Received 00th January 20xx,

1. College of Chemistry and Environmental Engineering, Yangtze University, Jingzhou 434023, P. R. China.
2. Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, P. R. China.

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A Cascade Oxidation/[4+1] Annulation of Sulfonium Salts for Synthesis of Polyfunctional Furans: DMSO as One-Carbon Source

**A novel DMSO-involved cascade reaction of stabilized sulfonium salts has been established for direct construction of polyfunctional furans. This one-pot sequential reaction involving in situ generated α-methylene sulfonium salts followed by [4+1] annulation with sulfur ylides. Notably, DMSO play a very important role in this transformation, not only as solvent but also as one carbon source.**

Over the past decades, the solvent-participated reaction is considered as an important synthetic strategy in organic chemistry.1 Due to its low toxicity and availability, dimethyl sulfoxide (DMSO) has been widely used as reactant to introduce a variety of functional groups in recent years,2 which served as the source of -CH2SMe,3 -Me,4 -CH2-,5 =CH2,6 =CH-,7 -CHO,8 -CN,9 -SMe,10 -SOMe,11 and -SO2Me.12 Despite these significant advancements, the development of new way to activate DMSO for the construction of more complex molecules in organic synthesis is greatly valuable.

Versatile sulfur ylides was usually perceived as 1,1'-dipole-type reagents, which have been widely utilized in [2+1] annulation for the synthesis of three-membered carbo- and heterocycles.13 In addition, sulfur ylides would also participate in [3+3] and [4+2] cycloaddition reactions in constructing diverse cyclic compounds.14 Particularly, the [4+1] annulation of sulfur ylides is unusual in the past decades. Until recent years, it has been developed as a powerful method to access various five-membered rings (furans, benzofurans, indolines, pyrrolines, isoxazolines, indoles and other compounds).15 For example, Xiao and coworkers reported a formal [4+1] annulation of stabilized sulfur ylides with α, β-unsaturated imines via one-pot two-step process giving a series of polysubstituted pyrroles (Scheme 1a).16 Furthermore, Chandrasekhar et al. developed a highly efficient and practical route for the syntheses of 2-aroyl benzofurans via a cascade [2+2] followed by [4+1] cycloaddition on arynes using stable sulfur ylides (Scheme 1b).17 In addition, Zhou and coworkers reported a facile [4+1] annulation of the o-QMs generated from 2-alkyl-substituted phenols and sulfonium salts, following DDQ oxidant for the synthesis of 2,3-disubstituted benzofurans (Scheme 1c).18 Herein, we report a cascade oxidation/[4+1] annulation reaction of stabilized sulfonium salts with DMSO for the direct construction of polyfunctional furans derivatives (Scheme 1d). It noteworthy that DMSO play a very important role in this transformation, not only as solvent but also as one carbon source.



**Scheme 1** The [4+1] Annulation of Sulfur Ylides.

Initially, we employed the annulation of benzoyl sulfonium salt (1a) and DMSO (used as the solvent) as a model reaction to screen the reaction conditions, and the results are summarized in Table 1. To our delight, the product furan **3a** was afforded in 61% yield when the reaction proceeded in the presence of TMEDA and K2S2O8 at 130 °C for 5 h (entry 1). Subsequently, other oxidants (Na2S2O8, (NH4)2S2O8 and Oxone) were also examined, and (NH4)2S2O8 was the best choice leading to 67% yield (entries 2–4). Later, various additives were screened, TFA has been proven to be the optimum choice, giving the 86% yield (entries 5–10). It is worth noting that the desired product **3a** could not be obtained in the absence of (NH4)2S2O8 (entry 11). Further investigation into other organic base (N,N-dimethylaniline, Et3N, DABCO) revealed that TMEDA was an efficient reagent for this transformation, affording a higher yield (entries 12–14). Moreover, decreased yields were obtained at lower reaction temperatures (entries 15–19).

Table 1 Optimization of the Reaction Conditions*a*



|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Entry | Addictive | Oxidant | Temp (°C) | Yield*b* (%) |
| 1 | - | K2S2O8 | 130 | 61 |
| 2 | - | Na2S2O8 | 130 | 58 |
| 3 | - | (NH4)2S2O8 | 130 | 67 |
| 4 | - | Oxone | 130 | 34 |
| 5 | TfOH | (NH4)2S2O8 | 130 | 71 |
| 6 | MsOH | (NH4)2S2O8 | 130 | 74 |
| 7 | TsOH∙H2O | (NH4)2S2O8 | 130 | 76 |
| 8 | TFA | (NH4)2S2O8 | 130 | 86 |
| 9 | HCl | (NH4)2S2O8 | 130 | 73 |
| 10 | H2SO4 | (NH4)2S2O8 | 130 | 77 |
| 11 | TFA | - | 130 | 0 |
| 12 | TFA | (NH4)2S2O8 | 130 | 68c |
| 13 | TFA | (NH4)2S2O8 | 130 | 8d |
| 14 | TFA | (NH4)2S2O8 | 130 | 32e |
| 15 | TFA | (NH4)2S2O8 | 120 | 79 |
| 16 | TFA | (NH4)2S2O8 | 110 | 71 |
| 17 | TFA | (NH4)2S2O8 | 100 | 64 |
| 18 | TFA | (NH4)2S2O8 | 90 | 43 |
| 19 | TFA | (NH4)2S2O8 | 80 | 28 |

