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# Chemistry of Dicationic Electrophiles: Superacid-Catalyzed Reactions of Amino Acetals

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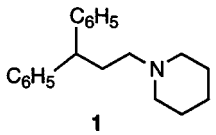
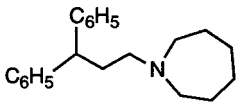
**Abstract:** Amino acetals are shown to form highly electrophilic systems in Bronsted superacids. It is proposed that amino acetals give dicationic electrophiles, and this proposal is supported by the direct observation of a dication by low-temperature $^{13}C$ NMR. When reacted with $C_6H_6$ and superacidic $CF_3SO_3H$, amino acetals are shown to provide 1-(3,3-diphenylpropyl)amines and 1-(2,2-diphenylethyl)-amines as condensation products in good yields (50−99%).

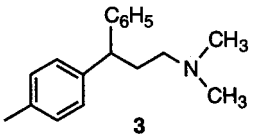
The 1-(3,3-diarylpropyl)amines are compounds having a variety of pharmacological activities.[1] In clinical applications, fenpiprane **1** and prozapine **2** are spasmolytics and tolpropamine **3** is an antihistaminic.[2] The 1-(3,3-diarylpropyl)amines have been prepared by a variety of synthetic routes,[2,3] yet there is only one report (in the patent literature) of these compounds being prepared by electrophilic aromatic substitution chemistry.[4] We have been studying the chemistry of reactive, dicationic electrophilic systems and recently reported a synthetic route to diarylpiperidines by the superacid-catalyzed reactions of piperidones with arenes.[5] The diarylpiperidines were prepared in good yields (80−99%). It was proposed that dicationic electrophiles are generated from piperidones by the protonation of the carbonyl and nitrogen base sites. Since it is well-known that acetal and ketal groups can form carboxonium ions in acid-catalyzed reactions,[6] we have explored the possibility of generating dicationic electrophiles from amino acetals with the goal of preparing compounds such as the 1-(3,3-diarylpropyl)amines. In this paper, we describe a general synthetic route to 1-(3,3-diarylpropyl)amines and related products, propose the formation of dicationic intermediates, and report the direct observation of a dicationic intermediate by low-temperature $^{13}C$ NMR.




**1**




**2**




**3**

Although a number of amino acetal compounds are commercially available, these compounds can be readily prepared by the reaction of amines with brominated acetals and $Na_2CO_3$ in anhydrous DMF.[7] To compare two common acetals, the dimethoxy acetals **4a**−**7a** and the dioxolane derivatives **4b**−**7b** were prepared and reacted with benzene in triflic acid ($CF_3SO_3H$, TfOH; Table 1).[8] Although both types of amino acetals give fair yields of the condensation products, the dimethoxy acetals give better yields of the 1-(3,3-diphenylpropyl)amines (**2**, **14**, **15**). Amino acetals **8**−**12** react with $C_6H_6$ in TfOH to give good yields of the 1-(2,2-diphenylethyl)amines **16**−**20**. In a typical reaction, the reagents (3 mmol of acetal, 20 mmol of TfOH, and 2 mL of $C_6H_6$) are stirred for 2 h at room temperature. Longer reaction times and heat caused reduction of yields for some of the acetals. Acetals **9**, **10**, and **12** were also reacted with $H_2SO_4$ and $C_6H_6$. Although some condensation products could be detected if the reactions were done at 90 °C, the $H_2SO_4$-catalyzed conversions were generally poor. Even at elevated temperatures, the condensation reactions do not proceed in $CF_3CO_2H$. In the patent literature, there is a report of amino acetals reacting with arenes in polyphosphoric acid or $H_2SO_4$.[4] However, in these earlier studies, the condensation reactions are done with strongly activated arenes, such as phenols and catechols. For less reactive arenes such as $C_6H_6$, the condensation reactions of amino acetals work best in superacidic TfOH. Interestingly for the TfOH reactions, the acetaldehyde derivatives (**8**−**13**) give slightly better yields than the propionaldehyde derivatives (**4a**,**b**−**7a**,**b**). When the formamide derivative **22** or the butyraldehyde derivative **23** are reacted under similar conditions, however, the expected condensation products are not formed.[9] Compound **13** reacted in TfOH and $C_6H_6$ to give product **21** as the only major product (eq 1) in about 50% yield (after column chromatography). Product **21** is the result of condensation and oxidation chemistry; however, it is not immediately clear if the benzylic position is oxidized during the TfOH reaction or during the workup.

