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Pummerer Synthesis of Chromanes Reveals a Competition between Cyclization and Reductive Chlorination

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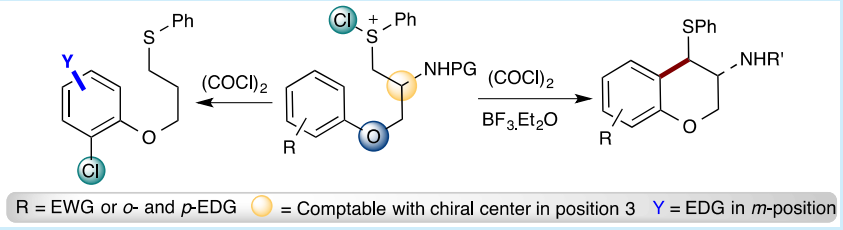
Supporting Information



ABSTRACT: The competition between an unprecedented reductive chlorination and the Pummerer reaction was studied and applied to the synthesis of benzofused oxygen heterocycles including 3-aminochromanes and in the intramolecular chlorination of activated aromatic rings. The use of $(COCl)_2$ as a Pummerer activator showed substantial activity, producing α-chlorinated sulfides that can undergo Pummerer–Friedel–Crafts cyclization. If the aromatic ring has electron-donating groups in position three, then the reaction follows a different pathway, yielding the reductive chlorination products, where the chlorine atom comes from a sulfonium salt.

Chromanes, which show diverse biological activities such as antitumor, antioxidant, antibacterial, antifungal, and anti-inflammatory effects, are privileged heterocycles in a remarkable number of natural products and pharmaceutical molecules.[1] Figure 1 shows some examples of active compounds with the chromane core in their structure: Cromakalim is a potassium channel opener, alenespirone reached phase II of pharmacological studies as a serotonin receptor agonist, etamicastat reached phase II for hypertension treatment, equol is a nonsteroidal estrogen metabolite produced by humans from soy, which acts as a selective agonist of ERβ, and sorbinil is an aldolase reductase inhibitor used in the treatment of diabetes complications. Because of the predominance of the chromane scaffold, considerable efforts in developing new and general methods to prepare them have been made for many years; nevertheless, methods to access functionalized chromanes remain limited.[2]

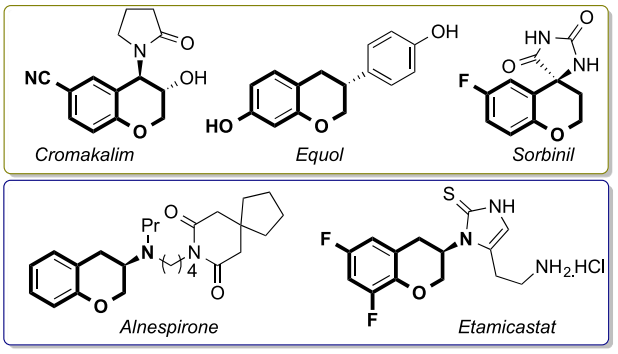


Figure 1. Structures of selected bioactive chromanes and aminochromanes.

The Pummerer reaction and its variants[3] have been successfully used in the synthesis of heterocyclic compounds;[4] however, the synthesis of benzofused oxygen heterocycles is mainly accomplished by interrupted Pummerer approaches (Scheme 1a).[5]

Classic Pummerer cyclizations using aromatic rings as nucleophiles are extremely limited (Scheme 1b),[6] presumably because of the competition between nucleophiles and the byproducts obtained[7] but also because β-hydrogens are undesirable because their elimination causes the formation of vinyl sulfides. Recently, Carter and coworkers[8] took advantage of this fact by applying the vinyl sulfides effectively in a Pummerer cyclization; unfortunately, the use of β-chiral centers is impractical in Carter's method. Another problem is the use of highly deactivated aromatic rings (carrying electron-withdrawing groups (EWGs)) as nucleophiles, whereas they are almost unreactive in all aforementioned situations.

