THE INTERRUPTED PUMMERER REACTION: DESIGN OF SULFOXIDES AND THEIR UTILITY IN ORGANIC SYNTHESIS

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Abstract – Acid anhydride-activated sulfoxides can undergo a variety of cascade reactions after reacting with nucleophiles on its sulfur atom. Originally regarded as an abnormal phenomenon that occurs under Pummerer reaction conditions, the reports of the reaction increased gradually, and research regarding sulfoxide reactivity has advanced. In recent years, the term ‘interrupted Pummerer reaction’ has been introduced, and the transformation has been actively incorporated into the development of new research areas. Such studies have yielded numerous valuable sulfoxides, which contribute to the precise reaction control and to the generation of practical products. Notably, the outcome of the interrupted Pummerer reaction is characteristic for each nucleophile.

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1. INTRODUCTION

Sulfur atoms exhibit several possible valences and can exist in several forms, such as sulfanes (sulfides), sulfoxides, sulfonium salts, sulfur ylides, and sulfuranes. Therefore, detailed studies have been conducted on the physical properties and chemical reactivity of sulfur atoms, and numerous intriguing studies have been reported. In addition, sulfur-containing products have attracted considerable attention as functional
materials, and have been utilized in various fields, such as polymer materials, electronic materials, pharmaceuticals, and agricultural chemicals. Sulfoxides are comprised of polarized S-O bonds and the sulfur atom is an asymmetric center, therefore, the features have elicited numerous studies. In addition, sulfoxides undergo various reaction processes following activation by acid anhydrides such as TFAA and Tf₂O. A particularly interesting example, namely the interrupted Pummerer reaction, involves a nucleophilic attack on the sulfur atom of the activated sulfoxide, which can be followed by various cascade reactions. Recently, vigorous research has been conducted regarding the utilization of this reaction for carbon-carbon bond formation and concise syntheses of natural products. Along with those reports, excellent reviews on C-H functionalization and [3,3]-sigmatropic transition via interrupted Pummerer reaction, and reactivity of sulfur (IV) species have emerged, recently. Based on our unexpected findings from an interrupted Pummerer reaction in 1997, our group has been conducting research on the reaction, with the aim of expanding its generality and developing new applications. In the process of the research, we realized that the type of nucleophiles is the most important factor for the determination of the reaction sequence and products.

In this review, we have classified the functionalization induced by interrupted Pummerer reaction according to the types of the nucleophile and the successive reactions.

2. REACTIONS OF ALCOHOLS
The most well-known reaction of activated sulfoxide and alcohol is the Swern oxidation. A hydroxy group is activated by a sulfonium salt, which is followed by elimination to afford carbonyl compounds. In Swern-type oxidations, sulfide was used as the leaving group to form the carbonyl compound. In contrast, sulfoxide moiety, generated by interrupted Pummerer reaction with sulfonium and alcohol, was used as the leaving group to install nucleophiles. Mukaiyama and coworkers developed the one-pot C-benzylation of sodium enolate using diphenyl sulfoxide (1) and Tf₂O system (Scheme 1). Benzyl alcohol 3 was activated by sulfonium species 2 in the presence of a base, and subsequent nucleophilic substitution by a sodium enolate, a soft nucleophile, delivers 4 with leaving sulfoxide moiety. Under these conditions, benzaldehyde derivatives were not obtained. The predominant formation of the C-alkylated product was explained by the fact that diphenyl sulfoxide is a soft leaving group.
As a similar concept as Mukaiyama, direct glycosylation with 1-hydroxy glycosyl donor 5 using the Ph₂SO-Tf₂O system accompanying the elimination of diphenyl sulfoxide (1) was demonstrated by Gin (Scheme 2). This dehydrative glycosylation method involves \textit{in situ} activation of the anomeric hydroxy group by the sulfonium salt 2. This procedure allows for the direct preparation of a wide variety of anomeric-substituted products 6,\(^8\)

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{MeO} & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

Scheme 2. Direct glycosylation with a 1-hydroxy glycosyl donor 5 using sulfonium salt 2

As a related glycosylating method, Wan’s group developed a glycosylation reaction with a novel glycosyl donor 8 bearing a 2-(2-propylsulfinyl)benzyl group as a recyclable leaving group (Scheme 3). Sulfoxide 8 was activated by Tf₂O and left from saccharide moiety. The following coupling with 7 gave disaccharide 9 and sulfoxide 10 in excellent yields.\(^9\)
In 1974, Martin reported the reaction of diaryldialkoxy sulfurane 12 towards cyclohexane-1,2-diols 11 (Scheme 4). The diol trans-11 gave cyclohexene oxide (13) in 97% yield by the intramolecular nucleophilic substitution of alcohol with eliminating diphenyl sulfoxide (1). However, the diol cis-11 produced cyclohexanone (14) by the elimination of 1 and 2-(2-thiophenyl)cyclohexanone (16) via the sigmatropic rearrangement of intermediate 15.10

Scheme 4. Reactions of diaryldialkoxy sulfurane (Martin’s sulfurane: 12) and diols 11
3. REACTIONS OF PHENOLS

