Halogenation of Resorcinol Derivatives

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Several types of resorcinols have been monobrominated in the ring in good yields with sodium bromide in the presence of 18-crown-6 on oxidation with m-chloroperbenzoic acid. Monoiodination takes place with 2′-(1-methylcyclohexen-3-yl)-5-(1,1-dimethylheptyl)-resorcinol when sodium iodide is employed. This new reagent system, MX/18-crown-6/m-CPBA ($M = K^+$, Na^+, $X = Br^-$, I^-), effects the regiospecific halogenation of activated aromatic ring over olefinic double bond.

Introduction

Halogenation is one of the most widely used and extensively studied aromatic substitution reaction.[1] Electron donating substituents in a benzenoid compound generally give ortho/para-isomers have similar physical properties their separation is tedious.[2]

Rozen *et al.* have shown that fluorination of 1-3-dimethoxybenzene with CH_3COOF produces only 4-substitution without 2-substitution and has attributed the result to steric hinderance at the 2-position.[3] Patrick *et al.* have reported a study of the reaction of $CsSO_4F/BF_3$ with several activated aromatic system.[4]

This paper describes some interesting features of the halogenation of resorcinol derivatives.

Experimental

IR spectra were recorded on Perkin-Elmer 457 Grating Infrared Spectrophotometer. H-NMR spectra were obtained on a Bruker WH-60, and WH-300 pulsed FT spectrometer. Chemical shift are given in parts per million downfield from Me_4Si internal standard. Mass spectra were recorded on Varian Mat, CH-5 Mass Spectrometer and LKB 2091-Gas Chromatograph-Mass Spectrometer. Melting point apparatus, Thomas Hoover. Chromatography; Analytical TLC was performed by using commercially available silica plate. Polygram Sil N-HR/UV_{254} and the plates were visualized with Fast Blue phenol reagent of charring with a solution of $MeOH:H_2SO_4$ (1:1). Medium pressure liquid chromatography was performed by ALTEX glass column, 1 meter long, internal diameter 9mm using FMI pump and silica gel 60(230-400 mesh) purchased from Merck, collective fraction with LKB 2070 or LKB 7000 Fraction Collectors of 2-10 m./min. "Acetylation in the usual way" means addition of acetic anhydride and pyridine (in a ratio of 1:2); the mixture is left overnight, poured onto ice, extracted with ether, saturated brine solution, then dried over $MgSO_4$, followed by filtration and evaporation to dryness in vacuo. "Worked up in the usual way" means addition of about 2 volumes of ether and 5 volumes of water, separation of the layers, washing the organic layer with a saturated brine solution, drying over $MgSO_4$, filtration and evaporation to dryness in vacuo.

Solvents and anhydrous reagents for the synthesis were purified and dried according to established procedures by distillation under argon or nitrogen from an appropriate drying agent[5]; CH_2Cl_2. The solvents for other chromatography and general used were purified by distillation and filtration according to standard procedure. The deuterated NMR solvents were used without further purification. The spectroscopic solvents were purchased from Aldrich, or Merck.

3-Chloroperbenzoic acid was purchased from Aldrich. 18-crown-6 was obtained from Sigma. Sodium bromide was obtained from Shimakyu. All reactions were run under an inert atomsphere of nitrogen (oxygen free) and reaction requiring anhydrous conditions were performed in flame-dried apparatus. Starting materials 2,3,4,5,6 and 7 were available from previous research.[6] Products 2a, 3a, 4a, 5a, 6a, and 7a were identified by comparison of IR, NMR and GC-MS spectral properties.

The general procedure is as follow. 2′-(1-methylcyclohexen-3-yl)-3′-ethyl-5′-(1,1-dimethylheptyl)-resorcinol (4) (358 mg, 1 mmol) 18-crown-6 (291 mg, 1.1 mmol) and sodium bromide (515 mg, 5 mmol) were stirred in methylenechloride (20 m*l*) under nitrogen at room temperature for 5 min. The solution of m-chloroperbenzoic acid (237 mg, 1.1 mmol) in methylenechloride (20 m*l*) was added dropwise with stirring over 10 min. The reaction mixture was vigorously stirred for additional 5 min, and was then worked up in the usual way. The reaction product was purified by medium pressure liquid chromatography on a silica column (elution with petroleum ether b.p. 60-80°C), to obtain 2′-(1-methyl-cyclohexen-3-yl)-6′-bromo-3′-ethyl-5′-(1,1-dimethylheptyl)-resorcinol (4a) (175 mg, 75%) an oil, UVmax(EtOH), 273 (ϵ 2830), 280nm(3000); NMR δ ($CDCl_3$), 0.84(3H, t, CH_3), 1.23(6H, brs, CH_3), 1.44(3H, t, J=3Hz, CH_3), 2.05(3H, s, CH_3), 3.34-3.64(1H, m, C-3H), 4.03(2H, q, J=4Hz, methylene H), 6.42(1H, m, C-2H), 6.65(1H, s, arom H); MS(20°), m/e 438(25), 436(M^+, $Br,^{79}$ 28), 396(6), 382(7), 356(62), 272(100); IR(film), 3505, 3430, 2944, 2875, 1605, 1590, 724$cm.^{-1}$

