An intriguing effect of lithium perchlorate dispersed on silica gel in the bromination of aromatic compounds by *N*-bromosuccinimide

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Abstract: A convenient and efficient procedure for electrophilic aromatic bromination has been developed by mixing of *N*-bromosuccinimide and an aromatic compound at room temperature on the surface of silica gel mixed with solid anhydrous $LiClO_4$. All of the substrates examined underwent clean electrophilic aromatic bromination in reaction times of a few minutes to afford the corresponding bromoarenes under neutral conditions in excellent yield. In the case of thiophenol, no substitution reaction occurred, and the corresponding disulfide was obtained in excellent yield.

Key words: LP-SiO_2, NBS, arenes, electrophilic bromination, regioselectivity.

Résumé : On a mis au point une méthode pratique et efficace d'effectuer une bromation aromatique électrophile donnant d'excellents rendements et qui implique la mise en contact, à la température ambiante et pendant quelques minutes, de *N*-bromosuccinimide et d'un composé aromatique à la surface d'un gel de silice mélangé avec du $LiClO_4$ anhydre solide. Tous les substrats ont donné lieu à des bromations aromatiques électrophiles propres conduisant, dans des conditions neutres, aux bromoarènes correspondants. Dans le cas du thiophénol, il ne se produit pas de réaction de substitution et le disulfure correspondant est obtenu avec un excellent rendement.

Mots clés : LP-SiO_2, NBS, arènes, bromation électrophile, régiosélectivité.

[Traduit par la Rédaction]

Introduction

Brominated arenes are versatile intermediates in the synthesis of a wide variety of biologically active compounds. They are also widely used for the preparation of products of commercial importance such as pharmaceuticals, agrochemicals, synthetic colorants, and performance chemicals (1). A popular method for the bromination of aromatic compounds is the reaction of molecular bromine with an arene, in a halogenated hydrocarbon (2) or acetic acid (3). However, in many cases, mixtures of mono-, di-, and polybrominated products are obtained. Another popular and mild, less hazardous, and inexpensive reagent that has been used for electrophilic aromatic bromination is *N*-bromosuccinimide (NBS) in CCl_4 (4). The major advantage of the use of NBS as a brominating agent is that the by-product succinimide can be easily recovered, converted to NBS, and reused. A variety of methods for such a reaction with NBS have been reported in the literature, including NBS-PTZ (5), NBS-PTSA (5), NBS-Amberlyst (6), NBS-NaOH (7), NBS-HZSM (8), and NBS-HBF_4/Et_2O (9). In addition, electrophilic bromination of activated aromatic compounds has been reported to be favored in polar solvents such as propylene carbonate (10), DMF (11), CH_3CN (12), and ionic liquids (13). Despite the apparent utility of these reagents, they have not been widely used for electrophilic aromatic bromination, which may be due to the variable results reported in terms of both products and yields. More recently, green protocols such as solid-state bromination (14) and Oxone®/sodium bromide (15) have been reported in the literature.

Results and discussion

In recent years, the use of lithium perchlorate in diethyl ether (LPDE) as a polar medium has attracted attention owing to the enhanced rate and selectivity observed for various organic transformations in this medium (16). The LPDE medium provides a convenient means to carry out reactions under neutral and easy workup conditions.

In continuation of our interest on the application of lithium perchlorate for various organic transformations (17), we herein describe a simple, efficient, and general method for the electrophilic bromination of aromatic rings by using NBS in CH_2Cl_2 catalyzed by solid lithium perchlorate dispersed on silica gel ($LiClO_4$–SiO_2). The general applicability of this reagent for a large number of aromatic compounds was investigated, and the results are summarized in Tables 1 and 2. The brominated compounds were identified on the basis of their ^{1}H NMR and mass spectral data, and by comparison of these data with those reported in the literature. The

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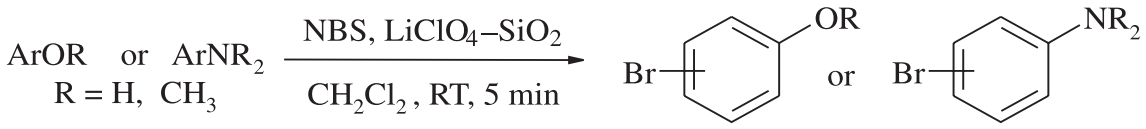
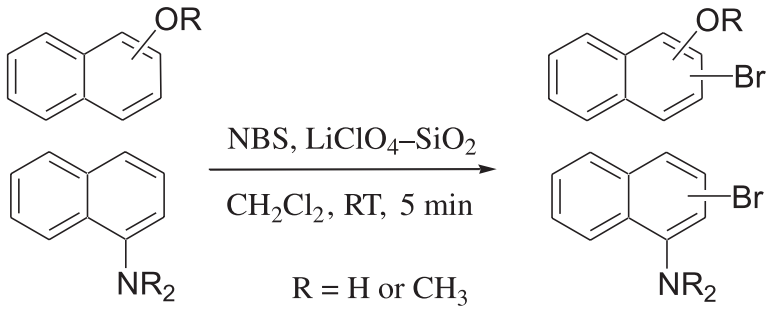
Table 1. Bromination of activated benzene derivatives by NBS in the presence of $LiClO_4$–SiO_2.



