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Superacid-catalyzed preparation of aryl-substituted piperidines via dicationic electrophiles

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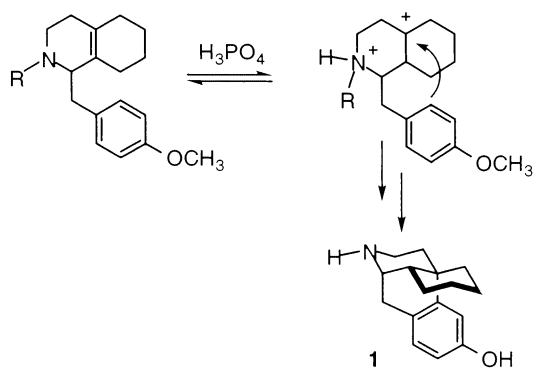
Abstract—The electrophilic chemistry of 1,2,3,6-tetrahydropyridines has been studied in the Bronsted superacid, CF_3SO_3H (triflic acid). The 1,2,3,6-tetrahydropyridines react with arenes to give aryl-substituted piperidines. It is proposed that the reactions occur through dicationic electrophilic intermediates. Depending upon substituents, either 1,4-dications or 1,3-dications are formed. The dicationic intermediates react with moderately deactivated arenes, such as *o*-dichlorobenzene. © 2001 Elsevier Science Ltd. All rights reserved.

Benzomorphans (i.e. **1**) are morphine analogues and can be prepared by the acid-catalyzed Grewe cyclization (Scheme 1).[1] The Grewe cyclization is typically done in strong acids such as H_3PO_4 or HBr. The cyclization involves formation of a diprotonated intermediate which undergoes an intramolecular reaction to give the benzomorphan ring system. Although the Grewe cyclization has been known for more than 50 years, there is only one report in the literature of an analogous intermolecular reaction to give an aryl-substituted piperidines.[2] Aryl-substituted piperidine rings are important substructures in a number of clinically important drugs and biologically active compounds.[3]



Scheme 1.

Aryl-substituted piperidines have been synthesized by ring-forming reactions with primary amines,[4] by the reaction of aryl-Grignard reagents with piperidones and related compounds,[3c,e] and by Pd-catalyzed reactions.[3e] However, some of these routes proceed through potentially toxic synthetic intermediates, such as the 4-aryl-1,2,3,6-tetrahydropiperidines.[5] Owing to the biological activities of the aryl-substituted piperidines, there is a continued interest in the development of synthetic routes to these compounds. We recently reported the preparation of diarylpiperidines by the reaction of piperidones with arenes in the Bronsted superacid CF_3SO_3H (triflic acid, TfOH).[6] Strong mineral acids such H_2SO_4 fail to catalyze the conversion of piperidones to diarylpiperidines. The results suggested TfOH is capable of generating diprotonated, dicationic electrophilic species from piperidones, while weaker acids do not generate the dicationic intermediates. In the following report, we describe the preparation of aryl-substituted piperidines (**8**–**13**) from 1,2,3,6-tetrahydropyridines (**2**–**7**) in TfOH. We also propose that the conversion occurs via dicationic intermediates.

When 1,2,3,6-tetrahydropyridine (**2**) is reacted with benzene in TfOH, 4-phenylpiperidine (**8**) is formed in 86% yield as the only major product (Table 1).[7] The *N*-methyl derivative (**3**) and the sterically crowded 1,2,3,6-tetrahydropyridine (**4**) also react in good yields with benzene in TfOH. In H_2SO_4, no reaction occurs between compound **2** and benzene. TfOH is at least 100 times more acidic than H_2SO_4 and these results suggest the diprotonated intermediate (**15**) is formed in the

