Effects of Solvent and of the Alkylating Agent upon Alkylation of the 2,6-Di-*t*-butyl-4-methylphenoxide Anion

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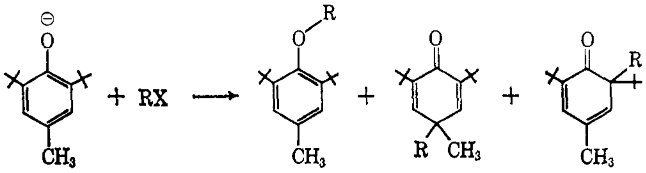
Alkylation of salts of 2,6-di-*t*-butyl-4-methylphenol gave mixtures of ethers, 2,5-cyclohexadienones, and 2,4-cyclohexadienones. The 2,4-cyclohexadienones lost *t*-butyl groups readily to give *o*-alkylated phenols. Allylic halides gave higher carbon/oxygen alkylation ratios and higher *ortho*/*para* ratios than saturated alkyl halides. Changing the solvent from dimethyl sulfoxide (DMSO) to *t*-BuOH increased the carbon/oxygen ratio and the *ortho*/*para* ratio.

In the course of our recent work on dienone–phenol rearrangements of 2,6-di-*t*-butylcyclohexadienones[1] we studied some alkylations of salts of 2,6-di-*t*-butyl-4-methylphenol. The 2,6-di-*t*-butylphenoxide anions are particularly suitable subjects for investigation of reactions of ambident anions, since the steric effects of the *t*-butyl group cause a high percentage of the reaction to occur at the *para* position. This is true even when the alkylating agents are saturated alkyl halides,[2] which have not been observed to react at the *para* position of other phenoxide anions. However, only one previous study of carbon/oxygen alkylation ratios in reactions of 2,6-di-*t*-butylphenoxide anions has been reported.[2] In this paper we record some further observations about these reactions.

The alkylations were run at room temperature in DMSO using sodium hydride or potassium *t*-butoxide as the base, or in *t*-butyl alcohol with potassium *t*-butoxide. As was expected, alkylations were complete in a few minutes in DMSO solution (except for reactions with isopropyl bromide), while reaction in *t*-butyl alcohol took several days.

Excellent yields of alkylated products were obtained when allyl bromide, crotyl bromide (*trans*-1-bromo-2-butene), or ethyl iodide were employed as the alkylating agents (see Table I). With isopropyl bromide, however, elimination was the principal reaction (particularly in DMSO), and it was necessary to repeat the reaction several times to obtain reasonable yields of alkylagtion products. While reactions in DMSO were homogeneous, reactions in *t*-butyl alcohol were carried out in stirred slurries of potassium 2,6-di-*t*-butyl-4-methylphenoxide. Since the phenoxide does have appreciable solubility in *t*-butyl alcohol, however, it seems most probable that the actual alkylations occur in solution, rather than on the surface of the solid salt.[3] That this is so was confirmed by one reaction with allyl bromide which was carried out in sufficient *t*-butyl alcohol to dissolve all the components. No change in the ratio of reaction products occurred.

TABLE I

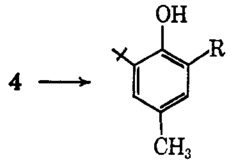


1 2 3 4

RX	Solvent	% alkylation	% **2**[a]	% **3**[a]	% **4**[a]
C_2H_5I	DMSO	81	77	23	0
C_2H_5I	*t*-BuOH	83	19	73	8
i-C_3H_7Br	DMSO	25[b]	60	40	0
i-C_3H_7Br	*t*-BuOH	60[b]	20	76	4[c]
$CH_2{=}CHCH_2Br$	DMSO	88	11	65	23
$CH_2{=}CHCH_2Br$	*t*-BuOH	84	3[d]	50	47
$CH_3CH{=}CHCH_2Br$	*t*-BuOH	91	2[d]	48	50
$CH_3CH{=}CHCH_2Br$	DMSO	94	9	70	22
$CH_2{=}CHCH_2Br$[e]	*t*-BuOH	22	2[d]	47[d]	52[d]

[a] Per cent of alkylated product. [b] Total alkylation after repeated reaction. See Experimental Section. [c] Estimated by ultraviolet, assuming ϵ_{320} 4000. [d] Analysis by v.p.c. [e] Reaction carried out in dilute, homogeneous solution.