Inspired by those difficulties, we reasoned that eluding the vinyl sulfide formation might be accomplished by reducing the acidity of β-hydrogens and the basic character of counterion in the Pummerer activator. Typical Pummerer activators are acetic anhydride, trifluoroacetic anhydride, and triflic anhydride; however, it was proven that oxalyl chloride may be used as a Pummerer activator[9] in an analogous process with Swern

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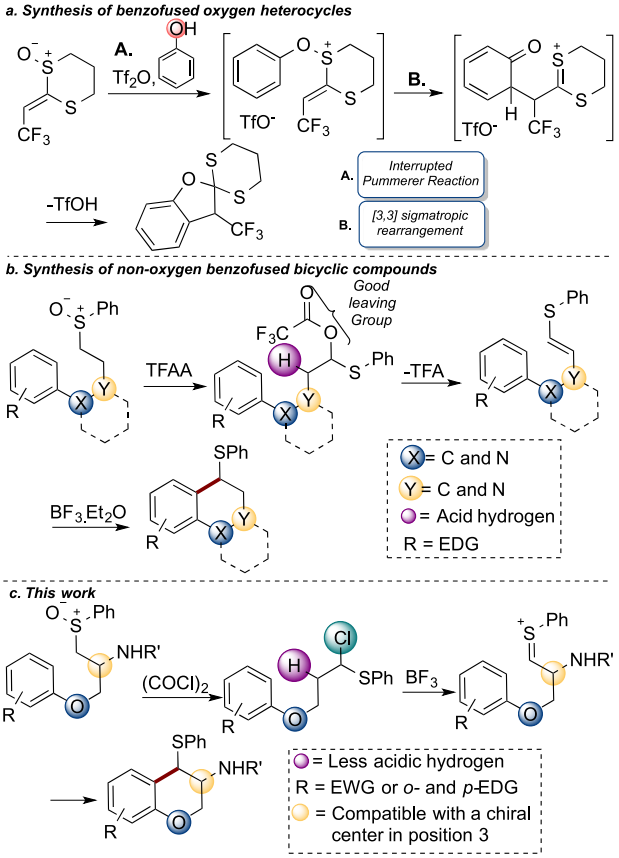
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 1. Synthesis of Benzofused Heterocycles by Pummerer Reaction, Previous and This Work

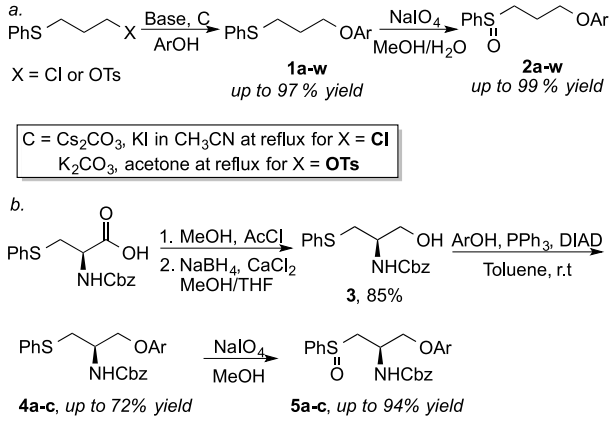


oxidation, forming highly reactive α-chlorinated sulfides and generating the thionium ion, which is the key intermediate in Pummerer chemistry. The counterion in this case is chloride, which is less basic than acetate or trifluoroacetate, and thus changing the CH_3COO^- or CF_3COO^- groups to Cl^- should be enough to reduce the elimination reaction and the cause of vinyl sulfide formation. Consequently, in making this simple change of reagents, we hoped to obtain the desired chromanes (Scheme 1c). Herein we report the successful cyclization of phenol ethers by the classic Pummerer reaction and our preliminary studies on the competitive reductive chlorination reaction issued from a special and unprecedented interrupted Pummerer reaction.

