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Tf_2O-mediated Reaction of Alkenyl Sulfoxides with Unprotected Anilines in Flow Microreactors

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Flow microreactors have allowed an efficient extended Pummerer reaction of ketene dithioacetal monoxides with anilines by precise control of unstable sulfonium intermediates and spatial separation of the generation of the intermediates and the nucleophilic attack to the intermediates. A new iodonium-mediated cyclization has been devised to convert the products, thioimidates, into indoles.

Keywords: Flow microreactor, Pummerer reaction, Indole

Organosulfur compounds are ubiquitous in nature and play important roles in organic synthesis as well as biochemistry and material science.[1] One notable feature of organosulfur chemistry lies in stable high-oxidation-state species such as sulfoxides, which enhances their usefulness as synthetic intermediates. Stable sulfoxides can be activated by the action of acid to induce sulfur-specific reactions.[2] The Pummerer rearrangement of alkyl sulfoxides is such a classical example.[3] In the last couple of decades, the Pummerer chemistry has been rapidly extending its frontier to alkenyl and aryl sulfoxides as substrates to lead to the exciting discovery of novel characteristic transformations including metal-free C(sp^2)–H functionalizations.[4–6]

In the modern Pummerer chemistry,[4–6] the choice of acidic activators is crucial. Strong activators such as triflic anhydride (Tf_2O) and trifluoroacetic anhydride are usually used to generate very reactive cationic sulfonium intermediates. However, it is generally difficult to control such short-lived intermediates. Indeed, during the course of our study, the reactions of alkenyl and aryl sulfoxides often resulted in the formations of complex mixtures, especially when Tf_2O was used as the activator.[4j,4k,5] Taming reactive short-lived sulfonium intermediates is important to extend the Pummerer frontier further.

Flow microreactors have emerged as a game-changing technology in organic synthesis, offering many practical advantages.[7] Most notably, flow microreactors enable to precisely control very unstable intermediates by virtue of extremely fast mixing of a reagent and a substrate and residence time (the duration between the addition of a reagent and that of the next reagent) as short as a few milliseconds.[8] We envisioned that flow microreactors would offer an opportunity to tame reactive short-lived sulfonium intermediates in the extended Pummerer chemistry.[9] As an additional advantage, flow microreactors allow spatial separation of the activation step and the nucleophilic trapping step: we can eliminate the possibility of unwanted direct nucleophilic attack of a reactive nucleophile onto an acid anhydride activator.

Here we disclose a new Tf_2O-mediated extended Pummerer reaction of ketene dithioacetal monoxides (KDMs) with nucleophilic unprotected anilines[10,11] taking advantage of flow microreactors. The setup to realize the target reaction is shown in Figure 1, consisting of two T-shape micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**). Phenyl KDM **1a** and Tf_2O were mixed together in **M1** and reacted in **R1** to generate reactive sulfonium species from **1a**. The species was then trapped with aniline (**2a**) in the presence of *i*Pr_2EtN in **M2** and **R2** to give a mixture of products.

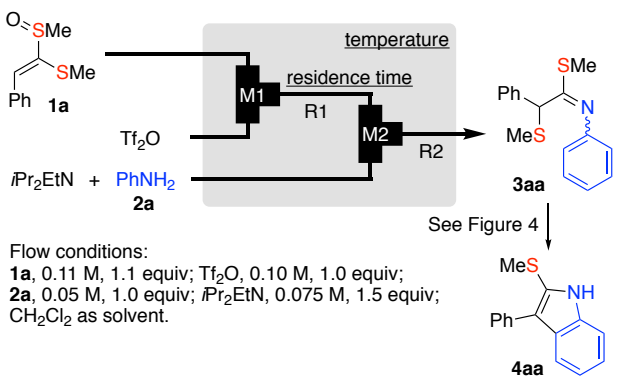


Figure 1. Setup for reaction of KDMs with anilines in flow microreactors.

