Synthesis and Characterization of 4-Amino-3, 5-dibromo-toluene from p-Toluidine

Charan Kamal Saini[*], Manpreet Kaur, Amandeep Kaur

ABSTRACT

O-toluidine ($CH_3C_6H_4NH_2$), a prominent toluidine isomer, is a precursor to herbicides, metolachlor, and acetochlor. It is a colorless liquid, with exception of yellow-ish commercial samples. Toluene, formally known as toluol, is a clear, water-insoluble liquid with the typical smell of paint thinners. Chemically it is a mono-substituted benzene derivative that is one in which a single hydrogen atom from the benzene molecule has been replaced by a univalent group, in this case, CH_3. Toluene reacts as a normal aromatic hydrocarbon towards electrophilic aromatic substitution. The methyl group makes it around 25 times more reactive than benzene in such reactions.

Keywords: 4- Amino-3, 5-dibromo-toluene, Bromine, Glacial acetic acid, Concentrate sulphuric acid.

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INTRODUCTION

Halogenated organic compounds form an important class of intermediates as they can be converted efficiently into other functionality by simple chemical transformations. The manufacture of a range of bulk and fine chemicals, including flame retardants, disinfectants, antibacterial, and antiviral drugs, involves bromination. Bromo aromatics are widely used as intermediates in pharmaceuticals, agrochemicals, and other specialty chemical products. Selective bromination of aromatic compounds is investigated, given the importance of the brominated compounds in organic synthesis. Consequently, a variety of methods for the bromination of aromatics have been reported in the literature.
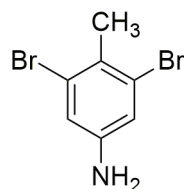
Structure of 4-Amino-3, 5-dibromo-toluene

Brominated aromatic compounds are widely used as building blocks for pharmaceuticals and other specialty chemicals. Most of the aromatic compounds are poorly soluble in water, and this has been a major limitation in the

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preparation of industrially important brominated compounds under aqueous conditions. Classical nuclear bromination of aromatic compounds involves: (a) Bromine; (b) A catalyst like $FeCl_3$, $FeBr_3$, iodine, thallium acetate etc.; (c) Absence of light, often yielding undesired co-products. The direct bromination of an aromatic system presents an environmental problem in large-scale operations. Besides, the bromination is wasteful as one-half ends up as hydrogen bromide, which renders the process more expensive. Oxybromination using HBr is highly toxic and corrosive and is as harmful as molecular bromine to the environment.[1,2]

### Reactions of Aromatic Compounds

Just like an alkene, benzene has clouds of electrons above

attack on an electrophile   sigma complex   substituted

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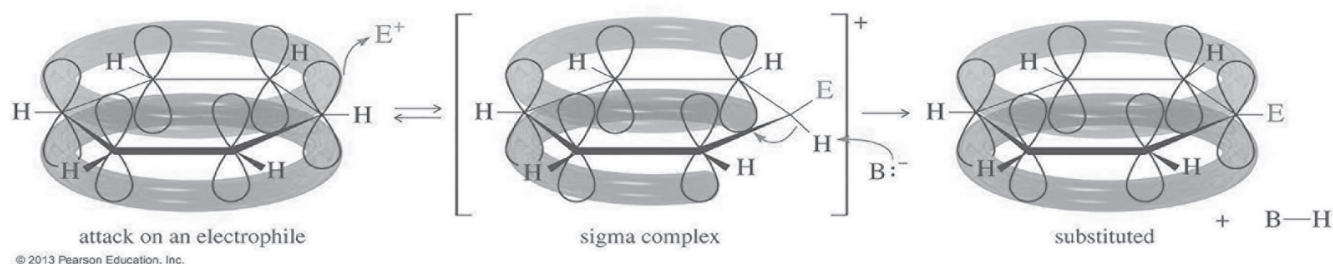
and below its sigma bond framework

Although the electrons are in a stable aromatic system, they are still available for reaction with strong electrophiles. This generates a carbocation which is resonance stabilized (but not aromatic).


