynamides. **a.** Intramolecular cyclizations of ynamides. **b.** Skeletal reorganization of *N*-Boc ynamides. **c.** Initial hypothesis. **d.** Skeletal reorganization divergence of *N*-sulfonyl ynamides.

Results

Reaction optimization.

We commenced our study by using *N*-sulfonyl ynamide **1a** and lithium base to investigate this reaction. As shown in Table 1, various bases were employed to treat with **1a** in THF at low temperature. We initially set the reaction using *n*-BuLi at -40 °C for 1 hour and then treated with MeOH, and a new

major product **2a** and a minor product **3a** were observed (entry 1). The standard analysis, including ^1H NMR, ^{13}C NMR and mass spectroscopy, was not able to identify these compounds. Gratifyingly, the X-ray analysis showed that **2a** was a thiete sulfone and **3a** was a propargyl sulfonamide, indicating an unusual skeletal reorganization occurring. This unexpected outcome prompted us to optimize the reaction. The next survey of lithium bases showed that LDA was superior to give **2a** in 72% yield (entry 2), while the utilization of LiHMDS would decrease the yield to 31% (entry 3). The use of NaHMDS and KHMDS as base could only give **3a** in very low yield (entry 4-5). The next screening of bases such as NaH, DBU and TEA showed inferior to shut down the reactivity even at room temperature, and **1a** was recovered (entries 6-8). When LDA was used as base and the temperature was varied to 0 °C or -78 °C, the yield of **2a** would slightly decrease (entries 9-10). Considering that lithiation was involved in this process, we tried to add ligands to increase the yield. The next using of TMEDA (*N,N,N',N'*-tetramethylethylenediamine) as ligand showed no improvement (entry 11). Interestingly, the utilization of DMPU (1,3-dimethyl-tetrahydropyrimidin-2(1*H*)-one) as ligand would give **3a** in good yield exclusively (entry 12, 79% yield). Therefore, the skeletal reorganization is divergent and could be determined by ligand.

Table 1. Reaction Optimization^a.

Entry	Base	Additive	Solvent	T [°C]	Yield (%) ^b	
					2a	3a

1	<i>n</i> -BuLi	none	THF	-40	60	19
2	LDA	none	THF	-40	72	18
3	LiHMDS	none	THF	-40	31	0
4	NaHMDS	none	THF	-40	0	14
5	KHMDS	none	THF	-40	0	16
6	NaH	none	THF	25	0	0
7	DBU	none	THF	25	0	0
8	TEA	none	THF	25	0	0
9	LDA	none	THF	0	68	19
10	LDA	none	THF	-78	65	21
11	LDA	TMEDA	THF	-40	63	16
12	LDA	DMPU	THF	-40	trace	79

^aReaction conditions: **1a** (0.2 mmol), base (0.3 mmol), additive (0.5 mmol), THF (2 mL), 1 hr, then MeOH (0.1 mL). For details, see Supplementary.

^bIsolated yields.

Reaction scope study. With the optimized reaction conditions in hand, we next tested the substrate scope of this skeletal reorganization divergence. The starting material *N*-sulfonyl ynamides could be easily prepared by coupling of sulfonamides and alkynyl bromides. As shown in Fig. 4, various ynamides **1** could participate well in this skeletal reorganization, leading to the corresponding thiete sulfones **2** in moderate to good yields. Diverse substitutions on the amino group of ynamides, including *n*-butyl, benzyl, *i*-propyl, cyclopentanyl and thiophene-3-ethyl, were found tolerable in this process (**2b-2d**). The (*S*)-1-phenylethyl amine derived ynamide **1g** could also engage in this reaction to give the chiral moiety tethered thiete sulfone **2g** in a moderate 56% yield. Other functional groups, such as alkene and protected alcohol, were also found compatible in this reorganization process to give the corresponding products (**2h** and **2i**), which might offer ample opportunities for the further derivatization. In addition, the

