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Three-Component Coupling Reaction Triggered by Insertion of Arynes into the S═O Bond of DMSO

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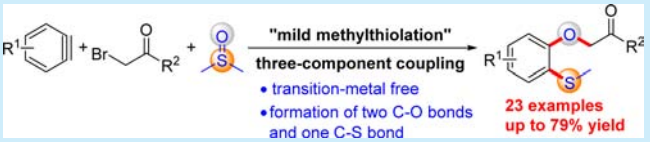
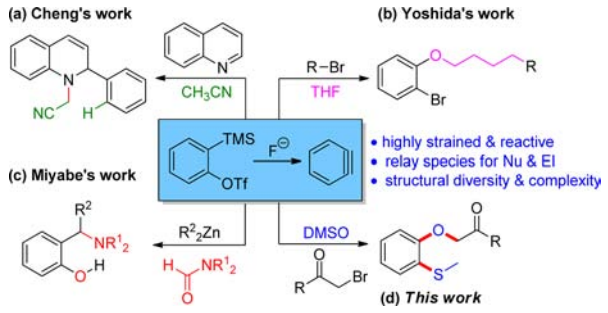
Supporting Information

ABSTRACT: An unprecedented three-component coupling reaction of arynes, α-bromo carbonyl compounds, and DMSO triggered by insertion of arynes into the S═O bond of DMSO has been developed. The reaction can generate a wide range of multisubstituted aryl methyl thioethers in good yields, wherein DMSO serves as both methylthiolation reagent and oxygen source.



Arynes represent a class of unique and highly versatile synthetic intermediates, and the past decades have witnessed a rapid revival in their application in organic synthesis since the discovery of a mild generation of arynes from *o*-silyl aryl triflate precursors by Kobayashi.[1,2] Owing to their high strain and low-lying LUMO, arynes could undergo various transition-metal-free nucleophilic attack readily by a wide range of neutral nucleophiles,[3] such as isocyanides,[4] aldehydes and ketones,[5] N-heteroaromatic compounds,[6] imines,[7] amines,[8] amides,[9] and thioureas,[10] to generate a diverse variety of highly reactive and versatile zwitterions. The resultant highly reactive 1,3- or 1,4-zwitterionic intermediates have provided a powerful platform for identifying or engineering new multicomponent reactions (MCRs) by employing appropriate electrophiles, thus leading to efficient construction of diversely functionalized 1,2-disubstituted arenes and biologically important carbo- and heterocycles.[11] In particular, the transition-metal-free three-component coupling reaction of arynes has enjoyed considerable advances over the past several years.[12] Among them, solvent-participated (e.g., THF,[4e] CH_3CN,[6a,8d] and DMF[9b−d]) MCRs of arynes are particularly intriguing and thus have attracted remarkable research effort, wherein these solvents act not only as a reaction medium but also as a reagent incorporated into the final products (Scheme 1). For example, the Cheng group pioneered a reaction of arynes, isoquinolines, and nitriles (Scheme 1a),[6a] while Yoshida and co-workers described an interesting three-component coupling reaction of benzyne, THF, and alkynyl (or polyfluoroaryl) bromides to produce the corresponding alkyl aryl ethers in moderate to high yields (Scheme 1b).[4e] Furthermore, the Miyabe group disclosed another powerful transformation of arynes, formamides and alkylzincs in a one-pot fashion for the synthesis of *ortho*-disubstituted arenes (Scheme 1c).[9b] It was found that the key to success for the desired reaction was the formation of formal [2 + 2] adduct (benzoxetene) or *ortho*-quinone methide via insertion of arynes into C═O π-bond of

Scheme 1. Aryne-Based Three-Component Coupling Reaction with Incorporation of Solvent



fomamides. Based on these elegant works, the third coupling components were subsequently extended to active methylene compounds,[9c,d] water,[9e] α-chlorinated methines,[9f] alcohols,[9g,h] and aroyl cyanides,[9i] by the groups of Miyabe, Yoshida, Shi, and Wang.

