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PII: S0040-4039(15)30050-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.09.008
Reference: TETL 46680

To appear in: *Tetrahedron Letters*

Received Date: 6 July 2015
Revised Date: 1 September 2015
Accepted Date: 4 September 2015

Please cite this article as: Tanaka, M., Kamito, Y., Lei, C., Tada, N., Itoh, A., Aerobic photooxidative bromination of aromatic compounds using carbon tetrabromide mediated by anthraquinone-2-carboxylic acid, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.09.008

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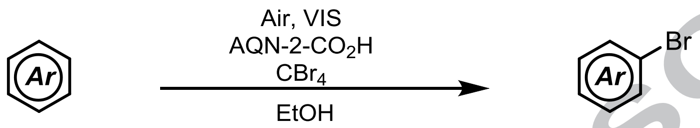

Tetrahedron Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

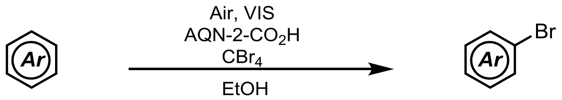
Keywords:
Aerobic
Anthraquinone-2-carboxylic acid
Photooxidation
Carbon tetrabromide
Air.

ABSTRACT

We developed the aerobic photooxidative bromination of aromatic compounds using carbon tetrabromide in the presence of anthraquinone-2-carboxylic acid under visible light irradiation.

Aryl bromides are important reagents in synthetic organic chemistry, especially in cross-coupling reactions.[1] Aryl bromide motifs are present in various useful products such as pharmaceuticals, agrochemicals, dyes, and fire-retardants. Moreover, several natural products such as 6,6′-dibromoindigo[2] and Tambjamine B[3] are aryl bromides.

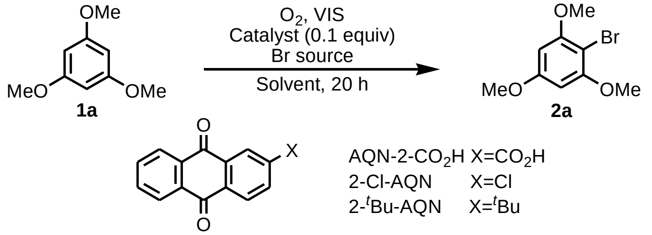
Various synthetic methods of aryl bromides have been developed using aryldiazonium,[4] aryl boronic acid derivatives,[5] or aryl triflate[6] as substrates. Of the various synthetic methods, the bromination of aryl C(sp^2)–H to C(sp^2)–Br using a representative brominating agent such as Br_2 or NBS has been a direct, economical, and reliable method.[7] Furthermore, oxidative bromination is enabled using easy to handle brominating agents, such as NH_4Br, LiBr, NaBr, and KBr, together with a suitable oxidant such as H_2O_2, MCPBA, or oxone.[8] Light is an important factor in many reactions[9] and can exhibit specific reactivity. However, the photo bromination of aromatic rings using bromine sources, such as HBr, NBS, and Br_2, is relatively rare.[10]



Scheme 1. Aerobic photooxidative bromination of aromatic compounds

Due to the increasing demand for more environmentally friendly syntheses, molecular oxygen has received much attention as an attractive oxidant, which is inexpensive and has a greater atom efficiency than that of other oxidants.[11] We have been studying aerobic photooxidative reactions using various photocatalysts, and discovered that compounds such as LiBr, $MgBr_2$, HBr, Br_2, NBS, and CBr_4 are effective bromine radical sources.[12] Among them, CBr_4 is an easy to handle air and moisture stable crystalline solid, and has been used for the Appel reaction and the Corey–Fuchs reaction. However, because of its stability, the bromination of aromatic rings using CBr_4 requires a high temperature ranging from 150 to 180 °C,[13] or lithiated aromatic compounds.[14] Thus, a more mild activation method of

Table1. Optimization of reaction conditions[a]