† American Chemical Society Scholar, 2001−2002.

(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) Reference 1b.

(3) Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 1915.

(4) Watanabe, Y.; Kamochi, Y.; Kido, K.; Kudo, T.; Nose, A. *Chem. Abstr.* **1974**, *81*, 91256z.

(5) Klumpp, D. A.; Garza, M.; Jones, A.; Mendoza, S. *J. Org. Chem.* **1999**, *64*, 6702.

(6) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 373−376. (b) Fukuzawa, S.; Tsuchimoto, T.; Hiyama, T. *J. Org. Chem.* **1997**, *62*, 151. (c) For an example of a superacid-catalyzed Friedel−Crafts reaction involving a heterocyclic acetal, see ref 7.

(7) Wardani, A.; Lhomme, J. *Tetrahedron Lett.* **1993**, *34*, 6411.

(8) (a) For a review of TfOH chemistry, see: Stang, P. J.; White, M. R. *Aldrichim. Acta* **1983**, *16*, 15. (b) Olah, G. A.; Prakash, G. K. S.; Sommer, J. In *Superacids*; Wiley: New York, 1985. (c) 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) Compound **23** was also reacted with a large excess of TfOH and $C_6H_6$ at 90 °C for 2 h with no conversion.

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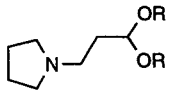
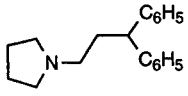
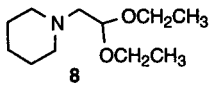
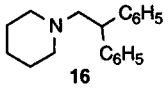
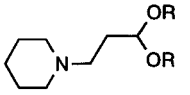
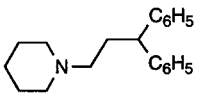
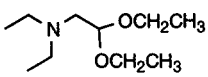
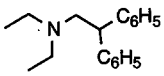
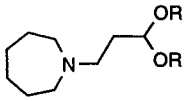
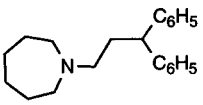
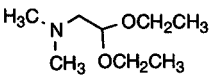
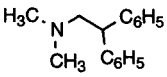
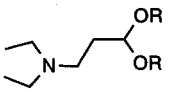
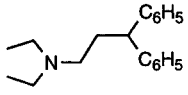
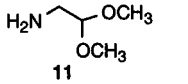
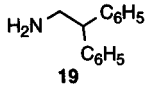
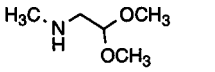
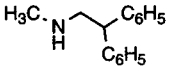
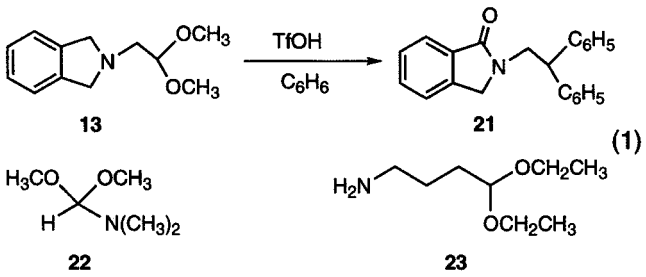
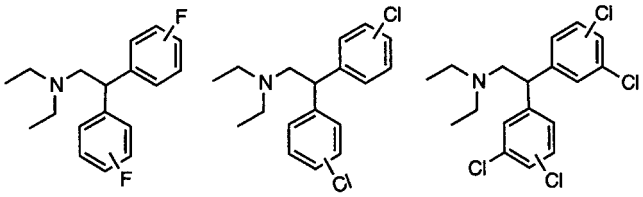
**TABLE 1. Products from the Reactions of Amino Acetals 4−12 with $CF_3SO_3H$ and $C_6H_6$**

