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Dicationic Electrophiles from Olefinic Amines in Superacid[⊥]

Yun Zhang, Aaron McElrea, Gregorio V. Sanchez, Jr., Dat Do, Alma Gomez, Sharon L. Aguirre,[†] Rendy Rendy, and Douglas A. Klumpp*,[§]

Department of Chemistry, California State Polytechnic University, 3801 West Temple Avenue, Pomona, California 91768

daklumpp@csupomona.edu

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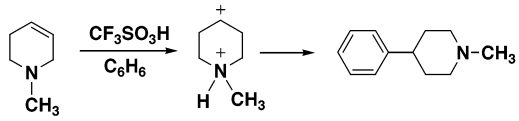
This paper describes the superacid-catalyzed chemistry of olefinic amines and related compounds. A variety of olefinic amines are found to react with benzene in CF_3SO_3H (triflic acid) to give addition products in good yields (75−99%), including the pharmaceutical agents fenpiprane and prozapine. A general mechanism is proposed that invokes the formation of reactive, dicationic electrophiles and the direct observation of a diprotonated species is reported from low-temperature NMR experiments. This chemistry is also used to conveniently prepare functionalized polystyrene beads having pendant amine groups.

Introduction

It has been more than 100 years since Friedel and Crafts first reported the chemistry of electrophilic aromatic substitution. Yet, this area of organic chemistry continues to be active with research in both mechanistic and synthetic studies.[1] One recent development involves the chemistry of superelectrophiles. The concept of superelectrophilic activation was first proposed by Olah and co-workers in 1975.[2] In studies involving the nitration of aromatic compounds, they observed that nitronium salts exhibit enhanced reactivities in Bronsted superacids. It was suggested that the nitronium electrophile is protosolvated in superacid to give a dicationic electrophile, or superelectrophilic intermediate. The Olah group also found similar electrophilic activation involving the acylation of aromatic compounds.[2] Following these pioneering studies, superelectrophilic activation has been studied extensively by both theoretical and experimental methods.[3]

We and others have recently reported several examples of dicationic electrophilic systems which are analogous to the superelectrophiles.[4] There are also a number of older reports in which dications were clearly involved in the chemistry, but the role of these reactive species was not generally appreciated.[5] In one of our recent studies, we reported that 1,2,5,6-tetrahydropyridines give dicationic intermediates in the Bronsted superacid CF_3SO_3H (triflic acid, TfOH; eq 1).[4a] The dicationic intermediates



(1)

react in good yields to give aryl-substituted piperidines from electrophilic aromatic substitution. Similarly, we found that piperidones condense with arenes in high yields with TfOH.[4b] Both these studies suggested that the ammonium cation plays a critical role in activating the nearby electrophilic site. In the following report, we describe further studies in the area of electrophilic chemistry involving these reactive intermediates. We show that a variety of olefinic amines and *N*-heterocycles can yield reactive dicationic electrophiles in TfOH and that these reactive intermediates can be used in electrophilic aromatic substitution reactions, including the functionalization of polystyrene resins. We also report the direct observation of a diprotonated species by low-temperature NMR.

Results

The 1-(3,3-diarylpropyl)amines belong to an important class of biologically active compounds.[6] For example,

[⊥] Dedicated to Professor George A. Olah on the occasion of his 75th birthday.

[†] American Chemical Society Scholar, 2001−2002.

[§] Present address: Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL 60115.

