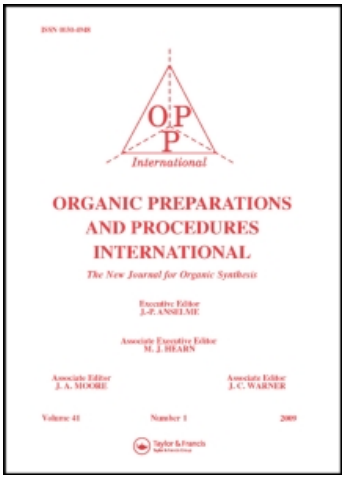

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ALKYLATION OF 2,6-DI-TERT-BUTYLPHENOL IN DIMETHYL SULFOXIDE

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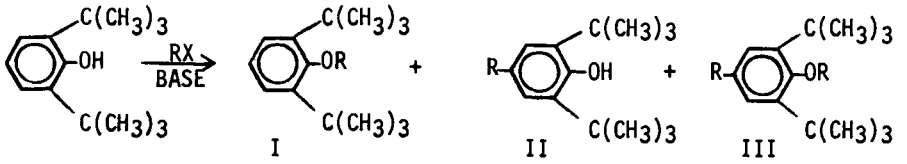
The alkylation in protic solvents of 2,6-di-t-butylphenol with its severely hindered hydroxy group gives primarily products C-alkylated in the para position rather than on oxygen.[1] Although the use of DMSO as a solvent greatly increases the amount of oxygen alkylation of normal phenols,[2] its utilization in the preparation of 2,6-di-t-butylphenoxy compounds from alkyl halides seems to have been overlooked.

2,6-Di-isopropylphenol was oxygen arylated with p-nitrochlorobenzene in DMSO at 90° using KOH as a base,[3] but the alkylation failed with 2,6-di-t-butylphenol. In our laboratories oxygen alkylation of 2,6-di-t-butylphenol with aliphatic halides, α-haloesters, and haloalkylamines with this reagent has been successful.



The reaction was cleaner and produced higher yields at 25-35° rather than at 90°. Approximately one equivalent of pulverized KOH pellets or a 50% aqueous solution of KOH was added to a solution of the phenol in DMSO. Potassium t-butoxide powder (Alpha Inorganics) was also effective as a base. Usually an excess of the alkyl halide was added and the reaction was stirred at room temperature overnight although it was essentially complete within

0.5 to 2 hrs. The total amount of phenol alkylated was sometimes low, but the unchanged phenol could readily be recovered by distillation of the product.

Table I shows a comparison of the results of alkylation of 2,6-di-t-butylphenol with some alkyl halides under a variety of conditions. The products were analyzed by vpc and separation by distillation confirmed the relative analyses and allowed identification of the products. The nature of the relatively small amount of non-volatile material present was not investigated.

TABLE I

Alkyl Halide	Base	Solvent	% Phenol Alkylated	% of Total Alkylated Product I	II	III
CH_3I	KOt-Bu	t-BuOH	95[a]	93[a]	7[a]	-
	KOH	DMSO	95-100	100	-	-
C_2H_5Br	KOt-Bu	DMSO	80	87	13	-
C_2H_5I	KOt-Bu	t-BuOH	90[a]	13[a]	67[a]	13[a]
C_3H_7Br	NaOEt	EtOH	22	-	99	-
	KOH	DMSO	63	46	52	2
	KOt-Bu	DMSO	69	48	41	11
	KOt-Bu	t-BuOH	39	0	99	-
	KOH	Me_2CO	10	33	66	-
	KOH	CH_3CN	20	40	60	-
	KOH	DMF	30	46	54	-
$BrCH_2COOEt$	KOH	DMSO	32	81	19	
$ClCH_2CN$	KOH	DMSO	33	100	-	
$ClCH_2CH_2N(Et)_2$	KOH	DMSO	35	100	-	

[a]These values determined from the data of Kornblum and Seltzer.[1]

Experimental

Alkylation of 2,6-di-t-butylphenol with n-propyl bromide. To a solution of 2 g. (0.01 mole) 2,6-di-t-butylphenol in 10 ml of DMSO was added 0.6 g. KOH (0.01 mole) dissolved in 1 ml of water. The resulting green solution was then treated with 5 g. (0.04 mole) of n-PrBr and the mixture stirred at room temperature for about 20 hrs. The originally green and then dark blue reaction was clear yellow at the end of this time. It was poured into 100 ml of 10% aqueous HCl, extracted 3 times with 30 ml portions of $CHCl_3$, the combined extracts washed twice with H_2O, dried over Na_2SO_4 and the solvent removed under vacuum. The light yellow oil remaining was analyzed by vpc (200^o isothermal column 5 ft., 4% SE 52 Chrom W. HMDS 80-100 mesh). The results are indicated in table I. Careful distillation of a larger run failed to completely separate the ether and the 4-propyl phenol. However, the samples were sufficiently enriched to allow nmr analysis which confirmed the structural assignments. The other alkyl halides were treated in a similar manner.

