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Regioselective, photochemical bromination of aromatic compounds using *N*-bromosuccinimide

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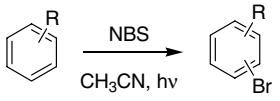
Abstract—Regioselective nuclear bromination of aromatic compounds is investigated with *N*-bromosuccinimide as the brominating agent under UV irradiation to afford the corresponding brominated compounds. The reaction proceeds at ambient temperature (30 ± 2 °C) without any catalyst. In most of the reactions, regioselectively mono-brominated products are obtained in good to high yields. The conversion and selectivity for bromination depend on the nature of the substituent on the aromatic ring.

Halogenated aromatic compounds belong to an important class of organic intermediates that are used as precursors of organometallic reagents in synthetic organic chemistry.[1] They can be used as potent, antitumor, antibacterial, antifungal, antineoplastic, antiviral, antioxidizing agents and also as industrial intermediates in the manufacture of pharmaceuticals and agrochemicals.[2] Various methods have been developed and reported for the bromination of aromatic compounds using a variety of brominating agents under various conditions.[3] Conventional, direct bromination involves the use of molecular bromine and metal halides including Br_2–Lewis acids,[4] $Br_2/SbF_3/HF$,[5] *N*-bromosuccinimide (NBS)/H_2SO_4,[6] NBS/SiO_2,[7] NBS/H_2SO_4/CF_3COOH,[8] NBS/PTSA,[9] NBS/NaOH,[10] Br_2/zeolites,[11] HBr/DMSO,[12] quaternary ammonium tribromide,[13] $KBrO_3$,[14] KBr/H_2O_2/Oxone,[15] and sodium monobromoisocyanourate.[16] Recently, bromination of aromatic compounds has been reported using hexamethylenetetraamine–Br_2[17] and KBr–benzyltriphenylphosphonium peroxo disulfate[18] and monosulfate,[19] under neutral conditions. In the reported reactions, the brominating agent used was either molecular bromine or Br_2 in combination with an acid or an oxidizing agent. These reagents are potentially hazardous, and it is difficult to handle and store elemental halogens.[20] From the 'green chemistry' point of view, the replacement of such harmful reagents with non-toxic, inexpensive, commercially available, non-polluting, and more selective reagents is an important goal. Among various brominating reagents, NBS [21] is environmentally friendly, easy to work with and is extensively used for allylic, benzylic, and aromatic nuclear bromination under mild conditions.[22] Recently, we reported α-bromination of aliphatic and aromatic ketones using NBS under UV–vis light irradiation at ambient temperatures without the use of a catalyst.[23] A major advantage of the use of NBS is that the by-product succinimide, can be easily recovered and recycled to NBS. Carreno et al.[24] reported aromatic ring bromination and benzylic bromination of substituted methyl anisoles using NBS in CH_3CN and CCl_4 under severe reaction conditions and with a long reaction time. However, photochemical nuclear bromination of activated aromatic compounds using NBS has not been studied so far. Here, we report the photochemical bromination of a number of substituted phenols and anilines, giving mono- and di-substituted derivatives, using NBS as the brominating agent at ambient temperature in acetonitrile, without a catalyst, in a very short time (Schemes 1 and 2). Optimization of the reaction conditions for the photochemical bromination of phenol with NBS was investigated as a model transformation.



Scheme 1. R = H, OH, OCH_3, NH_2, NMe_2, NHAc, CH_3 and NO_2.

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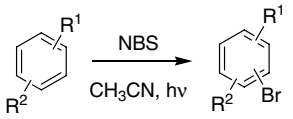


Scheme 2. R^1 and R^2 may be electron-donating or withdrawing groups. $R^1 = NH_2$, OH; $R^2 = NO_2$, OH, OCH_3, Cl, CH_3, CHO and COOH.

