Transition Metal-Catalyzed Oxidations. 11 [1]

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

Karsten Krohn, Hagen Rieger, Klaus Steingröver, and Ingeborg Vinke

Paderborn, Universität-GH, FB 13- Fachbereich Chemie und Chemietechnik

Received October 20th, 1998

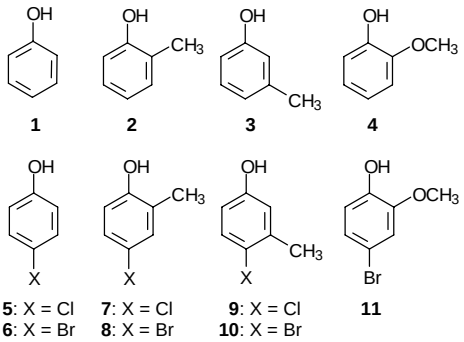
Dedicated to Prof. W. Pritzkow on the Occasion of his 70th Anniversary

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 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



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_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

  1436-9966/99/34101-59 $ 17.50 + .50/0

were formed when lithium bromide was added to the $TiCl(OiPr)_3$/TBHP system. To exclude the simultaneous formation of chlorides, we later used $TiBr(OiPr)_3$ that was prepared by mixing $TiBr_4$ with three parts of $Ti(OiPr)_4$ similarly as described for $TiCl(OiPr)_3$. 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 $Ti(OiPr)_4$ or the sterically even more bulky $Zr(OtBu)_4$ was treated with phenol. In fact, the amount of the *para*-product especially in the presence of $Zr(OtBu)_4$ 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 $TiCl(OiPr)_3$/TBHP or the related $TiBr(OiPr)_3$/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.

We thank the Deutsche Forschungsgemeinschaft for financial support of this work.

Experimental

For general methods and instrumentation see [21].

Preparation of Chloro- and Bromotitanium Triisopropoxides [14]

A solution of $Ti(OiPr)_4$ (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 $TiCl(OiPr)_3$ (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 °C/min to 160 °C, then 10 °C/min). The products were purified by column chromatography (CH_2Cl_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(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 CH_2Cl_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_2SO_4 (10 ml), and the aqueous phase was extracted twice with CH_2Cl_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_2SO_4 and then extracted three times with CH_2Cl_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_2Cl_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_2SO_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_2Cl_2 (10 ml) was treated at 0 °C with *tert*-butyl hypochlorite [26] in CH_2Cl_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_2Cl_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_2Cl_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

Address for correspondence:
Prof. K. Krohn
Fachbereich Chemie und Chemietechnik
der Univ.-GH Paderborn
Warburger Str. 100
D-33098 Paderborn
FAX: internat. code (0) 5251-60-3245
E-mail: kk@chemie.uni-paderborn.de