SHORT PAPER

J. Chem. Research (S), 2000, 266–268

An efficient conversion of *p*-hydroxybenzylic alcohols into *p*-hydroxybenzylic ethers and thioethers†

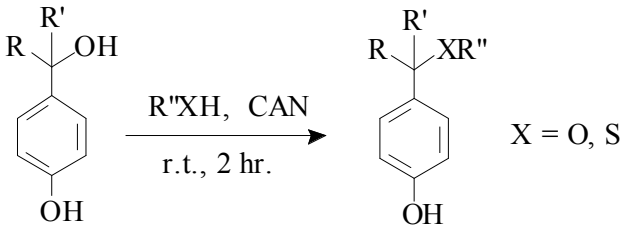
Biswanath Das*, Bollu Venkataiah and Purushotham Madhusudhan

Organic Chemistry Division-1, Indian Institute of Chemical Technology, Hyderabad-500 007, India

Different *p*-hydroxybenzylic alcohols were converted into *p*-hydroxybenzylic ethers and thioethers in excellent yields by treatment with alcohols and thiols respectively in the presence of catalytic amounts of ceric ammonium nitrate (CAN).

Radical methodology is a rapidly growing area in the field of synthetic organic chemistry. One of the most frequently used reagents for the oxidative generation of radicals is the strong one electron oxidant ceric ammonium nitrate (CAN). The latter has been used extensively[1–4] for the formation of C–C bonds *via* carbon-centered radicals. However, the application of CAN for the formation of carbon-oxygen and carbon-sulfur bonds is limited.[5,6] Previously the reagent has been used[7] for alcoholysis of allylic and tertiary benzylic alcohols. However, the conversion of primary and secondary benzylic alcohols into their corresponding ethers using CAN has not so far been reported. The application of the reagent for the formation of thioethers is also not yet known. We have utilized the reagent for a convenient conversion of *p*-hydroxybenzylic alcohols (primary, secondary and tertiary) into *p*-hydroxybenzylic ethers and thioethers by treatment with alcohols and thiols respectively.

Several *p*-hydroxybenzylic alcohols were treated with various alcohols in the presence of CAN to produce *p*-hydroxybenzylic ethers. The former on treatment with thiols under similar conditions afforded thioethers (Scheme 1, Table).



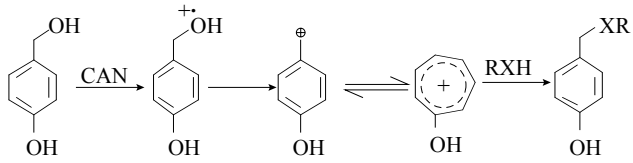
Scheme 1

The conversions were found to be highly efficient. The yields of the products were excellent. The *p*-hydroxybenzylic ether moiety has been found to be present in some bioactive molecules.[8,9] The present methodology can be utilized for the preparation of these ethers from the corresponding alcohols. Primary, secondary and tertiary *p*-hydroxybenzylic alcohols can be used. The presence of hydroxy group at the *para*-position of the starting primary and secondary benzylic alcohols is necessary as without having a hydroxyl group at the *para*-position these alcohols were found to yield no product under similar reaction conditions. Primary and secondary benzylic alcohols containing methoxy or other alkoxy groups at the *para*-position or even hydroxy group at the *ortho*-position also did not afford ethers (or thioethers) by treatment with alcohols (or thiols) in the presence of CAN. The structures of all the products were settled from analytical and spectroscopic data.

* To receive any correspondence. E-mail: biswanathdas@yahoo.com

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

The conversion of *p*-hydroxybenzylic alcohols into their corresponding ethers and thioethers may be rationalized by the generation of the benzylic cation which is formed by the one electron oxidant CAN (Scheme 2). The cation formed from primary and secondary alcohols is stabilized by the presence of the hydroxyl group at the *para*-position of the aromatic ring. However, for tertiary benzylic alcohols a hydroxyl group at the *para*-position is not necessary to form a stable benzylic cation.[7] The predicted mechanism involves C–O and C–S bond formation to produce ethers and thioethers respectively. The reaction of $^{\bullet}$OH with Ce(III) regenerates Ce(IV) and thus the conversion can be carried out with catalytic amount of CAN. However, the reaction proceeds faster with one molar equivalent of the reagent.



