Bioorganic & Medicinal Chemistry Letters, Vol.3, No.2, pp. 251-252, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

MONOCYCLIZATION OF *N*-(2,2-DIETHOXYETHYL)-1,2-DIPHENYLETHYLAMINES TO THE 4-ARYL-1-HYDROXY-2,3,4,5-TETRAHYDRO-1*H*-3-BENZAZEPINE RING SYSTEM

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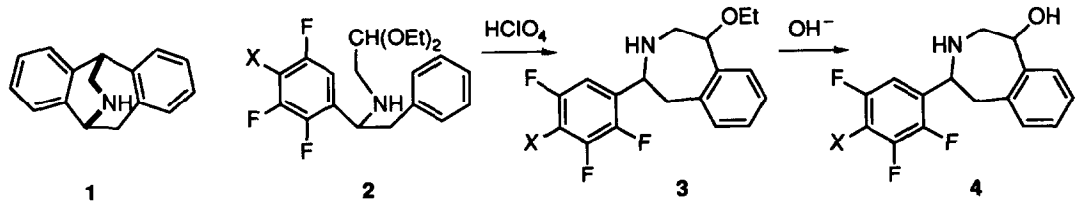
(*Received in USA* 17 *August* 1992)

Abstract: Treatment of *N*-(2,2-diethoxyethyl)-2-phenyl-1-(2,3,4,5-tetrafluorophenyl)ethylamine (**2a**) and *N*-(2,2-diethoxyethyl)-1-(4-amino-2,3,5-trifluorophenyl)-2-phenylethylamine (**2b**) with perchloric acid afforded monocyclized 4-aryl-1-hydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepines **4a,b**.

Dopamine and dopaminergic neurons are involved in various physiological and pathophysiological conditions of the central nervous system.[1,2] Certain phenyl-substituted 2,3,4,5-tetrahydro-1*H*-3-benzazepines have been shown to possess potent and selective agonist and/or antagonist activity at the D-1 dopamine receptor.[3] As part of our efforts to synthesize new *N*-methyl-D-aspartate receptor antagonists based on 10,5-(iminomethano)-10,11-dihydro-5*H*-dibenzo[a,d]-cycloheptene (**1**),[4] we found the new route herein reported to 4-aryl-1-hydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepines (e.g. **4a,b**). We believe the route may be useful for the preparation of a series of 4-aryl derivatives with a variety of electron withdrawing substituents on the 4-aryl ring. These new 3-benzazepines may have interesting dopaminergic activity. Also, conversion of **4b** into the corresponding fluorinated aryl azide might afford a new receptor photoaffinity label.[5]

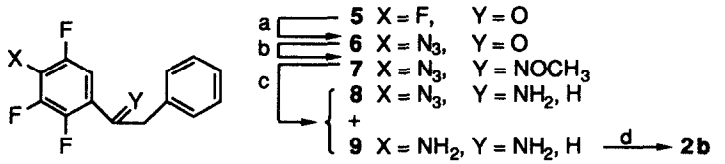
Our method takes advantage of the lack of reactivity of the phenyl group bearing the electron withdrawing substituents in **2a**[4a] and **2b** toward electrophilic attack by the respective carbocation intermediates produced by protonation of an ethoxy group by $HClO_4$ followed by loss of ethanol.[6] Thus benzazepines **4a,b** were obtained as oils in 50-60% yield after workup with aqueous NaOH. The corresponding ether **3** is a likely intermediate.[6]



1 **2** **3** **4**

a X = F **b** X = NH_2

Acetal **2b** was prepared by reaction of ketone **5**[4a] with sodium azide in refluxing acetone/water to give the azido-ketone **6**,[7] which was converted into its oxime methyl ether **7**.[7] Treatment with BH_3•THF at room temperature,[8] followed by basic hydrolysis, afforded a 2:1 mixture of the diamine **9**[7] and the azido-amine **8**,[7] respectively. Treatment of **9** with $BrCH_2CH(OEt)_2$ selectively alkylated the aliphatic amino group to give **2b**.[7]



a. NaN_3, acetone, H_2O, reflux (16%); b. CH_3ONH_2•HCl, pyridine, rt (97%); c. i) BH_3•THF, THF, rt ii) NaOH (2:1 ratio of **9** and **8**, 69%); d. $BrCH_2CH(OEt)_2$,DMF, K_2CO_3, 95°C (48%)

