**TFA-Mediated DMSO-Participant Sequential Oxidation/1,3-Dipolar Cycloaddition Cascade of Pyridinium Ylides for Assembly of Indolizines**



**ABSTRACT:** A trifluoroacetic acid (TFA)-mediated cascade oxidation/1,3-dipolar cycloaddition reaction of stabilized pyridinium salts with dimethyl sulfoxide (DMSO) has been developed in the presence of K2S2O8 and trimethylethylenediamine (TMEDA). In this transition-metal-free reaction, DMSO acts as a one-carbon source, thus providing a convenient method for the efficient and direct synthesis of various indolizine derivatives.

Indolizines are an important class of aromatic heterocycles. As a consequence of their unique electronic characteristics, they have found numerous applications in the fields of materials chemistry and photochemistry.1 Indolizine derivatives also possess a variety of biological activities, including antibacterial, anticonvulsant, antitumor and orexin receptor antagonist activities (Figure 1).2 Therefore, the development of efficient methods for the construction of functionalized indolizines from simple and available substrates would be highly valuable.



Figure 1. Selected examples bearing an indolizine skeleton.

Because of its availability, low toxicity and relative stability, dimethyl sulfoxide (DMSO) is commonly used as a polar solvent and mild oxidant in the synthesis of organic molecules.3 However, DMSO is not often considered as an important and versatile synthon in organic synthesis.4 Recently, the reactivity of DMSO has been explored in the synthesis of complex organic compounds, including DMSO-based methylthiomethylation (-CH2SMe),5 methylation (-Me),6 metheylenation (-CH2-),7 formylation (-CHO),8 cyanation (-CN),9 thiomethylation (-SMe),10 and methylsulfonylation (-SO2Me) reactions.11 Although DMSO has been used in syntheses to introduce various functional groups, to the best of our knowledge, there are fewer examples of its use in complicated sequential annulation/aromatization reactions to access heterocyclic aromatic rings.3, 12 For example, Zhang and coworkers reported an efficient copper-catalyzed annulation of amidines with DMSO for the synthesis of quinazolines via C–N bond forming reactions (Scheme 1a).13 Very recently, Chen et al. developed a palladium-catalyzed annulation of ortho-vinylanilines with DMSO leading to 4-aryl quinolones (Scheme 1b).14 In these methods, DMSO generally provides a “=CH-” fragment leading to six-membered cyclics, rather than five membered heterocycles. Herein, we report a transition-metal-free cascade oxidation/1,3-dipolar cycloaddition reaction of pyridinium ylides with DMSO that leads to indolizine derivatives (Scheme 1c).

**Scheme 1. DMSO-based Annulation/Aromatization reactions.**



Initially, we explored N-phenacylpyridinium iodide **1a** (0.2 mmol) as a model reactant. Heating reactant **1a** with DMSO at 130 °C for 8 h in presence of K2S2O8 and trimethylethylenediamine (TMEDA) afforded the desired indolizine **3a** in 71% yield (Table 1, entry 1). Encouraged by this result, we investigated other reaction conditions, including the variation of additive, oxidant and temperature. The results are summarized in Table 1. First, oxidants (K2S2O8, Na2S2O8, (NH4)2S2O8 and Oxone) were added to the reaction system (entries 1-4). K2S2O8 performed better than other oxidants. However, when the reaction was carried out in the absence of oxidant, we did not detect the formation of indolizine product **3a** (entry 11). Subsequently, a screen of various additives (TfOH, MsOH, TsOH∙H2O, HCl, H2SO4, and TFA) revealed that TFA is the best choice for the reaction (entries 5-10). Variation of the reaction temperature confirmed that 130 °C was the optimal condition for this protocol, with lower and higher temperatures affording decreased yields (entries 12-13).

**Table 1. Optimization of the Reaction Conditions*a***



|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| entry | additive | oxidant | temp (°C) | yield (%)*b* |
| 1 | - | K2S2O8 | 130 | 71 |
| 2 | - | Na2S2O8 | 130 | 66 |
| 3 | - | (NH4)2S2O8 | 130 | 59 |
| 4 | - | Oxone | 130 | 60 |
| 5 | TfOH | K2S2O8 | 130 | 78 |
| 6 | MsOH | K2S2O8 | 130 | 45 |
| 7 | TsOH∙H2O | K2S2O8 | 130 | 17 |
| 8 | HCl | K2S2O8 | 130 | 26 |
| 9 | H2SO4 | K2S2O8 | 130 | 30 |
| **10** | **TFA** | **K2S2O8** | **130** | **83** |
| 11 | TFA | - | 130 | 0 |
| 12 | TFA | K2S2O8 | 120 | 80 |
| 13 | TFA | K2S2O8 | 140 | 78 |
| *a*Reaction conditions: **1a** (0.2 mmol, 2.0 equiv), addictive (0.1 mmol, 1.0 equiv), oxidant (0.4 mmol, 4.0 equiv), TMEDA (0.1 mmol, 1.0 equiv), and DMSO (3 mL) for 8 h. *b*Isolated yields. | | | | |

