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An efficient regioselective NBS aromatic bromination in the presence of an ionic liquid

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ABSTRACT

A simple, efficient, and rapid method was developed for high-yielding regioselective monobromination of activated aromatic compounds using NBS in combination with ionic liquid 1-butyl-1-methylimidazolium bromide ([Bmim]Br) or dioxane. The ionic liquid is recyclable and can be reused with minimal loss in the catalytic efficiency if the ionic liquid is rapidly microwaved prior to reactions.

Advances in organic chemistry are usually measured by availability of simple, highly functionalized building blocks that can be used in the preparation of larger molecules with diverse properties and applications.[1] The bromination of aromatic substrates has been the subject of a great deal of interest in recent years due to the commercial importance of brominated compounds in the synthesis of natural products, as well as in the manufacturing of pharmaceuticals and agrochemicals. Bromoarenes[2] are starting points for the preparation of a diverse array of building blocks.[3] The preparation of brominated aromatic compounds with molecular bromine is a well-known reaction in organic chemistry.[4] This reaction requires transition metal-based catalysts and the side product generated in the course of these reactions is corrosive and toxic hydrogen bromide. In the case of active aromatic compounds, such as anilines and phenols, elemental bromination usually results in a complex mixture of mono-, di-, tri-, and even tetrabrominated products.[4]

It is especially difficult to perform selective monobromination of highly activated aromatic compounds, such as aniline and phenol derivatives. To perform selective monobromination of highly active aromatic compounds, several non-bromine bromination reagents have been developed, including, but not limited to, pyridinium tribromide,[5] 1-butyl-3-methylpyridinium tribromide,[6] poly 4-vinylpyridinium tribromide,[7] 1,2-dipyridiniumditribromide-ethane (DPTBE),[8] tetrabutylamonium tribromide,[9] 1-butyl-3-methylimidazolium tribromide,[10] [K.18-crown-6]Br_3,[11] bromine-1,4-dioxane,[12] hexamethylenetetramine-bromine,[13] DABCO-bromine.[14] Finally, there are, of course, other reagents that are widely used as a substitute for bromine in organic synthesis. One of them is 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one as a reagent of choice for selective monobromination of aniline derivatives.[15]

For the purposes of our studies presented here, we selected *N*-bromosuccinamide (NBS) to develop selective and simple procedures for the preparation of the highly valuable bromophenols and bromoanilines. NBS is a relatively safe and easy to handle source of bromine and NBS is a well-known synthetic organic reagent useful for bromination and/or oxidation of a wide variety of organic moieties under various reaction conditions.[16] Although electrophilic substitution of aromatic hydrocarbons by bromine is a well-known organic reaction[17] to date, there has been no simple, inexpensive, and high yield method developed for selective bromination of reactive aromatic hydrocarbons. For instance, if the highly activated aromatic compound is to be brominated, first it should be made less reactive through deactivation (by transformation of the amino group into an acetamido group) and following bromination the deactivation group must then be removed.[18] In this current study, we are presenting a simple and direct bromination of phenol, aniline, and their derivatives as examples of active aromatic compounds using NBS as the bromination reagent (Table 1). The reaction was found to be first order in the aromatic substrate and zero order in NBS.[19] A probable mechanism involves an attack by Br^+ or more likely Br^+-solvated ion on the aromatic substrate.[19]

There were two reaction media that we explored for NBS aromatic bromination; (a) the ionic liquid 1-butyl-3-methylimidazolium bromide [Bmim]Br[20] and (b) dioxane. In recent studies, Zheng and co-workers performed bromination of activated aromatics such as phenols, naphthols, methoxynaphthalenes, and anisole with 1-butyl-3-methylimidazolium tribromide [Bmim]Br_3.[21] The reagent was prepared as a stable liquid from [Bmim]Br and bromine. In our case, bromination starts with the in situ preparation of the bromination reagent, NBS/[Bmim]Br, by adding NBS into [Bmim]Br. This was immediately followed by adding the aromatic compound to be brominated. The reaction was completed in a few minutes and product was isolated by ether extraction.[24] In most of the cases, the isolated yields were almost quantitative and purity