In the reaction with phenols, sulfonium was used to functionalize the ortho-position of phenol through aryloxsulfonium species by combination with continuous reactions such as sigmatropic rearrangement or nucleophilic substitution. The reaction of activated DMSO with substituted phenols 17 produced o-methylthiomethylated products 18 by Sommlet-Hauser-type rearrangement, along with hemithioacetals 19 (Scheme 5).11

Scheme 5. ortho-Methylthiomethylation of phenols 17 reported by Moffatt

As the sequence of interrupted Pummerer reaction-[3,3]-sigmatropic rearrangement, the biaryl coupling of aryl sulfoxides 20 and phenols 21 has been reported by Yorimitsu and Osuka (Scheme 6).12 By the activation of aryl sulfoxides 20 with TFAA, interrupted Pummerer reaction and [3,3]-sigmatropic rearrangement were proceeded to give biaryls 22. Coupling reactions between heteroaromatic sulfoxides and substituted phenols or naphthols proceeded in high yields. The coupling product 22c was transformed into a helicene derivative 23.

Scheme 6. Biaryl coupling via interrupted Pummerer-sigmatropic rearrangement reactions sequence
They also reported that the treatment of CF$_3$-substituted ketene dithioacetal monoxide (CF$_3$-KDM) 24 with Tf$_2$O and phenols 25 afforded benzofurans 27 through ortho-functionalized phenol, involving the sequential [3,3]-sigmatropic rearrangement of sulfonium salts 26 (Scheme 7). With the addition of TFAA as a mild activator at ambient temperature, a variety of KDMs provided a practical and diversity-oriented route to multi-substituted benzofurans. They additionally reported that the 2-methylthio moiety in benzofurans could be applied to Pd- or Ni-catalyzed cross-coupling reactions with aryl magnesium or zinc reagents to give multi-substituted benzofurans 28. Repeating their sequential strategy after oxidizing sulfide moiety of the product realized the synthesis of oligoarenes. In addition, this strategy was applied to C-F arylation of polyfluorophenols.

Scheme 7. Benzofuran formation from ketene dithioacetal monoxide 24 and phenols 25

Procter reported that the reaction of benzothiophene S-oxides 29 with TFAA triggered an interrupted Pummerer reaction with phenols 30 to provide the corresponding intermediates 31 (Scheme 8). Consequent charge accelerated [3,3]-sigmatropic rearrangement of 31 placed the phenols at the C3-position of benzothiophenes to deliver 32 with complete regioselectivity.
Scheme 8. Construction of C3 aryl-benzothiophene from benzothiophene S-oxides 29 with phenols 30

In the case of 2-substituted benzothiophene S-oxides 33, the reaction of activated 33 and phenols 34 proceeded by the combination with [3,3]-sigmatropic rearrangement and subsequent cyclization of ortho-substituted phenols to form S,O-acetals 35 (Scheme 9). The successive oxidation of 35 provided the corresponding sulfones 36, which were cleaved with the treatment of base to rearomatize to a benzofuran scaffolds. Thus, the generated sulfinate motif was transformed with alkyl halides, or by Pd-catalyzed desulfinative coupling with aryl bromides, to produce various C3-arylated benzofurans 37.17

Scheme 9. Transformation from 2-substituted benzothiophene S-oxides 33 to 3-aryl-benzofurans 37

When 3-substituted benzothiophene S-oxides 38 was used, the cascade reaction, contains three reactions, occurred as follows (Scheme 10). As the first step, the activation of 3-substituted benzothiophene
S-oxides 38 caused an interrupted Pummerer reaction with the phenol derivatives 39 to yield sulfonium intermediates 40. With a lack of aromaticity, [3,3]-sigmatropic rearrangement proceeded as the second step, placing the phenols at the C3 position. As the third step [1,2]-migration of the generated benzo thiophenium intermediates 41 was assisted by BF$_3$·OEt$_2$ afforded ortho-substituted phenols 42. They additionally synthesized BTBF upon heating 42b under acidic conditions, which is the oxygen derivative of BTBT, a key component of OLEDs.$^{18}$

![Scheme 10. Interrupted Pummerer/sigmatropic rearrangement/migration cascade](image)

The sulfonium mediated coupling reaction utilized the elimination of sulfide was achieved by the interrupted Pummerer reaction-nucleophilic substitution sequence. The intermolecular coupling reaction of phenols or electron-rich arenes was studied using 1 and Tf$_2$O system. The reaction of 4-tert-butylphenol (43) with the electron-rich nucleophile such as dimethoxybenzene afforded the cross-coupled biaryl 44, involving the elimination of diphenyl sulfide as the leaving group (Scheme 11).$^{19}$

![Scheme 11. Biaryl coupling reaction of phenol 43 and electron-rich arene](image)
The catalytic system by re-oxidation of generated sulfide has been developed. 3-Methylbenzothiophene S-oxide (45) catalyzed the oxidative coupling of 2-naphths 46 (Scheme 12). Naphthoxysulfonium intermediates 47 was formed by an interrupted Pummerer reaction. Thus, another equivalent of naphths 46 engaged with 47 to produce BINOLS 48 and eliminate 3-methylbenzothiophene, which was re-oxidized with H$_2$O$_2$-TFA. This method was applied to the synthesis of (±)-nigerone (49), a compound exhibiting antitumor and antibacterial activities.\textsuperscript{20} Utilizing this concept, oxidative cross-coupling of phenols and various nucleophilic partners, including phenols, 1,3-diketones, and arenes has been reported through phenoxyxsulfonium intermediates with non-catalytic system.\textsuperscript{21}