Preparation of 2′-(1-methylcyclohexen-3-yl)-4′-bromo-olivetol(2a).

Under the conditions of general procedure we obtained (2a) (120mg, 62%), an oil, UVmax(EtOH), 282nm(ϵ 2470); NMR δ ($CDCl_3$), 0.90(3H, t, CH_3), 1.79(3H, brs, CH_3), 2.62 (3H, brt, benzylic H), 3.96(1H, br, C-3H), 5.62(1H, brs, C-2H), 6.35(1H, s, arom H); MS(20°), m/e 354(24), 352(M^+, Br^{79}, 99), 350(100), 310(34), 297(76), 285(42), 273(47), 228 (32); IR(film), 3410, 2915, 2859, 1614, 1563, 718cm^{-1}.

Preparation of 2′-(1-methylcyclohexen-3-yl)-4′-bromo-5′-(1,1-dimethylheptyl)-resorcinol(3a).

Under the conditions of general procedure we obtained (3a) (96mg, 63%), an oil, UVmax(EtOH), 273nm(ϵ 3536); NMR δ ($CDCl_3$), 0.84(3H, t, CH_3), 1.40(6H, s, CH_3), 1.78(3H, brs, CH_3), 4.04(1H, br, C-3H), 5.70(1H, brs, C-2H), 6.10(1H, s, OH), 6.54 (1H, d, J=8Hz, arom H); MS(20°), m/e 410(5), 408(M^+, Br^{79}, 7), 407(19), 343(20), 326(52), 245(100), 139

(81); IR(film), 3470, 2920, 2860, 1558, 724cm^{-1}.

Preparation of 2′-(1-cyclohexen-3-yl)-4′-bromo-olivetol (5a).

Under the conditions of general procedure we obtained (5a) (150mg, 44%), an oil, UVmax(EtOH), 280nm(ϵ 4380); NMR δ ($CDCl_3$), 0.87(3H, t, CH_3), 2.46(2H, t, benzylic H), 3.75-4.18(1H, m, C-3H), 5.75(1H, s, OH), 5.94(1H, brs, C-1H), 6.14(1H, d, J=4Hz, C-2H), 6.33(1H, s, arom H); MS (20°), m/e 340(74), 338(M^+, Br^{79}, 75), 312(14), 310(14), (297) (36), 295(32), 284(92), 282(86), 259(40), 203(100); IR(film), 3460, 2932, 1618, 1570, 726cm^{-1}.

Preparation of 2′-(1-cyclopenten-3-yl)-4′-bromo-5′-(1,1-methylheptyl)-resorcinol (6a).

Under the conditions of general precedure we obtained (6a) (60mg, 48%), an oil, UVmax(EtOH), 279(ϵ 2240), 285 sh nm (2180); NMR δ ($CDCl_3$), 0.90(3H, t, CH_3), 1.40(6H, s, CH_3), 4.52(1H, br, C-3H), 5.87(1H, s, OH), 6.02(1H, d, J=2Hz, C-1H), 6.11(1H, s, C-2H), 6.48(1H, s, arom H); MS (20°), m/e 382(43), 380(M^+, Br^{79}, 44), 326(9), 302(29), 297 (65), 295(61), 243(36), 228(100); IR(film), 3500, 2975, 2940, 2870, 1615, 1571, 735cm^{-1}.

Preparation of 2′-(1-methylcyclohexen-3-yl)-4′-iodo-5′-(1,1-dimethylheptyl)-resorcinol diacetate(7a).

Under the conditions of general procedure we obtained crude product(7). Compound(7) was acetylated in the usual way and the resulting oil was chromatographed on a silica column(elution with petroleum ether b.p. 60-80°) to obtain (7a) 101mg 57%), an oil, NMR δ ($CDCl_3$), 0.87(3H, t, CH_3), 1.24(6H, s, CH_3), 1.89(3H, brs, CH_3) 2.30(6H, s, $COCH_3$), 3.53(1H, brd, J=8Hz, C-3H), 5.58(1H, brs, C-2H), 6.62(1H, dd, J=10Hz, J=2Hz, arom H); MS(20°), m/e 357(M^+, (I^{127}, CCH_2), 14), 355(100), 340(12) 327(6), 313(74), 298(10), 271 (62), 230(63), 215(8), 201(8), 167(10), 149(24); IR(film), 2690, 2930, 2860, 1770, 1632, 1593cm^{-1}.

