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Dicationic electrophilic systems: the activation of carbocations and carboxonium ions by pyridinium groups and related heterocycles

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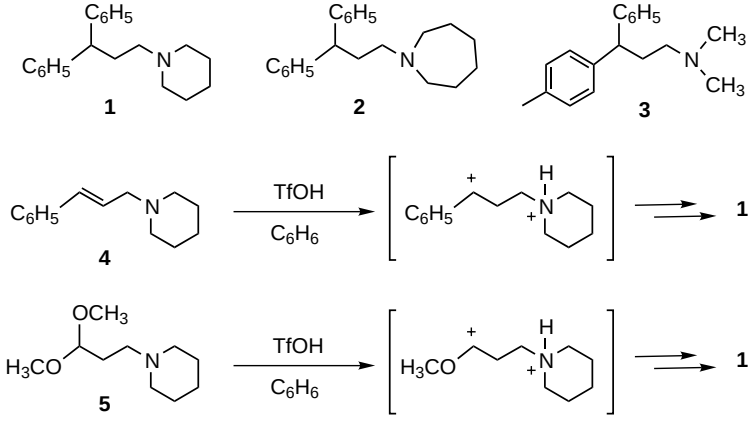
Abstract—*N*-Heterocycles can be alkylated with cinnamyl bromide to give the cationic salts **6**–**10** and subsequent reactions with C_6H_6 and superacidic CF_3SO_3H provide the addition products in good yields. Reactions of *N*-acetonylpyridinium salts give the condensation product from C_6H_6 and CF_3SO_3H and the dicationic intermediate can be directly observed using low temperature ^{13}C NMR spectroscopy. © 2002 Elsevier Science Ltd. All rights reserved.

The 1-(3,3-diarylpropyl)amines are compounds having a variety of pharmacological activities.[1] In clinical applications, fenpiprane **1** and prozapine **2** are spasmolytics and tolpropamine **3** is an antihistaminic.[2] We have recently reported two new synthetic routes to compounds like **1** and **2**, and both routes exploit the reactivities of dicationic electrophilic intermediates (Scheme 1).[3–5] Compound **1** has been prepared by the superacid-catalyzed (TfOH:triflic acid, CF_3SO_3H) reactions of the olefinic-amine (**4**) or the amino acetal (**5**). We hypothesized that novel analogues of **1** could also be prepared from *N*-pyridinium salts and related *N*-heterocyclic salts. In the following report, we describe the reactions of *N*-cinnamylpyridinium bromide (**6**) and other heterocyclic salts (**7**–**10**) with C_6H_6 in TfOH and propose the formation of dicationic electrophilic intermediates. We also describe our results from the reactions of *N*-acetonylpyridinium salts and report the direct observation of a dicationic intermediate.

The *N*-heterocyclic salts **6**–**10** are prepared by the reaction of cinnamyl bromide with the corresponding heterocyclic compound.[6] When these salts are allowed to react reacted in a solution of TfOH and C_6H_6, the addition products **11**–**15** are obtained in generally good yields (Table 1).[7] The pentenyl derivative (**16**) likewise gives the addition product **17** from TfOH and C_6H_6 (Eq. (1)). It is proposed that the salts (**6**–**10**) are regiose-



Scheme 1.

Keywords: superacid; heterocycle; electrophile; dication.

