

Transition Metal-Catalyzed Oxidations. 11 [1]

Para-Selective Chlorination and Bromination of Phenols with *tert*-Butyl Hydroperoxide and $\text{TiX}(\text{OiPr})_3$

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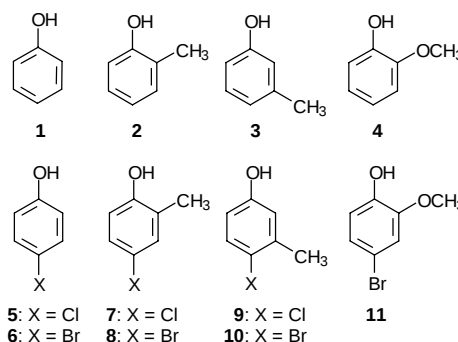
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Dedicated to Prof. W. Pritzkow on the Occasion of his 70th Anniversary

Keywords: Bromine, Chlorine, Oxidations, Titanium, Peroxides, Phenol**Abstract.** Mononuclear phenols **1–4** are chlorinated or brominated with high *para*-selectivity and in good yields to thehalides **5–11** with the $\text{TiX}_n(\text{OiPr})_m/\text{TBHP}$ system ($\text{X} = \text{Cl}$ or Br).

Selectivity is a major goal in modern synthetic chemistry [2]. This goal is relatively difficult to achieve in some electrophilic aromatic substitutions especially in the halogenation of phenols. Mixtures of *ortho*- and *para*-substitution products are usually formed which are often difficult to separate. We now report on surprisingly clean chlorinations and brominations with interesting *para*-position selectivity in the reactions of phenols with *tert*-butyl hydroperoxide (TBHP) in the presence of halogenated transitionmetal alkoxides such as $\text{TiX}(\text{OiPr})_3$ ($\text{X} = \text{Cl}$ or Br ; for a review on TBHP oxidations see [3]). The halogenating power of the $\text{TiX}_n(\text{OiPr})_m/\text{TBHP}$ system and the selectivities involved have not yet been systematically investigated. Pertrifluoroacetic acid is known to generate hypochlorite ions in the reaction with TiCl_4 that chlorinate phenol (**1**) with moderate *ortho*-selectivity (56:22) [4]. A reverse, but also very poor *para*-selectivity (67.5:25) is obtained when *meta*-chloroperbenzoic acid is used in presence of HCl [5].

Our preliminary chlorination experiments of 2-methylphenol (**2**) in dichloromethane at room temperature with $\text{TiCl}(\text{OiPr})_3/\text{TBHP}$ gave low yields but an interesting *para*-selectivity encouraging further studies. The reaction was finally (see Experimental for details) conducted in THF at -30°C with 0.1 molar solutions of the phenols **1–3**. Increasing the chlorine content of the titanium catalyst or the addition of lithium or magnesium chloride did not improve



the conversions that were in the range of 90–95% by GC analysis after 20 h of reaction time at -30°C . The corresponding *para*-chlorination products **5**, **7** and **9** were the only products detected by GC analysis; the isolated yields were 62, 58, and 47%, respectively [6]. For comparison, the most successful reagents for regioselective *para*-chlorination are listed in Table 1. With exception of a recent procedure of Hirano *et al.* [7] using sodium chlorite and a manganese(III)-salen complex in the chlorination of anisol some *ortho*-chlorination products (**3** – 8.7%) were always formed in the described procedures.

Next, we turned our attention to the bromination of the phenols **1–4**. Initially, we observed that bromination products

Table 1 Selection of reagents for *para*-selective chlorination of phenol **1**

Reagent	Ratio <i>ortho/para</i>	Dichloro product (%)	Yield <i>para</i> (%)
chlorodimethylsulfonium chloride [8]	3 : 97	–	84
<i>N</i> -chlorotriethylammonium chloride [9]	3 : 97	–	97 ^{b)}
<i>N</i> -chloropyridinium chloride [9]	3 : 97	–	95 ^{b)}
SO_2Cl_2 , cat.: Ph_2S , AlCl_3 [10]	8.7 : 91.3	–	89 ^{b)}
2,3,4,4,5,6-hexachlorocyclohexa-2,5-dienone [11]	5.6 : 94.4 ^{a)}	10 ^{a)}	85 ^{a)}
sodium chlorite, cat.: (salene)-mangan(III)-complex [7]	– ^{a)}	0 ^{a)}	98 ^{a)}