Results and Discussion

We report the further development of a new route to these types of compounds, which is preparatively simple, fast, and leads to the halogenated products in good yields. This reaction represents the halogenation of resorcinols by the newly formed halogen species. Initial experiments in this field were reported by M. Srebnik.[7]

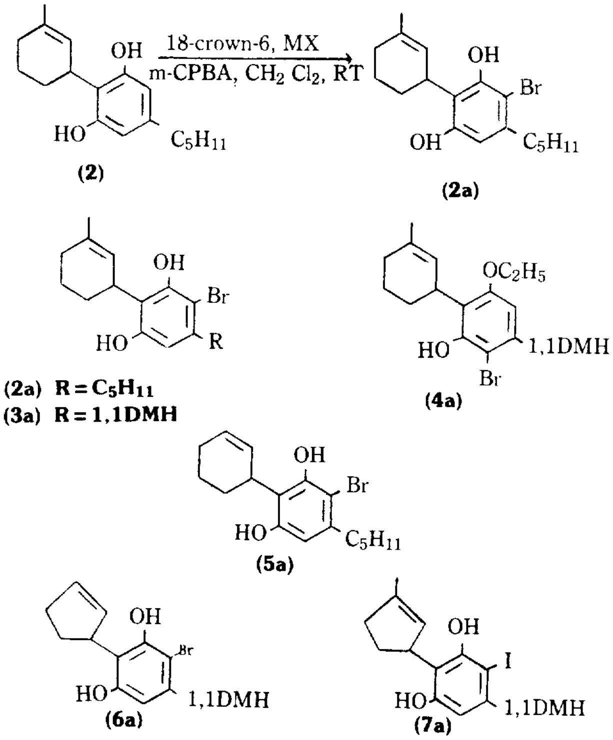
The halogenation invariably takes place with regiospecificity only on the aromatic ring, the product having the halogenated group ortho to one of the phenolic groups and para to the other.

The reactions described obove do not take place in the absence of a crown ether. Although 18-crown-6 is generally used with potassium salts[10b], in the present reactions the sodium salts led to a higher yield.

No epoxide formation is observed under the conditions described above even in the presence of double bonds which do not participate in the reaction (Scheme 1 and Table 1).

We have made some observations which throw additional light on the pathway through which the new reagent reacts, although the mechanism of the reaction is not yet established.

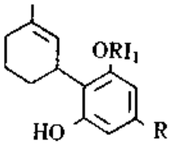
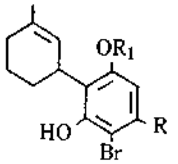
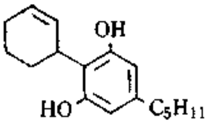
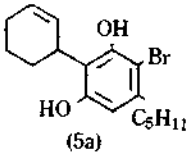
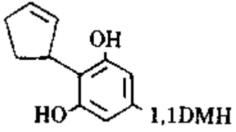
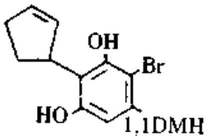
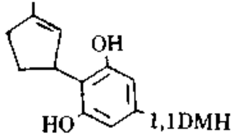
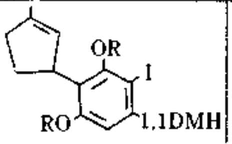
We assume that crown ether complexation of alkalimetal ions leads to increased halide reactivity. This solubilized halide ("naked" halide)[8,9] is oxidized by the m-chloroperbenzoic acid to afford a positive halogen species which attacks



1,1 DMH indicates 1,1-dimethylheptyl

Scheme 1

Table 1. Halogenation of resorcinols with MX / 18-crown-6 / m-CPBA

Resorcinols	Products	Yield	Ref.
 (2) R_1 = H, R = C_5H_{11} (3) R_1 = H, R = 1,1DMH (4) R_1 = C_2H_5, R = 1,1DMH	 (2a) R_1 = H, R = C_5H_{11} (3a) R_1 = H, R = 1,1DMH (4a) R_1 = C_2H_5, R = 1,1DMH	62% 63% 75%	10
 (5)	 (5a)	44%	10
 (6)	 (6a)	48%	10
 (7)	 (7a) R = H(Ac)	57%	10

the aromatic ring leading to a halonium ion[10b]; halogenation led to monohalogenated resorcinols. The suggested ready formation of a positive halogen species should make possible the introduction of various new synthetic methodologies.

