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Regioselective and efficient bromination of anilides on water using HBr and Selectfluor

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ABSTRACT

A metal-, additive-, and Br_2-free highly regioselective bromination of anilides using HBr and Selectfluor is presented. This reaction proceeded under mild conditions with high efficiency and good functional group tolerance, and water served as the solvent. In general, with substrates bearing no *para*-substituent, *para*-mono-bromination occurred exclusively, while *ortho*-mono-brominated anilides were the only products when *para*-positions were blocked. The incorporation of a stronger orienting group might result in a reversed regioselectivity, and the reaction was sensitive to steric hindrance.

Aryl halides are among the most valuable feed stocks in organic synthesis, especially in transition-metal-catalyzed coupling reactions, owing to their versatile reactivities in a wide range of transformations [1]. In this regard, aryl bromides are of particular importance and represent profoundly more desirable targets, for they are usually more reactive than corresponding chlorides, and far less expensive than their iodide congeners.

Bromoanilides in recent years have proved to be valuable synthons in the syntheses of important heterocycles such as benzoxazoles [2], benzimidazoles [3], benzothiazoles [4], benzoxazinones [5], phenanthridines [6], indoles [7], carbazoles [8], [3,4]-fused oxindoles [9], and benzisoxazolo[2,3-*a*]pyridinium tetrafluoroborates [10]. However, there are some issues related to their preparation. Bromoanilides are usually synthesized via bromination reaction of corresponding anilides [11–16]. Elemental bromine, which is highly volatile and corrosive, is traditionally used as the brominating reagent [11]. On the other hand, bromination of anilides with alternative reagents suffers from poor selectivities [12], long reaction times [12f,13], high temperatures [12f,14], and/or poor yields [13a], and/or requires commercially hardly available brominating reagents [15], precious catalysts or additives [12e,f,16], or large amounts of toxic copper salts [14].

What is more, most of those works are only shallow attempts, in which only one or a few brominated anilides were reported. Systematic studies are needed. An elegant one was disclosed by Bedford et al., in which *ortho*-bromination was achieved yet a palladium catalyst was required, and the selectivity was poor when, say, *N*-(*m*-tolyl)acetamide was employed (Scheme 1a) [12e]. A little earlier, they had reported a *para*-selective bromination of anilides, yet an elevated temperature of 120 °C and 4 equiv of copper salts were required, and the substrate scope was not thoroughly investigated (Scheme 1b) [14].

A complementary access to these bromides is the reaction of bromoanilines with acid chlorides, acid anhydrides, or carboxylic acids [4,9]. This methodology is frequently used in laboratory as well, but it is know that bromoanilines are generally prepared by deprotection of the parent anilides.

As a consequence, there is still an urgent need to develop a practical, selective and environmentally benign approach for bromoanilides synthesis. Herein, we present an efficient and highly regioselective bromination reaction of anilides, with HBr as a bromine source and Selectfluor as an oxidant. The reaction proceeded in the non-flammable, non-toxic and the most abundant solvent of water, with a broad substrate scope and without any additive [16] or metal catalyst ensuring regioselectivity (Scheme 1c).

We began the present study by investigating the bromination reaction of 4-methylacetanilide **1a** (Table 1). Much to our satisfaction, exposure of **1a** to 1.1 equiv of KBr and 1.2 equiv of Selectfluor

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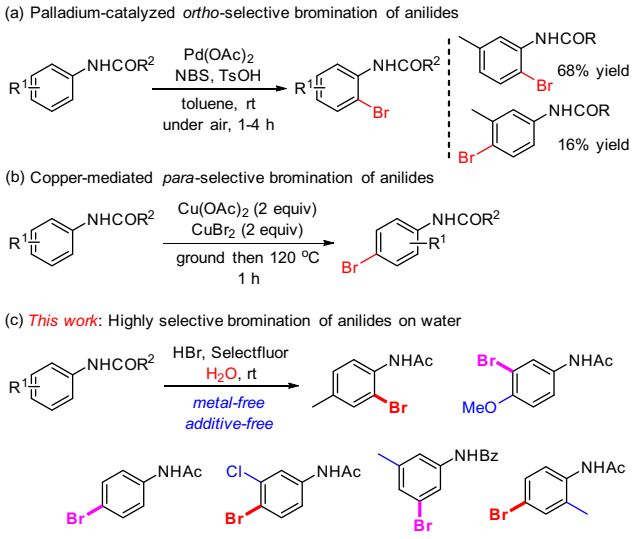
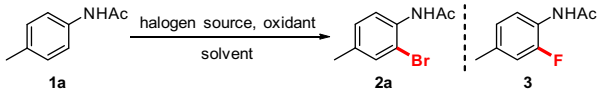
0040-4039/



