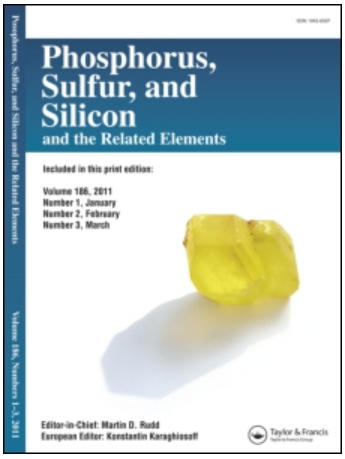

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Heterocyclic Synthesis using the Pummerer Reaction

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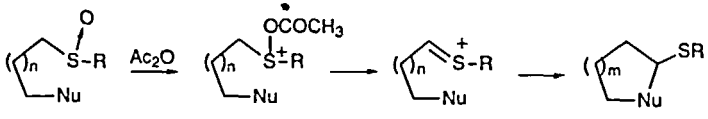
Many structurally diverse heterocyclic compounds can be easily accessed *via* the domino Pummerer/cycloaddition/N-acyliminium ion cyclization cascade.

Keywords: Pummerer reaction; *N*-acyliminium ion; cyclization; heterocycles; alkaloid synthesis; domino; tandem cascade

The Pummerer rearrangement of sulfoxides with acid anhydrides has been extensively utilized as a method for synthesizing α-substituted sulfides.[1-6] The initial step of the reaction involves acylation of the sulfoxide oxygen to form an acyloxy-sulfonium salt (**2**), thus converting this oxygen to a good leaving group. Removal of a proton from the α-carbon with elimination of the acyloxy group generates a thionium ion (**3**), which is trapped by one of the nucleophilic species present in the reaction medium. The finding that thionium ions may serve as electrophiles in electrophilic substitution chemistry has greatly extended the synthetic range of the Pummerer reaction.[4] Thus, both inter-[7] and intramolecular[8] versions of the process have been used to prepare a wide assortment of compounds. Currently,

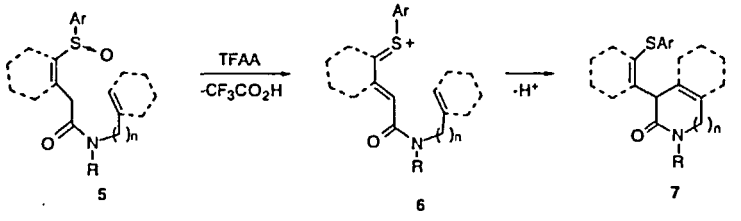
Pummerer-based transformations are finding widespread application in carbo-[9] and heterocyclic syntheses[10] by reaction of the initially generated thionium ions with internally disposed nucleophiles.

Scheme I



1 2 3 4

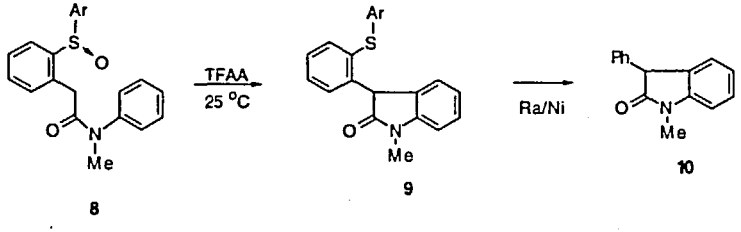
As part of our continuing interest in cascade transformations,[11] we have become interested in tandem induced Pummerer processes with the intention of assessing their viability as a general strategy for the synthesis of heterocyclic ring systems.[12] Domino cascade processes belong to a growing family of reactions which allow for the regio- and stereocontrolled formation of several carbon-carbon bonds and/or ring systems in a single operation.[13] Cationic reactions that proceed in a domino fashion are featured in the biosynthesis of important natural products, and synthetic applications of both biomimetic and nonbiomimetic cationic cyclizations have been widely developed.[14] Important contributions to this area have also been realized utilizing a combination of anionic, radical, carbenoid, and transition metal-catalyzed processes.[15] The combination of a sequence of individually powerful methods often has a value significantly greater than the sum of individual reactions and has become of great interest to the synthetic community. In this regard, we decided to investigated the vinylogous Pummerer reaction of vinyl sulfoxides such as **5** to determine whether these substrates could



be used as electrophilic reagents to trigger tandem carbon-heteroatom bond formation.[16] In this reaction, electrophilic attack proceeds at the nucleophilic oxygen atom of the sulfoxide and this is followed by proton loss to give the highly reactive intermediate **6** in which the γ-position is activated by the positively charged sulfur atom. Attack at the γ-carbon by a tethered π-bond could result in an overall annulation leading to various heterocyclic systems (*i.e.*, **7**).

