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# Iron-catalyzed bromination of aryl azides by *N*-bromosuccinimide: Efficient method for the synthesis of brominated aryl azides

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## Abstract

An efficient and mild protocol for bromination of aryl azides with *N*-bromosuccinimide (NBS) under $FeCl_3$ catalysis in 1,2-dichloroethane was developed. It is proved to be an efficient method for obtaining brominated aryl azides.

*Keywords:* Iron-catalyzed; Aryl azides; *N*-Bromosuccinimide; Bromination

Aryl azides are versatile intermediates with various applications in organic and bioorganic chemistry [1]. They are extensively employed in the synthesis of aryl nitrenes [2], aryl anilines [3], particularly nitrogen-containing five-membered heterocycles upon 1,3-dipolar cycloaddition [4]. In addition, aryl azides are well known for their use as photoaffinity labeling agents for proteins [5]. However, perhaps because of their partly less attractive properties (explosiveness, toxicity), very few bromination systems in the literature has been published for their bromination. Smith *et al.* [6] reported a method for bromination of phenyl azide with $Br_2$, the reaction gives the *para*-bromination product in low yield. Latyshev *et al.* [7] reported bromination of 1,3-diazido-2-methylbenzene using 1,4-dioxane dibromide affords the monobromination product in moderate yield, and the reaction requires long reaction time and the substrate scope is limited to electron-rich aryl azides. Thus, we still consider it highly desirable to develop milder and more efficient bromination method of aryl azides.

In recent years, iron as one of the transition metal catalysts was revealed to be of high interest in term of cost and efficiency [8]. To the best of our knowledge, although iron catalyzed the reaction of aromatic ring has been previously reported [9], iron-catalyzed bromination of aryl azides has been never studied.

Herein, we report an iron-catalyzed bromination reaction of aryl azides using NBS, which afford the corresponding brominated aryl azides **2** in moderate to good yield (Scheme 1).

To screen suitable reaction conditions, 1-azido-4-chlorobenzene **1a** has been used as model substrate. Initially, the reaction was carried out in the presence of $FeCl_3$ (20 mol%) and NBS (1.1 equiv.) in 1,2-dichloroethane (3 mL) at room temperature for 12 h, 49% isolated yield of 1-azido-2-bromo-4-chlorobenzene **2a** was obtained (Table 1, entry 1). Then we examined other catalysts, $FeCl_3$ proved to be superior to $Fe_2(SO_4)_3$ and $FeCl_2$ (Table 1, entries 1–3).

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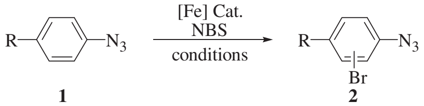


Scheme 1. Iron-catalyzed bromination of aryl azides **1** by NBS.

Table 1
Optimization of bromination of 1-azido-4-chlorobenzene **1a** to 1-azido-2-bromo-4-chlorobenzene **2a**.

| Entry | Catalyst (0.2 equiv) | Solvent (3 mL) | Temperature (°C) | Time (h) | Yield of **2a** (%)[a] |
|---|---|---|---|---|---|
| 1 | $FeCl_3$ | 1,2-Dichloroethane | 25 | 12 | 49 |
| 2 | $Fe_2(SO_4)_3$ | 1,2-Dichloroethane | 25 | 12 | 23 |
| 3 | $FeCl_2$ | 1,2-Dichloroethane | 25 | 12 | 27 |
| 4 | $Fe_2O_3$ | 1,2-Dichloroethane | 25 | 12 | 9 |
| 5 | $Fe(acac)_3$ | 1,2-Dichloroethane | 25 | 12 | 5 |
| 6 | none | 1,2-Dichloroethane | 25 | 12 | Trace |
| 7 | $FeCl_3$ | MeCN | 25 | 12 | 43 |
| 8 | $FeCl_3$ | 1,4-Dioxane | 25 | 12 | 0 |
| 9 | $FeCl_3$ | 1,2-Dichloroethane | 60 | 12 | 65 |
| 10 | $FeCl_3$ | 1,2-Dichloroethane | 80 | 12 | 72 |
| 11 | $FeCl_3$ | 1,2-Dichloroethane | 80 | 24 | 85 |

[a] Isolated yields.

