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Bromination of deactivated aromatic compounds

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Contents

I.	Introduction	421
II.	Bromination with molecular bromine and inorganic bromine compounds	421
III.	Bromination with organic *N*-bromo compounds	425
IV.	Conclusion	427

Abstract. The methods of bromination of aromatic compounds containing electron-withdrawing substituents are reviewed. The relevant reagents, catalysts, reaction media and putative reaction mechanisms are discussed. The bibliography includes 71 references.

I. Introduction

Aromatic compounds containing a bromine atom in the ring are of considerable importance for organic synthesis. Bromine is introduced into the aromatic ring to impart the desired consumer properties to the final product or to attain the required reactivity of the formed intermediate. Substances pertaining to the former group are produced on an industrial scale: fire retardants, fuel additives, pharmaceuticals and agrochemicals, dyes.[1] Compound of the latter group are much more diverse, as bromoarenes are able to undergo various reactions that involve bromine exchange. These reactions include nucleophilic aromatic halogen substitution,[2] electron-transfer substitution,[3] the Ullmann reaction,[4] palladium complex-catalyzed cross-coupling reactions[5,6] (the Mizoroki – Heck,[7,8] Suzuki – Miyaura,[9] Buchwald – Hartwig,[10] Negishi,[11] Stille,[12] Sonogashira[13] reactions).

The principal method of bromine introduction into aromatic molecules is the substitution of hydrogen under the action of an electrophilic brominating agent.[14] An alternative way is the transformation of an amine to the bromide *via* diazonium salts by the Sandmeyer reaction, or, which is less common, nucleophilic substitution of a bromide anion for the nitro group or another halogen atom.[2] The electrophilic brominating agents include molecular bromine, some inorganic bromine compounds and organic *N*-bromo derivatives. Electrophilic bromination easily proceeds when the activating electron-donating groups are present in the aromatic ring. The presence of deactivating electron-withdrawing substituents requires development of specific methods of bromination. However, this issue has not been considered in modern monographs.[14] The present paper is the first systematic review in this field.

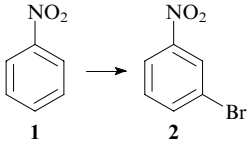
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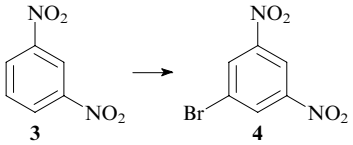
II. Bromination with molecular bromine and inorganic bromine compounds

The degree of deactivation of an arene depends on the overall electron-withdrawing effect of substituents in the aromatic system. Arenes can arbitrarily be divided into moderately deactivated and strongly deactivated ones. Compounds of the former group bear one electron-withdrawing group [NO_2, C(O)R, CHO, CN, CO_2R, SO_2R, *etc.*] in the ring, those of the latter contain two or more such groups. The bromination procedures applicable to monosubstituted arenes are not necessarily suitable for the disubstituted ones. The most popular model compound of the first type is nitrobenzene, 1,3-dinitrobenzene being an example of the second type.

Nitrobenzene (**1**) is transformed into 3-bromonitrobenzene (**2**) upon monobromination, while 1,3-dinitrobenzene (**3**) gives 5-bromo-1,3-dinitrobenzene (**4**).



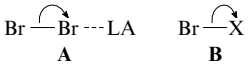
1 **2**



3 **4**

Unlike activated compounds, the deactivated arenes react with molecular bromine only in the presence of a

catalyst or a co-reagent. The reaction is carried out by direct contact of the substrate with bromine and a Lewis acid in an organic solvent or in sulfuric acid. Lewis acid (LA) catalysts ($FeBr_3$, $AlCl_3$) increase the electrophilicity of the reagent due to polarization of the Br—Br bond in the complex (**A**) formation. The co-reagent or a homogenous catalyst reacts with the bromine molecule resulting in the intermediate Br—X, where X is a nucleofugal group where a more electronegative atom is bound to bromine: fluorine, chlorine, oxygen, sulfur, nitrogen. Due to the polarization of the Br—X bond, this intermediate acts as an electrophilic brominating agent (**B**).



A **B**

Benzene is brominated at ambient temperature in the presence of iron filings or $FeBr_3$, whereas nitrobenzene (**1**) undergoes bromination into 3-bromonitrobenzene (**2**) upon heating at 135–140 °C for several hours (the yield is 60%–75%).[15] In a similar way, 2-bromo-4-nitrotoluene is obtained by bromination of 4-nitrotoluene at 70–80 °C (86%–90% yield).[16] When bromine is added to the molten complex of acetophenone and $AlCl_3$ at 80–85 °C, 3-bromoacetophenone is isolated in 70%–75% yield;[17] if less than 1 equiv. of $AlCl_3$ is employed, α-bromoacetophenone is formed in considerable amounts.