In our first trial, to our surprise, we did not obtain the expected indole **4aa** at all but thioimidate **3aa**[12] as the major product apparently through skeletal rearrangement (*vide infra*). Because we later found a new transformation that can easily convert **3aa** into **4aa** (*vide infra*), we started optimizing reaction conditions to obtain **3aa** efficiently.

Given that careful control of unstable sulfonium intermediates is important, we investigated the effects of the temperature of **R1** and the residence time in **R1** on the yield of **3aa** (Figure 2). In regard to the yield of **3aa** and the amounts of by-products, we concluded that the best combination is 0 ˚C and 1.0 s for the temperature and the residence time, respectively, to yield **3aa** in 91% GC yield. Probably because of the instability of the sulfonium species, a higher temperature and a longer residence time led to a lower yield of **3aa** (45% yield at 30 ˚C and for 24 s, for instance). The reaction at a temperature as low as 0 ˚C for a short residence time (0.24 s) resulted in a small decrease of

the yield of **3aa** (84%) because the activation of **1aa** with Tf_2O would be incomplete.

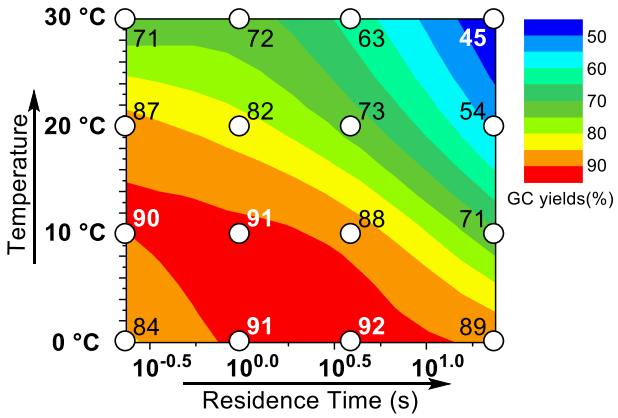


Figure 2. Temperature–residence time mapping for the reaction of KDM **1a** with aniline (**2a**) in the flow microreactor system.

With the optimized conditions in hand, we screened the reaction scope of anilines. As shown in Figure 3, the scope has proved to be very wide. Electron-rich as well as electron-deficient anilines similarly participated in the reaction to isolate **3aa**–**aj**. The propargyl ether, chloro, ester, and cyano groups in **3ad**, **3ae**, **3af**, and **3ah**, respectively, were compatible under the reaction conditions. The *ortho*-methyl substituent and 1-naphthyl skeleton had no influence on the yields of **3ak** and **3al**, respectively. It is worth noting that all the reactions invariably provided the products in high yields (84–88%), which underscores the advantage of the flow microreactor technology. In addition, the aniline-independent behavior strongly suggests that nucleophilic attack of anilines and the subsequent reactions in **R2** do not involve a yield-determining step and that control of the reactions in **R1** is crucial. Aliphatic cyclohexylamine reacted to furnish the corresponding thioimidate **5** in good isolated yield after careful purification albeit **5** is not so stable on silica gel (eq 1). *N*-methylaniline, a secondary amine, also reacted to yield the corresponding enamine **6** (eq 2).

