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Electrochemical C−H Amination: Synthesis of Aromatic Primary Amines via *N*-Arylpyridinium Ions

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Supporting Information

ABSTRACT: We have developed a new method for C−H amination of aromatic compounds based on electrochemical oxidation of aromatic compounds in the presence of pyridine followed by the reaction of the resulting *N*-arylpyridinium ions with an alkylamine. This new transformation serves as a powerful method for synthesizing aromatic primary amines from aromatic compounds without using metal catalysts and harsh chemical reagents. High chemoselectivity of the present method is demonstrated by C−H amination of aromatic compounds bearing a nitro group to give a key intermediate for the synthesis of VLA-4 antagonist.

Functionalized aromatic primary amines are relevant intermediates in the synthesis of organic functional materials such as dyes and pigments, and biological active medicinal and agrochemical compounds.[1] Therefore, a variety of protocols for synthesizing aromatic primary amines from corresponding aromatic compounds were developed. Among them, the most popular protocol is nitration of aromatic compounds followed by reduction of the nitro compounds.[2] Although various methods for reduction of nitroarenes have been developed, chemoselectivity is still a major concern in addition to safety issues of nitration.[3] Transition-metal-catalyzed amination serves as an alternative method, but it requires preintroduction of a halogen atom[4] or a metal[5] into aromatic compounds. Recently, transition-metal catalyzed direct amination of C−H bonds of aromatic compounds has been developed.[6] Although these methods are useful, development of a new method, which does not use metal compounds nor harsh chemical reagents, is desired to provide an efficient and chemoselective synthetic route to aromatic primary amines.

Electrochemical oxidation[7,8] serves as a powerful method for functionalize C−H bonds of aromatic compounds by the intermediacy of radical cations.[9] Recently, we developed an effective method for the metal- and chemical-oxidant-free C−H/C−H cross-coupling of two aromatic compounds using the "radical-cation-pool" method.[10]

On the basis of these backgrounds, we envisaged that the sequential transformations consisting of activation of aromatic compounds by electrochemical oxidation followed by nucleophilic attack of a nitrogen source and subsequent conversion of the introduced nitrogen functionality to an NH_2 group would serve as a powerful method for direct conversion of C−H to C−NH_2 in aromatic compounds.

We chose to use pyridine as nitrogen source for the following reasons: (1) high oxidation potential of pyridine enables selective oxidation of aromatic compounds in the presence of pyridine, (2) extremely high nucleophilicity of pyridine[11] leads to nucleophilic attack of pyridine to radical cation of aromatic compounds to give *N*-arylpyridinium ions,[12] (3) overoxidation is suppressed because of strong electron-withdrawing effect of a positive charge on the pyridinium nitrogen, avoiding introduction of multiple NH_2 groups, and (4) the *N*-arylpyridinium ion can be converted to NH_2 group by the attack of a suitable nucleophile,[13,14] although the process has not been utilized so far from a synthetic point of view. Here, we report that electrochemical oxidation of aromatic compounds in the presence of pyridine and a subsequent chemical reaction of the resulting *N*-arylpyridinium ions gave aromatic primary amines (Scheme 1). Because the method does not require the use of metal compounds, reducing reagents, and strong acids, it exhibits remarkable functional group compatibility.

Scheme 1. Electrochemical C−H Amination

We first chose to use anisole (**1**) as a substrate because oxidation potential of **1** is lower than that of pyridine (**2**). The electrochemical oxidation of **1** was carried out in a 0.3 M solution of Bu_4NBF_4 in CH_3CN/pyridine (100/5) in an H-type divided cell equipped with an anode consisting of fine fibers made from carbon felt and a platinum plate cathode at 25 °C. After 3.0 F/mol of electricity was consumed, the reaction mixture was treated with piperidine at 80 °C for 12 h to give 4-methoxyaniline in 69% yield (Table 1, entry 1).