Our studies began with an investigation of the Pummerer reaction of amido sulfoxide **8**. Treatment of **8** with trifluoroacetic anhydride (TFAA) in CH_2Cl_2 at 25 °C gave the 3-substituted oxindole **9** in 91% yield which could easily be reduced with Raney-nickel to 3-phenyloxindole **10**. We assume that the mechanism for the conversion of **8** to **9** proceeds by the sequential

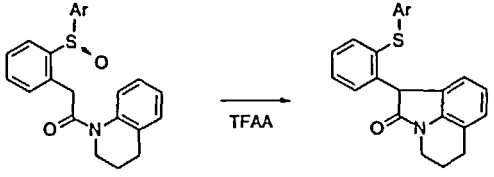
Scheme 3



set of reactions outlined in Scheme 2 where the *N*-phenyl group effectively traps the Pummerer-generated thionium ion in a Friedel-Crafts fashion.[17]

In a like manner, sulfoxide **11** afforded the tetrahydroquinolone derivative **12** in 85% isolated yield when treated with TFAA at room temperature.

Scheme 4

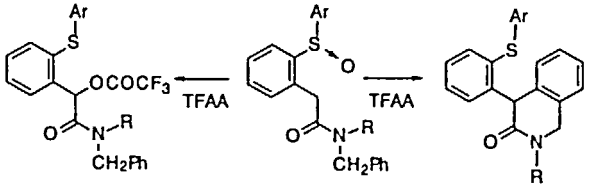


11; Ar=*p*-MeC_6H_4 **12**

Interestingly, treatment of the homologous *N*-benzyl-*N*-methylamido sulfoxide **13** 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 **14**) was formed which readily hydrolyzed to the corresponding alcohol upon work-up. On the other hand, when the related *tert*-butyl amide **15** was subjected to TFAA, the desired tetrahydroisoquinolone derivative **16** 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 carbon-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).[18] 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.[19] Due to the *N*-benzyl-*N*-methylamido sulfoxide **13** preferred *syn* (benzyl) geometry, the thionium ion is generated in an unfavorable conformation for π-cyclization and thus, no cyclization occurs. Moreover, the failure to isolate the tetrahydroisoquinolone derivative from the Pummerer reaction of **13** implies that the amide linkage does not rotate during the lifetime of the thionium ion. *N-tert*-Butylamides strongly favor the *Z*-rotamer[18] thereby suggesting that amido sulfoxide **15** 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 **15** is converted into tetrahydroisoquinolone **16.**

Scheme 5

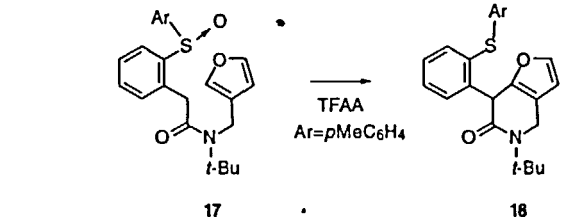


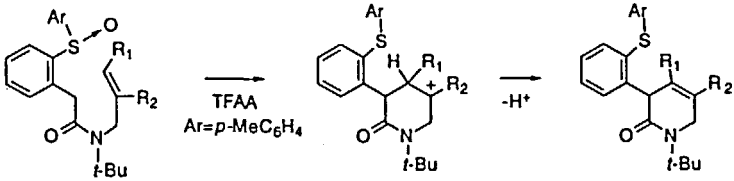
14; R=Me; Ar=*p*-MeC$_6$H$_4$ **13**; R=Me **15**; R=*t*-Bu **16**; R=*t*-Bu

