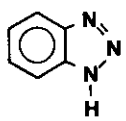
THE SYNTHESIS OF 5- AND 6-FORMYL-1-ETHOXY-1,2,3-BENZOTRIAZOLE

Dale Evans, M. Paul Serve, Balsubramaniam Ramalingam, Lisa Barna, and William Feld*

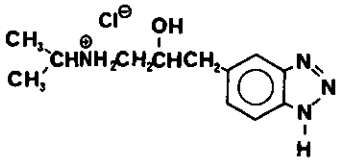
Department of Chemistry, Wright State University, Dayton, OH 45435, U.S.A.

Abstract - The bromination of 5- and 6-methyl-1-ethoxy-1,2,3-benzotriazole with NBS provided 5- and 6-bromomethyl-1-ethoxy-1,2,3-benzotriazole which were, by way of the Sommelet reaction, converted to 5- and 6-formyl-1-ethoxy-1,2,3- benzotriazole.

The 1,2,3-benzotriazole molecule 1 and its derivatives have been shown to possess a wide range of biological activity. Recently, the 1,2,3-benzotriazole derivative 2 was shown to possess significant β-adrenergic receptor blocking activity.[1] Compounds possessing the 1-hydroxy-2-aminoethyl group have been shown to be active in reducing the body's synthesis of epinephrine and thus are effective in reducing peripheral blood pressure.[2]

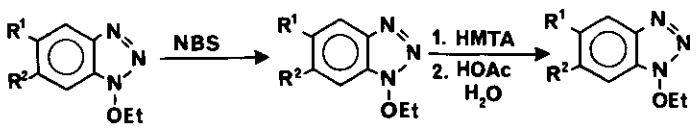


1



2

As part of our continuing effort to investigate new, biologically active 1,2,3-benzotriazole systems, we wish to report the synthesis of the previously unreported 5-formyl-1-ethoxy-1,2,3-benzotriazole (7) and 6-formyl-1- ethoxy-1,2,3-benzotriazole (8), a potential precursor of the 1-hydroxy-2-aminoethyl functional group.



3 $R^1 = CH_3$; $R^2 = H$
4 $R^1 = H$; $R^2 = CH_3$

5 $R^1 = CH_2Br$; $R^2 = H$
6 $R^1 = H$; $R^2 = CH_2Br$

7 $R^1 = CHO$; $R^2 = H$
8 $R^1 = H$; $R^2 = CHO$

Although several aldehyde preparations were examined, the procedure which proved most successful was the Sommelet reaction. Thus, treatment of 5-methyl-1-ethoxy-1,2,3-benzotriazole (3) and 6-methyl-1-ethoxy-1,2,3-benzotriazole (4) with N-bromosuccinimide yielded 5-bromomethyl-1-ethoxy-1,2,3-benzotriazole (5) and 6-bromomethyl-1-ethoxy-1,2,3-benzotriazole (6), respectively. Analytical samples of 5 and 6 were isolated by crystallization from hexane. Both ^{1}H and ^{13}C NMR spectra of 5 and 6 were consistant with the presence of the desired bromomethylbenzotriazoles. A complete ^{13}C assignment will be made in a future publication. Compounds 5 and 6 were subsequently converted to an intermediate salt by treatment with hexamethylenetetramine. Acidic hydrolysis of the intermediate salts yielded 5-formyl-1-ethoxy-1,2,3-benzotriazole (7) and 6-formyl-1-ethoxy- 1,2,3-benzotriazole (8), a potential precursor of the 1-hydroxy-2-aminoethyl functionality.

Although the preparation of 4-formyl-1-ethoxy-1,2,3-benzotriazole using the Sommelet reaction has thus far proved unsuccessful, we are presently investigating the preparation of both 4- and 7-formyl-1-ethoxy-1,2,3-benzotriazole. The failure of the Sommelet reaction to produce any of the 4-formyl derivative along with the low yields of the corresponding 5- and 6-formyl compounds may be due to the reported reduced capability of benzyl halides which are substituted with strong electron withdrawing groups to undergo the Sommelet reaction.[3]

EXPERIMENTAL

Infrared spectra were recorded on Perkin-Elmer 735-B or Nicolet 5-DX spectrophotometers. The ^{1}H and ^{13}C NMR spectra were obtained on Varian EM-360 or IBM AC-100 spectrometers. Elemental analyses were performed by Midwest Microlabs, Indianopolis, IN. Both 5- and 6-methyl-1-hydroxy-1,2,3-benzotriazole were prepared according to literature procedures.[4,5] Conversion to the 1-ethoxy derivatives was accomplished using the method of Feld.[6]

5-Formyl-1-ethoxy-1,2,3-benzotriazole (7).

