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Additive Pummerer reaction of heteroaromatic sulfilimines with carbon nucleophiles

Albert Padwa,* Shinji Nara and Qiu Wang

Department of Chemistry, Emory University, Atlanta, GA 30322, USA

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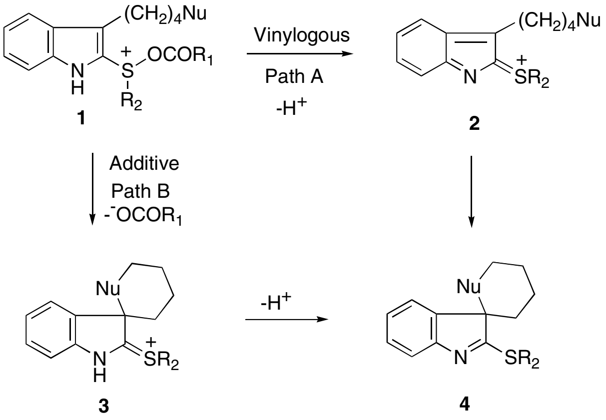
Abstract—The additive Pummerer reaction of several heteroaromatic sulfilimines has been investigated. The overall process involves the reaction of the sulfilimine with TFAA to produce a transient *N*-tosyl-*N*-trifluoroacetyl sulfonium ion. Nucleophilic attack at the adjacent vinyl carbon results in the ejection of the sulfonamide group and the resulting thionium ion loses a proton to give the observed product.

The finding that thionium ions may serve as electrophiles in electrophilic substitution chemistry has greatly extended the synthetic range of the Pummerer reaction.[1] Thus, both inter-[2] and intramolecular[3] versions of the process have been used to prepare a wide assortment of compounds. Currently, Pummerer-based transformations are finding widespread application in carbo- and heterocyclic syntheses by reaction of the initially generated thionium ions with various nucleophilic reagents.[4–7] When α,β-unsaturated sulfoxides are used for the Pummerer reaction, the initially formed oxysulfonium ion (i.e., **1**) may undergo reaction via two different routes.[6] These pathways differ primarily in the timing by which the leaving group on sulfur is lost. In the *vinylogous Pummerer* reaction (Path A),[8] the departing acyloxy group is discharged prior to nucleophilic attack. In the *additive Pummerer* process (Path B),[9] nucleophilic attack occurs simultaneous with acyloxy group departure. In either circumstance, the end result corresponds to electrophilic activation at the β-position of the unsaturated sulfoxide and the overall procedure represents a useful bond construct for cyclic ring systems.[6] An elegant application of the Pummerer β-activation approach was recently described by Feldman and co-workers for the synthesis of various 3,3-spirocyclic oxindoles (Scheme 1).[10]



Scheme 1.

As part of our continuing research program designed to explore the use of sulfonium ions for heterocyclic synthesis,[11] we became interested in developing some comparable additive Pummerer chemistry using sulfur–nitrogen ylides (sulfilimines). The properties of sulfilimines[12] are known to be similar to those exhibited by sulfoximines,[13] but the sulfilimines are more reactive, just as sulfonium ylides are more reactive than the corresponding oxosulfonium ylides. To demonstrate that vinyl sulfilimines can be induced to undergo the additive-Pummerer reaction,[14] we have examined the reaction of several aromatic and heteroaromatic substituted sulfilimines with carbon nucleophiles in the

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* Corresponding author. Tel.: +1 404 727 0283; fax: +1 404 727 6629; e-mail: chemap@emory.edu

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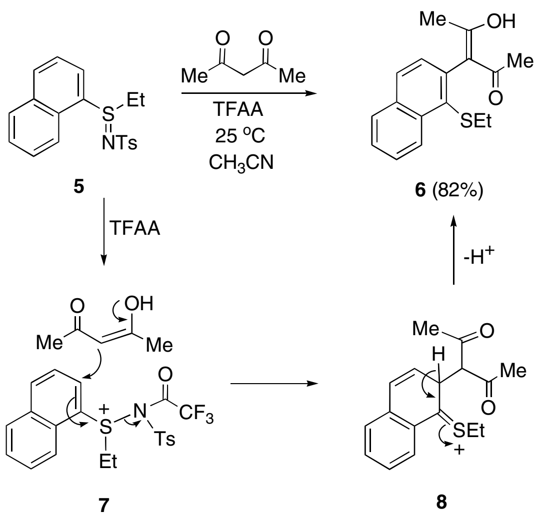


Scheme 2.

presence of trifluoroacetic anhydride. The results of these studies are described herein.