The effect of various solvents on the bromination of phenol was studied and the results are shown in Table 1. The reaction was complete within 3 min with no catalyst, in acetonitrile, with 99% conversion, to give *para*-bromophenol regioselectively in 88% yield. However, in hexane, the reaction was slower and less selective towards *para*-bromophenol (34%), also yielding *ortho*-bromophenol and 2,6-dibromophenol (Table 1, entry 9). The extent of conversion of phenol was in the order, $CH_3CN > DMSO > CHCl_3 \sim Et_2O > MeOH > DMF > DCM \sim THF > CCl_4 >$ hexane, whereas the selectivity for *para*-bromophenol decreased in the order, $CHCl_3 > Et_2O \sim MeCN > DMSO > DMF > THF > MeOH > CCl_4 >$ hexane. This observation suggests that more polar or more ionizing solvents enhance the reactivity of NBS and favor nuclear bromination. To establish the general applicability of NBS, various mono- and di-substituted aromatic compounds having electron-donating substituents were brominated in acetonitrile under UV–vis light. The mono-substituted phenols and their derivatives (α-naphthol, β-naphthol, 1- and 2-methoxynaphthalene and anisole) were readily brominated to afford the desired mono-brominated products with excellent selectivity (100%) and conversion (<97%) (Table 2, entries 1–5). The bromination of 1- and 2-methoxynaphthalene was carried out by Carreno et al. at room temperature in acetonitrile as solvent affording 94% and 92% yields of mono-brominated products in 2 and 3 h, respectively.[24] The same bromination carried out by us using UV–vis irradiation took only 3 min and gave 99% conversion and 100% selectivity.

Table 1. Effect of solvents on the bromination of phenol

Entry	Solvent	Conversion (%)	Selectivity (%)	
			Product[a]	Others[b]
1	MeCN	99	88	12
2	$CHCl_3$	89	91	9
2	DCM	83	32	68
4	Methanol	87	69	31
5	Et_2O	89	89	11
6	DMF	85	80	20
7	DMSO	92	83	17
8	THF	83	75	25
9	Hexane	43	34	66
10	CCl_4	46	47	53

Reaction conditions: temp = 30 ± 2 °C; substrate: reagent (mol) ratio = 1:1, the conversions are based on GC analysis. Products were characterized by NMR and GC–MS.

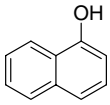
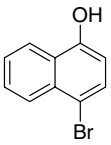
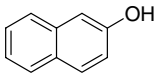
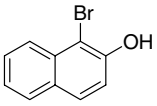
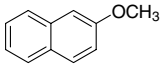
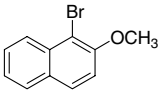
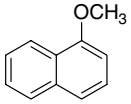
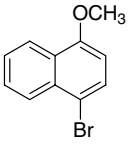
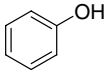
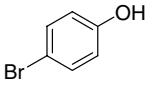
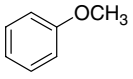
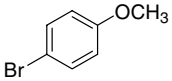
[a] *para*-Bromophenol.

[b] *ortho*-Bromophenol and 2,4-dibromophenol. All reactions were conducted for a duration of 3 min.

Benzene and nitrobenzene did not undergo bromination even after a prolonged reaction time (entries 6 and 7). Thus, less reactive aromatic substrates did not undergo nuclear bromination under these reaction conditions. Toluene was brominated at a benzylic position, rather than on the ring, requiring a longer reaction time (Table 2, entry 8). Aniline was brominated at the *para* position with 90% selectivity (2,4,6-tribromoaniline, 10% selectivity was also obtained), with 73% conversion (entry 9). *N*,*N*-Dimethylaniline was rapidly brominated at the *para* position to give 4-bromo-*N*,*N*-dimethylaniline within 1 min with 93% conversion and 100% selectivity (entry 10). Bromination of acetanilide afforded 4-bromoacetanilide with low conversion. To obtain the best yield of 4-bromoacetanilide, NBS was added in four portions,[23] which increased the conversion from 40% to 83% (entry 11).

