A General Route to Substituted Naphthols

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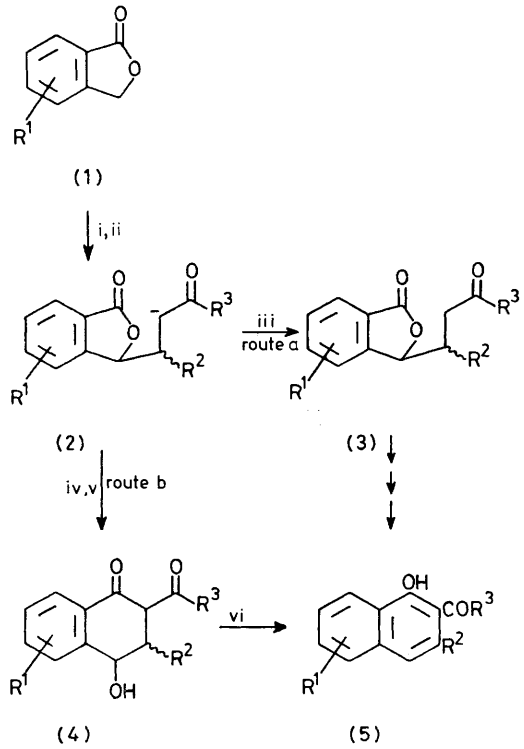
Summary A new synthetic method for the homologation of phthalides is described and exemplified by the formation of substituted naphthols.

THE aglycone portion of numerous naturally occurring phenols consists of linear di-, tri-, and tetra-cyclic systems containing two or more aromatic rings.[1] Such systems

include antibiotics and anti-tumour agents such as adriamycin,[2] daunorubicin,[3] carminomycin,[4] the olivomycins,[5] and chromomycins.[5,6] Synthetic routes to polycyclic phenols are limited but a recent publication outlined a proposed strategy for the linear extension of phenols using a six-stage process.[7] Herein we describe a comparable, but shorter, method for the production of naphthols from substituted benzenes.

Treatment of phthalides (**1**) with bases under protic conditions is known to generate species capable of undergoing addition to conjugated systems such as quinones and this has been developed as a means for obtaining precursors in the synthesis of naphthacenes.[8] A limitation of this process is the need to oxidise subsequently the phthalide–quinone conjugates [*e.g.*, related to (**3**)] and then treat them with Lewis acid catalysts in order to effect ring formation (Scheme, route a). The need to effect the cyclisation step

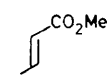
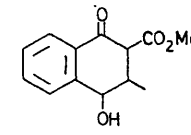
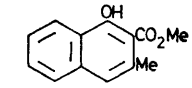
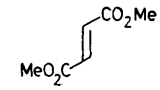
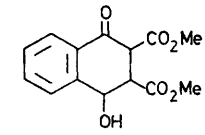
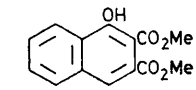
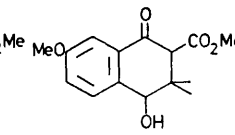
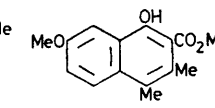
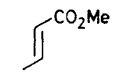
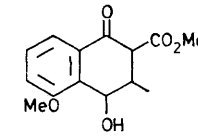
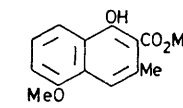


SCHEME. i, Base; ii, $R^2CH{:}CH{\cdot}COR^3$; iii, protic solvent; iv, aprotic solvent; v, H_3O^+; vi, CF_3CO_2H or BF_3–Et_2O.

under Lewis acid conditions could be avoided, it was argued, if the initial base-catalysed reactions could be carried out in an aprotic manner (Scheme, route b). Under these conditions the conjugate anion (**2**) would react by attacking the lactone ring before protonation, hence generating tetralone structures of the type (**4**), even though the related process, involving butenolides, is not reported to give cyclic products.[9] Subsequent dehydration should afford the naphthol (**5**). This alternative method proved feasible, thus considerably extending the scope of the earlier work.

Examples (see also Table) include the following reactions. Treatment of the phthalide (**1**; $R^1 = H$) with lithium di-isopropylamide in tetrahydrofuran at −40 °C generated the orange carbanion which reacted with added acrylonitrile.

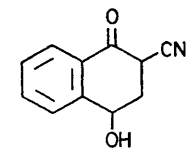
TABLE

(1) R^1	Reactant	Products[a] (Yield/%)	Naphthol (Yield/%)
H		 (48)	 (68)
H		 (44)	 (82)
5-MeO		 (41)	 (51)
3-MeO		 (58)	 (43)

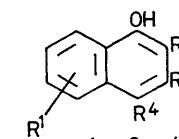
[a] As mixtures of epimers.

After acid work-up and ethereal extraction a solid was isolated (40%), which was identified as the hydroxytetralone (**6**); brief treatment of this with trifluoroacetic acid effected an almost quantitative dehydration to afford 2-cyano-1-hydroxynaphthalene (**7**), m.p. 176—177 °C (lit.[10] m.p. 178 °C).

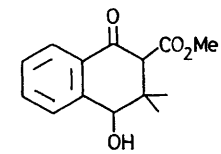
When methyl senecioate was employed the initial cycloadduct (**8**) underwent acid-catalysed dehydration with concomitant methyl migration yielding the naphthol (**9**)



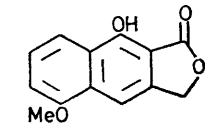
(6)



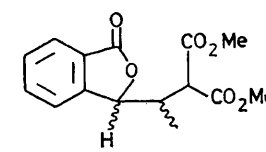
(7) $R^1 = R^3 = R^4 = H$; $R^2 = CN$
(9) $R^1 = H$; $R^3 = R^4 = Me$; $R^2 = CO_2Me$



(8)



(11)



(10)

(35%).† Use of dimethyl ethylidenemalonate afforded an epimeric mixture of the uncyclised adducts (**10**) (45%), presumably because the related anions of the type (**2**) are too stable to open the lactone ring.

An interesting ramification of this process is the reaction of 3-methoxyphthalide with 2-butenolide, in which the product, after dehydration, was the naphthol lactone (**11**). After protection of the phenolic group this could be used for further aromatic ring homologation.

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† All new compounds were characterised by spectral, microanalytical, and/or mass spectral means.

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