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Regioselective Monobromination of Free and Protected Phenols

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A comparative study of the advantages of using THF compared with DMF in regioselective monobromination reactions of highly activated polyphenols, their ethers, and their *tert*-butyl carbonate derivatives under mild conditions is described. Bromination with the common reagent *N*-bromosuccinimide in polar solvents provided an easy and fast approach to aromatic electrophilic substitution at the most electronically favored positions with respect to *O*-substituents. Tight control of the reaction temperature as well as short reaction times afforded better isolated yields (from 70% to quantitative) of bromides when THF was used as the solvent instead of the classically used DMF.

Introduction

Chemical functionalization of substituted benzenes provides compounds capable of modulating the physico-chemical and/or biological activities of natural products. Saframycins,[1] renieramycins,[2] ningalins,[3] ecteinascidins,[2c,2d,4] and lamellarins are an important group of marine natural products[5] possessing as a common structural motif polyhydroxy- and polymethoxybenzenes. These privileged structures are characterized by their cytotoxic activity and potential utility for cancer chemotherapy. Many total syntheses are based on Pd^0-catalyzed cross-coupling reactions leading to C–C bond formation.[6] Sequential regioselective bromination and Suzuki cross-coupling reactions have been used in the total synthesis of lamellarin D and in the preparation of a library of lamellarin analogues.[7]

Bromo- and iodobenzenes have been extensively used in cross-coupling reactions as reagents or precursors of the organometallic required for each reaction. Thus, efficient methodologies for the preparation of OH/OMe-substituted halobenzenes are required. Bromination of trihydroxybenzenes and their ether derivatives has been achieved using diverse combinations of reagents and conditions, the most common of which is bromine in halogenated solvents (e.g., CCl_4 and $CHCl_3$[8]) or in AcOH.[9] Bromination reactions have also been carried out with bromine with catalysts such as CF_3CO_2Ag,[10] tetrabutylammonium bromide with V_2O_5/H_2O_2, supported reagent systems such as $NaClO_2$, NaBr, and $Mn(acac)_3$ with Montmorillonite K10 or moistened silica gel.[11] The harsh reaction conditions associated with most bromination methods, namely the use of bromine and the consequent formation of polyhalogenated byproducts, has led to the development of reagents such as pyridinium bromide perbromide[12] which can be used preformed or can be generated in situ by the addition of pyridine to bromine.[13] *N*-Bromosuccinimide (NBS) has previously been used for the bromination of the aforementioned class of trihydroxy and trialkoxy substrates, whether in CCl_4 or with the heterogeneous system CCl_4/SiO_2 as Lewis acid to promote nuclear bromination.[14] Aromatic electrophilic substitution of activated systems with NBS is generally favored in polar solvents such as DMF and CH_3CN.[15] Ionic liquids[16] such as 1-butyl-3-methylimidazolium hexafluorophosphate have recently been reported as the solvents of choice for these kinds of substrates. We report herein a new and mild procedure for the regioselective monobromination of benzenetriol, its methyl and isopropyl ethers, and its *tert*-butyl carbonate.

Results and Discussion

The bromination reactions of trioxybenzenes using freshly crystallized NBS in either DMF or THF were evaluated. We chose these two highly polar solvents as it is known that polar solvents drive the bromination reaction through the stabilization of bromocyclohexadienone-type intermediates.[17] DMF[18] as well as MeCN[15] have been described previously as good solvents for nuclear bromination reactions of aromatic systems with NBS. However, the bromination of a polyphenol with NBS in THF has only been reported once,[19] and has only rarely been used for the bromination of monosubstituted methoxy- or benzyloxyanilines.[20]

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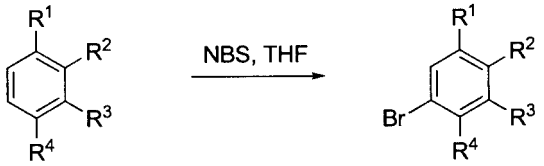
To the best of our knowledge, no comparative study on the role of solvent in polyphenols of benzenes has ever been carried out. The results of attempts to regioselectively brominate **1a**–**g** in THF and DMF are detailed in Table 1. Reaction progress was monitored by HPLC. Good-to-excellent yields of regioselectively monobrominated compounds were obtained. DMF and THF performed similarly in the bromination of the alkoxy-protected phenols, but THF gave higher yields with phenols (entries 1–4). Low-temperature reactions in THF probably allow more selectivity by avoiding polybromination and decomposition processes. Bromination of **1b** in DMF at room temperature (entry 3) gave a mixture of the starting material [retention time (t_r) = 3.6 min], **2b** (t_r = 6.2 min), a regioisomer (t_r = 6.6 min), and a dibromo derivative (t_r = 9.7 min). However, when this reaction was performed at –60 °C, the freezing point of DMF, **2b** was obtained in a yield of 28%. Although these reaction conditions were suitable for the monobromination of phenols with OH/OMe groups in positions 2 and 3 (entries 1–3), yields decreased dramatically with 1,2,4-trisubstituted phenols and methoxyphenols in both solvents. Bromination of 1,2,4-trihydroxybenzene (**1c**) in THF at –78 °C gave **2c** in 17% yield. The same reaction in DMF led to decomposition of the starting material (entry 4). In both cases (THF, DMF, entry 4) decomposition was observed during the purification process as a dark material adhered to the alumina pad. In contrast, excellent reaction yields were obtained for protected 1,2,4-trihydroxybenzenes. Bromination of **1d** in THF and in DMF afforded **2d** in 96 and 89% yields, respectively.