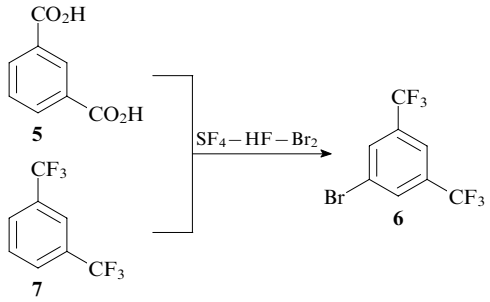
The reagent Br—X, which performs the attack, is, in most cases, formed during the reaction. The only compound of this type known as the reagent is bromine fluoride (X = F) characterized by its high reactivity; at the same time, it is instable and is of limited accessibility. This compound is prepared by passing fluorine with a flow of nitrogen into a solution of bromine in CCl_3F at −78 °C; the thus obtained BrF solution is added to the solution of a substrate in $CHCl_3$. Nitrobenezene is converted to 3-bromonitrobenzene in 95% yield in a reaction with this reagent (1.7 equiv.) at −40 °C, the reaction with 4.5 equiv. results in 3,5-dibromonitrobenzene (70% yield); 1,3- dinitrobenzene is transformed to 5-bromo-1,3-dinitrobenzene under the action of 7 equiv. of BrF (93% yield).[18] Since bromine fluoride cannot be stored and is to be prepared before each experiment, more stable bromine trifluoride was suggested. Its mixture with bromine is added to an excess of a substrate at 0–10 °C; the yield of bromonitrobenzene **2** is 80% based on the consumed substrate.[19]

$$BrF_3 + Br_2 \rightleftharpoons 3\,BrF.$$

The brominating agent in the equimolar mixture of Br_2 and $SbCl_5$ is presumably BrCl, this is used as a solution in an organic solvent. Both of the bromine atoms are consumed due to the oxidation of the bromide anion with $SbCl_5$. The reaction of nitrobenzene in refluxing dichloroethane at 84 °C for 3 h results in 3-bromonitrobenzene (63% yield), ethyl benzoate is converted into ethyl 3-bromobenzoate (74%), the reaction of acetophenone in CCl_4 (35 °C, 0.5 h) affords 3-bromoacetophenone (86%).[20]

$$2\,ArH + Br_2 + SbCl_5 \longrightarrow 2\,ArBr + SbCl_3 + 2\,HCl.$$

The bromination with the $SF_4—HF—Br_2$ system occurs with conversion of the carboxyl groups to trifluoromethyl groups.[21] Thus heating isophthalic acid (**5**) with the $SF_4—HF—Br_2$ mixture in an autoclave at 120 °C for 12 h results in 5-bromo-1,3-bis(trifluoromethyl)benzene (**6**) in 93% yield. 1,3-Bis(trifluoromethyl)benzene (**7**) reacts in a similar way, but 3-trifluoromethylnitrobenzene is not brominated even at 160 °C. Sulfur tetrabromide is presumably formed during the reaction.



Bromination of nitrobenzene and 4-nitrobenzoic acid with tetrabutylammonium tribromide $Bu^n_4N^+Br_3^-$ proceeds very fast (1–2 min) under solvent-free conditions and microwave irradiation at 90 °C; the yield of the 3-bromo-substituted product is 35%–45%.[22]

Reactions with molecular bromine in the medium or in the presence of oxoacids (AOH) and catalysts or different co-reagents occur presumably *via* the species BrOA. Their brominating activity is the higher the better leaving group is the AO^- anion, and is the higher the stronger the acid AOH.

Nitrobenzene is brominated in trifluoroacetic acid under the action of KBr and $Pb(OAc)_4$ at ambient temperature.[23] Red lead (Pb_3O_4) can be used instead of lead tetraacetate. At the molar ratio of $PhNO_2 : Pb_3O_4 : KBr = 1 : 2 : 2$, nitrobenzene **2** is formed in 90% yield.[24] The halogenating agent is believed to be the bromine trifluoroacetate ($CF_3\,CO_2Br$).

In the reaction of nitrobenezene (**1**) with equimolar amount of potassium bromate ($KBrO_3$) in sulfuric acid at ~30 °C, the yield of bromonitrobenzene **2** strongly depends on the acid concentration.[25] At the concentration of H_2SO_4 <40%, no bromination occurs; with 68% acid the yield of **2** reaches ~90%, and in 70% H_2SO_4 it drops to 15% due to the uncontrolled bromate decomposition.

Reaction of a deactivated substrate (nitrobenzene, benzoic acid, benzonitrile) with bromine and mercury(II) oxide at a molar ratio 1 : 1 : 2 in refluxing CCl_4 in the presence of a small amount of H_2SO_4 affords the corresponding 3-bromo-substituted products in 50%–79% yields.[26] Only one of the two bromine atoms of the molecule is consumed, the second forming a compound with mercury. The action of bromine and mercury oxide in concentrated H_2SO_4 and oleum results in polybromination products. Thus treatment of nitrobenzene with an excess of the $Br_2—HgO$ reagent (molar ratio 2 : 1) in 20% oleum at 60 °C for 2 h affords 91% pentanitrobenzene (**8**).[27] Presumably, the reaction of bromine with mercury oxide produces an unstable bromine monoxide (Br_2O), which is converted to bromosulfate ($BrOSO_2OH$) in concentrated sulfuric acid:

$$2\,Br_2 + HgO + 2\,H_2SO_4 \longrightarrow 2\,BrOSO_2OH + HgBr_2 + H_2O.$$

Bromination with molecular bromine in conc. H_2SO_4 can be effected in the presence of silver salts. The reaction of nitrobenzene (**1**) with equimolar amounts of bromine and silver sulfate[28] or silver trifluoromethanesulfonate[29] in conc. H_2SO_4 for 14–16 h without heating affords 3-bromonitrobenzene (**2**) in 70%–74% yield. 1,3- Dinitrobenzene

(**3**) does not react under the described conditions, but heating at 90 °C with silver trifluoromethanesulfonate in conc. H_2SO_4 affords 5-bromo-1,3-dinitrobenzene (**4**) in 71% yield.[29] The action of bromine and an eqimolar amount of Ag_2SO_4 in conc. H_2SO_4 at 100–110 °C for 32 h converts isophthalic acid (**5**) to 5-bromoisopthalic acid (**9**).[30] Presumably, the silver cation binds the bromide anion to generate bromosulfonate as the brominating reagent:

$$Br_2 + AgOSO_2R \xrightarrow{H_2SO_4} BrOSO_2OR + AgBr,$$

R = H, CF_3, Ar.