Despite these impressive advances, to our knowledge, there is no report on the use of DMSO in MCRs of arynes for new methodology developments.[13] As part of our ongoing research program in sulfur chemistry,[14] we envisioned that the use of cheap and commercially available DMSO as neutral nucleophile instead of DMF might also lead to formation of highly reactive formal [2 + 2] cycloaddition adduct through insertion of aryne into the S═O bond. Thus, exploration of such type of resultant intermediate should provide a novel platform for incorporating a S-containing moiety into valuable aromatic compounds. Herein, we describe a transition-metal-free three-component coupling reaction of arynes, α-bromo carbonyl compounds, and DMSO, which is triggered by insertion of arynes into the S═O bond (Scheme 1d). The reaction furnished a wide range of

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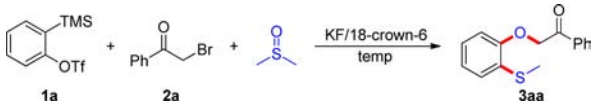
biologically and synthetically important aryl methyl thioethers in generally good yields.[15,16]

Initially, we investigated the reaction by employing benzyne, generated in situ from 2-(trimethylsilyl)aryl triflate **1a** by fluoride source and 2-bromo-1-phenylethanone **2a** in DMSO at room temperature.[17] To our delight, the reaction resulted in formation of the unexpected product **3aa** in 53% yield in the presence of KF and 18-crown-6 (Table 1, entry 1). The

Table 1. Optimization of Reaction Conditions[a]



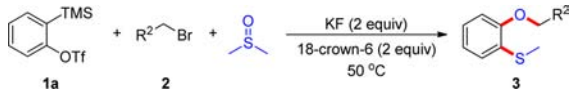
entry	temp (°C)	concn (M)	t (h)	yield[b] (%)
1	rt	0.1	4	53
2	40	0.1	4	65
3	50	0.1	4	66
4	60	0.1	4	61
5[c]	50	0.2	4	51
6[d]	50	0.07	4	70
7[d]	50	0.07	2	68
8[d,e]	50	0.07	6	76
9[d]	50	0.07	8	72

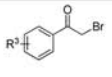
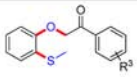
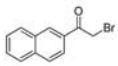
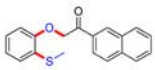
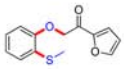
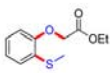
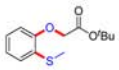
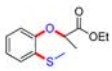
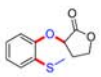
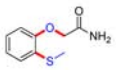
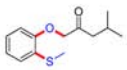
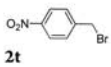
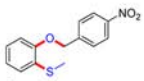
[a]Unless noted, reactions were carried out with **1a** (0.20 mmol), **2a** (0.40 mmol), KF (0.40 mmol), and 18-crown-6 (0.40 mmol) in DMSO (2.0 mL). [b]GC yield (using biphenyl as the internal standard). [c]DMSO (1.0 mL). [d]DMSO (3.0 mL). [e]Isolated yield = 68%.

structure of **3aa** has been fully characterized by NMR and X-ray crystallographic analysis.[18] Notably, this novel and catalyst-free process can generate two new C−O bonds and one C−S bond through only one operation. Encouraged by this result, we continued to screen reaction temperature and substrate concentration to further improve the chemical yield. It was found that increasing the reaction temperature to 50 °C provided a 66% yield of **3aa** (Table 1, entry 3). A brief survey of substrate concentration showed that slightly diluted reaction improved the yield to 70% (Table 1, entries 3, 5, and 6). Moreover, somewhat prolonged reaction time resulted in a 76% yield of **3aa** (Table 1, entry 8 vs 9). Hence, the optimal reaction conditions were established (Table 1, entry 8).