Alkylation took place at all possible sites on the phenoxide anion—at the oxygen atom to give ethers (**2**), the *para* carbon to give cross-conjugated cyclohexadienones (**3**), and at the *ortho* carbons to give linearly conjugated cyclohexadienones (**4**). The presence of **4** in the crude reaction mixtures could be demonstrated by their ultraviolet maxima at 320 mμ. Attempted isolation of **4** by chromatography on silica gel or neutral alumina, or by v.p.c., resulted in loss of *t*-butyl groups to give *o*-alkylated phenols (**5**).[4,5] Careful chromatography on basic alumina, however, did allow a minute yield (0.005% of **4**, R = $CH_2{-}CH{=}CH_2$) to be isolated from one run.



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As has been observed with other, less hindered, phenoxide ions,[6] the ratio of alkylation on carbon to alkylation on oxygen is much higher with allyl bromide and crotyl bromide than with saturated halides. A particularly interesting phenomenon is that the allylic halides gave much higher percentages of alkylation at the *ortho*

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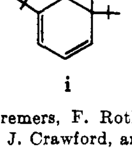
(1) B. Miller and H. Margulies, *Tetrahedron Letters*, **No. 22**, 1727 (1965); B. Miller, *ibid.*, **No. 22**, 1733 (1965).

(2) N. Kornblum and R. Seltzer, *J. Am. Chem. Soc.*, **83**, 3668 (1961).

(3) Alkylation on solid surfaces can give quite different results from alkylation in solution: N. Kornblum and A. P. Lurie, *ibid.*, **81**, 2705 (1959).

(4) B. Miller, *J. Org. Chem.*, **30**, 1964 (1965).

(5) In contrast, dienone i was reported to be stable to chromatography.[2]



i

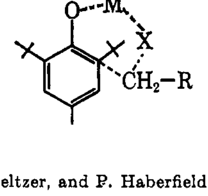
(6) *E.g.*, L. Claisen, F. Kremers, F. Roth, and E. Tietze, *Ann.*, **442**, 210 (1925); D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *J. Am. Chem. Soc.*, **80**, 1391 (1958); D. Y. Curtin and R. J. Fraser, *ibid.*, **80**, 6016 (1958).

carbons, rather than the less hindered *para* carbons, than do the saturated halides. This effect has not been observed in other systems, since saturated halides do not attack carbon atoms of less hindered phenoxide ions in homogeneous, relatively polar, reaction mixtures. It is far from clear why allylic halides should give higher *ortho/para* ratios. This may result, in part, from the lower selectivity of the more reactive allylic halides, but attack at oxygen is not similarly favored.

Ethyl iodide and isopropyl bromide give much higher percentages of carbon alkylation in *t*-butyl alcohol than they do in DMSO. It does not appear likely that this is due to the lower dielectric constant of *t*-butyl alcohol,[7] since the homogeneous reactions of **1** with triethoxyphosphonium bromide or triisopropoxyphosphonium bromide in benzene solution gave only oxygen alkylation.[4] Kornblum, Berrigan, and Le Noble[8] have pointed out the importance of the hydrogen-bonding power of the solvent in determining the positions at which allylic halides react with phenoxide ions. Solvents capable of forming strong hydrogen bonds with the anion appear to block attack at the oxygen atom by "selective solvation," and to cause alkylation at carbon instead. Although allylation of sodium phenoxide in *t*-butyl alcohol was found to occur exclusively on oxygen,[8] the much more basic 2,6-di-*t*-butyl-4-methylphenoxide ion might be expected to form strong hydrogen bonds with even such weak acids as *t*-butyl alcohol.[9] It may be noted that this represents the first evidence that alkylation of phenols at carbon by *saturated* halides can be encouraged by the use of hydrogen-bonding solvents.