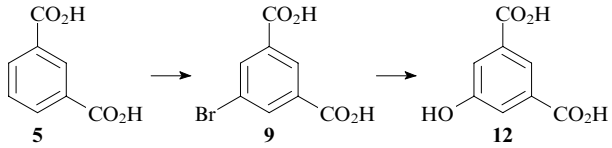
Oxidation of bromine with peroxysulfates in H_2SO_4 also possibly leads to bromosulfonate.

$$Br_2 + 4\text{-}ClC_6H_4SO_2{-}OO{-}SO_2C_6H_4Cl\text{-}4 \xrightarrow{H_2SO_4} 2\,BrOSO_2C_6H_4Cl\text{-}4.$$

3-Bromonitrobenzene (**2**) was obtained in 60% yield in the reaction of equimolar amounts of nitrobenzene (**1**), bromine and bis(4-chlorophenylsulfonyl) peroxide $4\text{-}ClC_6H_4SO_2{-}OO{-}SO_2C_6H_4Cl\text{-}4$ in conc. H_2SO_4 at 30 °C for 14 h.[29]

The formation of peroxosulfates probably accounts for bromination of a substrate with bromine in conc. H_2SO_4, which is carried out with continuous addition of aqueous hydrogen peroxide and heating.[31] Thus, treatment of 3,4-dichloronitrobenzene (**10**) with bromine in sulfuric acid and continuous introduction of H_2O_2 at 80 °C gives 3-bromo-4,5-dichloronitrobenzene (**11**); bromination of 4-chloronitrobenzene using H_2O_2 and a double amount of bromine leads to 3,5-dibromo-4-chloronitrobenzene.

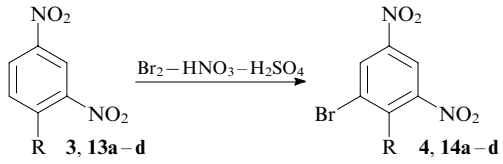
A procedure for the synthesis of 5-hydroxyisophthalic acid (**12**) was developed, which includes bromination of isophthalic acid (**5**) into 5-bromoisophthalic acid (**9**) with bromine in oleum and catalytic amounts of iodine.[32]



Heating of isophthalic acid (**5**) with bromine (molar ratio 1 : 0.6) in 20% oleum with 2% iodine at 102–105 °C for 6 h affords a reaction product containing 83%–91% of monobromoisophthalic acid (**9**) and 5%–8% of dibromo derivatives, which are removed in subsequent steps. Increasing the concentration of oleum up to 40% reduces the degree of dibromination.

According to a patent,[33] isophthalic acid (**5**) is brominated in oleum without any catalyst at elevated temperature under pressure. Thus heating of **5** with equimolar amount of bromine in 10% oleum in a sealed tube at 130 °C (22 h), affords 5-bromoisophthalic acid (**9**) in ~80% yield.

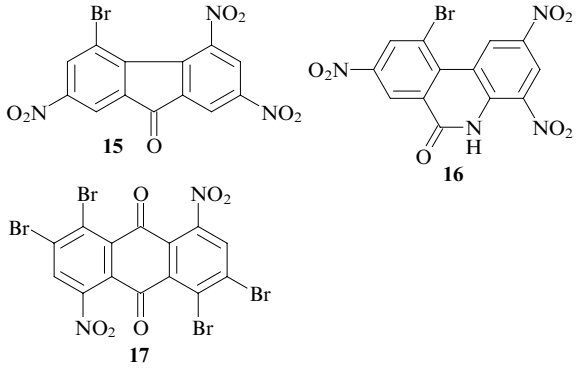
Nitric acid proved to be an efficient co-reagent of bromination of strongly deactivated compounds with molecular bromine.[31,34] Heating of 1,3-dinitrobenzene (**3**) in conc. H_2SO_4 with bromine and nitric acid (molar ratio 1 : 0.5 : 1) at 70–80 °C leads to 5-bromo-1,3-dinitrobenzene (**4**). In a similar way, dinitrobenzenes **13a–d** were brominated with the formation of the corresponding bromo derivatives **14a–d**.[31]



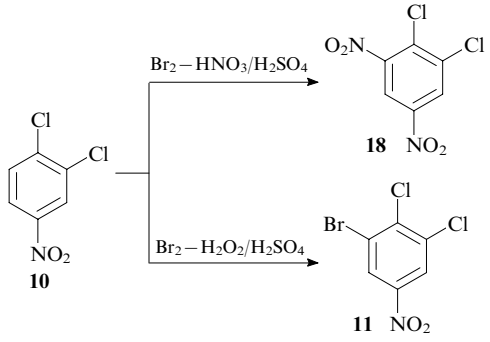
R = H (**3**, **4**), Cl (**a**), Br (**b**), F (**c**), Me (**d**).

