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Electrochemical Regioselective Bromination of Electron-Rich Aromatic Rings Using $^{n}Bu_4NBr$

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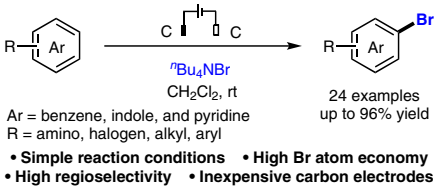

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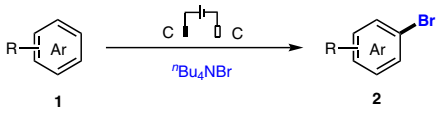
Abstract Electrochemical regioselective bromination of electron-rich aromatic rings using stoichiometric tetrabutylammonium bromide ($^{n}Bu_4NBr$) has been accomplished under mild conditions. This protocol provides an environmentally friendly and simple way for the construction of C–Br bond in moderate to high yields with wide functional group tolerance.

Key words electrochemistry, regioselective, bromination, aromatic ring, stoichiometric, tetrabutylammonium bromide

Aryl bromides are among the most common and important chemicals and are extensively present in various natural products and biologically active compounds.[1] Moreover, they are versatile starting materials and synthetic intermediates in organic synthesis, especially in transition-metal-catalyzed cross-coupling reactions.[2] Thus, efficient and mild methods to synthesize aryl bromides are of significant interest. Nowadays, considerable efforts have been devoted to the development of various effective brominating reagent systems,[1d,3] for example, Br_2, NBS, and bromide salts/oxidants. However, traditional methods generally suffer from certain drawbacks such as application of hazardous reagents, unavoidable overbromination, poor regioselectivity, production of metal salts as stoichiometric by-products, and the use of oxidants.[3] More recently, visible-light-mediated bromination of aromatic compounds using NBS with the help of erythrosine B has been reported.[4] While remarkable progress has been achieved, there is still an urgent need to develop a mild, operationally simple, cost-effective, site-selective, and environmentally benign approach for aryl bromides synthesis.

Organic electrosynthesis, which achieves redox reactions with traceless electric current, is accepted to be an environment-friendly and enabling synthetic tool.[5] In the past two decades, several important milestones in electrochemical C–H bond activation have been accomplished, such as halogenation,[6] azidation,[7] thiocyanation,[8] cross-coupling,[9] and annulation.[10] Electrochemical bromination of arenes has been studied in recent years.[11] For example, Thasan's group reported the two-phase (chloroform/water) electrochemical bromination of simple aromatic compounds using a large amount of NaBr;[12] Fuchigami's group disclosed a novel electrolytic system for anodic bromination using NaBr-PEG/MeCN system;[13] Liu and co-workers described the applications of electrochemical arene bromination on complex late-stage intermediates and drug molecules using a large excess NaBr in water and methanol/acetonitrile mixture.[14] In 2019, Lei's group reported the electrochemical oxidative halogenation of heteroarenes, arenes, alkenes, alkynes, and aliphatic hydrocarbons using NaX (X = Cl or Br) in DMF/H_2O under 80 °C and N_2 protection.[15] Mei's group disclosed the palladium-catalyzed electrochemical C–H bromination of benzamide derivatives using NH_4Br as the brominating reagent under divided cells.[16] It is noteworthy that these electrochemical bromination reactions were accomplished by using expensive platinum (Pt) electrode and a large excess NaBr or NH_4Br. In 2014, Baran's group discovered the byproduct bromoxiamycin (17% yields) during the synthesis of dixiamycin B by electrochemical oxidation of xiamycin A using Et_4NBr as electrolyte and carbon as electrode.[17] Inspired by the seminal work, we envisioned that aryl bromide **2** could be readily prepared from compound **1** via a one-pot direct electrochemical oxidative C–Br bond formation in an undivided cell with inexpensive carbon electrodes using equivalent $^{n}Bu_4NBr$ as electrolyte and Br source (Scheme 1). Herein, the details of these studies are presented.