With optimized conditions in hand, we investigated the scope of the *N*-(acylmethyl)pyridinium iodides **1** (Table 2). Notably, the electronic properties of the substituents on the aromatic ring system had little effect on the reaction. The pyridinium iodides bearing various electron-neutral (H), and electron-donating (4–Me, 3–OMe, 4–OMe, 3,4–2OMe, 3,4–OCH2O) substrates on the benzene ring were smoothly transformed into their corresponding products in 65–87% yields (entries 1–6). To our delight, good to excellent yields were also obtained for halo-substituted substrates (70–92%; entries 7–12). Heteroaryl (2-furyl and 2-thienyl) groups were also investigated, and good yields were afforded (75–82%; entries 13–14). In addition, even when the substrate contained sterically-hindered 1-naphthyl and 2-naphthyl groups, the corresponding products were obtained in 86% and 78% yields, respectively (entries 15–16). Finally, the structure of **3b** was determined by single-crystal X-ray diffraction analysis (see Supporting Information (SI)).

**Table 2. Scope of Pyridinium Ylides*a***



|  |  |  |  |
| --- | --- | --- | --- |
| entry | R | product | yield (%)*b* |
| 1 | Ph | **3a** | 83 |
| 2 | 4-MeC6H4 | **3b** | 72 |
| 3 | 3-MeOC6H4 | **3c** | 82 |
| 4 | 4-MeOC6H4 | **3d** | 65 |
| 5 | 3,4-(MeO)2C6H3 | **3e** | 76 |
| 6 | 3,4-(OCH2O) C6H3 | **3f** | 87 |
| 7 | 2-ClC6H4 | **3g** | 70 |
| 8 | 4-ClC6H4 | **3h** | 91 |
| 9 | 2,4-Cl2C6H3 | **3i** | 92 |
| 10 | 3,4-Cl2C6H3 | **3j** | 83 |
| 11 | 3-BrC6H4 | **3k** | 81 |
| 12 | 4-BrC6H4 | **3l** | 76 |
| 13 | 2-furyl | **3m** | 82 |
| 14 | 2-thienyl | **3n** | 75 |
| 15 | 1-naphthyl | **3o** | 86 |
| 16 | 2-naphthyl | **3p** | 78 |
| *a*Reaction conditions: pyridinium salts **1** (2.0 mmol, 2.0 equiv), TFA (1.0 mmol, 1.0 equiv), TMEDA (1.0 mmol, 1.0 equiv), and K2S2O8 (4.0 mmol, 4.0 equiv) was stirred in DMSO (5 mL) at 130 °C for 8 h. *b*Isolated yields. | | | |

Encouraged by these results, we further examined the scope of the *N*-phenacylpyridinium salts **1** (Scheme 2). Pyridinium salts with substituents 3, 5-2Me, 4-CO2Me, and 4-CN on the pyridinium group gave the corresponding products in 58-71% yields (**4a**, **4c** and **4d**). Unfortunately, the desired products **4c** and **4e** were not detected with 4-OMe or 4-I substituents on the pyridinium group. The isoquinolinium salt was also a suitable substrate for this transformation, leading to the corresponding product **4f** in 74% yield.

**Scheme 2. Scope of Pyridinium salts*a***



*a*Isolated products.

On the basis of our experimental results, a possible reaction mechanism was proposed (Scheme 3, using **3a** as an example). Initially, DMSO (**2**) is activated by K2S2O8 to furnish a thionium ion **2′**.15 This is attacked by the pyridinium ylide **1a****′**,derived from *N*-phenacylpyridinium iodide **1a** in presence of TMEDA, to furnish intermediate **I**. Next, intermediate **I** undergoes rapid elimination of methanethiol to form the propenyl ketone pyridinium **II**.This intermediate participates in a [3+2] cycloaddition reaction with pyridinium ylide **1a′**, converging on the tetrahydroindolizine **III**. Intermediate **III** is oxidized to dihydroindolizine **IV**, which eliminates pyridine to afford the desired product **3a**. It is worth noting that the potential intermediates **1a′**, **II**, **III**, and **IV** were also detected by ion trap mass spectrometry (ITMS) (see SI).

**Scheme 4. A Possible Mechanism**



In conclusion, we have developed a transition-metal-free cascade oxidation/1,3-dipolar cycloaddition reaction for the efficient and convenient synthesis of indolizine derivatives from readily available pyridinium salts and DMSO. DMSO plays a vital role in this transformation, not only serving as a solvent, but also as a one-carbon source. Studies on the application of this method to the synthesis of natural products are underway in our laboratory.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, product characterizations, crystallographic data, and copies of the 1H and 13C NMR spectra (PDF)

X-ray data for **3b** (CIF)

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**Notes**The authors declare no competing ﬁnancial interest.

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