

## A Novel Multicomponent Reaction of Arynes, $\beta$ -Keto Sulfones, and Michael-Type Acceptors: A Direct Synthesis of Polysubstituted Naphthols and Naphthalenes

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A novel multicomponent reaction of arynes,  $\beta$ -keto sulfones, and Michael-type acceptors is presented, providing an efficient method for the synthesis of polysubstituted naphthols and polysubstituted naphthalenes. Further investigation suggests that the tandem reaction may proceed via a sequential nucleophilic attack to arynes, intramolecular nucleophilic substitution followed by a Michael addition, and a ring closure—elimination process.

Polysubstituted naphthalenes have been used in many applications such as pharmaceuticals, plant protection agents, dyes, etc. In addition, some natural products that contain a naphthalene nucleus often exhibit biological activities<sup>1</sup> which makes their preparation of great interest in organic synthesis.<sup>2</sup>

Recently, the chemistry of arynes has received considerable attention due to its potential in synthetic applications.<sup>3</sup> Although their application has been extended to insertion of element– element  $\sigma$ -bond<sup>4</sup> and transition-metal-catalyzed reactions<sup>5</sup> to synthesize polysubstituted arenes, which are difficult to prepare

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by other strategies, multicomponent reactions of the arynes were rare<sup>6</sup> because of the difficulty associated with regulating the reactivity of arynes.

During our studies on the chemistry of arynes<sup>7</sup> and multicomponent reactions,<sup>8</sup> we were surprised to find that polysubstituted naphthols and naphthalenes could be obtained in moderate yields by a novel three-component reaction of arynes,  $\beta$ -keto sulfones, and Michael-type acceptors, in which the efficiency of bond formations was high with four new carbon– carbon bonds formed within in one operation (Scheme 1).

Initially, we studied the multicomponent reactions of o-(trimethylsilyl)phenyl triflate<sup>9</sup> 1a, benzenesulfonylacetate 2a, and diethyl fumarate **3a**. When  $\beta$ -sulfonylacetate **2a** was treated with 1.5 equiv of triflate 1a and 1 equiv of fumarate 3a in the presence of 2 equiv each of 18-crown-6 and KF as the source of fluoride to induce the generation of arynes at room temperature, the naphthol 4a was obtained only in a trace amount by using 2 equiv of K<sub>2</sub>CO<sub>3</sub> as base after 24 h (entry 1, Table 1). In order to optimize the reaction conditions, the effects of bases, amounts of reactants and bases, and temperature on the reaction were examined (Table 1). The experimental results showed that NaH is effective as the base to the reaction, while KF, K<sub>2</sub>CO<sub>3</sub>, and 'BuOK were ineffective (entries 1-4, Table 1). When 0.75 equiv of fumarate 3a was used, the yield of naphthol 4a increased to 58% (Table 1, entry 5). By increasing the amount of sodium hydride, the yield of naphthol 4a could be improved (entries 6 and 7, Table 1). When the reaction was performed at 65 °C, compound 4a was obtained in a better yield (69%) (entry 8, Table 1).

With the optimized reaction conditions in hand (entry 8, Table 1), the scope and the limitation of this reaction were examined. The results in Table 2 demonstrated that the reaction could proceed smoothly using maleic esters, fumaric esters, or ethyl acrylate as the Michael-type acceptors to afford naphthols in moderate yields (entries 1-4, Table 2). However, when methyl

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SCHEME 1. Multicomponent Reactions of Arynes,  $\beta$ -Keto Sulfones, and Michael-Type Acceptors

$$R = \bigcup_{i=1}^{M} \bigcup_{j=1}^{M} CO_2Et + \bigcup_{i=1}^{R} ZO_2Et + \bigcup_{i=1}^{R}$$

TABLE 1. Optimization of Three-Component Reactions of Benzyne,  $\beta$ -Sulfonylacetate 2a, and Fumarate  $3a^a$ 

TMS OTf +		+ COOEt Base	COOEt
1a	2a	3a	ÓH <b>4</b> a
entry	<b>3a</b>	base	yield <sup>b</sup>
	(equiv)	(equiv)	(%)
1 2	1	K <sub>2</sub> CO <sub>3</sub> (2) KF (2)	trace
3	1	NaH (2)	35
4	1	<sup>7</sup> BuOK (2)	mixture
5	0.75	NaH (2)	58
6	0.75	NaH (2.5)	63
$\frac{7}{8^c}$	0.75	NaH (3)	63
	0.75	NaH (2.5)	69

