

Proceeding Paper

# [Fe]-*t*-BuOCl—A New Efficient Catalytic System for Chlorination of Arenes <sup>†</sup>

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† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: <https://ecsoc-25.sciforum.net/>.

**Abstract:** Chlorine derivatives of aromatic compounds are widely used in organic chemistry as intermediates for the synthesis of pharmaceuticals. Despite the abundance of various chlorination methods, almost no work on the chlorination of organic compounds using *tert*-butyl hypochlorite in the presence of catalysts. We have developed a new iron-catalyzed method for chlorination of aromatic compounds using *tert*-butyl hypochlorite. The reactions take place with high conversion and selectivity. A new method for the chlorination of ethylbenzene and toluene with *tert*-butyl hypochlorite under the action of iron-containing catalysts to give 1-(chloroethyl)benzene and benzyl chloride in more than 50% yield was developed. A new iron-catalyzed method for the synthesis of 1,4-dichloro-2,3,5,6-tetramethylbenzene in 100% yield by chlorination of durene with *tert*-butyl hypochlorite was proposed. A method was developed for the synthesis of phenol and its derivatives (anisole and 4-nitrophenol) with the use of *tert*-butyl hypochlorite under the action of iron-containing catalysts with a quantitative yield of the reaction products. The developed methodology paves the way for the industrial use of the environmentally friendly reagent in the production of chlorine derivatives of aromatic compounds.

**Keywords:** anisole; chlorination; durene; ethylbenzene; iron-containing catalysts; phenol; *t*-BuOCl; toluene

**Citation:** Asadullin, R.R.; Bayguzina, A.R.; Ramazanov, I.R. [Fe]-*t*-BuOCl—A New Efficient Catalytic System for Chlorination of Arenes. *Chem. Proc.* **2021**, *3*, x. <https://doi.org/10.3390/xxxxx>

Academic Editor: Julio A. Seijas

Published: 15 November 2021

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## 1. Introduction

Chlorine derivatives of aromatic compounds are widely used in organic chemistry as intermediates for the synthesis of pharmaceuticals [1,2]. Various reagents are used for the chlorination of aromatic compounds: Cl<sub>2</sub>, SO<sub>2</sub>Cl<sub>2</sub>, *N*-chlorosuccinimide, PCl<sub>3</sub>, PCl<sub>5</sub> [3,4]. However, these reagents have significant disadvantages: a large amount of waste is generated, in particular, during the reaction, HCl is formed, which leads to equipment corrosion; a considerable duration of the experiment, and the reactions with their participation are nonselective, in addition, they are strong poisons. Therefore, the use of *tert*-butyl hypochlorite for the selective chlorination of aromatic compounds seems to be an interesting problem. But the chlorination method using *t*-BuOCl also has disadvantages: the need to carry out the reaction at a low temperature (0 °C), low selectivity of the reaction, the difficulty of isolating the target products, the need to use UV irradiation.

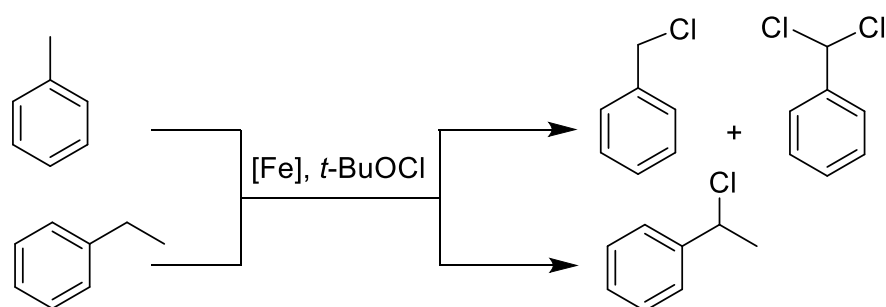
In the literature, there is practically no work on the chlorination of organic compounds using *tert*-butyl hypochlorite in the presence of catalysts. In this regard, the development of new, catalytic methods for chlorination of arenes using *t*-BuOCl is an important and urgent task.

## 2. Results and Discussion

At the first stage of the work, we tried to carry out the chlorination of alkylarenes using *tert*-butyl hypochlorite under the action of a catalyst using toluene as an example. The primary product of toluene chlorination is benzyl chloride. For the catalytic activity in the chlorination of arenes using *t*-BuOCl, we investigated the following series of iron-containing catalysts:  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ ,  $\text{FeCl}_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{Fe}(\text{C}_5\text{H}_5)_2$ ,  $\text{FeBr}_2$ . Iron complexes are one of the best catalysts for the activation of C–H bond in alkenes, aromatic compounds, alkenes, and alkynes [5]. In the absence of a catalyst, the reaction does not proceed.