Entry	Br source (equiv)	Catalyst	Solvent	Yield (%)[b]
1	CBr_4 (1.0)	AQN-2-CO_2H	EtOAc	20
2	CBr_4 (1.0)	AQN-2-CO_2H	$CHCl_3$	20
3	CBr_4 (1.0)	AQN-2-CO_2H	Toluene	33
4	CBr_4 (1.0)	AQN-2-CO_2H	THF	50
5	CBr_4 (1.0)	AQN-2-CO_2H	MeOH	55
6	CBr_4 (1.0)	AQN-2-CO_2H	EtOH	63
7	CBr_4 (0.25)	AQN-2-CO_2H	EtOH	93 (92)
8	CBr_4 (0.25)	2-Cl-AQN	EtOH	62
9	CBr_4 (0.25)	2-^{t}Bu-AQN	EtOH	67
10	CBr_4 (0.25)	Methylene Blue	EtOH	15
11	CBr_4 (0.25)	Anthracene	EtOH	26
12	CBr_4 (0.25)	Benzophenone	EtOH	46
13	CBr_4 (0.25)	Eosin Y	EtOH	35
14	CH_2Br_2 (0.5)	AQN-2-CO_2H	EtOH	0
15	$CHBr_3$ (0.33)	AQN-2-CO_2H	EtOH	49
16	NBS (1.0)	AQN-2-CO_2H	EtOH	17
17	Br_2 (0.5)	AQN-2-CO_2H	EtOH	52
18	HBr (1.0)	AQN-2-CO_2H	EtOH	35
19[c]	CBr_4 (0.25)	AQN-2-CO_2H	EtOH	93 (90)

[a] A solution of 1,3,5-trimethoxybenzene (**1a**, 0.3 mmol), Br source, and catalyst (0.1 equiv) in dry solvent (5 mL) purged with an O_2 balloon was stirred and irradiated externally with 21W fluorescent lamp for 20 h.

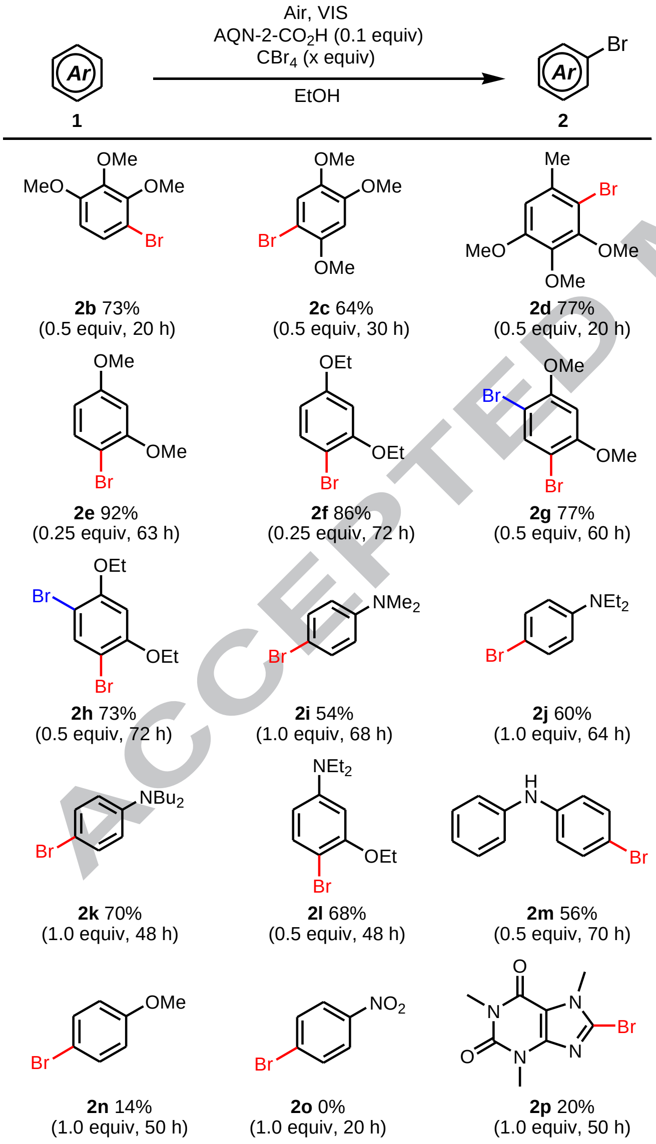
[b] ^{1}H NMR yields. Numbers in parentheses are isolated yields.

[c] The reaction was carried out under the air.

CBr_4 is desirable. Here, we report a detailed study of the photocatalytic bromination of aromatic compounds using CBr_4 as a brominating agent under aerobic photoirradiation conditions (Scheme 1).

To explore this approach, we selected 1,3,5-trimethoxybenzene (**1a**) as a test substrate to optimize the reaction conditions (Table 1). First, we screened the solvents in the presence of CBr_4 (1 equiv), AQN-2-CO_2H (0.1 equiv), and molecular oxygen (balloon) under photo-irradiation from 21 W fluorescent lamp (entries 1-6). The desired monobrominated product, 2-Bromo-1,3,5-trimethoxybenzene (**2a**), was produced most efficiently in moderate yields when using ethanol as solvents (entry 6). However, polybrominated products were also generated under the conditions. Interestingly, when the amount of CBr_4 was reduced to 0.25 equivalents, the yield was increased to 92% isolated yield (entry 7). Thus catalyst and bromine source were investigated using 1 equivalent of Br atom (entries 7-18), and revealed that combination of AQN-2-CO_2H and CBr_4 gave best result (entry 7). It is noteworthy that the reaction proceeded even under air atmosphere instead of oxygen atmosphere (entry 19).

