Electrophilic Bromination of *meta*-Substituted Anilines with *N*-Bromosuccinimide: Regioselectivity and Solvent Effect

Sandra Bartoli, Amalia Cipollone, Antonella Squarcia, Andrea Madami, Daniela Fattori*

Menarini Ricerche S.p.A., via Tito Speri 10, 00040 Pomezia (Rm), Italy
Fax +39(06)91184462; E-mail: dfattori@menarini-ricerche.it

Received 5 November 2008

Abstract: *N*-Bromosuccinimide-mediated electrophilic aromatic bromination of a series of anilines substituted with an electron-withdrawing group in the *meta* position was investigated. The regioselectivity of the reaction is markedly dependent on the polarity of the solvent and the bromination reaction can be tuned by appropriate selection of the reaction medium.

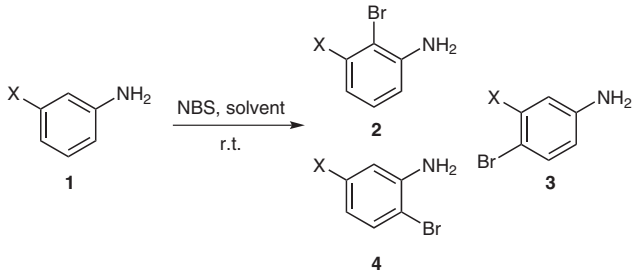
Key words: bromine, electrophilic aromatic substitution, regioselectivity, solvent effects

Brominated aromatic compounds are of considerable interest, both for their intrinsic properties (numerous biologically active molecules contain a brominated aromatic unit) and for their use as reactive intermediates in the synthesis of important drugs, because of their ability to undergo carbon–carbon and carbon–heteroatom bond-formation reactions.

Electrophilic aromatic bromination was probably one of the earliest reaction to be discovered and studied by organic chemists.[1] Its mechanism is generally regarded as starting from a π-complex B,[2] a pre-reactive intermediate that evolves into a σ-complex C (the Wheland intermediate), the formation of which represents the rate-determining step of the process in most cases (Scheme 1).[3]

N-Bromosuccinimide is a well-known reagent for electrophilic aromatic bromination. In 1979, Mitchell *et al.*[4] reported that *N*-bromosuccinimide in *N*,*N*-dimethylformamide is a mild and selective reagent for nuclear monobromination of reactive aromatic compounds. Since then, several regioselective methods have been developed that use *N*-bromosuccinimide alone[5] or in combination with a variety of additives, both for deactivated[6] and activated[7] *ortho*- and *para*-disubstituted substrates. Surprisingly neither the regioselectivity nor the solvent effect in the bromination of *meta*-substituted aromatics with *N*-bromosuccinimide has been extensively investigated.

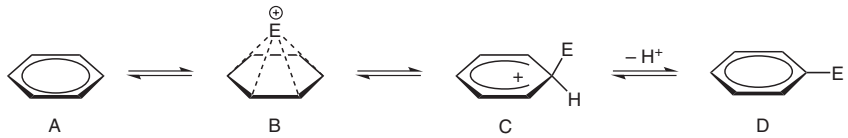
meta-Substituted anilines **1a**–**h** (Scheme 2), all of which contain an electron-withdrawing group, seemed to be appropriate starting points for our study, the aim of which was to explain some unexpected results obtained in our laboratories during routine synthetic work on analogous substrates. Bromination of **1a**–**h** by *N*-bromosuccinimide was studied in a panel of seven solvents.



Scheme 2 X = (**a**) NO_2; (**b**) CF_3; (**c**) CN; (**d**) CO_2Me; (**e**) COMe; (**f**) F; (**g**) Cl; (**h**) Br

The polarity of the solvents examined ranged from low in the case of dioxane [dielectric constant (ε) = 2.2] to high in the case of dimethyl sulfoxide (DMSO; ε = 47.2). The results obtained (Table 1) confirm that the regioselectivity of the reaction is markedly dependent on the solvent.