Alkylations with allyl and crotyl bromide similarly show an increased tendency for carbon alkylation in *t*-butyl alcohol, although the low percentages of oxygen alkylation even in DMSO make the effect less dramatic. In reactions of allylic halides, the principal effect of changing the solvent from DMSO to *t*-butyl alcohol is to increase the *ortho/para* alyklation ratio. The *ortho/para* ratio in the reactions of ethyl iodide and isopropyl bromide is also raised in *t*-butyl alcohol solution, although the much lower over-all tendency for the saturated halides to give *ortho* alkylation rather obscures the effect.

A possible explanation for the effects of solvents on the *ortho/para* ratio can be found in the work of Kornblum, Seltzer, and Haberfield.[7] They suggested that in solvents of low dielectric constant alkylation at carbon is facilitated by the attraction of the metal ion of the ion pair for the halide ion being produced in the reaction. A diagram of such a transition state for the alkylation of **1** is shown below. While Kornblum and his co-workers intended this argument to explain a preference for carbon *vs.* oxygen alkylation, its applicability in determining the *ortho/para* alkylation ratio is clear.



It should be noted that this argument does not conflict with our views on the importance of hydrogen bonding by the solvent, since hydrogen bonding to the anion of an ion pair could be quite significant.

Experimental Section[10]

Reaction of Potassium 2,6-Di-*t*-butyl-4-methylphenoxide with Allyl Bromide.—2,6-Di-*t*-butyl-4-methylphenol (44.0 g., 0.20 mole) was added to a solution of 22.4 g. (0.20 mole) of potassium *t*-butoxide in 400 ml. of *t*-butyl alcohol. The slurry was stirred for 0.5 hr. Allyl bromide (40.0 g., 0.33 mole) was added and the mixture was stirred until it became neutral to indicator paper (*ca.* 65 hr.). The precipitated salts were then dissolved in water and the mixture was extracted with methylene chloride. The methylene chloride layer was washed several times with water and dried over magnesium sulfate, and the solvent was evaporated to give 54.0 g. of light brown liquid, which was chromatographed on Fisher basic alumina (activity I). Elution with petroleum ether gave a ketonic fraction which was shown by ultraviolet spectra to be a mixture of 2,5- and 2,4-cyclohexadienones. Further elution with petroleum ether gave a fraction consisting of 2,6-di-*t*-butyl-4-methylphenol and a 2,4-cyclohexadienone. Finally, elution with methylene chloride gave 2-allyl-6-*t*-butyl-4-methylphenol. A slurry of the first fraction with silica gel in petroleum ether was stirred overnight and the product was rechromatographed on alumina to give 4-allyl-2,6-di-*t*-butyl-4-methylcyclohexadien-1-one[4] (21.9 g., 0.0843 mole, 42%), and 2-allyl-6-*t*-butyl-4-methylphenol.[4] Careful chromatography of the second fraction on basic alumina (activity III) gave, on elution with pentane, 3.1 g. of 2,6-di-*t*-butyl-4-methylphenol (0.0141 mole, 7.1%) and 26 mg. of 2-allyl-2,6-di-*t*-butyl-4-methylcyclohexadien-1-one as a yellow oil, $\lambda_{\max}^{\mathrm{MeOH}}$ 320 mμ (ϵ 3720).

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.1; H, 10.8. Found: C, 83.3; H, 10.8.

Further elution with chloroform gave 2-allyl-6-*t*-butyl-4-methylphenol. The combined yield of this phenol was 16.1 g. (0.079 mole, 39%).

The reactions of potassium 2,6-di-*t*-butyl-4-methylphenoxide with *trans*-1-bromo-2-butene and with ethyl iodide in *t*-butyl alcohol were carried out as described above, except that the linearly conjugated cyclohexadienones could not be isolated. The new products of these reactions were **2,6-di-*t*-butyl-4-ethyl-4-methylcyclohexadien-1-one**, m.p. 35.5–36° (*Anal.* Calcd. for $C_{17}H_{28}O$: C, 82.2; H, 11.3. Found: C, 82.5; H, 11.7.), and **2-*t*-butyl-6-ethyl-4-methylphenol**, obtained as a colorless oil (*Anal.* Calcd. for $C_{13}H_{20}O$: C, 81.2; H, 10.5. Found: C, 81.3; H, 10.7.).

