

Aza-Nazarov Reaction and the Role of Superelectrophiles

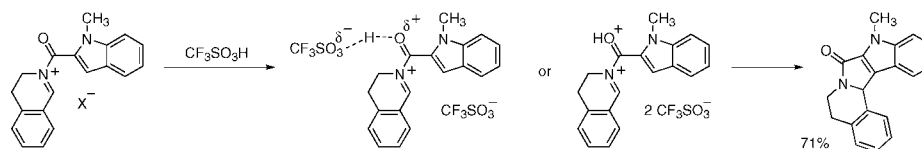
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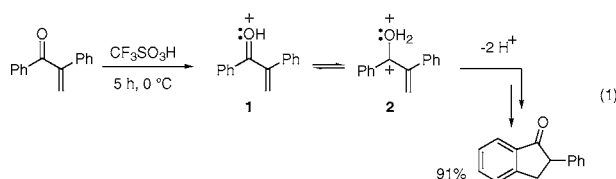
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ABSTRACT



The superacid-catalyzed reactions of *N*-acyliminium ion salts have been studied. The new conversions are remarkably similar to the Nazarov reaction and dicationic superelectrophilic species are thought to be involved. Experimental studies show that the cyclizations may be used to prepare varied heterocyclic products, while theoretical studies show that formation of the superelectrophiles can lead to very favorable reaction energetics.

The Nazarov reaction is a useful methodology for the synthesis of five-member carbocycles.¹ The conversion often involves the cyclization of divinyl ketones and related compounds in strongly acidic media. On the basis of the results from kinetic studies and theoretical calculations, Shudo and Ohwada demonstrated that the superacid-catalyzed Nazarov cyclization of 1-aryl-2-propen-1-ones to indanones involves dicationic or superelectrophilic intermediates (eq 1).^{2,3} It was proposed that the monocationic



carboxonium ion (1) is unreactive toward cyclization, but further protonation generates the dicationic superelectrophile (2), which leads to the cyclized product. By analogy to this

earlier work, we sought to determine if similar cyclizations with *N*-acyliminium salts could be done to provide a new route to nitrogen-containing heterocycles (i.e., aza-Nazarov reactions).⁴ Although a significant amount of electrophilic chemistry has been accomplished with *N*-acyliminium salts,⁵ their use in Nazarov-type cyclizations has not been reported. Herein we report our results from synthetic studies and discuss the role of superelectrophiles in these aza-Nazarov conversions.

Recently, we reported the superacid-catalyzed cyclizations of *N*-acyliminium salts to 3-oxo-1,2,3,4-tetrahydroisoquinolines and related products.⁶ Among the systems studied, salt

(2) Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774.

(3) Superelectrophile reviews: (a) Olah, G. A.; Klumpp, D. A. In *Superelectrophiles and Their Chemistry*; Wiley: New York, 2007. (b) Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, *37*, 211. (c) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767. (d) Olah, G. A.; Prakash, G. K. S.; Lammertsma, K. *Res. Chem. Intermed.* **1989**, *12*, 141.

(4) An earlier study of an aza-Nazarov reaction: Dieker, J.; Fröhlich, R.; Würthwein, E. U. *Eur. J. Org. Chem.* **2006**, 5339.

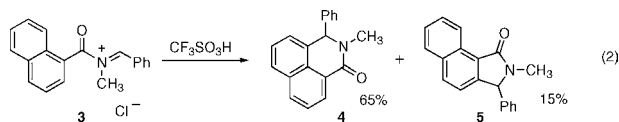
(5) (a) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833. (b) Pin, F.; Comesse, S.; Garrigues, B.; Marchalin, S.; Daiech, A. *J. Org. Chem.* **2007**, *72*, 1181. For reviews, see: (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (d) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

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[†] Northern Illinois University.

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(1) (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1. (b) Pellisier, H. *Tetrahedron* **2005**, *61*, 6479. (c) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577.