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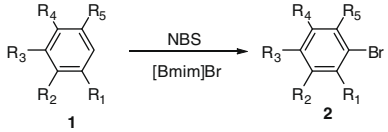
Table 1
Isolated yields of mono-brominated arenes[24,25]



1 2

a: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = NH_2$; **b**: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OH$;
c: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OCH_3$; **d**: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = N(CH_3)_2$;
e: $R_1 = NH_2$, $R_2 = R_3 = R_5 = H$, $R_4 = NO_2$; **f**: $R_1 = OH$, $R_2 = R_3 = R_5 = H$, $R_4 = NO_2$;
g: $R_1 = R_5 = H$, $R_2 = R_4 = CH_3$; $R_3 = OH$; **h**: $R_1 = R_5 = H$, $R_2 = CHO$, $R_3 = OCH_3$;
i: $R_1 = CHO$, $R_2 = R_4 = R_5 = H$, $R_3 = OCH_3$; **j**: $R_1 = (CH_3)_2N$, $R_2 = R_3 = R_5 = H$, $R_4 = CHO$

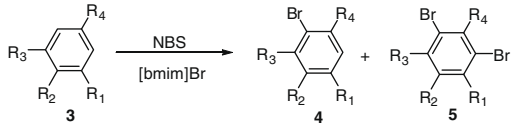
Compound	Time (min)	Isolated Yield (%)	Selectivity (%)
Ionic liquid/dioxane			
2a	5/5	85/91	100/100
2b	5/5	75/75	100/80
2c	8/5	93/95	100/100
2d	5/1	95/95	100/100
2e	4/2	90/80	100/100
2f	5/2	85/75	95/80
2g	2/1	98/95	100/100
2h	15/5	95/80	100/100
2i	15/5	93/85	100/95
2j	5/4	90/78	100/100

of the product was higher than 96%. However, it is important to emphasize that the ionic liquid must be dried to obtain these high yields. Commercially available [Bmim]Br must be dried under vacuum prior to use in these reactions. The presence of water substantially decreases both the isolated yield and the selectivity of the aromatic bromination.

To eliminate this problem of extensively drying the ionic liquid prior to use, we implemented microwave activation of the ionic liquid prior to reactions. The ionic liquid was microwaved for 15 s at microwave powers of 150 W prior to being added to the reaction mixture as a reagent. Alternatively, we have also prepared [Bmim]Br from 1-methylimidazole and butyl bromide.[22] In this case, the ionic liquid was used immediately after its preparation without drying. After bromination was completed (Table 1) the product (together with succinimide) was extracted from ionic liquid with ether. The remaining ionic liquid was microwaved at 150 W for 15 s and reused. We repeated the same reaction of bromination of phenol five times with recycling the ionic liquid without loss of selectivity or decreased isolated yield of 4-bromophenol. In addition, an additional reaction was performed on a large scale (10 g of anisole) with almost quantitative yield (97%) of 4-bromoanisole.

Bromination of benzene with one hydroxyl, amino, *N*,*N*-dimethylamino, or methoxy groups produced the single 4-brominated product in almost quantitative yield (Table 1, compounds **2a**–**d**). For *N*,*N*-dimethylaniline and anisole, the presence of an aldehyde, nitro, or carboxylic group did not change the outcome of the reaction nor the reaction time. Bromination occurred selectively in the *para* position with regard to the activating aromatic substituent (Table 1, compounds **2f**–**k**). Interestingly, for phenol and aniline with a carboxylic acid, aldehyde, or cyano group, the formation of the dibromo product is preferred over monobromo product (Table 2). We were not able to perform selective monobromination even when less than one equivalent of NBS was used. One can argue that the OH group is stronger aromatic activating group than OCH_3 and therefore, this might be an explanation for the ease of dibromination in these substrates. However, the same was not found for phenol and aniline, where the only product detected was the 4-bromophenol and 4-bromoaniline products, respectively. Based on our observations, we hypothesize that the presence of electron-withdrawing group in combination with OH or

