

Synthetic Methods and Reactions; 127¹. Regioselective *para* Halogenation of Phenols, Phenol Ethers and Anilines with Halodimethylsulfonium Halides

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Halodimethylsulfonium halides [bromodimethylsulfonium bromide and chlorodimethylsulfonium chloride] are efficient regioselective *para* halogenating agent for activated aromatics, such as phenol, anisole, diphenyl ether and *N*-alkylanilines. Dihalo and monohalo derivatives of diphenyl ethers were obtained depending upon the reaction conditions. Aniline itself is not suitable in the reaction due to the strong complexation of the lone electron pair of nitrogen with the sulfonium reagent.

Halogenation is one of the most widely used and extensively studied aromatic substitution reaction². Electron donating substituents in a benzenoid compound generally give *ortho/para* substitution, with the *ortho*-isomer frequently exceeding the *para*. As the *ortho*- and *para*-isomers have similar physical properties their separation is tedious. The halogenation of anilines and phenols is usually so fast that it can be carried out in dilute aqueous solutions of bromine and chlorine at room temperature. Primary aminobenzenes, consequently, are often converted to their corresponding acetanilides if monosubstitution is desired.

In order to bring about increased *para*-regioselectivity it was found that the reaction of 2,4,4,6-tetrabromocyclohexa-2,5-dienone with anilines³ and phenols⁴ in dichloromethane or chloroform solution gives extensive *para* substitution. In addition, complexes of bromine with carbon disulfide⁵,

ethylene dichloride⁶, dimethylformamide⁷, dioxane⁸, and dimethylsulfoxide⁹, have been used for bromination of reactive benzenoids. However, these complexes tend to give lower yields and also lead to di- or tri-substitution.

Recently Watson reported¹⁰ the use of sulfonyl chloride and sulfonyl chloride catalyzed by diphenyl sulfide and aluminum chloride or ferric chloride for the preparation of *para* chlorinated phenols. However, the highest *para/ortho* ratio obtained was 10.5 at temperatures above the melting point of the phenols. Furthermore, inevitable aromatic biproduct formation under these conditions also makes the reaction less attractive.

Our continued interest in selective aromatic substitutions combined with our previous experience with halodimethylsulfonium halides has led us to a study of the halogenation of reactive aromatic compounds with dimethylhalosulfonium halides.

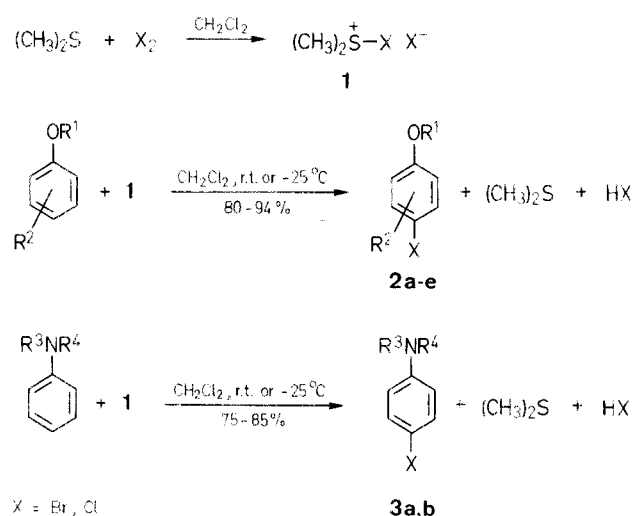
Since Meerwein's discovery in 1965 of the bromodimethylsulfonium ion^{11a} and Corey's subsequent use of chlorodimethylsulfonium chloride^{11b,c}, halodimethylsulfonium halides have become useful reagents.

In recent years we have demonstrated the remarkably facile use of halodimethylsulfonium halides in the synthesis of α -halo ketones¹², oxidation of thiols to disulfides¹³, and dethioacetalization reactions¹³. We now would like to report on their use as effective *para* regioselective aromatic halogenating agents for activated aromatics such as phenols, phenyl ethers and anilines.

Bromodimethylsulfonium bromide (BDMS) and chlorodimethylsulfonium chloride (CDMS) are easily prepared from dimethylsulfide and bromine or chlorine, respectively, as isolable, relatively stable crystalline compounds. Results for the bromination or chlorination of activated aromatic compounds with these reagents are given in the Table.

Phenols, phenyl ethers, and anilines react with BDMS or CDMS at -25 to 0°C in dichloromethane solution during

4–10 h to give the corresponding *para* halogenated products in pure form.



2	R ¹	R ²	3	R ³	R ⁴
a	H	H	a	CH ₃	CH ₃
b	H	<i>o</i> -CH ₃	b	COCH ₃	H
c	CH ₃	H			
d	CH ₂ CH ₃	H			
e	C ₆ H ₅	H			

Gaseous hydrogen halide and low boiling dimethyl sulfide formed in the reaction can be easily removed from the reaction mixture. As shown by data reported in the Table, highly selective *para* halogenation is achieved in all reactions. GLC analysis shows that the *para*-halogenated products are all in excess of 97%. Isolated product yields are from 75 to 94% showing that the reaction in general gives good to excellent yields.

