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Superacid catalyzed ring-opening reactions involving 2-oxazolines and the role of superelectrophilic intermediates

Douglas A. Klumpp,[a,*] Rendy Rendy[b] and Aaron McElrea[b]

[a]Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL 60115, USA
[b]Department of Chemistry, California State Polytechnic University, 3801 West Temple Avenue, Pomona, CA 91768, USA

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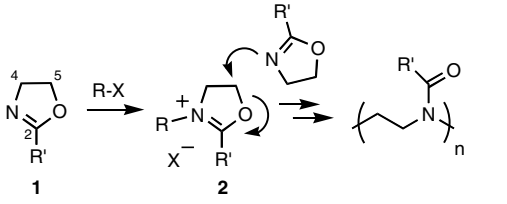
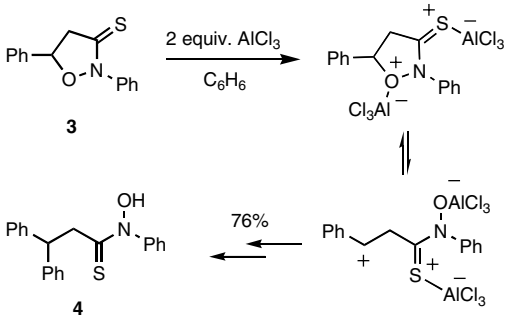
Abstract—A variety of 2-oxazolines are found to react with arenes in superacidic triflic acid, CF_3SO_3H. It is proposed that the 2-oxazolines are protonated twice in triflic acid and the resulting intermediates undergo ring-opening reactions to produce reactive, dicationic species. These superelectrophiles are capable of reacting with benzene and *o*-dichlorobenzene in high yields by Friedel–Crafts type reactions.

2-Oxazolines have been known for many years to undergo electrophilic ring-opening reactions with strong nucleophiles.[1] In particular, 2-oxazolines (**1**) give high molecular weight poly-*N*-acylethyleneimines by cationic ring-opening polymerizations (Eq. 1).[2] Cationic ring-opening can be promoted by alkylation, silylation, and acylation of the 2-oxazoline nitrogen (**2**) and subsequent attack of nucleophiles at the C-5 position.[1] While a variety of strong nucleophiles are known to effect ring-opening, there are few reports of very weak nucleophiles (like arenes) attacking 2-oxazoline cations and giving ring-opening products.[3] In a recent report, isoxazolidine **3** was reacted with an excess of aluminum chloride in benzene to give product **4** in good yield (Eq. 2).[4] It was proposed that product **4** arises from coordination of the isoxazolidine (**3**) with 2 equiv of $AlCl_3$ to generate a dicationic intermediate, which undergoes ring-opening to give product **4** by a Friedel–Crafts type reaction. We and others have published a number of studies in which dicationic, superelectrophilic intermediates are generated in Brønsted superacids.[5] In two of our recent studies, ring-opening reactions lead to highly reactive, dicationic electrophiles.[6] We report herewithin that substituted 2-oxazolines react in a Brønsted superacid, triflic acid (CF_3SO_3H, TfOH), to give superelectrophilic species and that these intermediates react readily with arenes in good yields. In this chemistry, the reactive



(1)



(2)

electrophiles are thought to be dicationic species composed of protonated amide groups and adjacent carbocationic centers.

As shown in Table 1, the oxazolines (**5**–**10**) react in TfOH and benzene to give the phenyl-substituted amides (**11**–**16**) in generally high yields.[7] In the case of oxazoline **9**, two major products are formed: the

* Corresponding author. Tel.: +1 815 753 6857; fax: +1 815 753 4802; e-mail: dklumpp@niu.edu

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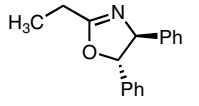
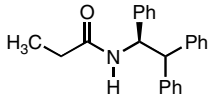
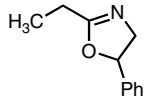
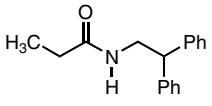
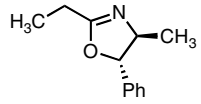
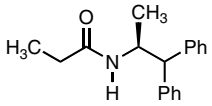
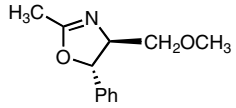
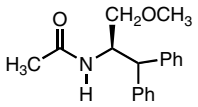
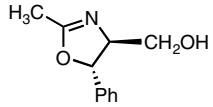
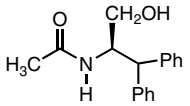
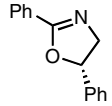
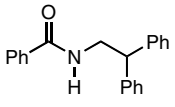
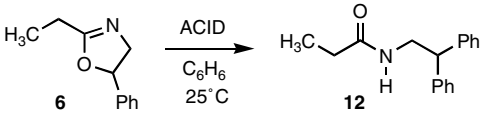
Table 1. Products and yields from the reactions of oxazolines (**5**–**10**) with CF_3SO_3H and C_6H_6[a]