3 was found to give product **4** as a major product, along with an unidentified minor product (eq 2). Isolation and characterization of this minor product revealed its identity to be that of structure **5**. This product arises from a reaction that is remarkably similar to the Nazarov cyclization (eq 1). This prompted us to examine other *N*-acyliminium salts. Varied salts were prepared and reacted in $\text{CF}_3\text{SO}_3\text{H}$ at 25 °C to give products from cyclization (Table 1).⁷ The desired *N*-acyliminium salts are prepared in situ by the reaction of the appropriate acid chloride with the imine (in CH_2Cl_2). The cyclization reaction is then accomplished by the addition of the acid. In general, the cyclization products are formed in fair to good yields from *N*-acyliminium salts having nucleophilic aryl groups. This includes (di- and tri-) methoxyphenyl groups, thienyl, and indole groups. Both acyclic and cyclic iminium groups undergo the reaction. For example, the isoindoloisoquinolone ring system (present in several natural product alkaloids) can be prepared readily from *N*-acyliminium salts such as **20** and **22**. The effect of the activated aryl group is seen in the contrasting chemistry of salts **14** and **16**. With the activated aryl group, salt **14** gives the expected cyclization product (**15**). However the benzoyl derivative (**16**) preferentially reacts at the benzyl group to give **17** as the only major product. Product **17** is considered to be the result of a Friedel–Crafts-type reaction. Cyclization with nonactivated aryl groups may, however, also be accomplished. This is seen in the cyclization of the benzoyl and halogen-substituted aryl groups (compounds **6a**, **6c**, and **8b**; done at 80 °C). Besides superacidic $\text{CF}_3\text{SO}_3\text{H}$, other Brønsted acids were found to catalyze the transformations, such as H_2SO_4 and $\text{CF}_3\text{CO}_2\text{H}$. The weaker acids were found to give the cyclization products at a reduced rate. For example, 2 equiv of $\text{CF}_3\text{SO}_3\text{H}$ were reacted with *N*-acyliminium salt **10** at 25 °C and within 10 min the cyclization to **11** was essentially complete. With 2 equiv of $\text{CF}_3\text{CO}_2\text{H}$, the same reaction had only produced 17% yield of compound **11**.

Our earlier results⁶ suggested that cyclizations to six-member rings can be favorable reaction paths (eq 2). In this respect, a number of systems were found to give the products containing six-member rings (Table 2). With salts **24** and **26**, the six-member-ring cyclizations occur instead of the Nazarov-type cyclization products (five-member rings).

The Nazarov reaction can involve both thermal and photochemical four π -electron electrocyclic closures.¹ In photolysis experiments, *N*-acyliminium salts were found to provide nitrogen heterocycles, but the photochemical conversions differ little from the acid-catalyzed thermal reactions. For example, photolysis of *N*-acyliminium salt **6a** in superacidic $\text{CF}_3\text{SO}_3\text{H}$ ($H_0 = -14.1$)⁸ provides compound **7a** in 56% yield, while photolysis in the weaker acid $\text{CF}_3\text{CO}_2\text{H}$ (H_0

Table 1. Results from the Reactions of *N*-Acyliminium Salts with $\text{CF}_3\text{SO}_3\text{H}$ (Isolated Yields Reported)

starting material	product	yield
		7a , R=H 53% 7b , R=OCH ₃ 72% 7c , R=Cl 71%
		9a , R=OCH ₃ 70% 9b , R=Cl 32%
		92%
		49%
		70%
		80%
		79%
		80%
		71%

–2.7) gives no cyclized product (eq 3). Without UV irradiation, the same conversion is observed in 53% yield in superacidic $\text{CF}_3\text{SO}_3\text{H}$ (80 °C, Table 1) and no cyclization product is obtained from **6a** in $\text{CF}_3\text{CO}_2\text{H}$. *N*-Acyliminium salt **30** does show differing chemistry from photolytic and thermal reaction conditions. Photolysis of **30** in $\text{CF}_3\text{CO}_2\text{H}$ gives compound **32** as the only major product (eq 4). It is proposed that cyclization initially occurs to give the stabilized cation **31** and subsequent ring closure and oxidation leads to product **32**. When salt **30** is reacted in $\text{CF}_3\text{CO}_2\text{H}$ without

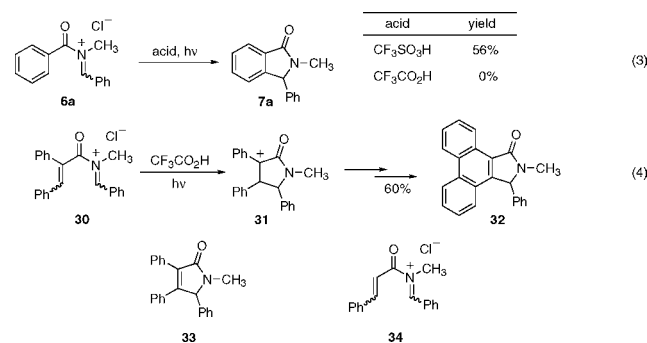
(7) These types of *N*-acyliminium ion salts are in equilibrium with the α -chloroamides, see ref 4c.