Sigma complex (arenium ion)
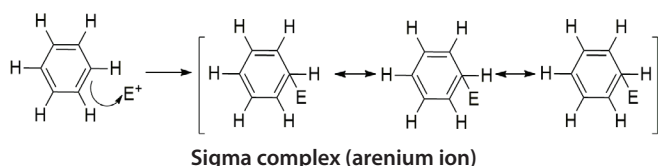
This carbocation is called a sigma complex because the electrophile is joined to the benzene ring through a new sigma bond. The sigma complex (also called an arenium ion) is not aromatic since it contains sp^3 carbon (which disrupts the required loop of *p* orbitals). The loss of aromaticity required to form the sigma complex explains the highly endothermic nature of the first step. (That is why we require strong electrophiles for reaction). The sigma complex wishes to regain its aromaticity, and it may do so by either a reversal of the first step (*i.e.,* regenerate the starting material) by loss of the proton on the sp^3 carbon (leading to a substitution product).
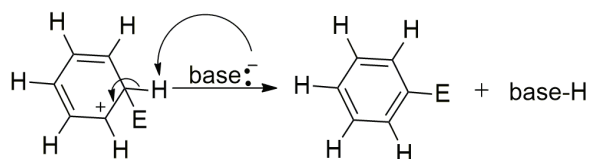

When a reaction proceeds this way, it is electrophilic aromatic substitution. A wide variety of electrophiles can be introduced into a benzene ring in this way, so electrophilic aromatic substitution is a very important method for the synthesis of substituted aromatic compounds.

Bromination: Bromination follows the same general mechanism for electrophilic aromatic substitution (EAS). Bromine itself is not electrophilic enough to react with benzene. But the addition of a strong lewis acid (electron pair acceptor), such as FeBr$_3$, catalyzes the reaction and leads to the substitution product. The bromine molecule reacts with FeBr$_3$ by donating a pair of its electrons to the lewis acid, which creates a more polar Br-Br bond, and thus a more reactive electrophile. Benzene now attacks this electrophile to generate the sigma complete.
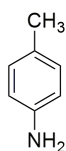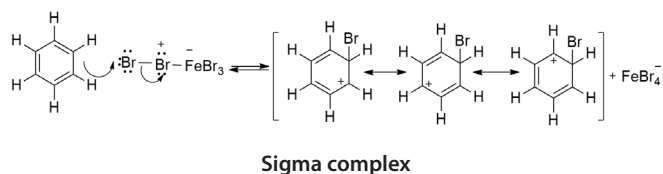

Structure of p-toluidine
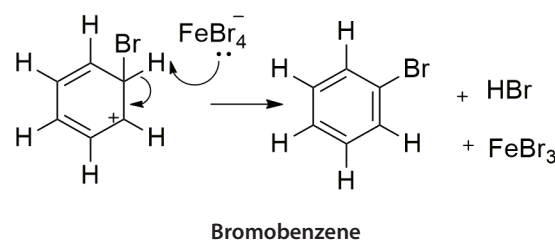
Step1: Formation of a stronger electrophile.

Br$_2$ + FeBr$_3$ intermediate
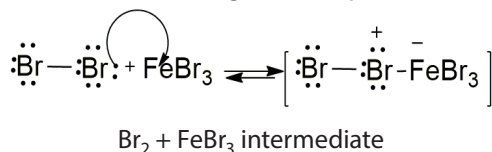
(a stronger electrophile than Br$_2$)

Step 2: Electrophilic attack and formation of the sigma complex.


Sigma complex

Step 3: Loss of a proton gives the products

Bromobenzene

Aromatic Substitution Reactions of p-toluidine Derivative

Aromatic amines can undergo electrophilic aromatic substitution reactions on the ring. The amino group is one of the most potent ortho, para-directing groups in electrophilic substitution. If the conditions of the reaction are not too acidic and its derivatives undergo rapid ring substitution. For example, p-toluidine, like phenol, brominates three times under mild conditions.
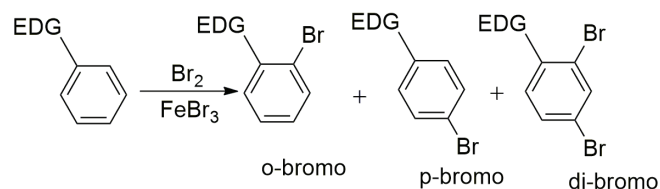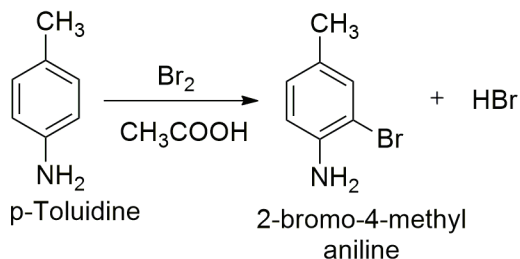