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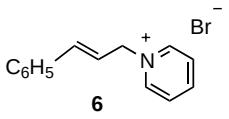
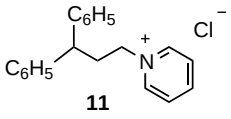
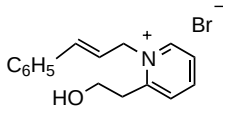
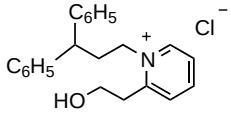
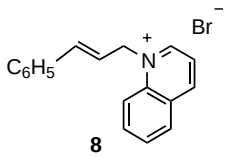
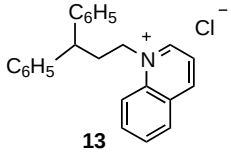
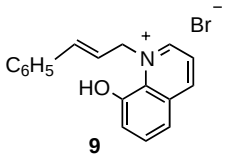
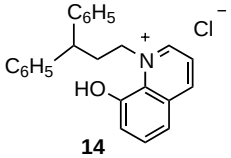
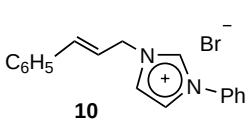
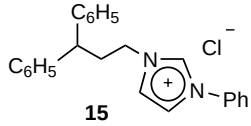
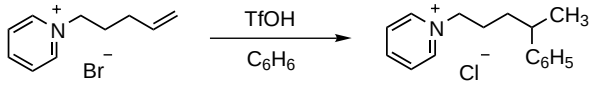
Table 1. Products (**11**–**15**) from the reactions of CF_3SO_3H and C_6H_6 with cinnamyl derivatives of *N*-heterocycles (**6**–**10**)

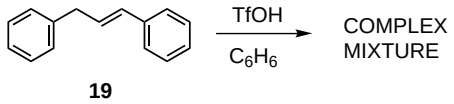
STARTING MATERIAL	PRODUCT	YIELD
 **6**	 **11**	89%
 **7**	 **12**	99%
 **8**	 **13**	90%
 **9**	 **14**	93%
 **10**	 **15**	86%

lectively protonated to give dicationic intermediates like **18** that react with benzene to provide the addition products (Eq. (2)). Despite the fact that TfOH has been used as an acid-catalyst in the polymerization of olefins,[8] there is no evidence of oligomerization of these salts. Due to electrostatic repulsion, the dicationic intermediates presumably cannot attack the olefinic sites of the unreacted starting materials.



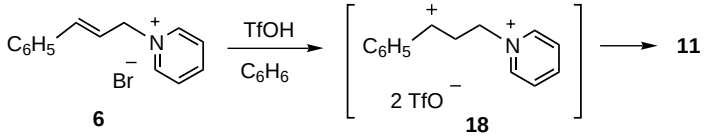
16 **17** (1)

The effects of the cationic heterocyclic groups can been seen by comparing the chemistry of salts **6**–**9** with the chemistry 1,3-diphenylpropene (**19**). Reaction of **19** with TfOH and C_6H_6 gives a complex mixture of >10 products and there is no evidence of the addition product, 1,1,3-triphenylpropane (Eq. (3)). This result suggests that the pyridium group activates the adjacent electrophilic (carbocationic) site and renders it more reactive towards C_6H_6. This activation is similar to the well known inductive effects of adjacent electron-withdrawing groups (-CF_3, -NO_2, and carbonyl groups) on electrophilic sites;[9] however, in the case of **18**, this activation may involve both inductive and electostatic effects.



19 (3)

The electrophilic activation of the pyridinium group is also seen with carboxonium ion electrophiles. When *N*-acetonylpyridinium bromide (**20**) is reacted with C_6H_6 and TfOH, the condensation product (**22**) is formed as the only product in 95% yield (Eq. (4)). Product **22** can also be prepared from hydroxyacetone



6 **18** (2)

