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Ring expansion reaction of α-sulfonyl cyclic ketones via insertion of arynes into C–C: a facile and mild access to medium- and large-sized benzannulated carbocycles

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ABSTRACT

Insertion of arynes into C–C of α-sulfonyl ketones was investigated, which lead to the ring expansion reactions when α-sulfonyl cyclic ketones were used. By ring expansions and desulfonylations, medium- and large-sized benzannulated cyclic ketones were obtained in moderate yields.

Medium- and large-sized carbocycles, which widely exist in natural products and artificial reagents,[1] are still challenging to be obtained, although a number of methods have been developed.[2] In these routes, harsh conditions were often required when the traditional intramolecular Wurtz couplings[3a,b] and Friedel–Crafts reactions[3c–e] were employed, limitations in scope of the samarium-participated reactions[3f,g] and generally strict experimental conditions of transition metal-participated reactions[3h–j] should also be considered. Hence, it is desirable to explore alternative facile and mild methods to synthesize medium- and large-sized carbocycles.

Arynes are active intermediates, and have been intensively studied because of the mildness and facility of the in situ generation of arynes induced by fluoride ions.[4] Insertion of arynes into element–element σ-bond could lead to formation of *ortho*-substituted arenes which are otherwise difficult to be synthesized by other methodologies, which has received considerable attentions in recent years.[5] The progress of insertion of arynes into C–C was especially significant and attractive for the convenience and efficiency in introducing two new C–C into *ortho*-positions of arene skeletons.[6]

As the so called auxiliary chemical chameleons,[7] organosulfones were often involved as activating groups, and could be replaced by other groups via various desulfonylation reactions[8] or undergo β-elimination to prepare unsaturated bonds[9] after the required synthetic operations, which made the use of sulfone groups classic in the synthesis of natural products.[8c,9a–c,f,g,10c] β-Keto sulfone, a kind of 1,3-difunctional organosulfone compound, has an active α-methylene and plays an important role in organic synthesis.[10] Based on our research on organosulfones[11] and arynes,[12] we would like to report a facile and mild insertion of arynes into C–C of acyclic and cyclic β-keto sulfone compounds.

We began our investigations on the insertion of arynes **1** into α-sulfonyl acyclic ketones **2**. To a dried THF solution of aryne precursor **1a** (1.0 mmol), 1-(phenylsulfonyl)propan-2-one **2a** (0.75 mmol), and 18-crown-6 (2 mmol), KF (2 mmol) was added rapidly. The resulting mixture was stirred at room temperature and monitored by TLC. The expected product **3a** was obtained in yield of 80% (Table 1, entry 1). When the acyl group of **2a** was replaced by the alkoxy carbonyl group, the insertion also proceeded smoothly in good yield (Table 1, entry 2). It was notable that the methyl group attached to α carbon of **2c** or **2d** did not affect the yield of **3c** or **3d** remarkably despite the conceivable steric strain of α-substituted substrates (Table 1, entries 3 and 4). Comparing with **1a**, another symmetrical aryne precursor, 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1b** also showed good adaptability for this route (Table 1, entry 5). Using the unsymmetrical 3-methyl-substituted aryne (from precursor **1c**), we got an 88% yield of product **3f** in perfect regioselectivity with

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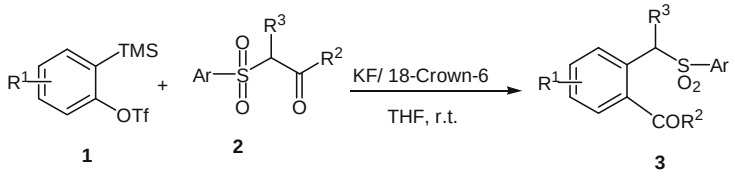
Table 1
Insertion reactions of arynes into α-sulfonyl acyclic ketones[a]



1 2 3

1a 2-(trimethylsilyl)phenyl trifluoromethanesulfonate

1b 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate

1c 2-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate

Entry	1	2				3	Yield[b] (%)
			Ar	R^2	R^3		
1	**1a**	**2a**	Ph	Me	H	**3a**	81
2	**1a**	**2b**	Tol	OEt	H	**3b**	81
3	**1a**	**2c**	Ph	OEt	Me	**3c**	82
4	**1a**	**2d**	Tol	OEt	Me	**3d**	76
5	**1b**	**2a**	Ph	Me	H	**3e**	78
6	**1c**	**2e**	Ph	OEt	H	**3f**	88[c]

[a] At ambient temperature, the mixture of **1** (1.0 mmol), **2** (0.75 mmol), KF (2 mmol), and 18-crown-6 (2 mmol) in 10 mL of THF was stirred for 12 h under nitrogen atmosphere.
[b] Isolated yields based on **2**.
[c] Regioselectivity determined by NOE.

the methyl group from aryne and the alkoxy carbonyl moiety in adjacent positions, which was determined by NOE experiment analysis (Table 1, entry 6) (Fig. 1).