In the absence of nitric acid, these deactivated aromatic compounds do not react. Introduction of an additional electron-withdrawing group (nitro or carboxyl group) into position 5 of the molecule prevents bromination. At the concentration of H_2SO_4 < ~90%, the brominating activity of the system drops, and at the concentration of H_2SO_4 below ~85% the system looses its activity. The described method was applied to a preparative-scale synthesis of 5-bromo-1,3- dinitrobenzene.[35,36] In an attempted bromination of 3-nitrobenzaldehyde, oxidation of the aldehyde group occurred resulting in 3-bromo-5-nitrobenzoic acid.[37]

This method has been extended to deactivated polycyclic compounds. It was shown that 2,4,7- trinitrofluoren-9-one is smoothly transformed to 5-bromo-2,4,7-trinitrofluoren-9-one (**15**), 2,4,8-trinitro-5*H*-phenanthridin-6-one gives 10-bromo-2,4,8-trinitro-5*H*-phenanthridin-6-one (**16**)[38] and 1,5-dinitroanthraquinone is converted to 3,4,7,8-tetrabromo-1,5-dinitroanthraquinone (**17**) using an excess of the brominating reagent.[39] Identification of 10-bromo-substituted trinitrophenanthridinone **16** formed in the nitration of 2-bromophenanthridinone was rationalized as a result of debromination and subsequent bromination of trinitrophenanthridinone;[38] this served as a reason to study bromination in the presence of nitric acid.



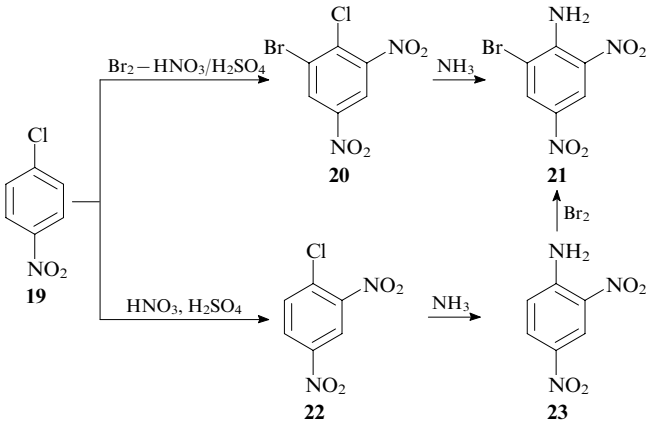
The competition between the bromination and nitration reactions of strongly deactivated aromatic compounds results in virtually exclusive bromination, while nitration prevailed in the case of moderately deactivated substrates. 3,4-Dichloronitrobenzene (**10**) is transformed upon action



of bromine and nitric acid mainly into 1,2-dichloro-3,5-dinitrobenzene (**18**), rather than into 3-bromo-4,5-dichloronitrobenzene (**11**). To avoid competitive nitration, the use of a different oxidant is reasonable. Compound **11** was successfully synthesized by the reaction of nitrobenzene **10** with bromine in sulfuric acid with gradual addition of hydrogen peroxide.[31]

The increase in the extent of deactivation of an aromatic compound results in greater suppression of nitration compared to bromination, which suggests the lesser substrate selectivity of the latter. This feature makes it possible to combine the nitration and bromination into one preparative step. 4-Chloronitrobenzene (**19**) is transformed to 5-bromo-4-chloro-1,3-dinitrobenzene (**20**) upon treatment with bromine and nitric acid in concentrated sulfuric acid due to initial selective nitration and subsequent bromination. Two-step synthesis of 6-bromo-2,4-dinitroaniline (**21**) from 4-chloronitrobenzene (**19**) (Scheme 1) is based on this procedure, compound (**21**) being a diazo component of dispersed dyes.[40,41] Simultaneous nitration – bromination and subsequent ammonolysis of 5-bromo-4-chloro-1,3-dinitrobenzene (**20**) are carried out instead of the traditional three-step synthesis *via* 2,4-dinitrochlorobenzene (**22**) and 2,4-dinitroaniline (**23**).

Scheme 1



If the concentration of H_2SO_4 is >90%, nitric acid exists in the form of nitronium salt;[42] when it acts as the oxidizing agent, it is reduced to dinitrogen tetroxide, which disproportionates in sulfuric acid into nitric acid and nitrosonium hydrogen sulfate (nitrosylsulfuric acid). The overall equation corresponds to consumption of 0.5 mol of nitric acid per mol of the aromatic substrate and complete consumption of bromine.

$$2\,HNO_3 + 2\,H_2SO_4 \rightleftharpoons 2\,NO_2^+HSO_4^- + 2\,H_2O,$$

$$Br_2 + 2\,NO_2^+HSO_4^- \longrightarrow N_2O_4 + 2\,Br^+HSO_4^-,$$

$$N_2O_4 + H_2SO_4 \longrightarrow HNO_3 + NO^+HSO_4^-,$$

$$2\,ArH + 2\,Br^+HSO_4^- \longrightarrow 2\,ArBr + 2\,H_2SO_4,$$

$$2\,ArH + Br_2 + HNO_3 + H_2SO_4 \longrightarrow 2\,ArBr + NO^+HSO_4^- + 2\,H_2O.$$

A comparison of various oxidants shows that their efficiency in the bromination reaction does not implicitly correlate with their redox potential.[31] Stronger oxidants, such as dichromates, bromates, chlorates (with their standard potential (E°) 1.36 – 1.45 V)[43] appear to be inefficient, while weaker oxidants, such as nitric acid, iodates, mercury oxide ($E^\circ = 0.80 - 1.08$ V)[43] bring about bromination. Probably, the electron transfer from bromine to the oxidant proceeds *via* an intermediate species, which undergoes dissociation and generates an electrophilic brominating reagent stabilized in a sulfuric acid medium. The efficiency of an oxidant depends on the energy barrier to the intermediate formation. The structure of the intermediate species can be specific for each oxidant, but the genuine brominating reagent formed in sulfuric acid is presumably the same. The bromine cation which is formed upon the electron transfer to the oxidant in the course of formation – dissociation of the intermediate is stabilized in a weakly nucleophilic medium by binding to the HSO_4^- counter-ion and forming associates with non-ionized sulfuric acid molecules: $Br^+HSO_4^- \cdot n\,H_2SO_4$. This associate is similar to the nitronium ion complex in sulfuric acid $NO_2^+HSO_4^- \cdot 2\,H_2SO_4$.[44] The ion pair of the complex can be considered as the boundary structure of the sulfohypobromite, in which the bromine – oxygen bond of the leaving group is strongly polarized.

