Substituted Naphthalenes and Naphthols from Benzynes and Dienolate Anions

By **Peter G. Sammes*** and **Timothy W. Wallace**, Chemistry Department, Imperial College, London SW7 2AY

A direct method for the preparation of substituted naphthalenes and naphthols from benzynes and dienolate anions is described. The naphthols are thus formed from conjugated esters and the naphthalenes from conjugated ketones. The scope and mechanism of the reaction have been briefly explored. Reaction between the dienolate anion from mesityl oxide and the benzyne from 2-(or 3-)bromoanisole produces 8-methoxy-1,3-dimethylnaphthalene in a regioselective manner.

SEVERAL studies on the participation of benzynes in cycloaddition reactions have been made.[1] For additions to conjugated, unsaturated, unhindered aldehydes, reaction across the carbonyl group is favoured,[2] whereas with conjugated ketones [3] and esters [4] addition proceeds by competing [2 + 2] and [2 + 4] processes involving the double bond.

Until recently the reaction of benzynes with dienolate anions remained unexplored, in contrast to a thorough study having been conducted on their reaction with enolate anions.[5,6] One reason for this omission was the previous lack of knowledge of how to form stable dienolate anions, but conditions for this have now been defined.[7] In this paper results of an introductory survey of the reaction are reported.[8] Other work in this area has also appeared recently.[9]

A typical reaction sequence was as follows. Formation of the dienolate anion, with lithium di-isopropylamide as base, was accomplished at −5 to −10 °C. An excess of the complex base sodium t-butoxide–sodamide [5,10] was then added and the mixture was cooled to −60 °C before addition of the benzyne precursor. The mixture was then allowed to warm slowly to room temperature in order to generate the benzyne intermediate. In this manner, for example, methyl 3-methylbut-2-enoate and benzyne produced 3-methyl-1-naphthol [11] (2; R^1 = H, R^2 = OH) in moderate (37%) yield. A slight improvement was observed when hexamethylphosphoric triamide was used as co-solvent (42%; see Table).

The relatively low yield observed for this reaction is partly offset by the directness of the method. For example, 5,8-dimethoxy-3-methyl-1-naphthol (2; R^1 = OMe, R^2 = OH), previously prepared by a seven-step synthesis,[12] was obtained by this method in 27% yield. Other examples of naphthol formation are noted in the Table.

Reaction of dienolate anions with benzynes

Benzyne precursor	Carbonyl compound	Product	Yield (%)	Conditions *
1-Bromo-2,5-dimethoxybenzene	(1; R = Me)	(2; R^1 = MeO, R^2 = Me)	34	*a*
			35	*b*
	(1; R = OMe)	(2; R^1 = MeO, R^2 = OH)[12]	27	*c*
Bromobenzene	(1; R = OMe)	(2; R^1 = H, R^2 = OH)[11]	37	*c*
			42	*d*
			<20	*e*
	MeC(OMe):CH·COMe	3-Methoxy-1-methylnaphthalene	7	*c*
			13	*f*
	MeC(OMe):CH·CO_2Me	3-Methoxy-1-naphthol	19	*c*
2-Bromoanisole	(1; R = Me)	(4)	42	*a*
3-Bromoanisole	(1; R = Me)	(4)	20	*a*

* [a] Sodamide. [b] Sodamide–sodium t-butoxide. [c] Lithium di-isopropylamide–sodamide–sodium t-butoxide. [d] As for *c*, plus hexamethylphosphoric triamide (HMPA) (1 ml). [e] As for *c*, with lithium t-butoxide in place of sodamide and sodium t-butoxide. [f] Lithium di-isopropylamide–sodamide–HMPA.

The reaction could also be applied to the preparation of substituted naphthalenes. Formation of the dienolate anion (1; R = Me) from mesityl oxide followed by reaction with the aryne from 2,5-dimethoxybromobenzene produced 1,4-dimethoxy-5,7-dimethylnaphthalene (2; R^1 = OMe, R^2 = Me) (27%). The ketonic side products noted in this reaction were not further investigated.

An interesting result was obtained with the 2- and 3-bromoanisoles. Both produced 8-methoxy-1,3-dimethylnaphthalene (4), indicating formation of the same aryne intermediate (3), which has precedent.[13] The substituent effect of the methoxy-group appears to

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[12] R. G. Cooke and H. Dowd, *Austral. J. Sci. Res.*, 1952, **5A**, 760.
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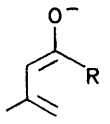
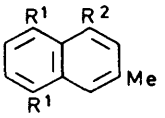
increase the acidity of the hydrogen atoms in the *ortho*-positions relative to those in the *meta*- and *para*-sites.