^{a)} selectivity for the chlorination of anisol; ^{b)} based on chlorination equivalent

were formed when lithium bromide was added to the $\text{TiCl}(\text{OiPr})_3/\text{TBHP}$ system. To exclude the simultaneous formation of chlorides, we later used $\text{TiBr}(\text{OiPr})_3$ that was prepared by mixing TiBr_4 with three parts of $\text{Ti}(\text{OiPr})_4$ similarly as described for $\text{TiCl}(\text{OiPr})_3$. The reaction of **1–4** was conducted at -40°C in THF, and Table 2 shows the results of the GC analysis comprising all reaction products. It must be mentioned that naphthol did not give clean halogenation products due to oxygenations described earlier [12]. The *para*-bromination products of **6**, **8**, **10**, and **11** were formed in high yields and selectivity (86–92%) with only small amounts of starting material (3–8%), dibromination products (2–8%) or very little *ortho*-product (3%, only one case). These results are comparable with the best known reagents for selective *para*-bromination compiled in Table 3. It should be stressed that in the procedure described here, readily available commercial reagents are used and environmentally safe (TiO_2) side products are formed.

The reason of the high *para*-selectivity was unclear, and we performed a few experiments to rule out some mechanistic alternatives. Although the redox potential is relatively unfavourable, it cannot be excluded that electrophilic chlorine species in particular hypochlorite or *tert*-butyl hypochlorite are generated from TBHP and the titanium catalyst [20]. Therefore, sodium hypochlorite and *tert*-butyl hypochlorite were treated with phenol (**1**) and the products carefully analyzed by GC. The results are summarized in Table 4. They clearly demonstrate that *ortho*-chlorophenol is formed predominantly with these reagents. However, it is possible that *para*-selectivity is caused by steric shielding of the phenolic *ortho*-positions after ligand exchange with the titanium alkoxide to form the phenolate. Accordingly, *tert*-butyl hypochlorite in combination with $\text{Ti}(\text{OiPr})_4$ or the sterically even more bulky $\text{Zr}(\text{OtBu})_4$ was treated with phenol. In fact, the amount of the *para*-product especially in the presence of $\text{Zr}(\text{OtBu})_4$ increased showing that steric shielding of the *ortho*-positions may be of some importance. However, the ratio of nearly 1:1 is far away from that observed with the $\text{TiCl}(\text{OiPr})_3/\text{TBHP}$ or the related $\text{TiBr}(\text{OiPr})_3/\text{TBHP}$ systems (see Tables 1 and 3) and steric shielding by formation of the titanium phenolate is not solely responsible for the observed

para-selectivity. It should be noted in this connection that electron-rich phenol ethers are also halogenated by the system but without the position selectivity typical for the investigated phenols.

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Experimental

For general methods and instrumentation see [21].

Preparation of Chloro- and Bromotitanium Triisopropoxides [14]

A solution of $\text{Ti}(\text{OiPr})_4$ (2.132 g, 7.5 mmol) in dry CH_2Cl_2 (10 ml) was treated at 0°C with TiCl_4 (0.474 g, 2.5 mmol) or TiBr_4 (0.919 g, 2.5 mmol) in dry CH_2Cl_2 (10 ml). The solutions were then allowed to warm to room temperature, and stirring was continued for 24 h. The 1 molar solutions can be used for one month if stored at 4°C .

Chlorination of Phenols (General Procedure)

A solution of the phenols **1–4** (1 mmol) in dry THF (10 ml) was treated with $\text{TiCl}(\text{OiPr})_3$ (1 mmol, 1 mol/l in CH_2Cl_2). The solution turned orange and was stirred 30 min and cooled to -30°C . A solution of TBHP (0.86 ml, 3 mmol, 3.5 mol/L in CH_2Cl_2) was then added dropwise within 5 min. The yellow mixture was stirred for 20 h at room temperature, quenched by addition 10% H_2SO_4 (10 ml), and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 (each 5 ml), the combined organic phases washed twice with 10% H_2SO_4 (each 5 ml), dried (MgSO_4), and the solvent was evaporated at reduced pressure. The crude product was analyzed by GC (starting temperature 80°C , heating rate $5^\circ\text{C}/\text{min}$ to 160°C , then $10^\circ\text{C}/\text{min}$). The products were purified by column chromatography ($\text{CH}_2\text{Cl}_2/n\text{-hexane}$ 10:1) and characterized by NMR and *m.p.*; for yields see Table 1; *m.p.* **5**: 41°C (Lit. [22] $43\text{--}44^\circ\text{C}$) **7**: *m.p.* $43\text{--}44^\circ\text{C}$ (Lit. [23] *m.p.* $48.5\text{--}49^\circ\text{C}$); **9**: *m.p.* $61\text{--}62^\circ\text{C}$ (Lit. [23] : *m.p.* $65\text{--}68^\circ\text{C}$).

