Tetrahedron Letters, Vol. 33, No. 42, pp. 6279-6282, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Apparent Proton-Catalyzed Meerwein-Ponndorf-Verley Type Reduction of 8-Chloro-6-(2-fluorophenyl)-1-methyl-6H-imidazo[1,5-a][1,4]benzodiazepine

Keith Ramig,* Michael A. Kuzemko, David Parrish

Synthesis Development Department, Hoffmann-La Roche Inc., 340 Kingsland St., Nutley, N J 07110-1199

Barry K. Carpenter*

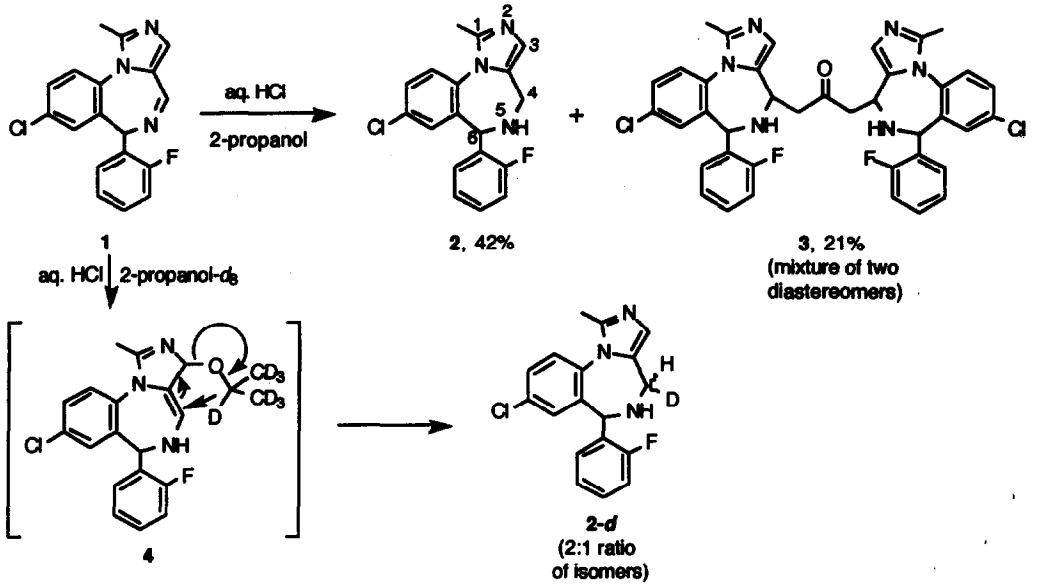
Cornell University, Department of Chemistry, Baker Laboratory, Ithaca, NY 14853-1301

Abstract: **When treated with 2-propanol in the presence of HCl, reduction of the C4-N double bond in 8-chloro-6-(2-fluorophenyl)-1-methyl-6H-imidazo[1,5-a][1,4]benzodiazepine occurs. Data are presented which indicate 2-propanol is the reductant in a two-step mechanism.**

The reduction of ketones and aldehydes by 2-propanol/aluminum isopropoxide (Meerwein-Ponndorf-Verley reduction) is a well-established synthetic procedure.[1] Although aluminium alkoxides are the most widely used catalysts, other Lewis acids have been used more recently.[2] We report here a novel and unexpected proton-catalyzed apparent Meerwein-Ponndorf-Verley type reduction of a C-N double bond.

We have found that treatment of 8-chloro-6-(2-fluorophenyl)-1-methyl-6H-imidazo[1,5-a][1,4]benzodiazepine (**1**)[3] with a solution of concentrated HCl (2.4 equiv. HCl) in 2-propanol at reflux, followed by basic aqueous work-up, yields a 2:1 mixture of 8-chloro-6-(2-fluorophenyl)-5,6-dihydro-1-methyl-6H-imidazo[1,5-a][1,4]benzodiazepine (**2**)[4] (42%) and 1,3-bis-[8-chloro-6-(2-fluorophenyl)-5,6-dihydro-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepin-4-yl]-2-propanone (**3**) as a mixture of two separable diastereomers[5] (21%) (Scheme 1). The remainder of the material balance was starting material and small amounts of unidentified compounds. When **1** was subjected to standard Meerwein-Ponndorf-Verley reduction conditions[6] (excess aluminum isopropoxide in 2-propanol at reflux or excess aluminum isopropoxide in xylenes at reflux), the starting material was recovered. The latter result was expected, as there is little if any precedent for reduction of imine double bonds under these conditions.

