A Convenient and General Synthesis of Alkanediyl Diphenols

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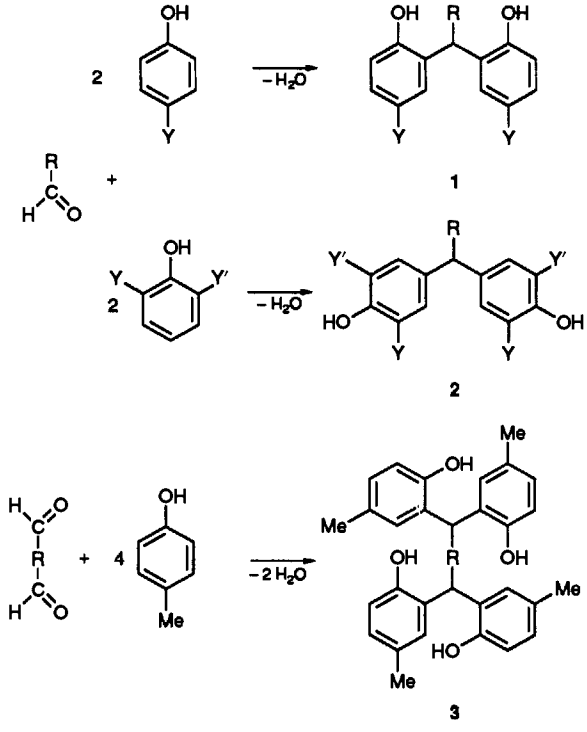
Alkanediyl diphenols are readily obtained in large quantities by the acid catalysed condensation of various aldehydes with an excess of the appropriate phenol.

The condensation of phenol with aldehydes usually involves coupling through the *ortho*- and *para*-position relative to the phenolic hydroxy group.[1] In various elegant studies, Casnati *et al.* have shown that this condensation can be restricted to the *ortho*-position by use of suitable metal phenolates in apolar solvents.[2] This pronounced regioselectivity, due to the coordination of the carbonyl oxygen to the metal cation, enabled the synthesis of linear oligomers (novolaks) of the all-*ortho* type, without the need for protection of the *para*-position.[3,4] The same conditions were also applied to the condensation of *para*-substituted phenols such as *p*-*tert*-butylphenol,[5] although less complicated procedures are possible in these cases. A recent paper by Sartori *et al.* described a similar condensation of aromatic dialdehydes with 2,4-dimethylphenol or *p*-*tert*-butylphenol using 'oxophilic metal phenolates'.[6] This prompted us to report briefly on our own results, which allow for the preparation of analogous compounds in a far simpler way and are also readily applicable to large quantities.

According to Sartori's procedure, the *p*-alkylphenol was refluxed in dry toluene first with NaH and then with $TiCl_4$, both applied in stoichiometric amounts, and refluxing was continued after the addition of a stoichiometric amount of the aldehyde. For the conversion of 5 mmol of aldehyde, toluene (180 cm^3) was used as the solvent and the final product (although formed in good yield) was purified by preparative TLC, which precludes the preparation of larger quantities.

Condensations, according to Scheme 1, can be achieved more efficiently without solvent, using an excess of the phenol and hydrochloric acid as the catalyst at temperatures between 60 and 150 °C, depending on the reactivity of the phenol. The molten phenol thus acts as solvent, suppressing by its excess various side reactions, like the formation of higher oligomers (in the case of *para*-substituted phenols with two free *ortho*-positions), the self condensation of aldehydes (aldol condensation of *e.g.* acetaldehyde, electrophilic self-substitution of *e.g.* salicylaldehyde) or even di- and tri-merisation of the quinomethanes eventually formed as intermediates.[7] The excess of phenol is easily removed (usually by steam distillation) and can be re-used. Pure products are obtained by a simple recrystallization, and quantities up to 0.5 mol can be prepared without difficulty in a single run on a laboratory scale. If no excess of phenol is required, for instance with phenols having only one reactive *ortho*- or *para*-position and with aldehydes which will not undergo aldol condensation, acetic acid may be used as a solvent to achieve a homogeneous reaction mixture.[8]

