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O-Alkylation of Phenols by Esters

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We have reported that methyl *p*-hydroxybenzoate adds to acrylonitirle and methyl acrylate in the presence of triton B or metal sodium to give compounds with cyanoethyl and methoxycarbonylethyl groups respectively.[1] In these reactions, good results were obtained below 150°C. However, when methyl methacrylate was used in place of acrylonitrile or methyl acrylate, no product was obtained under the conditions employed in the above reactions. Therefore, we carried out the reaction of potassium salt of methyl *p*-hydroxybenzoate with methyl methacrylate at 200°C, and the resulting mixture was analyzed by gas chromatography. As a result, the mixture was found to contain methyl *p*-anisiate and a dimer of methyl methacrylate. The latter is methyl 2-methyl-5-methoxycarbonyl-5-hexenoate [$CH_2{=}C(COOCH_3)CH_2CH_2CH(CH_3)COOCH_3$], whose structure was confirmed by instrumental analysis. This reaction is interesting as an *O*-alkylation of phenols.

This reaction was then also applied to other phenols, and good results were obtained there. Moreover, alkyl esters of acrylic acid and acetic acid were also found to be effective alkylating agents. The present paper will deal with the *O*-alkylation of phenols by esters.

Experimental

The NMR spectra were obtained on a Japan Electron Optics Laboratory spectrometer (JNM C-60HL), with TMS used as the internal standard. The mass spectra were obtained on a Hitachi mass spectrometer (RMU-6L), using an electron-accelerating voltage of 70eV. The IR spectrum was measured with a Japan Spectroscopic spectrometer (IRA-2). The gas chromatography was performed with a Yanagimoto apparatus (G80T).

Reaction of Potassium Salt of Methyl p-*Hydroxybenzoate with Methyl Methacrylate.* In a 300 m*l* autoclave, with an electro-magnetic stirrer, we placed 0.07 mol of potassium salt of methyl *p*-hydroxybenzoate and 0.7 mol (70.0 g) of methyl methacrylate containing 0.1 wt% of hydroquinone. After the air had been replaced by nitrogen, the mixture was heated to the prescribed temperature (it took about 30 min) and kept there for 5 hr. After cooling, the insoluble product was filtered off and the filtrate was washed with an aqueous alkaline solution and water. The mixture was found by gas chromatography to contain two main components (I and II).

The another reactions were carried out under the same conditions.

The components, I and II, were separated by gas chromatography and were analyzed by NMR, MS, IR, and elementary analysis. The results were as follows. Component I: NMR ($CHCl_3$); τ 2.98 (a part of the AB system, 2H, J=9.0 Hz), 3.07 (a part of the AB system, 2H, J=9.0 Hz), 6.07 (s, 3H), and 6.12 (s, 3H). Mass; *m/e* 168 (1.2%), 167 (9.9), 166 (M^+, 93.7), 136 (27.0), 135 (100), 107 (37.1), 92 (45.2), 77 (65.5), 64 (31.5), 63 (28.0), 50 (15.5), and 15 (12.6). Found: C, 65.18; H, 6.35%. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07%. Component II: NMR (neat); τ 3.92 (d, 1H, J=1.4 Hz), 4.45 (d, 1H, J=1.4 Hz), 6.29 (s, 3H), 6.38 (s, 3H), 7.5—7.9 (m, 3H), 8.1—8.5 (m, 2H), and 8.87 (d, 3H, J=7.3 Hz). Mass; *m/e* 200 (M^+, 1.0%), 141 (33.9), 140 (55.3), 126 (63.0), 125 (37.6), 109 (44.7), 88 (100), 81 (94.2), 59 (52.4), 57 (36.9), 56 (33.2), 53 (32.5), 41 (57.3), 39 (38.6), and 15 (57.6). IR (cm^{-1}); 1727 (s, broad), 1633 (m), and 945 (m). Found: C, 59.83; H, 8.15%. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05% On the basis of these data, these components, I and II, were identified as methyl *p*-anisiate and $CH_2{=}C(COOCH_3)$-$CH_2CH_2CH(CH_3)COOCH_3$ respectively.