Scheme 12. Sulfoxide-catalyzed oxidative coupling of 2-naphths 46

Another example of the phenol functionalization is reported by Huang et al. They identified that the reaction between activated sulfonium salts and phenols 50 in acetonitrile produced o-hydroxyarylсуlfonium salts 51 (Scheme 13). Treatment of 51 with the base under aqueous micellar conditions containing a surfactant, produced 53 by Smiles rearrangement of 52.\textsuperscript{22}
4. REACTIONS OF AMINES AND NITRILES

In the reactions with amines and nitriles, various reactions triggered by N-S bond formation have been reported. In 1975, Swern reported that activated DMSO reacted with amines 54 to give iminosulfuranes 55 (Scheme 14a). Moreover, compound 56, prepared from a sulfanilamide, was partially transformed to aniline 57 by successive Sommlet-Hauser rearrangement, following treatment with basic resins (Scheme 14b). 23

(a) Conversion of DMSO to iminosulfurane 55; (b) transformation of iminosulfurane to ortho-functionalized aniline 57

Wright reported that the treatment of 2-(benzylsulfinyl)benzanilide 58 with trichloroacetic anhydride (TCAA) afforded N-phenylbenzisothiazolone 59 in 84% yield along with benzyl trichloroacetate. In this reaction, the Pummerer cyclized product 60 was isolated in trace amounts (Scheme 15). 24
Kita reported that chiral sulfoxides, bearing an achiral amide group, gave β-lactams with high ee’s under silicon-induced Pummerer conditions (Scheme 16).\textsuperscript{25a} Sulfoxides (S)-61 were transformed into intermediates 62, which yielded chiral pseudo-isothiazolones 63 via axial attack by the amide anion. Successively, the rearrangement of amide moiety driven by N-S bond cleavage gave the β-lactams (R)-64.

The reactions of β-sulfinyl amine diastereomers 65 and 69 with TFAA were studied briefly by Zanda and coworkers (Scheme 17). X-Ray analyses of the products suggested that the S$_{N}$2 reaction of the trifluoroacetate anion occurred at the α-position of the sulfur atom in sulfurane intermediates 66 and 70. In addition, the presence of the four-membered cyclic σ-sulfurane 66 was detected by NMR spectroscopy in the reaction of diastereomer 65. The reaction rate of the other diastereomer 69 was faster than that of 65 owing to increased steric repulsion occurring in sulfurane intermediate 70.\textsuperscript{26}
Scheme 17. Competition of reactivity between β-amino sulfoxide diastereomers under Pummerer reaction conditions

The reaction of diphenyldialkoxy sulfurane 12 with secondary amide 73 resulted in cleavage of the amide moiety at room temperature to give sulfilimine 74 and benzoate 75 (Scheme 18). In the reaction of 12 with a tertiary amide, DMF, used as the solvent, remained intact.27

Scheme 18. Cleavage of secondary amide 73 into sulfilimine 74 and benzoate 75

Magnier developed the preparation of perfluoroalkylated sulfilimines 79 from activated perfluoroalkylated sulfoxides 76 and nitriles (Scheme 19a). The nitrogen atom of nitrile attacks the sulfur of sulfonium 77 to form the triflic imide intermediate 78. Consequently, the hydrolysis produced sulfilimines 79 in good yields.28 Additionally, they discovered that the use of aryl sulfoxide 80 at higher temperatures resulted in the electrocyclization of sulfilimino keteneacetal 81 to generate (perfluoroalkylsulfanyl)phenylacetonitrile 83 in good yields with a small amount of sulfilimine 82 (Scheme 19b).29
Scheme 19. Sulfilimine formation from nitriles and reactions thereof

Peng and Wang reported the α-arylation of alkyl nitriles 85 with aryl sulfoxides 84 (Scheme 20). $^1$H-NMR spectroscopy and DFT calculations revealed that the reaction pathway involved E1cB elimination from

Scheme 20. [3,3]- and [5,5]-sigmatropic rearrangements of ketenimine sulfonium intermediate
intermediate 86 and [3,3]-sigmatropic rearrangement.\textsuperscript{30a,c} When α-stannyl nitrile (X = SnBu\textsubscript{3}) was employed, the reaction proceeded under the milder reaction conditions with TFAA.\textsuperscript{30b} On using allyl nitrile (R\textsuperscript{2} = vinyl), γ-arylation of allyl nitrile was occurred by [5,5]-sigmatropic rearrangement of 88 to deliver sulfide 90.\textsuperscript{31}

Yorimitsu reported dehydrogenative coupling of aryl sulfoxides 91 with anilines 92 by their cascade strategy of interrupted Pummerer reaction-sigmatropic rearrangement through dication intermediates 93 to provide biaryls 94 (Scheme 21).\textsuperscript{32}