According to our experience these conditions are very general. Aliphatic aldehydes like acetaldehyde, propionaldehyde (example **1a**), lauraldehyde (decanal), isobutyric aldehyde, pivaldehyde (trimethylacetaldehyde) (example **1b**) have been used, as well as a large variety of aromatic aldehydes like benzaldehyde, *para*-substituted benzaldehydes [*p*-Cl, *p*-Me, *p*-NO_2 (examples **1c**, **2**)], salicylaldehyde and nitrosalicylaldehyde (example **1d**), pyridinecarbaldehydes, naphthaldehydes and iso- and tere-phthalaldehyde (examples **3a**, **3b**). As phenols, a variety of *para*-substituted phenols like *p*-cresol (examples **1a**, **1b**, **3a**, **3b**), *p*-*tert*-butylphenol (example **1d**), 2,4-dimethylphenol (and other 2,4-dialkylphenols), *p*-chlorophenol and *p*-nitrophenol (example **1c**) were used. In the latter case, somewhat higher reaction temperatures were necessary and the excess of *p*-nitrophenol was removed by extraction with hot water. 2,6-Disubstituted phenols can also be used under the same conditions, but if desired also with stoichiometric amounts (example **2**) and at lower temperatures. However singly *ortho*-substituted phenols would lead to a mixture of (*ortho*- and *para*-substituted) isomers. Here, the regioselectivity exerted by a metal cation could be helpful. Another advantage



	R	Y	Y′
1a	C_2H_5	Me	–
1b	CMe_3	Me	–
1c	*p*-$NO_2C_6H_4$	NO_2	–
1d	*o*-OH-*p*-$NO_2C_6H_4$	CMe_3	–
2	*p*-$NO_2C_6H_4$	Me	CMe_3
3a	*p*-phenylene	–	–
3b	*m*-phenylene	–	–

Scheme 1

of Sartori's conditions is the possibility to restrict the reaction to a single aldehyde group in dialdehydes.

In most cases, however, the acid catalysed condensation with an excess of phenol is clearly the method of choice to prepare di- or tetra-phenols of type **1**, **2** or **3** in large quantities, which are attractive as starting materials for the synthesis of calixarenes and similar macrocycles.

Experimental

Syntheses of the Diphenols **1a**, **1b** *and* **1d**.—A mixture of phenol (0.6 mol) and the required aldehyde (0.06 mol) was heated with stirring until a homogeneous melt had formed (60–70 °C for *p*-cresol and 100–110 °C for *p-tert*-butylphenol), then conc. HCl (4 cm^3) was added and the reaction continued for a further 6 h. The excess phenol was then removed by steam distillation and then the residue was recrystallized as indicated.

4,4′-*Dimethyl*-2,2′-(*propane*-1,1-*diyl*)*diphenol* **1a**. From *p*-cresol and propionaldehyde; (12.6 g, 82%) as white crystals, m.p. 154 °C [chloroform–light petroleum (40–80 °C)] (Found: C, 79.7; H, 7.9. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.86%). δ_H(200 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.2, Me), 2.13 (2 H, q, *J* 7.4, CH_2), 2.26 (6 H, s, Me), 4.28 (1 H, t, *J* 7.7, CH), 6.63 (2 H, s, OH), 6.67 (2 H, d, *J* 8.1, ArH), 6.84 (2 H, dd, *J* 8.1 and 1.8, ArH) and 7.08 (2 H, d, *J* 1.6, ArH); *m*/*z* 256 (M^+; 44%).

4,4′-*Dimethyl*-2,2′-(2,2-*dimethylpropane*-1,1-*diyl*)*diphenol* **1b**. From *p*-cresol and pivalaldehyde; (13.3 g, 78%) as white crystals, m.p. 184 °C [chloroform–light petroleum (40–80 °C)] (Found: C, 80.1; H, 8.6. $C_{19}H_{24}O_2$ requires C, 80.24; H, 8.51%); δ_H(200 MHz; $CDCl_3$) 1.14 (9 H, s, Me_3), 2.26 (6 H, s, Me), 4.44 (1 H, s, CH), 5.53 (2 H, s, OH), 6.66 (2 H, d, *J* 8.1, ArH), 6.82 (2 H, d, *J* 1.6, ArH) and 7.28 (2 H, s, ArH); *m*/*z* 284 (M^+; 6%).