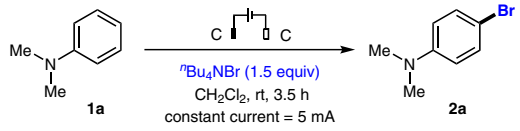


Scheme 1 Electrochemical bromination using ^{n}Bu$_4$NBr

We first identified the optimal reaction conditions for the electrochemical bromination of *N*,*N*-dimethylaniline (**1a**), which involved constant-current electrolysis using graphite rod as anode and cathode, in an undivided cell containing an electrolyte solution of ^{n}Bu$_4$NBr in CH_2Cl_2 at room temperature (Table 1). Under these mild conditions, the desired 4-bromo-*N*,*N*-dimethylaniline (**2a**) was isolated in 80% yield (Table 1, entry 1).[18] In comparison, reduced yields were obtained when the reaction conditions were modified in one of the following manners: changing the anode to RVC (Table 1, entry 2) or changing the cathode to Ni foam (Table 1, entry 3), using other solvents such as EtOH (Table 1, entry 4) or MeCN (Table 1, entry 5), or reducing the amount of ^{n}Bu$_4$NBr (Table 1, entry 6). It is worth to mention that increasing the amount of ^{n}Bu$_4$NBr does not improve the yield (Table 1, entry 7), indicating that stoichiometric ^{n}Bu$_4$NBr is sufficient for the reaction. A control experiment revealed that no **2a** was obtained in the absence of electric current (Table 1, entry 8). This result suggested that the reaction driving force should be the employment of electric energy.

Having optimized the reaction conditions, we next examined the scope of the bromination reaction by testing a series of aromatic substrates (Table 2). To our satisfaction, a variety of tertiary (**1a–f**), secondary (**1g**), and primary anilines (**1h**) were tolerated to afford *para*-brominated products in moderate to high yields (**2a–h**). Furthermore, a range of functional groups, including alkyl (**2i–o**), aryl (**2s–v**), alkoxy (**2t**, **2v**), halogen (**2n**,**o**,**u**), ester (**2q**), hydroxyl (**2r**), and even oxidation- and bromination-prone olefin (**2p**) substituents at the *N*-1 position of indoles, were well tolerated in the reaction system. Other heteroarene (pyridine) could also be regioselectively brominated in moderate yields (**2w**). Interestingly, the bromination proceeded smoothly at the *ortho* position instead to furnish the desired product **2x** in 42% yield when the *para* position was occupied (Scheme 2).

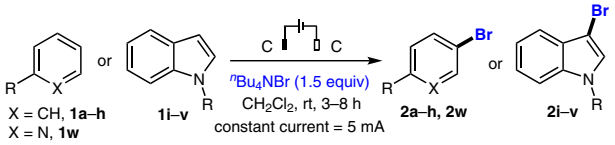
Table 1 Optimization of the Reaction Conditions[a]



Entry	Variation from standard conditions above	Yield (%)[b]
1	none	80
2	RVC as anode	72
3	Ni foam as cathode	58
4	EtOH instead of CH_2Cl_2	60
5	MeCN instead of CH_2Cl_2	24
6	^{n}Bu$_4$NBr (1.0 equiv)	60
7	^{n}Bu$_4$NBr (2.0 equiv)	80
8	no electric current	0

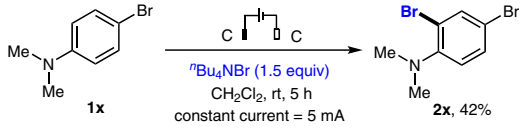
[a] Standard conditions: graphite rod anode (d = 5 mm), graphite rod cathode (d = 5 mm), constant current = 5 mA, **1a** (0.25 mmol), ^{n}Bu$_4$NBr (0.375 mmol), CH_2Cl_2 (5 mL), undivided cell, room temperature, 3.5 h.
[b] Isolated yield.

Table 2 Synthesis of Aryl Bromides **2**[a,b]