Table. Halogenation of Reactive Aromatics with Halodimethylsulfonium Halide

Benzenoid ^a	Product	Reaction Time [h]		Yield ^b [%]		b.p. [°C]/torr or m.p. [°C]		Reported ¹⁰ b.p. [°C]/torr or m.p. [°C]	
		X = Cl	X = Br	X = Cl	X = Br	X = Cl	X = Br	X = Cl	X = Br
phenol	4-halophenol (2a)	4	4	84	85	78–80/2.75	82–4/0.4	220/760	235–6/760
<i>o</i> -cresol	5-halo- <i>o</i> -cresol (2b)	5	4	80	81	80/1	88/1.5	220–5/760	235/760
anisole	4-haloanisole (2c)	4	8	80	94	48–50/0.4	55–6/1.5	198–202/760	198–220/760
phenetole	4-halophenetole (2d)	4	8	85	90	70–3/0.4	67–70/1.5	212/760	233/760
<i>N,N</i> -dimethylaniline	4-halo- <i>N,N</i> -dimethylaniline (3a)	4	8	75	84	90/1	89–90/1.5	233–6/760	264/760
acetanilide	4-haloacetanilide (3b)	4	8	85	80	176	165	178	167
diphenyl ether	4-halophenyl ether (2e)	4	8	87 ^c	94	87–90/0.25	80/0.5	100–4/0.4	124–8/3–4
diphenyl ether ^d	–	4	8	85 ^c	94 ^f	150/1.3	80/0.5	312–4/760 ¹⁷	124–8/3–4
<i>p</i> -cresol	–	10	10	NR ^g	NR ^g	–	–	–	–

^a In every case the ratio of benzenoid to BDMS is 1 : 1.2, unless otherwise mentioned.

^b Yields of the isolated products of > 98% purity as determined by GC and IR, ¹H-NMR, and ¹³C-NMR spectroscopy.

^c Reverse addition of CDMS (see experimental section).

^d In this case the ratio of diphenyl ether to BDMS is 1 : 2.4. Excess CDMS produced 4,4'-dichloro-diphenyl ether; however, excess BDMS had no effect, and only 4-bromophenyl phenyl ether was obtained.

^e Yield of 4,4'-dichloro-diphenyl ether.

^f Yield of 4-bromophenyl phenyl ether as only isolated product.

^g No reaction.

When less reactive aromatic compounds such as toluene were reacted under the same condition with halodimethylsulfonium halides, no halogenated products were obtained.

The observed high *para* selectivity is a consequence of the transfer halogenations going through a "late" arenium ion like transition state and of the bulky nature of the halogenating agents. When the *para* position is blocked, as in *p*-cresol, reaction with bromodimethylsulfonium bromide gives no halogenation.

The reaction of diphenyl ether with BDMS (1:1.2 molar ratio) affords exclusively 4-bromophenyl phenyl ether (the monobromination product). In contrast the major product of the reaction of diphenyl ether with CDMS is 4,4'-dichlorodiphenyl ether. This indicates the higher reactivity of CDMS against BDMS. Even if excess BDMS is used in the reaction with diphenyl ether (2.4:1) the only product was 4-bromophenyl phenyl ether. The same ratio of CDMS to diphenyl ether (2.4:1) gave 4,4'-dichlorodiphenyl ether. However, reverse addition of CDMS to the solution of diphenyl ether gives pure 4-chlorophenyl phenyl ether (see experimental section).

Phenols, phenyl ethers and anilines used were obtained from Aldrich Chemical Co. Chlorine gas (99%, Matheson) and bromine (Dow Chemical) were used as obtained. The halogenated aromatic products were analyzed by GLC. Product isolation was by distillation, and isolated products were also analyzed by ¹H- and ¹³C-NMR and IR spectroscopy.

Bromination with bromodimethylsulfonium bromide: General Procedure:

To a stirred solution of bromodimethylsulfonium bromide¹⁵ (5.45 g, 25 mmol) in dichloromethane (30 ml, dried over phosphorus pentoxide) at room temperature under nitrogen is added during 10 min a solution of the corresponding activated benzenoid (20 mmol). The reaction mixture is stirred for the appropriate time (see Table) at room temperature. Water (50 ml) is added to the mixture, which is then extracted with dichloromethane (2 × 20 ml). The combined organic extracts are washed with saturated solution of sodium carbonate (20 ml) and water (30 ml), dried over magnesium sulfate, and concentrated to afford almost pure product. All products are subject to distillation.

Chlorination with chlorodimethylsulfonium chloride: General Procedure:

To a magnetically stirred solution of chlorine (0.85 g, 12 mmol) in dichloromethane (10 ml, dried over P₂O₅) under nitrogen at -25°C (carbon tetrachloride/acetone) is added a solution of dimethylsulfide (0.93 g, 15 mmol) in dichloromethane (5 ml). A solution of benzenoid (10 mmol) in dichloromethane (10 ml) is then added and the stirring continued for the indicated time (see Table) at -25°C. At the end of the given period, the cooling bath is removed, and after 5 minutes the reaction mixture is diluted with water (15 ml). The organic layer is separated, and the aqueous layer extracted with dichloromethane (2 × 15 ml). The organic layers are combined and washed with a saturated solution of sodium carbonate (25 ml), followed by brine (10 ml). Drying the organic extracts over anhydrous magnesium sulfate and removal of solvent give almost pure product, which was further purified by distillation.

4-Chlorophenyl phenyl ether:

To a magnetically stirred solution of diphenyl ether (1.70 g, 10 mmol) in dry dichloromethane (10 ml) under nitrogen is added chlorodimethylsulfonium chloride (12 mmol; prepared as described in the above procedure and kept in an addition funnel equipped with a dry ice-acetone cooling coil) at -78°C. After the addition is complete, the reaction mixture is allowed to warm to -25°C and kept at this temperature for an additional 4 h. The cooling bath is then removed. After 5 minutes the reaction mixture is diluted with

water (15 ml), and extracted as described above. Removal of solvent after extraction gives almost pure product, which is further purified by distillation; yield: 1.78 g (87%), b.p. 87-90°C/0.25 torr.

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