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Regioselective Para Halogenation of Substituted Benzenes with Benzeneseleninyl Chloride and Aluminum Halide

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Synopsis. In the presence of aluminum halide, benzeneseleninyl chloride is an efficient regioselective halogenating reagent for activated aromatics such as toluene, phenol, anisole, phenetole, diphenyl ether, and *N*,*N*-dimethylaniline. Benzene and chlorobenzene are not halogenated under similar conditions.

Extensive studies on the halogenation of aromatic compounds have been reported.[1] Electron-donating substituents in a benzenoid compound generally give ortho- and para-substituted compounds, with the ortho-isomer frequently exceeding the para. Since the ortho- and para-isomers have similar physical properties, their separation is tedious. Many studies on the bromination of anilines and phenols have been reported in order to obtain a high para-regioselectivity.[2] However, these methods tend to give lower yields and also lead to di- or tri-substitution. The following three papers reportred recently are excellent methods for para-halogenation. Osa et al. found a high para-chlorination of anisole (para/ortho ratio=25/1) by an electrochemical anodic reaction in the presence of α-CD.[3] Watson found a high para chlorination of phenols (para/ortho ratio=10.5/1) by use of sulfuryl chloride catalyzed by diphenyl disulfide and aluminum chloride.[4] Olah et al. found that phenols and anilines gave more than 97% para-halogenated products by a reaction with bromodimethylsulfonium bromide or chlorodimethylsulfonium chloride.[5]

Recently, we reported that benzeneseleninyl chloride in the presence of aluminum chloride or bromide is an excellent vinylic chlorinating or brominating reagent of olefins, respectively, in one step under mild reaction conditions, and the reaction mechanism involving positive halogen (chloronium or bromonium ion) intermediate is proposed.[6] If such a positive halogen intermediate is formed under the reaction conditions, the electrophilic halogenation of aromatic compounds would also be expected by this method. We have investigated the halogenation of aromatic compounds with benzeneseleninyl chloride (**1**) in the presence of aluminum halide and found that aromatic compounds possessing electron donating-group are halogenated regioselectively at para-position in high yield. We report herein the results of these novel para-halogenations of aromatic compounds.

Benzeneseleninyl chloride (**1**), prepared from benzeneselenenyl chloride treated with ozone in dichloromethane, was allowed to react with anisole in the presence of aluminum chloride. *p*-Chloroanisole (**2a**) was formed in quantitative yield, and no formation of *o*-chloroanisole was detected by gas chromatography. Similarly, compound **1** was allowed to react with phenetole, diphenyl ether, and *N*,*N*-dimethylaniline in the presence of aluminum chloride in dichloromethane at room temperature to give *p*-chlorophenetole (**2b**), *p*-chlorodiphenyl ether (**2c**), and *p*-chloro-*N*,*N*-dimethylaniline (**2d**), respectively, in quantitative yield; and no corresponding ortho-isomer was detected by gas chromatography. These observations show that the chlorination of activated aromatics with **1** cata-

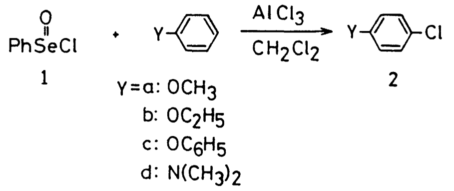


Table 1. Halogenation of Aromatic Compounds with Benzeneseleninyl Chloride and Aluminum Halide