(1)



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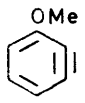

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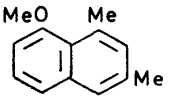

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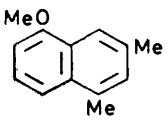
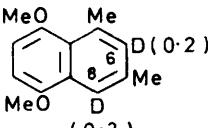


(5)



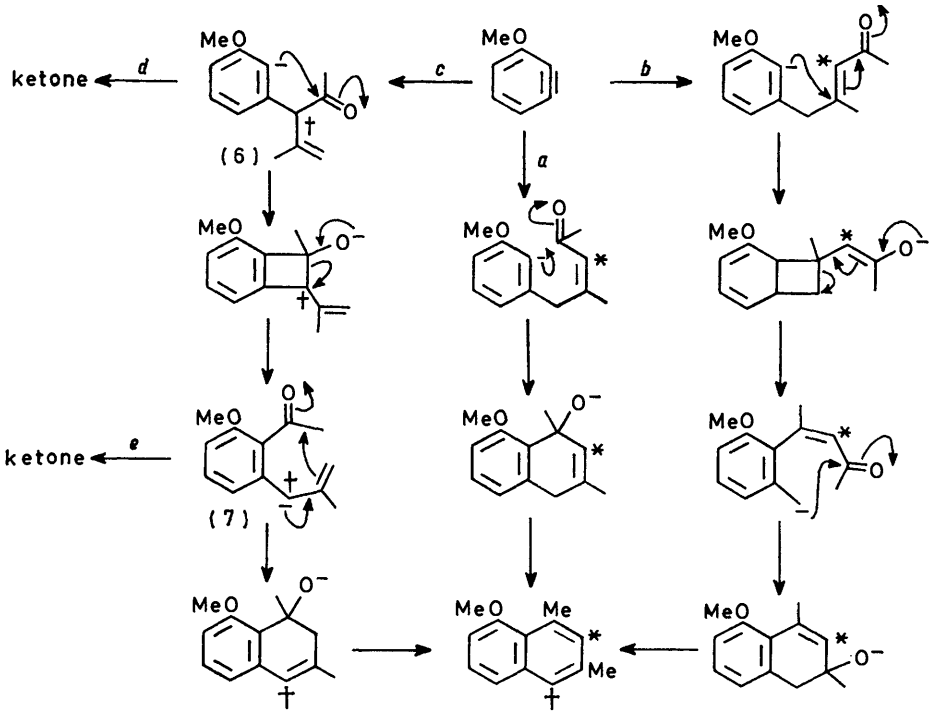
(9) (0·3)

As a result 3-bromoanisole reacts rapidly, *via* loss of the 2-H atom, producing the benzyne (3). That 3-bromoanisole produces a lower yield of the naphthalene (4) than the 2-isomer might also reflect this substituent effect of the methoxy-group. Self-condensation of the aryne produced in the former (*meta*) case is more likely to compete with reaction with the dienolate anion than in the case of the *ortho*-isomer, for which aryne formation is slower.

A regiospecific reaction is indicated in this example since none of the isomer (5) was observed. The assignment of structure to the product (4) was mainly based on ^{1}H n.m.r. comparison with the naphthalene (2; R^1 = OMe, R^2 = Me) (see Experimental section). The orientations of nucleophilic additions to benzynes of the type (3) have been rationalised by examining the transition states involved.[14] Introduction of electron-withdrawing groups, such as the methoxy-substituent, directs nucleophilic attack into the *meta*-position.[15] These mechanistic ideas are incorporated into Scheme 1.

Attack by the dienolate anion (1; R = Me) from the γ-position (Scheme 1, path a or b) can eventually lead to the observed product, as can, in this case, initial attack from the α-position (path c). In related work, on the reaction of the dienolate anion of mesityl oxide with benzyne itself, Caubère and his colleagues [9] have also isolated ketones, produced by alternative reactions of intermediates such as (6) and (7) (*e.g.* paths d and e, Scheme 1).

Previous work [16] on the reactivity of dienolate anions suggested that initial attack by the α-position (Scheme 1, path c) should be favoured over γ-attack, steric factors permitting. In an initial attempt to study the relative importance of α- and γ-attack in this instance, the deuteriated mesityl oxide (8) was prepared (Scheme 2)



SCHEME 1

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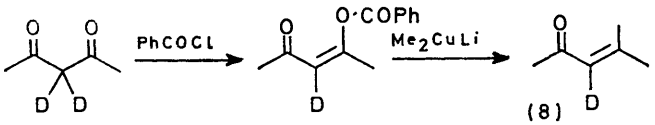
[16] Ref. 7; M. Tanabe and D. F. Crowe, *J.C.S. Chem. Comm.*, 1973, 564, and references cited therein.

(the route shown gave material with only 80% deuterium at the labelled position). Scheme 1 summarises the expected results. Attack by either path a or b should



SCHEME 2

lead to label in the asterisked position; initial α-attack (path c) should produce material labelled in the alternative site (†).

