A New Bromination Method for Phenols and Anisoles: NBS/HBF_4·Et_2O in CH_3CN

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For the bromination of phenols, bromine in halogenated hydrocarbons[1] or HOAc[2] is often the reagent of choice. However, with many substrates, mixtures of mono- and polybrominated compounds are obtained.[3] For the selective monobromination of phenols and other activated aromatics, milder and also less hazardous reagents like dioxane dibromide,[4] pyridinium hydrobromide perbromide,[5] DBU hydrobromide perbromide,[6] tetrabromocyclohexadienone,[7] tetraalkylammonium tribromides,[8] and hexamethylenetetramine tribromide[9] have been developed. These reagents yield selectively *para*-brominated phenols unless the *para*-position is substituted. A reagent which brominates phenol selectively in the *ortho*-position is Br_2/*t*-$BuNH_2$.[10]

Another popular and inexpensive reagent for aromatic brominations is *N*-bromosuccinimide (NBS) in CCl_4.[11] Alkylated aromatics are either brominated in the side chain with NBS and benzoyl peroxide (Wohl−Ziegler reaction) or in the aromatic nucleus when no radical initiator is present.[12] The nuclear bromination of activated aromatic compounds (alkylbenzenes, phenols, anisoles) with NBS is clearly favored by polar solvents like propylene carbonate,[13] DMF,[14] and CH_3CN.[15] NBS has also been used in aqueous NaOH for the bromination of methoxy benzoic acids[16] and in the presence of diisopropylamine for the selective *ortho*-bromination of phenols.[17] Benzene reacts with NBS only in the presence of stoichiometric amounts of Lewis acids or concd H_2SO_4.[18] Other acidic catalysts that were used with NBS for the bromination of activated aromatic substrates are aqueous H_2SO_4[19] or catalytic amounts of concd H_2SO_4,[20] TsOH,[21] silica gel,[22] and the zeolite HZSM-5.[23]

Herein we report a new method for the selective monobromination of phenols and anisoles with NBS in CH_3CN promoted by HBF_4·Et_2O or other strong acids.[24] The results are summarized in Table 1. In the course of process research directed towards a technical synthesis of the potassium channel opener Ro 31-6930,[25] we required 2-bromo-4-hydroxybenzonitrile. Bromination of 4-hydroxybenzonitrile with NBS in CH_3CN gave a mixture of starting material, the desired *ortho*-monobrominated phenol, and the corresponding dibromo compound (entry 1f). With stoichiometric H_2SO_4, selective monobromination was observed, but even after 24 h the reaction was not complete (entry 1e). CF_3SO_3H, FSO_3H, and HBF_4·Et_2O on the other hand resulted in selective monobrominations within 3−24 h (entries 1a,b,d) whereas $ClSO_3H$ gave about 9% dibromophenol (entry 1c). Even when 4-hydroxybenzonitrile was treated with 2 equiv of NBS and 2 equiv of HBF_4·Et_2O, only 6% dibromophenol was detected. This nicely demonstrates the high selectivity of this reagent. For all subsequent bromination experiments HBF_4·Et_2O was used. The bromination is highly *para*-selective for phenol itself (entry 7a) as well as for *ortho*- and *meta*-substituted phenols (entries 2a, 3a, 5a, 6a, 9a). *Para*-substituted phenols were brominated in the *ortho*-position (entries 4a, 8a). The yields were generally good to excellent. 4-Nitrophenol and 2-nitroanisole required FSO_3H for complete bromination (entries 10a, 12a). HBF_4·Et_2O led only to incomplete conversion (entries 10b, 12b). In the absence of acid, mixtures of compounds were obtained, often with the dibrominated compound dominating (entries 2−9b, 10c). The only exceptions were 2-methylphenol and 2-methoxyphenol (entries 13, 14). With these substrates, selective monobromination was achieved with and without acid. 2-Nitroanisole and 4-methoxybenzoic acid methyl ester were virtually inert toward NBS in the absence of acid (entries 12c, 11b).