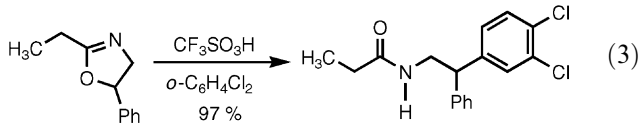
Starting material	Product	Yield (%)
 **5**	 **11**	96
 **6**	 **12**	99
 **7**	 **13**	97
 **8**	 **14**	95
 **9**	 **15**	40
 **10**	 **16**	88

[a] Isolated yields of pure products.

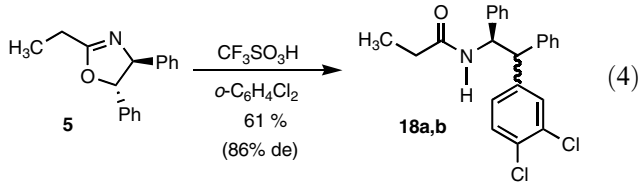


TIME	mL ACID (equiv.)	ACID	YIELD
12 hr	4.0 mL (80)	CF_3SO_3H	99%
12 hr	0.25 mL (5)	CF_3SO_3H	98%
0.5 hr	4.0 mL (80)	CF_3SO_3H	99%
12 hr	4.0 mL (80)	H_2SO_4	0%

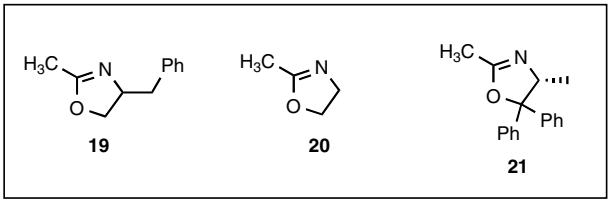
Figure 1. Yields of phenylated product (**12**) from reactions of 2-oxazoline **6** (0.57 mmol) in C_6H_6 (1.0 mL).



(3)



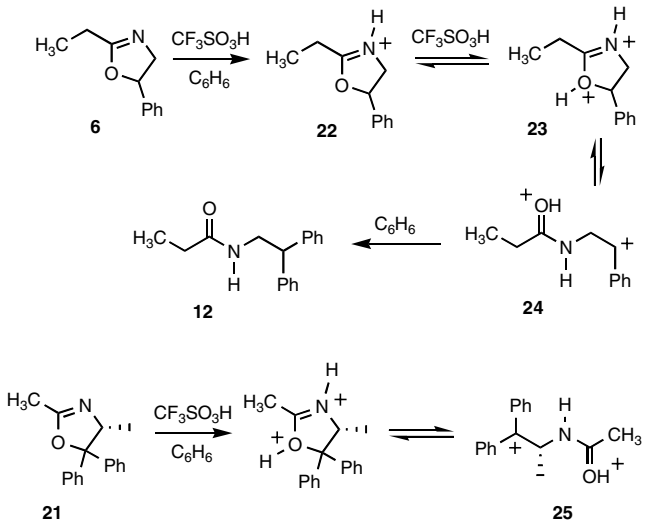
(4)



expected amide **15** (mol wt 269) and an unidentified 'dehydration' product (mol wt 251). After recrystallization ($CHCl_3$), the product (**15**) is obtained in 40% yield. Although the procedure has not been optimized, we have found that relatively small amounts of the superacid may be used to effect the conversion (Fig. 1). 2-Oxazoline **6** is converted to product **12** in high yield with as little as 5 equiv of TfOH.[8] When a large excess of H_2SO_4 was used instead TfOH, no ring opened product was obtained. With a large excess of TfOH, quantitative conversion of the 2-oxazoline (**6**) to the amide product (**12**) is accomplished in 30 min.

When 2-oxazoline **6** is reacted with TfOH and *o*-dichlorobenzene, the arylated product **17** is formed in very good yield (Eq. 3). *o*-Dichlorobenzene is a somewhat deactivated arene,[9] so the conversion of **6**–**17** must involve a reactive electrophilic intermediate. In the case of the optically active 2-oxazoline **5**, reaction with TfOH and *o*-dichlorobenzene gives the diastereomeric products (**18a**,**b**) in 61% overall yield and 86% diastereomeric excess (Eq. 4). Although compounds **18a** and **18b** separate on a DB-5 capillary GC column, the diastereomeric compounds were inseparable by column chromatography, so it is unknown, which is the major product. 2-Oxazolines **19**–**21** were also reacted with TfOH and benzene, but in each case the starting 2-oxazoline was the major component of the product mixture.