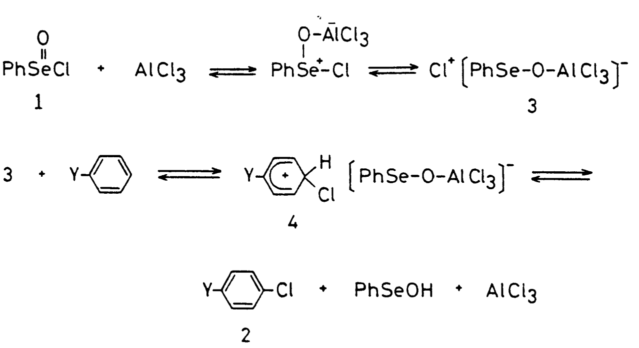
Aromatic compound	Aluminum halide	Reaction temp/°C	Reaction time/h	Product	Yield[a) /%	Isomer ratio para/ortho
Anisole	$AlCl_3$	Room temp	2	**2a** *p*-Chloroanisole	100(84)	100/0
Phenetole	$AlCl_3$	Room temp	3	**2b** *p*-Chlorophenetole	100(89)	100/0
Diphenyl ether	$AlCl_3$	Room temp	10	**2c** *p*-Chlorodiphenyl ether	100	100/0
N,*N*-Dimethylaniline	$AlCl_3$	Room temp	10	**2d** *p*-Chloro-*N*,*N*-dimethylaniline	95	100/0
Phenol	$AlCl_3$	40	2	**2e** *o*-Chlorophenol **2f** *p*-Chlorophenol	34 61	64/36
Toluene	$AlCl_3$	40	14	**2g** *o*-Chlorotoluene **2h** *p*-Chlorotoluene	30 35	54/46
Benzene	$AlCl_3$	40	24	—	0	—
Chlorobenzene	$AlCl_3$	40	48	—	0	—
Anisole	$AlBr_3$	Room temp	6	**5a** *p*-Bromoanisole	90(83)	100/0
Phenetole	$AlBr_3$	Room temp	8	**5b** *p*-Bromophenetole	94(86)	100/0
Diphenyl ether	$AlBr_3$	−10	6	**5c** *p*-Bromodiphenyl ether	92	100/0
N,*N*-Dimethylaniline	$AlBr_3$	−10	3	**5d** *p*-Bromo-*N*,*N*-dimethylaniline	99	100/0

a) Determined by GLC using an internal standard. Isolated yields are given in parentheses.

lyzed by aluminum chloride is regiospecific, and that the method is quite efficient for the synthesis of para-chlorinated aromatic compounds.

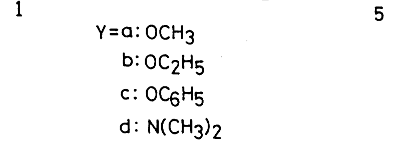
On the other hand, the reaction of **1** with phenol in the presence of aluminum chloride in dichloromethane at 40 °C gave a mixture of *o*- and *p*-chlorophenol (para/ortho ratio=64/36) in high yield. Similarly, the reaction of **1** with toluene under similar conditions afforded *o*- and *p*-chlorotoluene in 30 and 35% yield, respectively. The results show that both the yield and regioselectivity are lowered when the substituents on the benzene ring are OH or CH_3. Moreover, benzene and chlorobenzene were not chlorinated by **1** under similar reaction conditions. The results are summarized in the Table 1. These observations suggest that chlorination by this method is an electrophilic substitution on the activated aromatic nucleus.

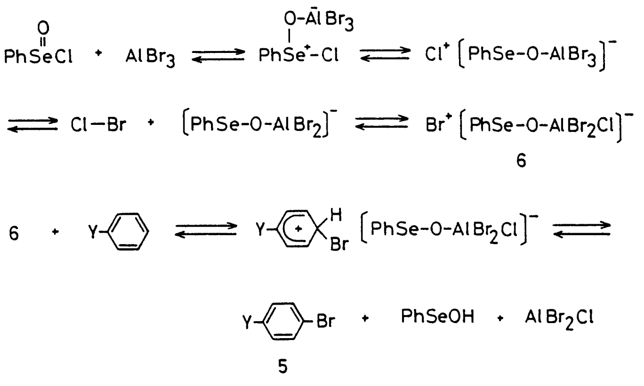
The reaction mechanism is accounted for by Scheme 1, which involves a chloronium ion intermediate.[6] The aluminum chloride interacts with the oxygen atom of **1** to give chloronium trichloro(phenylselenooxy)aluminum intermediate (**3**). The following electrophilic reaction of the chloronium ion toward aromatic nucleus affords para-chlorinated products via carbocation intermediate (**4**). The observed high para-selectivity is a consequence of the transfer chlorinations going through a "late" arenium ion like transition state and of the bulky nature of the halogenating reagent (**3**).