Monocyclization Procedure: Representative Example

Perchloric acid (70%, 0.11 mL, 1.3 mmol) was added to N-(2,2-diethoxyethyl)-1-(2,3,4,5-tetrafluorophenyl)-2-phenylethylamine (**2a**,[4a] 24 mg, 0.062 mmol) under nitrogen at 25 °C. The resulting pale brown mixture was stirred overnight, and 10% NaOH (3 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (2 x 5 mL), and the extract was dried (K_2CO_3) and concentrated in vacuo to give 19 mg of a pale brown oil. Flash chromatography (5% methanol/chloroform) afforded 9.5 mg (50%) of **4a** as a colorless oil. The ^1H NMR spectrum indicated the presence of only one diastereomer: ^1H NMR ($CDCl_3$) δ 1.61 (br s, 2H), 2.72 (d, J = 14.7, 1H), 3.09 (d, J = 12.8, 1H), 3.49 (dd, J = 12.8, 6.0, 1H), 3.55 (dd, J = 14.8, 10.9, 1H), 4.18 (d, J = 10.7, 1H), 4.68 (d, J = 6.0, 1H), 6.95-7.30 (m, 5H); m/e (rel. intensity) 311 (M^+, 21), 293 (M-H_2O, 100), 281 (22), 190 (34), 178 (51); HRMS 311.0924 (311.0933 calcd for $C_{16}H_{13}F_4NO$).[9]

Acknowledgment. This work was supported by the National Institute on Drug Abuse (Grant DA 06726) and Cambridge NeuroScience, Inc.

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2. Calne, D. B.; Larsen, T. A. in *Dopamine Receptors*; Kaiser, C., Kebabian, J. W., Eds.; ACS Symposium Series 224; American Chemical Society: Washington, DC, 1983; pp. 147-153.
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4. a) Gee, K.R.; Barmettler, P.; Rhodes, M.R.; McBurney, R.N.; Reddy, N.L; Hu, L.-Y.; Cotter, R.E.; Hamilton, P.N.; Smith, S.M.; Weber, E.; Keana, J.F.W., submitted. b) Hu, L.-Y.; Reddy, N.L.; McBurney, R.N.; Cotter, R.E.; Fischer, J.B.; Weber, E.; Gee, K.R.; Barmettler, P.; Rhodes, M.R.; Keana, J.F.W. *American Chemical Society 203rd National Meeting* **1992**, San Francisco, CA. c) Suzuki, T.; Takamoto, M.; Okamoto, T.; Takayama, H. *Chem. Pharm. Bull.* **1986**, *34*, 1888.
5. Keana, J. F. W.; Cai, S. X. *J. Org. Chem.* **1990**, *55*, 3640.
6. Acid-catalyzed cyclization of 2-(N-phenethyl)amino-1-arylethanol derivatives has been used to prepare 1-aryl-3-benzazepines. See, for example, Smalley, R. K. in *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, p. 533.
7. Compounds **2b** and **6-9** were colorless or pale yellow oils, chromatographically homogeneous, and gave satisfactory ^1H NMR spectra. The IR of **6** confirmed the presence of the azide group.
8. Feuer, H.; Braunstein, D. M. *J. Org. Chem.* **1969**, *34*, 1817.
9. For **4b**: ^1H NMR ($CDCl_3$) δ 1.61 (br s, 2H), 2.73 (d, J = 14.8, 1H), 3.05 (d, J = 12.8, 1H), 3.45 (dd, J = 12.8 and 6.1, 1H), 3.55 (dd, J = 14.8 and 10.9, 1H), 3.83 (br s, 2H), 4.09 (d, J = 10.7, 1H), 4.64 (d, J = 6.0, 1H), 7.01-7.12 (m, 2H), 7.19 (m, 3H); HRMS 308.1140 (308.1136 calcd for $C_{16}H_{15}F_3N_2O$).