Table 2
Non-selective bromination in the ionic liquid



3 4 5

a: $R_1 = OH$, $R_2 = CHO$, $R_3 = R_4 = H$; **b**: $R_1 = OH$ $R_2 = COOH$, $R_3 = R_4 = H$;
c: $R_1 = R_3 = H$; $R_4 = OH$, $R_2 = COOH$; **d**: $R_1 = R_3 = H$; $R_4 = OH$, $R_2 = COOH$;
e: $R_1 = NH_2$, $R_2 = COOH$, $R_3 = R_4 = H$; **f**: $R_1 = R_3 = H$; $R_4 = NH2$, $R_2 = COOH$;
g: $R_1 = NH_2$, $R_2 = CN$, $R_3 = R_4 = H$

Product	Time (min)	Conversion (%)	Mono/di (ratio)
4a/**5a**	2	80	2/3
4b/**5b**	2	65	2/3
4c/**5c**	3	85	2/3
4d/**5d**	2	100	1/4
4e/**5e**	5	50	1/4
4f/**5f**	4	100	2/3
4g/**5g**	2	70	2/3

NH_2 is required to facilitate these substrates bromination products. At the present time we do not have plausible explanation for outcome of this reaction.

We also utilized different solvents through the course of our studies, to determine what, if any, changes would occur in the regioselectivity or isolated yields of our bromination products. Therefore, we compared the ionic liquid/NBS-facilitated aromatic bromination with NBS/dioxane bromination. Using a bromine–dioxane complex for aromatic bromination is well documented.[12] Recently, NBS aromatic bromination in the presence of polyethylene glycol[23] suggests the possibility to utilize NBS-dioxane for aromatic bromination. Using this reagent mixture, we obtained excellent monobromination for phenol and aniline (Table 1). The isolation procedure following this reaction is exceptionally simple and the results were comparable to the ionic liquid-mediated bromination. However, when phenol and aniline derivatives with strong electron-withdrawing groups such carboxylic, nitro, formyl, and cyano were brominated, a complex mixture of mono- and dibromo products.

In conclusion, it can be stated that a new, very efficient aromatic bromination method was developed for bromination active aromatic compounds. *Para* monobromination was accomplished in a few minutes by using NBS as a safe bromine source and an ionic liquid as a recyclable reaction medium. It is necessary to microwave the ionic liquid prior to its use or reuse in the bromination process to activate the ionic liquid. The selectivity and isolated yield are almost identical after five times recycling of the ionic liquid. Furthermore, the reaction is also applicable to large scale aromatic bromination.

Acknowledgment

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24. *General procedure for synthesis of aromatic bromides using ionic liquids*: Into shortly (15 s) microwaved (150 W) 1-butyl-3-methylimidazolium bromide [Bmim]Br (0.5 g) and *N*-bromosuccinimide [NBS] (1 mmol) aromatic compound (1 mmol) was added. After the reaction was completed (a few minutes as monitored by TLC), the reaction mixture was extracted with ether (3×3 ml). The remaining ionic liquid was reused for next bromination following microwave activation again. Ether extract was washed with saturated $NaHCO_3$ (3×1 ml), and dried over anhydrous magnesium sulfate. The resulting product was isolated after evaporation of ether.
25. *General procedure for synthesis of aromatic bromides using Dioxane-NBS*: The corresponding aromatic compound (1 mmol) was dissolved in dioxane (2 ml) and NBS (1 mmol) was added in small portions. As the reaction completes, the reaction mixture was diluted with water (15 ml) and extracted with dichloromethane or ethyl acetate (3×15 ml). Combined organic extracts were washed with saturated $NaHCO_3$ (3×10 ml) and dried over anhydrous magnesium sulfate. The resulting product was isolated by evaporation of the solvent. If required, further product purification can be performed by column chromatography.