

Preparation of Methoxyphenols by Baeyer–Villiger Oxidation of Methoxybenzaldehydes

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Baeyer–Villiger oxidation of methoxybenzaldehydes with *m*-chloroperbenzoic acid in boiling dichloromethane, followed by hydrolysis of the resultant formates, is shown to be a convenient method for the preparation of methoxyphenols.

In connection with our work on depsidones we required a convenient route to some dimethoxymethylphenols. The Baeyer–Villiger oxidation of the corresponding methoxybenzaldehydes appeared to be an attractive method since the aldehydes are easily available. This type of oxidation had previously been carried out by using peracetic acid under a variety of conditions.^{1–6} The reported yields were often low^{3,4} (see however ref. 7), or the use of anhydrous peracetic acid was required.^{5,6}

We now report that such oxidations can conveniently be carried out by using the commercially available *m*-chloroperbenzoic acid in boiling dichloromethane. Under these conditions the formates were usually produced in almost quantitative yield and they were hydrolysed to the phenols under mild conditions. The overall yields for the more complex compounds (see Table) were generally high.

The required benzaldehydes were easily prepared by the Vilsmeier–Haack method. The usual literature procedure⁸ often gave rise to a violently exothermic

Benzaldehyde	Time of reflux (h)	Chemical shift [τ (CDCl ₃)] of formate proton	Yield (%) of phenol
2-Methoxy	18.5	1.93	60
3-Methoxy	29	1.84	31
4-Methoxy	5	1.74	92
4-Chloro-2-methoxy-3-methyl	48	1.84	82
4-Methoxy-2,5-dimethyl	21	1.87	92
2,4-Dimethoxy	16	1.91	80
3,4-Dimethoxy	24	1.84	83
2,4-Dimethoxy-3-methyl	24	1.88	96
2,4-Dimethoxy-5-methyl	24	1.95	65
2,4-Dimethoxy-6-methyl	50	1.89	89
2,4-Dimethoxy-3,6-dimethyl	12	1.89	88
3-Ethoxycarbonyl-2,6-dimethoxy-4-methyl	90	1.88	80
2,3,4-Trimethoxy	24	1.84	83
2,4,5-Trimethoxy	48	1.92	79
2,3,4,6-Tetramethoxy	96	1.88	82

reaction. The modification described (see Experimental section) was found to be preferable.

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EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. 'Light petroleum' refers to the fraction of b.p. 58–65°. N.m.r. spectra were determined for solutions in deuteriochloroform with a Varian A-60A spectrometer.

Vilsmeier–Haack Reactions.—The Vilsmeier complex was prepared by the dropwise addition of freshly distilled phosphoryl chloride (55 ml) to dry *NN*-dimethylformamide (100 ml) during 15 min with stirring and cooling in ice. The complex was allowed to warm to room temperature and was then added during 1–1.5 h to a stirred solution of the substrate (0.5 mol) in dry *NN*-dimethylformamide (100 ml) at 100–110° (bath). Heating and stirring were then continued until t.l.c. indicated that the substrate had been consumed (usually 1–2 h). The mixture was poured onto ice-water, made just basic by addition of aqueous sodium carbonate, and exhaustively extracted with ethyl acetate; the combined extracts were washed successively with dilute hydrochloric acid, water, and saturated brine, and finally dried (Na₂SO₄). The crude product was then purified by distillation under reduced pressure or by crystallisation. The following substituted benzaldehydes were obtained: 4-methoxy-2,5-dimethyl- from 2,5-dimethylanisole in 76% yield as an oil, b.p. 85–86° at 0.4 mmHg (lit.,⁹ 147–149° at 12 mmHg), which crystallised on cooling; 2,4-dimethoxy- (99%) from *m*-dimethoxybenzene as pale yellow needles, m.p. 68–69° (from ethanol) (lit.,¹⁰ 71–72°); 2,4-dimethoxy-6-methyl- (84%) from 3,5-dimethoxytoluene as needles, m.p. 65–66° (from dichloromethane-light petroleum) (lit.,¹¹ 64–66°); 2,4-dimethoxy-3-methyl- (83%) from 2,6-dimethoxytoluene as glistening needles, m.p. 52–53° (from light petroleum) (lit.,¹⁰ 54–55°); 2,4-dimethoxy-5-methyl- (87%) from 2,4-dimethoxytoluene¹² as needles, m.p. 118–119° (lit.,¹³ 117–118°) (from methanol); 2,4-dimethoxy-3,6-dimethyl- (93%) from β -orcinol di-*O*-methyl ether¹⁴ as needles, m.p. 49–50.5° (from light petroleum) (lit.,¹⁵ 47–48°); 2,4,5-trimethoxy- (88%) from 1,2,4-trimethoxybenzene¹⁶ as needles (from water), m.p. 112–112.5° (lit.,¹⁷ 114°); and 2,3,4,6-tetramethoxy- (86%) from 1,2,3,5-tetramethoxybenzene¹⁸ as needles (from light petroleum), m.p. 87–88° (lit.,¹⁹ 88–89.5°).