The synthesis of the staring sulfoxides was accomplished by the oxidation of the corresponding sulfides with $NaIO_4$ in the H_2O/MeOH mixture. The sulfides were obtained by two different methods, sequential nucleophilic substitutions with thiophenol and the corresponding phenol (Scheme 2a) or the Mitsunobu reaction of phenols with a phenyl cysteine derivative (Scheme 2b). Yields were good to excellent, and the reactions were performed on a 1 or 2 mmol scale in most of the cases (sometimes they were performed on the gram scale), showing the easy access to the starting materials and the scalability of this process. Experimental details and data for those experiments may be found in the Supporting Information.

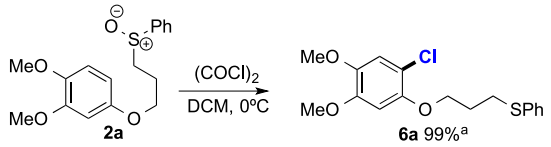
We mentioned that the previously described methods for classic Pummerer cyclization in the synthesis of heterocycles and carbocycles always used highly activated aromatic rings as nucleophiles, so we started our study with compound **2a**,

Scheme 2. Synthesis of Starting Materials



which should provide a suitable setup for cyclization. Nevertheless, the treatment of **2a** with oxalyl chloride afforded in quantitative yield a new sulfide **6a** issued from an intramolecular reductive chlorination (Scheme 3).

Scheme 3. First Reductive Chlorination of Aromatics with Sulfoxides



[a]Isolated yield. The reaction was performed on a 1 mmol scale.

To the best of our knowledge, no chlorinations of aromatic rings using chlorosulfonium salts have been described; in fact, the reactions of sulfonium salts with phenols and phenol ethers afford the alkylthioalkylation of the aromatic ring.[10] Moreover, the reactions of carbon, nitrogen, and oxygen nucleophiles with sulfonium ions by the interrupted Pummerer pathway always proceed by substitution on the sulfur atom, revealing new chemistry and amazing developments.[11] Similar aromatic halogenations (with I and Br) presumably evolve by the *in situ* formation of molecular halogens.[12] In original works by Swern[13] and Corey[14] (Corey–Kim oxidation), problems in the oxidation of unsaturated alcohols were reported, probably due to the presence of molecular chlorine in the reaction media;[15] however, the chlorination of allyl and vinyl nucleophiles using chlorosulfonium salts is very rare.[16] Even if sulfonium salts are known as electrophile sources,[17] the interrupted Pummerer reaction should be coexisting.

We then used highly activated aromatic rings (compounds **2b–f**) under the same reaction conditions (see Scheme 4). The reductive chlorination proceeded smoothly, and the chlorinated sulfides were obtained in good to excellent yield and with complete regioselectivity. Thus according to the literature, four possible scenarios were envisaged to explain the reductive chlorination: two using a nucleophilic chloride, illustrated as routes a and b in Scheme 5 (interrupted Pummerer approaches), one using an electrophilic chlorosulfonium salt (Scheme 5, route c), and one inspired by Jiao's work,[12a] where molecular halogen is formed *in situ* and acts as the electrophile (Scheme 5, route d).

The regioselective chlorination of compound **2a** makes routes a and d the least plausible. The dication intermediate in