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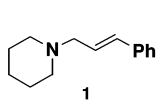
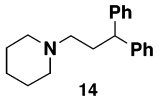
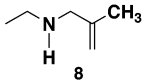
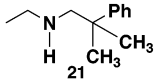
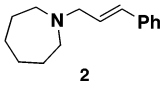
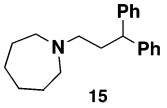
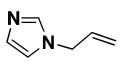
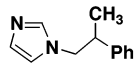
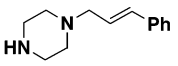
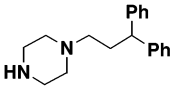
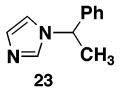
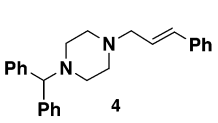
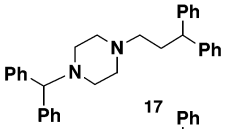
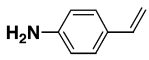
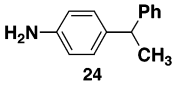
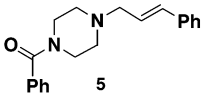
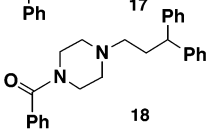
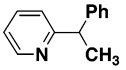
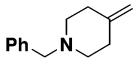
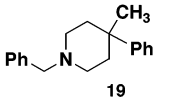
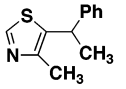
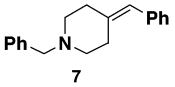
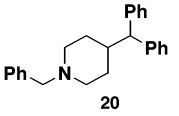
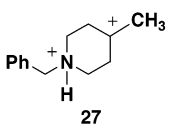
TABLE 1. Results from the Reactions of Olefinic Amines with C_6H_6 in TfOH

Starting Material	Product	% Yield	Starting Material	Product	% Yield
 1	 14	99%[a]	 8	 21	91%[a]
 2	 15	88%[a]	 9	 22	90%[b]
 3	 16	91%[a]	 10	 23	83%[c]
 4	 17	75%[a]	 11	 24	86%[c] 49%[a]
 5	 18	77%[a]	 12	 25	87%[c]
 6	 19	99%[a]	 13	 26	92%[c]
 7	 20	89%[a]			

[a] 25 °C. [b] 50 °C. [c] 80 °C.

fenpiprane (**14**) is an anti-allergic and anti-spasmodic drug while prozapine (**15**) is an anti-spasmodic and choleretic drug.[7] Fenpiprane (**14**) can be prepared in good yield from piperidine and cinnamyl bromide via the olefinic amine (**1**). When compound **1** is reacted with CF_3SO_3H (TfOH, triflic acid) and benzene, **14** is formed in high yield (Table 1). In general, cinnamyl-substituted *N*-heterocycles (**1**−**5**) give the 1-(3,3-diarylpropyl)amines (**14**−**18**) in good yields. Compounds **6** and **7** react to give products **19** and **20**, respectively, by protonation of the nitrogen base-sites and the exo-cyclic double bonds. In the case of **6**, diprotonation occurs to give the 1,4-dication (**27**), while **7** gives exclusively the 1,5-dication (**28**)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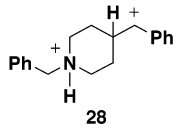
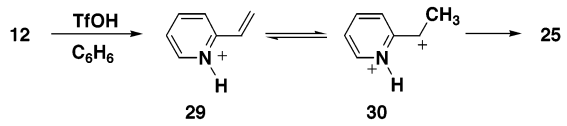

28

leading to product formation. These products are consistent with the formation of the most highly stabilized carbocation centers. Olefins **8** and **9** react by additions to the 2-methyl-2-propenyl and allyl groups and they give the respective addition products (**21** and **22**) in good yields. The vinyl group also reacts with benzene in superacid. The vinyl-substituted arenes **10**−**13** give the additions products in good yields, but in some cases the conversions require heating (Table 1). When the vinyl-substituted imidazole (**10**), pyridine (**12**), thiazole (**13**), or aniline (**11**) is reacted with TfOH and C_6H_6, protonation occurs at the 2-carbon of the vinyl group to give 1,1-diarylethane products (**23**−**26**).