| ACETAL | PRODUCT | % YIELD | ACETAL | PRODUCT | % YIELD |
|---|---|---|---|---|---|
|  **4a**, R = $CH_3$<br>**4b**, R = -$CH_2CH_2$ - |  **14** | 66%<br>30% |  **8** |  **16** | 75%[a] |
|  **5a**, R = -$CH_3$<br>**5b**, R = -$CH_2CH_2$ - |  **1** | 70%<br>74% |  **9** |  **17** | 99% |
|  **6a**, R = $CH_3$<br>**6b**, R = -$CH_2CH_2$ - |  **2** | 81%<br>51% |  **10** |  **18** | 97% |
|  **7a**, R = $CH_3$<br>**7b**, R = -$CH_2CH_2$ - |  **15** | 66%<br>65% |  **11** |  **19** | 95% |
| | | |  **12** |  **20** | 88% |

[a] Reference 5.

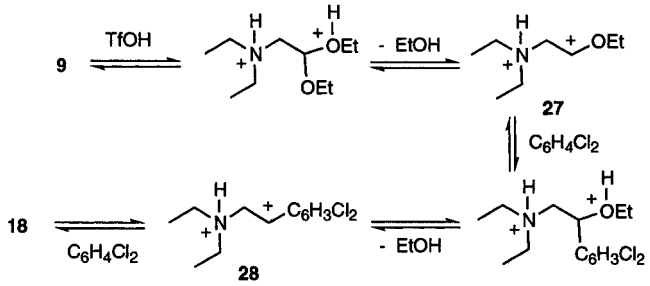


Acetal **9** reacts in TfOH with fluorobenzene, chlorobenzene, or 1,2-dichlorobenzene to give products (**24**−**26**).



The reactions give mixtures of regioisomers, and the yields parallel the relative deactivation of the arenes (nitrobenzene did not react). Despite the fact that 1,2-dichlorobenzene is a significantly deactivated arene,[10] a fair amount of the condensation products are formed. Therefore, acetal **9** must form highly electrophilic intermediates upon solvation in superacid. We propose a mechanism involving the formation of dicationic intermediates (Scheme 1). The dicationic electrophiles are the carboxonium−ammonium dication (**27**) and the carbenium−ammonium dication (**28**). Both of these dications are sufficiently electrophilic to react with benzene and halogen-substituted arenes.

**SCHEME 1**



In comparing the different types of amino acetals, the propionaldehyde and acetaldehyde derivatives give good yields of products, while the formamide (**22**) and butyraldehyde (**23**) derivatives give no condensation products. These results suggest that **22** does not form the dicationic intermediate **29**, due to the unfavorable proximity of the two charge centers. On the other hand, the condensation chemistry appears to work best with the acetaldehyde derivatives, while the propionaldehyde and (especially) the butyraldehyde derivatives yield poorer results. This trend may reflect the relative reactivities of the dicationic intermediates. Thus, the 1,3-dication (**27**) from the acetaldehyde derivative is more reactive than the analogous 1,4-dication (**30**) and the 1,5-dication (**31**) from the respective propionaldehyde and butyraldehyde derivatives. In the chemistry of dicationic electrophiles, proximity of the charge centers can influence the reactivity of

(10) (a) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, 1990; Chapter 2. (b) Olah, G. A. *Friedel−Crafts and Related Reactions*; Wiley: New York, 1964; Vol. 2; pp 597−640.