Scheme 1. Selective bromination of anilides.

in an aqueous medium of dichloromethane (DCM)/H_2O furnished 2-bromo-4-methylacetanilide **2a** in an excellent yield within 1 h (entry 1). Selectfluor serving as the oxidant is crucial, as evidenced by the fact that while *N*-fluorobenzenesulfonimide (NFSI, entry 2), $K_2S_2O_8$ (entry 4), H_2O_2 (30% aqueous, entry 5), *tert*-butyl hydroperoxide (TBHP, 70% aqueous, entry 6), di-*tert*-butyl peroxide (DTBP, entry 7), $Cu(OAc)_2$ (entry 8), AgOAc (entry 9), and $FeCl_3$ (entry 10) all proved ineffective, the use of $PhI(OAc)_2$ as the oxidant afforded brominated product **2a** in only 44% yield even after 8 h (entry 3). Then, other bromine sources were tested. It was found that excellent yields were also achieved by using tetrabutyl ammonium bromide (TBAB, entry 11) or $CuBr_2$ (entry 12), yet longer reaction times were required. When HBr (40% aqueous) was employed, the bromination proceeded rapidly and was completed within 20 min, delivering brominated anilide **2a** in 95% yield (entry 13). With Selectfluor as the oxidant and HBr as the bromine source, DCM alone was not a good solvent for this process, for the bromination took over 5 h to complete in it (entry 14). To our great delight, when the reaction was run under "on water" conditions [17], it was greatly accelerated and was completed within 5 min, yielding bromoanilide **2a** in 95% yield (entry 15). An excellent yield of **2a** was also achieved by using KBr rather than HBr, albeit in a longer reaction time (note e, entry 15). Organic MeCN (entry 16) and *N*,*N*-dimethylformamide (DMF, entry 18), were both excellent solvents as well, whereas the use of tetrahydrofuran (THF, entry 17) or ethanol (entry 19) delivered bromoanilide **2a** in only moderate yields even after fairly prolonged reaction times. With toluene

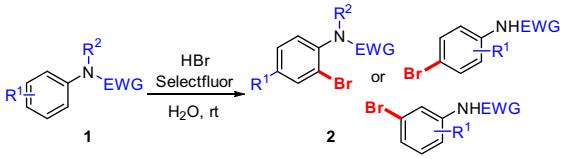
Table 1
Optimization of reaction conditions.[a]



Entry	Halogen source	Oxidant	Solvent	Time (min)	Yield (%)[b]
1	KBr	Selectfluor	DCM/H_2O[c]	60	94
2	KBr	NFSI	DCM/H_2O[c]	480	Trace (93)[d]
3	KBr	$PhI(OAc)_2$	DCM/H_2O[c]	480	44 (51)[d]
4	KBr	$K_2S_2O_8$	DCM/H_2O[c]	480	Nr
5	KBr	H_2O_2	DCM/H_2O[c]	480	Nr
6	KBr	TBHP	DCM/H_2O[c]	480	Nr
7	KBr	DTBP	DCM/H_2O[c]	480	Nr
8	KBr	$Cu(OAc)_2$	DCM/H_2O[c]	480	Nr
9	KBr	AgOAc	DCM/H_2O[c]	480	Nr
10	KBr	$FeCl_3$	DCM/H_2O[c]	480	Trace (91)[d]
11	TBAB	Selectfluor	DCM/H_2O[c]	70	93
12	$CuBr_2$	Selectfluor	DCM/H_2O[c]	100	92
13	HBr	Selectfluor	DCM/H_2O[c]	20	95
14	HBr	Selectfluor	DCM	300	90
15	HBr	Selectfluor	H_2O	5 (20)[e]	95 (93)[e] (95)[f]
16	HBr	Selectfluor	MeCN	10	93
17	HBr	Selectfluor	THF	480	53 (43)[d]
18	HBr	Selectfluor	DMF	5	94
19	HBr	Selectfluor	EtOH	480	41 (54)[d]
20	HBr	Selectfluor	Toluene	140	91
21	HCl or HI	Selectfluor	H_2O	480 (150)[g]	Nr (complex)[g]
22[g]	NaCl	Selectfluor	H_2O	1440	0[h] (83)[d]
23[g]	KI or KF	Selectfluor	H_2O	480	Nr
24[i]	HBr	Selectfluor	H_2O	10	94