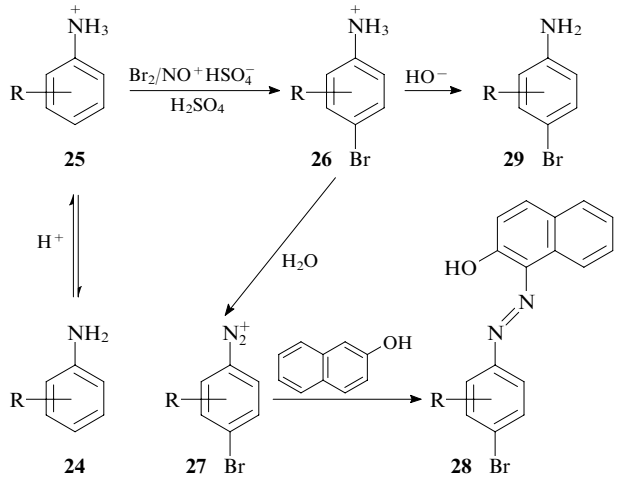
$$Br^+OSO_2OH^- \longleftrightarrow Br-OSO_2OH.$$

The formation of sulfohypobromite upon reaction of bromine with an oxidant in sulfuric acid presents a method of generation of electrophilic brominating agent that can overcome the low reactivity of the aromatic substrate.

Yet another way of the catalyst-assisted increase in the reactivity of the aromatic substrate is implemented in bromination of anilinium ions in sulfuric acid.

The ammonium group in the anilinium ion has distinct a *meta*-directing effect, it is a more potent electron-withdrawing group than the nitro group ($\sigma_n = 1.70$, $\sigma_m = 1.13$).[45] The anilines **24** in 92% – 100% sulfuric acid exist as anilinium ions **25**, they do not react with bromine. However, in the presence of nitrosonium hydrogen sulfate ($NO^+HSO_4^-$) in conc. H_2SO_4, bromination occurs smoothly, though not in the *meta*-, but in the *para*-position relative the ammonium group, with the formation of 4-bromoanilinium ions **26** (Scheme 2).[46,47] Nitrosonium hydrogen sulfate does not catalyze bromination of arenes with nitro groups and other deactivating substituents.

Scheme 2



R = H, 3-Me, 2-Cl, 3-Cl, 2-Br.

Treatment of the anilines **24** with bromine and nitrosonium hydrogen sulfate in conc. H_2SO_4 at ambient temperature or gentle heating and dilution of the reaction mixture

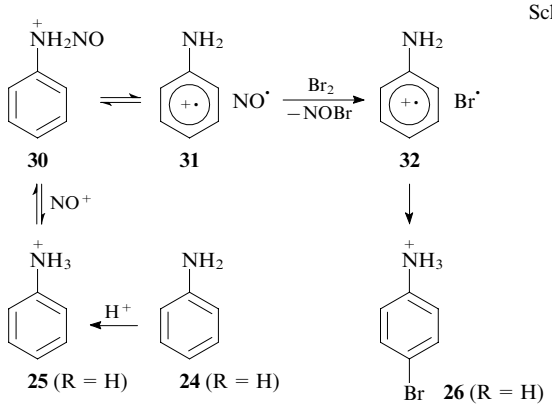
with water results in fair yields of 4-bromobenzenediazonium salts **27**, their subsequent azo coupling affords the bromo-containing azo compounds **28**. Azo coupling with 2-naphthol leads to 1-(4-bromophenylazo)-2-naphthols, while in the absence of the nitrosonium salt only 1-phenylazo-2-naphthols devoid of bromine are formed. Brominated amines in the form of bases **29** can be isolated under conditions that exclude diazotization (pouring the reaction mixture into an alkaline solution, or addition of compounds that decompose nitrous acid) (see Scheme 2).

Aniline derivatives with substituent (an alkyl group or a halogen atom) in the *meta*- or *ortho*-position, are brominated similarly to aniline, *i.e.*, in the *para*-position in the presence of nitrosonium hydrogen sulfate. If the *para*-position is occupied, no bromination occurs. The presence of the *meta*-nitro group prevents bromination. Secondary and tertiary alkylarylamines react in a same way, the respective 4-bromo derivatives were isolated and identified as the free bases. Nitrosonium hydrogen sulfate is not stoichiometrically consumed and can be used in catalytical amounts.[46,47]

The reaction of anilinium ions with bromine in sulfuric acid in the presence of nitrosonium hydrogen sulfate can serve as a valuable straightforward route to 4-bromobenzenediazonium salts from primary non-brominated amines. A vast number of preparative-scale syntheses based on diazonium salts[48] have been reported for various brominated aromatic compounds.

