Selective Hydrogenolysis of Bis(hydroxymethyl)aromatic Compounds

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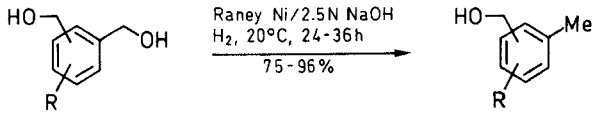
Selective hydrogenolysis of symmetric bis(hydroxymethyl)aromatic compounds has been performed over Raney nickel in alkaline solution for 24–36 h at 20°C. The yield of the corresponding monohydrogenolysis product was in the range of 75–96%. The usefulness of the reaction was demonstrated by the synthesis of 4-(bromomethyl)benzoic acid.

During our attempts to synthesize derivatives of 3,5-bis-(hydroxymethyl)-substituted benzenes, we have discovered that a single hydroxy group can be selectively removed by hydrogenolysis over Raney nickel in aqueous alkaline solution at 20°C and 1 atmosphere in high yield.

Hydrogenolysis of benzyl alcohols is a well-known reaction,[1] favored by the use of highly polar solvents.[2] Raney nickel is usually employed as the catalyst and is found to be especially active in alkaline medium.[3] By dissolving the bis(hydroxymethyl)aromatic compound in 2.5 N sodium hydroxide, hydrogenolysis proceeds rapidly at room temperature. Results of the hydrogenolysis of a series of bis(hydroxymethyl)aromatic compounds are presented in the Table. The hydrogen uptake proceeds linearly with time until about one equivalent has been consumed. At this stage the rate of uptake declines, especially in the case of 1,2- and 1,4-bis(hydroxymethyl)benzene. This appears not to be due to decreased solubility of the products in water, as suggested by the increased turbidity with time, since the same happened with 3,5-bis(hydroxymethyl)aniline, and -benzonitrile, the products of which are readily soluble in water. However, a chemisorption group (the hydroxy group[4]) is lost during the reaction, thereby decreasing the binding affinity for the metal surface. This is a possible explanation for the observed selectivity of the reaction, and the decline in the rate of hydrogen uptake with time.



R = H, CN, NH_2, CH_2NH_2

The possibility of further derivatization was demonstrated by the oxidation and bromination of 4-methylbenzyl alcohol with three equivalents of *N*-bromosuccinimide (NBS). When 4-methylbenzyl alcohol was treated with one equivalent of NBS, 4-methylbenzaldehyde was isolated as the only product, with NBS acting as an oxidation reagent for the benzylic alcohol group.[5,6] On addition of three equivalents of NBS the aldehyde was oxidized and the methyl group brominated, and 4-bromomethylbenzoic acid was obtained in 72% yield.

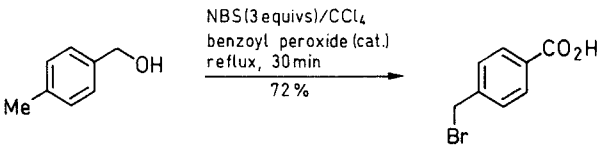
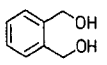
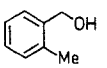
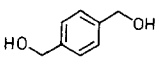
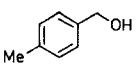
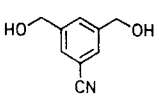
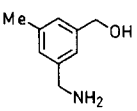
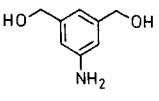
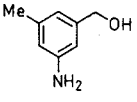


Table. Hydrogenolysis of Bis(hydroxymethyl)aromatic Compounds

Starting Material	Product[a]	Yield (%)	mp (°C)	Molecular Formula[b] or mp (°C)	^{1}H NMR (solvent/TMS)
		75	34–35	33–36[9]	$CDCl_3$: 1.60 (s, 1H), 2.36 (s, 3H), 4.70 (s, 2H), 7.20 (m, 4H)
		94–96	59–61	59–61[9]	methanol-d_4: 2.31 (s, 3H), 4.56 (s, 2H), 7.21 (2H, J = 8.85 Hz), 7.24 (2H, J = 8.85 Hz)
		82[c,d]	174–176	$C_9H_{14}ClNO$ (187.7)	D_2O: 2.34 (s, 3H), 4.13 (s, 2H), 4.60 (s, 2H), 7.21 (m, 3H)
		78[c]	217–219 (dec)	$C_8H_{12}ClN$ (157.6)	D_2O: 2.32 (s, 3H), 4.57 (s, 2H), 7.18 (m, 3H)

[a] Yield of isolated crude product. Attempts to extend the reaction to 2,6-bis(hydroxymethyl)-4-methylphenol failed.
[b] Satisfactory microanalyses obtained: C ± 0.37, H ± 0.02, Cl ± 0.33, N ± 0.16.
[c] Isolated as the hydrochloride.
[d] Three equivs of H_2 were consumed.