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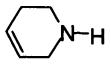
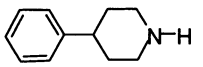
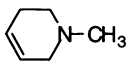
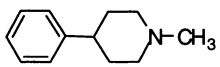
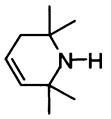
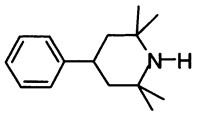
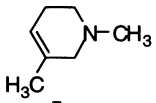
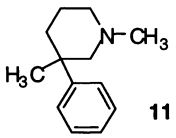
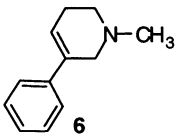
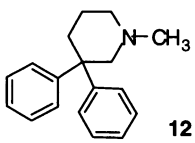
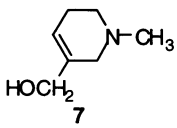
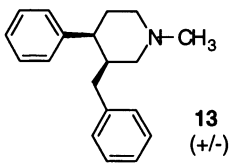
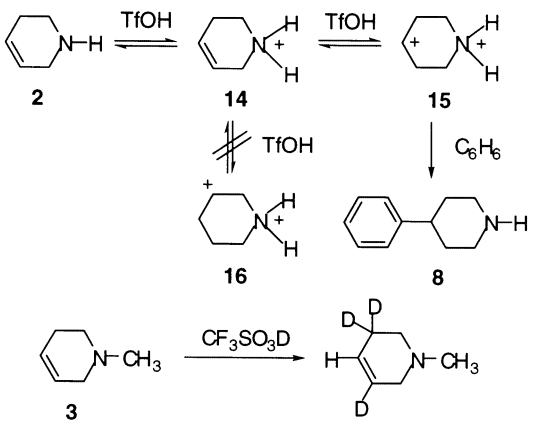
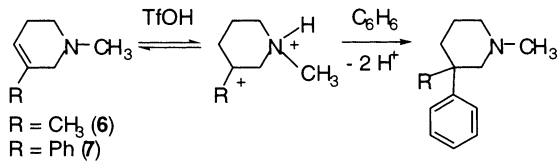
Table 1. Products from the reactions of 1,2,3,6-tetrahydropyridines **2**–**7** with C_6H_6 in CF_3SO_3H

Starting Material	Product	% Yield
 **2**	 **8**	86%
 **3**	 **9**	82%
 **4**	 **10**	67%
 **5**	 **11**	87%
 **6**	 **12**	99%
 **7**	 **13** (+/-)	60%



Scheme 2.



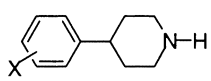
Scheme 3.

Bronsted superacid (Scheme 2).[8] Interestingly, TfOH has been used as an acid catalyst in the polymerization of olefins,[9] but there is no evidence of oligomerization or polymerization of **2** in the TfOH-catalyzed reaction. There is apparently a significant electrostatic repulsion between ions **14** and **15**, and therefore polymerization cannot take place. Moreover, 3-phenylpiperidine is not found as a product, which indicates protonation occurs exclusively at the nitrogen and 3-position of the ring. When compound **3** is reacted with deuterated acid, deuterium is slowly incorporated onto the ring (Scheme 2). Deuterium is incorporated at a significant rate only with CF_3SO_3D, while the weaker acids CF_3CO_2D and D_2SO_4 do not substitute deuterium at 25°C. GC–MS analysis indicates approximately 5% deuterium substitution at 25°C and 50% deuterium substitution at 80°C.[10] Moreover, NMR and GCMS data indicate that the olefinic proton at the 4-position is not substituted by deuterium. This provides further evidence that the 1,4-dication (**15**) is significantly more stable than 1,3-dication (**16**). In studies of bis-carbocations by Olah and others, it was observed that dicationic systems can be greatly destabilized by close proximity of the positive charges.[11]

When methyl and phenyl substituted 1,2,3,6-tetrahydropyridines (**5** and **6**) are reacted, arylation occurs exclusively at the 3-position (Table 1). Despite the unfavorable electrostatic effects in generating 1,3-dications, compounds **5** and **6** are protonated at the nitrogen and the 4-position (Scheme 3). The carbocationic centers are presumably stabilized by the resonance and/or inductive effects. The hydroxymethyl derivative **7** gives **13** as the only major product (Table 1). The structure of compound **13** was established by ^1H, ^{13}C, HETCOR, COSY, and DEPT NMR spectroscopy.[12] The mechanism of this conversion is presently being studied.