Table 2. Scope and limitations[a, b]



2b 73% (0.5 equiv, 20 h)

2c 64% (0.5 equiv, 30 h)

2d 77% (0.5 equiv, 20 h)

2e 92% (0.25 equiv, 63 h)

2f 86% (0.25 equiv, 72 h)

2g 77% (0.5 equiv, 60 h)

2h 73% (0.5 equiv, 72 h)

2i 54% (1.0 equiv, 68 h)

2j 60% (1.0 equiv, 64 h)

2k 70% (1.0 equiv, 48 h)

2l 68% (0.5 equiv, 48 h)

2m 56% (0.5 equiv, 70 h)

2n 14% (1.0 equiv, 50 h)

2o 0% (1.0 equiv, 20 h)

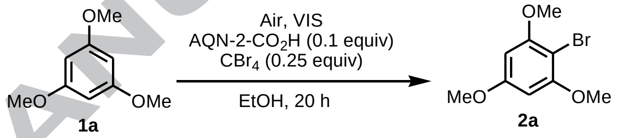
2p 20% (1.0 equiv, 50 h)

[a] Isolated yields. [b] A solution of **1** (0.3 mmol), CBr_4, and AQN-2-CO_2H (0.1 equiv) in dry EtOH (5 mL) was stirred under air and irradiated externally with a 21 W fluorescent lamp for the indicated time.

Table 2 shows the results of scope and limitations of the aerobic photooxidative bromination of aromatic compounds under the reaction conditions mentioned above.[15] Generally the corresponding brominated compounds are obtained by using electron rich substrates in good to high yields (**2b-f**, **2i-2m**). In addition, dibrominated compounds were selectively obtained in the presence of 0.5 equiv CBr_4 (**2g** and **2h**). On the other hand, anisole and nitrobenzene was poor substrate (**2n** and **2o**). In this reaction, caffeine was also brominated albeit in low yield (**2p**).

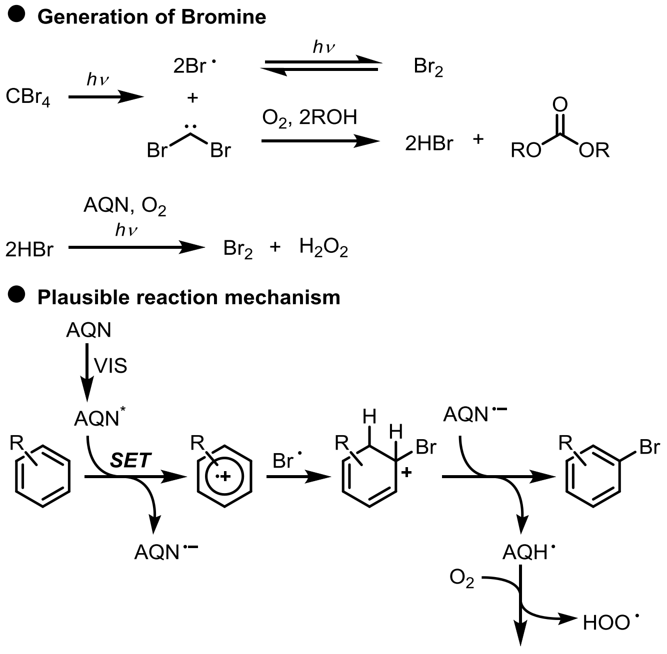
We also conducted a control experiments to elucidate reaction mechanism (Table 3). Oxygen environment and visible light irradiation were found to be essential for this reaction (entries 1 and 2). The yield was decreased to 17% when the reaction performed without AQN-2-COOH (entry3). Furthermore, the reaction performed with 1 equivalent of TEMPO, which led to the desired compound in 7% yield (entry 4). This result indicated that the radical intermediate is involved in this reaction mechanism. However, important feature of the mechanism is that this reaction may allow the selective bromination of aromatic C−H bond at most electron-rich and less hindered position without damaging at benzylic position.

Table 3. Study of reaction mechanism[a]



Entry	Changed conditon	Yield (%)[b]
1	Under Ar	7
2	In the dark	0
3	No catalyst	17
4	TEMPO (1.0 equiv) was added	7

[a] A solution of **1a** (0.3 mmol), CBr_4 (0.25 equiv), and AQN-2-CO_2H (0.1 equiv) in EtOH (5 mL) was stirred under air and irradiated externally with a fluorescent lamp for 20 h. [b] ^1H NMR yields.