When **1** was treated with 2-propanol-d_8 instead of 2-propanol, under the same conditions, **2-*d*** was isolated. The position and extent of deuteration in **2-*d*** were determined by comparison of the 400 MHz ^{1}H NMR spectra ($CDCl_3$) of **2** and **2-*d***. Two one-proton doublets (J = 14.4 Hz) at 4.05 and 3.56 ppm were



Scheme 1

assigned to the protons on C4 in **2**. In **2-*d***, both doublets had collapsed to singlets, while the intensity of the signal at 4.05 ppm had decreased to one-third of its former value and the intensity of the signal at 3.56 had decreased to two-thirds of its former value. No deuterium incorporation at other sites in **2-*d*** was detected.

The simplest mechanism consistent with the observations would involve hydride transfer from 2-propanol to N5-protonated **1**, giving **2** and protonated acetone. However, AM1 calculations[7] suggest that such a reaction would be endothermic by nearly 30 kcal/mol. Even considering the uncertainty in the calculations and the possible influence of the solvent on the energetics, this figure makes the simple mechanism seem improbable. One alternative that we currently favor involves attack of 2-propanol as a nucleophile at C3[8] of N5-protonated **1**, followed by a retro-ene fragmentation to **2** and acetone. Compound **3** is then formed as a double Mannich condensation product between **1** and acetone. As shown in Scheme 1, such a mechanism would be consistent with the results observed when 2-propanol-d_8 was used as solvent. Another alternative, which was suggested by a referee, starts with attack of 2-propanol on C4 of N-5 protonated **1**. Transfer of hydride to C4 with ejection of acetone would then complete the reduction.

To distinguish between these two alternatives, AM1 calculations were performed to determine the energetic feasiblity of each pathway. While addition of 2-propanol to C4 in both a *syn* and *anti* sense (with respect to the fluorophenyl group) is slightly more favorable than addition to C3 (*syn* addition to C4 is endothermic by 4.5 kcal/mol, *anti* addition is endothermic by 9.7 kcal/mol; the corresponding values for addition to C3 are 6.0 and 12.0 kcal/mol), a comparison of the activation enthalpies for the elimination of acetone in the *syn* C3 and *syn* C4 adducts (*syn* C3 adduct = 31.2 kcal/mol; *syn* C4 adduct > 50 kcal/mol) shows that the pathway involving initial addition to C3 is more likely.

ACKNOWLEDGMENT

We thank our colleagues from the Hoffmann-LaRoche Physical Chemistry Department for their help in obtaining and interpreting the NMR, IR, and mass spectra.

REFERENCES AND NOTES

1. For leading references, see: March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1985, pp. 811, 813-814.

2. Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045 and references therein.

3. Walser, A.; Benjamin, L. E. Sr.; Flynn, T.; Mason, C.; Schwartz, R.; Fryer, R. I. *J. Org. Chem.* **1978**, *43*, 936.