![Scheme 21. Functionalization of ortho position of anilines 92 by cascade process](image)

**5. REACTIONS OF ENOLIZABLE KETONES**

In the reaction with ketones, the attack of ketone on the sulfur atom triggered the successive reaction such as dealkylation or sigmatropic rearrangement. 3-Acetoxy-\(N,N\)-dialkylbenzo[\(b\)]thiophene-2-carboxamide 98 was readily obtained from sulfoxide 95 under heating in Ac\(_2\)O (Scheme 22). A plausible reaction

![Scheme 22. Formation of benzo[\(b\)]thiophene-2-carboxamide 98 by intramolecular reaction](image)
mechanism entails the interrupted Pummerer reaction of 96 and the cleavage of C\textsubscript{sp3}-S bond to remove ethyl acetate from the sulfonium salt 97.\textsuperscript{33}

Yorimitsu and Oshima group has investigated the reaction of 2-(2,2,2-trifluoromethylidene)-1,3-dithiane monoxide (100) with ketone (Scheme 23). The sulfoxide 100 was activated by Tf\textsubscript{2}O and the oxygen atom of acetophenone (99) executed a nucleophilic attack at the cationic sulfur atom. The resulting vinyloxysulfonium species 103 underwent [3,3]-sigmatropic rearrangement to form 101, which upon the acidic treatment, produced thioester 102 in 73% yield. Product 102 was further transformed into 3-trifluoromethylated furan, thiophene, and pyrrole.\textsuperscript{34}

Scheme 23. Reaction of ketene dithioacetal monoxide 100 with acetophenone (99)

Maulide disclosed that the reaction of Martin’s sulfurane (12) with active methylene compounds, such as 104, provided sulfur ylide 105 in high yields. Phenyl migration from sulfur to oxygen in ylide 105 led to the formation of 106 under thermolysis conditions (Scheme 24a).\textsuperscript{35} His group additionally developed the α-arylation of β-ketoester 107 using diphenyl sulfoxide (1). The complete \textit{ortho}-selectivity of 108 arises from the nucleophilic attack of 107 at the sulfur atom and sequential [3,3]-sigmatropic rearrangement (Scheme 24b).\textsuperscript{36} In the case of the simple carbonyl compounds, its silyl enol forms 109 proceeded the reaction with sulfoxide 1 and p-toluenesulfonic anhydride to generate α-arylated products 110 in moderate yields (Scheme 24c).\textsuperscript{37}
Scheme 24. Reactions of sulfurane and active sulfonium species with carbonyl compound

Peng reported the dearomatization of aryl sulfoxide 111 with silyl enol ether 112 by interrupted Pummerer/[3,3]-sigmatropic rearrangement/nucleophilic substitution cascade (Scheme 25). The activation of 111 with acid anhydride \((\text{R}_2\text{O})\) induced interrupted Pummerer reaction by the attack of the oxygen atom of 112. The following [3,3]-sigmatropic rearrangement and cyclization gave acetal 113. When 111 was treated with \(\text{Tf}_2\text{O}\), intermediate 113 was highly reactive to be captured by another 112 to provide 114. On using TFAA as \(\text{R}_2\text{O}\), the addition of external nucleophile was feasible to give 115 due to the intermediate 113 was less reactive than in the case of \(\text{Tf}_2\text{O}\).

Scheme 25. Dearomatization and functionalization of aryl sulfoxide 111 with 112
6. REACTIONS OF ALKENES AND ALKYNES

In the reactions with alkene and alkyne, sulfonium generates vinyl or allylsulfonium intermediate, which induces continuous reaction. During their studies on dimethyl sulfide ditriflate (DMSD), generated from DMSO and Tf₂O, Nenajdenko and Balenkova revealed that the reaction between DMSD and alkenes 115a-115d produced corresponding sulfonium salts 116a-116d. The consequent demethylation of the sulfonium salts with diethylamine delivered vinyl sulfides 117a-117d (Scheme 26).³⁹

\[
\begin{align*}
115a-115c & \quad \text{DMSO, Tf}_2O \quad \text{CH}_2\text{Cl}_2 \quad -30 \text{ to } -15 ^\circ \text{C} \quad 116a-116c \ (54-78\%) \quad 117a-117c \ (68-89\%)
\end{align*}
\]

Scheme 26. C(sp²)-H Thiomethylations by DMSD via vinylsulfonium intermediate 116

3-Arylbenzo[b]thiophene 121 was readily prepared from 118 under heating in Ac₂O (Scheme 27). A plausible reaction mechanism entails the interrupted Pummerer reaction of activated sulfonium intermediate 119 and the intramolecular attack of alkene moiety generated sulfonium intermediate 120. The sequential removal of the ethyl group afforded benzothiophene 121.⁴⁰

\[
\begin{align*}
118 & \quad \text{Ac}_2\text{O} \quad 100 ^\circ \text{C} \quad 119 \quad \text{AcO} \quad -\text{AcOH} \quad 120 \quad \text{AcO} \quad -\text{AcOEt} \quad 121 \ (77\%)
\end{align*}
\]