Electrophilic Aromatic Substitution Reaction

Synthetic chemistry has had an enormous impact on the pharmaceutical industry and drug discovery. This impact has made scientists search for new methodologies for the assembly of functional molecules. Although there are many aryl substitution reactions, electrophilic aromatic substitution (EAS) has been an extensively used method in many organic syntheses to prepare substituted aromatic systems. Electrophilic aromatic substitution has enabled the development of many modern pharmaceutical compounds such as sulfa drugs. Sulfathiazole and Sulfadiazine were among the two most effective sulfa drugs synthesized in the 1930s by the EAS method.
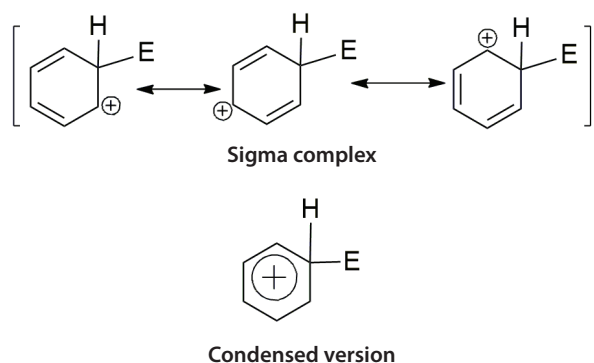
Electrophilic aromatic substitution reactions also were applied to the preparation of over-the-counter drugs like ibuprofen, in which EAS is the first step where a Friedel-Crafts acylation occurs. This method has also been utilized widely towards the development of anticancer agents. Therefore, the aromatic substitution procedure is highly utilized in many

organic syntheses. However, there are some difficulties with this method. One downside of this substitution reaction is it does not afford region-specific mono-substituted arenes, providing a mixture of *ortho* and *para*-substituted arenes as well as di-substituted derivatives. The bromination of an activated aromatic compound using molecular bromine resulted in the mixture of ortho, para, and di-substituted derivatives. [3,4]

p-Toluidine → 2-bromo-4-methyl aniline + HBr

Mechanistic Aspects

The general mechanism of electrophilic aromatic substitution (In gold-Hughes) involves a two-step reaction. The first step includes the attachment of an electrophile to the aromatic ring at a location containing a hydrogen atom. As a result, the π-bond gets replaced with two new sigma bonds, forming a carbocation intermediate, termed a wheel and adduct or sigma complex, causing the ring to lose its aromaticity. The second step proceeds rapidly by releasing the hydrogen from the sigma complex to resume the stabilization afforded by the aromatic ring. As an essential carbocation intermediate and the substituent properties or substituents, the sigma complex plays a vital role in governing the location where substitution occurs and the overall rate of the electrophilic substitution reactions.[5-7]

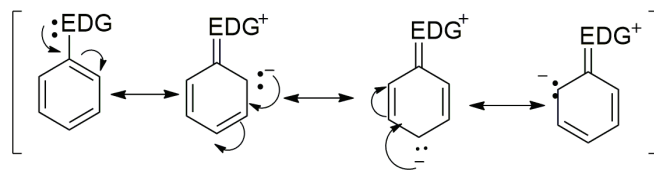

Sigma complex

Condensed version

In an electrophilic aromatic substitution reaction, the aromatic ring is considered an electron-rich aromatic, and electrophiles prefer to attack electron-rich substrates. This leads to consideration of the two different types of ring substituents; activating and deactivating groups. The aromatic ring can be activated by substituting activating or electron-donating groups (EDG) through a resonance electron-donating effect.

The electron-donating groups such as –OH, –OMe, –Me, –NH$_2$, –NHCH$_3$, –NMe$_2$, – NHCOCH$_3$, also act as ortho/para directors. Therefore, the aromatic systems that bear

activating groups direct the incoming electrophiles chiefly to the ortho/para positions. In contrast, deactivating or electron-withdrawing groups (EWG) deactivate the benzene ring by reducing the electron density on the ring through a resonance electron-withdrawing effect.

Moreover, –NO$_2$, –CHO, –COOH –COCH$_3$, –COOCH$_3$, and –CN, as EWGs direct the incoming substituent to the meta position. However, halogens are also electron-withdrawing groups but are ortho/para directors. [8,9]