Ethyl (2,6-di-t-butylphenoxy)acetate. To a solution of 49.4 g. (0.24 mole) of 2,6-di-t-butylphenol in 450 ml of DMSO was added 11.2 g. (0.2 mole) KOH and 33.4 g. (0.2 mole) of ethyl bromoacetate. The temperature rose to 40^o as the initial brown solution became green. After 19 hrs. at room temperature the solution was a clear yellow. The reaction mixture was poured into dilute HCl, extracted with $CHCl_3$, washed, dried and the solvent removed under vacuum. By vpc analysis, the residue (62.4 g.) consisted of 18.2 g. of ethyl (2,6-di-t-butylphenoxy)acetate, 4.5 g. of ethyl (3,5-di-t-butyl-4-hydroxyphenyl)acetate and 39.7 g. of unreacted 2,6-di-t-butylphenol. The yellow oil distilled at $124-130^o$ at 0.6 mm Hg, but the best fraction of the desired phenoxy ester obtained contained 97% desired ester and 3% of the phenylacetate derivative. IR: Carbonyl 1760, 1730 cm^{-1}. NMR: 3H triplet 1.28 δ (CH_3), 18H singlet

1.40 δ (t-butyl), 2H quartet 4.23 δ (ester CH_2), 2H singlet 4.32 δ (OCH_2COOR), 3H multiplet in aromatic region.

2,6-Di-t-butylphenoxyacetonitrile. To a stirred mixture of 11.2 g. (0.2 mole) pulverized KOH and 49.4 g. (0.24 mole) 2,6-di-t-butylphenol in 450 ml DMSO was added 15.1 g. (0.2 mole) chloroacetonitrile in 20 ml DMSO. The reaction turned dark green and the temperature rose to 39° and then subsided slowly. After 3 hrs, the reaction was poured into dilute HCl and extracted 3 times with $CHCl_3$. The combined extracts were washed with water, dried over Na_2SO_4 and the solvents removed under vacuum. The resulting red oil weighed 48 g. and vpc analysis showed it to contain 16 g. of 2,6-di-t-butylphenoxyacetonitrile and 32 g. of unreacted 2,6-di-t-butylphenol. Distillation afforded about 12 g. of an oil, bp 128-135° at 0.6 mm which crystallized on cooling. It was recrystallized from ethanol-water to yield 9 g. of colorless crystals, mp 71-73°.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.20; H, 9.30; N, 5.72.

IR: No phenolic OH. NMR: 3H multiplet 7.2 δ, 2H singlet 4.41 δ; 18H singlet 1.41 δ.

2-(2,6-Di-t-butylphenoxy)triethylamine hydrochloride. To a stirred mixture of 49.4 g. (0.24 mole) of 2,6-di-t-butylphenol and 22.4 g. (0.4 mole) of KOH in 450 ml DMSO was added 34.4 g. (0.2 mole) of solid 2-diethylaminoethyl chloride hydrochloride. The reaction warmed to 30°, but after ½ hour it had begun to turn green and the temperature had reached 35°. After 22 hours the reaction was poured into 1 liter of dilute HCl and extracted 3 times with $CHCl_3$. The combined extracts were washed 3 times with water, dried over Na_2SO_4 and the solvent removed under vacuum. The resulting red oil crystallized on standing.

It was recrystallized from $CHCl_3$-ether, it produced 28 g., mp 182-4°.

Anal. Calcd. for $C_{20}H_{35}NO \cdot HCl$: C, 70.25; H, 10.61; Cl, 10.37; N, 4.10. Found: C, 70.38; H, 10.61; Cl, 10.53; N, 4.10.

IR: No phenolic OH. NMR: 24H multiplet 1:43 δ (18 due to the t-butyl groups and 6 to the CH_3 triplets of the ethyl groups), 6H multiplet 3.3 δ ($-N-CH_2-$), 2H multiplet 4.16 δ ($-O-CH_2-$), 3H multiplet 7.21 δ (phenyl protons).

All microanalyses were performed by Midwest Microlab., Inc., Indianapolis, Indiana. All melting points and boiling points uncorrected. Nmr spectra were obtained using a Varian A-60 NMR Spectrometer.

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