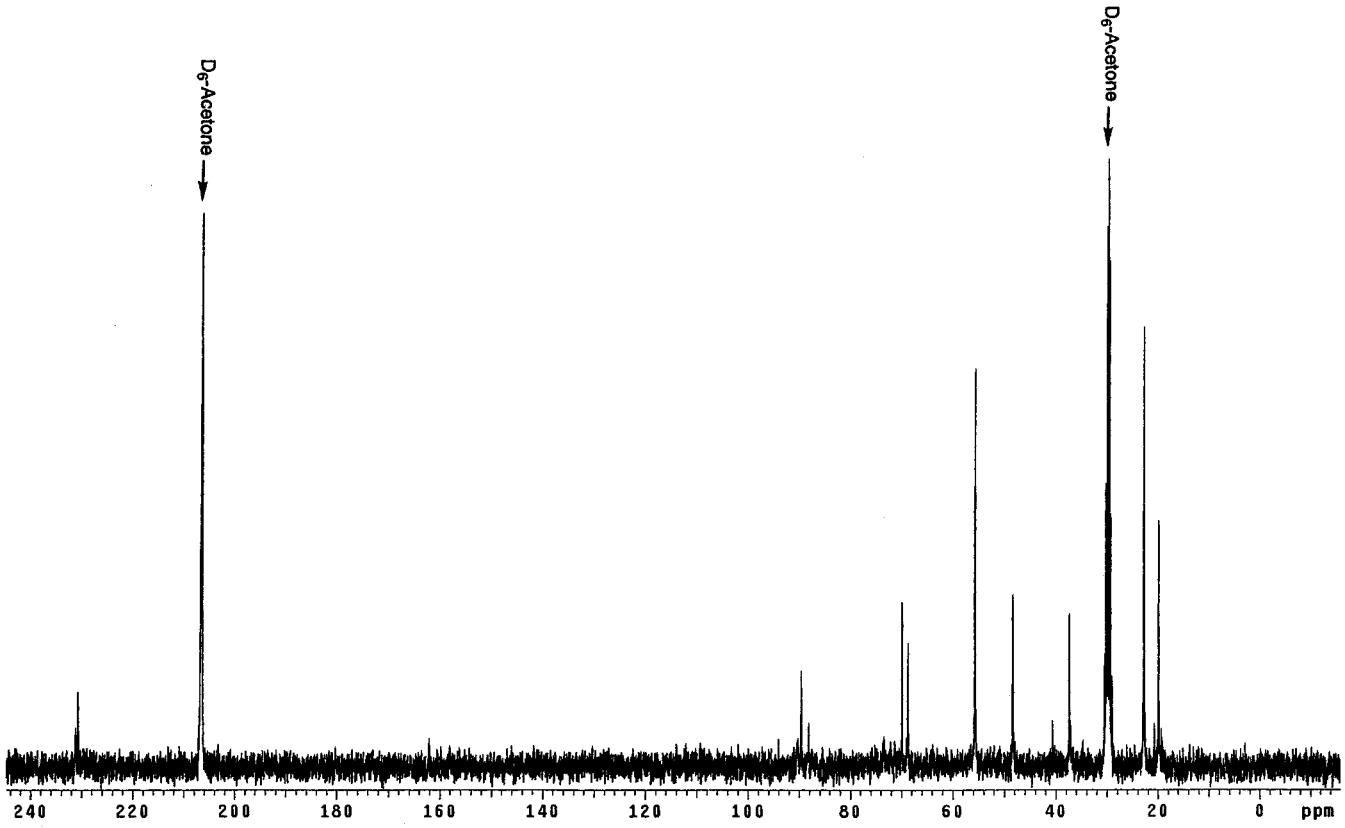
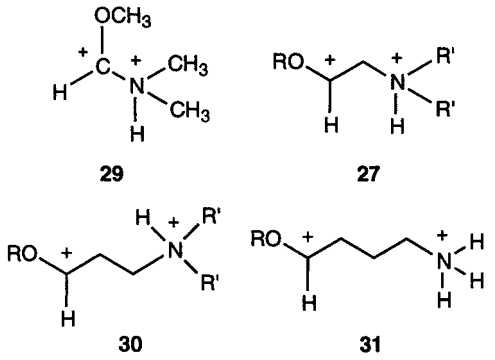