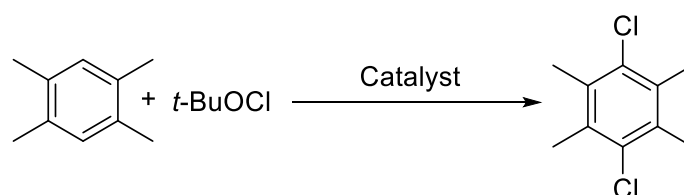
A new method for the chlorination of ethylbenzene and toluene with *tert*-butyl hypochlorite under the action of iron-containing catalysts has been proposed. The yield of 1-(chloroethyl)benzene and benzyl chloride reaches more than 50% under the following conditions: 20 °C, 5 h (ethylbenzene) and 3 h (toluene), with a molar ratio of catalyst and reagents: [catalyst]: [alkylbenzene]: [*tert*-butylhypochlorite] = 1: 100: 100 in  $\text{CH}_2\text{Cl}_2$  solution (Scheme 1).

To increase the degree of conversion of toluene, the temperature and reaction time were varied. It was found that the reaction of toluene with *tert*-butyl hypochlorite under the action of the iron-containing catalyst  $\text{FeBr}_2$  gives benzyl chloride and dichlorobenzyl chloride in a ratio of 9:1. The reaction was carried out at the following molar ratio of catalyst and reagents: [catalyst]:[toluene]:[*t*-BuOCl] = 1:100:100. The highest yield of benzyl chloride (65%) was observed at 40 °C in refluxing  $\text{CH}_2\text{Cl}_2$  for 14 h. Under the action of ultrasound, the reaction takes place within 3 h, while the conversion of toluene reaches 80%. At the same time the yield of benzal chloride increases ([benzyl chloride]: [benzal chloride] = 4: 1). The reaction was carried out with a threefold excess of *tert*-butyl hypochlorite.



**Scheme 1.** Chlorination of toluene and ethylbenzene using *t*-BuOCl.

A new method was proposed for the synthesis of 1,4-dichloro-2,3,5,6-tetramethylbenzene in quantitative yield by chlorination of 2,3,5,6-tetramethylbenzene (durene) with *tert*-butyl hypochlorite under the action of an iron-containing catalyst (Scheme 2). The yield of 1,4-dichloro-2,3,5,6-tetramethylbenzene reaches almost 100% under the following conditions: 20 °C, 5 h, with a molar ratio of catalyst and reagents: [ $\text{FeBr}_2$ ]:[ethylbenzene]:[*tert*-butylhypochlorite] = 1:100:100 in  $\text{CH}_2\text{Cl}_2$  solution.

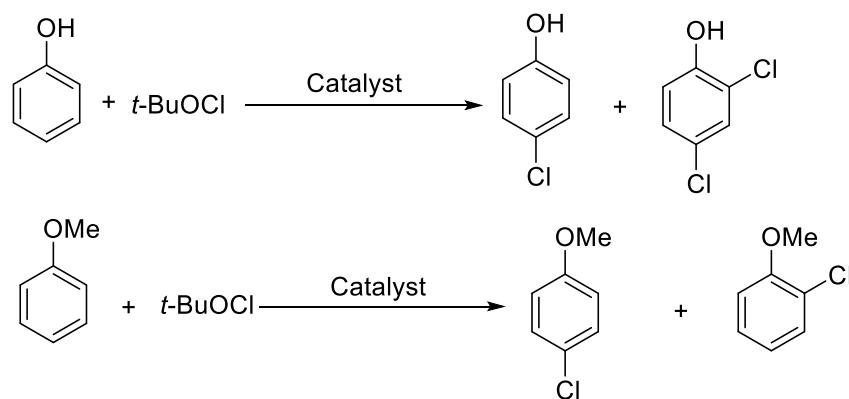


**Scheme 2.** Synthesis of 1,4-dichloro-2,3,5,6-tetramethylbenzene.

In order to study the effect of the substituent in arenes on the regularity of chlorination, we investigated the reaction of *tert*-butyl hypochlorite with phenol derivatives in the presence of iron-containing catalysts.

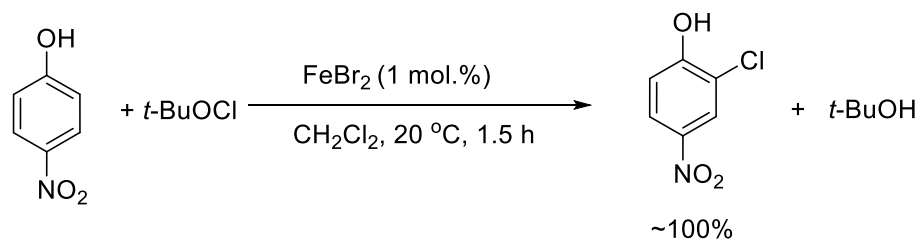
Chlorine derivatives of phenol are of particular interest, since they are produced on an industrial scale and are involved in the production of pharmaceuticals, dyes, herbicides, pesticides, and antiseptics [6].