Determination of Products. All the products were determined by gas chromatography, using dimethylaniline or nitrobenzene as the internal standard. The conditions were as follows: column, PEG 20M or Apiezone Grease L 2.25 m; temp. 200°C; He, 10 m*l*/min. Authentic samples of *O*-methyl products (anisole derivatives), if necessary, were prepared from phenols and dimethyl sulfate in aqueous alkali. Phenyl butyl ether was prepared by Williamson ether synthesis.

Results and Discussion

The reaction of alkali phenoxides with methyl methacrylate was carried out at 150, 200, and 250°C for 5 hr. In the gas chromatograms of those reaction mixtures, no products with retention times longer than that of methyl methacrylate were found, or if any were found, they were all minor products except for the *O*-methyl product and the dimer. Therefore, the resulting *O*-methyl product and dimer were determined by gas chromatography. The results are summarized in Table 1.

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[1] The 24th Annual Meeting of the Chemical Society of Japan, Osaka, 1971.

Table 1. O-Methylation of phenols by methyl methacrylate

R-C_6H_4-OM		MMA[a]/ RC_6H_4OM	Temp[b]	O-Methyl Product,	Dimer Yield
R	M	(mol/mol)	(°C)	Yield (%)[c]	(%)[d]
H	K	10	150	16.9	0.2
H	K	10	200	73.2	3.6
H	K	10/3	200	73.6	0.8
H	Na	10	150	8.9	0.2
H	Na	10	200	44.6	3.6
H	Na	10	250	59.6	12.9
H	Na	10/3	250	50.9	11.6
o-CH_3	K	10	200	29.4	5.1
m-CH_3	K	10	200	74.8	3.1
p-CH_3	K	10	200	84.5	6.8
p-CH_3	Na	10	200	69.4	1.8
o-Cl	K	10	200	13.9	2.7
p-Cl	K	10	200	48.9	3.7
p-$COOCH_3$	K	10	150	0.1	0.2
p-$COOCH_3$	K	10	200	11.9[e]	0.8[e]
p-$COOCH_3$	K	10	250	74.8	1.2
H	H	10	250	0.0	8.5
—	—	—	200	—	3.2[f]

a) MMA: Methyl methacrylate, 0.1 wt% of hydroquinone is contained.
b) Reaction time; 5 hr.
c) Yields are based on phenols used.
d) Yields are based on MMA used.
e) NMR, MS, and IR data are present in the experimental section.
f) MMA was heated in the absence of phenoxides.

Similar reactions were carried out in methyl acetate and acrylate in place of methyl methacrylate. O-methyl products were also obtained from both reactions, but an appreciable amount of polymer was formed in the latter and this complicated the post-treatment of the reaction mixture. The yields from both reactions were lower than those from the reactions in methyl methacrylate under comparable conditions, but the yield of the O-methyl product was not appreciably affected by the reaction temperature.

From the reactions of potassium phenoxide with ethyl methacrylate, acrylate, and acetate at 200°C for 5 hr, phenetole was obtained. Similarly, from the reaction of potassium phenoxide with butyl methacrylate and acetate, phenyl butyl ether was obtained. These results are listed in Table 2.

Patai and his co-worker reported that 2-alkoxynaphthalene was formed in the reaction of 2-naphthol (0.04 mol) with the ester (0.08 mol), in which methyl methacrylate, methyl acetate, ethyl acetate, and ethyl butyrate were included, in the presence of concentrated sulfuric acid (0.1 m*l*) at the reflux temperature.[2] The yield of 2-methoxynaphtalene from methyl acetate was 20—25%, that from methyl methacrylate was 45—50%, that of 2-ethoxynaphthalene from ethyl acetate was 40—45%, and that from ethyl butyrate, 20—25%. These results suggest that the alkylation was caused by the alkyl hydrogen sulfate formed from the ester and sulfuric acid.