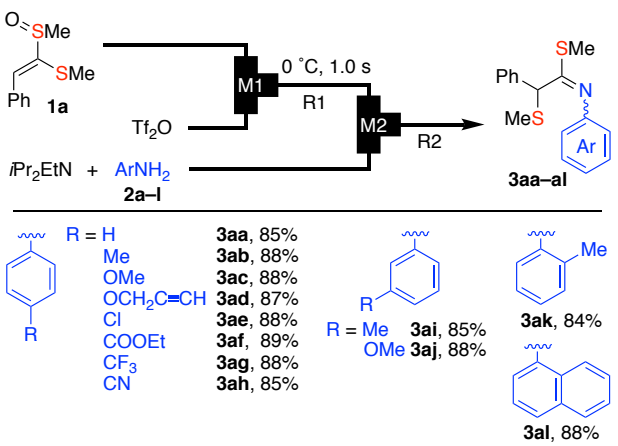
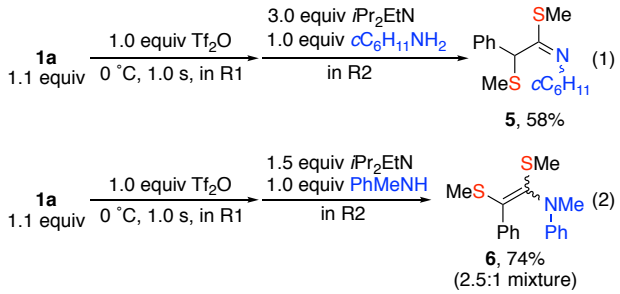
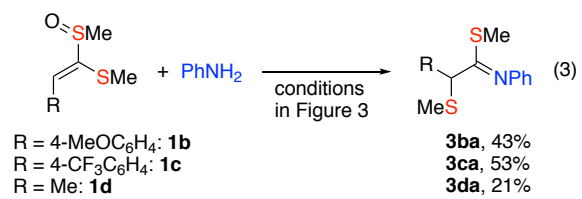


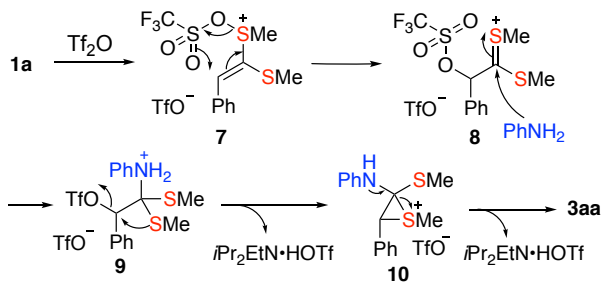
Figure 3. Scope of anilines.



The scope of KDMs was also investigated. Both electron-donating methoxy and electron-withdrawing CF_3 groups in **1b** and **1c** diminished the yields of the corresponding products (eq 3). The modest yields would originate from differences in the formation rate and stability of the key reactive sulfonium species generated from these electronically biased KDMs. This would be also the case for the alkyl-substituted KDM **1d**, and **3da** was obtained in only 21% yield. Further optimization study would be necessary for each KDM.



Although the exact reaction mechanism for the formation of thioimidates **3** is unclear at this moment, we suppose a mechanism in Scheme 1. KDM **1a** is activated by Tf_2O to yield sulfonium cation **7**. Cation **7** would undergo rapid rearrangement to yield benzylic triflate **8**.[13] Aniline injected in **M2** would react with **8** to yield **9** bearing an *N*,*S*,*S*-orthoester unit. Intramolecular substitution of the triflate with a nucleophilic methylsulfanyl group results in the formation of thiiranium cation **10**. Smooth ring-opening of **10** provides thioimidate **3aa**.[14]



Scheme 1. Supposed mechanism for thioimidate formation.

To convert thioimidates **3** into indoles, we needed to invent a new cyclization reaction. Taking advantage of the high electron density at the benzylic sulfide unit, we found that an oxidant, bis(pyridine)iodonium tetrafluoroborate, promotes cyclization to yield 2-methylsulfanyl-3-arylindoles

4 (Figure 4). The reaction scope is wide although the electron-deficient aniline units in **3ag** and **3ah** retarded the cyclization. The cyclization of *m*-methoxyaniline derivative **3aj** was exclusively regioselective to yield **4aj** albeit the corresponding *m*-methyl analogue **3ai** was converted to a regioisomeric mixture of **4ai**. By considering these electronic effects observed above, the cyclization is likely to proceed via oxidation of the benzylic sulfide by the iodonium reagent followed by Friedel-Crafts-type cyclization (Scheme 2). A substoichiometric amount of $(py)_2IBF_4$ was sufficient because MeSI generated *in situ* would also serve as an oxidant.