Various disubstituted aromatic compounds were brominated within 3 min with good to excellent conversions. Bromination of *ortho*-substituted electron-rich phenols and anilines occurred at the *para* position. Hydroxy derivatives of phenol (catechol, resorcinol, and hydroquinone, entries 12–14) gave the corresponding bromophenols with good conversion but low selectivity. The bromination of hydroquinone gave mono-brominated hydroquinone as the major product but oxidation as a side reaction gave benzoquinone as a minor product. Bromination of 2- and 4-chlorophenols gave the corresponding brominated products in good yields (entries 15 and 16). Methyl phenols underwent nuclear bromination rather than benzylic bromination to give the corresponding brominated products 4-bromo-3-methylphenol and 2-bromo-4-methylphenol, respectively (entries 17 and 18). It may be noted that Carreno et al. had earlier reported on the bromination of the respective ethers of the methyl phenols, which was completed within 0.5–3 h.[24] The bromination of 3-aminophenol gave 4-bromo-3-hydroxyaniline with low conversion, along with 2,6-dibromo-3-hydroxyaniline and 2,4,6-tribromo-3-hydroxyaniline as side products. When the reagent-to-substrate mol ratio was increased from 0.25:1 to 2:1, the conversion increased from 48% to 100% with no change in the product distribution (entry 19). 4-Nitrophenol and 2-hydroxybenzoic acid were brominated to give 2-bromo-4-nitrophenol and 4-bromo-2-hydroxybenzoic acid with 55% and 56% conversions and 78% and 100% selectivity, respectively (entries 20 and 21). While using a substrate to reagent ratio of 1:1.5 moles increased the conversion from 56% to 96% for 2-hydroxybenzoic acid. Bromination of vanilin afforded a brominated product with 88% conversion and 100% selectivity (entry 22). Both 2- and 4-chloroanilines were brominated with excellent conversion and selectivity for 4-bromo-2-chloroaniline and 2-bromo-4-chloroaniline, respectively (entries 23 and 24). 4-Methoxyaniline gave 2-bromo-4-methoxyaniline along with 2,6-dibromo-4-methoxyaniline as a minor product (entry 25). Bromination of 4-aminobenzoic acid and 4-nitroaniline yielded 4-amino-3-bromobenzoic acid and 2-bromo-4-nitroaniline, respectively, at 84% and 80% conversion levels and with 86% and 100% selectivity for the brominated products, respectively (entries 26

Table 2. Bromination of mono-substituted aromatics using NBS

Entry	Substrate	Product	Time (min)	Conv. (wt %)	Selectivity (%)	
					Product	Others
1			3	99	100	—
2			3	97	100	—
3			3	99	100	—
3a			3	99	100	—
4			3	99	88	12
5			20	98	100	
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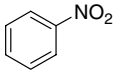
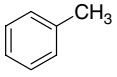
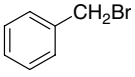
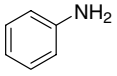
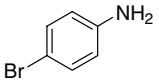
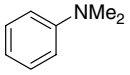
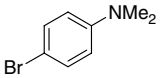
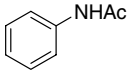
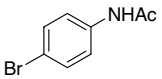
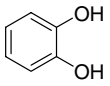
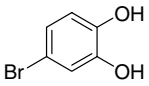
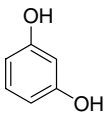
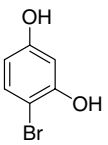
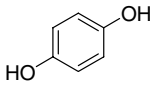
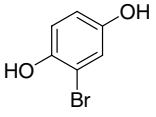
7		No reaction	180	—	—	—
8			15 30	76 95	100[b] 95	— 5
9			3	73	90	10
10			1	93	100	—
11			3 12	40 83[a]	100 99	— 1
12			3 12	58 77[a]	82 66	18 34
13			3	90	62	38
14			3 12	62 79[a]	45 47	55 53

(*continued on next page*)

Table 2 (*continued*)

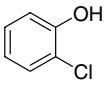
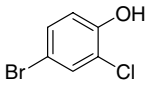
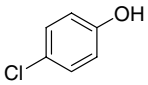
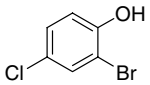
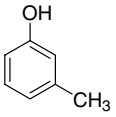
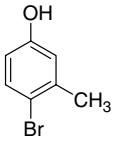
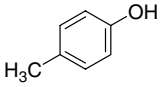
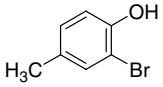
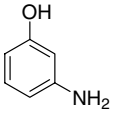
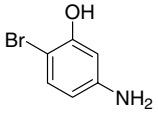
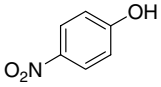
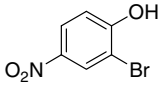
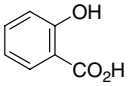
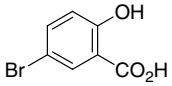
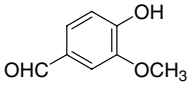
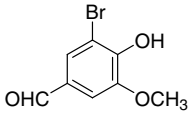
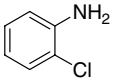
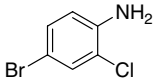
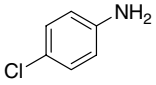
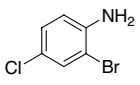
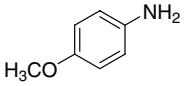
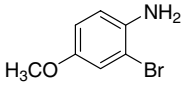
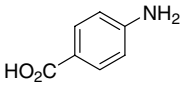
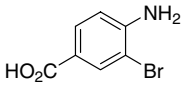
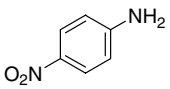
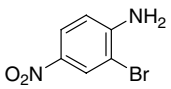
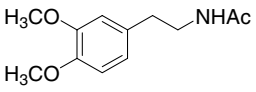
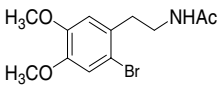
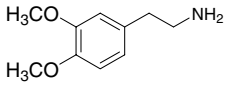
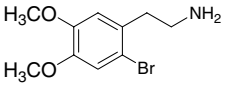
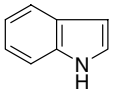
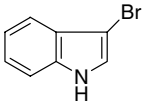
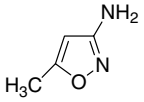
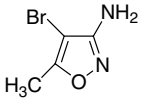
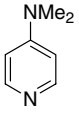
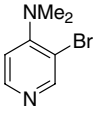
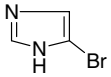
Entry	Substrate	Product	Time (min)	Conv. (wt %)	Selectivity (%)	
					Product	Others
15			3	85	74	26
16			3	65	94	6
17			3 12	89 99[a]	86 93	14 7
18			3 12	80 98[a]	93 92	7 8
19			3 3	60 100[c]	49 43	51 57
20			3	55	78	22
21			3 3	56 96[d]	100 100	— —
22			30	88	100	—
23			3	98	99	1
24			3	99	99	1
25			3	86	82	18
26			3	84	86	14
27			3 12	51 80[a]	78 100	22 —
28			30	100	100	—