SCHEME 1


12 → (TfOH, C_6H_6) → 29 ⇌ 30 → 25

We propose that the olefinic compounds (**1**−**13**) react through dicationic electrophilic intermedites. In the case of vinylpyridine **12**, protonation occurs at the nitrogen to give the monocation (**29**) and a second protonation gives the reactive dication (**30**, Scheme 1). The dicationic intermediate then reacts with benzene to give the final product (**25**). Despite the fact that TfOH catalyzes the polymerization of styrene,[8] there is no evidence for polymerization or oligomerization of any of the olefinic compounds (**1**−**13**) in the addition reactions. This suggests that the dicationic intermediate (i.e., **30**) is unable to react with the cationic olefin (**29**) due to repulsive electrostatic effects.

To characterize the proposed dicationic intermediates, low-temperature ^{13}C NMR studies were done with olefinic amines dissolved in $FSO_3H-SbF_5-SO_2ClF$. Initial efforts to observe dicationic species were not successful. For

(7) (a) Budavari, S.; O'Neil, M. J.; Smith, A.; Heckelman, P. E.; Kinneary, J. F., Eds. *The Merck Index*, 12th ed.; Merck Company: Whitehouse Station, NJ, 1996; No. 4031. (b) Keemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th ed.; Thieme: Stutgart, Germany, 2001; pp 1750−1751.

(8) Stang, P. J.; White, M. R. *Aldrichim. Acta* **1983**, *16*, 15.

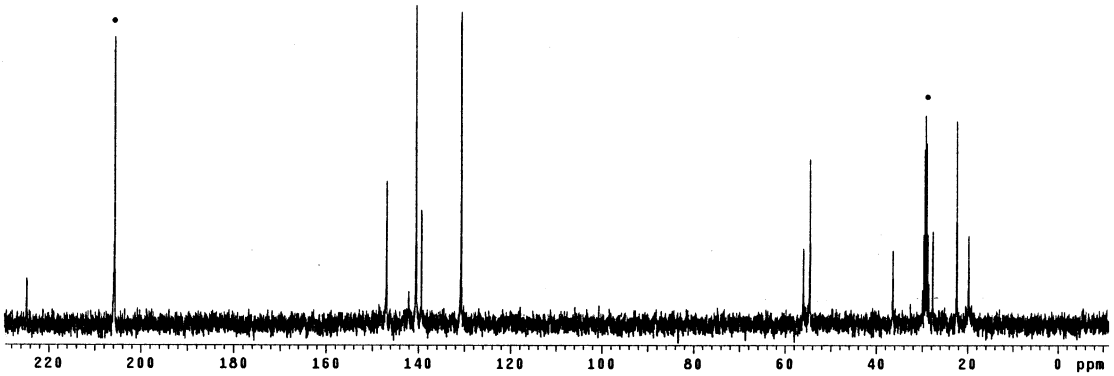
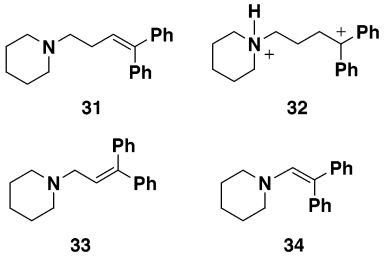


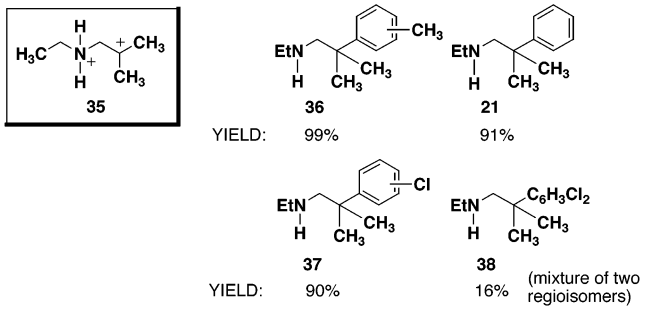
FIGURE 1. ^{13}C NMR of dication **32** in FSO_3H:SbF_5:SO_2ClF (1:1:1) at −30 °C; the • denotes the external standard peak (d_6-acetone).