<sup>*a*</sup> At ambient temperature, **2a** in the presence of base was stirred for 10 min, and the mixture was treated with **1a** and **3a** in the presence of KF and 18-crown-6 in THF for 5 h. <sup>*b*</sup> Isolated yields based on **3a**. <sup>*c*</sup> The reaction was conducted at 65 °C.

acrylate was employed, a mixture of naphthols **4d** and **4e** was isolated. We think naphthol **4d** may be the transesterification product of naphthol **4e** with ethanol, which was generated in the reaction (entry 5, Table 2). Cyclohex-2-enone is also effective for the reaction (entry 6, Table 2). However, when chalcone was used as the Michael-type acceptor, only a trace amount of the product **4g** was formed, probably due to the steric hindrance of the phenyl group in the substrate **3g** (entry 7, Table 2).

As well as unsubstituted aryne, substituted arynes could also be used in this reaction. When 4,5-dimethyl-1-(trimethylsilyl)phenyl triflate **1b** was selected as a substrate in the reaction, the naphthol **4h** was obtained in good yield (entry 8, Table 2). The reaction of 3-substituted arynes generated from triflate **1c** with  $\beta$ -sulfonylacetate **2a** and maleic esters also took place smoothly in excellent regioselectivity probably due to the steric hindrance of the methyl group in the ortho-positions of arynes (entries 9 and 10, Table 2). The regioselectivities of the products from 3-substituted arynes were determined by NOE experiment (Figure 1).

To extend this protocol, we used other  $\beta$ -ketone sulfones to prepare corresponding substituted naphthalenes (Table 3). To our delight, 2-(phenylsulfonyl)acetophenone **2b**, 1-(phenylsulfonyl)-2-propanone **2c**, or 2-(*p*-tolylsulfonyl)acetophenone **2d** is effective for this reaction, and the corresponding substituted naphthalenes **4** were obtained in good yields. In this transformation, it is necessary to increase the amount of sodium hydride to 3.5 equiv to remove the water generated during the reaction.

Next, we turned our attention to the mechanism of the reaction. Scheme 2 outlines a plausible pathway, which involves five reaction steps. First, the enolate of **2a** attacks the aryne to generate aryl anion **5**, which could undergo intramolecular nucleophilic addition to the carbonyl moiety of the ester to form anion **7** via benzocyclobutene anion **6**. Subsequently, the anion **7** would in turn attack the Michael-type acceptor, such as a fumarate, followed by 1,2-addition and elimination of benzene-sulfinic acid to generate naphthol **4a**.

## **TABLE 2.** Synthesis of Polysubstituted Naphthols by theThree-Component Reactions of Arynes<sup>a</sup>



<sup>*a*</sup> Reaction conditions: At ambient temperature, 1 mmol of **2a** in the presence of 2.5 mmol of NaH (65% in mineral oil) was stirred for 10 min, then the mixture was treated with 1.5 mmol of **1** and 0.75 mmol of **3** in the presence of 2.25 mmol of KF and 2.25 mmol of 18-crown-6 in 10 mL of THF at 65 °C. <sup>*b*</sup> Isolated yields based on **3**. <sup>*c*</sup> Determined by <sup>1</sup>H NMR analysis.





To infer the mechanism better, we tested the two key reaction steps: (A) the insertion of  $\beta$ -keto sulfones to arynes; (B) the synthesis of polysubstituted naphthols by the reaction of the products from (A) with Michael-type acceptors. Initially, our efforts focused on the reaction of 2-(trimethylsilyl)phenyl triflate **1a** with  $\beta$ -sulfonylacetate **2a**. When 0.75 equiv of  $\beta$ -sulfonylacetate **2a** reacted with triflate **1a** in the presence of 2 equiv of KF and 18-crown-6 in THF at room temperature, the insertion product **9a** was obtained in 85% yield after 4 h (Scheme 3).

ortho-Keto benzyl sulfones are important building blocks in organic synthesis, so we investigated the reaction of a variety of precursors of arynes and  $\beta$ -keto sulfones to generate ortho-

 
 TABLE 3. Synthesis of Polysubstituted Naphthalene by the Three-Component Reactions of Arynes<sup>a</sup>

TMS OTf +		<sup>2</sup> + COOEt KF/NaH/18-	C-6 COOEt
1a	2	3b	K∸ 4
entry		2	<b>4</b> , yield <sup>b</sup> (%)
1 2 3	2b, Ar 2c, Ar 2d, Ar	= Ph; $R^2$ = Ph = Ph; $R^2$ = CH <sub>3</sub> = <i>p</i> -(CH <sub>3</sub> )-Ph; $R^2$ = Ph	<b>4k</b> , 67 <b>4l</b> , 70 <b>4k</b> , 68

<sup>*a*</sup> Reaction conditions: At ambient temperature, 1 mmol of **2** in the presence of 3.5 mmol of NaH (65% in mineral oil) was stirred for 10 min, then the temperature was increased to 65 °C and the mixture was treated with 1.5 mmol of **1a** and 0.75 mmol of **3b** in the presence of 2 mmol of KF and 2 mmol of 18-crown-6 at 65 °C. <sup>*b*</sup> Isolated yields based on **3b**.

