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Vinylogous Pummerer Reaction of Amido-Substituted Sulfoxides as a Method for Preparing Oxindoles and Tetrahydroisoquinolones

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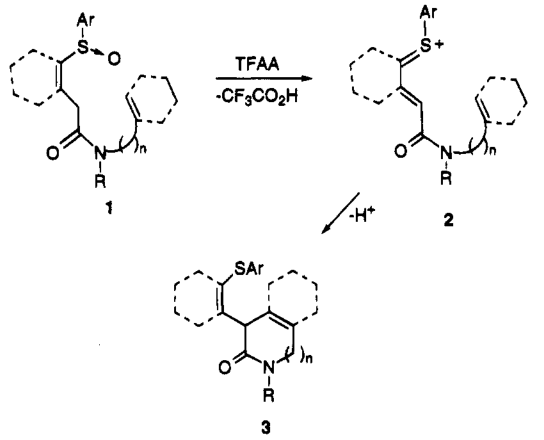
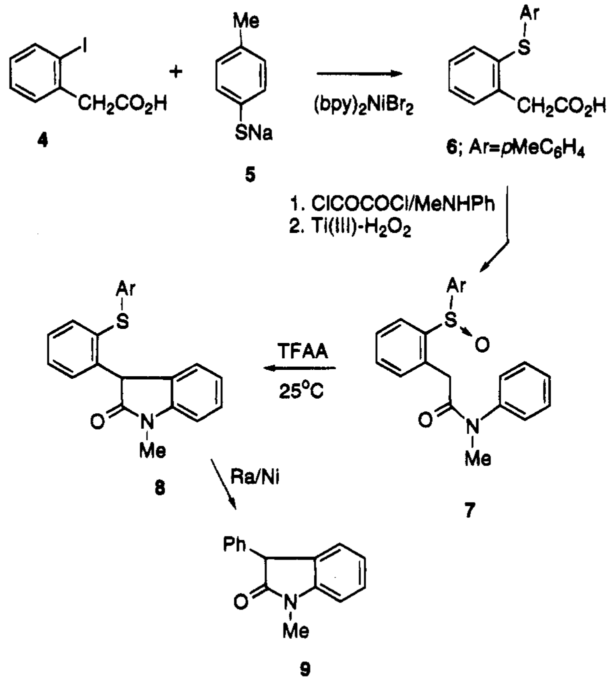
The Pummerer rearrangement has been widely studied and has received considerable attention as a synthetically useful process.[1-3] α-Acylthionium ions generated from α-acyl sulfoxides under Pummerer conditions are powerful electrophiles, reacting efficiently with nucleophilic carbon species. Bimolecular interception of the cation with various carbon−carbon double bonds is well known.[4] The intramolecular mode, which is in effect a π-cyclization route, has extended the usefulness of the Pummerer rearrangement.[5] The intermediate thionium ion can be effectively trapped by aromatic rings in Friedel−Crafts reactions, both inter- and intramoleculary.[6-8] There are also synthetically useful examples of *additive Pummerer rearrangements* involving the direct conversion of vinyl sulfoxides into disubstituted sulfides.[9-15] We wish to disclose here a novel reaction of aryl amido sulfoxides of type **1** which occurs upon treatment with trifluoroacetic anhydride. Electrophilic attack proceeds at the nucleophilic oxygen and is followed by proton loss to give the highly reactive intermediate **2** in which the γ-position is activated by the positively-charged sulfur atom. Attack at the γ-carbon by a tethered π-bond results in an annulation leading to oxindoles and tetrahydroisoquinolones. The overall transformation is illustrated in Scheme 1. The details of this new reaction are the subject of this Communication.

Scheme 1



Construction of the prerequisite amido sulfoxide necessary for thionium generation was accomplished by the bis(bipyridyl)nickel(II)-catalyzed thioarylation (83%) of 2-iodophenylacetic acid with sodium p-thiocresolate.[16] Conversion of the resulting acid **6** to the corresponding amide followed by titanium(III)−hydrogen peroxide oxidation[17] afforded sulfoxide **7** in 81% overall yield.