Plots of the molar fraction of isomers **3a**, **3d**, **3e**, and **3f** against ε (Figure 1a; curves for **3c**, **3d**, **3g**, and **3h** are not reported for the sake of clarity) show an almost linear correlation until ε reaches a value of around 20, where the curves reach a plateau. A similar trend is observed with solvent mixtures of tetrahydrofuran (ε = 7.5) with increasing fractions of water (ε = 80) (Figure 1b; curve for **3b**). Regardless of the nature of X, bromination seems to be very selective in polar media (DMF, DMSO), where **3** is formed almost exclusively.



Scheme 1 The accepted mechanism for aromatic electrophilic substitution

SYNTHESIS 2009, No. 8, pp 1305–1308
Advanced online publication: 16.03.2009
DOI: 10.1055/s-0028-1088016; Art ID: P12608SS

Table 1 Product Isomer Distributions in Selected Solvents[a]

Solvent (ε)	2a	3a	4a	2b	3b	4b	2c	3c	4c	2d	3d	4d	2e	3e	4e	2f	3f	4f	2g	3g	4g	2h	3h	4h
dioxane (2.2)	48	16	36	36	32	32	44	40	16	35	48	17	41	50	9	–	70	30	16	38	46	9	50	41
$CHCl_3$ (4.8)	46	21	33	33	37	30	35	50	15	27	55	18	37	56	7	–	75	25	12	44	44	10	52	38
DCE (10.4)	34	45	21	30	50	20	30	60	10	27	64	9	28	66	6	–	89	11	9	54	37	5	74	21
acetone (20.7)	10	85	5	15	70	15	15	78	7	8	85	–	10	86	–	–	>95	–	–	85	12	–	95	5
EtCN (27.7)	–	94	–	12	80	8	13	80	7	10	85	–	8	88	–	–	>95	–	–	90	9	–	95	–
DMF (38.0)	–	>95	–	9	88	–	11	85	–	12	85	–	6	90	–	–	>95	–	–	90	8	–	>95	–
DMSO (47.2)	–	>95	–	9	87	–	12	85	–	12	85	–	7	90	–	–	>95	–	–	90	8	–	>95	–

[a] 0–5% of an isomer is indicated by –.

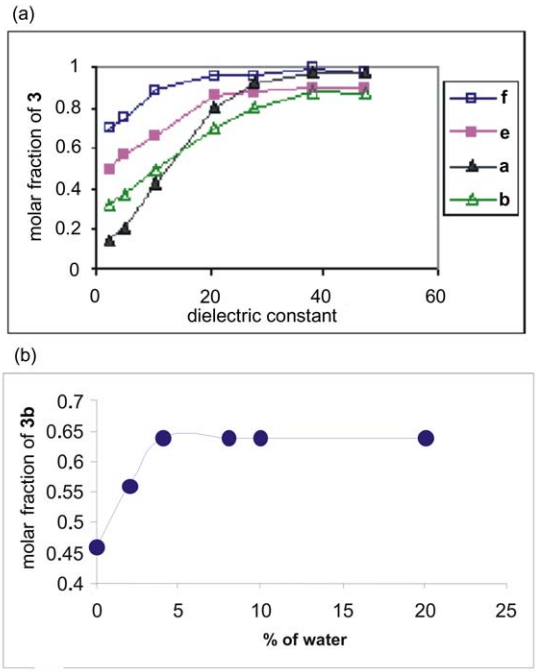


Figure 1 (a) Molar fractions of **3a**, **3b**, **3e**, and **3f** products plotted against the ε of the solvent; (b) molar fraction of **3b** obtained with various percentages of water in tetrahydrofuran.

Our experimental findings appear to confirm the so-called *ortho* effect[8] that occurs in the nitration of substrates containing both an electron-withdrawing substituent (such as NO_2, COR, or CO_2R) and an electron-donating substituent oriented *meta* to each other; this effect is sensitive to increasing quantities of water and it is enhanced by the polarity of the reaction medium.[8]

Hammond suggested that the deactivation of the position *para* to X in polar solvents could be due to a more effective 'interaction' (electron withdrawal) of the X group with the *para* position of the ring, which translates into a low electron density at the *para* carbon and in destabilization of the corresponding Wheland intermediate.[8] This is particularly true for deactivating substituents that have a relevant conjugation on the ring and are defined as *meta*-orientating. For the same reason, in polar solvents, the electron-donating NH_2 group activates the *para*-position more effectively, favoring the formation of isomers **3**.

