

## Regiospecificity in Reactions between Metal Phenoxides and Ketones. One-step Synthesis of *ortho*-Vinylphenols

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Ketones have shown to be useful vinylating agents of phenols. They react with aluminium phenoxides in xylene under reflux to give isomerically pure *ortho*-vinylphenol derivatives (3), in high yields.

We have recently reported<sup>1</sup> a preparatively useful procedure for the synthesis of *ortho*-vinylphenols *via* direct *C*-alkenylation of bromomagnesium phenoxides with cyclic acetals. This method is of wide applicability and gives the desired compounds in moderate to

The structures of compounds of type (3) were assigned on the basis of their spectral and elemental analyses or comparison with published data for *ortho*-vinylphenols (see Experimental section). The purity of all compounds prepared was checked by t.l.c. and g.l.c. techniques.

TABLE I

*Ortho*-Vinylation of aluminium phenoxides according to the Scheme

Phenol				Ketone		Product	Yield <sup>a</sup> (%)	B.p. (°C/Torr)	Lit. value (°C/Torr)	Ref.
R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>					
H	H	H	H	Me	H	(3a) <sup>b</sup>	56 (83)	122—123/16	50—52/0.7	3
Me	H	H	H	Me	H	(3b)	62 (95)	128—130/16	128—130/16	1
Bu <sup>t</sup>	H	H	H	Me	H	(3c)	64 (96)	128—129/16	127—129/16	1
Bu <sup>t</sup>	H	H	Me	Me	H	(3d)	70 (98)	130—131/16	130—132/16	1
H	H	H	H	Ph	H	(3e)	70 (96)	169—170/16	102—103/0.05	3
H	H	Me	H	Ph	H	(3f)	80 (90)	176—178/16	<i>c</i>	4
H	H	Cl	H	Ph	H	(3g)	61 (90)	180—184/16	<i>c</i>	4
H	H	H	H	Ph	H	(3h)	84 (96)	m.p. 117—119	m.p. 117—119	4
H	H	H	H	—C <sub>4</sub> H <sub>9</sub> —	H	(3i)	90 (98)	168—170/16	168—170/16	1
Me	H	H	H	—C <sub>4</sub> H <sub>9</sub> —	H	(3j)	91 (98)	160—161/16	158—161/16	1
H	H	H	H	—C <sub>3</sub> H <sub>7</sub> —	H	(3k)	87 (91)	169—170/16		
Bu <sup>t</sup>	H	H	H	—C <sub>3</sub> H <sub>7</sub> —	H	(3l)	85 (94)	170—173/16	168—170/16	1
H	H	H	H	—C <sub>6</sub> H <sub>13</sub> —	H	(3m)	84 (90)	164—166/16		
H	H	H	H	Me	Me	(3n) <sup>d</sup>	76 (95)	86—90/0.05		
H	H	H	H	Ph	Me	(3o) <sup>e</sup>	73 (90)	104—106/0.05	102/105/0.05 <sup>f</sup>	3

<sup>a</sup> Yields are not optimised and figures quoted refer to pure chromatographed product. Values in parentheses refer to yields based on consumed starting phenol. <sup>b</sup> 10—14% of 2'-hydroxy-2,4,4-trimethylflavan [(3a) dimer] also formed: colourless prisms from light petroleum, m.p. 96—97 °C (lit.,<sup>2</sup> m.p. 97 °C). <sup>c</sup> B.p. values not reported. <sup>d</sup> *E*:*Z* Isomer ratio = *ca.* 1:1 by <sup>1</sup>H n.m.r. analysis. <sup>e</sup> *E*:*Z* Isomer ratio = *ca.* 7:3 by <sup>1</sup>H n.m.r. analysis. <sup>f</sup> The value quoted refers to 5:2 *E*:*Z* isomer mixture.

good yields. Unfortunately use of open-chain acetals or simple ketones is precluded because of their instability under the reaction conditions.

Instead, we now show that use of aluminium phenoxides rather than bromomagnesium derivatives makes possible the application of ketones *per se* without protection of the carbonyl function. Thus, treatment of aluminium phenoxides (1) with a ketone (2) in xylene under reflux leads to the exclusive formation of 2-vinylphenols (3),<sup>†</sup> probably *via* an elimination process on the carbinol intermediate (4).