So that a cross-section of additional information could be obtained in regard to the *vinylogous Pummerer/π-cyclization protocol*, a series of different amido sulfoxides was needed to represent a variety of different π-bonds. Compounds ranging from substituted aromatics to simple alkenyl tethered systems were considered. Ultimately, substrates **17, 19**, and **20** were studied as they contain a range of synthetically interesting and easily attainable functionality. Exposure of the furanyl tethered amido sulfoxide **17** to TFAA in CH_2Cl_2 at 25 °C furnished **18** in 68%

yield. Similarly, reaction of *tert*-butylamido sulfoxides **19** and **20** with TFAA gave the cyclized dihydropyridones **22** and **23** in 67% and 54% yield, thereby demonstrating that tethered alkenes can also be used in these Pummerer-induced cyclizations.

Scheme 6





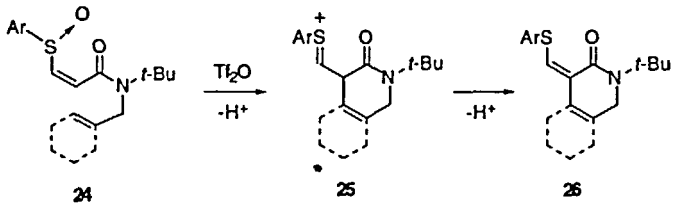
19; $R_1 = R_2 = (CH_2)_4$
20; $R_1 = C_2H_5$; $R_2 = CH_3$

22; $R_1 = R_2 = (CH_2)_4$
23; $R_1 = C_2H_5$; $R_2 = CH_3$

The *additive Pummerer* reaction of vinyl amido sulfoxides of type **24** also proceeded in a related fashion. In this case, activation of the vinylic sulfoxide C-C double bond by sulfoxide O-trifluoroacetylation is followed by intramolecular cyclization *via* nucleophilic addition of the tethered π-bond. The resulting thionium ion **25** undergoes deprotonation to furnish dihydropyridone **26** (Scheme 7).

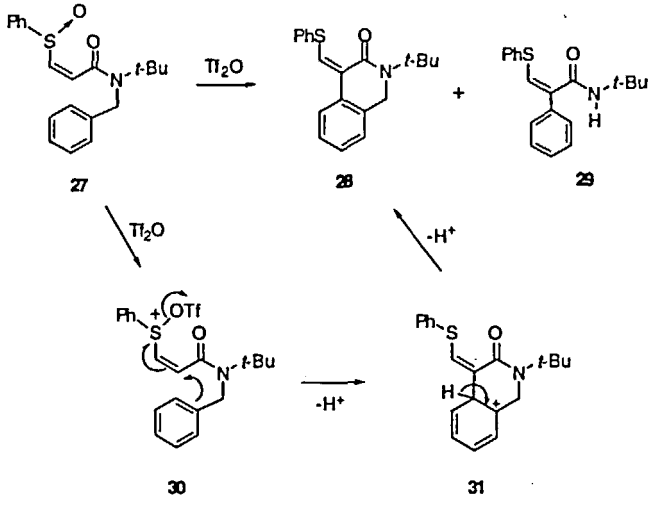
We also examined the chemistry of amido sulfoxide **27** and found that the Pummerer reaction gave rise to a mixture of dihydroisoquinoline **28** (32%) and the rearranged *N-tert*- butyl-2-

Scheme 7



phenyl-3-phenylsulfenyl acrylamide **29** (45%). The formation of **28** can be rationalized by the sequence of events outlined in

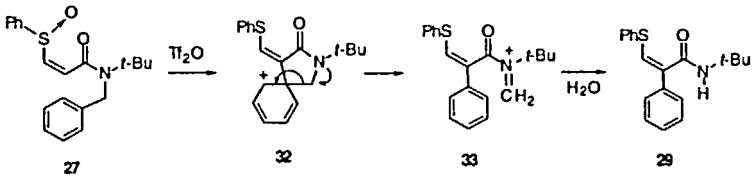
Scheme 8



Scheme 8. The critical step in this transformation involves a 6-*exo trig* cyclization of intermediate **30** to give **31** which is ultimately converted to **28**. A plausible mechanism for the formation of the rearranged enamide **29** from amido sulfoxide **27** is outlined in

Scheme 9. The first step involves *ipso* attack of the aromatic ring on the activated vinyl sulfoxide π-bond to produce the spiro substituted cyclohexadienyl cation **32**. Nitrogen assisted fragmentation of the C-C π-bond results in generation of acyl iminium ion **33** which is eventually converted to **29** on aqueous work-up.