The regioselectivity of the process was directed through a combination of electronic and steric effects enhanced by temperature control. Thus, bromination of **1a** and **1b** occurred only at positions 4 and 6 (*ortho* with respect to R^4, double favored effect), respectively, with no reaction observed at the less hindered position 5 (*meta* with respect to R^4, only one favored effect). The regioselectivity was evaluated through a NOESY (nuclear Overhauser effect spectroscopy) experiment. Formation of 6-bromo-2,3-dimethoxyphenol (**2b**) instead of the 4-bromo derivative was demonstrated by the positive NOE between C3–OMe (singlet at δ = 3.83 ppm) and the proton at position 4 (doublet at δ = 6.40 ppm) of the benzene ring (see the Supporting Information). The *para* disposition of the aromatic protons of compounds **2d**–**g** was demonstrated by the presence of two singlets in their respective ^{1}H NMR spectra. Bromination of **1d**–**g** (entries 5–9) occurred only at position 5 (*ortho* with respect to R^4, double favored effect), with no reaction at position 3 (bis *ortho*). These results clearly indicate that electronic effects are more important than steric effects in determining the orientation of electrophilic substitution. For instance, bromination of **1f** occurred at position 5, *ortho* to the isopropyloxy group, which is more hindered than the methoxy group, but not at position 3, where steric hindrance was too great.

The reaction times of these reactions are related to the nature of the oxygenated substituents. Phenols (entries 1–4) required longer reaction times than methoxy or isopropyl ethers (entries 5–7). Boc-protected phenol **1g** required a higher temperature and longer reaction time (entry 9). Attempts to brominate **1g** at –78 °C were unsuccessful (entry 8), however, high yields and regioselectivity were obtained for this reaction in DMF and THF at 0 °C.

The preparation of **2g** is an example of a bromination of a diprotected 1,3-dihydroxy-4-methoxybenzene in which the two protecting groups can be selectively removed under controlled acidic conditions.[21]

Table 1. Bromination of phenols and phenoxy ethers.



1 **2**

Entry	Comp.	R^1	R^2	R^3	R^4	THF			DMF		
						t /min	*T* /°C	% yield[a]	*t* /min	*T* /°C	% yield[a]
1	**a**	H	OH	OH	OH	60	–78	92	45	0	39
2	**b**	H	OMe	OMe	OH	70	–78	70	45	–60	28
3	**b**	H	OMe	OMe	OH	45	25	67	45	25	36[b]
4	**c**	OH	OH	H	OH	60	–78	17	45	0	dec.[c]
5	**d**	O*i*Pr	O*i*Pr	H	O*i*Pr	15	–78	96	15	0	89
6	**e**	OMe	O*i*Pr	H	OMe	15	–78	95	15	0	95
7	**f**	OMe	O*i*Pr	H	O*i*Pr	10	–78	quant.[d]	15	0	96
8	**g**	OMe	OBoc	H	O*i*Pr	60	–78	n.r.[e]	–	–	–
9	**g**	OMe	OBoc	H	O*i*Pr	45	0	quant.[d]	45	0	quant.[d]

[a] Yields of isolated products unless specified. [b] Percentage of **2b** in the reaction crude, as measured by HPLC, which also contained 38% of a regioisomer and 5% of a dibromo-2,3-dimethoxyphenol. [c] A complex mixture of decomposition products was obtained. [d] quant. = quantitative yield. [e] n.r. = no reaction, the starting material **1g** was recovered.

In conclusion, an effective procedure for the regioselective monobromination of activated phenols, their ethers, and Boc derivatives has been developed. THF was found to be a better solvent than DMF for free phenol substrates, however, similar yields were obtained for both solvents in the reactions of methoxy and protected phenols.