Scheme 27. Formation of 3-arylbenzo[b]thiophene 121 by attack of alkene moiety

As the combination of interrupted Pummerer reaction and nucleophilic substitution, Mukaiyama et al. developed the reaction of styrene derivative 122 with diphenylsulfonium to isolate 2-arylethenyl(diphenyl)sulfonium salt 123. The reaction of 123 with primary amine and base afforded the corresponding 2-arylziridine 124 in high yields, while that of sodium or potassium salt of cyclic imide provided α-imidostyrene 125 (Scheme 28a). The above reaction was applied to 1,1-disubstituted alkene 126 to obtain the corresponding allyl amine 129 (Scheme 28b). The reaction mechanism involved the
formation of vinylsulfonium intermediate 127, followed by double bond migration to allylsulfonium intermediate 128, and nucleophilic substitution with amine.\textsuperscript{41}

### Scheme 28. Formations of vinylsulfonium salt from styrene and their transformations

Procter revealed that C–H functionalization of alkenes 130 has been achieved by the combination of the interrupted Pummerer reaction and Negishi cross-coupling in a one-pot procedure (Scheme 29). In this reaction, sulfonium species 132, generated from readily available sulfoxide 131 and Tf\(_2\)O, was employed as the precursor for the cross-coupling reaction (Scheme 29a). In the case of alkyne 134, the same cascade

### Scheme 29. C-H Functionalizations via sulfonium species as precursor of Ni-catalyzed coupling
sequence proceeded on sp carbons to form internal alkyne 135 (Scheme 29b). Remarkably, the tetra-substituted alkenes 137 were achieved by incorporating the cyclization of substrates 136 into the cascade sequence (Scheme 29c).

As the reaction induced by the combination with sigmatropic rearrangement, Xu and Li reported the allylic C–H alkylation of alkene 138 (Scheme 30). In this reaction process, the formation of sulfonium salt by interrupted Pummerer reaction occurred successive [2,3]-sigmatropic rearrangement in the presence of a base to give 139. The reaction was applicable to trisubstituted and gem- and vic-disubstituted olefins.

Scheme 30. C–H Thioalkylation of allylic position of cyclohexene 138

Among their pioneering works on the aromatic Pummerer reaction, in 2004, Kita and Akai disclosed the regioselective alkylation of electron-rich heteroaryl sulfoxides 140 and 141, such as furans, thiophenes, and indoles under Pummerer reaction condition (Scheme 31).

Scheme 31. Regioselective C–C bond formation using aryl sulfoxides 140 and 141
In 2011, Procter’s group reported the sulfoxide-directed ortho-allylation of aryl and heteroaryl sulfoxides upon treatment with allylsilanes, exploiting the interrupted Pummerer-sigmatropic rearrangement cascade approach to functionalize aromatic rings (Scheme 32). Following the activation of sulfoxides with Tf₂O, the reaction with allylsilanes generated the allylsulfonium intermediates by an interrupted Pummerer reaction. Consecutive thio-Claisen rearrangement formed a C–C bond by transferring the allyl group to the ortho-position to afford allylated products with complete regioselectivity. 

They additionally expanded the regioselective C–H propargylation of aryl sulfoxides to yield 149, employing propargyltrimethylsilanes in the interrupted Pummerer reaction-triggered cascade sequence (Scheme 33). Furthermore, when non-prefuctionalized alkynes were used for the propargylation of aryl sulfoxides, the reaction occurred regioselectively. Alkyne was reacted with activated sulfoxides to
generate vinyltriflates 147. Consequently, sulfonium ylides 148 induced [3,3]-sigmatropic rearrangement to realize C–C bond formation and produced the desired compounds 149.

Benzo thiophene S-oxides 150 were used as instead of aryl sulfoxide in an interrupted Pummerer reaction with allyl- or propargyl-silanes 151 or 152 yielded C3 functionalized benzo thiophenes 153 or 154, respectively, by sequential [3,3]-sigmatropic rearrangement (Scheme 34). 16

![Scheme 34. C3-Alkylation using benzo thiophene S-oxides 150](image)

In the case of 3-substituted benzo thiophene S-oxides 155, C2 functionalized benzo thiophenes 158 or 159 were generated by consecutive [3,3]-sigmatropic rearrangement and additional [1,2]-migration due to the occupation of C3 position (Scheme 35). 18

![Scheme 35. C2-Alkylation of 3-substituted benzo thiophene S-oxides 155](image)
2-Substituted benzothiophene S-oxides 160 underwent the interrupted Pummerer reaction with styrene to form sulfonium intermediates 161 (Scheme 36). The continuous nucleophilic attack by alkyllithium-magnesium reagents on 161 proceeded opposite to the bulkiest sulfur ligand for the stereoselective ligand coupled products 162 or 163, respectively.48

Scheme 36. Cleavage of thiophene ring triggered by interrupted Pummerer reaction

The reaction of allyltrimethylsilane 164 and 2-(2,2,2-trifluoromethylidene)-1,3-dithiane monoxide (100) produced C2-allylated derivatives by the interrupted Pummerer reaction and successive [3,3]-sigmatropic rearrangement (Scheme 37). The C1-position of 165 can participate as a nucleophile in C–C bond formation via the thiol ester, as well as an electrophile, via dithiane chemistry.49