Treatment of **7** with TFAA in CH_2Cl_2 at 25 °C gave the 3-substituted oxindole **8** in 91% yield which could be easily reduced with Raney nickel to the known 3-phenyloxindole **9**.[18] We assume that the mechanism for the conversion of **7** to **8** proceeds by the sequential set of reactions outlined in Scheme 1 where the N-phenyl group effectively traps the Pummerer-generated thionium ion in a Friedel−Crafts fashion.[19]

In like manner, sulfoxide **10** afforded the tetrahydroquinolone derivative **11** in 85% isolated yield when treated with TFAA at room temperature. Reductive

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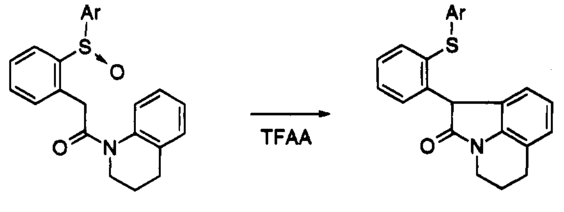
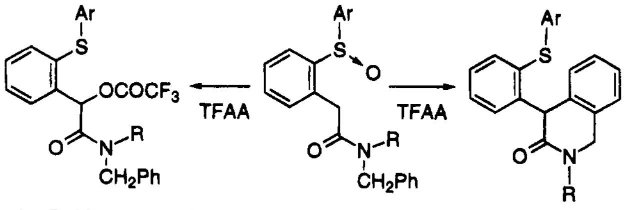
removal of the phenylthio group from these derivatives generally occurs in high yield using Raney nickel, and the overall reaction represents a new method for synthesizing a variety of 3-phenyl-substituted oxindoles.



10; Ar=*p*MeC$_6$H$_4$

11

Interestingly, treatment of the homologous *N*-benzyl-*N*-methylamido sulfoxide **12** with TFAA did not afford the product of internal cyclization on the aromatic ring. Instead, only the *normal Pummerer* product (*i.e.*, α-trifluoroacetoxy sulfide **13**; 66%) was formed which readily hydrolyzed to the corresponding alcohol on workup. On the other hand, when the related *tert*-butyl amide **14** was subjected to TFAA, the desired tetrahydroisoquinolone derivative **15** was obtained in 83% yield. The product distribution encountered coincides with the rotamer population of the starting amide. It is well known that rotation around the acyl-to-nitrogen bond is restricted, leading to the existence of two geometric isomers which are usually not separable due to the relatively low barrier to rotation (*ca.* 20 kcal/mol).[20] The preference for unsymmetrical N,N-disubstituted amides to exist predominantly with the larger substituent on nitrogen *syn* to the carbonyl oxygen is well documented.[21] Because the *N*-benzyl-*N*-methylamido sulfoxide **12** favors *syn* (benzyl) geometry, the thionium ion is generated in the wrong conformation for π-cyclization, and none occurs. Moreover, the failure to isolate the tetrahydroisoquinolone derivative from the Pummerer reaction of **12** also indicates that the amide linkage does not rotate during the lifetime of the thionium ion.[22] *N-tert*-Butylamides strongly favor the *Z*-rotamer,[20] thereby suggesting that amido sulfoxide **14** exists in the geometric orientation which places the benzylic group into the crucial conformation necessary for π-cyclization. This nicely accounts for the facility with which **14** is converted into tetrahydroisoquinolone **15**.

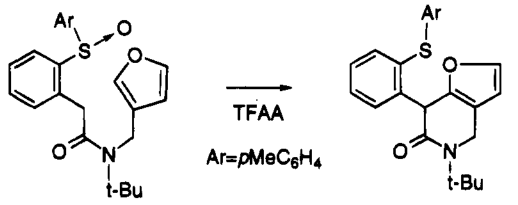


13; R=Me; Ar=*p*MeC$_6$H$_4$

12; R=Me
14; R=*t*-Bu

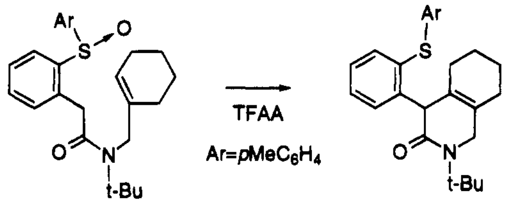
15; R=t-Bu

Two additional systems which illustrate the scope and variety of π-systems which can be employed in this cyclization are outlined below. Exposure of **16** to TFAA in CH$_2$Cl$_2$ at 25 °C afforded **17** in 68% yield. In like fashion, treatment of *tert*-butylamido sulfoxide **18** with TFAA gave the hexahydroisoquinolinone **19** in 67% yield, thereby demonstrating that tethered alkenes can also be used in these Pummerer-induced cyclizations.



16

17



18

19

In summary, the Pummerer-induced reaction of aryl amido sulfoxides with TFAA represents a highly efficient method for the synthesis of the oxindole and tetrahydroisoquinolone ring systems. We are currently investigating the generality of the process for the construction of other aza heterocycles and its application in target-oriented synthesis.

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Supporting Information Available: Procedures and characterization data (10 pages).

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(22) The fact that no cyclization occurred with amide **12** even though *ca.* 30% of the rotamer population is in the correct conformation indicates that the product distribution is determined by Curtin–Hammett kinetics in a more complex fashion than indicated. Further work is in progress to clarify this point.