Encouraged by the above results, especially the facile insertion into C–C of α-alkylated substrates (Table 1, entries 3 and 4), we envisioned that if the R^2 and R^3 groups of **2** joined together to construct a cycle, a ring expansion procedure of α-sulfonyl cyclic ketone might be realized via insertion of aryne. Under the conditions similar to Table 1, the reactions proceeded smoothly and the anticipated products were obtained from the ring expansions of α-sulfonyl cyclic ketones in moderate yields (Table 2). When 2-tosylcyclohexanone **4a** was used, we obtained 10-tosyl-7,8,9,10-tetrahydrobenzo[8]annulen-5(6*H*)-one **5a** containing benzannulated eight-membered carbocycle moiety in a yield of 44% after 48 h (Table 2, entry 1). α-Sulfonyl cyclic ketones bearing different sizes of carbocycles were employed too. Five-membered ring of 2-(phenylsulfonyl)cyclopentanone **4b** expanded to benzannulated seven-membered carbocycle in a shortened time of 30 h and with a higher conversion (Table 2, entry 2). For ring expansions of α-sulfonyl ketones bearing seven- and eight-membered rings, longer time was needed to finish the conversions of the starting materials, moderate yields of benzannulated nine- and ten-membered products **5c** and **5d** were synthesized (Table 2, entries 3 and 4). Symmetrically substituted aryne from precursor 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1b** also adapted to this ring expansion reaction and led to the formation of eight-membered benzo ring in 49% yield (Table 2, entry 5). Furthermore, the ring expansion reaction of α-sulfonyl cyclic ketone **4e** was carried out with the 3-substituted aryne from **1c** to clarify the regioselectivity, and the inseparable mixture of products 5f and 5f′ was obtained in the ratio of 11:1, where the methine group was predominantly introduced into the *meta* position of the methyl group which was determined by NOE experiment (Fig. 2).

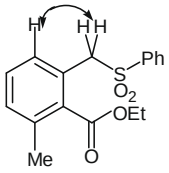


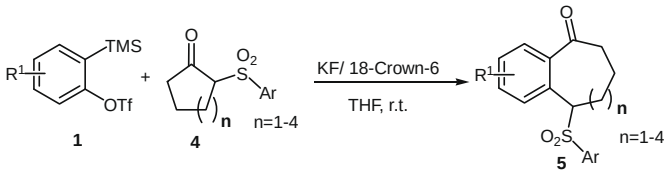
Figure 1. NOE experiment on **3f**.

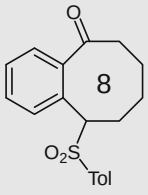
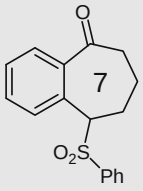
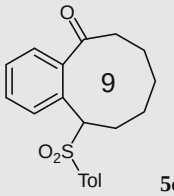
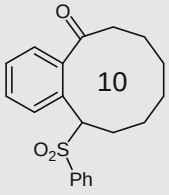
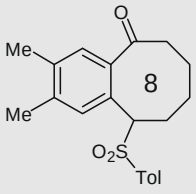
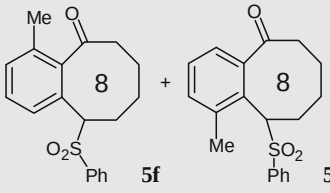
Based on the relative reports,[13] a plausible mechanism was outlined in Scheme 1. First, an aryl anion **8** is produced by the nucleophilic addition of in situ generated enolate anion **7** to aryne **6**. The key intermediate benzocyclobutanol anion **9** forms from the intramolecular nucleophilic attack of aryl anion to the carbonyl group of **8**. Following the opening of the benzocyclobutanol anion and subsequent protonation, the aimed ring expansion product **5** is obtained if α-sulfonyl cyclic ketone **4** is used. Presumably due to the steric congestion of **8** bearing cyclic ketone moiety in transforming to the key intermediate **9**, the competitive direct arylation occurs and the yield of **5** decreases. Contrarily, for reaction of α-sulfonyl acyclic ketone **2**, no matter α-position is substituted or not, this arylation route is suppressed greatly and the normal insertion product **3** is the main product. The regioselectivity in the *meta*-addition of 3-methyl-substituted aryne **1c** could be rationalized by the overwhelming steric strain between the methyl group and nucleophile rather than the electronic factor.[5h]