Scheme 9



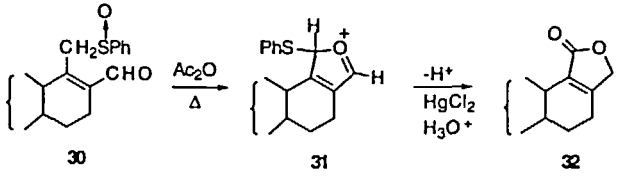
27 32 33 29

The above results demonstrate the potential of both the *vinylogous* and *additive* Pummerer reactions for the synthesis of nitrogen heterocycles. The reaction sequence involves formation of an electrophilic thionium ion intermediate which is intercepted by a π-nucleophile tethered on the amide nitrogen. The overall transformations represent highly effective methods for converting relatively simple starting materials into complex nitrogen heterocycles.

As part of our studies in this area, we have also been interested in another type of Pummerer cascade which we refer to as the *domino Pummerer/cycloaddition/N-acyliminium ion cyclization cascade*. Many structurally diverse heterocyclic compounds can be easily accessed *via* this method. Several years ago, De Groot and coworkers developed a procedure for butenolide formation in which the key step involves a Pummerer induced cyclization of aldehydic sulfoxides of type **30** into butenolides **32** (Scheme 10).[20] It was assumed that the neighboring carbonyl group attacks

the initially formed thionium ion to give an oxy-stabilized cation **31** which loses a proton to generate a 2-thio substituted furan which is subsequently converted to the butenolide upon hydrolysis. On the basis of this transformation we decided to explore the internal trapping of the Pummerer cation with adjacent carbonyl groups as a method to prepare a variety of substituted furans. The strategy

Scheme 10

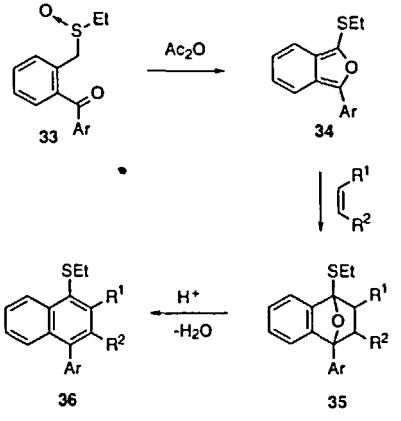


30 31 32

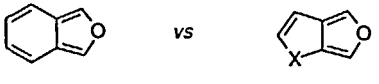
was first tested on ketosulfoxide **33** (Scheme 11). The α-thiocarbocation derived from the Pummerer reaction of **33** was readily intercepted by the adjacent keto group to produce isobenzofuran **34** as a transient intermediate which underwent a subsequent Diels-Alder cycloaddition with an added dienophile. The resulting cycloadduct **35** was readily converted to representatives of several types of arylnaphthalene lignans.[21]

As heteroaromatic isobenzofuran analogs **(37)** have not been extensively studied in the literature, we focused our attention on the Pummerer reaction of several *o*-heteroaroyl substituted sulfoxides as a method to generate reactive heteroaromatic *o*-xylylenes. Most notable among the heteroaromatic isobenzofurans**(38)** reported in recent years are the furo[3,4-*b*]furans, thieno[2,3-*c*]furans, furo[3,4-*d*]-isoxazoles, and furo[3,4-*b*]indoles[22].