The reactions of the corresponding *ortho*-disubstituted substrates showed no solvent dependence and resulted in exclusive formation of the isomer *para* to the amine and *meta* to X.

In the case of apolar solvents, the (**2** + **3**)/**4** ratio decreases: the reaction gives, in general, a mixture of isomers and, in some cases (dioxane or $CHCl_3$ as solvents and X = NO_2, CF_3, CN), the products **2** and **4**, in which the bromo substituent is *ortho* to the NH_2 group, predominate over **3**.

It is noteworthy that in some cases **2** predominates over **4**, as the former is the most sterically hindered of the three possible isomers. It is very likely this is a result of complex electronic effects that require further studies to be fully understood.

In conclusion, we found a solvent effect on the bromination of *meta*-substituted anilines by *N*-bromosuccinimide, which could be extended to a variety of other disubstituted aromatic substrates and to various electrophiles. This could be very useful for synthesis purposes, and a deeper understanding of this phenomenon could allow tuning of this important reaction without the aid of a catalyst.

Chemicals were purchased from commercial suppliers and used without further purification. Analytical HPLC was performed with a Merck–Hitachi L-6200A pump coupled to a Jasco 875 UV-multiwavelength detector: Waters SunFire column C_{18}, 5 μm, 150 × 4.6 mm. Eluents: A: H_2O + 0.1% TFA, B: CH_3CN + 0.1% TFA. Gradient: 20 to 80% solvent B in 20 min, flow rate 1.0 mL/min, λ = 220 nm. NMR spectra were recorded on a Bruker Avance spectrometer. Mass spectra were measured on a WATERS Alliance 2795 HPLC system fitted with a UV-PDA 996 diode array detector, a ZMD mass spectrometer, and a GL Science Inertsil ODS-3 column (50 × 3 mm; 3 μm) with ESI+ ionization (cone voltages: 20 V and 50 V, source temperature: 120 °C).

Bromination of 1a–h; General Procedure

To a solution of **1** (0.8 mmol) in the selected solvent (1 mL), a solution of NBS (0.8 mmol) in the same solvent (1 mL) was added batchwise at room temperature, and the reaction was monitored by HPLC and ^{1}H NMR. Mixtures of **2**, **3**, and **4** were obtained, with traces of dibrominated products. Yields were quantitative.

The compounds were isolated and purified either by flash chromatography or preparative HPLC, and characterized by ^{1}H NMR spectroscopy, MS, and, when not already reported or commercially available, by ^{13}C NMR spectroscopy (three cases only). Because of the different adsorption coefficients of isomers **2**, **3**, and **4**, the relative percentages obtained directly by HPLC are not correct. Correction factors for each isomer were obtained by comparing results from HPLC of the $CHCl_3$ reaction mixture to the corresponding ^{1}H NMR spectra. The resulting correction factors multiplied by the HPLC area gave the correct percentages for each reaction mixture.

2-Bromo-3-nitroaniline (2a)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 8.0 Hz, 1 H), 7.11 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.93 (dd, *J* = 8.0, 1.0 Hz, 1 H), 4.48 (br s, 2 H).

MS (ES): *m/z* = 217 $[M + H]^+$, 219 $[M + H]^+$.

4-Bromo-3-nitroaniline (3a)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.0 Hz, 1 H), 7.15 (d, *J* = 2 Hz, 1 H), 6.72 (dd, *J* = 8.0, 2.0 Hz, 1 H), 3.98 (br s, 2 H).

MS (ES): *m/z* = 217 $[M + H]^+$, 219 $[M + H]^+$.

2-Bromo-5-nitroaniline (4a)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.50 (m, 2 H), 7.18 (dd, *J* = 8.0, 2.0 Hz, 1 H), 5.95 (br s, 2 H).

MS (ES): *m/z* = 217 $[M + H]^+$, 219 $[M + H]^+$.

2-Bromo-3-(trifluoromethyl)aniline (2b)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 8.0 Hz, 1 H), 7.10 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.93 (dd, *J* = 8.0, 2 Hz, 1 H), 4.40 (br s, 2 H).