4,4′-*Di*-tert-*butyl*-4″-*nitro*-2,2′,2″-*methanetriyltriphenol* **1d**. From *p-tert*-butylphenol and 2-hydroxy-5-nitrobenzaldehyde; (21.0 g, 78%) as yellow crystals, m.p. 210 °C (from glacial acetic acid) (Found: C, 72.1; H, 7.1; N, 3.0. $C_{27}H_{31}O_5N$ requires C, 72.14; H, 6.95; N, 3.12%); δ_H(200 MHz; $CDCl_3$) 1.16 (18 H, s, CMe_3), 5.47 (3 H, br s, OH), 6.11 (1 H, s, CH), 6.64 (2 H, d, *J* 8.4, ArH), 6.73 (1 H, d, *J* 8.7, ArH), 6.97 (2 H, d, *J* 2.3, ArH), 7.12 (2 H, dd, *J* 8.4 and 2.3, ArH), 7.83 (1 H, d, *J* 2.6, ArH) and 7.96 (1 H, dd, *J* 8.8 and 2.6, ArH); *m*/*z* 449 (M^+; 94%).

Synthesis of 4,4′-*Dinitro*-2,2′-(4-*nitrophenylmethanediyl*)*diphenol* **1c**.—A mixture of *p*-nitrophenol (83.5 g, 0.6 mol) and *p*-nitrobenzaldehyde (9.1 g, 0.06 mol) was heated with stirring at 80–90 °C until a homogeneous melt had formed, then conc. HCl (4 cm^3) was added, and the bath temperature increased to 150 °C. After 8 h, the excess of *p*-nitrophenol was removed by extraction with hot water and the solid residue recrystallized to give the title diphenol **1c** (14.3 g, 58%) as yellow crystals; m.p. 297 °C (glacial acetic acid) (Found: C, 55.5; H, 3.2; N, 10.1. $C_{19}H_{13}O_8N_3$ requires C, 55.48; H, 3.19; N, 10.22%); δ_H(200 MHz; [$^2H_6$]DMSO) 6.06 (1 H, s, CH), 7.04 (2 H, d, *J* 8.9, ArH), 7.40 (2 H, d, *J* 8.6, ArH), 7.57 (2 H, d, *J* 2.6, ArH), 8.12 (2 H, dd, *J* 8.9 and 2.7, ArH), 8.20 (2 H, d, *J* 8.6, ArH) and 11.41 (2 H, s, OH); *m*/*z* 411 (M^+, 9%).

Synthesis of 2,2′-*Di*-tert-*butyl*-6,6′-*dimethyl*-4,4′-(4-*nitrophenylmethanediyl*)*diphenol* **2** *without an excess of Phenol*.—To the yellow solution of *p*-nitrobenzaldehyde (9.1 g, 0.06 mol) and 2-*tert*-butyl-6-methylphenol (19.7 g, 0.12 mol) in glacial acetic acid (100 cm^3) was added conc. sulfuric acid (4 cm^3) whilst stirring at room temperature. The red suspension formed was kept at 40 °C for 4 h and then diluted with ice–water. The yellow precipitate was filtered off, washed with water, dried (over P_2O_5 *in vacuo*) and recrystallized to give the title diphenol **2** (22.4 g, 81%) as yellow crystals; m.p. 158 °C [chloroform–light petroleum (40–80 °C)] (Found: C, 75.3; H, 7.6; N, 3.1. $C_{29}H_{35}O_4N$ requires C, 75.46; H, 7.64; N, 3.03%); δ_H(200 MHz; CDC_3) 1.33 (18 H, s, CMe_3), 2.18 (6 H, s, Me), 4.72 (2 H, s, OH), 5.38 (1 H, s, CH), 6.67 (2 H, d, *J* 1.8, ArH), 6.86 (2 H, d, *J* 1.8, ArH), 7.26 (2 H, d, *J* 8.3, ArH) and 8.11 (2 H, d, *J* 8.4, ArH); *m*/*z* 461 (M^+, 34%).

Synthesis of the Tetraphenols **3a** *and* **3b**.—The reaction was carried out as described for compounds **1a**, **1b** and **1d**, using a 20-fold excess of *p*-cresol (130 g, 1.2 mol) with respect to terephthalaldehyde (for **3a**) or isophthalaldehyde (for **3b**) (8.1 g, 0.06 mol).