The method outlined here offers an easy way to convert two equivalent functional groups into two different ones in a simple two-step procedure with good overall yield.

Raney Ni was freshly prepared[8] or purchased from Aldrich. 1,2- and 1,4-Bis(hydroxymethyl)benzenes were obtained from Aldrich. 3,5-Bis(hydroxymethyl)aniline was prepared from 5-nitroisophthalic acid by catalytic hydrogenation over Pd/C followed by Fischer esterification with EtOH and reduction with $LiAlH_4$. 3,5-Bis(hydroxymethyl)benzonitrile was prepared by the Sandmeyer reaction from 3,5-bis(hydroxymethyl)aniline.

^1H NMR spectra were recorded on a JEOL FX 90 Q spectrometer with TMS as an internal standard. Melting points were recorded on Büchi melting point apparatus and are uncorrected.

Hydrogenolysis of Bis(hydroxymethyl)aromatic Compounds; General Procedure:

Activated Raney nickel in EtOH (1–1.5 g) was washed several times with 2.5 N NaOH. The bis(hydroxymethyl) substrate (0.5–1.0 g) was dissolved in 2.5 N NaOH (50 mL) and flushed with N_2 before the Raney Ni was introduced. The reaction mixture was hydrogenated for 24–36 h at 20 °C. 0.9–1.1 Equivalents of H_2 were consumed and TLC showed only one major product. EtOH (50 mL) was added to give a clear solution. The Raney Ni was filtered, and the alkaline water/EtOH solution was evaporated in vacuo to one third of the original volume, and extracted with Et_2O (3 × 75 mL). The organic phase was separated, washed with brine (50 mL), and dried ($MgSO_4$). After evaporation in vacuo the crude product was further purified by recrystallization (Table).

In the case of 3,5-bis(hydroxymethyl)aniline, and -benzonitrile, the aqueous alkaline solution was extracted continuously with CH_2Cl_2 (150 mL) for 36 h. After evaporation in vacuo and redissolution in Et_2O (20 mL), addition of dry HCl (5 mL, 4.7 M) in Et_2O afforded the hydrochloride of the amine.

Bromination and Oxidation of 4-Methylbenzyl Alcohol to 4-(Bromomethyl)benzoic Acid:

4-Methylbenzyl alcohol (0.50 g, 4.1 mmol) was dissolved in CCl_4 (50 mL). NBS (2.18 g, 12.3 mmol) and benzoyl peroxide (0.05 g) were added, and the mixture was refluxed for 30 min. After cooling to r.t., water (40 mL) was added, and the mixture stirred for another 30 min. The two phases were separated, and the organic phase was evaporated in vacuo to dryness. The residue was recrystallized from EtOH/water (2:3, 50 mL), analyzed by ^1H NMR and elemental analyses, and identified as 4-(bromomethyl)benzoic acid; yield: 0.63 g (72%); mp 221–226 °C (Lit.[10] mp 227.5–229 °C, Lit.[11] mp 224–226 °C).

(1) Klabunovskii, E.I. *Russ. Chem. Rev.* **1966**, *35*, 546.
(2) Rylander, P.N. *Aldrichimica Acta* **1979**, *12*, 53.
(3) Augustine, R.L. *Catalytic Hydrogenation*; Marcel Dekker: New York, 1965, p 31.
(4) Hydroxy- and phenyl-(aryl-) groups are some of the chemisorption groups on Raney Ni, Mitsui, S.; Imaizumi, S. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 855.
(5) Filler, R. *Chem. Rev.* **1963**, *63*, 21.
(6) Hebbelynck, M.F.; Martin, R.H. *Bull. Soc. Chim. Belg.* **1951**, *60*, 54.
(7) Hydrogenation was accomplished in a low pressure apparatus described by Wibert K.B. In *Laboratory Technique in Organic Chemistry*; McGraw-Hill: New York, 1960, p 227.
(8) Linstead, R.P.; Elvirdge, J.A., Whalley, M. *A Course in Modern Techniques of Organic Chemistry*; Butterworths London, 1955, p. 51.
(9) Aldrich *Catalog Handbook of Fine Chemicals*, 1990–91.
(10) Daub, G.H.; Castle, R.N. *J. Org. Chem.* **1954**, *19*, 1571.
(11) Rich, D.H.; Gurwara, S.K. *J. Am. Chem. Soc.* **1975**, *97*, 1575.