ORGANIC LETTERS

2004
Vol. 6, No. 11
1789−1792

Dicationic Intermediates Involving Protonated Amides: Dual Modes of Reactivity Including the Acylation of Arenes

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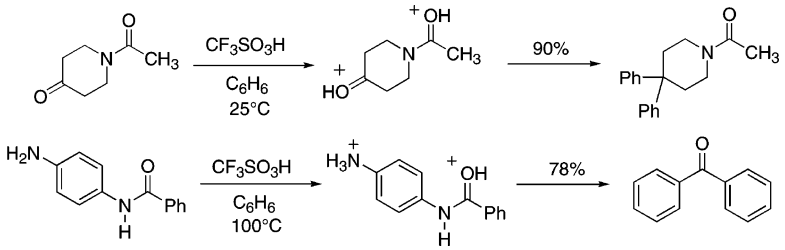
Received March 15, 2004

ABSTRACT



In the Brønsted superacid CF_3SO_3H (triflic acid), amides are able to form reactive, dicationic electrophiles. It is shown that these dicationic intermediates participate in two distinctly different types of electrophilic reactions. The protonated amide increases the reactivity of an adjacent electrophilic group, and the protonated amide group itself shows enhanced reactivity arising from an adjacent cationic charge. In the latter case, several types of amides are even capable of reacting with benzene by Friedel–Crafts acylation.

The amide functional group is an important structure in organic chemistry, biochemistry, and medicinal chemistry. Although the amide is a sturdy functional group, due in large part to its partial double-bond character, it can undergo acyl-transfer reactions with strong nucleophiles. For example, protease enzymes cleave peptide bonds by nucleophilic attack involving serine and cysteine residues.[1] Protonation of amides also enables the slow hydrolysis of peptides and amides. Even with protonated amides, however, acyl-transfer reactions are rare when the nucleophile is very weak, as in the case of aromatic nucleophiles. Friedel−Crafts acylations typically are done with more reactive functional groups, such as carboxylic acids, anhydrides, and acid chlorides.[2] There are few examples in the literature of acylations of arenes with amides or related compounds.[3]

Protonated amides have been thoroughly characterized by NMR, IR, and other methods,[4] and they have been estimated to have pK_a values around 0.0,[5] suggesting complete protonation in Brønsted superacids. Though the exact site of protonation was once a controversial topic, NMR studies

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(1) (a) Petsko, G. A.; Ringe, D. *Protein Structure and Function*; New Science Press: London, 2004. (b) Stryer, L. *Biochemistry*, 4th ed.; Freeman and Co.: New York, 1995; pp 218−227. (c) Keillor, J. W.; Brown, R. S. *J. Am. Chem. Soc.* **1991**, *113*, 5114.

(2) (a) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 733−750. (a) Olah, G. A. *Friedel−Crafts and Related Reactions*; Wiley-Interscience: New York, 1964; Vol. 3, pp 16−36.

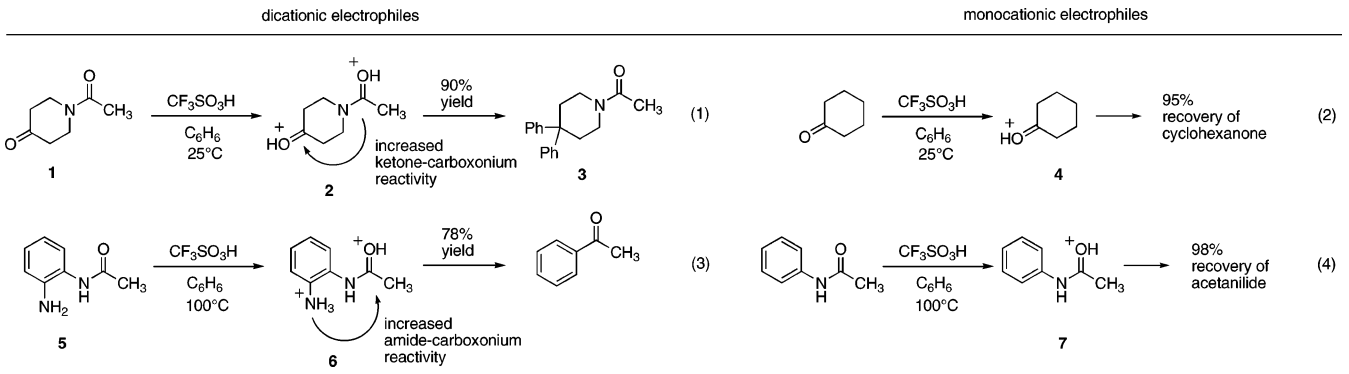
(3) (a) Anderson K. W.; Tepe, J. J. *Org. Lett.* **2002**, *3*, 459. (b) Majumdar, M. P.; Kudav, N. A. *Chem. Ind. (London)* **1976**, 1069. (c) Keumi, T.; Saga, H.; Kitajima, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1638.