NBS and HBF_4·Et_2O in CH_3CN is not suited for the bromination of hydroxybenzaldehyde or hydroxyacetophenone. Both compounds decomposed and in case of the

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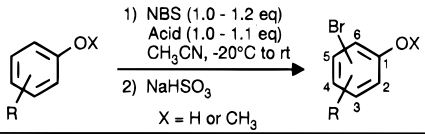
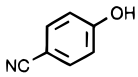
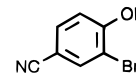
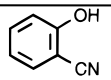
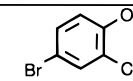
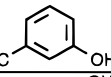
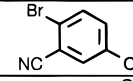
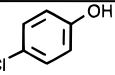
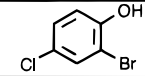
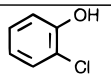
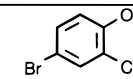
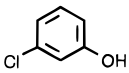
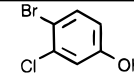
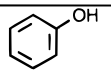
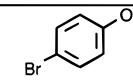
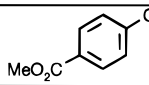
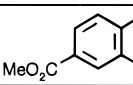
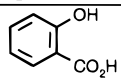
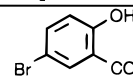
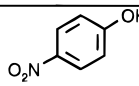
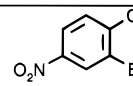
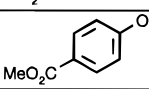
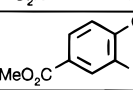
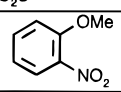
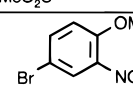
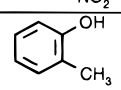
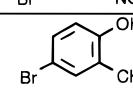
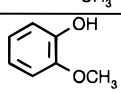
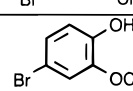
Table 1



Entry	Substrate	Acid	Time	Product Ratio[a]							Isolated Product	Yield
			(h)	S	2	4	6	2,4	2,6	4,6	2,4,6		(%)
1a		CF_3SO_3H	5	0	**97**	-	-	-	3	-	-		**94**[b]
1b		FSO_3H	3	2	**95**	-	-	-	3	-	-		**95**[c]
1c		$ClSO_3H$	5	5	**86**	-	-	-	9	-	-		nd
1d		HBF_4 Et_2O	24	1	**98**	-	-	-	1	-	-		**98**[c]
1e		H_2SO_4	24	28	**71**	-	-	-	1	-	-		nd
1f		—	5.5	44	**13**	-	-	-	43	-	-		nd
2a		HBF_4 Et_2O	3.5	0	-	**91**	9	-	-	0	-		**88**[d]
2b		—	3.5	29	-	**33**	4	-	-	34	-		nd
3a		HBF_4 Et_2O	5	4	18	**73**	2	0	0	0	3		**58**[d]
3b		—	5	50	2	**7**	15	<	12	>	14		nd
4a		HBF_4 Et_2O	4	0	**94**	-	-	-	6	-	-		**81**[d]
4b		—	4	36	**18**	-	-	-	47	-	-		nd
5a		HBF_4 Et_2O	7.5	0	-	**95**	3	-	-	2	-		**78**[d]
5b		—	3.5	36	-	**21**	6	-	-	37	-		nd
6a		HBF_4 Et_2O	2	0	4	**85**	4	<	4	>	3	0		**79**[d]
6b		—	1.5	40	6	**20**	5	<	6	>	3	20		nd
7a		HBF_4 Et_2O	1.5	0	2	**93**	-	5	0	-	0		**83**[d]
7b		—	5.5	30	11	**36**	-	10	1	-	12		nd
8a		HBF_4 Et_2O	4	2	**97**	-	-	-	1	-	-		**93**[c]
8b		—	4	42	**16**	-	-	-	42	-	-		nd
9a		HBF_4 Et_2O	5	3	-	**95**	2	-	-	0	-		**90**[e]
9b		—	5	14	-	**55**	5	-	-	26	-		nd
10a		FSO_3H	24	5	**95**	-	-	-	0	-	-		**86**[f]
10b		HBF_4 Et_2O	24	62	**38**	-	-	-	0	-	-		nd
10c		—	6.5	49	**14**	-	-	-	37	-	-		nd
11a		HBF_4 Et_2O	23	2	**97**	-	-	-	1	-	-		**94**[c]
11b		—	23	100	**0**	-	-	-	0	-	-		-
12a		FSO_3H	46	0	**100**	-	-	-	0	-	-		**91**[c]
12b		HBF_4 Et_2O	46	12	**88**	-	-	-	0	-	-		nd
12c		—	24	85	**15**	-	-	-	0	-	-		nd
13a		HBF_4 Et_2O	6	2	-	**93**	4	-	-	1	-		**86**[d]
13b		—	6	2	-	**95**	2	-	-	1	-		**87**[d]
14a		HBF_4 Et_2O	7	2	-	**80**	5-Br: 12		-	6	-		**72**[g]
14b		—	21	0	-	**88**	5-Br: 6		-	6	-		**81**[g]

[a] The product ratio was determined by GC and ^1H NMR. The structure of the by-products was elucidated by GC-MS, comparison with authentic standards or by isolation and spectroscopic characterization. S denotes substrate and the numbers the position of bromination. For simplification reasons the numbering is not in compliance with IUPAC nomenclature (see experimental part). [b] cryst. EtOAc/hexane. [c] crude yield. [d] chrom. CH_2Cl_2/*t*-BuOMe. [e] cryst. H_2O. [f] chrom. EtOAc/hexane 1:1. [g] chrom. hexane/ EtOAc/NEt_3 5:4:1.

acetophenone, a small amount of the α-brominated compound was isolated.