Scheme 37. Allylation of CF3-ketene dithioacetal monoxide 100

Gin and coworkers explored oxidative glycosylation with glycal 166 employing the combination of 1 and Tf2O (Scheme 38). An 18O-labeling study indicated the formation of an oxirane intermediate 167 from
disulfonium intermediate, which was followed by the addition of glycosyl acceptors (NuH) to afford C2-hydroxy-β-D-glucopyranoside 168a. When N-(TMS)acetamide was employed as the nitrogen transfer reagent, and 2-propanol as a glycosyl acceptor, the reaction regioselectively afforded C2-acetamidoglycoside 168b, along with sulfonium salt 169.50

Scheme 38. Oxidative glycosylations with glycal 166

7. REACTIONS WITH ARENES AND HETEROARENES

In the reactions with arene, various C–H functionalization were developed through arylsulfonium species by the combination with various continuous reaction. In 1992, Bates reported the ring closure of

Scheme 39. C-H Sulfenylation of heteroarenes by interrupted Pummerer reaction
2-(ethylsulfinyl)phenylpyrrole (170) and 2-(ethylsulfinyl)benzoylpyrrole (172), proceeding by sequential dealkylation to provide 171 and 173 (Schemes 39a and 39b). Furthermore, they found that the treatment of 174 with Tf₂O-pyridine produced the 9-membered heterocycle 176 by β-elimination of the sulfonium intermediate 175 (Scheme 39c).

In 2007, Yorimitsu and Oshima detailed the transformation of arylketene dithioacetal monoxide 177 into benzo[b]thiophene 178 by the combination of interrupted Pummerer reaction-dealkylation process (Scheme 40). Both E- and Z-stereoisomers of the substrate 177 underwent cyclization upon generation of the highly stabilized dication intermediate, followed by the removal of methyl group from 180.

Scheme 40. Formation of benzothiophene from ketene dithioacetal monoxide 177

In their synthesis of tetrahydroisoquinolines, Sano et al. established that subjecting 181 to Pummerer reaction conditions produced benzothiazepine salt 182 in 60% yield along with the desired product 183 (Scheme 41). The sulfonium salt 182 was hydrolyzed under acidic conditions by the cleavage of C₃sp3-S

Scheme 41. Competition between interrupted and standard Pummerer reactions
bond to afford alcohol 184.53

In their further research, the Pummerer cyclization of 185 and 186 was studied and revealed that the acidity of the α-proton on the α-acyl sulfoxide was pivotal in determining the reaction pathway (Scheme 42). Specifically, the reaction of α-acyl sulfoxide 185 with TFAA gave rise to a ylide, which upon Pummerer cyclization generated oxindole 187. In the case of alkyl sulfoxide 186, the electron-rich aryl moiety attacked the activated sulfur atom to give sulfuranes 188a and 188b.54

![Scheme 42. Distinct pathways governed by the acidity of the α-proton adjacent to the sulfinyl group](image)

Hartke discovered that the reaction between indole (189) and the activated DMSO with TFAA produced the isolable sulfonium salt 190. The treatment of the salt with K$_2$CO$_3$ afforded 191, which was transformed to $N$-methyl-3-methylsulfanylindole 192 with heat by methyl migration (Scheme 43).55

![Scheme 43. Methysulfanylation of indole and synthesis of bis(indol-3-yl)sulfide 195 by the combination with demethylation](image)
Based on this study, Suzuki’s group found that the treatment of 190 with secondary amine afforded 3-methylsulfanylindole (193) by demethylation. The sulfanylindole was oxidized to sulfoxide 194, which underwent the same reaction sequence as above to deliver diaryl sulfide 195.56

Procter achieved the C–H thio-arylation of aromatics 197 utilizing arylmethyl sulfoxides 196 for the synthesis of valuable diaryl sulfides 200. The method was operationally simple and employed readily available materials (Scheme 44). The interrupted Pummerer reaction was induced by the nucleophilic attack of 197 onto 198, generated in situ from aryl sulfoxide 196 and Tf₂O, to form diarylmethylsulfonium intermediate 199. Thus, the treatment of 199 with DBU afforded diaryl sulfide 200 by removal of the methyl group.57

![Scheme 44. C–H Thio-arylation of arenes 196](image)

Shoji and Morita developed the reaction between an activated sulfoxide and azulene (201) to give azulenesulfonium salt 202. Treatment of 202 with a secondary amine produced 1-azulenyl sulfide 203 by methyl

![Scheme 45. Formation of azulenesulfonium salts 202 and its reactions](image)
group elimination. The sulfide 203 was oxidized to the sulfoxide, which upon treatment with TFA delivered 1,1'-biazulene 204 (Scheme 45).