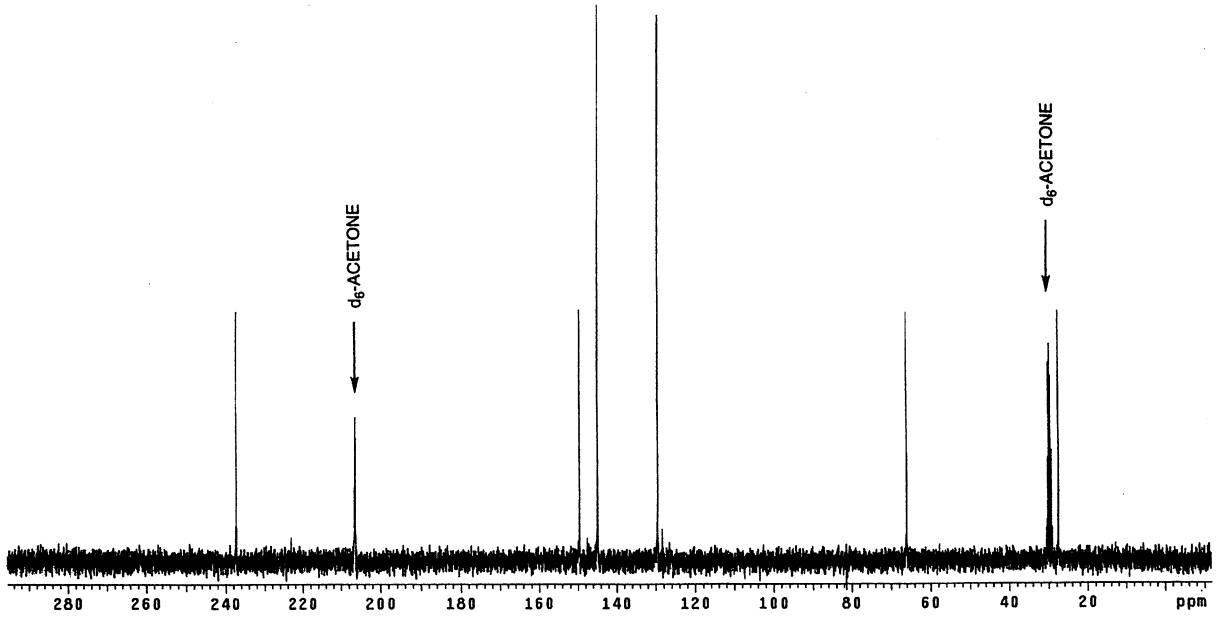
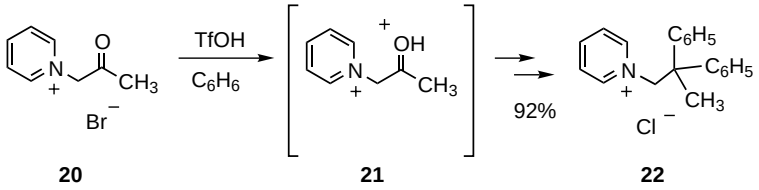
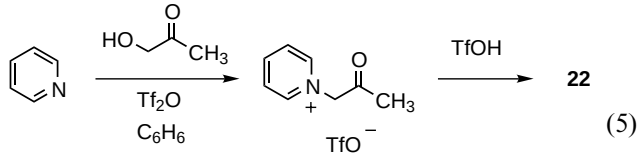


Figure 1. ^{13}C NMR spectrum of the dication **21** from the reaction of **20** with FSO_3H:SbF_5 (1:1) in SO_2ClF at −60°C.



(4)

and pyridine by in situ formation of the *N*-acetonylpyridinium salt (Eq. (5)). In contrast, ketones such as acetophenone or cyclohexanone do not react with benzene despite being almost completely protonated in TfOH. These results indicate that dication **21** is far more electrophilic than monocationic carboxonium ions (i.e. protonated cyclohexanone).



(5)

The dicationic species can also be directly observed by low temperature ^{13}C NMR. When compound **20** is dissolved in a solution of FSO_3H:SbF_5 (1:1) and SO_2ClF at −80°C, the dication **21** is formed cleanly (Fig. 1). The carboxonium carbon appears as a single resonance at 237 ppm, which is consistent with other reported values of carboxonium carbons.[10] The observation of **21** indicates that the dicationic intermediates can form appreciable concentrations in superacidic media. Efforts were also made to observe the dicationic species from compound **6**, but the pyridinium–carbenium dication (**18**) could not be detected as a cleanly formed ion. This may be the result of proton exchange reactions or even second protonation at the phenyl ring.