To gain insight into the nature of the active brominating species, ^{13}C NMR measurements were performed. Immediately after the addition of 1 (or 2) equiv of HBF_4·Et_2O to NBS in CD_3CN, the signal of the carbonyl group shifted from 176.27 to 177.33 ppm. After 5 h, however, the CO signal occurred at 184.16 ppm which corresponds to protonated succinimide (succinimide + 1 equiv of HBF_4·Et_2O: 183.98 ppm). The CO signal of neutral succinimide in CD_3CN is at 180.17 ppm. These results suggest protonation of NBS by HBF_4·Et_2O, followed by a slow cleavage of the N−Br bond under formation of succinimide and possibly bromonium tetrafluoroborate. To our knowledge, $BrBF_4$ has not yet been reported in the literature.[26]

In conclusion we developed an efficient new method for the selective monobromination of phenols and anisoles using NBS/HBF_4·Et_2O in CH_3CN. Bromonium tetrafluoroborate might be the actual brominating species. Further work regarding the halogenation of other activated

(26) The isolation of tribromine tetrafluoroborate (Br_3BF_4) has been reported: Šmalc, A. *Inst. Jozef Stefan Rep.* **1972**, *R-612*, 1−7.

aromatics with similar reagents is in progress and will be reported in due course.

Experimental Section

General. Unless otherwise indicated, all starting materials and reagents were obtained from commercial suppliers and used without further purification. Solvents for reactions, extraction, and chromatography were analytical grade. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 250 MHz. Low resolution EI mass spectra were obtained with an ionization voltage of 70 eV. GC analyses were performed on a crosslinked 5% Ph Me Silicone capillary column (0.25 μM, 30 m). Analytical HPLC employed a RP-18 column (250 × 4 mm) and a potassium phosphate buffer (0.03 M, pH 6)/CH_3CN gradient (1.2 mL/min, 50 °C). TLC was performed on precoated Merck glass plates (0.25 mm) with silica gel 60 F_{254}. Compound visualization was effected by UV light (254 nm).

General Procedure for the Bromination of Phenols and Anisoles. To a cold (−20 °C) solution of phenol or anisole (2 g)[27] in CH_3CN (20 mL) under argon was added acid (1.0−1.1 equiv) and then slowly NBS (1.0−1.2 eq) such that the temperature did not rise above −10 °C. After the addition, the cooling bath was removed and the reaction mixture allowed to warm up to rt. The progress of the reaction was followed by TLC, GC, or HPLC. Stirring was continued for the time indicated in Table 1. $NaHSO_3$ (38%, 10 mL) was added, and the reaction mixture was extracted with *t*-BuOMe (2 × 25 mL). Each organic layer was washed with H_2O (2 × 25 mL) and brine (25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure with a rotary evaporator. If necessary, the crude products were purified by crystallization or flash chromatography (230−400 mesh silica gel 60).

3-Bromo-4-hydroxybenzonitrile: mp 155−156 °C (lit.[28] mp 154−155 °C); ^{1}H NMR 6.06 (s, 1H), 7.09 (d, J = 8.5, 1H), 7.54 (dd, J = 8.5, 1.9, 1H), 7.80 (d, J = 1.9, 1H); MS 199, 197 (M^+, 100, 98).

5-Bromo-2-hydroxybenzonitrile: mp 157−158 °C (lit.[29] mp 158−159 °C); ^{1}H NMR 6.05 (s, 1H), 6.89 (d, J = 8.8, 1H), 7.57 (dd, J = 8.8, 2.4, 1H), 7.62 (d, J = 2.4, 1H); MS 199, 197 (M^+, 98, 100), 171, 169 (61, 63).

2-Bromo-5-hydroxybenzonitrile: ^{1}H NMR 5.20 (s, 1H), 6.97 (dd, J = 8.8, 2.8, 1H), 7.13 (d, J = 2.4, 1H), 7.53 (d, J = 8.8, 1H); MS 199, 197 (M^+, 100, 92).