Entry	Substrate	NBS (equiv.)	Product(s)	Yield (%)
1	Phenol	2	2,4-Dibromophenol	85
			4-Bromophenol	15
2	Aniline	2	2,4-Bromoaniline	98
3	*p*-Cresol	1	2-Bromo-4-methylphenol	95
4	*p*-Toluidine	1	2-Bromo-4-methyltoluidine	98
5	4-Hydroxyacetophenone	2	3,5-Dibromo-4-hydroxyacetophenone	80
			3-Bromo-4-hydroxyacetophenone	20
6	4-Aminoacetophenone	2	3,5-Dibromo-4-aminoacetophenone	90
7	4-Nitrophenol	2	2,6-Dibromo-4-nitrophenol	80
			2-Bromo-4-nitrophenol	20
8	4-Nitroaniline	2	2,6-Dibromo-4-nitroaniline	98
9[a]	Anisole	1	4-Bromoanisole	98
10	*N,N*-Dimethylaniline	1	4-Bromo-*N,N*-dimethylaniline	98
11	4-(*N,N*-Dimethylamino)benzaldehyde	1	3-Bromo-4-(*N,N*-dimethylamino)benzaldehyde	90
12	2-Aminobenzonitrile	1	2-Amino-4-bromo-benzonitrile	95
13	3-Anisidine	2.5	2,4,6-Tribromo-3-anisidine	10
			2,4-Dibromo-3-anisidine	90
14	4-Bromoaniline	1	2,4-Dibromoaniline	98
15	4-Chloroaniline	1	2-Bromo-4-chloroaniline	98

[a]Reaction time was 2 h, and 1.0 g of $LiClO_4$–SiO_2 was used.

Table 2. Bromination of naphthalene derivatives by NBS in the presence of $LiClO_4$–SiO_2.



Entry	Substrate	NBS (equiv.)	Product(s)	Yield (%)
1	2-Naphthol	1	1-Bromo-2-naphthol	98
2	1-Naphthol	2	2,4-Dibromo-1-naphthol	98
3	1-Naphthylamine	2	2,4-Dibromo-1-naphthylamine	98
4	2,7-Dihydroxynaphthalene	1	1-Bromo-2,7-dihydroxynaphthalene	98
5[a]	2-Methoxynaphthalene	2	1,4-Dibromo-2-methoxynaphthalene	98
6	Anthracene	2	9,10-Dibromoanthracene	100

[a]1.0 g of $LiClO_4$–SiO_2 was used.

starting materials used in this study were commercially available. The bromination reaction was studied at different temperatures and in solvents of different polarities (CH_3CN, CH_2Cl_2, CCl_4, MeOH, and 5 mol/L LPDE), using different molar ratios of NBS/arene. The optimized reaction conditions were found to be the simple stirring of a solution of arene (1 equiv.), NBS (1 equiv.), and 0.4 g $LiClO_4$–SiO_2 (1:4) in CH_2Cl_2 at room temperature, which afforded the product in good yield (Table 1). Without using solid $LiClO_4$ or SiO_2, the reaction is less selective and the reaction time is longer.

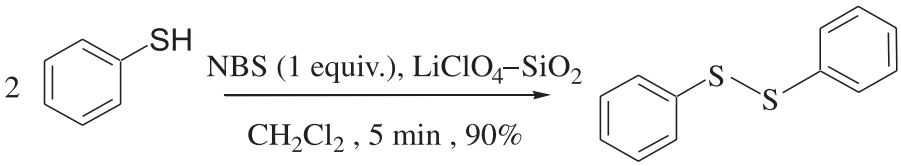
The data in Table 1 clearly show the general applicability of this method for a variety of aromatic compounds. In most cases, one product (either the monobromo- or the

Table 3. Bromination of activated pyridine and quinoline derivatives by NBS in the presence of $LiClO_4$–SiO_2.

Entry	Substrate	NBS (equiv.)	Product(s)	Yield (%)
1	2-Aminopyridine	2	5-Bromo-2-aminopyridine	90
			3,5-Dibromo-2-aminopyridine	10
2	8-Aminoquinoline	2	5,7-Dibromo-8-aminoquinoline	98

Note: Reaction time: 5 min.

