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Green Alternative of Bromination Reaction to Synthesize *Ortho*- and *Para*-bromoaromatic Secondary Amines

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Abstract: Elemental bromine (Br) is extremely reactive and as a result we do not find it as a free element in the environment. Bromine is found as a diatomic molecule in nature, named as molecular bromine (Br_2). But it is highly volatile in nature with a suffocating odour and evaporates voluntarily to generate a reddish colored fume. Br_2 is quickly absorbed by our lungs. Here monobromomalononitrile (MBM) have been used as brominating agent. It is much less toxic compared to molecular bromine. It is not volatile also. This bromination step is the key step for the synthesis of regioisomers *i.e*. *o* and *p*-bromoaromatic secondary amines.

Keywords: Monobromomalononitrile (MBM), *p*-Bromoaromatic secondary amines, *o*-bromoaromatic secondary amines

Introduction

Bromine (Br) is 35th element in modern periodic table. It has two isotopes written as $_{35}Br^{79}$ (50.686% relative mass abundance) and $_{35}Br^{81}$ (49.314% relative mass abundance). Elemental bromine (Br) is extremely reactive and as a result we do not find it as a free element in environment. Instead, bromine is found in nature as bromide ion (Br^-) mainly. Bromide ion is present as colorless soluble crystalline mineral bromide salts which is analogous to table salt (NaCl). Bromide ion is rarely found in the Earth's crust. However, bromide ion is present in the oceans due to its high solubility. Commercially the bromine is easily isolated mostly in the United States and Israel from brine evaporation ponds. It is noteworthy to mention that mass of bromine is almost one three-hundredth (0.00333333333) that of chlorine in the oceans. Other than bromide ion, bromine is found as a diatomic molecule in nature named as molecular bromine (Br_2). Molecular bromine (frequently we called as bromine only) is red-brown liquid at room temperature (boiling point 58.8°C (137.8°F)). But it is highly volatile in nature with a suffocating odour and evaporates voluntarily to generate a reddish colored fume. Br_2 is quickly absorbed by our lungs. Intake of molecular bromine in liquid form results in rapid and complete absorption from the intestine. Then molecular bromine is dispersed broadly into our tissues. The mainly of bromine is distributed into the extracellular fluid of the body. Unfortunately, this intake Br_2 is not metabolized by the body. It creates very toxicity in human body. Exposure to reddish bromine vapor may cause headache, lacrimation (the

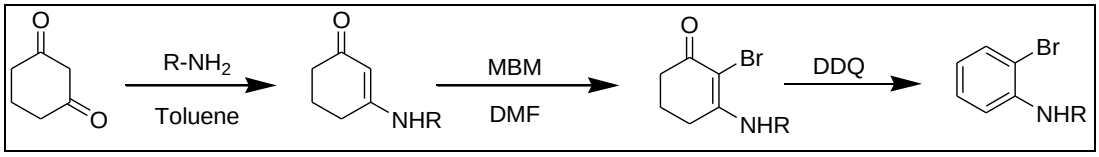
continuous flow of tears from eye), upper respiratory effects, and cough. Skin loss and skin discolouration have been observed following acute dermal exposure to bromine.

