N-Bromosuccinimide as a Regioselective Nuclear Monobrominating Reagent for Phenols and Naphthols

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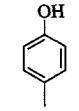
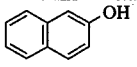
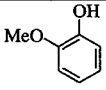
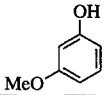
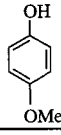
Abstract: A wide range of substituted phenols and naphthols were regioselectively monobrominated with *N*-bromosuccinimide, at *para* position in acetonitrile and at *ortho* position in carbon disulfide, under mild conditions in good yields. Methylphenols afforded only nuclear bromination products.

Bromination of phenols and derivatives can be achieved by a great variety of procedures.[1] Among them, the treatment with bromine in different solvents has been one of the more frequently utilized,[2] although the formation of polybrominated by-products and mixtures of regioisomers always emerged decreasing the yields of desired monobromophenols. In order to avoid polybrominations, the blocking of the more reactive positions of the aromatic ring by a group such as sulfonic acid, which can be removed after monobromination, has been applied.[3] The use of Br_2 in H_2O at different pH values[4] or in the presence of thallium acetate as catalyst,[5] and tetraalkylammonium bromides as brominating agents have also succeeded in the goal.[6] Very recently,[7] Oberhauser has developed an efficient new method for the selective monobromination of phenols and anisoles using NBS/ $HBF_4{\cdot}OEt_2$ in CH_3CN.

Other brominating systems have been successfully employed to obtain directly *para*-bromophenols in good yields.[7,8] Among them, NBS/ DMF,[8a] hexabromocyclopentadiene,[8b] hexamethylene tetramine tribromide,[8c] tetrabutylammonium tribromide[6] and tetraalkylammonium tribromides supported on polymers[8d,e] should be mentioned. Nevertheless, the regioselective preparation of *ortho*-bromophenols[9] remains nowadays as a not well solved question. The use of Br_2 or NBS in the presence of a primary or secondary amine[9b,c] or *N,N*-dibromomethylamine as brominating agent,[9d] have been described to give the *ortho*-regioselective bromination, although in both cases the formation of the dibrominated derivative was difficult to avoid. More recently, Buchwald has reported a method based on the regioselective insertion of borates or borinates in zirconocene complexes which after bromination and oxidation afforded the corresponding *ortho*-bromophenols.[9e]

Recently,[10] we have described the usefulness of *N*-bromosuccinimide[10a] and *N*-iodosuccinimide[10b] in CH_3CN for the regioselective halogenation of methoxybenzenes and naphthalenes under very mild conditions. In order to extend these good results, we wanted to study the ability of NBS to effect the regiocontrolled

Table 1. Bromination of Phenols and Naphthols with NBS in 0.25 M solutions

Entry	Substrate	Solvent	% *p*-Br[a] (isolated yield)	% *o*-Br[a] (isolated yield)	% of poly-bromination[a]	*o/p* or *p/o* Ratio
1		CH_3CN	**77** (73)	9	7	**8.6**
2		CH_2Cl_2	21	75	2	3.6
3		CCl_4	9	83 (80)	4	9.2
4		CS_2	5	**80** (75)	7	**16**
5		CH_3CN	**85** (80)	5	2	17
6		CS_2	18	**64**[b] (60)	3	3.6
7		CH_3CN	----	**90** (87)	5	
8		CS_2	----	**76** (68)	12	
9		CH_3CN	**97** (94)	3	----	32.3
10		CS_2	20	80	----	4
11		CS_2[c]	9	**91** (86)	----	10.1
12		CH_3CN	----	**100**[d] (95)	----	
13		CS_2	----	**100**[d] (95)	----	
14		CH_3CN	**78** (75)	11	6	7.1
15		CS_2	41	46	8	1.1
16		CS_2[c]	34	**53** (50)	8	1.6
17		CH_3CN	**50** (45)	35	4	1.4
18		CS_2	13	46[e]	18	3.5
19		CS_2[c]	8	**65**[e] (55)	14	8.1
20		CH_3CN	----	**90** (86)[f]	5	
21		CS_2	----	**90** (85)[f]	----	

[a] The rest up to 100% were starting materials. [b] Obtained as an unseparable 60:40 mixture of 2-bromo-5-methylphenol and 2-bromo-3-methylphenol. [c] In 0.01 M solutions. [d] Obtained as 1-bromo-2-naphthol. [e] Obtained as 2-bromo-5-methoxyphenol. [f] Isolated as the corresponding *p*-toluenesulphonate from the crude bromination mixture

monobromination of phenols and naphthols. The results reported herein show the possibility of synthesizing *p*-bromophenols from phenols by using NBS in CH_3CN and *o*-bromophenols from NBS in CS_2 under very mild conditions and in good to excellent yields and regioselectivities.