Scheme 2. Plausible reaction mechanism

Scheme 2 shows a plausible path of this oxidative photo bromination of aromatic compounds, which is postulated by the necessity of molecular oxygen, continuous irradiation, and AQN-2-CO_2H in this reaction. The major path is illustrated above in scheme 2. The bromine radical is generated by homolysis of C-Br bond along with dibromomethyl carbene. The dibromomethyl carbene produces hydrogen bromide in the presence of solvent and oxygen. Then, the hydrogen bromide is reoxidized to bromine. In this reaction, we suppose that bromine atom is installed to the arene by aromatic electrophilic substitution reaction. On the other hand, the minor path is illustrated below in scheme 2. The excited AQN, which is formed by absorption of visible light, causes SET and produces radical cation species.[15] This radical species react with bromine radical and the product is aromatized again via deprotonation and AQN hydroxyl radical is formed. The generated AQN hydroxyl radical are reoxidized under the photooxidative condition and the catalytic cycle is established.

In conclusion, we developed the aerobic photooxidative bromination of aromatic compounds using CBr_4 in the presence of the catalytic amounts of AQN-2-CO_2H under photo-irradiation from fluorescent lamp.

Acknowledgment

This work was supported by Grant-in-Aid for Young Scientists (B)(No. 24790015) from the Japan Society for the Promotion of Science (JSPS).

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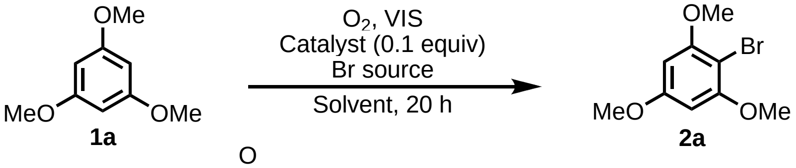
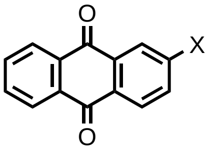
16. Typical procedure: A pyrex test tube containing solid of 1,3,5-Trimethoxybenzene (**1a**, 0.3 mmol), carbon tetrabromide (0.075 mmol), AQN-2-CO_2H (0.03 mmol) and dry EtOH (5 mL) was irradiated for 20 h at room temperature with stirring by a 21 W fluorescent lamp under air. The reaction mixture was concentrated *in vacuo,* quenched with aq. $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (hexane : ethyl acetate = 6 : 1) provided 2-bromo-1,3,5-trimethoxybenzene (**2a**) (66.8 mg, 90%,) as a white solid.

Table1. Optimization of reaction conditions[a]





AQN-2-CO_2H X=CO_2H
2-Cl-AQN X=Cl
2-^{t}Bu-AQN X=^{t}Bu

Entry	Br source (equiv)	Catalyst	Solvent	Yield (%)[b]
1	CBr_4 (1.0)	AQN-2-CO_2H	EtOAc	20
2	CBr_4 (1.0)	AQN-2-CO_2H	$CHCl_3$	20
3	CBr_4 (1.0)	AQN-2-CO_2H	Toluene	33
4	CBr_4 (1.0)	AQN-2-CO_2H	THF	50
5	CBr_4 (1.0)	AQN-2-CO_2H	MeOH	55
6	CBr_4 (1.0)	AQN-2-CO_2H	EtOH	63
7	CBr_4 (0.25)	AQN-2-CO_2H	EtOH	93 (92)
8	CBr_4 (0.25)	2-Cl-AQN	EtOH	62
9	CBr_4 (0.25)	2-^{t}Bu-AQN	EtOH	67
10	CBr_4 (0.25)	Methylene Blue	EtOH	15
11	CBr_4 (0.25)	Anthracene	EtOH	26
12	CBr_4 (0.25)	Benzophenone	EtOH	46
13	CBr_4 (0.25)	Eosin Y	EtOH	35
14	CH_2Br_2 (0.5)	AQN-2-CO_2H	EtOH	0
15	$CHBr_3$ (0.33)	AQN-2-CO_2H	EtOH	49
16	NBS (1.0)	AQN-2-CO_2H	EtOH	17
17	Br_2 (0.5)	AQN-2-CO_2H	EtOH	52
18	HBr (1.0)	AQN-2-CO_2H	EtOH	35
19[c]	CBr_4 (0.25)	AQN-2-CO_2H	EtOH	93 (90)

[a] A solution of 1,3,5-trimethoxybenzene (**1a**, 0.3 mmol), Br source, and catalyst (0.1 equiv) in dry solvent (5 mL) purged with an O_2 balloon was stirred and irradiated externally with 21W fluorescent lamp for 20 h.

[b] ^{1}H NMR yields. Numbers in parentheses are isolated yields.

[c] The reaction was carried out under the air.