In order to evaluate the reactivities of the dicationic intermediates, compound **2** was reacted with a series of substituted benzenes in TfOH (Fig. 1). The overall yields parallel the deactivation of the arenes relative to benzene. Although chlorobenzene and *ortho*-dichlorobenzene are moderately deactivated arenes,[13] compound **2** reacts in TfOH to give fair amounts of the products. However, even at elevated temperature (80°C), **2** does not react with nitrobenzene. In all cases, the reactions give mixtures of regioisomers in the products.

In conclusion, aryl-substituted piperidines have been prepared in fair to good yields by the superacid-catalyzed reactions of 1,2,3,6-tetrahydropyridines with benzene and other arenes. This methodology is an



X:	CH_3	F	Cl	Cl_2	NO_2
YIELD:	94%	76%	69%	42%	0%

Figure 1. Products and yields from the reactions of **2** with substituted benzenes.

improvement over a similar $AlCl_3$-catalyzed reaction, which gives low yields of aryl-piperidines.[2] It is proposed that the 1,2,3,6-tetrahydropyridines are protonated twice in CF_3SO_3H to generate reactive, dicationic electrophiles.[14] While the 1,4-dications are preferred over the isomeric 1,3-dications, substitution by alkyl or aryl groups can reverse this trend.

Acknowledgements

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7. Reaction conditions: 0.2 g of the tetrahydropyridine is dissolved in 1.0 mL of C_6H_6, and 3.0 mL of CF_3SO_3H is slowly added. After stirring for at least 4 hours at 25°C, the mixture is poured over ice, made basic with NaOH, and extracted with $CHCl_3$. The resulting organic solution is dried with $MgSO_4$ and concentrated to give the product. All products were fully characterized by ^1H and ^{13}C NMR, GCMS, and high resolution mass spectrometry. CF_3SO_3H can be quantitatively recycled, see: Booth, B. L.; El-Fekky, T. A. *J. Chem. Soc., Perkin 1* **1979**, 2441.
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10. 0.05 g of **3** is reacted with 1.0 g TfOD for 18 h.
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12. ***N*-Methyl-3,3-diphenylpiperidine (12)**: mp 38–40°C; ^1H NMR (300 MHz, $CDCl_3$) δ, ppm: 1.62 (m, 2H), 2.32 (m, 2H), 2.35 (s, 3H), 2.46 (m, 2H), 2.90 (m, 2H), 7.18 (m, 4H), 7.28–7.37 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 22.5, 34.8, 46.5, 46.6, 56.2, 65.6, 125.7, 127.6, 128.1, 147.7. HRMS calcd for $C_{18}H_{21}N$ 251.1674, found 251.1668. ***N*-Methyl-*cis*-(3-benzyl-4-phenyl)piperidine (13)**: ^1H NMR (300 MHz, $CDCl_3$) δ, ppm: 0.80–0.90 (m, 1H), 1.47–1.65 (m, 4H), 1.81–1.90 (m, 1H), 2.1 (s, 3H), 2.4 (m, 1H), 2.7 (m, 1H), 2.8 (m, 1H), 3.5 (m, 1H), 7.05–7.30 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 25.3, 29.34, 36.7, 46.6, 56.2, 57.1, 61.2, 126.1, 126.2, 127.9, 128.0, 128.5, 128.6, 143.5, 143.7. HRMS calcd for $C_{19}H_{23}N$ 265.1830, found 265.1828.
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14. For recent examples dicationic electrophiles, see: (a) *Stable Carbocation Chemistry*; Prakash, G. K. S.; Schleyer, P. v. R., Eds.; Wiley: New York, NY, 1997; (b) Klumpp, D. A.; Jones, A.; Lau, S.; DeLeon, S.; Garza, M. *Synthesis* **2000**, *8*, 1117; (c) Miller, J. P.; Jeon, I.; Wilson, G.; Athans, A. J. *Org. Lett.* **1999**, *1*, 1771; (d) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767.