Studies using ^1H and ^{13}C NMR spectroscopy show that the anilinium ion **25** (R = H) in conc. H_2SO_4 remains unchanged in the presence of bromine, but is transformed into the 4-bromoanilinium ion **26** (R = H) following the introduction of nitrosonium hydrogen sulfate (Scheme 3).[46] The resulting cation **26**, like the starting anilinium cation **25**, is not diazotized with nitrosonium hydrogen sulfate in conc. H_2SO_4 and remains intact, as evidenced by NMR spectroscopy. Only upon reduction of the acidity after dilution with water, diazotization occurs and 4-bromobenzenediazonium salt is formed. The fact that bromination is impossible in the absence of nitrosonium hydrogen sulfate demonstrates that it is just the anilinium ion rather than aniline that is the reaction substrate, because aniline itself is extremely easily converted to 2,4,6-tribromoaniline under the action of bromine.[49]

Scheme 3

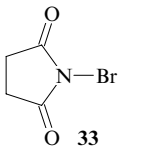


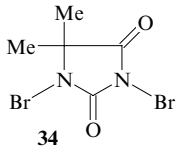
The reactivity of aromatic amines towards the nitrosonium cation is discussed in relation to the mechanisms of diazotization[48] and nitrosation[50] in a strongly acidic medium. The protonated aromatic amine reacts with the nitrosonium cation to give the *N*-nitrosoammonium ion **30**, which is stable against elimination of a proton in concentrated sulfuric acid. It is deprotonated in a less acidic medium with subsequent diazotization. A characteristic feature of the *N*-nitrosoammonium ions is their ability to undergo both heterolytic (dinitrozation) and homolytic N—N bond cleavage with the formation of the NO• radical and a radical cation of the aromatic substrate in the latter case. The key step is the transformation of the *N*-nitrosoammonium ion **30** into the radical ion pair **31**, which is then attacked by the reagent (see Scheme 3). The reaction of the intermediate **31** with the Br_2 molecule leads to substitution of the bromine atom for NO followed by recombination of the radicals within the radical ion pair **32**. The bromine atom covalently binds to the ring carbon atom with the highest spin density.[51] The other bromine atom of the Br_2 molecule binds to NO that is displaced from the radical ion pair **31** with the formation of nitrosyl bromide, which dissociates in sulfuric acid into the bromide anion and the nitrosonium cation; thus, the latter is regenerated.

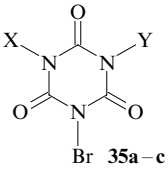
The described mechanism is similar to that of nitrosonium-catalysed nitration of *N*,*N*-dimethylanilinium[52] and anilinium[53] ions. Unlike the nitration of anilinium ions, which follows both catalytic an non-catalytic routes, bromination occurs only in the presence of the nitrosonium ion. This is a regioselective aromatic substitution in the *para*-position to the ammonium group, which is generally a *meta*-directing group.

III. Bromination with organic *N*-bromo compounds

N-Halo reagents have broad application in organic synthesis for halogenation and other transformations (see, *e.g.*, the reviews[54,55]). Deactivated arenes are brominated using bromo derivatives of cyclic imides: *N*-bromosuccinimide (**33**), 1,3-dibromo-5,5-dimethylhydantoin (**34**), mono-, di- and tribromo-isocyanuric acid (**35a**–**c**).







X = Y = H (**a**),
X = Br, Y = H (**b**),
X = Y = Br (**c**).

These *N*-bromo compounds are crystalline; their use allows one to avoid handling of molecular bromine. All *N*-bromo imides are obtained by bromination of the corresponding imides. For example, tribromoisocyanuric acid (**35c**) is prepared[56] by treating aqueous alkaline solutions of cyanuric acid with KBr and oxone ($2\,KHSO_5 - KHSO_4 - K_2SO_4$), the active component of the latter being potassium peroxosulfate. The bromoimides **33**–**35a**,**b** are produced on an industrial scale. 1,3-Dibromo-5,5-dimethylhydantoin (**34**) (bromantin) and sodium salt of monobromoisocyanuric acid (**35a**) are used for water disinfection in swimming pools and as bleaching agents in pulp-and-paper industry.[1]

The two CO groups adjacent to the nitrogen atom of cyclic *N*-bromoimides provide for polarization of the N—Br bond thus bringing about the electron density deficiency on the bromine atom. This is quite sufficient for halogenation of activated aromatic compounds with *N*-bromoimides in organic media[55] and even in aqueous alkaline solutions,[57]

but deactivated compounds are brominated only in the presence of strong acids, their reactivity depending on the strength and concentration of the acid. Reactions with *N*-bromoimides were carried out in aqueous sulfuric acid, in trifluoroacetic acid with addition of H_2SO_4, in dichloromethane with addition of TfOH or H_2SO_4, in boron trifluoride monohydrate, in concentrated sulfuric acid.

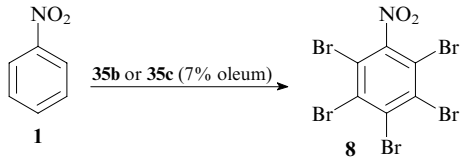
The reaction of *N*-bromosuccinimide in aqueous H_2SO_4 with an excess of nitrobenzene (**1**) at 85–90 °C resulted in 3-bromonitrobenzene (**2**) in 70% yield (on reacted substrate).[58] The action of *N*-bromosuccinimide in trifluoroacetic acid in the presence of 98% H_2SO_4 (10% by volume) at the molar ratio substrate : reagent = 1 : 1.5 affords 3-bromonitrobenzene (**2**) from nitrobenzene in 88% yield at 25 °C for 24 h and 5-bromo-1,3-dinitrobenzene (**4**) from 1,3-dinitrobenzene (**3**) in 45% yield at 45 °C for 48 h.[59] In the absence of sulfuric acid, the reaction does not occur, and the increase in the content of H_2SO_4 favours bromination.