In summary, we have found that cationic analogues of 1-(3,3-diarylpropyl)amines can be prepared in good yields from the salts of *N*-heterocycles. The chemistry is driven by the activation of the carbocationic electrophiles. This activation arise from the influence of the cationic heterocyclic groups and a similar activation is demonstrated for a carboxonium system.[11]

Acknowledgements

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References

1. (a) Giringauz, A. *Medicinal Chemistry*; Wiley-VHC: New York, 1997; (b) *Pharmaceuticals*; McGuire, J. L., Ed.; Wiley-VHC: New York, 2000; Vol. 2.
2. (a) Andersson, P. G.; Schink, H. E.; Osterlund, K. *J. Org. Chem.* **1998**, *63*, 8067; (b) Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 1915.
3. Klumpp, D. A.; Aguirre, S. L.; Sanchez, G. V., Jr. *Abstract of Papers*, 223nd National Meeting of the American Chemical Society, Orlando, CA, April 2002; Ameri-

can Chemical Society: Washington, DC, 2002; Abstract ORGN 345.

4. (a) Sanchez, G. V.; Klumpp, D. A.; de Leon, S. *Abstract of Papers*, Pacifichem2000, Honolulu, HI, December 2000; American Chemical Society: Washington, DC, 2000; Abstract 90005894; (b) Klumpp, D. A.; Sanchez, G. V., Jr.; Aguirre, S. L.; Zhang, Y.; de Leon, S. *J. Org. Chem.* **2002**, *67*, 5028.
5. For related studies, see: (a) Klumpp, D. A. *Recent Res. Dev. Org. Chem.: Part I* **2001**, 193; (b) Klumpp, D. A.; Aguirre, S. L.; Sanchez, G. V., Jr.; de Leon, S. J. *Org. Lett.* **2001**, *3*, 2781.
6. General procedure for preparation of cationic salts **6**–**10**: 1.0 g of the *N*-heterocycle is dissolved in 10 mL of Et_2O and 1.0 equiv. of cinnamyl bromide is added. The mixture is stirred for 1 day, or until a gel forms. The solvent is removed by vacuum, the gel is redissolved in MeOH, and a small amount of Et_2O is added. On cooling in a freezer, crystals of the salts (**6**–**10**) begin to appear within 1–2 days.
7. General procedure for preparation of addition products **11**–**15**: 0.2 g of the precursor salt (**6**–**10**) is added to a stirred solution of 4 mL TfOH and 1 mL C_6H_6. ***Caution**: TfOH protonates bromide to produce HBr gas and so the reaction vessel must be fitted with an outlet for pressure relief*. After 4 h, the reaction mixture is poured over about 10 g of ice and extracted into $CHCl_3$. The organic phase is then washed with water followed by brine. The solution is dried with $MgSO_4$ and concentration gives product (**11**–**15**, purity 90–99% by NMR).
8. (a) For a review of TfOH chemistry, see: Stang, P. J.; White, M. R. *Aldrichim. Acta* **1983**, *16*, 15; (b) TfOH may be quantitatively recycled. For a procedure, see: Booth, B. L.; El-Fekky, T. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2441.