For convenience in interpretation of the results, the benzyne from 2,5-dimethoxybromobenzene was selected for reaction with the dienolate anion of the ketone (8). ^1H N.m.r. analysis of the derived naphthalene (9), confirmed by a mass spectral estimation, showed that it contained an excess of 0.5 deuterium atoms, distributed in the ratio 0.3 : 0.2 in positions 8 and 6, respectively. Although the reasons for the loss of the label during reaction were not explored the result indicates that, although α-attack appears to predominate, γ-attack forms an important part of the reaction pathway.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 157G spectrophotometer and u.v. spectra with a Unicam SP 800 instrument for ethanolic solutions. ^1H N.m.r. spectra were recorded with a Varian T60 instrument for solutions in deuteriochloroform (tetramethylsilane as internal reference). An A.E.I. MS9 instrument was used for the mass spectra. T.l.c. was carried out on silica gel GF_{254} with chloroform–petroleum mixtures as eluant.

Typical reaction conditions (see Table) are exemplified.

3-*Methoxy*-1-*naphthol* (*Conditions* c).—Di-isopropylamine (0.85 g) in tetrahydrofuran (THF) (5 ml) under dry nitrogen at −10 °C was treated with butyl-lithium in hexane (2.1M; 4 ml). After 15 min methyl 3-methoxybut-2-enoate (0.80 g) in THF (5 ml) was added, followed, after a further 2 h, by sodamide (0.34 g) and sodium t-butoxide (0.21 g). The mixture was cooled to −70 °C before addition of bromobenzene (0.24 g) in THF (4 ml), and the mixture was then allowed to reach ambient temperature overnight. Hydrochloric acid (2N) was added and the mixture extracted with chloroform (3 × 25 ml). Isolation of the product from the extract by preparative t.l.c. gave the *title compound* (50 mg, 19%) as a viscous oil, which was rapidly oxidised in air. The freshly eluted material had *m/e* 174 (100), 131 (80), 104 (39), and 103 (46%) (Found: M^+, 174.0678. $C_{11}H_{10}O_2$ requires *M*, 174.0681); τ 1.8—2.0 (1H, m, aromatic), 2.2—2.9 (3H, m, aromatic), 3.24 (1H, d, *J* 2 Hz, H-2 or H-4), 3.47 (1H, d, *J* 2 Hz, H-4 or H-2), 4.5br (1H, s, OH), and 6.13 (3H, s, Me).

1,4-*Dimethoxy*-5,7-*dimethylnaphthalene* (2; R^1 = OMe, R^2 = Me) (*Conditions* b).—Sodamide (0.66 g) and sodium t-butoxide (0.36 g) in THF (10 ml) at 0 °C were stirred for 0.5 h before dropwise addition of mesityl oxide (0.54 g) in THF (5 ml). After a further 1 h, 1-bromo-2,5-dimethoxybenzene (0.32 g) in THF (5 ml) was added. The mixture was stirred at room temperature for 90 h, then quenched (2N-HCl) before extraction of the title compound into chloroform and isolation by preparative t.l.c. The sublimed *naphthalene* (0.114 g, 35%) had m.p. 56—58°; $\nu_{max.}$ 1 625, 1 610, 1 275, 1 245, 1 205, 1 135, 1 100, and 1 055 cm^{-1}; $\lambda_{max.}$ 220, 245s, 247.5, 300i, 309, 323.5, and 338 nm (ε 31 400, 19 400, 19 600, 5 300, 6 400, 6 300, and 5 700), τ 2.13br (1H, s, H-8), 2.92br (1H, s, H-6), 3.34 (2H, s, H-2 and -3), 6.05 and 6.14 (6H, 2 × MeO), 7.15 (3H, s, 5-Me), and 7.55 (3H, s, 7-Me) (Found: C, 77.7; H, 7.6. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.5%).

The reaction was also carried out under conditions a, with sodamide (0.64 g) alone, the yield being similar (34%).

8-*Methoxy*-1,3-*dimethylnaphthalene* (4) (*Conditions* a).—Mesityl oxide (0.52 g) in THF (5 ml) was added dropwise to a stirred suspension of sodamide [from sodium (0.45 g)] in THF (10 ml) under dry nitrogen at room temperature. The mixture was then stirred for a further 30 min, *o*-bromoanisole (0.32 g) in THF (2 ml) was added, and the mixture was again stirred at room temperature, for 39 h. The solution was quenched (2N-HCl; 50 ml) before extraction into dichloromethane. Preparative t.l.c. gave the *title compound* (132 mg, 42%), m.p. (after sublimation) 58—59°, $\nu_{max.}$ 1 615, 1 585, 1 280, 1 240, 1 095, 855, 805, and 755 cm^{-1}, $\lambda_{max.}$ 225, 294.5, 306.5, 312.5, 321, and 327 nm (ε 51 800, 7 100, 4 800, 4 900, 1 400, and 4 700), τ 2.62br (1H, s, H-5), 2.97br (1H, s, H-7), 2.6—3.4 (3H, m, aromatic), 6.12 (3H, s, MeO), 7.13 (3H, s, 1-Me), and 7.59 (3H, s, 3-Me) (Found: C, 83.6; H, 7.7. $C_{13}H_{14}O$ requires C, 83.8; H, 7.6%).