(8) Olah, G. A.; Prakash, G. K. S.; Sommer, J. In *Superacids*; Wiley: New York, 1985.

Table 2. Results from the Reactions of *N*-Acylium Salts with CF₃SO₃H (Isolated Yields Reported)

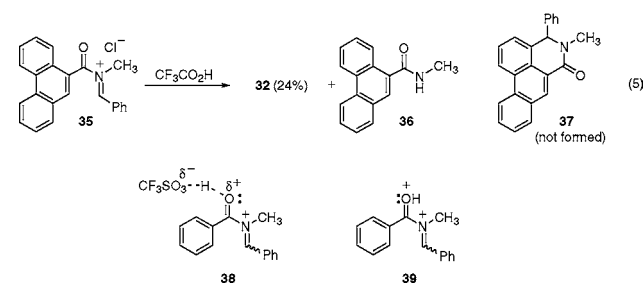
starting material	product	yield
		87%
		41%
		78%

UV irradiation, the cyclization product **33** is formed, albeit in low yield (16% isolated yield), along with unidentified minor products. Photolysis of **33** in CF₃CO₂H provides quantitative cyclization to **32**. The *N*-cinnamoyliminium salt **34** does not cyclize under thermal or photochemical reaction conditions, suggesting the importance of stabilization of the intermediate carbocation (such as **31**). Similar observations



have been made in the Nazarov cyclizations.⁹ Interestingly, the reaction of *N*-acylium ion salt **35** with CF₃CO₂H (no UV irradiation) gives **32** as the only major cyclization product, along with a substantial amount of the iminium ion hydrolysis products **36** (formed upon workup; eq 5). Cyclization to the six-member ring (i.e., **37**) does not occur.

For all of the reported cyclizations, the presence of acid catalysts is essential. When *N*-acylium salt **10** is gener-



ated in acetonitrile, no cyclization occurs (even at 80 °C). The dramatic effect of superacidity in the reaction of **6a** to **7a** and the need for acidic media in general suggests the involvement of superelectrophiles in the conversions. These could be the protosolvated species (**38**) or the fully formed dicationic superelectrophile (**39**). To further explore the superelectrophilic activation in this cyclization, we studied the reactions using DFT calculations (Figure 1). In calcula-

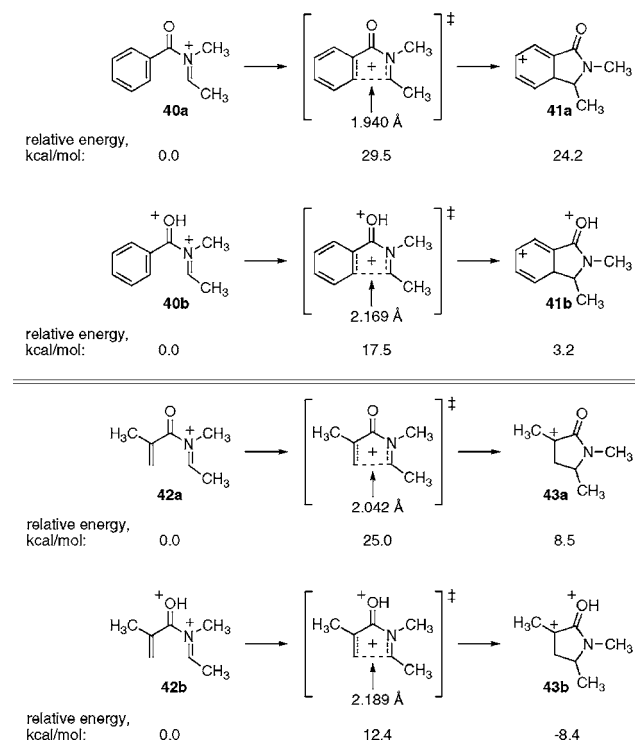


Figure 1. Calculated structures and free energies (B3LYP/6-311++G(d,p) level) of *N*-acylium ions (**40a** and **42a**), the corresponding superelectrophiles (**40b** and **42b**), transition states, and product ions (**41a,b** and **43a,b**).

