Transition Metal-Catalyzed Oxidations. 11 [1]

Para-Selective Chlorination and Bromination of Phenols with *tert*-Butyl Hydroperoxide and TiX(O*i*Pr)$_3$

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Abstract. Mononuclear phenols **1**–**4** are chlorinated or brominated with high *para*-selectivity and in good yields to the halides **5**–**11** with the TiX$_n$(O*i*Pr)$_m$/TBHP system (X = 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 TiX(O*i*Pr)$_3$ (X = Cl or Br; for a review on TBHP oxidations see [3]). The halogenating power of the TiX$_n$(O*i*Pr)$_m$/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 TiCl(O*i*Pr)$_3$/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

5: X = Cl   7: X = Cl   9: X = Cl   11
6: X = Br   8: X = Br   10: X = Br
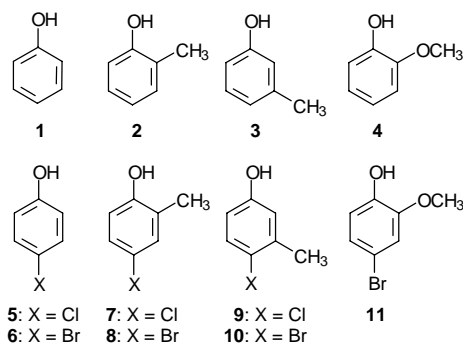
the conversions that were in the range of 90–95% by GC analysis after 20 h of reaction time at −30 °C. The corresponding *para*-chlorination products **5**, **7** and **9** were the only products detected by GC analysis; the isolated yields were 62, 58, and 47%, respectively [6]. For comparison, the 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 *ortho/para*	Dichloro product (%)	Yield *para* (%)
chlorodimethylsulfonium chloride [8]	3 : 97	–	84
N-chlorotriethylammonium chloride [9]	3 : 97	–	97 [b]
N-chloropyridinium chloride [9]	3 : 97	–	95 [b]
SO$_2$Cl$_2$, cat.: Ph$_2$S, 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 TiCl(O*i*Pr)$_3$/TBHP system. To exclude the simultaneous formation of chlorides, we later used TiBr(O*i*Pr)$_3$ that was prepared by mixing TiBr$_4$ with three parts of Ti(O*i*Pr)$_4$ similarly as described for TiCl(O*i*Pr)$_3$. 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 Ti(O*i*Pr)$_4$ or the sterically even more bulky Zr(O*t*Bu)$_4$ was treated with phenol. In fact, the amount of the *para*-product especially in the presence of Zr(O*t*Bu)$_4$ 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 TiCl(O*i*Pr)$_3$/TBHP or the related TiBr(O*i*Pr)$_3$/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.

Experimental

For general methods and instrumentation see [21].

Preparation of Chloro- and Bromotitanium Triisopropoxides [14]

A solution of Ti(O*i*Pr)$_4$ (2.132 g, 7.5 mmol) in dry CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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 TiCl(O*i*Pr)$_3$ (1 mmol, 1 mol/l in CH$_2$Cl$_2$). 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$_2$Cl$_2$) was then added dropwise within 5 min. The yellow mixture was stirred for 20 h at room temperature, quenched by addition 10% H$_2$SO$_4$ (10 ml), and the phases were separated. The aqueous phase was extracted twice with CH$_2$Cl$_2$ (each 5 ml), the combined organic phases washed twice with 10% H$_2$SO$_4$ (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 °C/min to 160 °C, then 10 °C/min). The products were purified by column chromatography (CH$_2$Cl$_2$/*n*-hexane 10:1) and characterized by NMR and *m.p.*; for yields see Table 1; *m.p.* **5**: 41 °C (Lit. [22] 43–44 °C) **7**: *m.p.* 43–44 °C (Lit. [23] *m.p.* 48.5–49 °C); **9**: *m.p.* 61–62 °C (Lit. [23] : *m.p.* 65–68 °C).