4,4′,4″,4‴-*Tetramethyl*-2,2′,2″2‴-(*p-phenylenemethanediyl*)-*tetraphenol* **3a**. White crystals (21.6 g, 68%), m.p. 257 °C (glacial acetic acid) (Found: C, 81.4; H, 6.5. $C_{36}H_{34}O_4$ requires C, 81.48; H, 6.46%); δ_H(200 MHz; [$^2H_6$]acetone) 2.13 (12 H, s, Me), 6.20 (2 H, s, CH), 6.66 (4 H, br s, ArH), 6.73 (4 H, d, *J* 8.1, ArH), 6.85 (4 H, dd, *J* 8.1 and 1.9, ArH), 6.99 (4 H, s, ArH) and 7.90 (4 H, s, OH); δ_H(200 MHz; $CDCl_3$) 2.17 (12 H, s, Me), 4.90 (4 H, v br s, OH), 5.80 (2 H, s, CH), 6.68 (4 H, br s, ArH), 6.70 (4 H, d, *J* 8.3, ArH), 6.92 (4 H, dd, *J* 8.1 and 1.7, ArH) and 7.09 (4 H, s, ArH); *m*/*z* 530 (M^+, 37%).

4,4′,4″,4‴-*Tetramethyl*-2,2′,2″,2‴-(m-*phenylenemethanediyl*)*tetraphenol* **3b**. White crystals (20.4 g, 64%), m.p. 86 °C (glacial acetic acid) (Found: C, 81.5; H, 6.4. $C_{36}H_{34}O_4$ requires C, 81.48; H, 6.46%); δ_H(200 MHz; [$^2H_6$]acetone) 2.10 (12 H, s, Me), 6.16 (2 H, s, CH), 6.61 (4 H, br s, ArH), 6.70 (4 H, d, *J* 8.1, ArH), 6.82 (4 H, br d, *J* 8.1, ArH), 6.91 (2 H, d, *J* 7.4, ArH), 7.01 (1 H, br s, ArH), 7.15 (1 H, t, *J* 7.8, ArH) and 7.87 (4 H, s, OH); δ_H(200 MHz; $CDCl_3$) 2.15 (12 H, s, Me), 5.00 (4 H, v br s, OH), 5.74 (2 H, s, CH), 6.61 (4 H, d, *J* 2.0, ArH), 6.66 (4 H, d, *J* 8.2, ArH), 6.90 (4 H, dd, *J* 8.1 and 1.9, ArH), 7.00 (1 H, s, ArH), 7.02 (2 H, br d, *J* 7.5, ArH) and 7.25 (1 H, t, *J* 7.5, ArH); *m*/*z* 530 (M^+, 43%).

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft and the European Community for financial support.

References

1 With formaldehyde, this condensation is the basic reaction in the formation of phenolic resins: A. Knop and L. A. Pilato, *Phenolic Resins*, Springer, Berlin, Heidelberg, 1985; A. Knop, V. Böhmer and L. A. Pilato, *Phenol–Formaldehyde Polymers* in *Comprehensive Polymer Science*, eds G. C. Eastmond, A. Ledwith, S. Russo and P. Sigwalt, Pergamon Press, Oxford, 1989, vol. 5.
2 G. Casnati, G. Casiraghi, A. Pochini, G. Sartori and R. Ungaro, *Pure Appl. Chem.*, 1983, **55**, 1677; and references cited therein.
3 G. Casiraghi, G. Sartori, F. Bigi, M. Cornia, E. Dradi and G. Casnati, *Makromol. Chem.*, 1981, **182**, 2151.
4 G. Casiraghi, M. Cornia, G. Ricci, G. Casnati, G. D. Andreetti and L. Zetta, *Macromolecules*, 1984, **17**, 19.
5 G. Casiraghi, M. Cornia, G. Ricci, G. Balduzzi and G. Casnati, *Makromol. Chem.*, 1983, **184**, 1363.
6 G. Sartori, F. Bigi, R. Maggi, A. Pstorio, C. Porta and G. Bonfanti, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1879.
7 C. Bavoux, M. Perrin, H. Goldmann and V. Böhmer, *J. Chem. Soc., Perkin Trans. 2*, 1989, 2059; and references cited therein.
8 The analogous acid catalysed condensation of 4-substituted resorcinols is possible in ethanol: M. Tabatabai, W. Vogt and V. Böhmer, unpublished results, see also *Tetrahedron Lett.*, 1990, **31**, 3295.

Paper 4/06289B
Received 14*th October* 1994
Accepted 15*th November* 1994