SCHEME 2. Plausible Pathway of Multicomponent Reactions



SCHEME 3. Insertion of  $\beta$ -Sulfonylacetate 2a to Aryne



keto benzyl sulfones. As shown in Table 4, we initially used the simple aryne precursor 1a to generate an aryne. When 2aand 1-(phenylsulfonyl)-2-propanone 2b were treated with arynes, the insertion products could be obtained smoothly in good yields (entries 1 and 2, Table 4), but when 2-(*p*-tolylsulfonyl)acetophenone 2d was used, the product was a mixture of 9cand 10c in a ratio of 3:1. We believe that the product 10c was formed from the reaction of the intermediate benzyl anion with a second aryne.

In addition to simple arynes, substituted arynes were also examined. When 4,5-dimethyl-2-(trimethylsilyl)phenyl triflate **1b** and 3-methyl-2-(trimethylsilyl)phenyl triflate **1c** were used to conduct this reaction, the insertion products could be obtained smoothly. The regioselectivities of the products from 3-substituted arynes were determined by NOE experiment (Figure 2). The regioselectivities of the reaction were excellent, and the products were monosubstituted at the ortho-position.

Next, we examined the reaction of *ortho*-keto benzyl sulfones with Michael-type acceptors, which afford the expected polysubstituted naphthalenes (Table 5).

In summary, a novel three-component reaction of arynes,  $\beta$ -keto sulfones, and Michael-type acceptors for the synthesis of polysubstituted naphthols and naphthalenes has been devel-





<sup>*a*</sup> At ambient temperature, **1** (1.0 mmol) and **2** (0.75 mmol) in the presence of 2 mmol of KF and 2 mmol of 18-crown-6 in 10 mL of THF were stirred for 12 h. <sup>*b*</sup> Isolated yields based on **2**. <sup>*c*</sup> Determined by <sup>1</sup>H NMR analysis.



FIGURE 2. NOE experiment on 5g.



SO <sub>2</sub> I	Ph +	R <sup>1</sup> NaH	$R^{2}$ or $H^{2}$	R R
9		3	4	
entry	9	Michael-type acceptor	products	yield <sup>b</sup> (%)
1	9a	<b>3</b> a	4a	78
2	9a	3c	<b>4</b> c	85
3	9a	3f	<b>4f</b>	76
4	9b	3a	41	73

 $^a$  The mixture of **9** (1.0 mmol) and **3** (1.0 mmol) in the presence NaH was stirred at 65 °C for 4 h.  $^b$  Isolated yields.

oped. The reaction may proceed via nucleophilic attack on the arynes, intramolecular nucleophilic substitution, Michael addition, ring closure, and elimination. It is the first example of successful trapping of the intermediate benzyl anion with electrophiles. To understand the mechanism better, the insertion

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of  $\beta$ -keto sulfones to arynes was also examined. The *ortho*keto benzyl sulfones were obtained with good yields under mild reaction conditions. Further studies including the generation methods of arynes, the reaction mechanism, and synthetic applications of arynes are underway in our laboratory.

## **Experimental Section**

General Procedure for Synthesis of Polysubstituted Naphthols and Naphthalenes via a Multicomponent Reaction of Arynes. At ambient temperature, 1 mmol of 2 in the presence of 2.5 mmol or 3.5 mmol of NaH (65% in mineral oil) was stirred for 10 min in 10 mL of dry THF, then the mixture was treated with 1.5 mmol of 1 and 0.75 mmol of 3 in the presence of 2 mmol of KF and 2 mmol of 18-crown-6 in THF at 65 °C. After completion of the reaction (monitored by TLC), 5 mL of water was added to the mixture, then diluted with dichloromethane (15 mL) and washed. The organic layer was dried over MgSO<sub>4</sub>. Removal of the solvent in vacuum and purification of the residue by silica gel chromatography with *n*-hexane—EtOAc (4:1) as eluent gave the product **4**.

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**Supporting Information Available:** Experimental procedures, spectral data for products, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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