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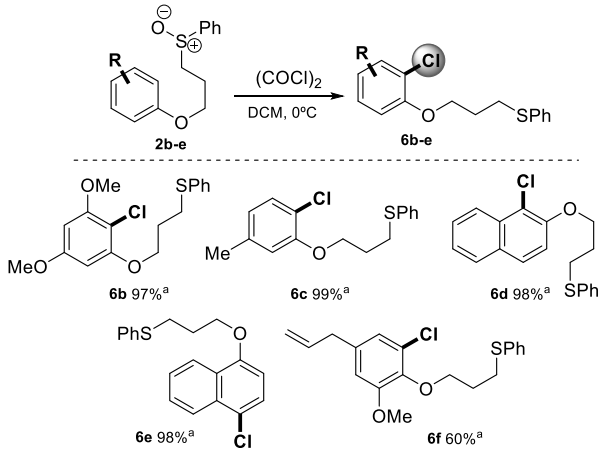
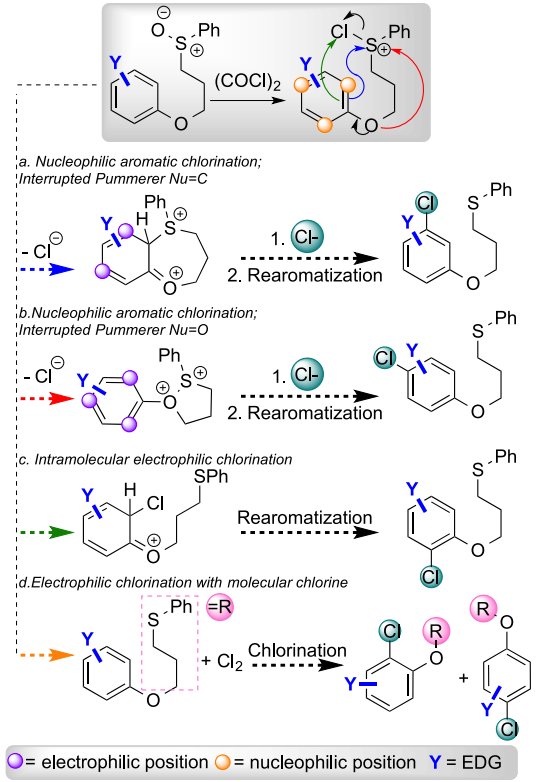
Scheme 4. Reductive Chlorination of Activated Aromatic Rings



[a]Isolated yields.

Scheme 5. Plausible Pathways for Reductive Aromatic Chlorination

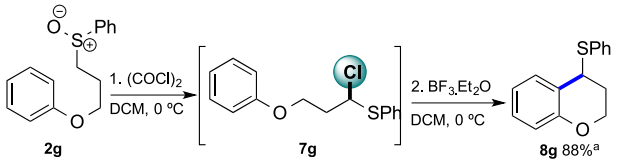


pathway b should be very unstable and consequently unsuitable as a reaction intermediate; however, the usual interrupted Pummerer reaction with phenols proceeds with the oxygen as the nucleophile. Even if routes b and c should provide the same products, it seems reasonable to expect that route b provides the chlorination product in the less hindered four-position because those products were not observed in the crude reaction mixture (only products **6b–d** were observed). We can conclude that route c looks to be the most realistic for the chlorination reaction. When the reaction is performed using the 1-naphthol derivative (see compound **6e**), position four is more nucleophilic than position 2,[18] instigating the reaction to proceed intermolecularly.

According to Jiao's results[12a] the reaction between dimethyl sulfoxide (DMSO) and hydrogen halides (HBr and HI) generates the reduction of DMSO to dimethyl sulfide (DMS) and the formation of molecular halogens, which are electrophilic enough to react with highly activated aromatics. The entire regioselectivity of our reaction suggests that in our case the molecular halogen is not formed; however, we performed the reaction with a polyfunctional substrate to demonstrate the absence of molecular chlorine. Product **6f** was isolated in 60% yield, and the sole byproduct observed by careful analysis of the crude ^{1}H nuclear magnetic resonance (NMR) was identified as the chromane issued by the reaction of a thionium intermediate with the aromatic as a nucleophile (*vide infra*). It is necessary to underscore that cyclization products (chromanes) were not observed with either +*I* (compound **6c**) groups or with +*M* (compounds **6a**,**b**) groups. Because the chlorination on the double bond or the allylic carbon was not observed, we ratify route (c) as being responsible for the chlorination of aromatics.