[a] Reaction conditions: **1a** (0.5 mmol), halogen source (0.55 mmol), oxidant (0.6 mmol), solvent (3.0 mL), room temperature.
[b] Isolated yields.
[c] The ratio is 1:1 (v:v).
[d] Recovery of **1a**.
[e] KBr was used instead of HBr.
[f] TEMPO (2.0 equiv) was additionally added.
[g] The reaction was stirred at 100 °C.
[h] *Ortho*-fluorinated product **3** was isolated in 13% yield.
[i] The reaction was run using 20.1 mmol (3.0 g) of **1a**, 22.1 mmol of HBr, and 24.1 mmol of Selectfluor in 120.7 mL water at room temperature.

Table 2
Regioselective bromination of anilides on water.[a]



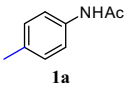
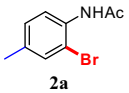
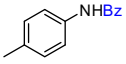
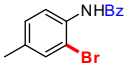
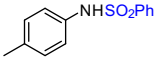
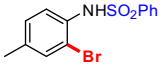
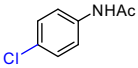
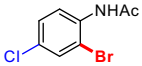
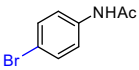
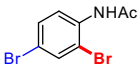
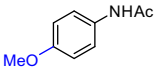
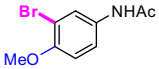
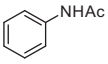
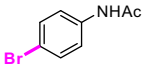
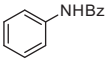
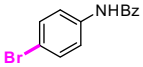
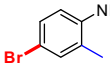
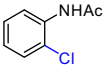
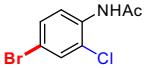
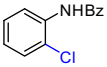
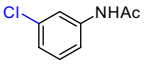
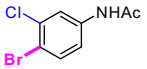
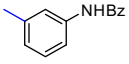
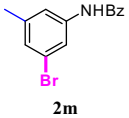
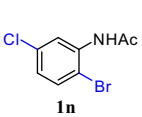
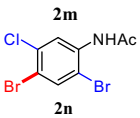
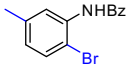
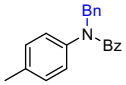
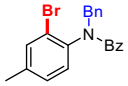
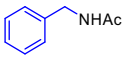
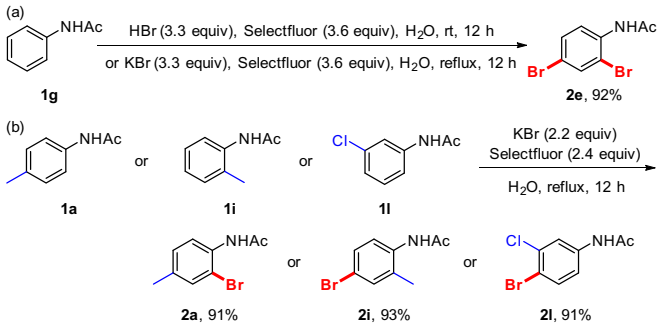
Entry	Anilides	Products	*t* (min)	Yield (%)[b]
1	 **1a**	 **2a**	5	95
2	 **1b**	 **2b**	240	90
3	 **1c**	 **2c**	80	93
4	 **1d**	 **2d**	210	95
5	 **1e**	 **2e**	150	96
6	 **1f**	 **2f**	15	91
7	 **1g**	 **2g**	30	95
8	 **1h**	 **2h**	150	91
9	 **1i**	 **2i**	15	94
10	 **1j**	 **2j**	60	90
11	 **1k**	 **2k**	1440	91
12	 **1l**	 **2l**	10	92
13	 **1m**	 **2m**	210	94
14	 **1n**	 **2n**	1440	90

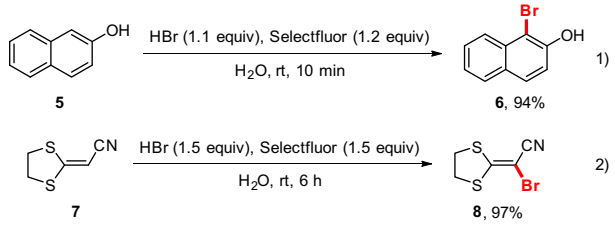
Table 2 (*continued*)