Table 2 Bromination of the phenols **1–4**

Substrate	<i>ortho</i> -Product (%)	<i>para</i> -Product (%)	Dibrominated product (%)	Starting material (%)
phenol (1)	3	88	6	3
2-methylphenol (2)	–	92	3.5	4.5
3-methylphenol (3)	–	90	2	8
2-methoxyphenol (4)	–	86	8	6

Table 3 Selected reagents for selective *para*-bromination of phenol **1**

Reagent	Ratio <i>ortho/para</i>	Dibrominated product (%)	Yield <i>para</i> (%)
2,4-diamino-1,3-thiazol hydrotribromide [13]	1 : 3	–	83
tetrabutylammonium tribromide [14]	–	–	93
bis(dimethylacetamid) hydrotribromide [15]	–	2.5	92
4,4-dibrom-3-methylpyrazol-5-one [16]	7.6 : 92.4	3	94
benzyltrimethylammonium tribromide [17] ^{a)}	8 : 92	traces	–
bromodimethylsulfonium bromide [18]	3 : 97	–	85
<i>N</i> -bromsuccinimid/DMF [18]	–	–	70
hexabromocyclopentadiene [19]	–	–	80

^{a)} bound on a polymeric matrix

Table 4 Comparison of the selectivity of hypochlorites in the reaction with phenol **1**

Reagent	<i>ortho</i> -product (%)	<i>para</i> -product (%)	dichloro product (%)
sodium hypochlorite	77	18	5
<i>tert</i> -butyl hypochlorite	60	38	2
<i>tert</i> -butyl hypochlorite/Ti(OiPr) ₄	53	46	1
<i>tert</i> -butyl hypochlorite/Zr(OtBu) ₄	49	49	2

tert-butyl hydroperoxide; regioselectivity

Bromination of Phenols (General Procedure)

A solution of the phenol (**1**) (1 mmol) in THF (10 ml) was treated with TiBr(OiPr)₃ (1 ml, 1 mol) and stirred 30 min at room temperature. A solution of TBHP (0.57 ml, 2 mmol, 3.5 mol/l in CH₂Cl₂) at –40 °C was then added within 5 min. The cooling bath was removed after 2 h at –40 °C, and stirring was continued for 30 min. The orange mixture was quenched by addition of 10% H₂SO₄ (10 ml), and the aqueous phase was extracted twice with CH₂Cl₂ (each 7.5 ml). The combined organic phases were extracted three times with 5% NaOH (each 5 ml), the aqueous phase was acidified to pH 2 with 10% H₂SO₄ and then extracted three times with CH₂Cl₂ (each 5 ml). The combined organic phases were dried (MgSO₄), and the solvent was evaporated at reduced pressure. The crude products were analyzed by GC (see Table 3); the pure bromides were obtained by filtration through a batch of silica gel and crystallization. **6**: (75%) *m.p.* 62 °C (Lit. [24] *m.p.* 66.4 °C); **8**: (73%) *m.p.* 34–35 °C (Lit. [25] *m.p.* 35–36 °C); **10**: (78%) *m.p.* 61 °C (Lit. [18] *m.p.* 60–61 °C); **11**: (80%) *m.p.* 58 °C (Lit. [25] *m.p.* 61–62 °C).

Chlorination of Phenols with Sodium Hypochlorite

A solution of the phenol (**1**) (1 mmol) in CH₂Cl₂ (10 ml) was treated at 0 °C with an aqueous solution of sodium hypochlorite (5 ml, 11 mmol). The resulting emulsion was stirred 4 h at room temperature. The organic phase was washed twice with 10% H₂SO₄ (5 ml), dried (MgSO₄), and the solvent was evaporated at reduced pressure. The crude oily residues were analyzed by GC (comparison with authentic samples; ratio of *ortho*- to *para* products see Table 4).

Chlorination of Phenol (**1**) with *tert*-Butyl Hypochlorite

A solution of phenol (**1**) (1 mmol) in CH₂Cl₂ (10 ml) was treated at 0 °C with *tert*-butyl hypochlorite [26] in CH₂Cl₂ (2 ml, 2.5 ml, 0.8 mol/L). The mixture was allowed to warm to room temperature and was stirred for 24 h. The solution was then extracted three times with 10% NaOH (each 5 ml), acidified to pH 2 and again extracted three times with CH₂Cl₂ (each 5 ml). The solvent was evaporated at reduced pressure and the *ortho* to *para* ratio analyzed by GC.

Chlorination of Phenol (**1**) with *tert*-Butyl Hypochlorite in Presence of Ti(OiPr)₄ or Zr(OtBu)₄

The phenols were equilibrated for 30 min at room temperature in CH₂Cl₂ (10 ml) with 1 mmol with Ti(OiPr)₄ or Zr(OtBu)₄. The reactions were then performed as described above and the *ortho* to *para* ratios analyzed by GC (ratio see Table 4).

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