2-Bromo-4-chlorophenol: mp 31−32 °C (lit.[30] mp 33−34 °C); ^{1}H NMR 5.56 (s, 1H), 6.95 (d, J = 8.7, 1H), 7.19 (dd, J = 8.7, 2.4, 1H), 7.46 (d, J = 2.4, 1H); MS 210, 208, 206 (M^+, 23, 100, 75).

4-Bromo-2-chlorophenol:[31] mp 49−50 °C (lit.[30] mp 48−49 °C); ^{1}H NMR 5.51 (s, 1H), 6.91 (d, J = 8.7, 1H), 7.29 (dd, J = 8.7, 2.3, 1H), 7.47 (d, J = 2.3, 1H); MS 210, 208, 206 (M^+, 22, 100, 78).

4-Bromo-3-chlorophenol: mp 67−68 °C (lit.[32] mp 67.5−69 °C); ^{1}H NMR 5.50 (s, 1H), 6.63 (dd, J = 8.7, 2.8, 1H), 6.97 (d, J = 2.8, 1H), 7.43(d, J = 8.7, 1H); MS 210, 208, 206 (M^+, 24, 100, 82).

4-Bromophenol: mp 66−68 °C; ^{1}H NMR 5.42 (s, 1H), 6.72 (dm, J = 8.9, 2H), 7.32 (dm, J = 8.9, 2H).

Methyl 3-bromo-4-hydroxybenzoate:[33] mp 105 °C (lit.[39] mp 106−107 °C); ^{1}H NMR 3.89 (s, 3H), 5.92 (s, 1H), 7.05 (d, J = 8.5, 1H), 7.92 (dd, J = 8.5, 2.0, 1H), 8.19 (d, J = 2.0, 1H); MS 232, 230 (M^+, 32, 33), 201, 199 (99, 100).

5-Bromo-2-hydroxybenzoic acid: mp 167 °C (lit.[34] mp 166 °C); ^{1}H NMR 6.92 (d, J = 8.9, 1H), 7.60 (dd, J = 8.9, 2.5, 1H), 8.03 (d, J = 2.5, 1H), 10.39 (s, br, 1H).

2-Bromo-4-nitrophenol: mp 114−115 °C (lit.[4] mp 112−114 °C); ^{1}H NMR 6.20 (s, br, 1H), 7.13 (d, J = 9.0, 1H), 8.16 (dd, J = 9.0, 2.6, 1H), 8.44 (d, J = 2.6, 1H); MS 219, 217 (M^+, 98, 100), 189, 187 (49, 51).

Methyl 3-bromo-4-methoxybenzoate: mp 97−98 °C (lit.[35] mp 99−100 °C); ^{1}H NMR 3.90 (s, 3H), 3.96 (s, 3H), 6.92 (d, J = 8.7, 1H), 7.99 (dd, J = 8.7, 2.1, 1H), 8.23 (d, J = 2.1, 1H); MS 246, 244 (M^+, 73, 72), 215, 213 (97, 100).

4-Bromo-1-methoxy-2-nitrobenzene: mp 84−85 °C (lit.[36] mp 85−85.5 °C); ^{1}H NMR 3.96 (s, 3H), 6.99 (d, J = 8.9, 1H), 7.64 (dd, J = 8.9, 2.5, 1H), 7.98 (d, J = 2.5, 1H); MS 233, 231 (M^+, 100, 97), 203, 201 (29, 30), 186, 184 (92, 87), 172, 170 (58, 59), 157, 155 (46, 43).

4-Bromo-2-methylphenol: mp 63−64 °C (lit.[37a] mp 62−64 °C); ^{1}H NMR 2.22 (s, 3H), 4.67 (s, 1H), 6.64 (d, J = 8.5, 1H), 7.17 (dd, J = 8.5, 2.4, 1H), 7.24 (d, J = 2.4, 1H); MS 188, 186 (M^+, 99, 100), 107 (60), 77 (30).

4-Bromo-2-methoxyphenol:[38] ^{1}H NMR 3.89 (s, 3H), 5.55 (s, 1H); 6.79 (d, J = 8.0, 1H), 6.96 (d, J = 2.1, 1H), 6.98 (dd, J = 8.0, 2.1, 2H); Diff-NOE irradiation at 3.89 results in 11% pos NOE at 6.96. MS 204, 202 (M^+, 100, 98), 189, 187 (74, 72), 161, 159 (42, 41).

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(27) The bromination of 4-hydroxybenzonitrile with NBS/CF_3SO_3H was performed at a 200 g scale (entry 1a).

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