The electron-donating group with a lone pair can stabilize the sigma complex formed by the attack of an electrophile at one of the ring positions bearing a negative charge delocalizing the positive charge over several positions. When the donating group has a delocalized unshared pair of electrons, the sigma complex distributes the positive charge on the aromatic carbons showing the unshared electron pairs in the ground state along with the 3 and 5 positions. As a result, the incoming electrophile is more willing to react with opposing charge positions 2, 4, and 6 resulting in an ortho/para-substituted product. In contrast to the electron-donating groups, all electron-withdrawing groups with π-bonds to electronegative atoms destabilize the sigma complex by increasing the positive charge in the ring. As a result, the electrophile primarily attacks the 3 and 5 positions, which then causes meta substituted products.
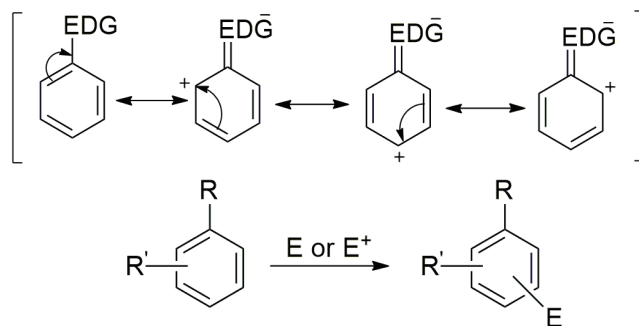
Various types of tri-substituted benzene ring and di-substituted benzene. Dots and circles are symbols showing the locations of the added substituent. A dot inside a circle (bull's eyes) is a symbol showing the highest probability of product outcomes, and the check marks illustrate the actual locations of the electrophile placement in reactions.[12-13]

Para-selective Bromination

In order to reduce health and safety risks, diminishing toxic waste, the cost efficiency, and Milder reaction condition, the study of the combination of N-halo succinimides (NXS) as

a green halogenation agent with various Medias has been the focus of scientists for a long time. NXS is a great source of X+ can be used efficiently in the radical substitution and electrophilic aromatic halogenations like bromination, iodination, and chlorination of various deactivated and activated aromatic systems under highly mild conditions, providing mono or di-brominated products in high selectivity and good yields. [14,15]
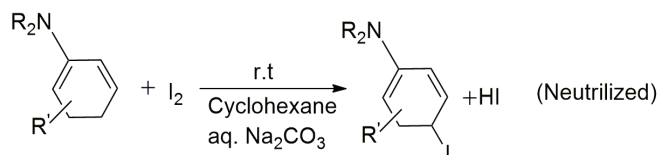
Moreover, all stated disadvantages, some of these methods have a failing in that the starting materials and the solvents must be used in large excess. A number of acid-catalyzed NBS bromination strategies suffering from these shortcomings and did not continue to be of interest are listed here, including NBSHBF4.

PROCEDURE

(10.7g, 0.1moL) of p-toluidine was dissolved in 45mL of glacial acetic acid taken in two necked (250 mL) RBF placed in a copper bath and provided with a mechanical stirrer and a dropping funnel. The solution was stirred, and (52.8g, 0.33moL) of bromine in 40 mL of glacial acetic acid was added slowly (1.5 hours) from the dropping funnel while stirring. The flask was cooled in ice during the addition of bromine, as the reaction being exothermic. The flask's content was poured into 200 mL of ice-cold water in (500mL) beaker with vigorous stirring. The solid separated was filtered, washed with water, dried, and which upon recrystallization from rectified spirit gave 22,700 g (15.660%) mp 75–76°C. 4-amino-3,5-dibromo-toluene was added to an ice-cold mixture solution of 40mL of rectified spirit and 10 mL of concentrated sulphuric acid contained in a three-necked (500mL) RBF placed in a copper bath and provided with a mechanical stirrer and a dropping funnel. The solution was stirred and cooled to –5°C, and then an ice-cold solution (7.4 g, 0.107 moL) of pure sodium nitrite in 15 mL of water taken in the dropping funnel was added slowly and was added slowly while stirring, taking care of the mixture. Then the mixture is filtered with the help of the filtration method, and the product is further dried in a hot air oven, and 4- Amino-3, 5- dibromo-toluene is formed as a brominated product.

BROMINATION OF P-TOLUIDINE

This reaction was performed in a clean, dry 25mL round-bottom flask equipped with a clean magnetic stir bar. One equivalent of NBS (1.78g, 10mmoL) was weighed and transferred to the flask, followed by adding 20mL of acetonitrile. Once the NBS dissolved into the solution, 1 equivalent of p-toluidine (0.91mL, 10mmoL) was added slowly to the stirred reaction using a glass syringe. The reaction mixture was well mixed with stirring at room temperature for 10 min. After workup with DI water and dilution with MTBE, a sample was taken and analyzed by GC, resulting in a 98.1% yield of 4-bromo-p-toluidine. The reaction mixture was transferred to a separator funnel with the aid of MTBE and DI water. The solution was washed with DI water three times. The organic layer was separated and washed once with brine and dried over sodium sulphate to give 4-bromo-p-toluidine in 98.7% purity. The concentrated product's melting point was 50–52°C.[24, 25]
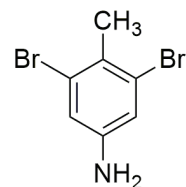