Scheme 2

In summary, we have developed an efficient and useful method for the conversion of *p*-hydroxybenzylic alcohols into *p*-hydroxybenzylic ethers and thioethers by reacting with alcohols and thiols respectively in the presence of CAN. The conversion is high-yielding. The methodology will find important synthetic utility.

Experimental

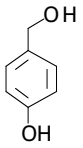
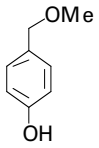
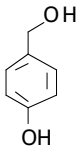
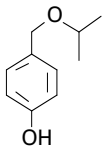
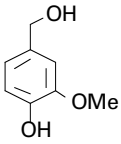
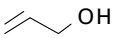
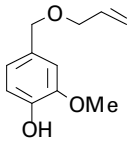
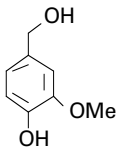
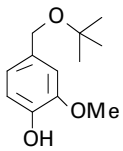
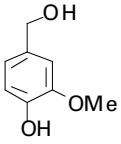
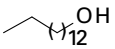
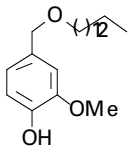
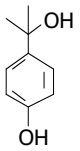
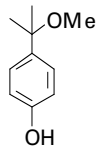
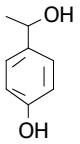
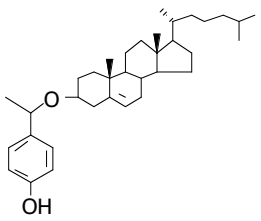
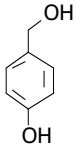
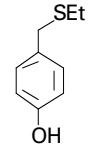
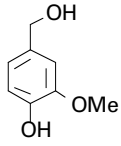
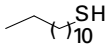
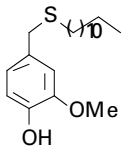
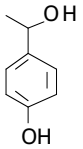
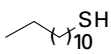
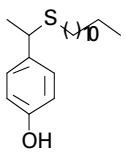
Melting points were measured in a Buchi-510 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectometer using TMS as internal standard, IR spectra on Nicolet 740 FTIR spectrophotometer and mass spectra on VG Micromass 7070 H (70 eV).

General procedure for the preparation of ethers and thioethers: The *p*-hydroxybenzylic alcohol (0.5 mmole) was dissolved in an appropriate alcohol or thiol (20 ml). The solution was cooled to 0°C. CAN (274 mg, 0.5 mmole) was added. The mixture was magnetically stirred for 2 h at room temperature. Excess reacting volatile alcohol was then removed for the preparation of an ether. The reaction mixture was poured on water (20 ml). The mixture was extracted with $CHCl_3$ (3 × 20 ml) and the concentrated extract was subjected to column chromatography over silica gel. The column was eluted with hexane-EtOAc (4:1). Removal of volatiles afforded *p*-hydroxybenzylic ether or thioether.

For preparation of the ethers and thioethers of the entry numbers 5, 7, 9, and 10, MeCN (20 ml) was used as solvent (and was removed after completion of reaction) as both the starting alcohol (0.5 mmole) and the reacting alcohol/thiol (0.5 mmole) are solids or viscous materials.

4-Methoxymethylphenol: Viscous mass; IR : υ_{max} 3288, 1615, 1520, 1187 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 7.12 and 6.65 (2H each, d, J = 8.0 Hz, Ar–H), 4.38 (2H, s, Ar–CH_2–), 3.35 (3H, s, –OMe); MS : *m/z* 138 ($M^{+\cdot}$); Anal. calcd. for $C_8H_{10}O_2$: C, 69.57; H, 7.25. Found : C, 69.68; H, 7.21.