We chose 2-methylphenol as a model to find the best conditions for regioselective *o*- and *p*-brominations. This compound was submitted to reaction with NBS in 0.25M solutions of solvents of different polarity at rt for 1h (see Table, entries 1-4). As can be seen, in the polar CH_3CN (entry 1) the *p*-bromide was the major regioisomer, being the *o*-bromo derivative predominant in CH_2Cl_2, CCl_4[11] and CS_2 (entries 2-4). The best *o/p* ratio was obtained in CS_2 (entry 4). Thus, we chose CH_3CN and CS_2 for further reactions on different phenols and naphthols which were treated with NBS in the same conditions as above.[12] The results are collected in the Table.

First, we studied brominations of 3- and 4-methylphenol. When the *para* position with respect to the hydroxy group was occupied, only *o*-bromide was detected in both type of solvents (entries 7 and 8) along with small amounts of starting materials and dibrominated by-products. When the *para* position was free, as in 3-methylphenol, we obtained different mixtures of *o*- and *p*-bromides, being the *o*-bromo derivative the major component when apolar CS_2 was used (entry 6), and the *p*-bromide predominant when the reaction was carried out in CH_3CN (entry 5). In the former case, an inseparable mixture of two regioisomeric *o*-bromides, 2-bromo-5-methylphenol and 2-bromo-3-methylphenol in a 60:40 ratio (entry 6) was formed. We never observed bromination at the benzylic positions in the reaction of methylphenols in both type of solvents (entries 1-8).

The bromination of α-naphthol followed a similar pattern: 4-bromo-1-naphthol was formed in CH_3CN (entry 9) whereas 2-bromo-1-naphthol resulted working in CS_2 (entry 10). Reaction of β-naphthol in both solvents (entries 12 and 13) yielded 1-bromo-2-naphthol as the sole product, as expected from the high reactivity of the α position.

The regioselectivity observed in the apolar solvent CS_2 could be a consequence of the association by hydrogen bonding between the reagent NBS and the hydroxylic proton of the substituted phenol as a previous step of the intramolecular bromination, which therefore will be directed mainly at the *ortho* position. The use of a polar solvent such as CH_3CN minimizes the importance of these association. As a consequence, the less hindered and usually more activated *para* position, shall be more prone to react, yielding the *p*-bromide as the major component.[13]

The results obtained in the bromination of 2-, 3- and 4-methoxyphenols reinforced the above mentioned considerations. As can be seen from the Table (entries 14-21), we obtained mixtures of *o*- and *p*-bromides in all cases except when the *para* position was not free (entries 20 and 21), where 2-bromo-4-methoxyphenol was obtained in good yields in both solvents. In CH_3CN, the *p*-bromide was clearly predominant in the case of 2-methoxyphenol (entry 14) whereas for 3-methoxyphenol a poor 1.4 *p/o* ratio resulted (entry 17) due to the influence of the OMe group which have a higher activating effect on C-2 than on C-4,[10a] thus compensating the influence of the OH group. The same effect of the OMe group must be responsible of the obtention of a sole *ortho*-bromide in the conditions of entry 18, whereas in the case of 3-methylphenol (entry 6), a 60:40 mixture of the two possible *ortho*-bromides was obtained. Finally, the low *o/p* ratio observed in the bromination of 2-methoxyphenol in CS_2 (entry 15) could be explained by assuming the intramolecular association between the OMe and OH groups, making more difficult the asociation of the latter with NBS.

When brominations were carried out under diluted conditions (0.01 M), favouring intramolecular associations, a significant increase of the *ortho*-regioselectivity was observed in the reactions of α-naphthol (entry 11) and 3-methoxyphenol (entry 19), this effect being less important for 2-methoxyphenol (entry 16) and scarcely significant for 2- and 3-methylphenols.

In conclusion, the preparative obtention of *para*- and *ortho*-bromophenols and naphthols can be regioselectively achieved with NBS under mild conditions and good yields, by choosing respectively CH_3CN or CS_2 as solvents.

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(11) A similar regioselectivity had been pointed out in ref. 8a in the reaction of phenol with NBS in CCl_4.

(12) Representative procedure: to a solution of 1 mmol of the phenol in 0.25 M solutions of CH_3CN or CS_2, 1 mmol of NBS was added. The mixture was stirred at room temperature for 1h, the solvent evaporated and the residue treated with 10 mL of ethyl ether and water (3 x 5 mL). The ethereal phase was dried over $MgSO_4$, filtered and evaporated, and the crude bromo derivative was obtained and purified by flash chromatography.

(13) A predominance of *p*-bromides was also observed when brominations of 2- and 3-methylphenols with the NBS/CS_2 system were carried out in the presence of 1.1 equiv. of DMSO, a solvent able to break the hydrogen bond association between NBS and the OH group of phenols.