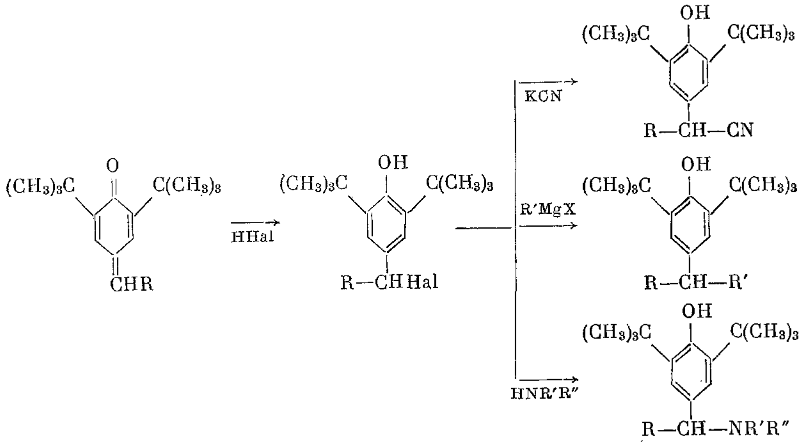
REACTION OF α-ALKYL-4-HYDROXY-3,5-DITERT-BUTYLBENZYL HALIDES WITH CERTAIN NUCLEOPHILIC AGENTS

A. A. Volod'kin, V. V. Ershov,
G. D. Ostapets-Sveshnikova,
and I. S. Belostotskaya

UDC 542.91 + 547.56

We had earlier [1, 2] demonstrated that 4-hydroxy-3,5-ditert-butylbenzyl bromide reacts readily with strong nucleophilic agents. These reactions were utilized for the production of functional derivatives of sterically hindered phenols [3, 4], possessing carcinolytic activity [5, 6]. The lability of the bromine atom in 4-hydroxybenzyl bromide naturally depends upon the presence and nature of substituents in the benzyl position. In view of this, we studied the reactivity of certain α-alkyl-4-hydroxy-3,5-ditertbutylbenzyl bromides (chlorides) with secondary amines, sodium cyanide, and organomagnesium compounds. The original hydroxybenzyl halides were produced by the reaction of hydrogen bromide (chloride) with the corresponding α-alkyl-2,6-ditert-butylmethylenequinones, the synthesis of which was described earlier [7]. The reaction proceeds readily when an ether solution of the methylenequinone is shaken with hydrochloric acid or 40% hydrobromic acid. Good results were also obtained by passing hydrogen bromide (chloride) into an ether solution of the methylenequinone (see Table 1). α-Alkyl-4-hydroxy-3,5-ditert-butylbenzyl bromides (chlorides) (I)-(VIII) represent white crystalline substances, which darken rapidly in air. The lability of the bromine atom is not reduced in comparison with 4-hydroxy-3,5-ditert-butylbenzyl bromide unsubstituted in the α-position [1], and as a result of the reaction, normal alkylation products are formed:



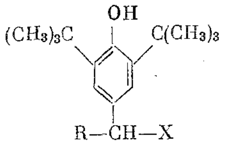
The indicated transformations proceed equally readily with α-alkyl-4-hydroxy-3,5-ditert-butylbenzyl bromides (chlorides), and the yields of the final products of the reaction are 70-90%. Increasing the volumes of the substituents in the benzyl position has an appreciable effect only in the Grignard reaction. Although the reaction of α-methyl-4-hydroxy-3,5-ditert-butylbenzyl bromide with excess methyl magnesium iodide proceeds with a 78% yield of 4-isopropyl-2,6-ditert-butylphenol, with α-isopropyl-4-hydroxy-3,5-ditert-butylbenzyl bromide under analogous conditions, only 42% of 4-isoamyl-2,6-ditert-butylphenol is formed.

EXPERIMENTAL

α-Alkyl-4-hydroxy-3,5-ditert-butylbenzyl Halides (I)-(VIII). Into a solution of 0.01 mole of α-alkyl-2,6-ditert-butylmethylenequinone and 40 ml of ether was passed a stream of hydrogen chloride (bromide) for 10 min, after which the solvent was evaporated, and the residue dissolved in hexane and crystallized at −78° (Table 1).

Institute of Chemical Physics, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6, pp. 1081-1083, June, 1966. Original article submitted November 1, 1965.