example, compound **1** is dissolved in $FSO_3H-SbF_5-SO_2ClF$ (1:1:1) at −30 °C, and a clean spectrum was not obtained. Similar results occur when compound **8** dissolved the superacidic solution. However, when compound **31** is dissolved in $FSO_3H-SbF_5-SO_2ClF$ (1:1:1)

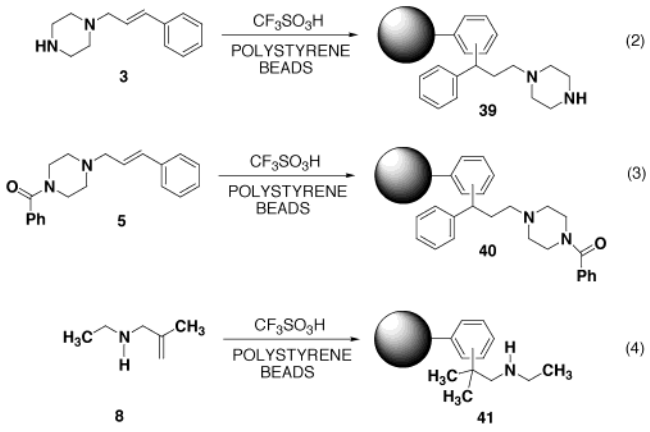


at −30 °C, a clean ^{13}C NMR spectrum results and the olefinic carbons are replaced by a new signal in the aliphatic region and another at 225 ppm (Figure 1). The downfield signal is consistent with the formation of the diphenyl-substituted carbocation center. The dication **32** shows no signs of decomposition at −30 °C in the superacidic solution. The stability of **32** is evidently due to the stabilization by the two phenyl groups and the relatively large distance between the two charge centers.[9] Neither olefin **33** or **34** gave spectra of the corresponding dications in $FSO_3H-SbF_5-SO_2ClF$ at −30 °C, but instead gave complex spectra. The difficulty in observing the dications from **1**, **8**, **33**, and **34** may be due to rapid equilibration with the monocationic species.

In previous studies, we and others have shown that dicationic electrophiles are often capable of reacting with deactivated arenes.[10] Compound **8** was reacted with monosubstituted benzenes in TfOH and the results indicate that the diprotonated species (**35**) is a fairly reactive electrophile. When **8** is reacted with TfOH and toluene, benzene, chlorobenzene, or *o*-dichlorobenzene, the respective addition products **36**, **21**, **37**, and **38** are formed. Nitrobenzene is unreactive toward compound **8** in TfOH. The yields of products roughly correlate with the deactivation of the arenes. Despite the high level of deactivation of *o*-dichlorobenzene,[11] the dicationic electrophile **35** is still capable of reaction with this arene. The reactivity of this electrophilic system may stem from two effects: an electrostatic effect arising from the two charge centers on the electrophile and also a decreased neighboring group stabilization of the carbcationic center.



In addition to the reactions with benzene, olefinic amines can also be used to functionalize polystyrene resins. Compounds **3**, **5**, and **8** can be reacted with polystyrene beads in the presence of TfOH to give the functionalized polymers **39**, **40**, and **41**, respectively (eqs 2−4). Amine-functionalized resins have been useful as



acid-scavenging reagents and reaction scaffolds for combinatorial synthesis.[12] Although acid-catalyzed cleavage of polystyrene is known, we found that the functionalized polymers **39**−**41** can be prepared by using polystyrene

(9) We have found evidence that the distance between charge centers can dramatically influence reactivity, see: Klumpp, D. A.; Garza, M.; Sanchez, G. V.; Lau, S.; DeLeon, S. *J. Org. Chem.* **2000**, *65*, 8997.