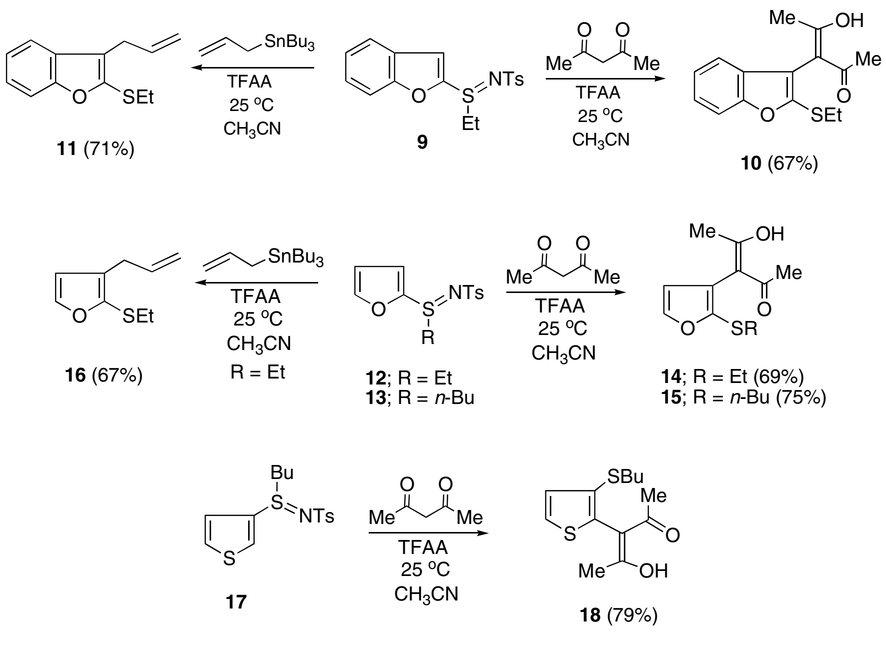
Our studies began with an investigation of the additive-aromatic Pummerer reaction of naphthyl-substituted sulfilimine **5**. Treatment of **5** with 2 equiv of trifluoro-acetic anhydride (TFAA) in the presence of 1.5 equiv of 2,4-pentanedione at 25 °C in CH$_3$CN afforded 2-(2,4-dioxopent-3-yl)-1-(ethylthio)naphthalene (**6**) in 82% yield.[15] We assume that the mechanism for the conversion of **5** to **6** proceeds by the sequential set of reactions outlined in Scheme 2 where the nitrogen atom of the sulfilimine reacts with TFAA to produce sulfonium ion **7**. Nucleophilic attack at the 2-position of the naphthalene ring by 2,4-pentanedione leads to intermediate **8** which undergoes a subsequent loss of a proton to produce product **6** which preferentially exists in the enol form.

Next, we turned our attention to the related reaction of several heteroaromatic substituted sulfilimines. The results we obtained showed that these cyclizations also proceeded at room temperature in CH$_3$CN and allowed for the nucleophilic installation of a carbon functional group on the heteroaromatic nucleus in good yield.[16]

In addition to 2,4-pentanedione, allyltributylstannane was also used as the trapping nucleophile and the additive Pummerer-type reaction proceeded in comparable yield. In all the cases examined (Scheme 3), a single product was isolated and the formation of other regioisomers was not observed by NMR analysis of the crude reaction mixture.

Bolstered by these positive results, we next examined the reaction of sulfilimine **17**, derived from the reaction of 3-thiobutylthiophene with chloroamine-T (the sodium salt of *N*-chloro-*p*-toluenesulfonamide).[17] Since thiophene has a lower lying HOMO than furan and possesses a higher degree of aromaticity,[18] it was not clear whether the additive Pummerer-like reaction would take place with this heteroaromatic system. We found, however, that no significant difference in yield occurred when **17** was treated with TFAA in the presence of 2,4-pentanedione in CH$_3$CN. The reaction took place cleanly to give the C2-substituted thiophene **18** in 79% yield with exclusive regiochemistry.

In conclusion, we have disclosed a novel additive Pummerer reaction of heteroaromatic sulfilimines with carbon nucleophiles. The overall process involves the reaction of the aromatic sulfilimine with TFAA to produce a transient *N*-tosyl-*N*-trifluoroacetyl sulfonium ion. Nucleophilic attack at the adjacent vinyl carbon results in the ejection of the sulfonamide group and the resulting thionium ion then loses a proton to give the observed product. The sulfur functionality left on



Scheme 3.

the heteroaromatic ring can be utilized for further synthetic manipulations and studies along these lines are currently under investigation in our laboratory.

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