4. Walser, A.; Fryer, R. I. (Hoffmann-La Roche Inc.) **U. S. Patent 4,401,597**, issued 30 Aug. 1983.

5. Compound **3**, one diastereomer (R_f in 10% MeOH/CH_2Cl_2 = 0.29): 400 MHz ^1H NMR ($CDCl_3$) ∂ 2.52 (s, 6 H, 2 X Me), 3.10-3.23 (m, 4 H, 2 X CH-C$\underline{H}_2$), 4.14 (dd, J = 4.70, 8.12 Hz, 2 H, 2 X C$\underline{H}$-CH_2), 5.01 (s, 2 H, C$\underline{H}$-N), 6.74 (s, 2 H, chloroaromatic), 6.87 (s, 2 H, 2 X imidazole), 7.05 (t, J = 9.24 Hz, 2 H, fluoroaromatic), 7.18 (t, J = 7.48 Hz, 2 H, fluoroaromatic), 7.27 (d, J = 8.33 Hz, 2 H, chloroaromatic), 7.32-7.37 (m, 2 H, fluoroaromatic), 7.41 (d, J = 8.33 Hz, 2 H, chloroaromatic), 7.47 (t, J = 7.20 Hz, 2 H, fluoroaromatic) ppm; ^{13}C NMR ($CDCl_3$) ∂ 14.2 (Me), 46.1 (CH, CH_2), 53.7 (CH), 115.6, 116.1, 123.1, 124.6, 125.4, 125.9, 126.2, 128.0, 128.7, 128.8, 129.7, 129.9, 132.2, 134.1, 134.2, 137.5, 144.9, 157.8, 162.7, 207.0 (C=O) ppm; IR ($CHCl_3$) 1487 (C=O), 2967 (N-H) cm^{-1}; HRMS (+) FAB calcd. for $C_{34}H_{33}Cl_2F_2N_6O$ (M+H, $Cl^{35}Cl^{37}$) 711.2032, found 711.2017.

Compound **3**, other diastereomer (R_f in 10% MeOH/CH_2Cl_2 = 0.25): 400 MHz ^1H NMR ($CDCl_3$) ∂ 2.53 (s, 6 H, 2 X Me), 3.09 (dd, J = 17.4, 3.29 Hz, 2 H, CH-C$\underline{H}_2$), 3.24 (dd, J = 17.4, 9.45 Hz, 2 H, CH-C$\underline{H}_2$), 4.15 (dd, J = 9.45, 3.29 Hz, 2 H, 2 X C$\underline{H}$-CH_2), 4.99 (s, 2 H, C$\underline{H}$-N), 6.78 (s, 2 H, chloroaromatic), 6.89 (s, 2 H, 2 X imidazole), 7.06 (t, J = 9.40 Hz, 2 H, fluoroaromatic), 7.19 (t, J = 7.48 Hz, 2 H, fluoroaromatic), 7.29 (d, J = 8.40 Hz, 2 H, chloroaromatic), 7.32-7.35 (m, 2 H, fluoroaromatic), 7.40 (m, 4 H, chloro- and fluoroaromatic) ppm; ^{13}C NMR ($CDCl_3$) ∂ 14.2 (Me), 45.7 (CH), 46.0 (CH_2), 53.9 (CH), 115.6, 116.1, 123.3, 124.6, 125.3, 125.8, 126.0, 128.0, 128.6, 128.8, 129.7, 129.9, 132.1, 134.0, 134.2, 137.5, 144.8, 157.7, 162.7, 206.9 (C=O) ppm; IR ($CHCl_3$) 1486 (C=O), 2965 (N-H) cm^{-1}; HRMS (+) FAB calcd. for $C_{34}H_{33}Cl_2F_2N_6O$ (M+H, $Cl^{35}Cl^{37}$) 711.2032, found 711.2024. Samples of both diastereomers for spectral comparison were prepared independently by treatment of **1** with acetone in aqueous HCl/*t*-butanol.

6. Wilds, A. L. *Org. React.*, **1944**, *2*, 178.

7. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

8. Based on AM1 calculations, *cis* geometry can be tentatively assigned to the major isomer of **2-*d***. Attack of 2-propanol at C3 to form the adduct in which the fluorophenyl and 2-propoxide groups are in a *syn* relationship is calculated to be 6.0 kcal/mol more favorable than attack to form the adduct in which the fluorophenyl and 2-propoxide groups are in an *anti* relationship (*vide supra*).

(Received in USA 13 April 1992; accepted 24 July 1992)