The reaction seems to proceed by the initial one-electron oxidation of an aromatic compound to produce the radical cation. The subsequent attack of pyridine followed by one-electron oxidation and elimination of a proton gives the *N*-arylpyridinium ion. In fact, the regioselectivity of the reaction is consistent with the lowest unoccupied molecular orbital (LUMO) of the radical cation of anisole (**1**) obtained by DFT calculations (Figure 1a). The amino group is introduced to the carbon bearing hydrogen with the largest coefficient of the LUMO of the radical cation of **1**. Because the LUMO of

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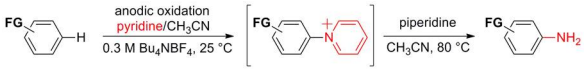
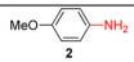
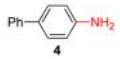
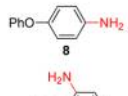
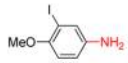
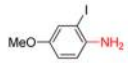
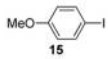
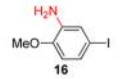
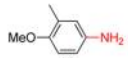
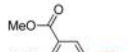
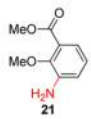
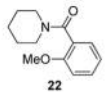
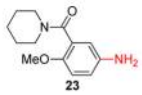
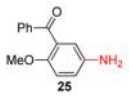
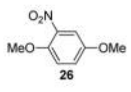
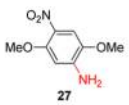
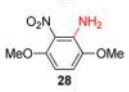
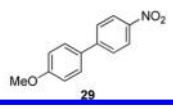
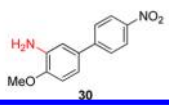
Table 1. Synthesis of Functionalized Aromatic Primary Amines by Electrochemical C−H Amination[a]



entry	substrate	product	electricity (F/mol)	yield[b] (%)
1	 1	 2	3.0	69
2	 3	 4	3.5	71
3	 5	 6	3.0	99
4	 7	 8  9	3.5	92 (**8**:**9** = 57:43)
5	 10	 11	3.0	81
6	 12	 13  14	3.5	97 (**13**:**14** = 66:34)
7	 15	 16	3.5	84
8	 17	 18	3.0	74
9	 19	 20  21	4.5	92 (**20**:**21** = 70:30)
10	 22	 23	3.5	97
11[c]	 24	 25	7.0	66
12	 26	 27  28	3.5	95 (**27**:**28** = 70:30)
13	 29	 30	3.5	quant

[a]The reactions were carried out on a 0.20 mmol scale. [b]Isolated yields are given. [c]$LiClO_4$ was used as a supporting electrolyte.

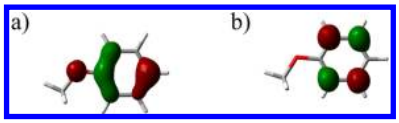


Figure 1. The lowest unoccupied molecular orbitals of (a) radical cation of **1** and (b) **1** obtained by DFT calculations (B3LYP/6-31G*).

neutral **1** has no coefficient at the 4-position, a mechanism involving initial formation of the zwitter ion by the nucleophilic attack of pyridine to **1** followed by one-electron oxidation is excluded (Figure 1b). The reaction of the *N*-arylpyridinium ion with piperidine proceeds by the addition of piperidine to 2-position of *N*-arylpyridinium ion followed by ring opening and hydrolysis of imine (Figure 2).

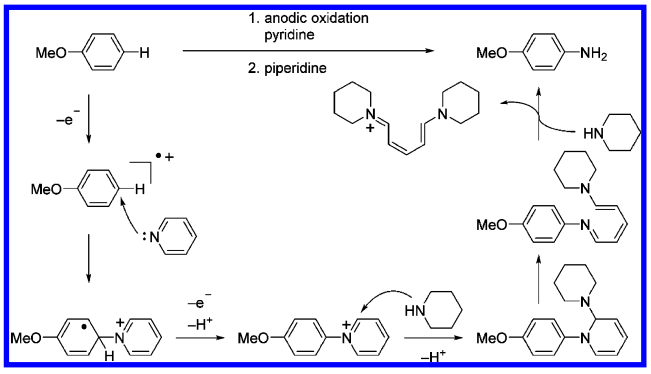


Figure 2. Proposed reaction mechanism of C−H amination of aromatic compounds via *N*-arylpyridinium ion.

π-Extended aromatic compounds such as biphenyl, naphthalene, and diphenylether gave corresponding primary amines in good yields (Table 1, entries 2−4). Functional group compatibility of the present transformation is remarkable. Iodoanisoles gave the corresponding iodine-substituted aniline derivatives in very good yields (Table 1, entries 5−7). These results are notable because iodo-substituents are often not compatible with the oxidation of aromatic compounds[15] and the reduction of nitro groups to amino groups.[16] 2-Methyl anisole is also a suitable substrate and benzylic C−H was not affected (entry 8). Anisoles with an electron-withdrawing group such as ester, amide, and ketone functionalities also gave the corresponding aniline derivatives in good yields (entries 9−11). It should be emphasized that the present transformation is compatible with nitro groups. For example, anisoles bearing a nitro group gave corresponding aniline derivatives in excellent yields without affecting the nitro group (entries 12 and 13). This contrasts sharply with the conventional nitration/reduction process. Furthermore, regioselectivities of the amination of these π-extended aromatic compounds and functionalized anisoles are predictable based on the DFT calculations (Figure 3).