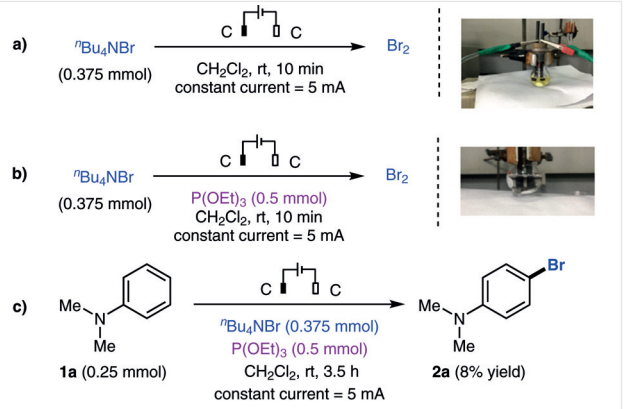
Entry	R	Time (h)	Product	Yield (%)
1	$(Me)_2N$	3.5	**2a**	80
2	^{n}BuMeN	3	**2b**	81
3	BnMeN	5	**2c**	55
4	pyrrolidin-1-yl	4	**2d**	91
5	piperidin-1-yl	3	**2e**	62
6	morpholino	5	**2f**	72
7	MeNH	6	**2g**	35
8	NH_2	3	**2h**	33
9	Me	8	**2i**	92
10	^{n}Bu	3	**2j**	85
11	Bn	3.5	**2k**	80
12	*o*-$MeC_6H_4CH_2$	3	**2l**	96
13	*m*-$MeC_6H_4CH_2$	3	**2m**	83
14	*o*-$ClC_6H_4CH_2$	3	**2n**	82
15	*p*-$BrC_6H_4CH_2$	3	**2o**	93
16	allyl	3	**2p**	71
17	EtO_2CCH_2	4	**2q**	54
18	$HOCH_2CH_2$	5	**2r**	79
19	Ph	3	**2s**	80
20	*o*-$MeOC_6H_4$	3	**2t**	73
21	*o*-FC_6H_4	4	**2u**	89
22	*m*-$MeOC_6H_4$	3	**2v**	81
23	NH_2	5.5	**2w**	37

[a] Standard conditions: graphite rod anode (d = 5 mm), graphite rod cathode (d = 5 mm), constant current = 5 mA, **1** (0.25 mmol), ^{n}Bu$_4$NBr (0.375 mmol), CH_2Cl_2 (5 mL), undivided cell, room temperature, 3–8 h.
[b] Isolated yield.



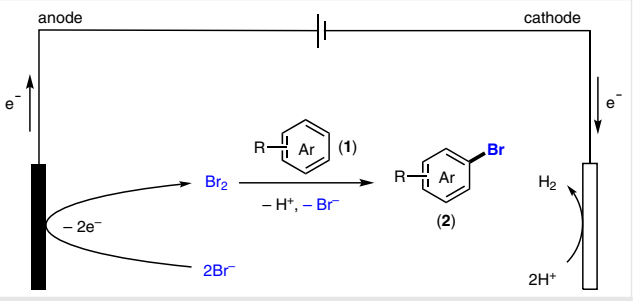
Scheme 2 Electrochemical bromination of compound **1x**

Control experiments showed that red-brown Br_2 was generated on the surface of the anode and the solution became yellow in color when ^{n}Bu$_4$NBr was directly electrolysis under the standard conditions (Scheme 3, a). Moreover, the solution remains colorless when radical scavenger P(OEt)$_3$ was added, suggesting that a radical process should be involved for formation of Br_2 (Scheme 3, b). Indeed, only 8% yield of product **2a** was isolated when P(OEt)$_3$ was added in our system (Scheme 3, c).



Scheme 3 Control experiments

Based on the observations above and literature reports,[11,19] a possible mechanism for the electrochemical bromination reaction was proposed (Scheme 4). As a start, the Br^- anions were oxidized on the anode to Br_2. The reaction of Br_2 with compound **1** afforded the aryl bromide **2** with the regeneration of Br^- anion for the next cycle. Thus, stoichiometric ^{n}Bu$_4$NBr is sufficient for full conversion of the aromatic substrates. The slow generation of Br_2 in situ is important for highly regioselective bromination of aromatic substrates in our strategy.



Scheme 4 Proposed mechanism

In summary, we have successfully developed an electrochemical bromination of electron-rich aromatic rings using stoichiometric ^{n}Bu$_4$NBr under undivided cell. This reaction could be carried out at room temperature without the use of any catalysts, oxidants or additives. This process offers an alternative to conventional methods that require chemical oxidants and represents an environmentally benign tool for regioselective oxidative C–Br bonds formation.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611545.

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(18) **4-Bromo-*N*,*N*-dimethylaniline (2a) – Typical Procedure**
A 10 mL distillation flask equipped with a magnetic stir bar was charged with *N*,*N*-dimethylaniline (**1a**, 0.25 mmol), CH_2Cl_2 (5 mL), and $^nBu_4NBr$ (0.375 mmol). The resulting suspension was stirred until complete dissolution. The flask equipped with graphite rod anode (d = 5 mm) and graphite rod cathode (d = 5 mm). The reaction mixture was stirred and electrolyzed at a constant current of 5 mA under room temperature for 3.5 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL), washed successively with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum ether–dichloromethane 3:1) afforded the desired product **2a** (80% yield) as a white solid; mp 54–55 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 2 H), 6.60 (d, J = 9.0 Hz, 2 H), 2.93 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.5, 131.6, 114.1, 108.5, 40.5.
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