Materials and Methods

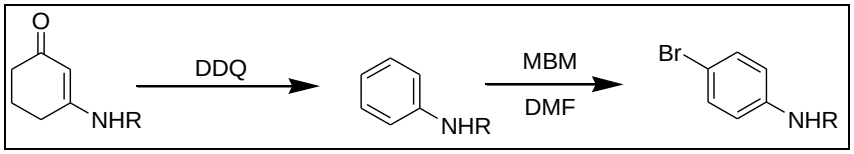
Organic molecules having bromine (Br) are very imperative in the research field of organic synthesis because of the profitable implication of starting/intermediate bromoorganics for the building of very important natural products. Bromoorganics are very useful as starting materials or intermediates in the production of agrochemicals and pharmaceuticals compounds. Besides, an enormous number of already marketed products such as pesticides, fire retardants, herbicides, insecticide etc. have bromo functionality [1]. Various metal catalyzed cross-coupling reactions are used for formation of new C–C bond using with organ-bromides as starting materials. Thus, the bromine containing organic compounds have mammoth impact on Heck coupling reactions [2], Stille and Suzuki coupling reactions [3] and Sonogashira coupling reaction [4] and other hetero coupling reaction [5]. The use of molecular bromine (Br_2) is the conventional technique of bromination reaction. As already discussed, molecular bromine is very toxic and corrosive in nature; use of molecular bromine as brominating agent should be avoided. In addition, unwanted side product(s) are obtained even after very careful control bromine addition and experimental temperature [6]. Thus, less toxic and milder brominating agents are urgently required for the bromination reaction on organic compounds [7-13]. Here, monobromomalononitrile (MBM) have been used as brominating agent. It is much less toxic compared to molecular bromine. It is not volatile also. This bromination step is the key step for synthesis of regioisomers *i.e*. *o*- and *p*-bromoaromatic secondary amines.

Results & Discussion

Two strategies are planned to get region-isomers of bromoaromatic secondary amines. Ortho-bromoaromatic secondary amines can be obtained using **scheme 1** whereas para-bromoaromatic secondary amines can be obtained using **scheme 2**. Main advantages of the two schemes are i) there is less chance to form other isomers; ii) mild brominating agent MBM is used; iii) use of toxic molecular bromine is avoided; iv) Generally, incorporation of groups at the ortho position by aromatic electrophilic substitution reaction is not easy. Para product is generally formed as a major for such reaction considering steric hindrance. But scheme 1 gives *o*-bromoaromatic secondary amines selectively; and v) The bromo-compounds can be further utilized to get various biphenyl systems via coupling reactions.



Scheme 1. Synthesis of *o*-bromoaromatic secondary amines from 1,3-cyclohexanone



Scheme 2. Synthesis of *p*-bromoaromatic secondary amines from 1,3-cyclohexanone

General procedure for the preparation of monobromomalononitrile (MBM)

A solution of malononitrile (3.3 g, 0.05 mol) in ice cool water (10 ml) and 2-propanol (10 ml) was cooled in an ice-cold water-bath at 20^{o}C. Then bromine (8.0 g, 0.05 mol) was added slowly into the solution with constant stirring, during which the temperature of the reaction mixture will rise and the colour of bromine will disappear immediately. After the addition of bromine, the reaction mixture was stirred at room temperature for 15 min and left at 0^{o}C for 10 h. The solid monobromomalononitrile was precipitated out from the reaction mixture and filtered off through suction.

General procedure for enamine synthesis

1,3-Cyclohexanone (1 equivalent) and 2^{o} amine (1 equivalent) were taken in a benzene solvent and refluxed using Dean-Stark apparatus for 0.5-1 hr. Then benzene was distilled and solid material (enamine) was isolated.

General procedure for enamine synthesis for bromination reaction using MBM

Enamine (1 equivalent) was taken in THF solvent at 0^{o}C. Then MBM (1 equivalent) was added under staring condition. Reaction was left at room temperature under staring condition for 1 hr. Then THF was removed under vacuum. The result mixture was extracted with ethylacetate and water. Organic layer was collected and evaporated. Brominated compounds were isolated.

Aromatization reaction with DDQ

Brominated compound (1 equivalent) and DDQ (2.5 equivalent) were mixed together in dichloromethane solvent. The reaction mixture was refluxed for 2-3 hrs. Then the organic layer (DCM) was collected in work up step by adding water. The product was isolated after column chromatography.

Conclusion

Here, monobromomalononitrile (MBM) has been used as a brominating agent. It is much less toxic compared to molecular bromine. It is not volatile also. This bromination step is the key step for the synthesis of regioisomers *i.e.*, *o* and *p*-bromoaromatic secondary amines.

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