Structure of 4- Amino- 3, 5-dibromo-toluene

In the face of sustainable and eco-friendly organic synthesis demands, clean organic reaction processes that do not use harmful organic solvents are encouraged and are in great demand today. The direct bromination of aromatic compounds with molecular bromine in solution often results in polybromination, and when brominated in the presence of oxidants, they also get oxidized rather than undergoing substitution. Although bromination of aromatic compounds by elemental bromine is a well-known organic reaction, bromination using elemental bromine usually results in a complex mixture of mono-, di-, tri-, and even tetra-brominated products. Hence to date, there has been no simple, inexpensive, instant, easily available, and high yield method developed that can be commercialized for the said purpose. Various new bromination techniques have been employed along with the conventional reagent "bromine" to increase efficiency and selectivity. Still, the use of toxic and expensive reagents, catalysts, VOSs, low yields, and discharge of corroding HBr waste circumvent these processes from industrial application. Oxybromination, on the other hand, can be a good alternative. Yet, these reactions require a great excess of the reagents, strongly acidic conditions, expensive, dangerous pollutants to the environment. Alternative analogues of bromine, such as organic tribromides and various tribromide-ionic liquids have also been used for the bromination of aromatic compounds.

Nevertheless, these brominating agents are saddled with various drawbacks, including their low atom economy, toxic and corrosive HBr disposal by-product waste, poor recycling of spent reagent, and the molecular bromine required for their preparation. Hence, to eliminate a two-step bromination wherein these reagents are first prepared using molecular bromine before bromination of aromatic compounds, we have effectively utilized molecular bromine and an environmental-friendly reagent NH_4Br for

an instant and facile bromination for industrially important compounds. Due to the above reasons, molecular bromine is still a target alternative for industrial chemists to develop an environmental-friendly brominating system that works under ambient conditions; keeping this in mind, we find an aq NH4Br-Br$_2$ system to be a better alternative.

p-Toluidine → 2-bromo-4-methyl aniline + HBr
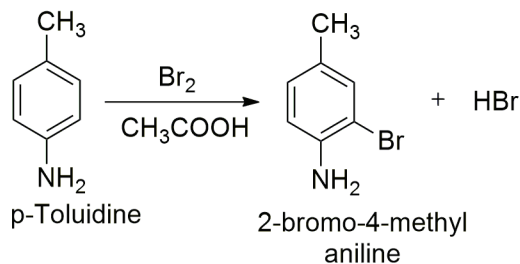
Synthesis Recycling of HBr

Molecular bromine carries significant industrial advantages, including low price, less favourable E-factors14, and high productivity. This last factor (the amount of substance produced per unit reactor volume per unit time), often ignored in laboratory studies, is crucial in all large-scale processing. As other bromine sources cannot match these advantages of Br2. Viable industrial oxybromination reagents must feature alternative benefits. The aqueous filtrate obtained after separating the bromination product was neutralized by adding $Ca(OH)_2$ (0.7409 g, 10 mmol). Initially, the pH of the aqueous filtrate was <3. When $Ca(OH)_2$ was added in small lots to aqueous filtrate, Br$_2$- of HBr was transformed into $CaBr_2$ (at pH 7). After separating CLS (22.6 mg), the aqueous mixture obtained containing $CaBr_2$ was concentrated to precipitate $CaBr_2$ (1.997 g) as a crystalline solid.
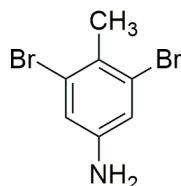
Structure of 4- Amino- 3, 5- dibromo-toluene

Uses of Bromination

One of the major uses of bromine is as water purifier/disinfectant as an alternative to chlorine. Brominated compounds are used for water treatment in swimming pools and hot tubs and are also used to control algae and bacterial growth in industrial processes.

Result

The practical yield of 3,5-Dibromotoluene 1.125 g was calculated.

IR (KBr) ῡ max cm^{-1}

3423, 3309 (N- H stretch of –NH2, antisymmetric and symmetric, Respectively)

2967, 2875 (C-H stretch of methyl, antisymmetric and symmetric, Respectively)

1450, 1375 (C-H bend of methyl, antisymmetric and symmetric, Respectively)

(1,2,3,5-tetrasubstituted, out of plane C-H bend, lone Hydrogen atom, aromatic) 733 (c- br stretch, aromatic)

PMR (CDCl$_3$) δ ppm

7.750	(s, 2H aromatic)
4.275	(br. S, 2H, -NH$_2$ exchangeable)
2.650	(s, 3H, -CH$_3$)

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