Regioselective Mono-*O*-alkylation of some Pyrocatechoxide Dianions

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In dimethyl sulphoxide the dianions derived from 2,3- or 3,4-dihydroxybenzaldehydes and 4-methylesculetin afford products corresponding to alkylation at the less acidic site while the monoanions give the isomeric phenols.

It seemed to us that a method for the regio-controlled partial *O*-alkylation of polyphenolic compounds could be devised for substrates where the hydroxy groups differ in acid strength, provided the factors governing *C*-alkylation of mono- and di-carbanions[1] operate in phenoxides also. In dimethyl sulphoxide (DMSO),† *O*-alkylation of some pyrocatechoxide dianions indeed gave products not directly accessible through routine

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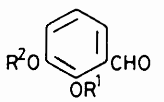
† The use of lithium di-isopropylamide–tetrahydrofuran gave inferior results.

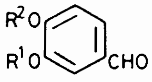
Table 1. Alkylation of catechols in DMSO.[a]

Pyrocatechol	Alkyl halide	NaH: pyrocatechol	Product[b]	% Yield[c]	M.p. C t/°C
(1)	$PhCH_2Cl$	2.2	**(2)**	65(80)	84—85
(1)	$PhCH_2Cl$	1.1	**(3)**[d]	44(50)	90—91
(1)	MeI	2.2	**(4)**	58(85)	43—44
(1)	MeI	1.1	**(5)**	52(66)	113—115
(6)	$CH_2=CHCH_2Cl$	2.2	**(7)**	42	66—67
(6)	$CH_2=CHCH_2Cl$	1.1	**(8)**	36	Oil
(6)	MeI	2.2	**(9)**	52	78—79
(6)	MeI	1.1	**(10)**	50	105—106
(11)	MeI	3.0	**(12)**	48	212—213
(11)	MeI	1.1	**(13)**	38	200—201

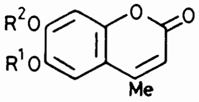
[a] The pyrocatechol (0.018 mol) was stirred with the calculated amount of NaH in DMSO (5 ml) for 1 h and the alkyl halide (0.018 mol) added. The mixture was worked up after 17 h at 25 °C. [b] All new compounds gave satisfactory analysis and ^1H n.m.r. data. Known compounds were compared with authentic samples. [c] Yields are for pure products isolated after crystallisation or chromatography; yields based on n.m.r. analysis (where applicable) of crude mixtures are shown in parentheses. T.l.c. and n.m.r. analysis always revealed negligible amounts of isomeric phenols but the original pyrocatechols and dialkylation products were present (*ca.* 10%). [d] Also obtained on benzylation using aqueous sodium hydroxide.



(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = CH_2Ph$
(3) $R^1 = CH_2Ph$, $R^2 = H$
(4) $R^1 = H$, $R^2 = Me$
(5) $R^1 = Me$, $R^2 = H$

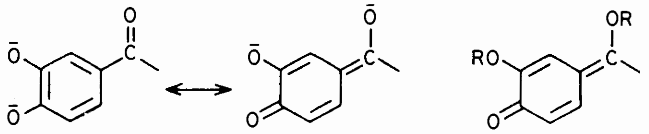


(6) $R^1 = R^2 = H$
(7) $R^1 = CH_2CH{=}CH_2$, $R^2 = H$
(8) $R^1 = H$, $R^2 = CH_2CH{=}CH_2$
(9) $R^1 = Me$, $R^2 = H$
(10) $R^1 = H$, $R^2 = Me$



(11) $R^1 = R^2 = H$
(12) $R^1 = Me$, $R^2 = H$
(13) $R^1 = H$, $R^2 = Me$

(monoanion) procedures (Table 1). The one-step preparation of **(12)**, earlier[2] obtained from 4-methylesculetin **(11)** through a benzylation–methylation–debenzylation sequence (32% overall yield), illustrates the utility of this procedure in natural product synthesis.



(14) (15)

Scheme 1

Since the use of only 1 mol. equiv. of the alkylating agent led to yields in excess of 50%, carbonyl *O*-alkylation [**(14)**→**(15)**, Scheme 1] followed by hydrolysis during aqueous work-up seems untenable as the major reaction course.[3] The observed regio-selectivity may thus be attributed to greater reactivity of the anionic site which is not stabilised through carbonyl conjugation.

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References

1 H. C. House, 'Modern Synthetic Reactions,' 2nd edn., Benjamin, California, 1972, ch. 9.
2 L. Velluz and G. Amiard, *Bull. Soc. Chim. Fr.*, 1948, 1109.
3 As suggested for the formation (17.4%) of (7) in the reaction of (6) with allyl iodide in tetrahydrofuran–NaH; A. Reitz, M. A. Avery, M. S. Verlander, and M. Goodman, *J. Org. Chem.*, 1981, **46**, 4859.