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

Substrate	*ortho*-Product (%)	*para*-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 *ortho/para*	Dibrominated product (%)	Yield *para* (%)
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
N-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	*ortho*-product (%)	*para*-product (%)	dichloro product (%)
sodium hypochlorite	77	18	5
tert-butyl hypochlorite	60	38	2
tert-butyl hypochlorite/Ti(O*i*Pr)$_4$	53	46	1
tert-butyl hypochlorite/Zr(O*t*Bu)$_4$	49	49	2

tert-butyl hydroperoxide; regioselectivity

Bromination of Phenols (General Procedure)

A solution of the phenol (1 mmol) in THF (10 ml) was treated with TiBr(O*i*Pr)$_3$ (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 CH$_2$Cl$_2$) 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% H$_2$SO$_4$ (10 ml), and the aqueous phase was extracted twice with CH$_2$Cl$_2$ (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% H$_2$SO$_4$ and then extracted three times with CH$_2$Cl$_2$ (each 5 ml). The combined organic phases were dried (MgSO$_4$), 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 mmol) in CH$_2$Cl$_2$ (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% H$_2$SO$_4$ (5 ml), dried (MgSO$_4$), 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 CH$_2$Cl$_2$ (10 ml) was treated at 0 °C with *tert*-butyl hypochlorite [26] in CH$_2$Cl$_2$ (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 CH$_2$Cl$_2$ (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(O*i*Pr)$_4$ or Zr(O*t*Bu)$_4$

The phenols were equilibrated for 30 min at room temperature in CH$_2$Cl$_2$ (10 ml) with 1 mmol with Ti(O*i*Pr)$_4$ or Zr(O*t*Bu)$_4$. The reactions were then performed as described above and the *ortho* to *para* ratios analyzed by GC (ratio see Table 4).

References

[1] Part 10: K. Krohn, J. Küpke, Eur. J. Org. Chem. **1997**, 679
[2] Selectivity, a Goal for Synthetic Efficiency (Edit.: W. Bartmann; B. M. Trost), Verlag Chemie, Weinheim 1983
[3] K. Krohn, Synthesis **1997**, 1115
[4] G. K. Chip, J. S. Grossert, Can. J. Chem. **1972**, *50*, 1233
[5] K. H. Chung, H. J. Kim, H. R. Kim, E. K. Ryu, Synth. Commun. **1990**, *20*, 2991
[6] Some loss occurred during workup.
[7] M. Hirano, S. Yakabe, H. Monobe, T. Morimoto, Can. J. Chem. **1997**, *75*, 1905
[8] G. A. Olah, L. Ohannesian, M, Arvanaghi, Synthesis **1986**, 868
[9] J. R. L. Smith, L. C McKeer, J. M. Taylor, J. Chem. Soc., Perkin Trans. II **1987**, 1533
[10] W. D. Watson, J. Org Chem. **1985**, *50*, 2145
[11] A. Guy. M. Lemaire, J.-P. Guette, Tetrahedron **1982**, 2339
[12] K. Krohn, H. Rieger, K. Khanbabaee, Chem. Ber. **1989**, *122*, 2323
[13] L. Forlani, Synthesis **1980**, 487
[14] S. Kajigaeshi, T. Kakinami, T. Okamoto, H. Nakumura, M, Fujikawa, Bull. Chem. Soc. Jpn. **1987**, *60*, 4187
[15] V. A. Mikkhailov, V. A. Savelova, M. Y. Rodygin, Russ. J. Org. Chem. **1993**, *29*, 1868
[16] S. H. Mashraqui, C. D. Mudaliar, H. Hariharasubrahmanian, Tretrahedron Lett. **1997**, *38*, 4865
[17] K. Smith, D. M. James, I. Matthews, M. R. Bye, J. Chem. Soc., Perkin Trans.1 **1992**, 1877
[18] R. H. Mitchell, Y.-H. Lai, R. V. Williams, J. Org. Chem. **1979**, *44*, 4733
[19] B. Fuchs, Y. Belsky, E. Tartakovsky, J. Zizuashvili, S. Weinman, J. Chem. Soc., Chem. Commun. **1982**, 778
[20] We thank Prof. E. Pritzkow for drawing our attention to that possibility.
[21] K. Krohn, A. Michel, U. Flörke, H.-J. Aust, S. Draeger, B. Schulz, Liebigs Ann. Chem. **1994**, 1093
[22] G. Norwitz, N. Nataro, P. N. Keliher, Anal. Chem. **1986**, *58*, 639
[23] M. Fujio, Bull. Chem. Soc. Jpn. **1975**, *48*, 2127
[24] A. Schoenberg. R. F. Heck, J. Am. Chem. Soc. **1974**, *96*, 7761
[25] J. Delobelle, M. Fetizon, Bull. Soc. Chem. Fr. **1961**, 1900
[26] C. Walling, J. A. McGuinness, J. Am. Chem. Soc. **1969**, *91*, 2053

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