$Fe_2O_3$ and $Fe(acac)_3$ proved to be inefficient (Table 1, entries 4, 5), and the absence of iron catalyst gives trace product (Table 1, entry 6). The reaction also showed a strong solvent dependence. Except 1,2-dichloroethane, other solvents such as MeCN, dioxane proved to be inappropriate (Table 1, entries 7, 8). After that we examined temperature and reaction time influence in the reaction. To our delight, the yield of **2a** could be improved when the temperature was increased to 80 °C and the reaction time was extended to 24 h. On the basis of these results, the optimal conditions involved the following parameters: $FeCl_3$ as catalyst, 1,2-dichloroethane as solvent, with reaction temperature at 80 °C for 24 h.

Under the optimized conditions, the substrate scope of this iron-catalyzed bromination reaction of aryl azides was investigated and these newly developed conditions appeared to be general for a spectrum of aryl azides (Table 2). The aryl azides were obtained from the anilines employing standard diazotization conditions [10]. The reaction conditions are compatible with various functionalities such as chloro (**2a**), bromo (**2b**), ethers (**2c**, **2d**), methoxy (**2e**) and methyl (**2f**, **2f′**). It was observed that azidobenzene could also proceed smoothly with good yield (**2g**). The substitution on the aromatic ring had almost no influence on the yield of the reaction, as systems substituted with electron-withdrawing (**2a**–**2d**), electron-donating groups (**2e**, **2f**, **2f′**) provided similar results. But the electronic factors had shown some effect on the reaction time. In general, electron-rich aryl azides (**2e**, **2f**, **2f′**) gave shorter reaction time than electron-deficient counterpart (**2a**–**2d**).

The reaction of heterocyclic azide such as thiazole (**2h**) proceeded with moderate yield 77% and gives good regioselectivity. Bromination of naphthalene (**2i**) gives disubstituted product, bromine atom was added to both *ortho* and *para* positions of azide group simultaneously in yield 67%.

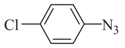
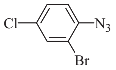
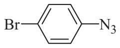
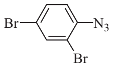
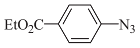
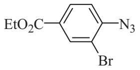
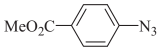
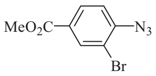
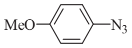
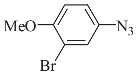
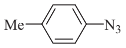
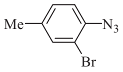
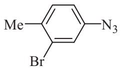
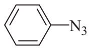
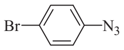
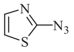
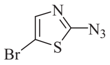
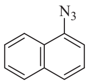
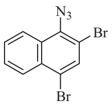
In summary, we have successfully employed $FeCl_3$ as catalyst for the direct bromination aryl azides to corresponding brominated derivatives in moderate to good yield. This is a versatile method to accomplish the synthesis of a series of brominated aryl azides from aryl azides in a single-step operation.

## 1. Experimental

$^1H$ and $^{13}C$ NMR spectra were recorded using a Bruker AM-500 spectrometer. High resolution mass spectra were determined using a Finnigan-NAT GC/MS/DS 8430 spectrometer.