Scheme 11



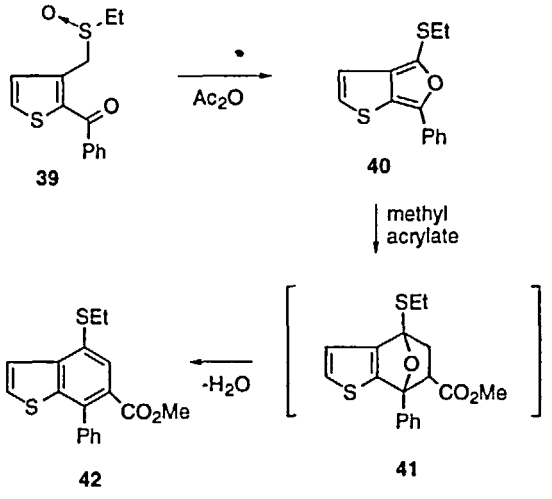
These 10π-systems are isoelectronic with the pentalene dianion and have been of some theoretical interest. MO calculations on these heteroisobenzofurans indicate that they possess little or no aromatic character, and this is reflected in their high chemical reactivity.[22] Using the domino Pummerer Diels-Alder sequence we were able to synthesize several thieno[2,3-c]furans and furo[3,4-b]indoles.[23] In the presence of a suitable dienophile, the reactive o-xylylene underwent [4+2]-cycloaddition followed by an acid-catalyzed ring-opening and aromatization to give hetero-aromatic naphthalene derivatives (Scheme 12). The domino Pummerer cyclization-cycloaddition sequence also occurred intramolecularly using unactivated alkenyl tethers of variable length. The results clearly indicate that the domino cascade



37 **38**; X = O, S, N

process is a powerful method for the construction of complex heteroaromatic *o*-quinodimethanes.

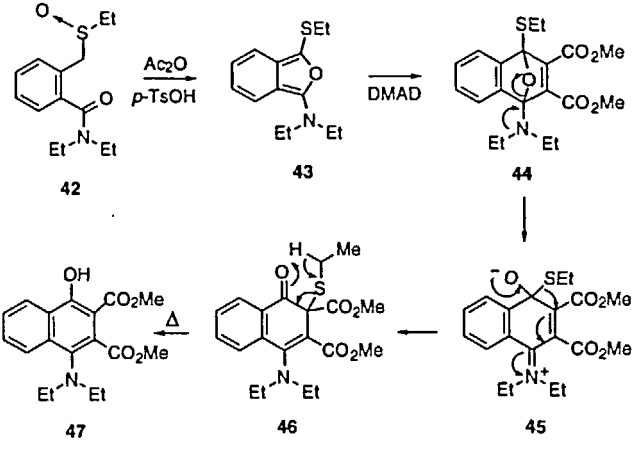
Scheme 12



Prompted by the above results, we became interested in extending the Pummerer promoted cyclization reaction of *o*-amido substituted sulfoxides since this would allow for the rapid stereocontrolled synthesis of a variety of azapolycyclic products. Indeed, the *domino Pummerer/Diels-Alder sequence* readily afforded 2-amino substituted isobenzofurans as transient species which were too labile to isolate but underwent rapid [4+2]-cycloaddition with added dienophiles.[24] When dimethyl acetylenedicarboxylate (DMAD) was used as the trapping agent, the initially formed iminium ion **45** could not undergo proton loss (Scheme 13). Instead, **45** rearranged by means of a 1,2-ethylthio

shift to afford the tetralone derivative **46**. Compound **46** was converted to naphthol **47** in high yield upon further heating. This process presumably proceeds by elimination of thioacetaldehyde in a hetero-retro-ene fashion, for which there is ample precedence in the literature.[25]

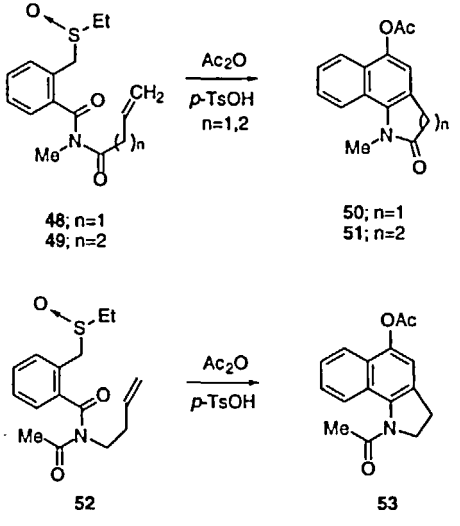
Scheme 13



In order to access synthetically more valuable targets, we focused our attention on an intramolecular variation of the *domino amido-Pummerer-Diels-Alder reaction sequence.* The one-pot intramolecular cascade process occurred smoothly when the olefin tether was activated by an ester or when a carbonyl group was located adjacent to the nitrogen atom of the 2-amino substituted isobenzofuran (Scheme 14).[24] The intramolecular cycloaddition behavior of the incipient isobenzofurans in response to the presence of a C=O group is striking. Five and six ring-membered precursors **48** and **49** delivered cyclized products bearing a