The other products obtained (**2**, $R = C_2H_5$ and $R = CH_2—CH{=}CH—CH_3$; **3**, $R = CH_2—CH{=}CH—CH_3$; and **5**, $R = CH_2—CH{=}CH—CH_3$) were identified by comparison with previously prepared samples.[4]

Reaction of Potassium 2,6-Di-*t*-butyl-4-methylphenoxide with Isopropyl Bromide in *t*-Butyl Alcohol.—The reaction was carried out as described above, except that 100 g. of isopropyl bromide replaced the allyl bromide. After stirring for 6 days, the reaction mixture was neutral. Potassium *t*-butoxide (11.2 g.) was added and the mixture was stirred for 15 min. Isopropyl bromide (50 g.) was added, and stirring was continued for an additional 6 days. Potassium *t*-butoxide (6 g.) and isopropyl bromide (25 g.) were added as before. After stirring 3 more days, the reaction mixture was worked up as above to give **isopropyl 2,6-di-*t*-butyl-4-methylphenyl ether**[4] (15%), **2,6-di-*t*-butyl-4-methylphenol** (32%), and **2,6-di-*t*-butyl-4-isopropyl-4-methylcyclohexadien-1-one**, m.p. 22–22.5° (43%).

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.3; H, 11.5. Found: C, 82.1; H, 11.1.

Alkylations in Dimethyl Sulfoxide.—Sodium hydride (0.1 mole) was dissolved in DMSO in a nitrogen atmosphere, and 0.1 mole of 2,6-di-*t*-butyl-4-methylphenol was added. The alkyl halide (allyl bromide, 1-bromo-2-butene, or ethyl iodide) (0.1 mole)

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(7) N. Kornblum, R. Seltzer, and P. Haberfield, *J. Am. Chem. Soc.*, **85**, 1148 (1963).

(8) N. Kornblum, P. J. Berrigan, and W. J. Le Noble, *ibid.*, **85**, 1141 (1963).

(9) Solvation of sodiodiphenylacetophenone in *t*-butyl alcohol causes appreciable alkylation on carbon rather than oxygen: H. D. Zook and T. J. Russo, *ibid.*, **82**, 1258 (1960).

(10) All melting points are corrected. Microanalyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. V.p.c. analyses were carried out on a 2% XE60 column at 160°.

was added. After 10 min., methylene chloride was added and the mixture was extracted several times with water and dried over magnesium sulfate. The solvent was evaporated and the products were chromatographed as usual.

The reaction with isopropyl bromide was carried out as described above. V.p.c. analysis of the initial reaction, however, showed that only *ca.* 2% of the phenol was alkylated. The product was therefore redissolved in DMSO and 0.1 mole of NaH, followed by 0.1 mole of isopropyl bromide, was added and the reaction was allowed to become neutral to indicating paper. Addition of NaH and DMSO was repeated seven times. The reaction mixture was then worked up as usual.

Coupling of Aromatic Rings. I. The Pyrolysis of Aryl Sulfides and Aryl Sulfones to Substituted Biphenyls

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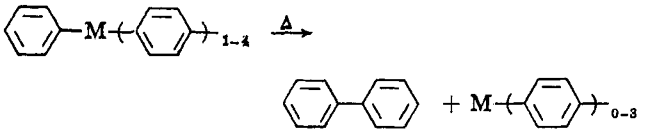
Pyrolysis of *p*-tolyl sulfide and *p*-tolyl disulfide on α-Fe embedded in a γ-Fe_2O_3 matrix yielded *p*-bitolyl in 60% conversion and 90% yield per pass. No decrease of activity for the catalyst was observed after *ca.* 50 passes, and no observable isomer redistribution preceded the coupling reaction. Pyrolysis of *p*-tolyl sulfone on alumina yielded *p*-bitolyl and a considerable amount of biphenyl. No observable isomer redistribution preceded this coupling reaction.

Pyrolysis of di- to pentaphenyl metalloids yielded biphenyl, frequently in high conversions.