(4) (a) Olah, G. A.; White, A. M.; O'Brien, D. H. *Chem. Rev.* **1970**, *70*, 561. (b) Olah, G. A.; Laali, K. K.; Wang, Q.; Prakash, G. K. S. *Onium Ions*; Wiley-Interscience: New York, 1998; pp 280−281.

(5) Arnett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223.

10.1021/ol049512z CCC: $27.50
Published on Web 04/29/2004

Table 1. Reactions of Amides **1** and **5** in Superacid, the Proposed Dicationic Intermediates, and Comparisons to Monocationic Intermediates



have provided strong evidence for protonation at the carbonyl group in most cases.[4]

During the past two decades, an active area of research has involved superelectrophilic and dicationic intermediates.[6] Olah was the first to propose the concept of superelectrophilic reactivity, and since these early reports, this concept has been extended to many systems, including enzymes.[6] In studies related to Olah's superelectrophilic activation, we and others have shown that stable cationic groups are capable of significantly increasing the reactivities of adjacent electrophilic groups.[7] For example, phosphonium, ammonium, or pyridinum cations have been shown to greatly increase the reactivities of adjacent carboxonium ions.[8]

In this paper, we show that protonated amides can increase the reactivities of adjacent electrophilic groups, such as the carboxonium ion. The direct observation of a dicationic species is also reported. Moreover, we show that protonated amides can have enhanced electrophilic reactivities when adjacent to cationic groups. This is demonstrated in several Friedel−Crafts acylations of benzene using amides.

When amide **1** is reacted with C_6H_6 in superacidic CF_3SO_3H (triflic acid, TfOH), the condensation product (**3**) is formed in good yield (Table 1, eq 1). It is proposed that the diprotonated intermediate **2** is formed and this dication is sufficiently electrophilic to attack benzene. Under the same reaction conditions, cyclohexanone does not react with C_6H_6 (eq 2), despite the fact that the carbonyl group is completely protonated, giving the monocationic carboxonium ion (**4**). This suggests that the protonated amide group enhances the electrophilic reactivity of the ketone−carboxonium group in dication **2**. When amide **5** is reacted with C_6H_6 in TfOH, dication **6** is formed, and this leads to an acyl-transfer reaction and the product acetophenone (eq 3). The analogous, monocationic intermediate (**7**) from acetanilide is largely unreactive to benzene (eq 4). The amide−carboxonium group in dication **6** is clearly more reactive than the amide−carboxonium group of monocation **7**. This suggests that the adjacent cationic ammonium group enhances the electrophilic reactivity of the amide−carboxonium group in the dication. Thus, protonated amides can be part of two types of reactive dications: the protonated amide group can activate an adjacent electrophilic center or the protonated amide group may itself be activated by an adjacent cationic group.

These two modes of reactivity are demonstrated in several related systems (Table 2). Friedel−Crafts acylation of benzene is seen with amides **8**−**10**. Though amide **9** produces a diprotonated intermediate (**17**) with significant resonance stabilization, acyl transfer still occurs giving benzophenone. In the case of amide **10**, reaction occurs at the amide instead of the ketone, and dication **18a**,**b** is proposed as the intermediate. This conversion can be explained by noting that the ketone-carboxonium ion is stabilized by resonance interactions, including withdrawing electron density from the nitrogen (i.e., **18b**). Like amide **1**, the piperidone derivatives **11** and **13** undergo condensation at the ketone group. The piperidone derivatives (**1**, **11**, and **13**) generate ketone−carboxonium ions (i.e., **2**) that do not have significant resonance stabilization, and so the nucleophilic attack occurs at the ketone−carboxonium ions. The β-ketoamide (**15**) generates dication **19** to give the condensation product **16** in high yield.