The C-H functionalization by interrupted Pummerer reaction-dealkylation sequence was applied to the synthesis of polymer. Poly(p-phenylene sulfide) (PPS) 207 was synthesized by the self-condensation of methyl(p-thiophenoxy)phenyl sulfoxide 205 in TfOH (Scheme 46). The demethylation of 206 was conducted in refluxing pyridine to give polymer 207. The average of the molecular weight was determined to be above $M_w = 2 \times 10^5$ by GPC analysis. The methodology was utilized for the synthesis of oligo(p-phenylene)ladder 208 and poly(thiaheterohelicene) 209.

As the sequence of interrupted Pummerer reaction-sigmatropic rearrangement, Procter developed a cascade reaction with allyl sulfoxide 211 to achieve regioselective C-H allylation of heteroarenes 210 (Scheme 47). Allyl sulfoxide 211 was treated with TFAA and the resulting interrupted Pummerer reaction with aromatics 210 formed allylarylsulfonium intermediates 212. The consecutive charge-accelerated [3,3]-sigmatropic rearrangement produced dual vicinal functionalized heteroarenes 213.

Scheme 46. Synthesis of poly(p-phenylene sulfide) and functional polymers

Scheme 47. Synthesis of poly(a-phenylene)ladder and poly(thiaheterohelicene)
The cascade sequence was applied for the synthesis of dihydrobenzothiophene. Interrupted Pummerer reaction-sigmatropic rearrangement generated allylsulfonylarene 216 from arene 214 (Scheme 48). And then, the cyclization of 216 and removal of the methyl group afforded dihydrobenzothiophene 215.61

Scheme 48. Construction of dihydrobenzothiophene scaffold 215 by combination with sigmatropic rearrangement and demethylation

In the reaction of the interrupted Pummerer reaction-intermolecular coupling reaction system, sulfonium species was utilized as the precursor of transition metal-catalyzed coupling reaction. Yorimitsu developed the sequence of interrupted Pummerer and metal-catalyzed coupling reactions for the formation of
triphenylenes 221 (Scheme 49). In their report, sulfonium salts were utilized as the substrate of palladium-catalyzed coupling reaction. The sulfonium 218 was coupled with an aromatic group to produce biaryl 219. The formation of thiophenium salt 220 was followed by intramolecular coupling to give triphenylene 221. 

Scheme 49. Synthesis of triphenylene 221 utilizing palladium-catalyzed coupling with sulfonium salts

Cowper and Lewis used arylsulfonium salt 222 from azulene (201) as the precursor of Suzuki-Miyaura coupling reaction with aryl boronates to generate biaryl product 223 in good yields (Scheme 50a). Instead of continuous Suzuki-Miyaura coupling, the combination with Negishi coupling in a one-pot procedure was reported by Procter to obtain biaryl 225 from non-prefunctionalized arene 224 (Scheme 50b).

Scheme 50. Sequential systems of interrupted Pummerer and metal-catalyzed coupling reaction
As the application of sulfonium mediated coupling reaction, a metal-free method was developed. The reaction with electron-rich arenes 226 as substrate and the coupling partner produced homo-coupled biaryls 228 in moderate yield via sulfonium intermediates 227 (Scheme 51).

![Scheme 51. Transition metal-free coupling of arenes 226 via sulfonium species](image)

Recently, the novel C-H functionalization system was reported consisting of interrupted Pummerer and photoredox catalyzed coupling reactions. The treatment of arenes 229 with dibenzothiophene S-oxide (230) and Tf₂O generated thiophenium intermediates 231, the key intermediate of the following photoredox catalyzed radical coupling to obtain biaryls 232 (Scheme 52).

![Scheme 52. Heterocoupling of arenes by interrupted Pummerer and photoredox reactions](image)

Versatile C₅₋₇-H functionalizations induced by interrupted Pummerer reaction have been reported by Ritter’s group. This strategy realized to functionalize complex arenes 233 utilized thianthrenium salts 236 (Scheme 53a) that are ready to engage in a various transformation as shown by Scheme 53b, via both
transition metal and photoredox catalysis (Scheme 53a). This transformation provides access to a large number of derivatives of complex small molecules (Scheme 53b).

Scheme 53. Synthesis of thianthrenium salts 236 and versatile functionalizations thereof
While pursuing novel synthetic strategies for indole alkaloids, Kawasaki found that the products obtained under Pummerer reaction conditions varied depending on the substituent group R\(^1\) on the indole nitrogen of tetrahydrocarbazoles (Scheme 54). In the case of 237, where R\(^1\) is acetyl, elimination of the \(\alpha\)-proton, followed by cyclization proceeded to give the Pummerer cyclized product 239. When R\(^1\) is hydrogen, as in 238, substitution at the sulfur atom forms the sulfonium intermediate 240. Subsequently, intermediate 240 isomerizes to enamine 241, which engages in an S\(_{N}2'\) reaction at the 2\(\alpha\)-position to provide product 242 utilizing high leaving group ability of sulfide moiety.\(^{66}\)

![Scheme 54. Reaction pathways controlled by the nucleophilicity of the indole core](image)

With the objective of developing an intermolecular version of the above-mentioned reaction, we investigated the reaction of activated sulfonium species with tetrahydrocarbazoles 243 (Scheme 55). Consequently, the DMSO-TFAA system effectively afforded indole derivatives functionalized at the 2\(\alpha\)-position such as 244. Carbon and heteroatom nucleophiles were directly introduced by a one-pot procedure in excellent yields.\(^{67}\)

Under the mediation of the active sulfonium species, the tryptophan analog 245 and an indole nucleophile assembled 3a-(3-indolyl)pyrroloindolines as a mixture of diastereomers (Scheme 56). The addition of 2,6-di-tert-butylpyridine (DTBP) was essential to avoid the coupling of indole at the C2 position of the tryptophan. The cascade reaction, encompassing the substitution of dialkylsulfonium, cyclization to the
pyrroindoline structure, and installation of a nucleophile, produced 3a-(3-indolyl)pyrroloindolines 246a and 246b as a mixture of diastereomers. Then, 246b was induced to (+)-gliocladin C (247).