Entry	Anilides	Products	*t* (min)	Yield (%)[b]
15[c]	 **1o**		1440	Nr
16[c]	 **1p**	 **2o**	1440	56
17[c]	 **4**		1440	Nr

[a] Reaction conditions: **1** (0.5 mmol), HBr (0.55 mmol), Selectfluor (0.6 mmol), H_2O (3.0 mL), room temperature.
[b] Isolated yields.
[c] KBr was used instead of HBr, and the reaction was run at 100 °C.



Scheme 2. Attempts of multibromination of acetanilides.



Scheme 3. Bromination of naphthalen-2-ol and 2-(1,3-dithiolan-2-ylidene) acetonitrile.

as the solvent, the bromination took a much longer time to complete (entry 20). Water was chosen as the solvent for further studies for reasons of efficiency, cost, safety, and environmental concerns. Though there is no unifying theory that explains the rate acceleration observed under heterogeneous aqueous conditions to date, the increase in interfacial area, trans-phase hydrogen-bonding between the water surface and the transition states, and the cohesive energy density of the solvent might be key factors responsible for the on-water effect [17].

When the model reaction under optimized conditions was doped with 2 equiv of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), the results were unaffected (note f, entry 15), while when the reaction was heated under otherwise optimal conditions, reddish-brown vapors were observed in the condenser, suggesting that a radical pathway could be ruled out, and that there might be Br_2 generated in situ, which might be the actual brominating reagent. However, as Br_2 is known to be readily produced via oxidation of a bromide ion with a wide range of oxidants [18], and in this protocol Selectfluor was unique and essential (entries 1–10), Selectfluor might be more than an oxidant here.

Attempts to achieve chlorination, iodination and fluorination reactions of **1a** by using chlorine, iodine and fluorine sources met with no success. While no reaction occurred by using HCl (37% aqueous) or HI (47% aqueous, entry 21) at room temperature, or by using KI or KF (entry 23) in refluxing water, the use of HCl or HI at 100 °C resulted in complex mixture (note f, entry 21), probably due to the hydrolysis of amides. Interestingly, the use of NaCl as the "halogen source" at refluxing temperature gave *N*-(2-fluoro-4-methylphenyl)acetamide **3** in 13% yield after 24 h (entry 22). To document the practicality of our protocol, a multigram-scale experiment was carried out, and the yield of **2a** was not compromised (entry 24).

Under the optimized reaction conditions (entry 15, Table 1), the substrate scope was then explored (Table 2). It proved that substrates **1a-c** with different electron-withdrawing *N*-protecting groups, including acetyl (entry 1), benzoyl (entry 2), and phenylsulfonyl (entry 3), all worked well to furnish the *ortho*-brominated products **2a-c** in excellent yields [19]. Acetanilides **1d,e** bearing a chloro or bromo group at the *para*-position could also be brominated, providing expected 2-bromoacetanilides **2d,e** in excellent yields (entries 4 and 5). Surprisingly, the reaction of anilide **1f** having a methoxy group *para* to the amide group gave *meta*-selective product **2f** exclusively, as evidenced by the ^{1}H NMR spectroscopic analysis of the crude reaction mixture, in 91% yield within 15 min (entry 6). This reversed regioselectivity reflected the fact that the methoxy is a stronger orienting group than the amide. In all of the above cases, no di-brominated products were observed.

It is worthy of notice that generally when there was no *para*-substituent on the benzene ring, *para*-mono-bromination occurred exclusively. For example, 4-bromoanilides **2g,h** were efficiently synthesized in excellent yields from acetanilide **1g** and benzanilide **1h**, respectively (entries 7 and 8), and no regioisomeric *ortho*- or *meta*-brominated product, or di- or tri-brominated anilide was detected by ^{1}H NMR spectroscopic analyses of the crude reaction mixtures. Anilides **1i-l** with a methyl or chloro group at either the *ortho*- (entries 9–11) or *meta*-position (entry 12) were also competent substrates in this transformation, and 4-brominated products **2i-l** were afforded in 90–94% yields. The *para*-bromination still proceeded smoothly when *N*-(2-bromo-5-chlorophenyl) acetamide **1n** with two electron-withdrawing groups (EWGs) on the benzene ring was used, affording polyhalogenated anilide **2n** in 90% yield (entry 14). This reaction was rather sensitive to steric hindrance, since incredible *meta*-selectivity was observed by

