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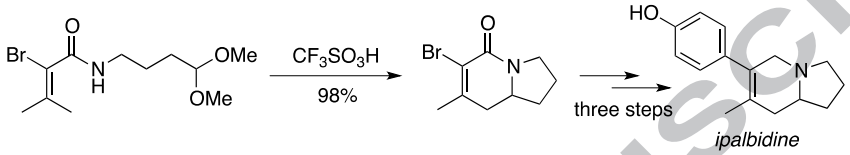

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Superacid-Promoted Synthesis of Indolizidine Derivatives

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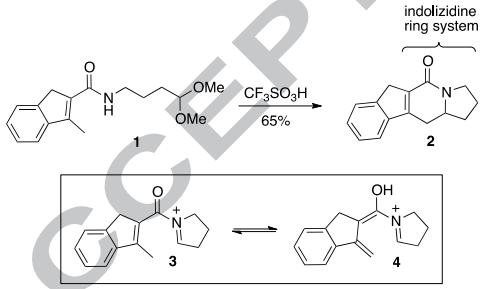
ABSTRACT

A series of amido-acetals were reacted with the Brønsted superacid, CF_3SO_3H, to provides indolizidine derives by a cyclization cascade. A mechanism is proposed involving formation of a vinylogous enol which undergoes a 6π-electrocyclization reaction with an adjacent N-acyl iminium ion group. With aryl substituents, there is a strong tendency for the N-acyl iminium ion group to undergo Friedel-Crafts type cyclizations with the aryl group. The synthetic methodology was used to prepare the alkaloid natural product, *ilpadine*.

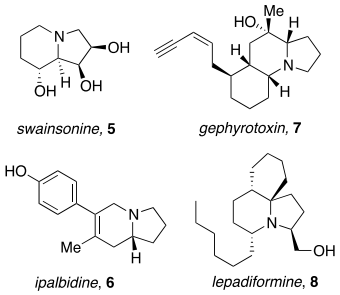
Introduction

During the course of studies related to the aza-Nazarov reaction, we observed an unexpected transformation involving an amido-acetal (**1**, Scheme 1).[1] The superacid-promoted chemistry



Scheme 1.

leads to the tetracyclic compound (**2**) in reasonably good yield. This conversion may be understood to be the result of two cyclizations. First, the amido-acetal undergoes cyclization to the *N*-acyliminium ion (**3**) by well-known acid-catalyzed condensation chemistry.[2] Second, ion **3** exists in equilibrium with the vinylogous enol **4** and this species may undergo a 6π-electrocyclization to give the final product (after a deprotonation). Interestingly, this cyclization cascade gives the indolizidine ring-system. The indolizidines are a well-known class of alkaloids, many of which exhibit biological activities.[3] Examples of indolizidine natural products include, swainsonine (**5**), ipalbidine (**6**), gephyrotoxin (**7**), and lepadiformine (**8**). This class of alkaloids is a frequent target in synthetic studies due to its diverse structures and useful biological activities.[4] Thus, new synthetic routes to the indolizidines are potentially valuable.



In the following manuscript, we describe our studies of cyclization cascades with amido-acetals providing a series of indolizidine derivatives. The scope of the transformation is explored and the mechanism is examined through the use of theoretical calculations. Several unexpected Friedel-Crafts-type cyclizations were observed with aryl-substituted amido-acetals. The new synthetic method has been used to prepare the indolizidine natural product, *ipalbidine* (**6**).

Results and Discussion

Our studies began with the preparation of amido-acetals from appropriate unsaturated carboxylic acids or derivatives. Thus, amido-acetals **9** and **10** were prepared from crotonoyl chloride and 3,3-dimethylacryloyl chloride, respectively, and the 4-aminobutyraldehyde acetals. When these substrates are reacted in superacid, compound **9** provides only the amide product **11**, while compound **10** gives the expected indolizidine **12** in nearly quantitative yield (eqs 1-2). The conversion to indolizidine **12** prompted further studies of the scope of this chemistry. A series of amido-acetals were prepared and reacted with superacid, providing several novel indolizidine derivatives (Table 1). This includes the 2-pentenoic acid derivative **13** to