aniline derived ynamide (**1j**) was also applicable to deliver the desired product **2j** in 77% yield. The structure of **2j** was further confirmed by X-ray diffraction (for more details, see Supplementary). For the variation of sulfonyl groups, a variety of substitutions were also tested and found amenable in this process to access functionalized thiete sulfones (**2k-2q**). In detail, *N*-methylsulfonyl and *N*-benzylsulfonyl ynamides could reorganize to corresponding thiete sulfones in moderate yield (**2k-2m**), and the structure of **2k** was confirmed by X-ray diffraction (for more details, see Supplementary). When *N*-cycloalkylsulfonyl ynamides like *N*-cyclopentanylsulfonyl ynamides and *N*-cyclohexanylsulfonyl ynamides were used, the skeletal reorganization could deliver *spiro*-fused thiete sulfones in moderate to good yields (**2n-2q**), and the structure of **2q** was also verified by X-ray diffraction (for more details, see Supplementary). With respect of the substitution at the β -position of ynamides, a set of aryl groups functionalized with 2-chloro, 3-methyl, 4-methyl, 4-pentyl, 4-methoxy, 4-fluoro or 4-chloro were tolerable to furnish the corresponding products in good yields (**2r-2x**), and these substituents did not show any significant electronic and steric effects with the yields. Other aryl groups, including 2-naphthyl, 3-pyridinyl and thiophene-2-yl, were suitable in this process to produce the products successfully (**2y-2a'**), and the structure of **2a'** was confirmed by X-ray analysis (for more details see Supplementary). Meanwhile, the cyclohexenyl substituted ynamide **1d'** could smoothly transform to the corresponding product **2b'** in 51% yield. Notably, silyl substitution was compatible with the process as well. For example, the TIPS-substituted ynamide **1e'** could reorganize to product **2c'** in 70% yield with retention of TIPS group, while the TMS-substituted ynamide **1f'** could transformed to product **2d'** in a remarkable 94% yield accompanied with TMS desilylation. Since the amino-containing full-substituted thiete sulfones are synthetically challenging⁶⁶, this skeletal reorganization of ynamides provides a robust and efficient approach toward these molecules with the achievement of structural diversity and molecule complexity.

Fig. 4. Scope of thiete sulfones. Standard condition: **1** (0.2 mmol), LDA (0.3 mmol), THF (2 mL), -40 °C, 1 hr, then treated with MeOH (0.1 mL). Yields refer to isolated products. ^a0.6 mmol LDA was used. ^bProduct of desilylation.

Next, the scope for another skeletal reorganization toward propargyl sulfonamide was also investigated. As shown in Fig. 5, a variety of ynamides were treated with LDA and DMPU toward the formation of propargyl sulfonamides, and the amino substitutions like *n*-butyl, cyclopentanyl, thiophene-3-ethyl, and protected alcohol, were compatible with this process (**3b-3e**). With respect to the sulfonyl substitutions, the cyclopentanyl and cyclohexanyl were applicable in the process to deliver the corresponding products in good yields (**3f-3i**). Meanwhile, alkynes with substitution on the aryl ring, including 2-fluoro, 2-chloro, 3-methyl, 4-methyl, 4-pentyl, and 4-fluoro, could well engage in this skeletal reorganization process to deliver the corresponding propargyl sulfonamides in good yields (**3j-3o**). The naphthyl and pyridinyl groups were also applicable to deliver the products smoothly (**3p-3q**). This skeletal reorganization involves an interesting 1,3-alkyne migration from *N*-atom to *C*-atom. Propargyl sulfonamide is a versatile synthon and their synthesis is challenging by conventional methods. Thus, this protocol provides a simple and efficient method to these molecules from readily available materials along with the fascinating process.

Fig. 5. Scope of propargyl sulfonamides. Standard condition: **1** (0.2 mmol), LDA (0.3 mmol), DMPU (0.5 mmol), THF (2 mL), -40 °C, 1 hr, then treated with MeOH (0.1 mL). Yields refer to isolated products.