carbonyl within the newly formed rings in good to excellent yields. Externalization of the C=O as in **52** likewise led to a facile internal cyclization. Removal of the C=O functionality, however, suppressed intramolecular cycloaddition in favor of the traditional Pummerer reaction. The reactivity discrepancy can be rationalized

Scheme 14

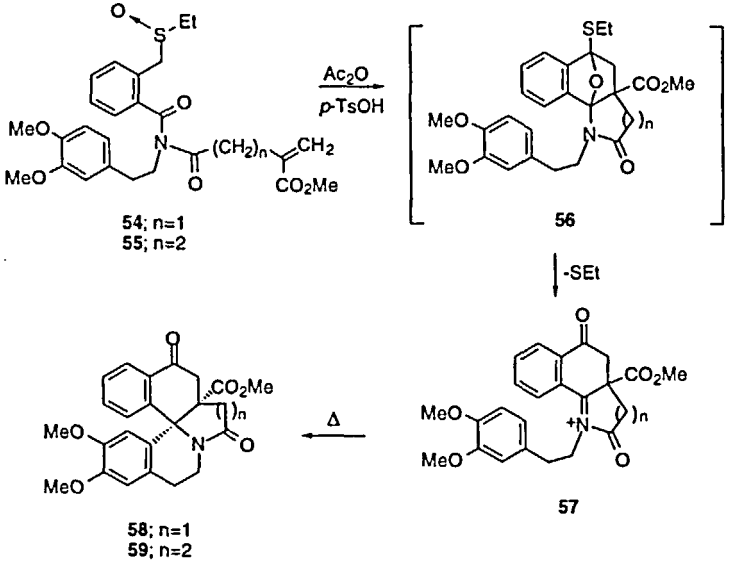


in terms of steric effects in the transition states. The incorporation of an amido group is clearly of synthetic advantage as it offers the opportunity to accelerate intramolecular cycloaddition by steric adjustment of ground-state and transition state energies either separately or simultaneously.

Having established the facility with which *N*-acyliminium ions can be formed from the Pummerer reaction of *o*-amido substituted

sulfoxides, we next focused our attention on the final cyclization step of the proposed cascade process.[26] In order to avoid the deprotonation (aromatization) step, we prepared sulfoxides **54** and **55**, each possessing a carbomethoxy group attached to the olefin tether. This substituent was selected not only to prevent deprotonation, but also because the presence of an electron