Table 2 (*continued*)

Entry	Substrate	Product	Time (min)	Conv. (wt %)	Selectivity (%)	
					Product	Others
29			30	98	100	—
30			12	85	100	—
31			3	85	100	—
32			30	95	100	—
33			30	85	82	18

Reaction conditions: temp = 30 ± 2 °C; solvent = acetonitrile, substrate: reagent (mol) ratio = 1:1; conversions are based on GC analysis. Products were characterized by ^{1}H NMR and GC–MS.

[a] Portion-wise addition of NBS.

[b] Benzylic bromination.

[c] 2:1 ratio of reagent to substrate.

[d] 1.5:1 ratio of reagent to substrate.

and 27). Synthetically useful and protected homoveratrylamine and veratrylamine were mono-brominated with excellent conversions (entries 28 and 29), but the reactions were sluggish compared to those of other aromatic compounds.

Some heterocyclic aromatic compounds were also brominated under similar reaction conditions to yield the desired products (entries 30–33). Indole was brominated at C-3 with 85% conversion and 100% selectivity. Imidazole gave a tri-bromo product without exposure to UV–vis light. A similar reaction at −10 °C afforded 5-bromoimidazole as the major product accompanied by tribromoimidazole as a minor product (entry 33).

The mechanism of these brominations is believed to involve radicals. [25] This was confirmed by adding to the reaction mixture a 2,2-diphenyl-1-picrylhydrazyl (DPPH) methanol solution and recording the UV–vis spectrum.[23,26] A blue shift in the absorption wavelength, from λ_{max} at 516 nm for DPPH in methanol to 385 nm for DPPH in the reaction mixture confirmed the formation of free radicals but this does not confirm that the radicals are involved in the substitutions.

The present study demonstrates an efficient and simple procedure for nuclear monobromination of aromatic compounds with NBS under UV–vis light irradiation. The selectivity and reactivity depend upon the nature of the substituents on the aromatic ring. Aromatic compounds having electron-donating substituents were brominated readily with high conversion and invariably with high selectivity for the mono-brominated products. However, with electron-withdrawing substituents, the bromination was slow and resulted in lower conversions. The reported photochemical methodology provides a convenient route to a number of brominated aromatics in good yield and within short reaction times.

General reaction procedure

A mixture of substrate (1 mmol) and NBS (1.05 mmol) was stirred in 5 ml of acetonitrile under an N_2 atmosphere in the presence of a Philips HPL-N (250 W, λ_{max} = 200–600 nm) lamp fitted with a water circulation arrangement at room temperature (30 ± 2 °C). To obtain the best yields of the products, NBS was added, in some cases, in four aliquots (each time 0.25 equiv at 3 min intervals). After completion (monitored by GC), the reaction mixture was quenched with cold water and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography over silica gel (60–120 mesh) using ethyl acetate and petroleum ether as eluents. The product was analyzed by GC (HP 5890) using a capillary column (HP-5). The GC–MS spectra were taken on a Shimadzu GC–MS QP5050A spectrometer equipped

with a DB-5 column to identify the products. All compounds gave satisfactory data and were identical with authentic samples.

Acknowledgments

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