Synthetic applications and mechanism study. To demonstrate the synthetic utility of this skeletal reorganization, an 8 mmol scale reaction was conducted (Fig. 6a). Under the standard reaction conditions, **1a** could be selectively transformed to **2a** and **3a** in gram-scale, indicating that these skeletal reorganization processes were practical. Considering that these processes may involve lithium intermediates which could offer opportunities for divergent functionalization of products, the derivatization was carried out. For example, when ynamide **1** were treated with LDA, various electrophilic reagents instead of MeOH were used to quench the reaction, and those electrophilic groups such as

methyl, allyl, propargyl, protected ethanol-2-yl, acetate and acetyl, were found placed on the amino group (Fig. 6b). This result not only indicated that a lithium amino intermediate is involved in the reorganization process, but also offered a vast potential for further derivatization of thiete sulfone skeletons. Similarly, when the LDA/DMPU mediated skeletal reorganization process of ynamide **1a** was quenched with MeI, a *N*-methyl propargyl sulfonamide product **5** was obtained in good yield (Fig. 6c). This experiment suggested the existence of sulfonamide anion intermediate after this skeletal reorganization process.

a) Gram-scale experiments

b) Electrophilic reagents-quenched reorganization toward *N*-functionalized thiete sulfones

c) MeI-quenched reorganization toward *N*-methyl propargyl sulfonamide

Fig. 6. Synthetic applications. **a.** Gram-scale reaction. **b.** Electrophilic reagents-quenched reorganization toward *N*-functionalized thiete sulfones, for details of electronic reagents, see Supplementary. **c.** MeI-quenched reorganization toward *N*-methyl propargyl sulfonamide.

In order to view more insights into the reaction, the mechanism exploration was conducted. For example, the crossover reaction was carried out to test whether any intramolecular group exchange was involved in the process. As shown in Fig. 7a, when ynamide **1r** and **1x** were subjected in one-pot under the standard reaction condition, **2q** and **2v** were exclusively formed in 79% and 73% yields respectively, and this excluded the possibility of intermolecular group exchange. Besides, treating *N*-acetyl ynamide **1o'** with LDA at 0 °C for 1 hour and then quenching the reaction with water could exclusively deliver a TIPS-tethered acetyl amide compound **6** in 59% yield (Fig. 7b). We assumed that the *in situ* generated lithium enolate **B** might undergo an anionic 4-*exo-dig* cyclization to deliver intermediate **C**, and the workup of water would lead to protonation and the following hydrolysis of methylene-1,3-oxazetidine would finally give the amide product **6**. This outcome indicated that anionic 4-*exo-dig* cyclization is more favored than 5-*endo-dig* cyclization in similar processes of ynamides.

a) Crossover experiment

b) Reaction of *N*-acetyl ynamide

Fig. 7. Mechanistic experiments. a. Crossover reaction. **b.** Reaction of *N*-acetyl ynamide.

Based on these results, a plausible reaction mechanism for this skeletal reorganization divergence is proposed (Fig. 8). Initially, the α -position of sulfonyl group would undergo lithiation upon treatment with LDA to deliver **A**, and then a 4-*exo-dig* cyclization would occur to generate four-membered β -sultam intermediate **B**^{63-64, 67-68}. At this stage, **B** shows a ligand-dependent divergent reactivity: (1) In the absence of ligands, intermediate **B** presumably undergoes a 1,3-sulfonyl migration to form lithium thiete sulfone intermediate **C**⁶⁹⁻⁷⁰, which could be protonated by MeOH to deliver product **2**. When MeOH was replaced by other electrophilic reagents, intermediate **C** could be functionalized directly to obtain *N*-substituted thiete sulfone products. (2) In the presence of DMPU, intermediate **B** might coordinate with DMPU to form **D**. Subsequently, intermediate **D** may undergo a β -elimination to generate lithium propargyl sulfonamide **E**, and the following protonation would furnish product **3**. In terms of the structure of compounds **3**, this skeletal reorganization process can be regarded as a 1,3-alkyne migration.

Fig. 8. Plausible mechanism.

Discussion

In summary, we have discovered an unprecedented skeletal reorganization divergence of *N*-sulfonyl ynamides. Upon treatment with lithium base, the *N*-sulfonyl ynamides would undergo lithiation/cyclization and the sequential ligand-determining 1,3-sulfonyl migration or β -elimination. Therefore, this protocol not

only represents a new skeletal reorganization mode, but also provides facile and selective access to privileged molecules from the easily accessible ynamides.