Under the optimized conditions, the scope of this reaction was first examined by using a variety of α-bromo carbonyl compounds, and the representative results are highlighted in Table 2. In addition to **1a**, various electron-donating and electron-withdrawing groups at *ortho*-, *meta*-, or *para*-positions of the phenyl ring of α-bromo carbonyl compounds were well-tolerated, affording the corresponding products **3ab**−**3ak** in 31−77% yields (entries 1−11). Note that the substrates bearing electron-donating substituents generally give superior yields over the ones with electron-withdrawing groups. Moreover, reactions of α-bromo carbonyl compounds bearing a fused ring (**2l**) or heterocycle (**2m**) can also result in the formation of the corresponding products **3al** and **3am** in 55 and 61% yield, respectively (entries 12 and 13). Importantly, an array of α-bromoesters (**2n**−**2q**) with variable steric hindrance and α-bromoamide (**2r**) have proved to be suitable for the reaction with formation of products **3an**−**3ar** in moderate to good yields (51−76%) (entries 14−18). To our delight, the reaction of alkyl-substituted α-bromoketone **2s**, benzyne, and DMSO proceeded smoothly to give the product **3as** in 79% yield.

Table 2. Substrate Scope of α-Bromo Carbonyl Compounds and Benzyl Bromide[a]



entry	substrate **2**	product		yield[b] (%)
				
1	**2a**	**3aa**	R^3 = H	70
2	**2b**	**3ab**	R^3 = 2-MeO	75
3	**2c**	**3ac**	R^3 = 3-MeO	69
4	**2d**	**3ad**	R^3 = 4-MeO	74
5	**2e**	**3ae**	R^3 = 4-Me	77
6	**2f**	**3af**	R^3 = 3-Cl	40
7	**2g**	**3ag**	R^3 = 4-F	68
8	**2h**	**3ah**	R^3 = 4-Cl	59
9	**2i**	**3ai**	R^3 = 4-Br	45
10	**2j**	**3aj**	R^3 = 4-CN	31
11	**2k**	**3ak**	R^3 = 2,4-F_2	57
12	 **2l**	 **3al**		55
13	 **2m**	 **3am**		61
14	 **2n**	 **3an**		76
15	 **2o**	 **3ao**		69
16	 **2p**	 **3ap**		51
17	 **2q**	 **3aq**		59
18	 **2r**	 **3ar**		52
19	 **2s**	 **3as**		79
20	 **2t**	 **3at**		59

[a]Unless noted, reactions were carried out with **1a** (0.40 mmol), **2** (0.80 mmol), KF (0.80 mmol), and 18-crown-6 (0.80 mmol) in DMSO (6.0 mL) at 50 °C for 6 h. [b]Isolated yield.

Furthermore, 4-nitrobenzyl bromide **2t** can successfully participate in the reaction to furnish the desired product **3at** in 59% yield (entry 20). Notably, product **3ah** was found to

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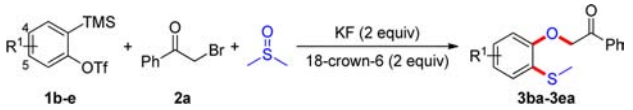
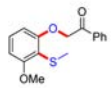
exhibit in vitro activities against intracellular *Leishmania amazonesis* and *Leishmania donovani amastigotes*.[19] Accordingly, products **3aa**−**3at** can provide a small library of candidates for related biological studies.

Encouraged by these results, we further investigated the scope of this three-component reaction by using diversely substituted aryne precursors under standard conditions (Table 3). In the case of symmetrical arynes, both 4,5-dimethyl- and

Table 3. Substrate Scope of Arynes[a]



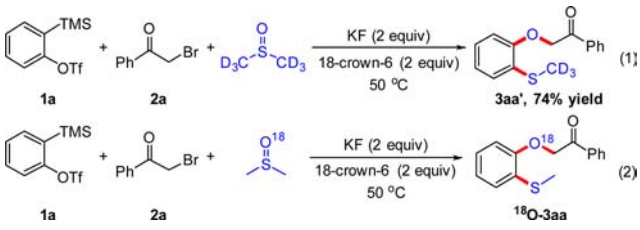
entry	aryne **1**	product	R^1	yield[b] (%)
1	**1b**	**3ba**	R^1 = 4,5-Me_2	35
2	**1c**	**3ca**	R^1 = 4,5-F_2	52
3	**1d**	**3da** and **3da'**	**3da:** R^1 = 5-Me	73
			3da': R^1 = 4-Me	
4	 **1e**	 **3ea**		72

[a]Unless noted, reactions were carried out with **1b**−**e** (0.40 mmol), **2a** (0.80 mmol), KF (0.80 mmol), 18-crown-6 (0.80 mmol) in DMSO (6.0 mL) at 50 °C for 6 h. [b]Isolated yield.