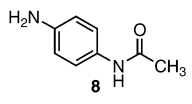
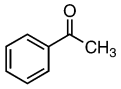
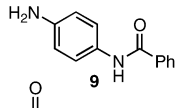
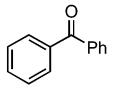
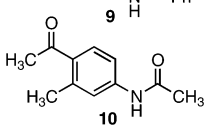
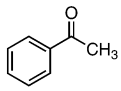
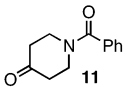
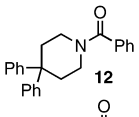
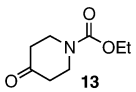
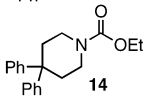
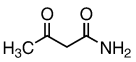
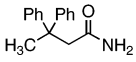
In an attempt to extend the chemistry to carbocations, the reactions of unsaturated amides were also studied (Scheme 1). Cinnamamide derivatives (**20**, **23**, and **25**) react with benzene to give addition products (**22**, **24**, and **26**) in good yields, presumably through the diprotonated intermediates such as **21**. The pyridine derivative **27** is found to give indanone **28** as the only major product. Similar to the Friedel−Crafts acylations involving **5** and **8**−**10**, the pyridinum ring appears to enhance the electrophilic reactivity of the protonated amide group in dication **29**. When amides

(6) (a) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767. (b) Nenajdenko, V. G.; Shevchenko, N. E.; Balenkova, E. S.; Alabugin, I. V. *Chem. Rev.* **2003**, *103*, 229. (c) Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, in press. (d) Klumpp, D. A. *Recent Res. Dev. Org. Chem.* **2001**, *5*, 193−205, Part I.

(7) (a) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1998**, *63*, 2810. (b) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (c) Conroy, J. L.; Sanders, T. C.; Seto, C. T. *J. Am. Chem. Soc.* **1997**, *119*, 4285. (d) Koltunov, K. Y.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 4330.

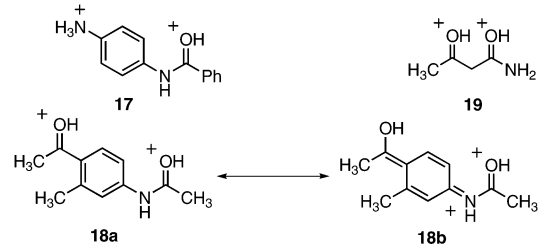
(8) (a) Zhang, Y.; Aguirre, S. A.; Klumpp, D. A. *Tetrahedron Lett.* **2002**, *43*, 6837. (b) Klumpp, D. A.; Lau, S. *J. Org. Chem.* **1999**, *64*, 7309. (c) Klumpp, D. A.; Garza, M.; Jones, A.; Mendoza, S. *J. Org. Chem.* **1999**, *64*, 6702. (d) Zhang, Y.; Klumpp, D. A. *Tetrahedron Lett.* **2002**, *43*, 6841.

Table 2. Reactions of Amides with CF_3SO_3H and C_6H_6

starting material	product	yield
 **8**		78%[a]
 **9**		80%[a]
 **10**		83%[a]
 **11**	 **12**	99%[b]
 **13**	 **14**	97%[b]
 **15**	 **16**	99%[b]

[a]Reaction done at 100°C, yield determined by GC-FID analysis with internal standard. [b]Reaction done at 25°C, isolated yield.

proposed intermediates:



22 or **24** are heated (100 °C) with excess TfOH (300 equiv), no indanone is formed.[9] However, amide **26** gives the indanone **28** by reaction with TfOH at 100 °C. Amide **26** can form a dicationic intermediate (**30**), and the protonated (piperazine) nitrogen activates the protonated amide group, leading to cyclization.

Dicationic intermediates involving protonated amides can be directly observed. Amide **1** was dissolved in solutions of varying acidity and studied by low-temperature ^{13}C NMR spectroscopy (Table 3). As the acidity of the solution increases, the carbonyl signals move downfield toward apparent limiting values of 176.3 and 242.2 ppm in SbF_5-FSO_3H (1:1). These values are consistent with the formation of the diprotonated species **2**. The experimental values are in reasonably good agreement with the calculated GIAO chemical shift values, determined from the optimized structure (B3LYP/6-311g(d,p)//B3LYP/6-311g(d,p) level of theory).[10] Given that there is little change in the ^{13}C spectra between TfOH (H_o −14) and SbF_5-FSO_3H (H_o −22), this further suggests that the triflic acid-catalyzed conversion involves the dicationic intermediate **2**.