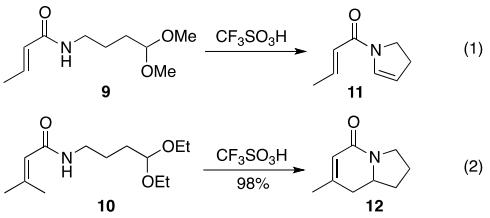
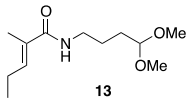
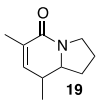
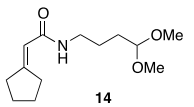
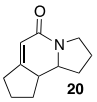
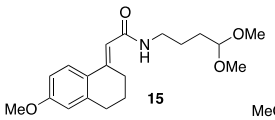
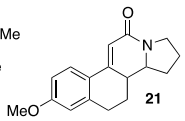
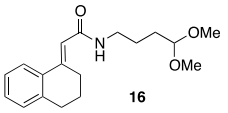
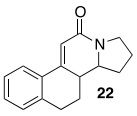
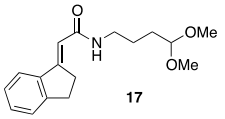
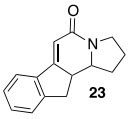
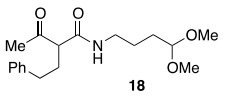
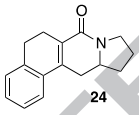


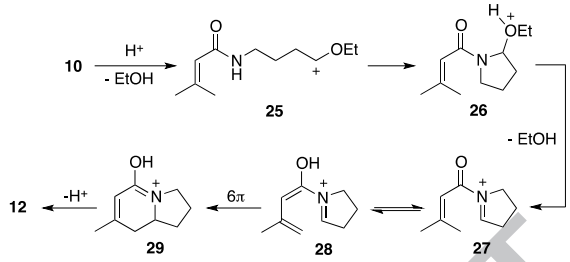
Table 1. Products and yields from the reactions of amido-acetals (**13-20**).

amido-acetals	cyclization products	yields[a]
 **13**	 **19**	87%
 **14**	 **20**	77%
 **15**	 **21**	99%
 **16**	 **22**	74%
 **17**	 **23**	47%
 **18**	 **24**	57%

[a]Isolated yield

provide the methyl-substituted indolizidine **19**. Ring-fused products may also be generated from this chemistry. For example, the cyclopentane derivative (**14**) gives ring-fused product **20**, while the aza-steroidal ring system is prepared in good yield from the cyclization of acetals **15** and **16**. A similar product (**23)** is prepared in 47% yield from the indanyl derivative **17**. Product **24** is formed in good yield by a cyclization cascade involving **18** (for a mechanistic explanation, see equation 4).

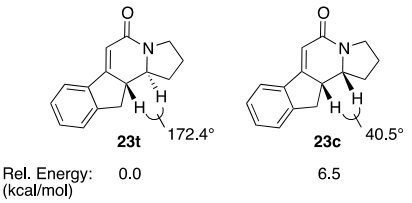
All of the above transformations may be explained by formation of the respective *N*-acyliminium ions and subsequent cyclization via the vinylogous enol (Scheme 2). For example, amido-acetal **10** is initially ionized in the superacid to give the carboxonium ion **25.** This species undergoes cyclization to **26** and elimination of methanol to provide the *N*-acyl iminium ion **27**. Since *N*-acyl iminium ions are not sufficiently electrophilic to insert directly into a C-H σ-bond, the conversion likely involves tautomerization to the vinylogous enol **28** followed by a 6π electrocyclization to give **29**. The conversions are best done in excess superacid, suggesting that the tautomerization occurs through a dicationic intermediate. This would involve protonation of the carbonyl oxygen and subsequent deprotonation of the γ-carbon to give intermediate **28**. Intermediate **28** is then favorably disposed to undergo a 6π electrocyclization reaction. Although the amido-acetal from crotonoyl chloride (**9**) did not



Scheme 2.

provide the desired indolizidine (eq 1), the observed product **11** is consistent with the proposed mechanism. This product likely arises by formation of an *N*-acyl iminium ion without the accompanying tautomerization to the vinylogous enol. Consequently, cyclization does not occur and product **11** is formed by deprotonation.

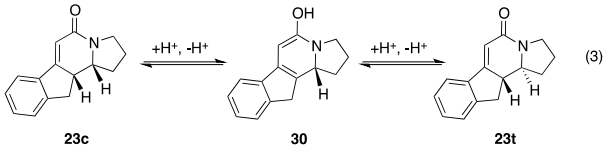
For products **20-23**, there exists the possibility of two stereoisomers, the cis and trans ring junction products. Likewise, compound **19** has a similar potential for stereoisomerism. Both NMR and GC analysis suggest that a single stereoisomer is formed in the cyclization cascades. If the proposed mechanism is correct, then the final cyclization step should occur by a thermal, 6π electrocyclization. According to the Woodward-Hoffman rules of orbital symmetry, this would require a disrotatory ring closure and this produces the cis ring junction for compounds **20-23**. Analysis of compound **23** was done by correlated NMR spectroscopic methods and the multiplet analysis method described by Hoye and coworkers.[5] The results indicate the coupling constant between the ring junction protons is 10.3 Hz – a value consistent with the trans ring junction rather than the cis ring junction. Both stereoisomers of **23** were modelled with DFT calculations (gas-phase B3LYP 6-311G (d,p) level, Scheme 3)