TABLE 1. 4-(α-Substituted)alkyl-2,6-ditert-butylphenols



Cpd. No.	R	X	B.p., °C	M.p., °C	Yield, %	Found %		Gross formula	Calculated %	
						C	H		C	H
I	CH_3	Cl	—	54—56	92	71,62 71,54	9,66 9,48	$C_{16}H_{25}OCl$	71,48	9,37
II	C_2H_5	Cl	—	66—67	87	72,41 72,21	9,67 9,42	$C_{17}H_{27}OCl$	72,18	9,36
III	$CH(CH_3)_2$	Cl	—	60—62	81	72,76 72,87	9,81 9,89	$C_{18}H_{29}OCl$	72,81	9,85
IV	n-C_4H_9	Cl	—	26—28	82	73,67 73,86	10,07 9,84	$C_{19}H_{31}OCl$	73,40	10,06
V	CH_3	Br	—	45—47	95	61,39 61,62	8,22 8,36	$C_{16}H_{25}OBr$	61,34	8,04
VI	C_2H_5	Br	—	44—45 *	84	62,54 62,81	8,13 8,33	$C_{17}H_{27}OBr$	62,38	8,28
VII	$CH(CH_3)_2$	Br	—	44—46	86	63,58 63,79	8,91 8,82	$C_{18}H_{29}OBr$	63,33	8,56
VIII	n-C_4H_9	Br	—	57—59	76	64,21 64,18	8,64 8,77	$C_{19}H_{31}OBr$	64,21	8,79
IX	CH_3	CN	—	79—80	85	78,88 78,99	10,03 10,10	$C_{17}H_{25}NO$	78,70	9,71
X	C_2H_5	CN	—	86—88	90	78,92 78,91	10,02 10,19	$C_{18}H_{27}NO$	79,09	9,95
XI	$CH(CH_3)_2$	CN	—	85—87	79	79,33 79,54	10,13 10,25	$C_{19}H_{29}NO$	79,39	10,17
XII	CH_3	NC_4H_8O	—	72—74	84	75,28 75,32	10,61 10,56	$C_{20}H_{33}NO_2$	75,18	10,41
XIII	C_2H_5	NC_4H_8O	—	28—30	88	75,76 75,66	10,41 10,43	$C_{21}H_{35}NO_2$	75,63	10,58
XIV	$CH(CH_3)_2$	NC_5H_{10}	—	107—110	91	80,17 80,15	11,61 11,47	$C_{23}H_{39}NO$	79,93	11,38
XV	CH_3	CH_3	112—114	—	78	81,89 81,91	11,09 11,17	$C_{17}H_{28}O$	82,19	11,36
XVI	C_2H_5	C_2H_5	127—128	—	72	82,37 82,44	11,53 11,61	$C_{19}H_{32}O$	82,56	11,68
XVII	$CH(CH_3)_2$	CH_3	132—134	—	42	82,71 82,86	11,72 11,81	$C_{19}H_{32}O$	82,55	11,68

---

* Literature data [8]: m.p. 45°.

α-Alkyl-4-hydroxy-3,5-ditert-butylbenzonitriles (IX)-(XI). To a solution of 1 g of sodium cyanide in a mixture of 5 ml of water and 20 ml of alcohol we added 0.01 mole of (I)-(VIII) in 15 ml of ether. The mixture was boiled for 2 h, after which it was diluted with water, acidified with 2 N HCl, the organic layer extracted with ether, dried, and the solvent distilled off under vacuum. The residue was crystallized from heptane (see Table 1).

4-(α-N,N-Dialkylamino)alkyl-2,6-ditert-butylphenols (XII)-(XIV). To 0.05 mole of the amine in 40 ml of absolute ether we added 0.01 mole of (I)-(VIII) in 20 ml of ether. After 30 min, the reaction mixture was washed with water, acidified with 2 N HCl, and the aqueous layer above the ether treated with 2 N NaOH. The ether extracts were dried, the solvent distilled off under vacuum, and the residue crystallized from hexane (see Table 1).

4-Alkyl-2,6-ditert-butylphenols (XV)-(XVII). To an ether solution of 0.03 mole of the alkyl magnesium iodide was added 0.01 mole of (I)-(VIII) in 20 ml of ether. After 2 h, 20 ml of water was added to the solution, the ether layer removed, washed with water, and dried with calcium chloride. The solvent was distilled off and the residue distilled under vacuum (see Table 1).

The authors would like to thank N. M. Émanuél' for his constant interest in this work during its performance.

CONCLUSIONS

1. Eight α-alkyl-4-hydroxy-3,5-ditert-butylbenzyl halides were produced by addition of the hydrogen halides to α-alkyl-2,6-ditert-butylmethylenequinones.

2. α-Alkyl-4-hydroxy-3,5-ditert-butylbenzonitriles and 4-(α-N,N-dialkylamino)alkyl-2,6-ditert-butylphenols were produced by the reactions of α-alkyl-4-hydroxy-3,5-ditert-butylbenzylbromides (chlorides) with sodium cyanide and secondary amines.

3. A new method of synthesizing 4-sec-alkyl-2,6-ditert-butylphenols was proposed.

LITERATURE CITED

1. A. A. Volod'kin and V. V. Ershov, Izv. AN SSSR, Otd. Khim. N., 1962, 342.
2. A. A. Volod'kin, G. D. Ostapets-Sveshnikova, and V.V. Ershov, Izv. AN SSSR, Ser. Khim., 1965, 2188.
3. A. A. Volod'kin and V. V. Ershov, Izv. AN SSSR, Otd. Khim. N., 1962, 1292.
4. Yu. Bruk and R. Yu. Rachinskii, Zh. Obshch. Khimii, 34, 2983 (1964).
5. N. M. Émanuél', N. P. Konovalova, and L. M. Dronova, Dokl. AN SSSR, 143, 737 (1962).
6. G. A. Kukushkina, L. B. Gorbacheva, and N. M. Émanuél', Dokl. AN SSSR, 146, 1206 (1962).
7. V. V. Ershov, A. A. Volod'kin, and G. D. Ostapets-Sveshnikova, Izv. AN SSSR, Ser. Khim., 1966, 928.
8. J. Hamada and T. Fujisaki, J. Chem. Soc. Japan 82, 898 (1961).