To a sealed tube were added 1,2-dichloroethane 3 mL, aryl azide (0.5 mmol), $FeCl_3$ (16 mg, 0.1 mmol), NBS (97 mg, 0.55 mmol). The mixture was stirred at 80 °C and the reaction was monitored by TLC. After reaction completed, the system was extracted with $Et_2O$ (3 × 30 mL). The organic layer was separated, washed with water and

Table 2
$FeCl_3$-catalyzed bromination of aryl azides **1** to brominated aryl azides **2**.

| Entry | Azide **1** | Product **2** | | Time (h) | Yield (%)[a] | Ref. |
|---|---|---|---|---|---|---|
| 1 |  |  | **2a** | 24 | 84 | |
| 2 |  |  | **2b** | 24 | 78 | [11] |
| 3 |  |  | **2c** | 24 | 81 | [12] |
| 4 |  |  | **2d** | 24 | 80 | [13] |
| 5 |  |  | **2e** | 4 | 86 | [14] |
| 6 |  |  | **2f** | 4 | 43 | [11] |
| | |  | **2f′** | | 40 | [15] |
| 7 |  |  | **2g** | 4 | 89 | [16] |
| 8 |  |  | **2h** | 4 | 77 | [17] |
| 9[b] |  |  | **2i** | 4 | 67 | [18] |

[a] Isolated yields.

[b] 2.2 equiv. NBS was added.

saturated brine, and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent gave the crude product, which was subjected to column chromatography (silica gel, EtOAc–petroleum ether) to afford brominated aryl azides **2**. The structure of these compounds has been elucidated by spectral ($^1$H NMR, $^{13}$C NMR) data [19].

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[18] G. Mitchell, C.W. Rees, J. Chem. Soc. (1987) 403.

[19] Spectroscopic data. 1-Azido-2-bromo-4-chlorobenzene **2a**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.10 (d, 1H, $J = 8.6$ Hz), 7.32 (dd, 1H, $J = 8.6$, 2.3 Hz), 7.56 (d, 1H, $J = 2.3$ Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 119.1, 120.1, 128.7, 130.6, 133.5, 137.6. HRMS: *m/z* calcd. for $C_6H_3BrClN_3$ 230.9199, found 230.9198. 1-Azido-2,4-dibromobenzene **2b**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.04 (d, 1H, $J = 8.5$ Hz), 7.46 (dd, 1H, $J = 8.5$, 2.1 Hz), 7.70 (d, 1H, $J = 2.1$ Hz). Ethyl 4-azido-3-bromobenzoate **2c**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.40 (t, 3H, $J = 7$ Hz), 4.38 (q, 2H, $J = 7$ Hz), 7.21 (d, 1H, $J = 8.5$ Hz), 8.02 (dd, 1H, $J = 8.5$, 1.5 Hz), 8.23 (d, 1H, $J = 1.5$ Hz). Methyl 4-azido-3-bromobenzoate **2d**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 3.92 (s, 3H), 7.22 (d, 1H, $J = 8.5$ Hz), 8.01 (dd, 1H, $J = 8.5$, 1.9 Hz), 8.23 (d, 1H, $J = 1.9$ Hz). 4-Azido-2-bromo-1-methoxybenzene **2e**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 3.88 (s, 3H), 6.87 (d, 1H, $J = 8.8$ Hz), 6.94 (dd, 1H, $J = 8.8$, 2.7 Hz), 7.23 (d, 1H, $J = 2.7$ Hz). 1-Azido-2-bromo-4-methylbenzene **2f**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.31 (s, 3H), 7.06 (d, 1H, $J = 8.0$ Hz), 7.14 (dd, 1H, $J = 8.0$, 1.0 Hz), 7.37 (s, 1H). 4-Azido-2-bromo-1-methylbenzene **2f'**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.37 (s, 3H), 6.88 (dd, 1H, $J = 8.2$, 2.3 Hz), 7.19 (d, 1H, $J = 8.5$ Hz), 7.21 (d, 1H, $J = 2.5$ Hz). 1-Azido-4-bromobenzene **2g**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.92−6.94 (d, 2H, $J = 8.8$ Hz), 7.47−7.49 (d, 2H, $J = 8.8$ Hz). 2-Azido-5-bromothiazole **2h**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.36 (s, 1H), 1-Azido-2,4-dibromonaphthalene **2i**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.61−7.68 (m, 2H), 7.91 (s, 1H), 8.18 (d, 1H, $J = 7.8$ Hz), 8.26.(d, 1H, $J = 8.5$ Hz).