Methods

General procedure for the synthesis of thiete sulfones 2. An oven-dried schlenk tube equipped with a magnetic stirrer bar was purged with argon three times. Ynamide **1** (0.2 mmol) was dissolved in 2 mL anhydrous THF and added by a syringe. The mixture was cooled to -40 °C and LDA (2 mol/L in THF, 0.15 mL, 0.3 mmol) was added dropwise. The reaction was stirred at -40 °C for another 1 h. MeOH (0.1 mL) was added to quench the reaction and then the mixture was concentrated under vacuum to obtain the residue, which was further purified by silica gel column chromatography using ethyl acetate/petroleum ether as eluent to give thiete sulfones **2**.

General procedure for the synthesis of propargyl sulphonamides 3. An oven-dried schlenk tube equipped with a magnetic stirrer bar was purged with argon three times. Ynamide **1** (0.2 mmol) was dissolved in 2 mL anhydrous THF and added by a syringe. DMPU (62 µL, 0.5 mmol) was added and the mixture was cooled to -40 °C. Subsequently, LDA (2 mol/L in THF, 0.15 mL, 0.3 mmol) was added dropwise. The reaction was stirred at -40 °C for another 1 h, and then MeOH (0.1 mL) was added to quench the reaction. The mixture was concentrated under vacuum to obtain the residue, which was further purified by silica gel column chromatography using ethyl acetate/petroleum ether as eluent to give propargyl sulphonamides **3**.

Data availability

Data for the crystal structures reported in this paper have been deposited at the Cambridge Crystallographic Data Center (CCDC) under the deposition numbers CCDC: 1999861 (**2a**), 1999862 (**2b**), 1999863 (**2j**), 1999864 (**2k**), 1999865 (**2q**), 1999866 (**2a'**). Copies of these data can be obtained

free of charge via www.ccdc.cam.ac.uk/data_request/cif. All other data supporting the findings of this study, including experimental procedures and compound characterization, are available within the paper and its Supplementary Information files, or from the corresponding authors on request.

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Author contributions

L. Zeng, Y. Lin and J. Li performed experiments. S. Cui conceived and directed the project and wrote the paper. All authors discussed the results and commented on the manuscript.

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Figures

a) Skeletal reorganization

b) Sun's work

c) Liu's work

d) Zhu's work

Figure 1

Skeletal reorganization. a Skeletal reorganization. b In-catalyzed skeletal reorganization of oxetanes. c Radical-initiated skeletal reorganization of olefines. d In-catalyzed skeletal reorganization of kojic acid- or maltol-derived alkynes.

Figure 2

Representative molecules containing the structures of sulfur-containing four-membered ring.

a) Intramolecular cyclizations of ynamides

b) Evans' work: skeletal reorganization of *N*-Boc ynamides

c) Our initial hypothesis

d) This work: skeletal reorganization divergence of *N*-sulfonyl ynamides

Figure 3

Skeletal reorganization of ynamides. a. Intramolecular cyclizations of ynamides. b. Skeletal reorganization of *N*-Boc ynamides. c. Initial hypothesis. d. Skeletal reorganization divergence of *N*-sulfonyl ynamides.

Figure 4

Scope of thiete sulfones. Standard condition: **1** (0.2 mmol), LDA (0.3 mmol), THF (2 mL), -40 °C, 1 hr, then treated with MeOH (0.1 mL). Yields refer to isolated products. ^a0.6 mmol LDA was used. ^bProduct of desilylation.

Figure 5

Scope of propargyl sulfonamides. Standard condition: **1** (0.2 mmol), LDA (0.3 mmol), DMPU (0.5 mmol), THF (2 mL), -40 °C, 1 hr, then treated with MeOH (0.1 mL). Yields refer to isolated products.

a) Gram-scale experiments

b) Electrophilic reagents-quenched reorganization toward *N*-functionalized thiete sulfones

c) Mel-quenched reorganization toward *N*-methyl propargyl sulfonamide

Figure 6

Synthetic applications. a. Gram-scale reaction. b. Electrophilic reagents-quenched reorganization toward *N*-functionalized thiete sulfones, for details of electronic reagents, see Supplementary. c. Melquenched reorganization toward *N*-methyl propargyl sulfonamide.

a) Crossover experiment

b) Reaction of *N*-acetyl ynamide

Figure 7

Mechanistic experiments. a. Crossover reaction. b. Reaction of *N*-acetyl ynamide.

Figure 8

Plausible mechanism.

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