Table 1 Conversion of *p*-hydroxybenzylic alcohols into *p*-hydroxybenzylic ethers and thioethers

Entry	Starting alcohol	Reacting alcohol/thiol	Product	Isolated yield (%)
1.		MeOH		91
2.				87
3.				87
4.				89
5.				85
6.		MeOH		81
7.		Cholesterol		72
8.		EtSH		83
9.				79
10				71

4-Isopropoxymethylphenol: Viscous mass; IR : υ_{max} 3290, 1620, 1514, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.15 and 6.65 (2H each, d, *J* = 8.0 Hz, Ar–H), 6.98 (1H, brs, –OH), 4.43 (2H, s, Ar–CH_2–), 3.75 (1H, m, –OCH<), 1.22 (6H, d, *J* = 7.0 Hz, 2 × –Me); MS : *m/z* 166 ($M^{+\cdot}$); Anal. calcd. for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found : C, 72.21; H, 8.49.

4-Allyloxymethyl-2-methoxyphenol: Viscous mass; IR : υ_{max} 3457, 1611, 1517, 1274, 1154 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.89–6.73 (3H, m, Ar–H), 5.92 (1H, m, CH_2=C*H*–), 5.60 (1H, brs, –OH), 5.28 (1H, dd, *J* = 14.0, 2.0 Hz, CH_2=CH–), 5.16 (1H, dd, *J* = 7.0, 2.0 Hz, CH_2=CH–), 4.42 (2H, s, Ar–CH_2–), 3.99 (2H, d, *J* = 4.0 Hz, OCH_2–CH=), 3.90 (3H, s, –OMe); MS : *m/z* 194 ($M^{+\cdot}$); Anal. calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found : C, 68.13; H, 7.18;

4-(*tert*-Butoxymethyl)-2-methoxyphenol: Viscous mass; IR : υ_{max} 3455, 1608, 1518, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.90–6.76 (3H, m, Ar–H), 5.73 (1H, brs, –OH), 4.38 (2H, s, Ar–CH_2–), 3.88 (3H, s, –OMe), 1.33 (9H, s, 3 × –Me); MS : *m/z* 210 ($M^{+\cdot}$); Anal. calcd. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.58. Found : C, 68.62; H, 8.55.

2-Methoxy-4-tetradecyloxymethylphenol: Viscous mass; IR : υ_{max} 3441, 1612, 1517, 1154 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.89–6.73 (3H, m, Ar–H), 5.63 (1H, brs, –OH), 4.40 (2H, s, Ar–CH_2–), 3.90 (3H, s, –OMe), 3.41 (2H, t, *J* = 7.0 Hz, –OCH_2–CH_2–), 1.70–1.55 (2H, m, –CH_2–Me), 1.43–1.25 (20H, brs, –$(CH_2)_{10}$–), 0.91 (3H, t, *J* = 7.0 Hz, –Me); MS : *m/z* 350 ($M^{+\cdot}$); Anal calcd. for $C_{22}H_{38}O_3$: C, 75.43; H, 10.86. Found : C, 75.49; H, 10.91.

4-(1-Methoxy-1-methylethyl)phenol: Viscous mass; IR : υ_{max} 3275, 1615, 1512, 1202 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.22 and 6.74 (2H each, d, *J* = 8.0 Hz, Ar–H), 5.55 (1H, brs, –OH), 3.00 (3H, s, –OMe), 1.49 (6H, s, 2 × –Me); MS : *m/z* 138 ($M^{+\cdot}$); Anal. calcd. for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found : C, 72.32; H, 8.39. %.