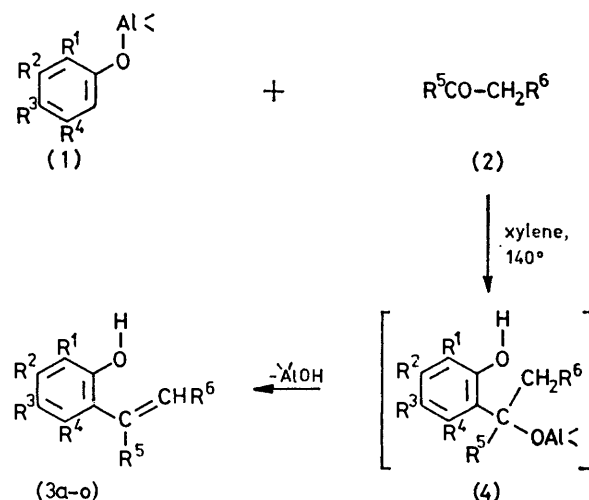
The results listed in Table 1 show that the reaction is general with respect to both the phenol and ketone. Limitations only arise in the presence of strong electron-withdrawing substituents (nitro- and cyano-phenols) and sterically hindered ketones such as camphor or β-methyl-α-tetralone.

Our technique avoids the use of an excess of any reagent and, especially in the case of cyclic ketones, it appears more efficient than the *ortho*-vinylation methods previously reported.<sup>1-6</sup>

<sup>†</sup> Extensive studies on production of 2-vinylphenol dimers *via* acid-catalysed condensation between phenols and ketones have been reported.<sup>2</sup>

Analytical samples were >99% pure as judged by these analyses.

Titanium(IV), tin(IV), and boron(III) phenoxides are slightly less reactive substrates as can be seen from



SCHEME

Table 2. Both the yields and phenol conversion diminish with their use, whereas the specificity remains excellent. By contrast, phenoxymagnesium bromide as well as alkali phenolates seem quite inert and after aqueous work-up, the starting phenol is recovered unchanged.\*

TABLE 2

*ortho*-Vinylolation of some metal phenoxides (PhOM) with cyclohexanone under comparable conditions <sup>a</sup>

Metal	Recovered phenol (%) <sup>b</sup>	Yield of (3i) (%) <sup>b</sup>	Selectivity (%) <sup>b</sup>
Al <sup>III</sup>	5	93	98
Ti <sup>IV</sup>	47	41	78
Sn <sup>IV</sup>	55	40	89
B <sup>III</sup>	77	18	78
Li	96		
Na	100		
K	99		
MgBr	97		

<sup>a</sup> Reaction system was: PhOM (20 mmol equiv.), cyclohexanone (20 mmol), and xylene (15 ml), at reflux for 20 h.

<sup>b</sup> By g.l.c. analysis.

It must be concluded, once more, that aluminium as well as other co-ordinating metal counterions in aprotic apolar solvents are very powerful 'directors' in electrophilic reactions involving phenolates.<sup>8,9</sup> It should be also emphasized that this approach serves as a convenient, high-yield, approach to a number of *ortho*-substituted phenols and their derivatives.

#### EXPERIMENTAL

All chemicals were reagent grade and were used without further purification. Aluminium hydride (0.5M in tetrahydrofuran) was prepared from LiAlH<sub>4</sub> and 100% H<sub>2</sub>SO<sub>4</sub> (0.5 mol) in tetrahydrofuran solution according to Brown's method.<sup>10</sup> Sodium and potassium phenoxides were prepared from phenol and Na or K wire in xylene solution; lithium phenoxide from phenol and BuLi in xylene; phenoxymagnesium bromide was obtained from phenol and ethylmagnesium bromide as previously described.<sup>9</sup> Titanium(IV) and tin(IV) phenoxides were prepared from phenol and titanium(IV) or tin(IV) ethoxides in non-equilibrating conditions. Boron(III) phenoxide was obtained from ROC/RIC Chem. Corp. <sup>1</sup>H n.m.r. spectra were obtained on a Varian XL-100 spectrometer; the spectra were run on saturated CDCl<sub>3</sub> solution with SiMe<sub>4</sub> as internal standard. A Perkin-Elmer 125 spectrometer was used for the i.r. spectroscopy; samples were run neat between KBr plates. The mass spectra were acquired with a Varian-Mat CH-5 mass spectrometer using 70 eV electron impact and 8 kV accelerator voltage. U.v. spectra were determined on a Cary model 14 instrument in 95% EtOH. Thin-layer chromatograms were run on glass plates coated with Merck Kieselgel F 254 in hexane-ethyl acetate (8 : 2 v/v) solvent. Merck 70-230 mesh ASTM silica gel was used for column chromatography. All microanalyses were performed by Istituto di Chimica Farmaceutica dell'Università di Parma, Italy.