The action of 1,3-dibromo-5,5-dimethylhydantoin (**34**) in dichloromethane with addition of equimolar amounts of TfOH or H_2SO_4 at 30–40 °C on nitrobenzene and trifluoromethylbenzene at the molar ratio substrate : acid : reagent = 1 : 1 : 0.5 affords 3-bromonitrobenzene (**2**) and 3-bromotrifluoromethylbenzene in 75%–87% yield and 81%–86% yields, respectively.[60] 1,3-Dinitrobenzene does not react under these conditions. Weak acids ($pK_a \geqslant -2$) are inefficient for conducting this transformation. In the absence of a strong acid, even such moderately deactivated substance as methyl benzoate is not brominated.[61] The molar ratio substrate : reagent = 1 : 0.5 shows that both bromine atoms of dibromohydantoin are consumed. It is of note that the reactivity of the latter is higher than that of *N*-bromosuccinimide (**33**).[60, 62]

Bromination proceeds most successfully in concentrated sulfuric acid. The reaction of arenes containing two deactivating *meta*-substituents with *N*-bromosuccinimide (1.2 equiv.) in conc. H_2SO_4 at 60 °C for 1.5–2.5 h, 1,3-dinitrobenzene (**4**), 1,3-dinitro-4-chlorobenzene (**13a**), 3-nitrobenzoic acid and 3-nitrobenzaldehyde leads to the corresponding 5-bromo derivatives in 87%, 84%, 83% and 92% yields, respectively.[36] The fact that the aldehyde group remains intact should be noted, as in other conditions[30, 35] it is oxidized to the carboxyl group. According to the patent,[63] dimethyl isophthalate is transformed into dimethyl 5-bromoisophthalate in 85% yield upon treatment with *N*-bromosuccinimide (**33**) in conc. H_2SO_4 (40 °C, 8 h). 1,3-Bis(trifluoromethyl)benzene (**7**) is successfully brominated with dibromohydantoin (**34**) in conc. H_2SO_4 at 0 °C for 24 h to 5-bromo-1,3-bis(trifluoromethyl) benzene (**6**) in the yield of 87%.[64]

The importance of high acidity was confirmed by carrying out bromination with *N*-bromosuccinimide (**33**) in boron trifluoride monohydrate ($BF_3 \cdot H_2O$), which is only slightly less acidic ($-H_0 = \sim 12$) than triflic acid ($-H_0 = 14.1$).[65] Boron trifluoride monohydrade, obtained by passing BF_3 into water with cooling, was mixed with equimolar amounts of a substrate and *N*-bromosuccinimide and stirred for several hours. Non-deactivated compounds reacted at ambient conditions, but nitrobenzene required heating at 100–105 °C in a sealed tube for 6 h, as without heating the yield of bromonitrobenzene was very low.[65] 1,3-Dinitrobenzene (**3**) is more deactivated than nitrobenzene; bromination of the former in conc. H_2SO_4 possessing lesser acidity ($-H_0 = \sim 10$)[45] with *N*-bromosuccinimide occurs easier (see above)[36] than that of the latter in $BF_3 \cdot H_2O$. Thus, it is not the high acidity itself, but rather the nature of the protolytic solvation that is important.

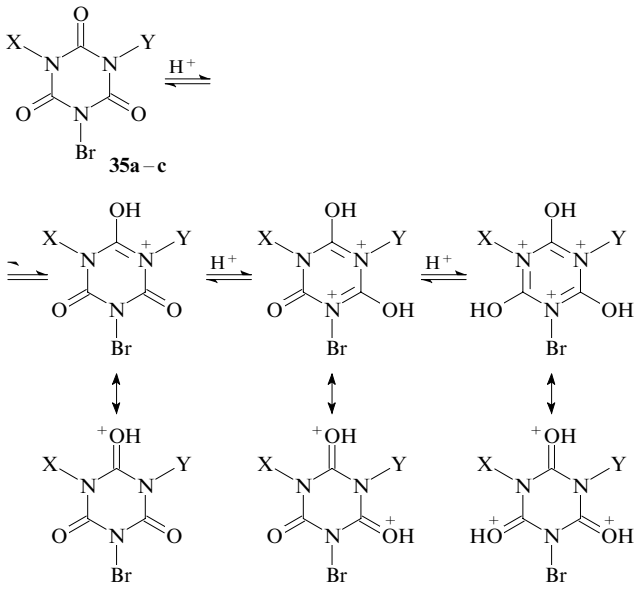
N-Bromo derivatives of isocyanuric acid in concentrated sulfuric acid are powerful brominating reagents. The reaction of sodium monobromoisocyanurate (**35a**) (50% excess) with nitrobenzene (**1**) in conc. H_2SO_4 at 40 °C for 12 h leads to 3-bromonitrobenzene (**2**) in 95% yield, the reaction of 1,3-dinitrobenzene (**3**) leads to 5-bromo-1,3-dinitrobenzene (**4**) (65%).[62] Dibromoisocyanuric acid (**35b**) (0.5 mol) reacts with deactivated substrates (1 mol) in 96% H_2SO_4 at 20 °C effects bromination of nitrobenzene in 5 min, of 1,3-dinitrobenzene in 20 min, the yields of the corresponding monobromo derivatives are 86%–88%.[66, 67] The increase in the acid concentration enhances the system reactivity: in 15% oleum 1,3- dinitrobenzene (**3**) undergoes monobromination in 1 min. Under the action of 2.5 mol of dibromoisocyanuric acid (**35b**), nitrobenzene is transformed into pentabromonitrobenzene (**8**) at 20° C in 93% yield.[68] Similar results were obtained with tribromoisocyanuric acid (**35c**). Pentabromonitrobenzene (**8**) is formed in 2 min in the reaction of nitrobenzene with tribromoisocyanuric acid (**35c**) (molar ratio 1:1.67) in 7% oleum at ambient temperature.[69]