Utilizing excess Raney Ni in EtOH as the hydrogenolysis reagent at reflux, the aryl sulfonyl groups of ring expansion products **5b** and **5d** were successfully hydrogenolyzed to form the corresponding medium-sized benzannulated cyclic ketone 6,7,8,9-tetrahydrobenzo[7]annulen-5-one **11a** and large-sized one 7,8,9,10,11,12-hexahydrobenzo[10]annulen-5(6*H*)-one **11b** in high yields, which were difficult to access by other methods (Scheme 2).[14]

In conclusion, we have disclosed the insertion reactions of arynes into C–C of α-sulfonyl acyclic and cyclic ketones. The *ortho*-substituted arenes or benzannulated carbocycles which were

Table 2
Ring expansion reactions of arynes and cyclic β-keto sulfones[a]



Entry	1	4	Ar	*n*	5	Yield[b] (%)
1	**1a**	**4a**	Tol	2	 **5a**	44
2	**1a**	**4b**	Ph	1	 **5b**	58[c]
3	**1a**	**4c**	Tol	3	 **5c**	51[d]
4	**1a**	**4d**	Ph	4	 **5d**	39[d]
5	**1b**	**4a**	Tol	2	 **5e**	49
6	**1c**	**4e**	Ph	2	 **5f** + **5f'**	55 (11:1)[e]

[a] At ambient temperature, the mixture of **1** (1.0 mmol), **4** (0.75 mmol), KF (2 mmol), and 18-crown-6 (2 mmol) in 10 mL of THF was stirred for 48 h under nitrogen atmosphere.
[b] Isolated yields based on **4**.
[c] Stirred for 30 h.
[d] Stirred for 60 h.
[e] Stirred for 120 h and the ratio of the inseparable products was determined by ^{1}H NMR.

difficult to get by other routes have been synthesized very facilely and directly in good or moderate yields. Through the ring expansion methods, five- to eight-membered carbocycles of α-sulfonyl cyclic ketones were enlarged by C=C of arene units to conduct for-

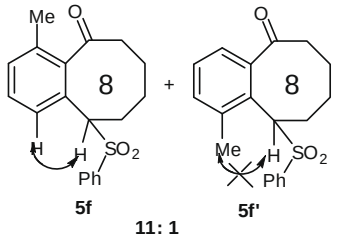
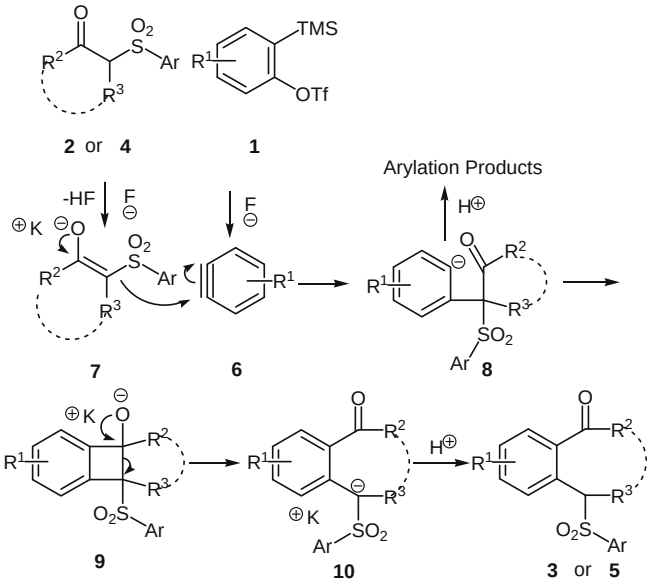
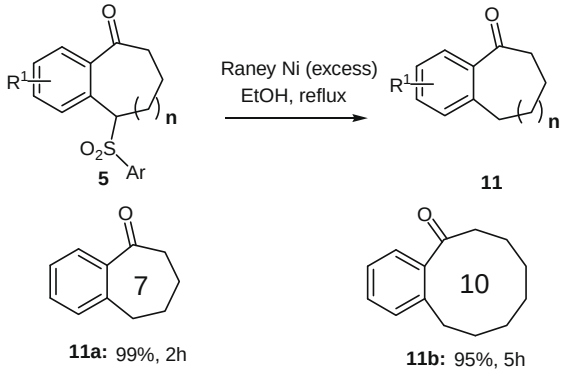


Figure 2. NOE experiment on the mixture of **5f** and **5f'**.



Scheme 1. The plausible mechanisms for insertion of arynes into C–C and ring expansion processes.



Scheme 2. Hydrogenolysis of aryl sulfonyl-substituted ring expansion products.

mation of seven- to ten-membered benzo rings. After being required in the ring expansion procedure, the redundant aryl sulfonyl groups were exchanged to hydrogen atoms via the hydrogenolysis effect induced by Raney Ni, and benzo cyclic ketones were obtained in high yields. The details of mechanism and further applications of products are being investigated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.001.

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