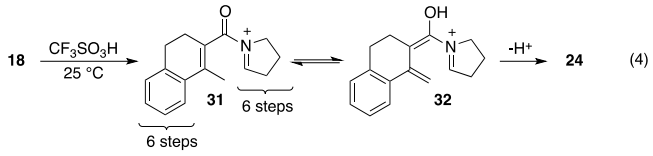
Scheme 3.

and the trans stereoisomer (**23t**) is found to be significantly more stable than the cis stereoisomer (**23c**).[6] Upon examination of the optimized structures, the trans stereoisomer **23t** has a H-C-C-H dihedral angle of 175° at the ring junction carbons while the cis stereoisomer (**23c**) has a H-C-C-H dihedral angle of 77°. Whereas a dihedral angle of 175° would be expected to give a coupling constant in the range of 10.3 Hz, a dihedral angle of 77° would not give such a coupling constant (based on the Karplus equation).[7] These data clearly suggest the trans stereoisomer **23t** is formed in the superacid-promoted cyclization. How could this occur when a Woodward-Hoffman 6π electrocyclization gives the cis stereoisomer? There are two possibilities. First, cyclization may not be a formal Woodward-Hoffman-type pericyclic reaction. The cyclization may be an electrophilic reaction involving an iminium ion with neighboring π-bonds, one that forms the trans stereoisomer directly. Alternatively, a Woodward-Hoffman-type electrocyclization could provide the cis stereoisomer but then it isomerizes quickly to the more stable trans stereoisomer. This chemistry can be considered to occur through the vinylogous enol (**30**) and reprotonation steps (eq 3).

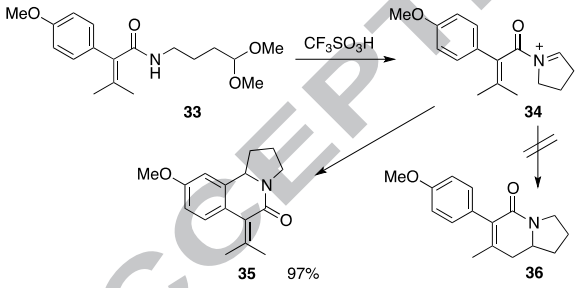
Since this type of tautomerization is likely involved in the cyclization, it seems reasonable to expect similar chemistry with compound **23** and other indolizidine products.



In the case of acetal **18**, three independent cyclizations occur to give product **24** (eq 4). The initial stages of the reaction provide the dihydronaphthalene ring by cyclization of the β-ketoamide (**18**). This process involves 6 reaction steps to complete the cyclodehydration chemistry (including proton transfers and the Friedel-Crafts reaction).[8] Similarly, the iminium ion formation requires 6 reaction steps. Product **24** likely arises from cyclization of the vinylogous enol **32** – a process that adds 4 more reaction steps from **31** to **24**. Thus, the conversion of acetal **18** to product **24** occurs by a sixteen-step process and it leads to three new rings.

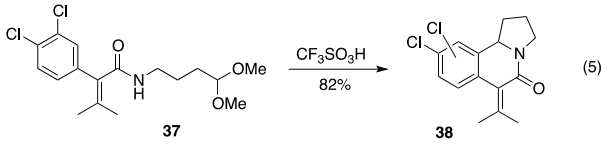


Other aryl-substituted amido-acetals did not provide good yields of the expected indolizidines, but rather cyclizations occurred from Friedel-Crafts type reactions. We prepared the 4-methoxyphenyl derivative (**33**) in an approach to the synthesis of the indolizidine natural product, *ipalbidine* (**6**, Scheme 4). Rather than providing the indolizidine product **36**, cyclization of

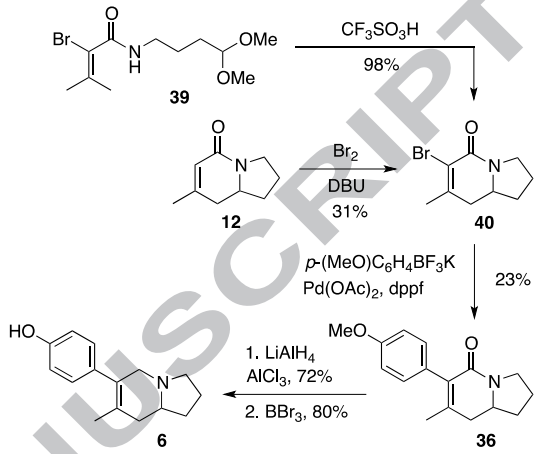


Scheme 4

the *N*-acyliminium ion **34** leads to product **35** in excellent yield. This product clearly arises from reaction of the *N*-acyliminium ion at the *para*-methoxy phenyl group. When a less nucleophilic aryl group is used - the 3,4-dichlorophenyl group - the same type of cyclization products is obtained (eq 5). Evidently, the Friedel-Crafts-type reaction is rapid even with a mildly deactivated aryl group, as the cyclization product (**38**) is obtained in 82% yield as a mixture of regioisomers.