(10) (a) Olah, G. A.; Wang, Q.; Sandford, G.; Oxyzoglou, A. B.; Prakash, G. K. S. *Synthesis* **1993**, 1077. (b) Reference 4g.

beads having a 2% cross-linking of divinylbenzene. Under these reaction conditions, analysis with a bright-field, optical microscope indicates there is little damage to the polystyrene beads. However, if marcoporous beads (polystyrene-*co*-divinylbenzene) are used, the beads show massive structural damage. Microscopic cracks and pitting is evident on the surface of the porous beads. Evidently, the macroporous beads absorb significant quantities of TfOH prior to any amine functionalization and the superacid cleaves some of the polystyrene surface.

Conclusion

In summary, we have found that olefinic amines and heterocycles react with arenes in the Bronsted superacid, CF_3SO_3H. We propose that olefinic amines are protonated twice to generate reactive dicationic intermediates. These doubly charged electrophiles are sufficiently reactive to attack moderately deactivated arenes such as *o*-dichlorobenzene. Polystyrene beads can be conveniently functionalized by olefinic amines in reactions catalyzed by TfOH.

Experimental Section

Compounds **1** and **2** were prepared from the reactions of cinnamyl bromide with the appropriate heterocycle; compounds **6** and **7** were prepared from *N*-benzyl-4-piperidone with use of CH_3PPh_3Br:$NaNH_2$ and $(C_6H_5)CH_2PPh_3Br$:BuLi, respectively, and standard Wittig reaction procedures.[13] All other olefinic amines were purchased from commercial suppliers. Products **14**, **16**, **17**, **19**, **20**, **23**, **24**, and **25** are known compounds.[14] Products **36**, **37**, and **38** were obtained as inseparable mixtures of regioisomers. The triflic acid was purchased from 3M and distilled from an argon atmosphere prior to use. Polystyrene beads were purchased from commercial suppliers. Microscopic analysis of functionalized polymers was done with a Nikon Eclipse E-400 with Nikon Plan lenses, using a Tungsten−halogen light source and an objective of 40× (standard bright-field configuration).

General Synthetic Procedure (Products 14−26). Approximately 0.2 g of the olefin is suspended in 2 mL of benzene and 3 mL of TfOH is added. After being stirred for at least 3 h, the mixture is poured over ice, and it is made basic with concentrated NaOH. The mixture is then extracted with $CHCl_3$ and the organic phase is washed with brine, dried with $MgSO_4$, and concentrated under vacuum.

1-Benzoyl-4-(3,3-diphenylpropyl)piperazine (18). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20−2.26 (m, 8H), 3.38−3.50 (m, 2H), 3.71−3.88 (m, 2H), 4.03 (t, J = 7.1 Hz, 1H), 7.00−7.51 (m, 15H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.8, 42.3, 47.9, 49.2, 53.1, 53.7, 56.9, 126.5, 127.3, 128.1, 128.7, 128.8, 129.9, 136.1, 144.9, 170.5 ppm. MS *m*/*z* (EI) 384 (M^+), 203, 105. HRMS (DEI) calcd for $C_{26}H_{28}N_2O$ 384.220164, found 384.220624.

Ethyl(2-methyl-2-phenylpropyl)amine (21). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, J = 6.6 Hz, 3H), 1.23 (s, 1H), 1.36 (s, 6H), 2.56 (q, J = 6.6 Hz, 2H), 2.75 (s, 2H), 7.15−7.40 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3, 27.7, 38.8, 45.0, 62.4, 126.0, 126.2, 128.5, 148.1 ppm. MS *m*/*z* (EI) 177 (M^+), 91, 58. HRMS (DEI) calcd for $C_{12}H_{20}N$ 178.159575 (MH^+), found 178.159111.

Ethyl(2-methyl-2-phenylpropyl)amine (21). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, J = 7.5 Hz, 3H), 1.23 (s, 1H), 1.36 (s, 6H), 2.56 (q, J = 7.5 Hz, 2H), 2.75 (s, 2H), 7.16−7.40 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3, 27.7, 38.8, 45.0, 62.4, 126.0, 126.2, 128.5, 148.1 ppm. MS *m*/*z* (EI) 177 (M^+), 162, 58. HRMS calcd for $C_{12}H_{20}N$ 178.159575 (MH^+), found 178.159111.

