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Tandem Pummerer Diels-Alder Sequence for the Preparation of α-Thio Substituted Naphthalene Derivatives

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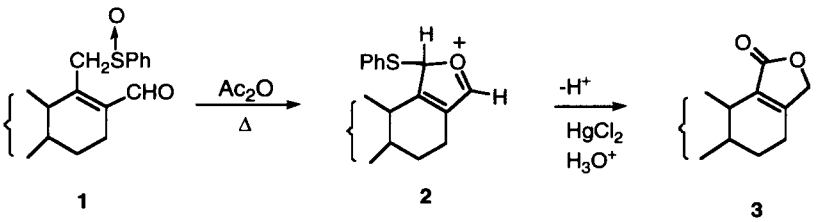
Abstract: The α-thiocarbocation generated from the Pummerer reaction of an *o*-benzoyl substituted sulfoxide is intercepted by the adjacent keto group to produce an α-thio-isobenzofuran as a transient intermediate which undergoes a subsequent Diels-Alder cycloaddition with added dienophiles.

The traditional Pummerer rearrangement is a reaction in which a sulfoxide, when treated with an acid or an anhydride, is converted to an α-substituted sulfide.[1,2] The finding that sulfenium ions may serve as electrophiles in electrophilic substitution chemistry has greatly extended the synthetic range of the Pummerer rearrangement.[3] Thus, both intra-[4] and intermolecular[5] versions of the process have been used to prepare a wide assortment of compounds. The Pummerer reaction continues to attract substantial research effort.[3] In particular, Pummerer-based transformations are finding widespread applications in carbo-[6] and heterocyclic synthesis,[7] by reaction of the intermediate thionium (α-thiocarbocations) with internally-disposed nucleophiles.[8] In the realm of carbon-carbon bond formation, most success has been achieved using intramolecular interception of the Pummerer thionium ion intermediate, and in this respect the β-keto sulfoxide functionality has proved to be the electrophilic partner of choice. Far fewer examples exist for heteroatom interception of the Pummerer intermediate.[9,10]

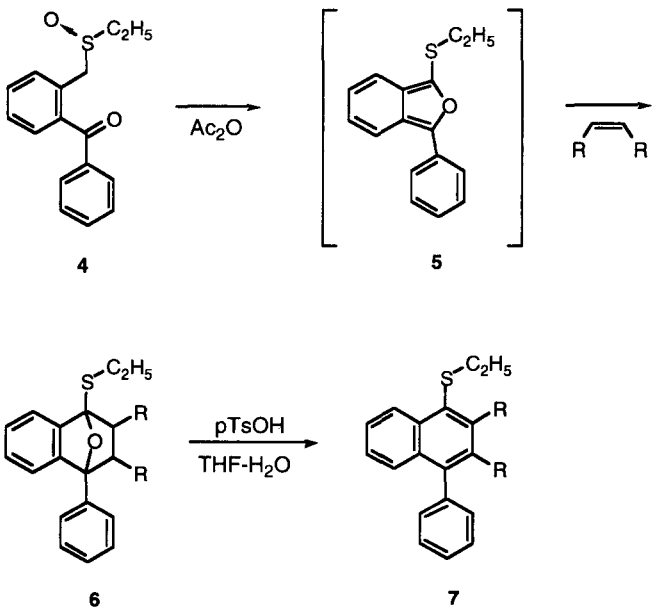
De Groot and coworkers[11] developed an efficient procedure for butenolide formation in which the key step involves a Pummerer induced cyclization of aldehydic sulfoxides of type **1** into butenolides **3**. It was assumed that the neighboring carbonyl group attacks the initially formed thionium ion to give an oxy-stabilized cation **2** which loses a proton to generate a 2-thio substituted furan which is subsequently converted to the butenolide upon hydrolysis.