*a)* Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), addictive(0.2 mmol, 1.0 equiv), and oxidant(3.0 equiv), TMEDA (0.4 mmol, 2.0 equiv) in DMSO at 130 °C for 5 h. b) Isolated yield. c) N,N-dimethylaniline instead of TMEDA. d) Triethylamine replaced of TMEDA. e) DABCO instead of TMEDA

With the optimized conditions in hand, we subsequently investigated the substrate scope of this reaction, as shown in Table 2. The results indicate that the electronic effect had little effect on the reaction. Various sulfonium salts bearing electron-donating (4-Me, 3,4-2Me, 3-OMe, 4-OMe, 4-Ph) substituents attached to benzene ring afforded the corresponding products in good to excellent yields (**3a**–**3e**, and **3n**). Much to our satisfaction, sulfonium salts with electron-withdrawing groups (4-NO2, 4-CN) could be converted into corresponding products in moderate to good yield (**3l** and **3m**). Furthermore, the halo-substituted (4-F, 3-Cl, 4-Cl, 3,4-2Cl, 3-Br, 4-Br) substrates worked well to produce the expected products **3f-3k** in good yields (76-87%). 2-Benzofuryl and 2-naphthyl also provided the furan products in 68% and 79% yield, respectively (**3o** and **3p**). Moreover, alkyl sulfonium salts were not tolerated in this [4+1] annulation reaction and we could not gain tert-butyl and cyclopropyl products (**3q** and **3r**). Finally, the structure of **3a** was determined by single-crystal X-ray diffraction analysis (see electronic supplementary information (ESI)).

Table 2 Scope of Sulfonium Salts*a*



*a*Reactions were performed with **1** (2.0 mmol, 1.0 equiv), Cu2O (10 mol %), TFA (2.0 mmol, 1.0 equiv), (NH4)2S2O8 (6.0 mmol, 3.0 equiv) and TMEDA (4.0 mmol, 2.0 equiv) in DMSO at 130 °C for 5 h. Isolated products. b) Lack of TFA.

In order to gain insight into the mechanism of furan formation, we performed a series of control experiments depicted in Scheme 2. Initially, when the model reaction was carried out in standard condition for 0.5 h, desired product **3a** and dihydrofuran compound **4a** was obtained in 45% and 42% yields, respectively (Scheme 2a). Under the standard reaction, dihydrofuran **4a** could easily transform into the furan product **3a** in excellent yield (Scheme 2b). It is possible that **4a** is an intermediate in this reaction.



**Scheme 2** Control Experiments.

Based on the abovementioned experimental results, a possible reaction mechanism for this reaction was proposed as shown in Scheme 3 (**3a** as example). Initially, DMSO (**2**) is activated by (NH4)2S2O8 to furnish a thionium ion **2'**, at the same time, benzoyl sulfonium salt **1a** transformed into the corresponding sulfur ylide **1a′** in presence of TMEDA. Later, the thionium ion **2'** was attacked by sulfur ylide **1a′** leading to the intermediate **A**. Quickly, the intermediate **A** underwent the following elimination of methanthiol to form α-methylene sulfonium intermediate **B**.6b, 6d The intermediate **B** quickly transformed into compound **B′**,19 which further participated in a [4+1] cycloaddition reaction with sulfur ylide **1a′** to converge on dihydrofuran **4a** by removing dimethyl sulfide. The dihydrofuran **4a** carried out oxidative aromatization reaction furnishing the desired product **3a**. In addition, the intermediates **A**, **B**, **B′**,and **4a** were detected by MS (see ESI).



**Scheme 3** A Possible Mechanism

In conclusion, we have developed a cascade oxidation/[4+1] annulation for the synthesis of polyfunctional furans from stabilized sulfonium salts and DMSO. DMSO play a very important role in this transformation, not only as solvent but also as one carbon source reagent. This reaction provide an efficient and practical strategy to activated DMSO for the construction of complex compounds from simple substrates. Further studies on the method for the synthesis of natural products are in progress in our laboratory.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (Grants 21472056, 21772051 and 21801022) for financial support. This work was also supported by the Yangtze Youth Talents Fund (No. 2016cqn25) and the Doctoral Scientific Research Startup Foundation of Yangtze University (No. 801090010135).

Conflicts of interest

There are no conflicts to declare.

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