Experimental Section

Reactants and solvents were purified according to literature procedures.[22] HPLC/MS spectra were recorded with a Waters Alliance LC/MS System consisting of a Waters ZQ mass detector, a photodiode array detector, and an Alliance HPLC system equipped with an XTerra C_{18} column (150×4.6 mm, 5 μm). ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury 400 MHz and a Gemini 200 MHz spectrometer. The multiplicity of the carbon atoms was assigned through DEPT and gHSQC experiments and typical abbreviations for off-resonance decoupling are used: (s) singlet, (d) doublet, and (q) quartet. The same abbreviations were used for the multiplicity of signals in the ^{1}H NMR spectra, as well as (h) heptet and (br. s) broad singlet. Spectra were referenced to appropriate residual solvent peaks ([D$_6$]DMSO or $CDCl_3$). IR spectra were obtained on a Thermo Nicolet FT-IR spectrometer. HRMS: were recorded with a Bruker Autoflex high-resolution mass spectrometer.

General Procedure for the Bromination Process: Solid NBS (1 mmol) was added to a cooled solution of the aromatic compound (1 mmol) in THF or DMF (5 mL) and the reaction mixture was stirred at the indicated temperature until complete consumption of the starting material. The mixture was allowed to reach room temperature and the solvent evaporated under reduced pressure. The resulting residue was taken up in EtOAc, filtered through a pad of neutral alumina, and dried. Pure products were characterized as detailed below.

4-Bromo-1,2,3-trihydroxybenzene (2a):[7a] Starting from 1,2,3-trihydroxybenzene (3.86 g, 30.3 mmol), **2a** (5.69 g, 27.8 mmol, 92%) was obtained as a yellowish solid using THF as solvent. IR (film): $\tilde{\nu}$ = 3116, 2962, 1401, 1261, 1094, 1021, 800 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.26 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H), 6.72 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H), 6.83 (s, 1 H, OH), 7.09 (s, 1 H, OH), 7.34 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 99.5 (s), 108.0 (d), 121.4 (d), 134.4 (s), 143.4 (s), 145.5 (s) ppm. MS (ESI-TOF): *m*/*z* (%) = 203 (100) [MBr^{79}], 205 (97) [MBr^{81}]. HRMS: calcd. for $C_6H_4O_3Br$: 202.9349; found 202.9346.

6-Bromo-2,3-dimethoxyphenol (2b):[23] Starting from 2,3-dimethoxyphenol (3.36 g, 21.8 mmol), **2b** (3.57 g, 15.3 mmol, 70%) was obtained as a yellowish oil using THF as solvent. IR (film): $\tilde{\nu}$ = 3440, 2941, 1466, 1429, 1204, 1168, 1089 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 6.13 (s, 1 H, OH), 6.40 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 7.13 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0 (q, OMe), 61.1 (q, OMe), 100.2 (s), 105.1 (d), 126.7 (d), 136.3 (s), 146.7 (s), 151.9 (s) ppm. MS (ESI-TOF): *m*/*z* (%) = 255 (100) [MBr^{79}Na], 257 (98) [MBr^{81}]. HRMS: calcd. for $C_8H_9O_3NaBr$ 254.9627; found 254.9620.

1-Bromo-2,4,5-trihydroxybenzene (2c): Starting from 1,2,4-trihydroxybenzene (300 mg, 2.4 mmol), **2c** (83 mg, 0.4 mmol, 17%) was obtained as a yellowish oil using THF as solvent. IR (film): $\tilde{\nu}$ = 3334, 1457, 1289, 1133, 837 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.03 (br. s, OH), 5.36 (br. s, OH), 5.48 (br. s, OH), 6.97 (s, 1 H), 7.16 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 98.3 (d), 104.8 (d), 115.3 (s), 141.8 (s), 144.4 (s), 149.4 (s) ppm. MS (ESI-TOF): *m*/*z* (%) = 203 (100) [MBr^{79}], 205 (97) [MBr^{81}].

1-Bromo-2,4,5-tris(isopropyloxy)benzene (2d): Starting from 1,2,4-tris(isopropyloxy)benzene (4.01 g, 15.9 mmol), **2d** (5.05 g, 15.3 mmol, 96%) was obtained as a yellowish oil using THF as solvent. IR (film): $\tilde{\nu}$ = 2976, 2932, 1489, 1384, 1200, 1109 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.30 (d, *J* = 6.4 Hz, 6 H, Me), 1.31 (d, *J* = 6.0 Hz, 6 H, Me), 1.34 (d, *J* = 6.0 Hz, 6 H, Me), 4.34 (h, *J* = 6.4 Hz, 1 H), 4.39 (h, *J* = 6.0 Hz, 1 H), 4.44 (h, *J* = 6.0 Hz, 1 H), 6.60 (s, 1 H), 7.02 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 (q), 22.2 (q), 72.6 (d), 73.3 (d), 73.4 (d), 105.2 (s), 109.1 (d), 123.2 (d), 144.3 (s), 149.0 (s), 149.4 (s) ppm. MS (ESI-TOF): *m*/*z* (%) = 353 (98) [MBr^{79}], 354 (23) [MBr^{79} + 1], 355 (100) [MBr^{81}], 356 (21) [MBr^{81} + 1]. HRMS: calcd. for $C_{15}H_{23}O_3NaBr$: 353.0728; found 353.0723.