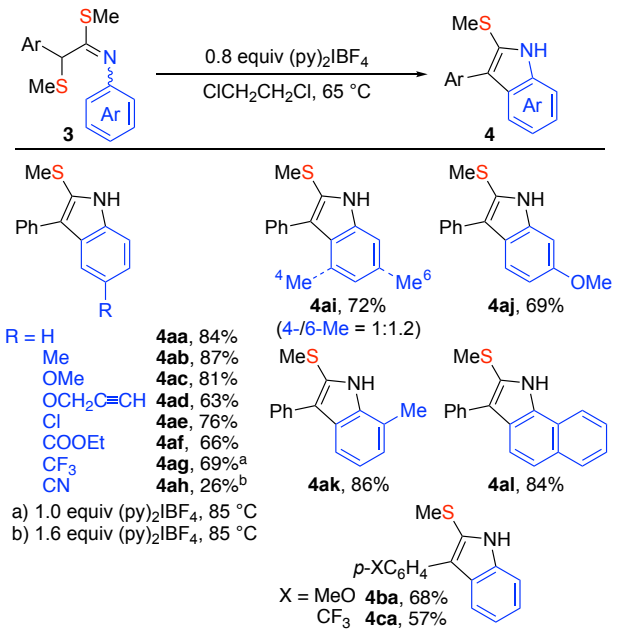
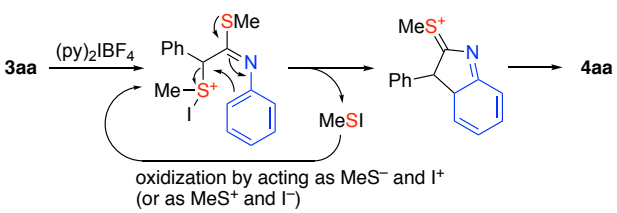
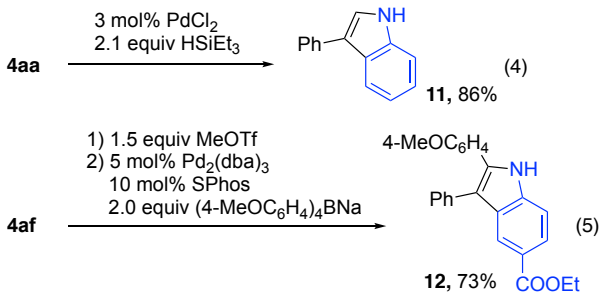


Figure 4. Iodonium-promoted cyclization into indoles.



Scheme 2. Supposed mechanism for indole formation.

N-Unprotected indoles **4** bearing a 2-methylsulfanyl group underwent various substitution reactions at the 2-position. Palladium-catalyzed reduction of **4aa** with triethylsilane[15] took place smoothly to yield **11** (eq 4). *S*-Methylation of **4af** followed by Suzuki-Miyaura arylation with tetraarylborate provided 2-arylindole **12** (eq 5).[5g,16,17]



In summary, we have developed an efficient extended Pummerer reaction of ketene dithioacetal monoxides with unprotected anilines, taking advantage of flow microreactors. The flow microreactors allowed us to precisely control unstable sulfonium intermediates and to spatially separate the generation of the intermediate and the nucleophilic attack onto the intermediates. The products are useful thioimidates that undergo iodonium-mediated cyclization into indoles of interest. The 2-methylsulfanyl group in the indole products participate in several transformations including palladium-catalyzed cross-coupling reactions. Further extension of Pummerer-type chemistry using flow microreactors is now in progress.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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12 Thioimidates **3** undergo fast *E*/*Z* isomerization even at room temperature.

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14 As far as we investigated, the formation of *i*Pr$_2$EtN•HOTf in **M2** did not cause clogging. This indicates the solubility of the ammonium salt in dichloromethane is reasonably high. In case of clogging, washing with acetone should be suitable.

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17 Although we conducted Suzuki-Miyaura arylation with neutral organoboron compounds and bases, these attempts did not give good results and side reactions such as demethylation by base proceeded.