Scheme 15

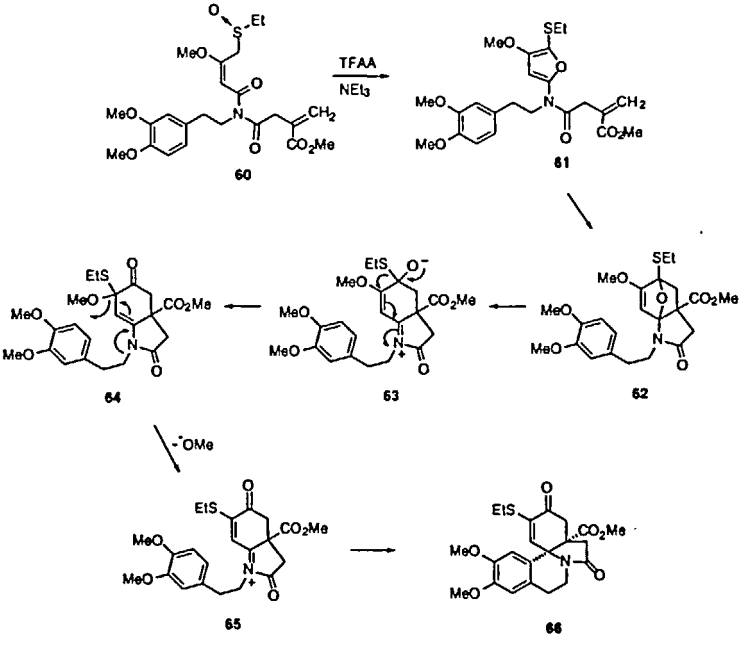


withdrawing group on the double bond enhances [4+2]-cycloaddition based on FMO considerations. *N*-Acyliminium ion **57** derived from the internal cycloadduct **56** underwent stereoselective spirocyclization to furnish the *cis*-3,4-benzoerythrinane **58** or homoerythrinane derivative **59** in good yield (Scheme 15). The overall triple cascade sequence represents an efficient one-pot approach towards the erythrinane

alkaloid skeleton[27] in which the spirocyclic ABC skeleton is assembled in a single operation.

A synthesis of (±)-erysotraamidine (**69**) was undertaken in order to further test the viability of the triple cascade process as an entry into the erythrinane skeleton. The requisite starting imido-

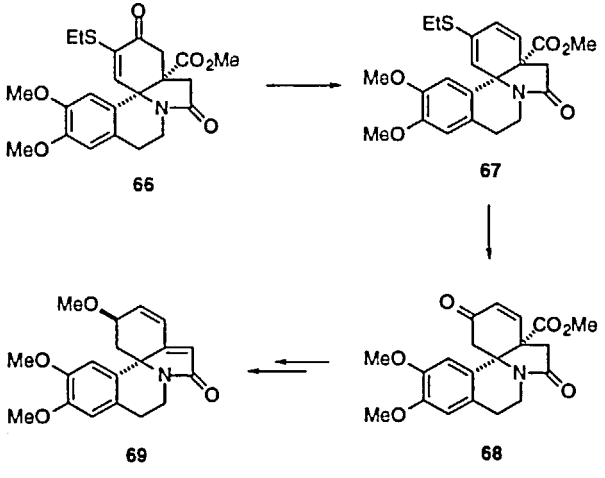
Scheme 16



sulfoxide **60**, possessing both a dienophilic and diactivated aromatic π-tether, was efficiently synthesized from known starting materials. Subjection of **60** to the Pummerer conditions gave compound **66** as a single diastereomer in 83% yield. The *cis* A/B ring fusion present in **66** was unequivocally established by an X-ray crystallographic analysis and is identical to the stereochemical

relationship found in the naturally occurring Erythrina alkaloids. The conversion of **60** into **66** is believed to follow the pathway outlined below (Scheme 16). The initially formed α-thiocarbocation intermediate generated from the Pummerer reaction of **60** is intercepted by the adjacent imido carbonyl to produce the α-amido substituted furan **61**. This transient intermediate undergoes a subsequent intramolecular Diels-Alder cycloaddition across the tethered π-bond to furnish cycloadduct **62**. Nitrogen-assisted ring opening of the oxabicyclic bridge results in the formation of zwitter-

Scheme 17



ionic intermediate **63** which undergoes a 1,2- thioethyl shift followed by methoxide ion ejection. Cyclization of the diactivated-aromatic tether onto *N*-acyliminium ion **65** ultimately provides the tetracyclic amide **66**.

With a supply of **66** in hand, this enone was converted into the corresponding vinyl triflate which, in turn, was subjected to a

palladium catalyzed formate reduction to give **67**. The resulting thio-substituted diene was subsequently transformed into ketone **68** *via* a titanium mediated hydrolysis.[28] The present sequence constitutes a formal synthesis of (±)-erysotramidine (**69**) based on the successful conversion of **68** into **69** by Tsuda and coworkers.[29]

In conclusion, our investigations have shown that many structurally diverse heterocyclic compounds can be easily accessed *via* the *domino Pummerer/ cycloaddition/N-acyliminium ion cyclization cascade.* The key step in this process involves the generation of an amino-substituted furan by a Pummerer induced cyclization reaction. After the Diels-Alder reaction occurs, the [4+2]-cycloadduct undergoes a subsequent fragmentation to generate a reactive *N*-acyliminium ion. This triple cascade is applicable toward the preparation of a broad range of alkaloids. It is a reasonable expectation that future years will see a continued evolution of this unique domino cascade toward other synthetic targets.

Acknowledgment

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