MS (ES): *m/z* = 240 $[M + H]^+$, 242 $[M + H]^+$.

4-Bromo-3-(trifluoromethyl)aniline (3b)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 9.0 Hz, 1 H), 6.99 (d, *J* = 3.0 Hz, 1 H), 6.68 (dd, *J* = 9.0, 3.0 Hz, 1 H), 3.85 (br s, 2 H).

MS (ES): *m/z* = 240 $[M + H]^+$, 242 $[M + H]^+$.

2-Bromo-5-(trifluoromethyl)aniline (4b)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 2.0 Hz, 1 H), 6.86 (dd, *J* = 8.0, 2.0 Hz, 1 H), 4.33 (br s, 2 H).

MS (ES): *m/z* = 240 $[M + H]^+$, 242 $[M + H]^+$.

3-Amino-2-bromobenzonitrile (2c)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 8.0 Hz, 1 H), 7.07 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.97 (dd, *J* = 8.0, 1.5 Hz, 1 H), 4.35 (br s, 2 H).

MS (ES): *m/z* = 197 $[M + H]^+$, 199 $[M + H]^+$.

5-Amino-2-bromobenzonitrile (3c)
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 1.5 Hz, 1 H), 6.76 (dd, *J* = 8.0, 1.5 Hz, 1 H), 3.97 (br s, 2 H).

MS (ES): *m/z* = 197 $[M + H]^+$, 199 $[M + H]^+$.

3-Amino-4-bromobenzonitrile (4c)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.0 Hz, 1 H), 6.99 (s, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 4.35 (br s, 2 H).

MS (ES): *m/z* = 197 $[M + H]^+$, 199 $[M + H]^+$.

Methyl 3-Amino-2-bromobenzoate (2d)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (t, *J* = 7.5 Hz, 1 H), 7.09 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.87 (dd, *J* = 7.5, 1.5 Hz, 1 H), 4.22 (br s, 2 H), 3.90 (s, 3 H).

MS (ES): *m/z* = 230 $[M + H]^+$, 232 $[M + H]^+$.

Methyl 5-Amino-2-bromobenzoate (3d)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 9.0 Hz, 1 H), 7.10 (d, *J* = 3.0 Hz, 1 H), 6.65 (dd, *J* = 9.0, 3.0 Hz, 1 H), 3.91 (s, 3 H), 3.50 (br s, 2 H).

MS (ES): *m/z* = 230 $[M + H]^+$, 232 $[M + H]^+$.

Methyl 3-Amino-4-bromobenzoate (4d)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.5 Hz, 1 H), 7.44 (d, *J* = 2.0 Hz, 1 H), 7.28 (dd, *J* = 8.5, 2.0 Hz, 1 H), 4.23 (br s), 3.91 (s, 3 H).

MS (ES): *m/z* = 230 $[M + H]^+$, 232 $[M + H]^+$.

1-(3-Amino-2-bromophenyl)ethanone (2e)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (t, *J* = 8.0 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 4.10 (br s), 2.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.6, 145.3, 143.2, 128.5, 118.0, 117.6, 105.1, 30.8.

MS (ES): *m/z* = 214 $[M + H]^+$, 216 $[M + H]^+$.

1-(5-Amino-2-bromophenyl)ethanone (3e)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.0 Hz, 1 H), 6.73 (d, *J* = 1.5 Hz, 1 H), 6.61 (dd, *J* = 8.0, 1.5 Hz, 1 H), 3.78 (br s, 2 H), 2.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.8, 146.3, 142.5, 134.8, 118.8, 115.4, 106.6, 30.8.

MS (ES): *m/z* = 214 $[M + H]^+$, 216 $[M + H]^+$.

1-(3-Amino-4-bromophenyl)ethanone (4e)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 1.0 Hz, 1 H), 7.18 (dd, *J* = 8.0, 1.0 Hz, 1 H), 4.20 (br s), 2.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 144.7, 137.7, 133.2, 119.6, 115.0, 105.9, 27.1.

MS (ES): *m/z* = 214 $[M + H]^+$, 216 $[M + H]^+$.