1-(2-Phenylpropyl)-1*H*-imidazole (22). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (d, J = 6.9 Hz, 3H), 3.02−3.10 (m, 1H), 4.02 (d, J = 7.5 Hz, 3H), 6.72 (s, 1H), 6.97 (s, 1H), 7.60−7.23 (m, 2H), 7.18−7.36 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.8, 41.9, 54.5, 119.4, 127.2, 127.3, 129.0, 129.4, 137.6, 142.9 ppm. MS *m*/*z* (EI) 186 (M^+), 105, 82. HRMS (EI^+) calcd for $C_{12}H_{14}N_2$ 186.115699, found 186.115742.

4-Methyl-5-(1-phenylethyl)thiazole (26). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.67 (d, J = 6.9 Hz, 3H), 2.35 (s, 3H), 4.38 (q, J = 6.9 Hz, 1H), 7.19−7.33 (m, 5H), 8.57 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.5, 24.2, 37.8, 126.8, 127.2, 128.9, 129.5, 145.1, 149.4, 149.5 ppm. MS *m*/*z* (EI) 203 (M^+), 188. HRMS calcd for $C_{12}H_{13}NS$ 203.076871, found 203.077637.

Cinnamylpiperazine Functionalized Polystyrene 39. A 1.0-g sample of polystyrene is suspended in 15 mL of $CHCl_3$ and 0.2011 g (1.0 mmol) of *trans*-1-cinnamylpiperazine (**3**) is added. To this solution is added 4 mL of triflic acid and the solution is stirred overnight at room temperature and then poured over about 50 g of ice. The solution is made basic with 1.0 M NaOH, and after an hour of stirring, the functionalized polymer is filtered off and rinsed thoroughly with deionized water. The solids are rinsed three times with anhydrous ether and then dried with heating under vacuum to yield approximately 1.2 g of a granular, tan solid. Anal. Calcd for 1.0 mmol of cinnamylpiperazine/g of polystyrene: C, 89.77; H, 7.90; N, 2.32. Found: C, 81.26; H, 7.32; N, 0.93. FTIR (KBr, cm^{-1}) 3448, 3020, 1380.

1-Benzoyl-4-cinnamylpiperazine Functionalized Polystyrene 40. A 1.0-g sample of polystyrene is reacted with 0.2013 g (0.66 mmol) of 1-benzoyl-4-cinnamylpiperazine (**5**) and 4 mL of triflic acid in $CHCl_3$, using the procedure described above, to yield approximately 1.2 g of a granular, tan solid. Anal. Calcd for 0.66 mmol of 1-benzoyl-4-cinnamylpiperazine/g of polystyrene: C, 90.0; H, 7.57; N, 1.50. Found: C, 88.18; H, 7.45; N, 0.98. FTIR (KBr, cm^{-1}) 3018, 2918, 1628, 1607, 1495, 1449.

Ethyl(2-methylallyl)amine Functionalized Polystyrene 41. A 1.0-g sample of polystyrene is reacted with 0.20 mL (1.52 mmol) of ethyl(2-methylallyl)amine (**5**) and 1 mL of triflic acid in 5 mL of $CHCl_3$, using the procedure described above, to yield approximately 1.1 g of a granular, tan solid. Anal. Calcd for 1.52 mmol of ethyl(2-methylallyl)amine/g of polystyrene: C, 89.75; H, 8.43; N, 1.82. Found: C, 88.60; H, 7.85; N, 0.71. FTIR (KBr, cm^{-1}) 3438, 3022, 2914, 1603, 1490, 1445, 1386.

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Supporting Information Available: Analytical data (^{1}H and ^{13}C NMR spectra) for new compounds and literature citations for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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