M = Br,[1] I,[2] S,[3] Se,[3] P,[4] Sb,[5] As[6]

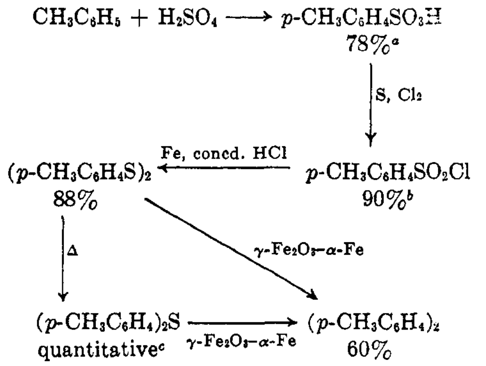
Bis(*p*-methoxyphenyl) sulfide when heated with Raney nickel gave *p,p'*-dimethoxybiphenyl in 50% conversion, and when *p*-tolyl disulfide was heated with Raney nickel, *p*-bitolyl was obtained in 84% conversion.[6] In our search for simple routes to substituted biphenyls proceeding with no isomer redistribution before the coupling step, pyrolysis of metalloids looked promising indeed. Unfortunately, most of the above starting materials require multistep syntheses and the elimination of sulfur with Raney nickel proceeded with a mild detonation, as also observed by others.[7] We have extended our search for new coupling reactions in two directions: (a) heterogeneous reactions in vapor phase on a solid catalyst support, and (b) homogeneous reactions in solution. In this paper we report two novel coupling reactions which proceed with the elimination of –S–, $-S_2-$, and $-SO_2-$ linkages in vapor phase on solid supports to yield substituted biphenyls.

Results

Bitolyls from Tolyl Sulfides and Tolyl Disulfides.—The most economic conversion of toluene to *p*-tolyl sulfide or disulfide was obtained by the route summarized in Chart I.

CHART I

SYNTHESIS OF *p*-BITOLYL FROM *p*-TOLYL SULFIDE AND *p*-TOLYL DISULFIDE



[a] Reference 8, p. 461. [b] W. Meves and W. Ohse, German Patent 499,052; *Chem. Abstr.*, **24**, 4055 (1930). [c] Reference 12.

We have found that the reduction of *p*-toluenesulfonyl chloride with iron powder in concentrated hydrochloric acid yielded directly *p*-tolyl disulfide in 88% over-all conversion. Reduction of the sulfonyl chloride with iron powder in 75% sulfuric acid gave 20% of the *p*-tolyl disulfide and about 80% of the iron salts of *p*-toluenethiol. *p*-Toluenethiol was dimerized in quantitative conversions to *p*-tolyl disulfide in an alkaline aqueous solution using Cu^{II} ions and air or in a sulfuric acid solution employing Fe^{III} ions and air.[8]

Attempts to synthesize *p*-tolyl sulfide or disulfide directly from toluene and sulfur, sulfur dichloride, or disulfur dichloride in the presence of Lewis acids such as $FeCl_3$, $SbCl_5$, $AlCl_3$, and HF yielded smaller over-all conversions to the *para* derivative and the separation of the resulting isomers by distillation proved impractical.

When *p*-tolyl sulfide was heated with a tenfold excess of degassed Raney Nickel, *p*-bitolyl could be isolated in up to 84% conversion.[6] In our hands this dimerization reaction was very sensitive to the weight

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(1) A. P. Nesmeyanov, T. P. Tolstaya, and L. S. Isaeva, *Dokl. Akad. Nauk USSR*, **125**, 330 (1959); *Chem. Abstr.*, **53**, 19927 (1959).

(2) W. Baker, N. J. McLean, and J. F. W. McOmie, *J. Chem. Soc.*, 922 (1963).

(3) H. Hauptmann and W. F. Walter, *Chem. Rev.*, **62**, 347 (1962); G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, **12**, 356 (1962).

(4) G. Wittig and M. Rieber, *Ann.*, **562**, 187 (1949).

(5) G. Wittig and K. Clauss, *ibid.*, **577**, 26 (1952).

(6) H. Hauptmann, B. Wladislaw, L. L. Nazario, and W. F. Walter, *ibid.*, **576**, 45 (1962).

(7) W. H. F. Sasse, *J. Chem. Soc.*, 3046 (1959).

(8) For discussion, see A. Schöberl and A. Wagner, "Methoden der organischen Chemie," Houben-Weyl, Vol. 9, Georg Thieme Verlag, Stuttgart, 1955, p. 60.