

Simple One-step Route to Substituted Anthraquinones

By PETER G. SAMMES*

(Department of Chemistry, The City University, St. John Street, London EC1V 4PB)

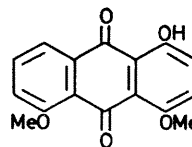
and DAVID J. DODSWORTH

(Departamento de Química, Universidad Simón Bolívar, Caracas, Venezuela, Apartado Postal 80659)

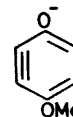
Summary A new synthetic method for the preparation of functionalized anthraquinones is described.

ALTHOUGH we have previously described the use of phthalide anions under aprotic conditions for the preparation of substituted naphthols,¹ recent communications on closely related topics²⁻⁴ have prompted us to report our preliminary results on a simple one-step procedure for the preparation of substituted anthraquinones.

Recent methods available for the preparation of synthetic precursors of these systems include the conjugate



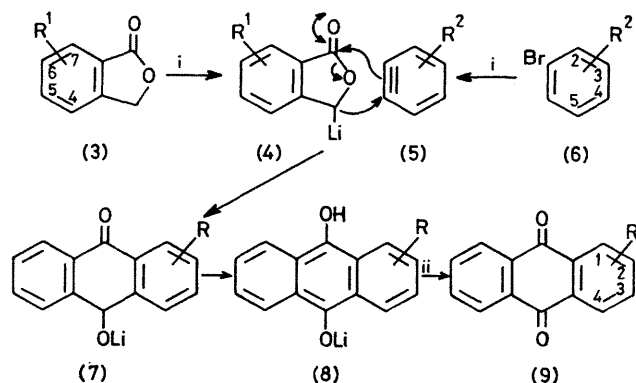
(1)



(2)

addition of acyl anions to $\alpha\beta$ -unsaturated esters⁵ and a recently described eight-stage method⁴ which gave (1) in an overall yield of 18.3% from *N*-phenyl-*m*-anisamide. We

describe herein a shorter method for the preparation of substituted anthraquinones (9), that involves the nucleophilic addition of lithium phthalides (4) to benzyne (5); the overall reaction sequence is indicated in the Scheme.



SCHEME. i, lithium di-isopropylamide; ii, H_3O^+ , air. For compound (9):

- a; R = H
 b; R = 1-MeO
 c; R = 2-MeO
 d; R = 2,3-(MeO)₂
 e; R = 1,4-(MeO)₂
 f; R = 2-Me
 g; R = 1,2-benzo
 h; R = 1-HO, 4-MeO

Addition of the lithium phthalide (4) to the benzyne (5), generated *in situ* by reaction of the substituted bromobenzene with lithium di-isopropylamide, would be expected to give the 10-hydroxyanthrone derivative (7). Formation of (7) is presumed to occur *via* nucleophilic addition of the phthalide anion to the benzyne followed by intramolecular cyclization with concomitant opening of the lactone ring. It is known that 10-hydroxyanthrones (7) are converted into the enol form (8) under basic conditions;⁹ acidification of the reaction medium followed by air oxidation of the unstable anthrahydroquinone (8) would thus give the anthraquinone (9). The experimental procedure is exemplified by the preparation of anthraquinone (9a). Treatment of phthalide (1 equiv.) with lithium di-isopropylamide (2.2 equiv.) in tetrahydrofuran at -60°C gave the orange carbanion. At -45°C the solution of the carbanion was treated with bromobenzene (1 equiv.) in tetrahydrofuran. After warming to room temperature the reaction mixture was stirred in contact with air. Acid work-up and chloroform extraction gave a mixture from which was

readily separated anthraquinone (9a), m.p. $269\text{--}271^\circ\text{C}$ (sublimation) (mixed m.p. $273\text{--}275^\circ\text{C}$), in 28.5% yield. When the lithium phthalide was treated with 2 equiv. of benzyne the yield of isolated anthraquinone increased to 74.5%. The use of substituted phthalides and substituted benzyne precursors permits the preparation of a wide range of substituted anthraquinones; examples include the following reactions (see also Table). Treatment of 5,6-di-

TABLE. Preparation of the anthraquinones (9)

(3) R ¹	(6) R ²	Product	% Yield ^a
H	H	(9a)	28.5 (74.5 ^b)
4-MeO	H	(9b)	51.4 ^b
H	4-MeO	(9c)	44.7
5,6-(MeO) ₂	H	(9d)	32.3
H	2,5-(MeO) ₂	(9e)	46.3
H	4-Me	(9f)	40.0
H	2,3-benzo	(9g)	61.7
H	2-HO, 5-MeO	(9h)	25.8

^a All with 1 equiv. of benzyne precursor except where stated.
^b 2 equiv. of benzyne precursor used.

methoxyphthalide (1 equiv.) with lithium di-isopropylamide gave the corresponding lemon-green carbanion which reacted with the benzyne precursor (1 equiv.) to give 2,3-dimethoxyanthraquinone (9d), m.p. $248\text{--}250^\circ\text{C}$ (lit.,⁸ 237°C), in 32.3% yield. Similarly the reaction of lithium phthalide with 1,4-dimethoxybenzyne gave 1,4-dimethoxyanthracene (9e), m.p. $175\text{--}177^\circ\text{C}$ (lit.,⁹ $170\text{--}171^\circ\text{C}$), in 46% yield. The aryne generated from 1-bromonaphthalene also reacted with lithium phthalide to give 1,2-benzanthraquinone (9g), m.p. $166\text{--}167^\circ\text{C}$ (lit.,¹⁰ 168°C). Interestingly, lithium phthalide (4) reacted with the anionic benzyne (2), generated from 2-bromo-4-methoxyphenol, to give the hydroxyanthraquinone (9h), m.p. $170\text{--}171^\circ\text{C}$ (lit.,¹¹ $167\text{--}168^\circ\text{C}$).

In all cases the anthraquinones were readily identified and separated either by direct crystallisation from the reaction mixture or by chromatography; yields have not been optimised. The preparation of anthraquinones from phthalides and related species would seem to offer a general reaction of wide scope. Since the addition of carbanions to arynes occurs regioselectively, further control on the eventual substitution pattern of the anthraquinone is also possible with this method.

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