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Bayer-Villiger Reactions.—The benzaldehyde (10 mmol) and *m*-chloroperbenzoic acid (40 ml) were heated under reflux in dry dichloromethane (40 ml) for the specified time. (The reaction can be conveniently followed by n.m.r. spectroscopy.) Most of the dichloromethane was removed by distillation and the residue was dissolved in ethyl acetate. The solution was washed with aqueous sodium hydrogen carbonate until effervescence ceased, and then with saturated brine, and dried (Na_2SO_4). Removal of the solvent left the crude formate which was dissolved in a little methanol and hydrolysed under nitrogen (0.5–1 h) with a slight excess of aqueous 10% potassium hydroxide at room temperature. Work-up in the usual way gave the following phenols: 2-methoxy- as prisms (from pentane), m.p. 25–26° (lit.,²⁰ 28.3°); 3-methoxy- as an oil [the aryloxyacetic acid formed needles (from light petroleum), m.p. 111.5–112.5° (lit.,²¹ 111–113°)]; 4-methoxy- as blades, m.p. 52–54° (lit.,²² 53°) (from light petroleum) [the formate formed needles, m.p. 32–34° (lit.,²³ 32–33°) (from pentane)]; 4-chloro-2-methoxy-3-methyl- as plates by sublimation at 30° and 0.5 mmHg, m.p. 44–45° (Found: C, 55.7; H, 5.2. $\text{C}_9\text{H}_9\text{ClO}_2$ requires C, 55.65; H, 5.25%), τ 2.99 and 3.27 (2H, ABq, J 8 Hz, ArH), 4.07br (1H, s, OH), 6.26 (3H, s, OMe), and 7.70 (3H, s, Me) (the preparation of the starting aldehyde will be reported in a future publication); 4-methoxy-2,5-dimethyl- as needles, m.p. 88.5–89.5° (lit.,²⁴ 90°) (from light petroleum); τ 3.44br (2H, s, ArH), 5.27br (1H, s, OH), 6.26 (3H, s, OMe), and 7.80 and 7.87 (each 3H, s, OMe); 2,4-dimethoxy- as prisms, m.p. 25–27° (lit.,²⁵ 28°) (from pentane); 3,4-dimethoxy- as plates, m.p. 79° (lit.,¹ 81.5°) (from light petroleum) [the formate formed prisms, m.p. 56° (lit.,² 57°) (from ethanol)]; 2,4-dimethoxy-3-methyl- as plates (from pentane), m.p. 32.5–34° (lit.,⁴ b.p. 132° at 15 mmHg) (Found: C, 62.55; H, 7.65. Calc. for $\text{C}_9\text{H}_{12}\text{O}_3 \cdot 0.25\text{H}_2\text{O}$: C, 62.6; H, 7.6%), τ 3.24 and 3.48 (2H, ABq, J 8.5 Hz, ArH), 4.62br (1H, s, OH), 6.22 (6H, s, OMe), and 7.82 (3H, s, Me); 2,4-dimethoxy-5-methyl- as needles (from light petroleum), m.p. 95.5–96° (lit.,⁴ 96°), τ 3.38 and 3.68