In summary we have described a new halogenation reagent which is easy to handle and which has certain advantages over the existing ones used in halogenation of resorcinols and bromination of monoethyl resorcinol, in particular as regards monohalogenation, regiospecificity and, in most cases, yields.

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References

1. (a) G. A. Olah, Y. D. Vankar, M. Arvanaghi and G. K. S. Prakash, *Synthesis,* 720 (1979); (b) Y. Ogata and K. Aoki, *J. Am. Chem. Soc.,* ; **10** 6187, (1968); (c) E. B. Merkushev, N. D. Simakhina and G. M. Koveshnikova, *Synthesis,* 486 (1980).

868 (1986).

3. O. Lerman, Y. Tor, D. Hebel and S. Rozen, *J. Org. Chem.,* **49,** 806 (1984).
4. T. B. Patrick and D. L. Darling, *J. Org. Chem.,* **51,** 3242 (1986).
5. B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith and A. R. Tatchell, "Vogel's Textbook of Practical Organic Chemistry", 4th edition, Longman Inc., New York (1978).
6. S. H. Baek, Doctoral thesis, The Hebrew Univ. of Jerusalem, Israel (1986).
7. M. Srebnik, Doctoral thesis, The Hebrew Univ. of Jerusalem, Israel (1984).
8. (a) D. J. Sam and H. E. Simmons, *J. Am. Chem. Soc.,* **96** , 2252 (1974); (b) C. L. Liotta and H. P. Harris, *ibid.,* **96,** 2250 (1974).
9. (a) R. N. Greene, *Tetrahedron Lett.,* 1793 (1972); (b) M. J. Maskornick, *ibid.,* 1797 (1972); (c) I. Belsky, *J. C. S. Chem. Comm.,* 237 (1977).
10. (a) A. Fischer and G. N. Henderson, *Can. J. Chem.,* **61,** 1045 (1983); (b) M. Srebnik, R. Mechoulam and I. Yona, *J. Chem. Soc. Perkin Trans.* I, 1423 (1987).

Purification of $TiCl_4$ by Adsorption Technique

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Titanium tetrachloride is purified using adsorption column packed with activated silica gel. When 120 m*l* of titanium tetrachloride was passed through an adsorption column filled with 7 g silica gel, iron content in titanium tetrachloride has been reduced from 7 ppm to less than 1 ppm, and aluminum from 46 ppm to 11 ppm, while silicon content being unchanged at about 60 ppm.

Introduction

Various methods currently in use for the preparation of high-purity titanium dioxide require titanium tetrachloride as a source material. The quality of titanium dioxide depends on the purity of the titanium tetrachloride used. Titanium tetrachloride is highly volatile; consequently, distillation may serve as a reasonably effective and convenient method of removing nonvolatile impurities[1-3]. However, it is difficult to remove low level volatile impurities such as iron (III), aluminum, silicon chlorides, etc.

It has been reported that ferric chloride, as well as heavy metal chlorides are removed from silicon tetrachloride efficiently by adsorption on silica gel[4].

In the present study, an attempt has been made to purify titanium tetrachloride by passing titanium tetrachloride through column packed with activated silica gel.

Experimental

Purification of $TiCl_4$ by the adsorption method

Since the titanium tetrachloride is very sensitive to moisture, the experiment was performed in a glove box under flowing dry N_2 gas. Some silica gel was also placed in the glove box. A blower was used inside the glove box for forced air convection. The separation column was constructed so that $TiCl_4$ was kept in a closed system during the separation as shown on Figure 1.

As the adsorbent, purified silica gel[5] of 70-230 mesh was used; it was activated by heating in air at 270 ± 10°C for 18 hours prior to use[6]. About 7 g of the activated silica gel was packed a portion of the adsorption column about 25 cm long. $TiCl_4$ was allowed to drop on top of the adsorbent at a rate of about 1 m*l* min^{-1} while suction was applied, until a liquid column was formed in the delivery tube. After standing for 30 minutes, $TiCl_4$ was allowed to flow while draining at a rate of 0.1 m*l* min^{-1}. After flowing every 40 m*l*, about 2 m*l* of the eluent was collected in a vessel containing 20 m*l* of distilled 6M HCl for chemical analysis.

After passing about 150 m*l* of $TiCl_4$, the silica gel in the top 6 cm portion of packing was transferred to 50 m*l* beaker with 6M HCl. The remainder was transferred to 100 m*l*