1-Bromo-2,5-dimethoxy-4-isopropyloxybenzene (2e):[14e,24] Starting from 1,4-dimethoxy-2-isopropyloxybenzene (1.22 g, 6.21 mmol), **2e** (1.63 g, 5.92 mmol, 95%) was obtained as a yellowish oil using THF as solvent. IR (film): $\tilde{\nu}$ = 2975, 2934, 1501, 1382, 1201 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (d, $^3J_{H,H}$ = 6.0 Hz, 6 H, Me), 3.78 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 4.48 (h, $^3J_{H,H}$ = 6.0 Hz, 1 H), 6.57 (s, 1 H), 7.03 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (q, Me), 56.7 (q, OMe), 57.1 (q, OMe), 72.4 (d), 102.1 (s), 103.7 (d), 117.3 (d), 145.5 (s), 147.2 (s), 150.2 (s) ppm. MS (ESI-TOF): *m*/*z* (%) = 274 (95) [MBr^{79}], 275 (19) [MBr^{79} + 1], 276 (79) [MBr^{81}], 305 (5) [MBr^{81} + 1]. HRMS: calcd. for $C_{11}H_{16}O_3Br$: 274.0205; found 274.0277.

1-Bromo-2,4-bis(isopropyloxy)-5-methoxybenzene (2f): Starting from 1,3-bis(isopropyloxy)-4-methoxybenzene (1.56 g, 6.96 mmol), **2f** (2.11 g, 6.95 mmol, quant) was obtained as a yellowish oil using THF as solvent. IR (film): $\tilde{\nu}$ = 2977, 2934, 1496, 1386, 1211, 825 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, $^3J_{H,H}$ = 6.4 Hz, 6 H, Me), 1.35 (d, $^3J_{H,H}$ = 6.0 Hz, 6 H, Me), 3.80 (s, 3 H, OMe), 4.44 (h, $^3J_{H,H}$ = 6.0 Hz, 1 H), 4.46 (h, $^3J_{H,H}$ = 6.4 Hz, 1 H), 6.60 (s, 1 H), 7.02 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (q), 22.4 (q), 56.8 (q), 72.4 (d), 74.2 (d), 105.4 (s), 108.7 (d), 117.0 (d), 144.4 (s), 147.2 (s), 148.8 (s) ppm. MS (ESI-TOF): *m*/*z* (%) = 302 (92) [MBr^{79}], 303 (57) [MBr^{79} + 1], 304 (83) [MBr^{81}], 305 (47) [MBr^{81} + 1]. HRMS: calcd. for $C_{13}H_{20}O_3Br$: 303.0596; found 303.0590.

4-Bromo-5-isopropyloxy-2-methoxyphenyl *tert*-Butyl Carbonate (2g): Starting from 5-isopropyloxy-2-methoxyphenyl *tert*-butyl carbonate (0.312 g, 1.11 mmol), **2g** (0.400 g, 1.11 mmol, quant) was obtained as a yellowish oil using THF as solvent. IR (film): $\tilde{\nu}$ = 2978, 2935, 1764, 1502, 1139 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (d, $^3J_{H,H}$ = 6.0 Hz, 6 H, Me), 1.52 (s, 9 H, Me), 3.78 (s, 3 H, OMe), 4.37 (h, $^3J_{H,H}$ = 6.0 Hz, 1 H), 6.76 (s, 1 H), 7.12 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1 (q), 27.6 (q), 56.6 (q), 73.5 (d), 83.6 (s), 110.5 (s), 111.9 (d), 116.6 (s), 117.2 (d), 139.5 (s), 145.9 (s), 148.3 (s) ppm. MS (ESI-TOF): *m*/*z* (%) = 383 (100) [MBr^{79}], 384 (11) [MBr^{79} + 1], 385 (97) [MBr^{81}], 386 (9) [MBr^{81} + 1]. HRMS: calcd. for $C_8H_9O_3NaBr$: 383.0470; found 383.0465.

Supporting Information (see also the footnote on the first page of this article): NMR spectra of the products.

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