Scheme 55. Traceless functionalization of indoles 243 using sulfonium salt

Scheme 56. Formation of 3a-substituted pyrroloindole 246 mediated with sulfonium salt
The reaction between a sulfonium species and tryptamine 248a generated a pyrroloindoline intermediate 249, which was reacted with another tryptamine, 248b or 248c, to give hetero-coupled bispyrroloindoline structures 250a and 250b by a one-pot procedure (Scheme 57). This method enables rapid access to heterodimeric bispyrroloindoline alkaloids, such as calycanthidine (251), and chimonanthidine (252).

Scheme 57. One-pot synthesis of bispyrroloindole structures 250

For the synthesis of 3a-nitrogen-substituted pyrroloindoline alkaloids, we explored the use of N-nucleophiles (Scheme 58). Tryptamine 248a was treated with DMSO, Tf₂O, DTBP, and aniline to give

Scheme 58. Synthesis of 3a-aminopyrroloindoles 253
the desired 3a-anilinopyrroloindoline 253a in 91% yield. The use of diphenylamine as a nucleophile produced 253b in 76% yield. However, the reaction with alkylamines such as benzylamine provided the corresponding amino product 253c in low yield. The utility of this reaction was demonstrated by accessing C3a-N1'-linked bistryptamines, including (±)-psychotriasine (255), which were successfully synthesized by the use of 5-bromo-2,3-dihydrotryptamine 254, and consecutive DDQ oxidation (Scheme 59).70

Scheme 59. Application to the synthesis of (±)-psychotriasine (255)

Our group extended the above-discussed intermolecular interrupted Pummerer reaction to an asymmetric version (Scheme 60).71 Oae reported that the chiral sulfonium center was partially racemized by the formation of sulfurane under Pummerer reaction conditions.72 Kita improved enantioselectivity of intermolecular Pummerer reaction using O-silylated ketene acetal73ab and ethoxy vinyl ester.73c Thus, we assumed that the chiral center exists around the sulfoxide moiety. The reaction using binaphthyl sulfoxides 256 and 257 resulted in moderate yields and ees. Sulfoxide 258, activated with TFAA in EtCN, provided the highest enantioselectivity (entry 7). The synthetic utility of this reaction was demonstrated by the total synthesis of (+)-psychotriasine in 91% ee.
Scheme 60. Enantioselective pyrroloindoline synthesis by asymmetric interrupted Pummerer reaction

<table>
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<tr>
<th>entry</th>
<th>sulfoxide</th>
<th>acid anhydride</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
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</thead>
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<td>256</td>
<td>Tf₂O</td>
<td>DCM</td>
<td>41</td>
<td>61</td>
</tr>
<tr>
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<td>257</td>
<td>Tf₂O</td>
<td>DCM</td>
<td>40</td>
<td>58</td>
</tr>
<tr>
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<td>258</td>
<td>Tf₂O</td>
<td>DCM</td>
<td>94</td>
<td>35</td>
</tr>
<tr>
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<td>DCM</td>
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<td>2</td>
</tr>
<tr>
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<td>DCM</td>
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<tr>
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<td>EtCN</td>
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<tr>
<td>7</td>
<td>258</td>
<td>TFAA</td>
<td>EtCN</td>
<td>73</td>
<td>93</td>
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</tbody>
</table>

Scheme 61. C2-Functionalization of indole derivatives 261 via iminium intermediate 262
During the formation of the C3a-substituted pyrroloindoline structure, we discovered that the nucleophilic addition competed between C3a at pyrroloindoline and C2 at indole. When C3-substituted indoles reacted with sulfonium species derived from DMSO and Tf₂O, iminium intermediates was formed. Nucleophiles added to intermediates, and the ensuing rearomatization, afforded C2,C3-disubstituted indoles in good yields (Scheme 61).

In conclusion, a large amount of studies has been conducted exploiting the reactivity of active sulfonium species, and useful reactions in synthetic organic chemistry, such as the Swern oxidation and the Pummerer reaction, have been developed. Initially, the interrupted Pummerer reaction was regarded as a side reaction occurring under Pummerer reaction conditions. However, research focused on this reaction is currently expanding dramatically, owing to the unexpected formation of valuable products, a variety of reaction modes, ease of sulfoxide synthesis, and mild reaction conditions. In the future, the development of novel sulfoxides and the elegant reaction design will further advance this research field.

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REFERENCES


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