1,3,5-Trinitrobenzene reacts with neither di- nor tribromoisocyanuric acid.

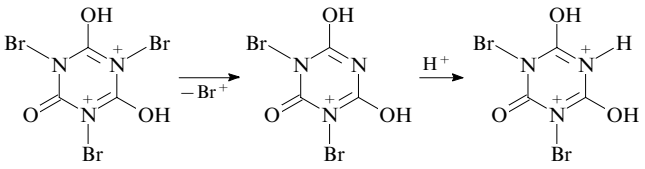
The role of the acid in the halogenation with *N*-bromoimides is protonation of the reagent. O-Protonation of cyclic imides with strong Brønsted acids leads to cations where the nitrogen atom takes part in delocalization of the positive charge. The presence of several protonation sites poses a question of the degree of protonation. The bromo derivative of cyanuric acid subsequently adds one proton producing mono-, di- and triprotonated forms, which coexist in an equilibrium (Scheme 4).

Scheme 4



X, Y = H, Br.

In the ^{13}C NMR spectrum of tribromoisocyanuric acid (**35c**) in 98% H_2SO_4 , two different signals for the carbonyl groups are present (δ 147.13 and 146.18), which relate to the monocation spectrum.[69] The high concentration of the monoprotonated form does not imply that it is responsible for the bromination action. Polyprotonated forms possess much higher activity. The bromination proceeds as transfer of Br^+ from the polyprotonated form of the reagent to the aromatic substrate, and reprotonation, *e.g.*:



As the reagent completely donates its bromine to the substrate, the di- and monobromo derivatives succeed tribromoisocyanuric acid in the reaction. Thus, the question of their comparative activity makes no sense.

The driving force of the Br^+ transfer from the protonated reagent is the tendency to reduce the intermolecular charge repulsion. The higher the degree of protonation the stronger the Coulomb repulsion and the higher the electrophilicity of the reagent, which can be thus adjusted by the acidity of the medium. The transfer of Br^+ from the reagent to the substrate with assistance of the medium (concentrated sulfuric acid) can be accompanied by association with the HSO_4^- counter-ion and protosolvation by H_2SO_4 molecules with the formation of electrophilic bromosulfonate as the brominating reagent, same as it is suggested for bromination with molecular bromine.

There is no common opinion on which protonated species transfers Br^+. It was suggested,[69] based on quantum chemical calculations (using the density functional method, DFT), that the diprotonated form of tribromoisocyanuric acid is responsible for the high brominating activity, as the triprotonated form is so strongly destabilized by the mutual charge repulsion that it does not actually exist. However, an analogous DFT-calculation for trichloroisocyanuric acid leads to the conclusion that it is the protosolvated trication that is the key intermediate.[70] The DFT calculations [65] show that the triprotonated species is preferrable even for *N*-halogenosuccinimides. The highly protonated form of *N*-halogenoimides is a superelectrophile, which emerges, in accord with the proposed terminology, due to superelectrophilic activation.[71]

IV. Conclusion

The inertness of aromatic compounds containing electron-withdrawing groups to bromine required the development of specific bromination methods. Reagents have been found that form *in situ* intermediates upon reaction with bromine, where bromine is bound to a more electronegative atom, and that represent electrophilic reagents. Reactions with bromine and nitric acid or some other oxidants in concentrated sulfuric acid allows bromination of strongly deactivated arenes with two electron-withdrawing substituents. The Br^+ cation formed upon dissociation of the said intermediate is stabilized in the concentrated sulfuric acid medium due to binding to the counter-ion HSO_4^- and protosolvation with the non-ionized acid molecules.

Cyclic *N*-bromoimides are powerful reagents for the electrophilic bromination in concentrated sulfuric acid, where they exist as the di- or tri-protonated species. The driving force for the N—Br bond cleavage in the protonated molecule is the mutual repulsion of the charges. The transfer of Br^+ from the reagent to the substrate in concentrated sulfuric acid can be similar to that taking place in the bromination with molecular bromine.

While bromine is introduced into the *meta*-position relative to the electron-withdrawing group in the electrophilic bromination, bromination of arenes with a very strong electron-withdrawing group (an ammonium group), in concentrated sulfuric acid is directed to the *para*-position. The reaction is catalyzed by nitrosonium hydrogen sulfate and does not occur in the absence of the catalyst. The role of the catalyst is the activation of the substrate by generating the *N*-nitrosoammonium ion and its reaction with bromine presumably according to a radical ion mechanism.

The developed methods for the introduction of bromine into the aromatic ring bearing electron-withdrawing substituents make it possible to obtain bromosubstituted aromatic compounds important for organic synthesis. The discovered approaches to the activation of the brominating agent, and, in some cases, the aromatic substrate, can be useful for further studies in the field of directed organic synthesis.

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