*Preparation of o-Vinylphenols (3a-o) from Aluminium Phenoxides and Ketones in Xylene: General Procedure.*—To 3 ml of a 0.50M-tetrahydrofuran solution of aluminium hydride was added dropwise with stirring under nitrogen

\* 75–85% of starting cyclohexanone recovered. 15–25% of cyclohexylidenecyclohexanone also formed *via* phenolate-catalysed self-condensation of cyclohexanone.<sup>7</sup>

a solution of the phenol (20 mmol) at ambient temperature; the mixture was then allowed to reflux for 15 min. The solvent was distilled off and anhydrous xylene (15 ml) was added with vigorous stirring.† After cooling to ca. 20 °C, the ketone (20 mmol) was added and the pale yellow solution stirred at reflux for 20 h. After cooling, the mixture was quenched with aqueous NH<sub>4</sub>Cl, and extracted with diethyl ether. After drying (Na<sub>2</sub>SO<sub>4</sub>), the solvent was removed under reduced pressure and the residual oil chromatographed on silica gel (100 g, hexane-ethyl acetate, 8 : 2 v/v) to give *o*-vinylphenols (3a–o) which can be further purified by bulb-to-bulb distillation under reduced pressure. The yields and the physical properties for all the isolated compounds are shown in Table 1. Spectroscopic data for compounds (3a), (3e), (3o),<sup>3</sup> and (3b–d), (3i), (3j), (3l),<sup>1</sup> and (3e–h)<sup>4</sup> were reported in previous papers. Analytical and significant spectroscopic data for the new compounds prepared, as well as <sup>1</sup>H n.m.r. data and assignments for (3o), are reported here.

*2-Cyclopentenylphenol (3k).*—This compound had the following physical properties:  $n_D^{20}$  1.550 3;  $\nu_{\max}$  (neat) 3 280, 2 950, 1 632, 1 461, and 758 cm<sup>-1</sup>;  $\lambda_{\max}$  232 (log  $\epsilon$  3.86), 257 (3.90), and 295 nm (3.44);  $\delta$  2.04 (2 H, m, CH<sub>2</sub>), 2.60 (4 H, m, CH<sub>2</sub>), 5.66 (1 H, s, OH), 5.94 (1 H, bs, CH), 6.5–7.1 (4 H, m, aromatic); *m/e* 160 (C<sub>11</sub>H<sub>12</sub>O) (rel. intensity 100), 145 (31), 131 (35), 107 (51), and 91 (30) (Found: C, 82.5; H, 7.45. C<sub>11</sub>H<sub>12</sub>O requires C, 82.46; H, 7.55%).

*2-Cyclo-octenylphenol (3m).*—This compound had the following physical properties:  $n_D^{20}$  1.542 0;  $\nu_{\max}$  (neat) 3 250, 2 900, 1 600, 1 465, 1 445, and 754 cm<sup>-1</sup>;  $\lambda_{\max}$  220 (3.72), 252 (3.53), and 279 nm (3.12);  $\delta$  1.7 (8 H, m, CH<sub>2</sub>), 2.41 (4 H, m, CH<sub>2</sub>), 5.70 (1 H, t, *J* 8.2 Hz, CH), 6.7–7.3 (4 H, m, aromatic), 8.10 (1 H, bs, OH); *m/e* 202 (C<sub>14</sub>H<sub>18</sub>O) (40), 201 (38), 131 (37), 121 (100), 107 (26), and 91 (31) (Found: C, 83.1; H, 8.8. C<sub>14</sub>H<sub>18</sub>O requires: C, 83.12; H, 8.97%).