9. (a) Shudo, S.; Ohwada, T. In *Stable Carbocation Chemistry*; Prakash, G. K. S.; Schleyer, P. v. R., Eds.; Wiley: New York, 1997; (b) Creary, X. *Chem. Rev.* **1991**, *91*, 1625.
10. Olah, G. A.; Burrichter, A.; Rasul, G.; Yudin, A. K.; Prakash, G. K. S. *J. Org. Chem.* **1996**, *61*, 1934.
11. Analytical data for new compounds: (a) 1-(3,3-Diphenylpropyl)pyridinium chloride (**11**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 2.78 (m, 2H), 4.15 (t, $J=7.5$ Hz, 1H), 4.78 (t, $J=6.8$ Hz, 1H), 7.0–7.4 (m, 10H), 7.83 (m, 2H), 8.25 (m, 1H), 9.04 (d, 2H); ^{13}C NMR (125 MHz) δ, ppm: 36.6, 48.8, 61.3, 127.0, 127.7, 128.5, 129.1, 143.0, 144.7, 145.4; mp 113–115°C ($MeOH:Et_2O$). (b) 1-(3,3-Diphenylpropyl)-2-(2-hydroxyethyl)pyridinium chloride (**12**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 2.77 (m, 2H), 3.13 (t, $J=6.0$ Hz, 2H), 3.88 (t, $J=5.7$ Hz, 2H), 4.18 (t, $J=7.5$ Hz, 1H), 4.63 (m, 2H), 7.2–7.4 (m, 10H), 7.83 (m, 1H), 8.01 (d, $J=6.9$ Hz, 1H), 8.40 (m, 1H), 8.77 (d, $J=5.1$ Hz, 1H); ^{13}C NMR (125 MHz) δ, ppm: 35.0, 35.9, 48.8, 57.3, 59.7, 125.9, 126.8, 127.6, 128.7, 129.8, 143.5, 145.1, 145.5, 157.4; oil. (c) 1-(3,3-Diphenylpropyl)quinolinium chloride (**13**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 2.81 (m, 2H), 4.35 (t, $J=7.8$ Hz, 1H), 5.19 (t, $J=7.2$ Hz, 2H), 7.1–7.3 (m, 11H), 7.90 (m, 2H), 8.06 (m, 1H), 8.22 (m, 1H), 8.87 (d, $J=8.4$ Hz, 1H), 8.87 (d, $J=6.0$ Hz, 1H); ^{13}C NMR (125 MHz) δ, ppm: 35.6, 48.7, 57.3, 118.2, 122.7, 127.2, 127.8, 128.6, 129.1, 130.1, 130.3, 131.2, 136.1, 137.6, 143.0, 147.3; mp 140–143°C ($MeOH:Et_2O$). (d) 1-(3,3-Diphenylpropyl)-8-hydroxyquinolinium chloride (**14**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 2.71 (m, 2H), 4.18 (t, $J=7.8$ Hz, 1H), 5.24 (t, $J=6.6$ Hz, 2H), 6.9–7.15 (m, 10H), 7.4–7.6 (m, 4H), 8.28 (d, $J=7.5$ Hz, 1H), 8.51 (d, $J=8.1$ Hz, 1H), 9.02 (d, $J=5.4$ Hz, 1H); ^{13}C NMR (125 MHz) δ, ppm: 37.7, 49.2, 63.2, 120.8, 121.2, 122.2, 126.8, 127.8, 128.6, 128.9, 129.4, 131.2, 132.2, 143.1, 147.2, 149.9. (e) 1-(3,3-Diphenylpropyl)-3-phenyl-3*H*-imidazol-1-ium chloride (**15**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 2.71 (m, 2H), 4.10 (t, $J=7.8$ Hz, 1H), 4.40 (t, $J=6.9$ Hz, 2H), 7.0–7.6 (m, 17H), 9.75 (s, 1H); ^{13}C NMR (125 MHz) δ, ppm: 35.6, 49.2, 49.9, 120.8, 122.0, 123.3, 127.0, 127.8, 129.0, 130.5, 130.7, 134.5, 135.7, 143.2; oil. (f) 1-(2,2-Diphenylpropyl)pyridinium chloride (**22**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ, ppm: 1.68 (s, 3H), 5.59 (s, 2H), 7.1–7.4 (m, 10H), 7.76 (m, 2H), 8.40 (m, 1H), 8.80 (d, $J=5.1$ Hz, 2H); ^{13}C NMR (125 MHz) δ, ppm: 25.2, 48.5, 70.8, 127.0, 127.5, 128.9, 143.8, 145.6, 145.7; mp 75–82°C ($CHCl_3$).