tions at the B3LYP/6-311++G(d,p) level,¹⁰ the monocationic *N*-acylium ion (**40a**) is compared to the analogous superelectrophile (**40b**). The cyclization of the monocation **40a** is found to have a free energy of activation of 29.5 kcal/mol. Compared to **40a**, the cyclic intermediate (**41a**) is less stable by 24.2 kcal/mol. In the superelectrophilic reaction, the free energy of activation is estimated to be 17.5 kcal/mol and the cyclic intermediate **41b** is less stable than **40b** by only 3.2 kcal/mol. Even more pronounced effects are seen in the cyclization of the methylacryloyl derivative **42**. Reaction of the monocationic *N*-acylium ion **42a** leads to the cationic intermediate (**43a**) in an endergonic reaction step. However, the superelectrophilic *N*-acylium ion

(9) (a) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278. (b) Denmark, S.; Jones, T. *J. Am. Chem. Soc.* **1982**, *104*, 2642.

(10) (a) Frisch, M. J.; et al. *Gaussian 03*, Revision B.04; Gaussian, Inc.: Wallingford, CT, 2004; see the Supporting Information for the full list of authors and details of the calculations. (b) For a review of calculational models used in the study of superelectrophiles, see ref 3a, Chapter 2.

(42b) leads to the cyclic intermediate (43b) in an exergonic reaction step. The free energy of activation is likewise significantly reduced by superelectrophilic activation.

These results suggest that superelectrophilic activation facilitates the cyclizations by destabilizing the *N*-acyliminium ion. This leads to the large decrease in the activation energies, an earlier transition state (note forming bond length), and more favorable reaction energetics. As described by Shudo and Ohwada in their studies of the Nazarov reaction,² dications like 40b exhibit more effective charge delocalization into the aryl ring, which facilitates the cyclization. Charge–charge separation is likely an important driving force in the formation of intermediates like 41b. From the synthetic reactions, it is seen that the *N*-acyliminium ion cyclization may involve even somewhat deactivated aryl groups. Although many cyclizations involving *N*-acyliminium ions have been described over the years, few examples have involved deactivated aryl groups.^{4c,d} Indeed, our own previous efforts were unsuccessful in preparing 3-oxo-1,2,3,4-tetrahydroisoquinolines from the superacid-promoted reactions of *N*-acyliminium ions having dichlorophenyl groups.⁶ Several examples of intermolecular reactions involving *N*-acyliminium ions and deactivated arenes have been reported and these conversions have required highly acidic conditions.¹¹ The observed high reactivities of the *N*-acyliminium ion systems in the above reactions (Table 1) are consistent with the formation of superelectrophiles. At present, it is not certain if the observed aza-Nazarov reactions are pericyclic reactions of the Woodward–Hoffmann type (i.e., four π -electron electrocyclizations) or if the conversions are more accurately described as Friedel–Crafts-type reactions. Further experimental studies are required to perhaps

distinguish between these two mechanistic possibilities. It should also be noted, however, that 5-endo-trig cyclizations are disfavored according to Baldwin's rules.¹² Consequently, the four π -electron electrocyclization mechanism may be the best way to account for these observed reactions.¹³

In summary, we have found that *N*-acyliminium ion salts undergo a cyclization reaction with acid catalysts. The reaction is similar to the Nazarov cyclization; however, varied *N*-heterocyclic products can be prepared. Many intramolecular reactions of *N*-acyliminium ions have been previously described.^{5c,d} However, our present studies reveal a new mode of cyclization involving conjugated π -systems within the *N*-acyliminium ions. In certain cases, the reactions are shown to be sensitive to acid strength. Theoretical calculations also show a dramatic effect with the protonation of the *N*-acyliminium ion, including a much more favorable free energy of activation and reaction. These results suggest the involvement of superelectrophilic species in these cyclization reactions.

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Supporting Information Available: Experimental procedures, characterization data, and spectra for new compounds, computational data including atomic coordinates, and thermodynamical parameters (ΔH , ΔS , and ΔG at 298 K and 1 atm) for the calculated species. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) We thank a reviewer for this insightful suggestion.