Scheme 1.



dibromoarene) was formed in a short reaction time and in good yield. In all cases, the crude products were monitored by GC and checked for the presence of any by-products. Some general trends are apparent from the data in Table 1. First, the reactivity of the substrate seems to be related to the electron density on the aromatic ring. Thus, the nucleus must be sufficiently activated before significant reactions occurred. This reagent is not effective for benzene, toluene, or naphthalene, and amino derivatives give slightly easier and cleaner reaction than hydroxyl derivatives. The presence of electron-donating or electron-withdrawing groups on the aniline or phenol did not affect the rates or the yields of the reactions. For example, *p*-methylaniline, *p*-nitroaniline, *N,N*-dimethylaniline, and *p*-(*N,N*-dimethylamino)benzaldehyde gave the monobromo product in short reaction times and in high yields (Table 1, entries 4, 8, 10, and 11). *p*-*S*ubstituted anilines were brominated at the ortho position. In the case of aniline (Table 1, entry 2), 1-naphthylamine (Table 2, entry 3), and 4-aminoacetophenone (Table 1, entry 6), as well as 8-aminoquinoline (see Table 3, entry 2), in the presence of 2 equiv. of NBS dibromination occurred at the 2 and 4 positions in high yields. It is noteworthy that the direct bromination of aniline with bromine in solution often results in polybromination and requires the protection of amino groups. The results with the derivatives of phenol are somewhat different. For example, under the above reaction conditions, phenol gave dibromophenol (Table 1, entry 1), while 2-naphthol (Table 2, entry 1), 2,7-dihydroxynaphthalene (Table 2, entry 4), and *p*-substituted phenols gave only monobrominated products in short reaction times and with high yields (except in the case of 4-nitrophenol). 1-Naphthol (Table 2, entry 2) and 3-anisidine (Table 1, entry 13) produced the corresponding dibromo derivatives. The bromination of methoxybenzene required a long reaction time with 1 g of $LiClO_4$–SiO_2 (Table 1, entry 9), but 2-methoxynaphthalene gave the dibromo product in excellent yield with 1 g of $LiClO_4$–SiO_2 (Table 1, entry 13). Comparison of our results with those reported in the literature clearly shows that higher reactivity and higher selectivity are obtained with $LiClO_4$–SiO_2 than with SiO_2 (18).

We next investigated bromination of 2-aminopyridine and 8-aminoquinoline. The most direct approach to the bromination of pyridine derivatives is the direct electrophilic halogenation of the activated pyridines in polar protic solvents, such as water and ethanol. In the reported procedures, with the use of common organic solvents such as CH_3CN, CS_2, CH_2Cl_2, and CCl_4, mixtures of monobromo and dibromo products were formed, with long reaction times (19, 20). We have found that NBS/$LiClO_4$–SiO_2 is suitable for the regioselective monobromination of aminopyridine and dibromination of 8-aminoquioline with excellent yields and a reaction time of a few minutes (Table 3).

To extend the scope of this reagent, we have also investigated bromination of anthracene and thiophenol. NBS in CCl_4 is a common brominating agent for anthracene and affords a mixture of mono- and dibromoanthracene in good yields (21). We found that bromination of anthracene with 2 equiv. of NBS using the NBS/$LiClO_4$–SiO_2 reagent yieled 9,10-dibromoanthracene as the sole product. On the other hand, bromination of thiophenol was not successful, and coupling of thiol groups to form the disulfide in excellent yields was observed (Scheme 1).

In conclusion, we have developed a simple, general, and efficient method for electrophilic bromination of activated arenes under mild conditions, mediated by $LiClO_4$ dispersed on SiO_2 in CH_2Cl_2. The absence of side-chain bromination products in this procedure clearly indicates that an electrophilic aromatic substitution mechanism operates in this reaction medium; the remarkable enhancement in reaction rates and regioselectivity could be explained by increased polarization of the N—Br bond of NBS in this ionic process. This procedure also can be applied to polycyclic aromatic compounds. Furthermore, the $LiClO_4$–SiO_2 reagent is cheap, stable, easy to handle, and nontoxic. The present method would be useful in organic synthesis. We are currently extending this methodology to the use of NXS (X = Cl, I).

Experimental

General procedure for the bromination of aromatic compounds with NBS

NBS (1–2 eqiuv.) was added slowly to a stirred solution of an aromatic compound (2 mmol) and 0.4 g of $LiClO_4$–SiO_2 (1:4) in CH_2Cl_2 (20 mL). When the addition was complete, the reaction mixture was stirred at room temperature and the progress of the reaction monitored by TLC and GC. Complete conversion was achieved for most of the substrates. The reaction mixture was filtered, and the catalyst

was recovered and washed with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with water and dried over anhydrous sodium sulfate and concentrated under reduced pressure using a rotary evaporator. Almost pure crude product was obtained in most cases. Further purification was carried out by short column chromatography on silica gel (ethyl acetate: petroleum ether). All compounds are known and were characterized on the basis of their spectroscopic data (GC, MS, NMR) and by comparison of these data with those reported in the literature.

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