*2-(2-Hydroxyphenyl)but-2-ene (3n).*—This compound had the following physical properties:  $n_D^{20}$  1.527 2;  $\nu_{\max}$  (neat) 3 500, 2 940, 1 570, 1 485, 1 450, and 756 cm<sup>-1</sup>;  $\lambda_{\max}$  225 (3.87) and 278 nm (3.36);  $\delta$  1.84 (1.42 H, double q, *J* 6.5 and 1.5 Hz,  $\omega$ -CH<sub>3</sub> of *E*-isomer), 1.80 (1.57 H, double q, *J* 6.5 and 1.5 Hz,  $\omega$ -CH<sub>3</sub> of *Z*-isomer), 1.96 (1.57 H, quint., *J* 1.5 Hz,  $\alpha$ -CH<sub>3</sub> of *Z*-isomer), 1.98 (1.42 H, quint., *J* 1.5 Hz,  $\alpha$ -CH<sub>3</sub> of *E*-isomer), 5.91 (1 H, bs, OH), 5.64 (0.53 H, qq, *J* 6.5 and 1.5 Hz, =CH of *Z*-isomer), 5.84 (0.47 H, qq, *J* 6.5 and 1.5 Hz, =CH of *E* isomer), 6.5–7.3 (4 H, m, aromatic); *m/e* 148 (M<sup>+</sup>) (Found: C, 80.95; H, 8.4. C<sub>10</sub>H<sub>12</sub>O requires: C, 81.04; H, 8.16%). The n.m.r. intensities indicate that the product is a mixture containing ca. 1 part of *E*-isomer and 1 part of *Z*-isomer.

*1-(2-Hydroxyphenyl)-1-phenylpropene (3o).*—This compound had the following physical properties:  $\delta$  1.61 (2.06 H, d, *J* 7.0 Hz, CH<sub>3</sub> of *E*-isomer), 1.75 (0.94 H, d, *J* 7.0 Hz, CH<sub>3</sub> of *Z*-isomer), 5.37 (1 H, bs, OH), 5.86 (0.32 H, q, *J* 7.0 Hz, =CH of *Z*-isomer), 6.26 (0.68 H, q, *J* 7.0 Hz, =CH of *E*-isomer), and 6.3–7.5 (9 H, m, aromatic). *E* : *Z* ratio = ca. 7 : 3.

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† Conveniently, aluminium salts of phenol, 2- and 4-methylphenol, and 4-chlorophenol can be prepared directly from the phenol (melt) and aluminium turnings at 150–160 °C.

## REFERENCES

- <sup>1</sup> G. Casiraghi, G. Casnati, G. Puglia, G. Sartori, and G. Terenghi, *J. Chem. Research*, (S) 1977, 96; (M) 1977, 1123.
- <sup>2</sup> W. Baker, R. D. Curtis, and J. F. W. McOmie, *J. Chem. Soc.*, 1952, 1774; W. Baker and D. M. Besly, *ibid.*, 1940, 1103.
- <sup>3</sup> B. A. M. Oude-Alink, A. W. K. Chan, and C. D. Gutsche, *J. Org. Chem.*, 1973, 38, 1993.
- <sup>4</sup> G. Casiraghi, G. Casnati, G. Puglia, G. Sartori, and G. Terenghi, *Synthesis*, 1977, 122 and references quoted therein.
- <sup>5</sup> J. B. Niederl and E. A. Storch, *J. Amer. Chem. Soc.*, 1933, 55, 4549.
- <sup>6</sup> J. Gripenberg and T. Hase, *Acta Chem. Scand.*, 1966, 20, 1561.
- <sup>7</sup> G. Casnati, A. Pochini, G. Salerno, and R. Ungaro, *J.C.S. Perkin I*, 1975, 1527.
- <sup>8</sup> A. G. Kolka, J. P. Napolitano, and G. G. Ecke, *J. Org. Chem.*, 1956, 21, 712; G. G. Knapp, T. H. Coffield, J. P. Napolitano, H. D. Orloff, and C. J. Worrel, 'Chemistry and Application of Phenol *ortho*-Alkylation,' Seventh World Petroleum Congress Preprints, Mexico City, Mexico 1967; J. Wolters, 'Ortho-Alkylering van Fenolen,' Drukkerij Bronder Offset N.V., Rotterdam, 1970.
- <sup>9</sup> G. Casiraghi, G. Casnati, M. Cornia, A. Pochini, G. Puglia, G. Sartori, and R. Ungaro, *J.C.S. Perkin I*, 1978, 318.
- <sup>10</sup> H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, 1966, 88, 1464.