(each 1H, s, ArH), 4.74br (1H, s, OH), 6.19 and 6.28 (each 3H, s, OMe), and 7.91 (3H, s, Me); 2,4-dimethoxy-6-methyl- as plates, m.p. 103–104° (lit.,²⁵ 107°) (from dichloromethane–light petroleum), τ 3.67br (2H, s, ArH), 4.75 (1H, s, OH), 6.14 and 6.26 (each 3H, s, OMe), and 7.76 (3H, s, Me); 2,4-dimethoxy-3,6-dimethyl- as prisms, m.p. 68.5–69° (from light petroleum) (Found: C, 65.75; H, 7.65. $\text{C}_{10}\text{H}_{14}\text{O}_3$ requires C, 65.9; H, 7.75%), τ 3.61 (1H, s, ArH), 4.83br (1H, s, OH), 6.26 (6H, s, OMe), and 7.78 and 7.90 (each 3H, s, Me); 3-ethoxycarbonyl-2,6-dimethoxy-4-methyl- as plates, m.p. 83–86° (from light petroleum) (Found: C, 60.25; H, 6.9. $\text{C}_{12}\text{H}_{16}\text{O}_5$ requires C, 60.0; H, 6.7%), τ 3.51 (1H, s, ArH), 5.25br (1H, s, OH), 5.60 (2H, q, $\text{CH}_2\cdot\text{CH}_3$), 6.10 and 6.12 (each 3H, s, OMe), 7.72 (3H, s, Me), and 8.60 (3H, t, $\text{CH}_2\cdot\text{CH}_3$) [the starting aldehyde, prepared by methylation of ethyl 3-formyl-2-hydroxy-4-methoxy-6-methylbenzoate¹⁵ with methyl sulphate and potassium carbonate in *NN*-dimethylformamide, was obtained as an oil, b.p. 150–155° (bath) at 0.8 mmHg, τ –0.38 (1H, s, CHO), 3.37 (1H, s, ArH), 5.59 (2H, q, $\text{CH}_2\cdot\text{CH}_3$), 6.08 and 6.11 (each 3H, s, OMe), 7.61 (3H, s, Me), and 8.59 (3H, t, $\text{CH}_2\cdot\text{CH}_3$)]; 2,3,4-trimethoxy- as an oil, τ 3.41 (2H, apparent s, ArH), 4.67br (1H, s, OH), and 6.05, 6.11, and 6.20 (each 3H, s, OMe) [benzoate, m.p. 69° (lit.,²⁵ 70 and 80°, dimorphic) (from dichloromethane–light petroleum), τ 1.66–1.83 (2H, m, ArH), 2.25–2.64 (3H, m, ArH), 3.10 and 3.32 (2H, ABq, J 8 Hz, 6- and 5-H), 6.06 (3H, s, OMe), and 6.11 (6H, s, OMe)] (the starting aldehyde was obtained by the method of ref. 26); 2,4,5-trimethoxy- as prisms, m.p. 61–62° (lit.,²⁵ 62°) (from ether–light petroleum), τ 3.42 and 3.44 (each 1H, s, ArH), 5.53vbr (1H, s, OH), 6.17 (3H, s, OMe), and 6.20 (6H, s, OMe) [the formate formed needles (from light petroleum), m.p. 78–80° (lit.,⁶ 78–80°)]; and 2,3,4,6-tetramethoxy- as plates, m.p. 87–88° (from light petroleum) (Found: C, 56.65; H, 6.4. $\text{C}_{10}\text{H}_{14}\text{O}_5$ requires C, 56.05; H, 6.6%), τ 3.67 (1H, s, ArH), 4.33br (1H, s, OH), and 6.05 and 6.15 (each 6H, s, OMe).

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