(9) Following aqueous workup, the reaction of **24** shows evidence of hydrolytic cleavage.

(10) For details of the calculations, see the Supporting Information.

Scheme 1

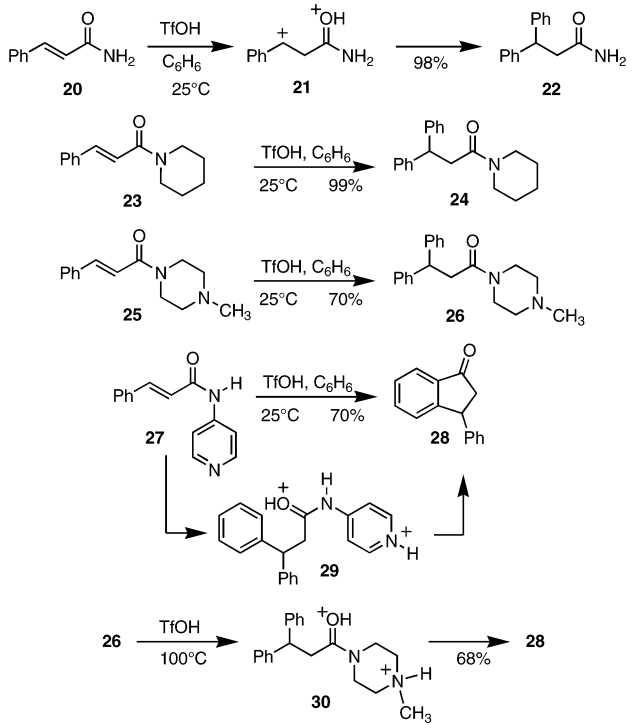
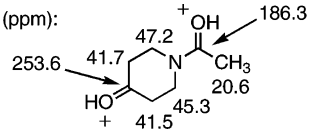


Table 3. Results from Low-Temperature (−80 °C) ^{13}C NMR Studies of Amide **1** Dissolved in SO_2ClF and Strong and Superacids (Experiments with $CDCl_3$ and CF_3CO_2H Were Done at −10 °C without SO_2ClF) and a Comparison to Theoretical Values

solvent/acid	H_O	^{13}C NMR signals
$CDCl_3$	n/a	21.7, 40.6, 40.9, 41.3, 45.0, 169.5, 207.3
100 % CF_3CO_2H	- 2.7	17.5, 37.3, 37.7, 42.3, 44.7, 175.6, 213.0
CF_3CO_2H : CF_3SO_3H (1 : 1)	- 9.0	17.5, 36.3, 36.8, 40.3, 42.5, 175.9, 238.2
CF_3SO_3H	- 14	18.0, 36.6, 37.0, 40.4, 42.6, 176.1, 240.9
FSO_3H	- 15	17.9, 36.5, 36.9, 40.3, 42.5, 176.0, 241.1
SbF_5 : FSO_3H (1 : 1)	- 22	18.1, 36.7, 37.1, 40.4, 42.6, 176.3, 242.2
calculated values (ppm): **2**		

In summary, we have found evidence for the formation of dicationic intermediates involving protonated amides. While similar dicationic intermediates have been proposed

in earlier reports,[11] the present work demonstrates that the protonated amide group can increase the reactivity of an adjacent electrophilic group. Moreover, cationic groups such as pyridinum and ammonium can increase the electrophilic reactivities of protonated amides. The heightened reactivity of these dicationic electrophiles has enabled amides to be used in Friedel−Crafts acylations.[12] Further studies are in progress to determine the scope of both of these types of electrophilic activation.

Acknowledgment. The support of the NIH (SO6GM-53933-0251) and Northern Illinois University is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization of compounds **3**, **12**, **16**, and **23**; computational methods, results, and ^{13}C NMR spectrum for dication **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049512Z

(11) (a) Koltunov, K. Y.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 8943. (b) Staskun, B. *J. Org. Chem.* **1964**, *29*, 1153. (c) Koltunov, K. Y.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* **2004**, in press. (d) Martin, A.; Jouannetaud, M.-P.; Jacquesy, J.-C. *Tetrahedron Lett.* **1996**, *37*, 2967.

(12) The exact mechanism of acylation may involve direct reaction of the dicationic intermediate with the arene, or the dicationic intermediate may form a mixed anhydride, which then leads to product formation.