To a solution of N-bromosuccinimide (0.03 moles) in 75 ml of carbon tetrachloride was added 3 (0.03 mol) and 0.01 g of benzoyl peroxide. After refluxing for 24 h, the reaction mixture was cooled and filtered. Two 20 ml washings with cold carbon tetrachloride were combined with the filtrate and the solution was evaporated. An analytical sample of 5 was obtained by crystallization of the residue from hexane: mp 75.5-77.5°C; ^{1}H NMR ($CDCl_3$) δ 1.5 (t, 3H, J= 8.0 Hz, $-CH_3$), 4.7 (s, 2H, $-CH_2Br$), 4.6 (q, 2H, J = 8.0 Hz, $-OCH_2-$), 7.3-8.0 (m, 3H, aromatic); ^{13}C NMR ($CDCl_3$) δ 13.6 ($-CH_3$), 32.9 ($-CH_2-Br$), 77.0 ($-O-CH_2-$), 109.3 (Ar, CH), 120.1 (Ar, CH), 127.4 (Ar), 129.4 (Ar, CH), 134.6 (Ar), 143.4 (Ar). Anal. calcd. for $C_9H_{10}N_3OBr$: C, 42.21; H, 3.94; N, 16.41. Found: C, 42.31; H, 3.98; N, 15.88. The residue from the previous step was

dissolved in 20 ml of chloroform and added to a solution of hexamethylenetetramine (0.03 moles) in 70 ml of chloroform. It should be noted that it appears to be imperative that a solution of the bromomethyl compound be added to a solution of hexamethylenetetramine for a successful reaction. After refluxing for 24 h, the reaction mixture was cooled and filtered. The precipitate was washed three times with 50 ml of cold chloroform, air dried, and used in the next step without further purification. The salt was dissolved in 50 ml of 50% aqueous acetic acid solution and refluxed for 2 h. On cooling, the solution was poured into 200 ml of water. The precipitate formed was recrystallized from methanol/water. The yield of 7 was 21% based on the methyl derivative: mp 92-93°C; IR (KBr) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.5 (t, 3H, $-CH_3$); 4.7 (q, 2H, $-CH_2-$); 8.0 (m, 3H, aromatic), 10.2 (s, 1H, -CHO); ^{13}C NMR ($CDCl_3$) δ 13.7 ($-CH_3$), 77.3 ($-O-CH_2-$), 109.8 (Ar, CH), 125.5 (Ar, CH), 126.7 (Ar, CH), 130.6 (Ar), 133.8 (Ar), 143.0 (Ar), 190.8 (C=O). Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.74 ; N, 21.98. Found: C, 56.27; H, 4.81; N, 22.19.

6-Formyl-1-ethoxy-1,2,3-benzotriazole (8).

To a solution of N-bromosuccinimide (0.03 moles) in 75 ml of carbon tetrachloride was added 4 (0.03 moles) and 0.01 g of benzoyl peroxide. After refluxing for 24 h, the reaction mixture was cooled and filtered. Two 20 ml washings with cold carbon tetrachloride were combined with the filtrate and the solution was evaporated. An analytical sample of 6 was obtained by crystallization of the a portion of the residue from hexane: mp 77-78.5°C; ^1H NMR ($CDCl_3$) δ 1.5 (t, 3H, J = 8.0 Hz, $-CH_3$), 4.7 (s, 2H, $-CH_2-Br$), 4.6 (q, 2H, J = 8.0 Hz, $-OCH_2-$), 7.3-8.0 (m, 3H aromatic); ^{13}C NMR ($CDCl_3$) δ 13.6 ($-CH_3$), 32.4 ($-CH_2-Br$), 76.5 ($-O-CH_2-$), 109.3 (Ar, CH), 120.1 (Ar, CH), 127.4 (Ar, CH), 129.4 (Ar), 134.6 (Ar), 143.4 (Ar). Anal. Calcd for $C_9H_{10}N_3OBr$: C, 42.21; H, 3.94; N, 16.41. Found: C, 42.19; H, 3.65; N, 15.86. The remaining residue was treated as previously described above. The yield of 8 was 15% based on the methyl derivative: mp 92-93°C; IR (KBr) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.5 (t, 3H, $-CH_3$); 4.7 (q, 2H, $-CH_2-$); 8.0 (m, 3H, aromatic), 10.2 (s, 1H, -CHO); ^{13}C NMR ($CDCl_3$) δ 13.3 ($-CH_3$), 77.3 ($-O-CH_2-$), 112.5 (Ar, CH), 121.1 (Ar, CH), 124.1 (Ar, CH), 127.8 (Ar), 135.8 (Ar), 145.9 (Ar), 190.9 (C=O). Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.74 ; N, 21.98. Found: C, 56.27; H, 4.81; N, 22.19.

ACKNOWLEDGEMENT

We acknowledge a grant from the National Science Foundation (CHE-8310555) for the purchase of a Nicolet 5-DX infrared spectrometer.

REFERENCES

1. H. Obase, N. Tatsuno, K. Gato, J. Shigenobu, Y. Kasuya, Y. Yamada, K. Fugii, and S. Yada, Chem.Pharm.Bull., 1978, 26, 1443.
2. W.C. Vineck, C.S. Aldrich, R.J. Borchardt, and G.L. Grunewald, J.Med.Chem., 1981, 24, 7.
3. S.J. Angyal, P.J. Morris, J.R. Tetaz, and J.G. Wilson, J.Chem.Soc., 1950, 2141.
4. J.W. Munson and T.G. Hodgkins, J.Heterocycl.Chem., 1978, 15, 545.
5. A.K. Macbeth and J.R. Price, J.Chem.Soc., 1936, 111.
6. W.A. Feld, R. Paessun, and M.P. Serve, J.Macromol.Sci.Chem., 1981, A 15(5), 891.

Received, 19th January, 1987