Because we observed the chromane as a minor product in the reaction of **2f**, we reasoned that using less activated aromatics should provide a suitable scenario for cyclization. The reaction of compound **2g** with oxalyl chloride (Scheme 6)

Scheme 6. Classic Pummerer Cyclization with an Unstable *α*-Chlorosulfide as Intermediate



[a]Isolated yield. The reaction was performed on a gram scale.

afforded a completely different product, the *α*-chlorinated sulfide **7g** (aliphatic chlorination). This compound is very unstable and was identified via ^{1}H NMR, which was measured immediately after the evaporation of the solvent and the excess of oxalyl chloride. Fortunately, the subsequent addition of BF_3·Et_2O allowed us to isolate the desired chromane **8g** in very good yield.

With these results in hand, we decided to study the scope of the reaction. To our delight, the cyclization may be performed via a *one-pot* reaction, and it is a general reaction that can be achieved with both electron-donating groups (EDGs) and electron-withdrawing groups (EWGs); (see Scheme 7).

As demonstrated in Scheme 4, the use of strong EDGs afforded the aromatic chlorination products. Consequently, we started our screening of substrates using weakly deactivating groups (I, Cl, and F), trying to induce the aliphatic chlorination and then the formation of the thionium ion. Fortunately, the reaction proceeded smoothly no matter the position of the substituent, and the products **8h–j** were obtained in excellent yield. The use of EDGs in position two or four also afforded the cyclization products in good to excellent yield (products **8k–o**). It is probable that when position two has the influence of two activating groups, it is extremely reactive, making the reaction with the chlorosulfonium salt faster than the formation of the thionium ion and thus avoiding the aliphatic chlorination. This is only possible with substrates

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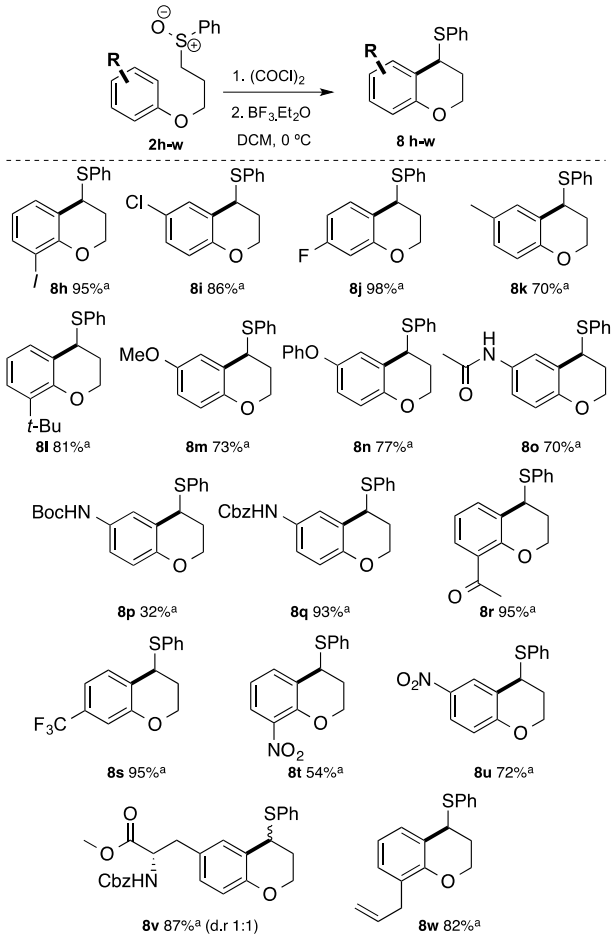
Scheme 7. General Scope of Cyclization



[a]Isolated yields.

bearing an activating group in position three or with substrates with more than two activated groups; however, the aromatic chlorination products were observed in the crude ^{1}H NMR spectra as the minor products (<10%). The reaction of a −NHBoc-substituted ring gave the product **8p** in very low yield, presumably because the Boc group is cleaved under the reaction conditions, and thus we changed the group to a Cbz group and obtained very good yields (product **8q**), proving the compatibility of our method with this protecting group. We then turned our attention to moderate (MeCO) and strong deactivators (NO_2 and CF_3). Pleasantly, the reaction worked very well with moderate deactivators (product **8r**) and the strong EWG CF_3 (product **8s**). In the case of the NO_2 group, the reaction worked well enough compared with the previously described Pummerer cyclizations (products **8t**,**u**). Finally, we used a tyrosine derivative (product **8v**) to prove the tolerance to other functional groups and to obtain a more functionalized product, which may serve as a precursor to polycyclic systems.[19] The chromane was successfully obtained.