To demonstrate the utility of the electrochemical C−H amination, we synthesized a key intermediate for the synthesis of VLA-4 antagonist **31**[17] (Figure 4). Starting material **32** was prepared from commercially available **33** in one step (quantitative yield). The electrochemical oxidation of **32** in the presence of pyridine followed by treatment with piperidine gave **31** in 89% isolated yield. In the previous work reported in the literature, synthesis of **31** requires protection and deprotection steps of the amino group because the amino group should be introduced prior to the introduction of the

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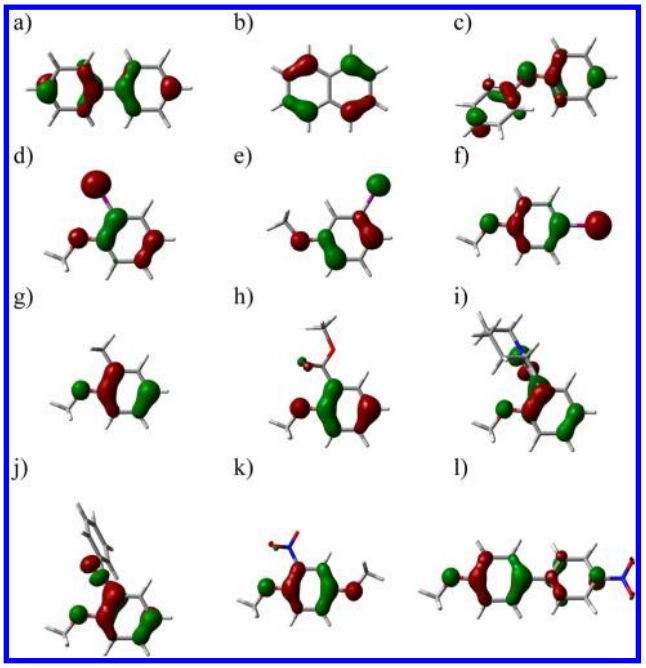

Figure 3. The lowest unoccupied molecular orbitals of radical cation of (a) **3**, (b) **5**, (c) **7**, (d) **10**, (e) **12**, (f) **15**, (g) **17**, (h) **19**, (i) **22**, (j) **24**, (k) **26**, and (l) **29** obtained by DFT calculations (UB3LYP/6-31G*).

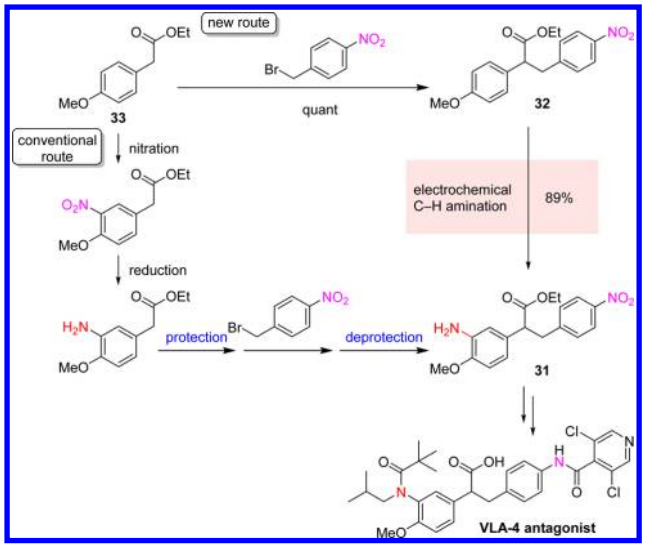

Figure 4. Synthesis of a key intermediate for the synthesis of VLA-4 antagonist **31**.

nitro group. However, the present method enabled the direct amination in the presence of the nitro group avoiding the protection and deprotection of the amino group, demonstrating the power of the present method from view points of redox economy,[18] step economy,[19] and protecting-group-free synthesis.[20]

In conclusion, we have developed an efficient method for the C−H bond amination of aromatic compounds by integration of the electrochemical and chemical reactions.[21] The present method provides chemoselective metal-free routes to the aromatic primary amines having a variety of functionalities including iodo and nitro groups. Currently, we are working to expand the scope of the present method for the synthesis of complex molecules containing Ar-NH_2 functionalities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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