employing *N*-(*m*-tolyl)benzamide **1m** having a bulkier *meta*-substituent, with 3-bromoanilide **2m** produced as the only product in 94% yield (entry 13), and since the use of *N*-(2-bromo-5-methylphenyl)benzamide **1o** proved fruitless after 24 h at refluxing temperature with KBr as the bromine source (entry 15). *N*-Benzyl-*N*-(*p*-tolyl)benzamide **1p** was also a challenging substrate, providing 4-bromoanilide **2o** as the only product in only a moderate yield even under those enhanced conditions (entry 16), whereas even in refluxing water no reaction occurred by using substrate **4** with a benzene ring unconjugated with the amide group (entry 17). In these cases, KBr was used instead of HBr to prevent the hydrolysis of amides. At this stage, the origin of these impressive selectivities remains unclear, yet it might be related to the structure and nature of Selectfluor, which avoided the assistance of a metal salt [12e,f] or an additive [16].

Di-brominated product **2e** could be afforded in 92% yield from acetanilide **1g** either by utilizing HBr as the bromine source at ambient temperature or by using KBr under reflux, whereas no tribromination occurred with 3.3 equiv of bromine source and 3.6 equiv of Selecfluor even after 12 h (Scheme 2a). On the other hand, only mono-bromo-anilides **2a,i,l** were produced when *para*-, *meta*-, or *ortho*-substituted substrates **1a,i,l** were exposed to 2.2 equiv of KBr and 2.4 equiv of Selecfluor in refluxing water for 12 h (Scheme 2b). These results suggest that when the *para*- and another positions of anilides were both substituted the bromination could not proceed, which might be attributed to the steric effect and represents one limitation of the current methodology.

This protocol could be extended to some other electron-rich compounds. For example, subjecting 2-naphthol **5** to our optimized reaction conditions afforded 1-bromonaphthalen-2-ol **6** in 94% yield within 10 min (Eq. (1), Scheme 3), while α-cyano ketene ethylene dithioacetal **7** reacted with 1.5 equiv of HBr and 1.5 equiv of Selectfluor to deliver brominated dithioacetal **8** in 97% yield after 6 h (Eq. (2), Scheme 3).

In conclusion, a metal- and additive-free highly regioselective bromination of anilides on water using HBr and Selectfluor has been developed, which provides an easy and practical access to bromoanilides under mild conditions with high efficiency and good functional group tolerance, and without the handling of hazardous liquid bromine. This reaction preferred to take place at the less-hindered *para*-position, unless it was blocked or a stronger orienting group was incorporated into the substrates, which led to *ortho*- or sometimes *meta*-bromination. This protocol has promising applications and it was extended to some other electron-rich compounds such as 2-naphthols and ketene dithioacetals.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.092.

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[19] *General procedure for the bromination of anilides (**1a** as an example):* To a stirred suspension of *N*-(*p*-tolyl)acetamide **1a** (75 mg, 0.5 mmol) and Selectfluor (213 mg, 0.6 mmol) in water (3.0 mL) was added HBr (40% aqueous, 0.08 mL, 0.55 mmol), and the mixture was stirred for 5 min at room temperature. After **1a** was consumed, as indicated by thin-layer chromatography (TLC), the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (2.0 mL) and water (20.0 mL), and extracted with CH_2Cl_2 (10.0 mL) three times. The residue obtained after evaporation of the solvent was purified by column chromatography on silica gel (petroleum ether–ethyl acetate = 6:1, v/v) to afford *N*-(2-bromo-4-methylphenyl)acetamide **2a** as a white solid (108 mg, 95% yield): mp 82-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.22 (s, 3H), 2.30 (s, 3H), 7.11 (dd, J = 1.2, 8.3 Hz, 1H), 7.35 (s, 1H), 7.51 (brs, 1H), 8.17 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.13, 135.28, 133.15, 132.44, 129.02, 121.86, 113.17, 24.82, 20.55; HRMS (ESI-TOF) Calcd for $C_9H_{11}BrNO^+$ ([M + H]$^+$) 228.0019. Found 228.0021.