4-(1-Cholest-5-en-3-oxyethyl)phenol: White solid, m.p. 162–163°C (MeOH); IR : υ_{max} 3305, 1620, 1510, 1182 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.15 and 6.75 (2H each, d, *J* = 8.0 Hz, Ar–H), 5.24 (1H, dd, *J* = 12.0, 4.0 Hz, H–6), 4.78 (1H, brs, –OH), 4.52 (1H, q, *J* = 7.0 Hz, Ar–CH<), 3.06 (1H, m, H–3), 1.34 (3H, d, *J* = 7.0 Hz, –Me), 1.02 (3H, s, –Me), 0.89 (3H, d, *J* = 7.0 Hz, –Me), 0.83 (6H, d, *J* = 7.0 Hz, 2 × –Me), 0.68 (3H, s, –Me); MS : *m/z* 506 ($M^{+\cdot}$); Anal. calcd. for $C_{35}H_{54}O_2$: C, 83.00; H, 10.67. Found : C, 83.12; H, 10.58;

4-Ethylthiomethylphenol: Viscous mass; IR : υ_{max} 3282, 1614, 1518, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.08 and 6.70 (2H each, d, *J* = 8.0 Hz, Ar–H), 3.60 (2H, s, Ar–CH_2–), 2.41 (2H, q, *J* = 7.0 Hz, –SCH_2–), 1.22 (3H, t, *J* = 7.0 Hz, –Me); MS : *m/z* 168 ($M^{+\cdot}$); Anal. calcd. for $C_9H_{12}SO$: C, 64.29; H, 7.14. Found : C, 64.33; H, 7.22.

4-Dodecylthiomethyl-2-methoxyphenol: Viscous mass; IR : υ_{max} 3460, 1620, 1510, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.85–5.68 (3H, m, Ar–H), 5.42 (1H, brs, –OH), 3.90 (3H, s, –OMe), 3.60 (2H, s, Ar–CH_2–), 2.35 (2H, t, *J* = 7.0 Hz, –S*CH*$_2$–CH_2–), 1.60–1.48 (2H, m, –CH_2Me), 1.38–1.22 (18H, brs, –$(CH_2)_9$–), 0.88 (3H, t, *J* = 7.0 Hz, –Me); MS : *m/z* 338 ($M^{+\cdot}$); Anal. calcd. for $C_{20}H_{34}SO_2$: C, 71.00; H, 10.06. Found : C, 69.92; H, 10.11;

4-(1-Dodecylthioethyl)phenol: Viscous mass; IR : υ_{max} 3294, 1620, 1512, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.18 and 6.74 (2H each, d, *J* = 8.0 Hz, Ar–H), 5.17 (1H, brs, –OH), 3.86 (1H, q, *J* = 7.0 Hz, Ar–CH<), 2.25 (2H, m, –SCH_2–), 1.48 (3H, d, *J* = 7.0 Hz, >CH-Me), 1.40–1.12 (20H, brs, –CH_2)$_{10}$–), 0.90 (3H, t, *J* = 7.0 Hz, –CH_2-Me); MS : *m/z* 322 ($M^{+\cdot}$); Anal. calcd. for $C_{20}H_{34}SO$: C, 74.53; H, 10.56. Found : C, 74.44; H, 10.61.

The authors thank CSIR, New Delhi for financial assistance.

Received 15 February 2000, accepted 5 May 2000
Paper 99/161

References

1 T-L. Ho, *Synthesis*, 1973, 347.
2 H.B. Kagan and J.L. Namy, *Tetrahedron*, 1986, **42**, 6573.
3 G.A. Molander, *Chem. Rev*., 1992, **92**, 29.
4 V. Nair, J. Mathew and J. Prabhakaran, *J. Chem. Soc. Rev*., 1997, **26**, 127.
5 J-H. Ye, J. Xue, K-Q. Ling and J-H. Xu, *Tetrahedron Lett*., 1999, **40**, 1365.
6 V. Mair, T.G. George, L.G. Nair and S.B. Panicker, *Tetrahedron Lett*., 1999, **40**, 1195.
7 N. Iranpoor and E. Mothaghineghad, *Tetrahedron*, 1994, **50**, 1859.
8 S.E. Drewes and D.G. Roux, *Biochem. J*., 1965, **50**, 1859.
9 Y. Imakura, S. Kobayashi and A. Mima, *Phytochemistry*, 1985, **24**, 139. # IICT Communication No. 4318.