A method has been developed for the synthesis of phenol and its derivatives by *tert*-butyl hypochlorite under the action of iron-containing catalysts with a quantitative yield of reaction products. The reactions were carried out at 20 °C for 5–24 h with the following molar ratio of catalyst and reagents: [catalyst]:[reagent]:[*tert*-butylhypochlorite] = 1:100:300 in CH<sub>2</sub>Cl<sub>2</sub> or CCl<sub>4</sub> (Scheme 3).



**Scheme 3.** Chlorination of phenol and anisole with *t*-BuOCl.

4-Nitrophenol reacts with *tert*-butyl hypochlorite in the presence of iron-containing catalysts (FeBr<sub>2</sub>, Fe(C<sub>5</sub>H<sub>5</sub>)<sub>2</sub>, FeCl<sub>2</sub> • 4H<sub>2</sub>O), at 20 °C for 0.5–5 h at a molar ratio [catalyst]:[4-nitrophenol]:[*t*-BuOCl] = 0.1–1:100:100–120, preferably [FeBr<sub>2</sub>]:[4-nitrophenol]:[*t*-BuOCl] = 1:100:100 in CH<sub>2</sub>Cl<sub>2</sub> (Scheme 4). The yield of 2-chloro-4-nitrophenol (active ingredient of the antifungal drugs “Nitrofungin”) was almost 100% in 1.5 h.



**Scheme 4.** Synthesis of 2-chloro-4-nitrophenol (nitrofungin).

### 3. Conclusions

Thus, as a result of the study, a method was developed for the catalytic chlorination of substituted arenes using *tert*-butyl hypochlorite. The reactions take place under mild conditions with high conversion and selectivity.

### 4. Experimental Part

Commercially available reagents were used. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker Avance 400 spectrometer (100.62 MHz for <sup>13</sup>C and 400.13 MHz for <sup>1</sup>H). When recording the <sup>1</sup>H and <sup>13</sup>C NMR spectra, SiMe<sub>4</sub> and CDCl<sub>3</sub> were used as an internal standards, respectively. Mass spectra were measured using Finnigan 4021 instrument with an ionizing electron energy of 70 eV and an ionization chamber temperature of 200 °C. The

elemental analysis of the samples was determined on Carlo Erba elemental analyzer, model 1106.

#### 2-Chloro-4-nitrophenol

To a 100-mL flask was added 0.016 g (0.072 mmol) of FeBr<sub>2</sub>, 1 g (7.2 mmol) of 4-nitrophenol, 2 mL of CH<sub>2</sub>Cl<sub>2</sub>. Then 0.82 mL (7.2 mmol) of freshly prepared *t*-BuOCl was added. The reaction mixture was stirred at room temperature (~20 °C) for 1 h on a magnetic stirrer with a reflux condenser. After the end of the reaction, the reaction mixture was neutralized with a 10% aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (stirring on a magnetic stirrer for 0.5–1 h), the organic layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> and filtered off. The solvent was distilled off and the solid residue was washed 3 times with water (5 mL). The yield of 2-chloro-4-nitrophenol is 1.25 g (~100%). Mp = 110–111 °C.

**Author Contributions:** Conceptualization, A.R.B.; methodology, A.R.B.; software, I.R.R.; validation, I.R.R.; formal analysis, R.R.A.; investigation, R.R.A.; resources, I.R.R.; data curation, A.R.B.; writing—original draft preparation, A.R.B.; writing—review and editing, I.R.R.; visualization, A.R.B.; supervision, A.R.B.; project administration, A.R.B.; funding acquisition, I.R.R.

**Funding:** The work was carried out within the framework of the state assignment of the Ministry of Education and Science (No.AAAA-A19-119022290009-3 and No.AAAA-A19-119022290008-6).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Acknowledgments:** The authors thank the Shared Facility Center «Agidel», Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, for the registration of NMR and mass spectra and for the elemental analysis of new compounds.

## References

1. Hassan, J.; Seignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl–Aryl Bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.* **2002**, *102*, 1359–1470. doi:10.1021/cr000664r.
2. Nicolaou, K.C.; Bulger, P.G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling reactions in total synthesis. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489. doi:10.1002/anie.200500368.
3. Smith, K.; Butters, M.; Paget, W.E.; Goubet, D.; Fromentin, E.; Nay, B. Selective mono-chlorination of aromatic compounds. *Green Chem.* **1999**, *1*, 83–90. doi: 10.1039/A901395D.
4. De la Mare, P.B.D. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, UK, 1976; pp. 96–121.
5. Khusnutdinov, R.I.; Bayguzina, A.R. New advances in the catalysis of organic reactions by iron compounds. *Russ. Chem. Rev.* **2020**, *89*, 824–857. doi:10.1070/rcr4943.
6. Muller, F.; Caillard, L. Chlorophenols. In *Ullmann's Encyclopedia of Industrial Chemistry*, 7th ed.; Wiley-VCH: Weinheim, Germany, 2011; volume 9, pp. 47–48. doi:10.1002/14356007.a07\_001.pub2.