The reaction was repeated on the same scale with *m*-bromoanisole. After a similar reaction time the products were isolated, to give the naphthalene (4) (66 mg, 20%).

3-*Methoxy*-1-*methylnaphthalene* (*Conditions* c).—Di-isopropylamine (0.85 g) in THF (5 ml) under nitrogen was treated with butyl-lithium in hexane (2.1M; 4 ml). After 15 min, 4-methoxypent-3-en-2-one (0.89 g) in THF (5 ml) was added, followed, after 3 h, by sodamide (0.32 g) and sodium t-butoxide (0.28 g). The mixture was cooled to −70 °C before addition of bromobenzene (0.24 g) in THF (2 ml). The mixture was then allowed to warm to room temperature during 15 h, before work-up in the usual manner. The *title compound* was isolated as a solid (17 mg, 7%) by sublimation; m.p. 48—49°, $\lambda_{max.}$ 231, 265, 275, 286, 315, and 330 nm (ε 57 000, 3 700, 4 500, 3 700, 1 400, and 1 800); τ 1.8—2.8 (4H, m, 5-,6-,7-, and 8-H), 2.94br (2H, s, 1- and 3-H), 6.07 (3H, s, MeO), and 7.34 (3H, s, Me) (Found: C, 83.5; H, 7.0. $C_{12}H_{12}O$ requires C, 83.7; H, 7.0%).

A reaction in which the sodium t-butoxide was omitted and bromobenzene in THF (2 ml) and HMPA (1 ml) were added (conditions f) afforded the naphthalene (33 mg, 13%).

4-*Methyl*[3-$^2H_2$]*pent*-3-*en*-2-*one*.—Acetylacetone was treated with ^2H_2O containing a trace of sodium deuterioxide, extracted with chloroform, isolated, and re-exchanged with fresh ^2H_2O. N.m.r. and mass spectral examination showed that the material was >90% dideuteriated. A sample (12 g) was benzoylated with triethylamine and benzoyl chloride in THF (10 ml) at room temperature for 2 h. Water (100 ml) was added and the mixture extracted with ether. The extract was washed with H_2O (50 ml) and saturated NaCl solution (50 ml) before drying and distilling. The fraction of b.p. 125—127° at 1.2 mmHg was collected. The 4-benzoyloxy[3-^2H]pent-3-en-2-one (13.3 g, 56%) was shown to be a mixture of *E*- and *Z*-isomers and to contain *ca.* 80% deuterium in the vinylic position by n.m.r. spectroscopy.

A sample of this material was used as follows. Me_2CuLi, prepared as a suspension of copper(I) iodide (13.14 g) and

methyl-lithium (2.3M in ether; 60 ml) in ether (70 ml) was added to the benzoate (12.8 g) in ether (100 ml) under nitrogen at −70 °C. The temperature was then allowed to rise to −20 °C during 30 min before addition of 2N-HCl (150 ml), followed by water (100 ml). The ether layer was isolated and worked up as usual to give the ketone as a brown liquid. This was purified as its semicarbazone before liberating the labelled mesityl oxide with aqueous oxalic acid. The product was purified by distillation to produce the title compound (1.53 g, 25%), b.p. 132—135° [stored over molecular sieve (3A)]. The mass spectrum showed *m/e* 100 (17), 99 (100), and 98 (35%). Integration of the n.m.r. spectrum showed the presence of *ca.* 20% of the residual vinylic protons.

Preparation of the Labelled Naphthalene (9).—This was carried out by procedure *a*, with the labelled mesityl oxide (0.5 g), 1-bromo-2,5-dimethoxybenzene (0.35 g), and sodamide [from sodium (0.46 g)] in THF (7 ml). Isolation in the manner described above gave the deuteriated naphthalene (118 mg, 34%), τ (CCl_4) 2.13br (0.7H, s, 8-H) and 3.00br (0.8H, s, 6-H), the rest of the spectrum being similar to that for the unlabelled material. Its mass spectrum showed *m/e* 219 (4%), 218 (25), 217 (97), and 216 (100) [unlabelled material, *m/e* 219 (0), 218 (trace), 217 (13), and 216 (100)].

We thank the S.R.C. for a research studentship (to T. W. W.) and Professor Caubère for correspondence on this work.

[5/048 *Received*, 8*th January*, 1975]