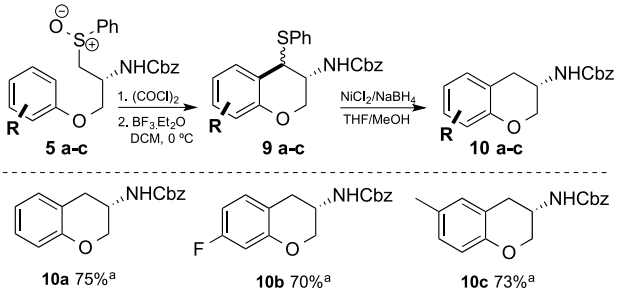
The reaction with sulfoxide **2w** enabled us to isolate compound **8w** in excellent yield, and no chlorination of the double bond or allylic carbon was observed, thereby demonstrating the absence of molecular chlorine or radicals in the reaction media. Compounds of Schemes 4 and 7 showed an apparent generality: The more activated the ring (more nucleophilic), the easier it reacted with the sulfonium salt to afford the reductive chlorination product (aromatic chlorination). Even though the eugenol was highly activated, it also produced the corresponding chromane in extremely low yield (detected by ^{1}H NMR), indicating that aliphatic chlorination is a competing reaction and the cyclization is feasible with any substituents, with the exception of activating groups in position three and rings with more than two activating groups, as mentioned above.

In a nutshell, the reaction of type-**2** compounds with oxalyl chloride proceeds by the formation of a chlorosulfonium salt,[20] which is a common intermediate for aromatic or aliphatic chlorinations. When the phenol aromatic ring has extra EDGs in position 3 or more than two EDGs as substituents, it is nucleophilic enough to react with the chlorosulfonium salt, yielding the aromatic chlorination product. On the contrary, with less nucleophilic aromatics, the chlorosulfonium salt participates in a typical Pummerer pathway, which means a β-elimination to generate the electrophilic thionium ion, followed by its reaction with chlorine, producing the aliphatic chlorination. The BF_3 is used to regenerate the thionium ion and induce its cyclization.

Nevertheless, we needed to prove the compatibility of our method with β-chiral centers. To this end, we chose 3-aminochromanes because they are very important structures in medicinal chemistry,[1d,21] and the starting materials are easily prepared from commercially available phenylcysteine, as shown in Scheme 2 and in the Supporting Information.

Scheme 8 shows the results of the synthesis of 3-aminochromanes. The reaction works as expected, but no

Scheme 8. Synthesis of 3-Aminochromanes



[a]Isolated yield.

control over the new chiral center was observed, and a 1:1 mixture of two diastereomers was obtained; however, the SPh group was easily reduced in a *one-pot* procedure using a mixture of $NiCl_2$ and $NaBH_4$, and the protected amino chromanes (products **10a**−**c**) were obtained in very good overall yield and without racemization.[22] This synthesis also shows the versatility of the SPh group, which can be reduced, oxidized, and used in further transformations, as demonstrated in this category of heterocycles.[2k]

In summary, this work illustrates a new Pummerer cyclization that provides a solution to previously described problems in this kind of chemistry; we also successfully applied the reaction to functionalized molecules carrying substituents in both aromatic and aliphatic rings. Most importantly, this method is compatible with chiral centers, which are β to the sulfoxide. Finally, we showed our preliminary results in reductive chlorinations of aromatic rings using sulfonium salts as a source of electrophilic chlorine. The development of this chemistry offers wonderful applications in synthetic organic chemistry and is continuously growing, and we are

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Org. Lett. XXXX, XXX, XXX−XXX

working to make this chlorination general and applicable in highly functionalized molecules. The results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02520.

Complete experimental details and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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