Scheme 1.

When a reaction of **1** with anisole was carried out in the presence of aluminum bromide instead of aluminum chloride in dichloromethane at room temperature, *p*-bromoanisole (**5a**) was obtained in 90% yield and no formation of the ortho-isomer was observed. Similarly, compound **1** was allowed to react with phenetole, diphenyl ether, and *N*,*N*-dimethylaniline in the presence of aluminum bromide to give *p*-bromophenetole (**5b**), *p*-bromodiphenyl ether (**5c**), and *p*-bromo-*N*,*N*-dimethylaniline (**5d**) in high yield, respectively. The results show that benzeneseleninyl chloride in the presence of aluminum bromide is a quite efficient para-brominating reagent of activated aromatics. The results indicate that a bromonium ion is involved in this reaction as a reactive intermediate, as shown in Scheme 2.





Scheme 2.

In conclusion, benzeneseleninyl chloride in the presence of aluminum chloride and aluminum bromide is a versatile chlorinating and brominating reagent at the para-position of activated benzenes.

Experimental

Measurement. Gas chromatography was performed by using a Hitachi 163 and 263-10 gas chromatograph using SE 30 (10 %), 1 m column. Mass spectra were determined with a JEOL JMX-DX 300 mass spectrometer with JEOL JMA 5000 Mass Data System at an ionizing voltage of 20—70 eV.

Materials. Benzeneselenenyl chloride of Nakarai Chemicals was distilled prior to use; bp 82 °C/3 mmHg (120 °C/20 mmHg) (1 mmHg=133.322 Pa).[7] Benzeneseleninyl chloride (**1**) was prepared by ozonization of benzeneselenenyl chloride with stirring in dry dichloromethane at −70 °C until the orange-red color has faded to a light yellow[8] by introducing ozone prepared by a Nippon Ozone Model O-3-2 ozonizer. The benzeneseleninyl chloride prepared was used to the reaction with aromatic compounds in situ since the compound is extremely hygroscopic and care must be taken to avoid moisture. Toluene, chlorobenzene, phenol, anisole, phenetole, diphenyl ether, and *N*,*N*-dimethylaniline used were obtained from Tokyo Kasei Co.

General Procedure for the Reaction of Benzeneseleninyl Chloride (1) with Aromatic Compound. To a stirred solution of benzeneseleninyl chloride, prepared from benzeneselenenyl chloride (192 mg, 1 mmol) by ozonization at −70 °C in dichloromethane (20 cm^3), was added corresponding aromatic compound (1 mmol) and aluminum halide (1 mmol) under nitrogen-gas bubbling. The mixture was allowed to raise the temperature at 40 °C or room temperature and was stirred for an appropriate time (see Table 1). Water (30 cm^3) was added to the reaction mixture, which was then extracted with dichloromethane (20 $cm^3 \times 2$). The combined organic extracts were washed with saturated solution of sodium carbonate (20 cm^3) and water (30 cm^3), and dried over magnesium sulfate. The halogenated aromatic products were analyzed by GLC and GC-MS comparing with their authentic samples, and the yields were determined by using acetophenone as the internal standard.

General Procedure for the Isolation of Para-Halogenated Benzenes. The halogenation of substituted benzene (30 mmol) by benzeneseleninyl chloride (10 mmol) in the presence of aluminum halide (10 mmol) in dichloromethane (300 cm^3) was carried out in a similar procedure shown above. The reaction mixture was quenched by water (50 cm^3); then dichloromethane was evaporated. The organic layer was extracted with ether (300 cm^3), dried over magnesium sulfate; the solvent was evaporated, and the residue was subjected to the silica-gel chromatography by using hexane as an eluent to give *p*-halogenated benzene. The product was further purified (if necessary) by gel-permeation chromatography on a JAI LC-08 liquid chromatograph with a JAIGEL-1m column (20ϕ×600 mm×2) using chloroform as an eluent.

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