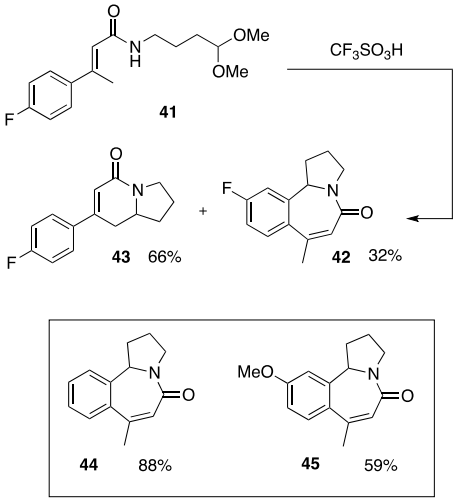
In order to access the desired aryl-substituted indolizidine (**36**), an alternative approach was developed. The amido-acetal (**39**) was prepared from the known 2-bromo-3,3-dimethylacrylic acid and this substrate provides the brominated indolizidine (**40**) in nearly quantitative yield (Scheme 5). The same substance may be prepared by bromination of the indolizidine **12**. Using Suzuki coupling, the aryl-substituted indolizidine **36** is obtained. A similar Stille coupling with 4-methoxyphenyltributyl tin was not



Scheme 5.

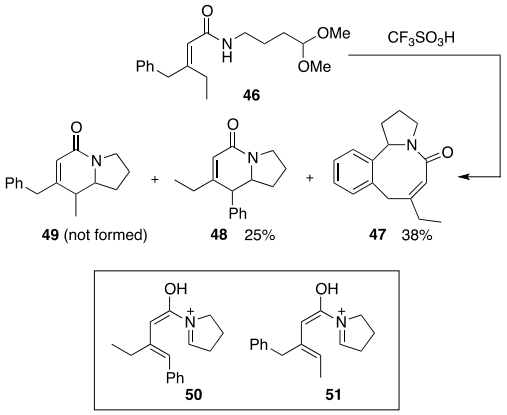
successful. Indolizidine **36** was then converted to the natural product *ipalbidine* (**6**) by carbonyl reduction and demethylation of the aryl ether.[9]

When the aryl group is installed at the 3-position of the acrylamide, both the Friedel-Crafts and indolizidine products may be obtained. Thus, the 4-fluorophenyl derivative **41** gives the products **42** and **43** from the electrocyclization and Friedel-Crafts reactions, respectively. The indolizidine product (**43**) is the major product – isolated in 66% yield. With phenyl and 4-



Scheme 6.

methoxyphenyl derivatives, the Friedel-Crafts-type products (**44-45**) are isolated as the major products. Amido-acetal **46** gives two major products from reaction in superacid. The Friedel-Crafts-type reaction leads to the unusual tricyclic product **47**, isolated in 38% yield. The indolizidine **48** is also isolated as a minor product in 25% yield. Product **48** evidently arises from the vinylogous enol (**50**). Interestingly, product **49** is not observed – suggesting the other potential vinylogous enol (**51**) does not



Scheme 7.

form. Formation of intermediate **50** may be favored somewhat by conjugation available with the phenyl group.

In summary, we have found that indolizidine derivatives may be prepared in fair to excellent yields by cyclization cascades involving amido-acetals. A mechanism is proposed in which an *N*-acyliminium ion is in equilibrium with a vinylogous enol intermediate. The vinylogous enol undergoes cyclization, perhaps through a 6π-electrocyclization, and the indolizidine framework is produced. Although aryl substituent groups are tolerated in some cases, we have found several examples in which cyclizations occur at the aryl group by Friedel-Crafts chemistry. Aryl-substituted indolizidines can also be accessed by Suzuki coupling with a brominated indolizidine - a strategy which was used to prepare the natural product, *ipalbidine*.

Acknowledgments

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Supplementary Material

Experimental procedures and analytical data. This supplementary data can be found in the online version, at

Bullet Points:

•Cascade reaction leading to the indolizidine ring system
•Superacid-promoted condensation and electrocyclization
•Synthesis of the alkaloid natural product, *ipalbidine*