The proposed mechanism for the ring-opening and arylation of the 2-oxazolines (**5**–**10**) is outlined in Scheme 1. Protonation of both the nitrogen and oxygen base sites of the 2-oxazoline **6** leads to the formation of the cyclic dication (**23**), which is in equilibrium with the ring-opened dication (**24**). Ring-opening produces a dication (**24**) composed of a carbocationic site and a protonated



Scheme 1.

amide group. Ring-opening is facilitated by the resonance stabilization of carbocation and increased charge–charge separation in the ring-opened dication (**24**), compared to the cyclic dication (**23**). Dication **24** then reacts with benzene to give the final product **12**. It is also plausible that the nucleophile (benzene) directly attacks **23** at the 5-position in an S_N2-like ring-opening reaction (Eq. 1). However, the direct ring-opening reaction seems unlikely given that 2-oxazolines **19** and **20** (which should also form cyclic dications) do not react with benzene. Furthermore, it is unlikely that benzene reacts with the monocation **22**, otherwise some product (**12**) would have also formed in H_2SO_4 (Fig. 1). In the case of 2-oxazoline **21**, its low reactivity may be explained by stability of the carbocationic site on the ring-opened dication **25** (Scheme 1). Despite the fact that Lewis acids catalyze the polymerization of 2-oxazolines,[2] no polymer is formed in any of the reactions studied. This is consistent with the complete protonation of 2-oxazolines in excess TfOH.

In summary, we have found that 2-oxazolines react in Brønsted superacids to generate diprotonated, superelectrophilic species. When the 2-oxazoline is substituted with a phenyl group at the 5-position, ring-opening occurs and the resulting dicationic intermediate is capable of reacting with benzene and *o*-dichlorobenzene in good to excellent yield by a Friedel–Crafts type reaction.[10] Further studies are in progress to determine the scope of this chemistry and the role of superelectrophilic intermediates.

Acknowledgements

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7. Oxazolines were purchased from commercial suppliers (**6**–**9**, **19**–**20**) or prepared from the appropriate aminoalcohols and orthoesters using Corey's procedure: Saravanan, R.; Corey, E. J. *J. Org. Chem.* **2003**, *68*, 2756.
8. For a review of triflic acid catalyzed chemistry, see: (a) Stang, P. J.; White, M. R. *Aldrich Acta* **1983**, *16*, 15; (b) Triflic acid can be quantitatively recycled, see: Booth, B. L.; El-Fekky, T. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2441.
9. Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, 1990; Chapter 2.
10. Products were characterized by ^{1}H NMR, ^{13}C NMR, low resolution mass spectroscopy, and high resolution mass spectroscopy: Product **11**: Mp 165–167 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 0.93 (t, J = 7.5 Hz, 3H), 2.01 (m, 2H), 4.30 (d, J = 9.9 Hz, 1H), 5.75–5.88 (m, 2H), 7.04–7.32 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm 9.9, 30.0, 55.7, 58.0, 126.7, 127.2, 127.3, 127.4, 128.4, 128.6 (two carbons), 128.8, 128.8, 141.4, 141.6, 141.7, 172.9. EI-MS 256, 162, 106. HRMS (DCI/NH_3): $C_{23}H_{24}NO$ (M+H) calcd 330.185790, found 330.186639. Product **12**: Mp 62–65 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 1.03 (t, J = 7.5 Hz, 3H), 2.04 (q, J = 7.5 Hz, 2H), 3.88 (m, 2H), 4.26 (t, J = 7.8 Hz, 1H), 7.18–7.32 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm 10.2, 29.8, 44.1, 50.8, 127.0, 128.4, 128.9, 142.4, 174.3. EI-MS 253 (M+), 180, 105. HRMS: $C_{17}H_{19}NO$ calcd 253.146664 (M+), found 253.145603. Product **14**: Mp 147–150 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 1.77 (s, 3H), 3.09 (m, 1H), 3.19 (s, 3H), 3.37 (m, 1H), 4.26 (d, J = 11.3 Hz, 1H), 4.88 (m, 1H), 5.72 (d, J = 9.4 Hz, 1H), 7.12–7.33 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ, ppm 23.1, 51.2, 52.0, 58.8, 71.9, 126.4, 126.5, 128.0 (two carbons), 128.3, 128.5. EI-MS 283 (M+), 196, 116. HRMS: (DCI/NH_3): calcd 284.165054, found 284.163968.