**FIGURE 1.** $^{13}C$ NMR of ions **33** and **34** in $FSO_3H/SbF_5/SO_2ClF$ at −80 °C.

the intermediates. Proximity effects were also observed in two other recent studies involving dicationic electrophiles.[11]




When the acetal derivative of octanal (**32**) is reacted with TfOH and $C_6H_6$, a complex mixture of products is formed and 1,1-diphenyloctane is not present in the mixture. Acetal **32** and the amino acetals (**4**−**13**) exhibit much different chemistry in the superacid-catalyzed reactions. This suggests that acetal **32** reacts primarily through monocationic intermediates, and if any dicationic intermediates are formed, they form in very low concentrations.

To characterize the cationic intermediates arising from the amino acetals, acetal **5b** was studied in acidic solution by NMR. When **5b** is dissolved in $CF_3CO_2H$ and analyzed by $^{13}C$ NMR at −10 °C (acetone-$d_6$ external standard), the spectrum is consistent with that of the monoprotonated, ammonium cation.[12] Seven resonance signals appear: 20.1, 22.4, 25.8, 52.4, 54.1, 64.5, and 101.4 ppm. In a mixture of $SbF_5$:$FSO_3H$ (ca. 1:1) with $SO_2ClF$ at −80 °C, compound **5b** gives a $^{13}C$ NMR spectrum (Figure 1) consistent with that of a dicationic intermediate. Upon ionization, the acetal carbon signal disappears and a new signal forms at 231 ppm. Close examination of the downfield signal reveals that it is split into a pair of peaks. This suggests the formation of the isomeric dicationic structures **33** and **34**. Two other carbon atoms also appear to give split peaks for the isomeric structures: one carbon at about 89 ppm and one carbon at 70 ppm. These peaks are likely the methylene groups adjacent to the caboxonium ion. The remaining $^{13}C$ signals are isochronous for structures **33** and **34**. It is well known that carboxonium ions can form cis and trans isomers.[13] Although there are very few published $^{13}C$ NMR spectra of carboxonium ions similar to **33** and **34**, the $^{13}C$ NMR spectrum of methylated trifluoroacetone **35** was recently reported and the carboxonium carbon appeared at 222 ppm.[14] These data are consistent with

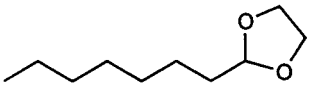
(11) (a) Klumpp, D. A.; Beauchamp, P. S.; Sanchez, G. S., Jr.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* **2001**, *42*(34), 5821. (b) Klumpp, D. A.; Garza, G.; Sanchez, G. V.; Lau, S.; DeLeon, S. *J. Org. Chem.* **2000**, *65*, 8997. (c) See also: Prakash, G. K. S.; Rawdah, T. N.; Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 390.

(12) $^{13}C$ NMR data for **5b**: ($\delta$, $CDCl_3$) 24.6, 26.2, 31.6, 54.3, 54.8, 65.1, 103.8

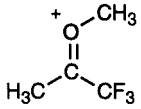
(13) Olah, G. A.; Prakash, G. K. S.; Laali, K.; Li, Q. in *Onium Ions*; Wiley: New York, 2000.

(14) Olah, G. A.; Burrichter, A.; Rasul, G.; Yudin, A. K.; Prakash, G. K. S. *J. Org. Chem.* **1996**, *61*, 1934.