1 **2** **3**

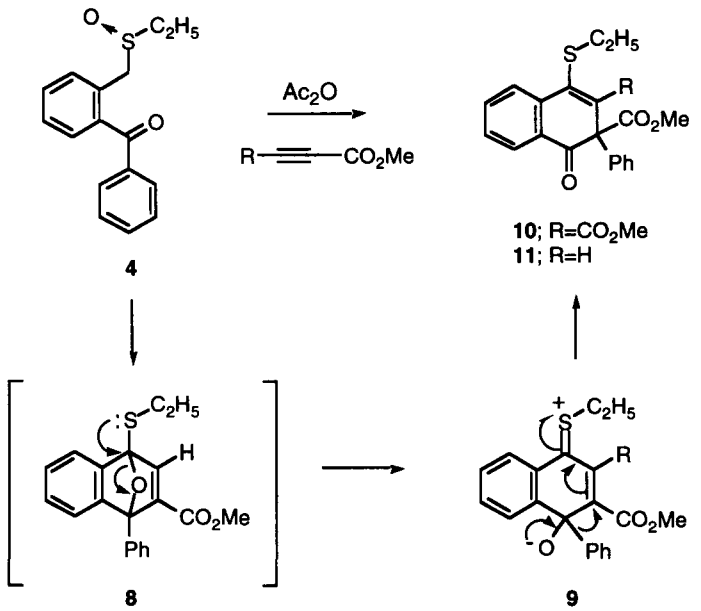
During the course of our own studies in this area, we established the effectiveness of this method for the synthesis of the isobenzofuran ring system. In this communication we report that treating an *o*-thio-substituted phenyl ketone with acetic anhydride in the presence of various dienophiles results directly in the formation of substituted naphthalenes *via* a tandem Pummerer-Diels Alder sequence.

Keto sulfoxide **4** was easily prepared in 5 steps from the commercially available 2-methyl benzophenone using standard synthetic procedures.[12] When heated to 120°C with acetic anhydride in the presence of an appropriate dienophile, the sulfoxide smoothly underwent a *tandem Pummerer-cyclization-Diels-Alder reaction* to produce the corresponding cycloadduct **6** as a mixture of diastereomers. Further reaction of cycloadduct **6** with *p*-toluenesulfonic acid in THF at 25°C afforded the α-thio-substituted naphthalene **7** in essentially quantitative yield.[15,16] When an unactivated dienophile such as cyclohexene was used (high lying LUMO), the cycloaddition reaction proceeded in low yield and only the α-thio-substituted naphthalene **7d** was isolated. This is presumably due to a poor matching of the frontier molecular orbitals.



6a (maleic anhydride); 87% (1.7:1)
6b (N-phenyl maleimide); 73% (10:1)
6c (*trans*-1,2-*bis*(phenylsulfonyl)ethylene); 69% (1:1)
7d (cyclohexene); 6%

Acetylenic dienophiles did not give the expected cycloadduct **8** but instead afforded the rearranged tetralone derivative **10** (or **11**). Thus, treatment of **4** with acetic anhydride in the presence of dimethyl acetylenedicarboxylate gave tetralone **10** in 38% isolated yield. An analogous reaction occurred using methyl propiolate producing tetralone **11** as the exclusive product in 51% isolated yield. The structure of **11** was assigned on the basis of its spectral data and was further established by an X-ray crystal analysis.[17] The mechanism of this unusual reaction has not been unequivocally



proven, but one reasonable possibility is outlined below. Here it is proposed that the cyclization-cycloaddition sequence produces the expected cycloadduct **8** which then rearranges to **10** (or **11**) *via* intermediate **9**. The key step involves oxabicyclic ring opening which is driven by the lone pair of electrons on sulfur and this is followed by a pinacol type rearrangement of **9** proceeding by way of a 1,2-phenyl shift.[18] The formation of adduct **11** as a single regioisomer is consistent with FMO theory.[19] The most favorable FMO interaction is between the HOMO of the isobenzofuran and the LUMO of methyl propiolate. The atomic coefficient at the ethylthio substituted position in the isobenzofuran ring is larger than at the phenyl position in the HOMO and this nicely accommodates the high regioselectivity encountered.

In conclusion, α-thiocarbocations derived from *o*-benzoyl substituted sulfoxides can be intercepted by the adjacent carbonyl group to give isobenzofurans. The cyclization can be performed in tandem with a Diels-Alder reaction to give 4+2-cycloadducts which are readily converted to α-thio

substituted naphthalene derivatives. We are currently investigating the generality of this process for the construction of aza-polycyclic ring systems and its application in target oriented synthesis.

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12. Conversion of the ketone to the corresponding dimethoxy ketal with methanol was followed by NBS bromination. The resulting benzylic bromide was converted to the ethyl sulfide using the method of Ono and coworkers.[13] Hydrolysis followed by oxidation of the sulfide using the general procedure of Leonard and Johnson[14] afforded **4** in 42% overall yield.
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16. All new compounds were completely characterized (IR; ^{1}H-NMR, ^{13}C-NMR and analytical data). Yields reported correspond to isolated products.
17. We wish to thank Mark A. Semones for the X-ray determination of compound **11**.
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