Regioselective Cleavage of Aromatic Methyl Ethers by Methanesulphonic Acid in the Presence of Methionine

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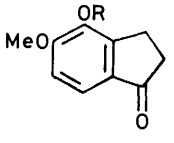
Addition of methionine as a methyl group acceptor facilitates acidolysis of aromatic methyl ethers such as anisole and *p*-methoxytoluene. Veratraldehyde and 4,5-dimethoxyindan-1-one gave isovanillin and 4-hydroxy-5-methoxyindan-1-one, respectively, indicating the usefulness of the reagent for regioselective cleavage.

We have noted previously [1] the formation of *S*-methylmethionine bismethanesulphonate salt along with phenol from methionine and methanesulphonic acid in the presence of anisole. This suggested that the methanesulphonic acid–methionine system might be applicable to the cleavage of aromatic ethers.

Treatment of anisole with 1.1 equiv. of methionine and 20 equiv. of methanesulphonic acid at room temperature overnight gave phenol in 54% yield. G.l.c. of an n-hexane extract of the reaction mixture showed that the cleavage proceeded quantitatively. *p*-Methoxytoluene gave *p*-cresol in 90% yield in the same manner. T.l.c. showed that both reactions were reasonably fast and clean. When *p*-methoxyacetophenone was treated with the same reagent at room temperature, no *p*-hydroxyacetophenone nor *S*-methylmethionine salts were detected by t.l.c. Elevation of the reaction temperature (to 60 °C) and prolongation of the reaction time (to 72 h) eventually gave *p*-hydroxyacetophenone in 30% yield, accompanied by 36% of the starting material.

Treatment of veratraldehyde with 1.1 equiv. of methionine and 20 equiv. of methanesulphonic acid at 50 °C for 24 h furnished isovanillin in 68% yield. Furthermore, 4,5-dimethoxyindan-1-one (1), treated similarly, gave 4-hydroxy-5-methoxyindan-1-one (2) in 70% yield; the product showed a methoxy-singlet at δ 3.90 in its n.m.r. spectrum [solvent $(CD_3)_2SO$]. Irradiation



(1) R = Me

(2) R = H

at the frequency of the methyl signal caused an intramolecular nuclear Overhauser effect (enhancement 22%) on the signal of an aromatic proton responsible for a component of the AB-type quartet centred at δ 7.08, confirming that the remaining methoxy-group was at position 5. These results indicate the usefulness of the methionine–methanesulphonic acid system for regioselective cleavage of aromatic ethers.

Although some sulphides other than methionine may accept alkyl groups in this reaction, methionine is preferable because of its bifunctionality, which makes isolation of the phenolic product(s) convenient.

Diethyl ether in the methionine–methanesulphonic acid system gave *S*-ethylmethionine ethyl ester, characterised as its dipicrate salt.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto microscope hot-stage apparatus. N.m.r. spectra were obtained with a Varian HA-100 spectrometer (tetramethylsilane as internal standard).

Phenol from Anisole.—A mixture of anisole (540 mg, 5 mmol), methionine (820 mg, 5.5 mmol), and methanesulphonic acid (6.5 ml, *ca.* 100 mmol) was kept at room temperature overnight, then thoroughly extracted with n-hexane. The extract was washed with a small amount of brine, dried, and evaporated to leave phenol (280 mg, 54%).

p-*Cresol from* p-*Methoxytoluene.*—*p*-Methoxytoluene (243 mg) was treated as above; the mixture was diluted with water, and extracted with ether. The extract was washed with brine, dried, and evaporated to leave *p*-cresol (198 mg, 90%).

p-*Hydroxyacetophenone from* p-*Methoxyacetophenone.*—*p*-Methoxyacetophenone (158 mg) was treated with the same reagents at 60 °C for 72 h to give *p*-hydroxyacetophenone (43 mg, 30%) and starting material (36%) by the usual work-up.

Isovanillin from Veratraldehyde.—Treatment of veratraldehyde (330 mg) with methionine (329 mg) and methanesulphonic acid (2.6 ml) at 50 °C for 24 h gave isovanillin (205 mg, 68%).

4-*Hydroxy*-5-*methoxyindan*-1-*one* (2).—A mixture of 4,5-dimethoxyindan-1-one (1) (511 mg), methionine (436 mg),

[1] H. Irie, N. Fujii, H. Ogawa, H. Yajima, M. Fujino, and S. Shinagawa, *J.C.S. Chem. Comm.*, 1976, 922; *Chem. and Pharm. Bull. (Japan).*, in the press.

and methanesulphonic acid (3.5 ml) was set aside at 22 °C for 72 h, then diluted with ice–water. The precipitate was crystallised from acetone to give *4-hydroxy-5-methoxyindan-1-one* (2) (332 mg, 70%), m.p. 198—202° (Found: C, 67.6; H, 5.6. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%); $\nu_{max.}$ (Nujol) 3 300—3 000 (OH) and 1 698 cm^{-1} (CO); δ [$(CD_3)_2$-SO] 7.13 (1 H, d, *J* 8 Hz, H-7), 7.03 (1 H, d, *J* 8 Hz, H-6), 3.90 (3 H, s, OMe), 2.95 (2 H, t, *J* 5 Hz, H_2-3), and 2.56 (2 H, t, *J* 5 Hz, H_2-2).

S-*Ethylmethionine Ethyl Ester Dipicrate Salt*.—A mixture of ether (1.1 ml), methionine (301 mg), and methanesulphonic acid (3 ml) was heated under reflux for 24 h and washed thoroughly with ether. The ether-insoluble residue was taken up in a small amount of water. A saturated solution of picric acid in water was added, to give S-*ethylmethionine ethyl ester dipicrate salt* (540 mg), m.p. 67—74° (from ethanol) (Found: C, 38.3; H, 4.1; N, 14.6; S, 4.8. $C_9H_{20}NO_2S,C_6H_2N_3O_7,C_6H_3N_3O_7$ requires C, 38.0; H, 3.8; N, 14.8; S, 4.8%).

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