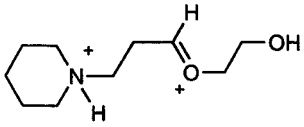
the proposed structures (**33** and **34**) as the ionization product from amino acetal **5b**.



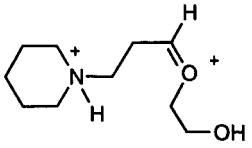
**32**



**35**



**33**



**34**

We have found that amino acetal compounds **4**−**13** react with benzene in superacidic triflic acid to give condensation products in good yields. It is proposed that the reactions occur through dicationic, electrophilic intermediates. The acetal functional groups react in acid to form carboxonium ions (**27**, Scheme 1) and the adjacent ammonium cations induce an electrostatic or inductive effect upon the carboxonium ions. The resulting destabilized carboxonium ions are sufficiently electrophilic to react with benzene, chlorobenzene, and 1,2-dichlorobenzene.

## Experimental Section

Compounds **8**−**12** and the bromoacetals were purchased from commercial sources and used as received. Trifluoromethanesulfonic acid was purchased from a commercial source and distilled under a dry, inert atmosphere immediately prior to its use. Benzene was dried with sodium prior to use. All products were fully characterized by $^1$H and $^{13}$C NMR and mass spectroscopy. Known compounds were found to be consistent with published analytical data. Low-temperature NMR experiments were done according to published procedures.[15]

**Typical Procedure. 2-Methylamino-1,1-diphenylethane (20).** Methylaminoacetaldehyde dimethyl acetal (**12**) (0.37 g, 3.11 mmol) was dissolved in 2.0 mL of benzene, and 3.0 mL of TfOH was slowly added. After 4 h of stirring, the mixture was poured over ice and neutralized with NaOH. The product was then extracted into $CHCl_3$ and the organic phase washed with water and then brine, dried with $MgSO_4$, and concentrated in vacuo. Crude **20** (0.58 g, 2.75 mmol, 88%) was isolated as a clear oil. $^1$H NMR and GC analysis of the crude product indicates a purity in excess of 95%. Further purification was achieved by vacuum distillation.

**2-(2,2-Diphenylethyl)-2,3-dihydroisoindol-1-one (21).** In anhydrous DMF, aminoacetaldehyde dimethyl acetal (**11**) was reacted with exactly 1 equiv of α,α′-dibromo-*o*-xylene to yield crude **13**. Crude **13** (ca. 0.2 g) was dissolved in 2 mL of $C_6H_6$, and 2 mL of TfOH was added slowly. Following 2 h of reaction, the mixture was poured over several grams of ice, made basic with 12 M NaOH, and extracted twice by $CHCl_3$. The organic extracts were washed with water, washed with brine, and dried with $MgSO_4$. Concentration under reduced pressure and purification by column chromatography (1:1, hexane/ether) afforded compound **21** (0.17 g) as a white, crystalline solid: mp 162−164 °C (hexane/ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.04 (s, 2H), 4.24 (d, 2H, $J$ = 8.1 Hz), 4.51 (t, 1H, $J$ = 8.1 Hz), 7.15−7.35 (m, 11H), 7.40−7.50 (m, 2H), 7.80 (d, 1H, $J$ = 6.6 Hz); $^1$H NMR (125 MHz, $CDCl_3$) $\delta$ 47.8, 50.4, 50.8, 122.8, 123.9, 127.1, 128.1, 128.3, 128.9, 131.4, 132.8, 141.5, 142.1, 169.0; IR (NaCl, cm$^{-1}$) 1685; MS (*m*/*z*) 313 ($M^+$), 165, 146, 91. HRMS (DEI) *m*/*z* 313.147164, calcd $C_{22}H_{19}NO$ 313.146664.

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**Supporting Information Available:** General procedure for the preparation of amino acetals **4a**−**7a** and **4b**−**7b**; analytical data for compounds **14**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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