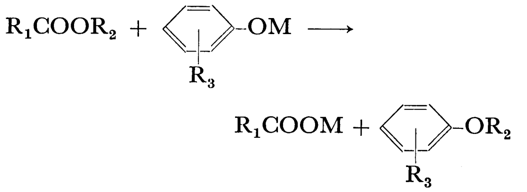
Table 2. O-Alkylation of phenols by esters

R-C_6H_4-OM		Ester[a]	Temp.[b]	O-Alkyl Product	
R	M		(°C)	Alkyl	Yield(%)[c]
H	K	AcOMe	200	CH_3	41.1
H	K	AcOMe	250	CH_3	54.6
H	Na	AcOMe	200	CH_3	54.8
m-CH_3	K	AcOMe	250	CH_3	73.6
p-Cl	K	AcOMe	250	CH_3	50.0
H	K	AcOEt	200	C_2H_5	49.4
H	K	AcOEt	250	C_2H_5	46.4
H	Na	AcOEt	200	C_2H_5	49.4
H	Na	AcOEt	250	C_2H_5	49.0
H	K	AcOBu	250	n-C_4H_9	52.8
H	Na	AcOBu	250	n-C_4H_9	22.0
H	K	MA	200	CH_3	41.6
H	K	EA	200	C_2H_5	17.9
H	K	MMA	200	CH_3	73.2
H	K	EMA	200	C_2H_5[d]	46.4
H	K	BMA	200	n-C_4H_9	29.9

a) Ester/RC_6H_4OM(mol/mol) = 10; MA, EA, EMA, and BMA are methyl acrylate, ethyl acrylate, ethyl methacrylate, and butyl methacrylate, respectively. These esters contain 0.1 wt% of hydroquinone.
b) Reaction time; 5 hr.
c) Yields are based on phenols used.
d) The structure was confirmed by NMR and IR.

Pierce and his co-worker reported that anisole was formed in the reaction of sodium phenoxide with methyl trichloroacetate at room temperature in carbon tetrachloride, although the reaction of sodium phenoxide with ethyl trifluoroacetate gave no phenetole, but only phenyl trifluoroacetate.[3]

The reaction process treated in this paper may be expressed as in Eq. (1), where R_1 is isopropenyl, ethenyl or methyl, where R_2 is methyl, ethyl, or butyl, where



$$R_1COOR_2 + R_3C_6H_4\text{-}OM \longrightarrow R_1COOM + R_3C_6H_4\text{-}OR_2 \qquad (1)$$

R_3 is a substituent on a phenyl nucleus, and where M is sodium or potassium. If the oxygen atom of phenol attacks the carbonyl carbon atom of the ester, the resulting product would be the phenyl ester; this is the reaction of sodium phenoxide with ethyl trifluoroacetate reported by Pierce and his co-worker.[3] However, in the present reactions, the oxygen atom of phenoxides must attack the alkyl carbon atom adjacent to the ether linkage and the alkyl-oxygen cleavage must occur. This mechanism is supported by the formation of phenetole and phenyl butyl ether described above. The reactions will be favored, thus, by a greater charge separation between oxygen and alkali atoms of alkali phenoxides. Therefore, the potassium salts must give better results than the sodium salts. On the contrary, the reaction will not be favored by an electron-attracting group, such as chloro and

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[2] S. Patai and M. Bentov, *J. Amer. Chem. Soc.*, **74**, 6118 (1952).

[3] A. C. Pierce and M. M. Joullié, *J. Org. Chem.*, **27**, 3968 (1962).

methoxycarbonyl groups, as an *ortho* substituent. Higher alkyl esters, such as butyl and ethyl esters, will also reduce the yield of the *O*-alkyl product. The results listed in Tables 1 and 2 are almost all consistent with the above idea.

The reaction with methyl methacrylate proceeded in two directions, the one being an *O*-methylating reaction, and the other, a dimerization of methyl methacrylate. The latter reaction has been reported by Albisetti and his co-workers; they determined the structure of the resulting dimer by a chemical technique.[4] The yield of the dimer was not affected by the molar ratio of methyl methacrylate: phenoxides (Table 1), suggesting that the two reactions—that is, an *O*-alkylation and a dimerization of methacrylate (methyl, ethyl, or butyl ester)—proceed independently of one other.

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4) C. J. Albisetti, D. C. England, M. J. Hogsed, and R. M. Joyce, *J. Amer. Chem. Soc.*, **78**, 472 (1956).