4,5-difluoro-substituted 2-(trimethylsilyl)phenyl triflates (**1b** and **1c**) can be tolerated in the reaction to afford the desired product **3ba** and **3ca** in 35 and 52% yield, respectively (entries 1 and 2). In the case of 4-methyl-substituted benzyne precursor **1c**, the reaction gave rise to a mixture in an almost 1:1 regioisomeric ratio (**3da** and **3da'**) with 73% total yield (entry 3). We also carried out the reaction with benzyne precursor **1e** under the standard conditions (entry 4). The reaction with the in situ-generated 3-methoxylbenzyne proceeded smoothly and led to exclusive formation of **3ea** in 72% yield, with the oxygen moiety at the *meta*-position of the MeO group. This result suggested that the reaction involves an initial nucleophilic coupling process.[7]

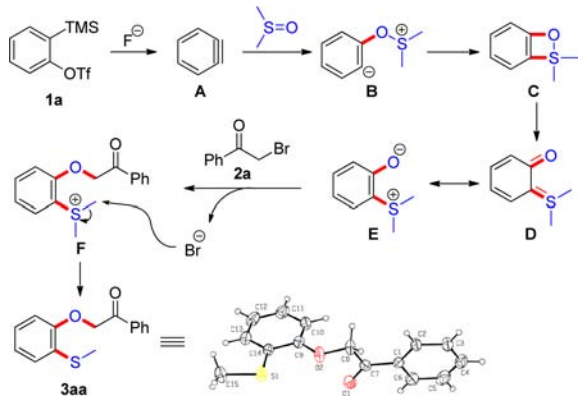
In order to gain some insight into the mechanism, we carried out a deuterium-labeling study in the reaction of **1a**, **2a**, and DMSO-d_6 (Scheme 2, eq 1). Complete deuterium incorporation at the carbon of methylthio moiety was observed by the ^{1}H NMR analysis, which confirmed that DMSO served as the source of the methylthio group. In addition, an O^{18}-labeled DMSO experiment with **1a** and **2a** was also performed, and obvious detection of ^{18}**O-3aa** by mass analysis suggested that the oxygen of newly formed C−O bond originated from DMSO (Scheme 2, eq 2).

Scheme 2. Labeling Experiments



On the basis of the above results and previous literature,[9] we proposed a possible mechanism to account for the formation of aryl methyl thioethers (Scheme 3). First, the highly reactive

Scheme 3. Proposed Mechanism



benzyne intermediate **A**, generated in situ from precursor **1a** by fluoride source, underwent a nucleophilic attack by oxygen of DMSO to generate the zwitterion **B**. Then, an intramolecular cyclization of **B** formed the intermediate **C**, which isomerized to α-carbonyl sulfur ylide **D** via a ring-opening process. The zwitterion **E** is a resonance structure of α-carbonyl sulfur ylide **D**. An intermolecular S_N2 nucleophilic attack of oxygen anion of zwitterion **E** to α-bromo carbonyl ketone **2a** resulted in the formation of intermediate **F**. Finally, the resultant bromine anion from α-bromo carbonyl ketone **2a** would abstract methyl cation of intermediate **F** to give the product **3aa**.[17,20]

In conclusion, we have developed a new three-component coupling reaction of arynes, α-bromo carbonyl compounds, and DMSO triggered by insertion of arynes into the S=O bond of DMSO. In this transformation, DMSO served as both methylthiolation reagent and oxygen source. Remarkably, the reaction allowed for an unusual construction of two new C−O bonds and a C−S bond in a one-pot fashion, affording a variety of synthetically and biologically important aryl methyl thioethers in generally good yields.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) Please see the Supporting Information for more details.

(18) CCDC 998873 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

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