4-Bromo-3-fluoroaniline (3f)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (t, *J* = 9.0 Hz, 1 H), 6.47 (dd, *J* = 10.0, 2.0 Hz, 1 H), 6.37 (dd, *J* = 9.0, 2.0 Hz, 1 H), 3.62 (br s, 2 H).

MS (ES): *m/z* = 190 $[M + H]^+$, 192 $[M + H]^+$

2-Bromo-5-fluoroaniline (4f)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 9.0, 6.0 Hz, 1 H), 6.48 (d, *J* = 10.0, 3.0 Hz, 1 H), 6.37 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.18 (br s, 2 H).

MS (ES): *m/z* = 190 $[M + H]^+$, 192 $[M + H]^+$

2-Bromo-3-chloroaniline (2g)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (t, *J* = 8.0 Hz, 1 H), 6.85 (d, *J* = 8.0, 1 H), 6.65 (dd, *J* = 8.0, 1 H), 3.93 (br s, 2 H).

MS (ES): *m/z* = 206 $[M + H]^+$, 208 $[M + H]^+$, 210 $[M + H]^+$.

4-Bromo-3-chloroaniline (3g)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 9.0 Hz, 1 H), 6.79 (d, *J* = 2.5 Hz, 1 H), 6.45 (dd, *J* = 9.0, 2.5 Hz, 1 H), 3.75 (br s, 2 H).

MS (ES): *m/z* = 206 $[M + H]^+$, 208 $[M + H]^+$, 210 $[M + H]^+$.

2-Bromo-5-chloroaniline (4g)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.5 Hz, 1 H), 6.76 (d, *J* = 2.0 Hz, 1 H), 6.60 (dd, *J* = 8.5, 2.0 Hz, 1 H), 4.15 (br s, 2 H).

MS (ES): *m/z* = 206 $[M + H]^+$, 208 $[M + H]^+$, 210 $[M + H]^+$.

2,3-Dibromoaniline (2h)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (dd, *J* = 7.5, 2.0 Hz, 1 H), 6.96 (t, *J* = 7.5 Hz, 1 H), 6.69 (dd, *J* = 7.5, 2.0 Hz, 1 H), 4.00 (br s, 2 H).

MS (ES): *m/z* = 254 $[M + H]^+$, 252 $[M + H]^+$, 250 $[M + H]^+$.

3,4-Dibromoaniline (3h)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.5 Hz, 1 H), 6.97 (d, *J* = 2.5 Hz, 1 H), 6.50 (dd, *J* = 8.5, 2.5 Hz, 1 H), 4.10 (br s, 2 H).

MS (ES): *m/z* = 254 $[M + H]^+$, 252 $[M + H]^+$, 250 $[M + H]^+$.

2,5-Dibromoaniline (4h)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.5 Hz, 1 H), 6.91 (d, *J* = 2.0 Hz, 1 H), 6.74 (dd, *J* = 8.5, 2.0 Hz, 1 H), 4.14 (br s, 2 H).

MS (ES): *m/z* = 254 $[M + H]^+$, 252 $[M + H]^+$, 250 $[M + H]^+$.

Acknowledgment

We wish to thank Dr. A. Ettorre for NMR studies, Dr. T. F. Gale for proofreading, and Dr. C. A. Maggi for support.

References

(1) Couper, A. S. *Ann. Chim. Phys.* **1858**, *53*, 469.
(2) (a) Lenoir, D. *Angew. Chem. Int. Ed.* **2003**, *42*, 854.
(b) Vasilyev, A. V.; Lindemann, S. V.; Kochi, J. K. *New J. Chem.* **2002**, *26*, 582.
(3) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry. Part A: Structure and Mechanism*; Plenum Press: New York, **1984**, 489–503.
(4) Mitchell, R. H.; Lai, Y.-H.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733.
(5) De Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. *Synthesis* **2006**, 221.
(6) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15700.
(7) Ganguly, N. C.; De, P.; Dutta, S. *Synthesis* **2005**, 1101.
(8) Hammond, G. S.; Hawthorne, M. F. In *Steric Effects in Organic Chemistry*; Wiley: New York, **1956**, 164–200.