



## Facile aerobic photo-oxidative syntheses of $\alpha,\alpha$ -dibromoacetophenones from aromatic alkynes with 48% aq HBr

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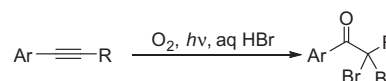
### ABSTRACT

We report a useful method for facile aerobic photo-oxidative synthesis of  $\alpha,\alpha$ -dibromoacetophenones from aromatic alkynes with 48% aq HBr. This method provides the synthesis of  $\alpha,\alpha$ -dibromoacetophenones using inexpensive and easily handled bromine sources, harmless visible light, and molecular oxygen.

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$\alpha,\alpha$ -Dibromoacetophenones are important intermediates in organic synthesis, and have been used in the synthesis of pharmaceutically important heteroaromatics.<sup>1</sup> Reaction of  $\alpha,\alpha$ -dibromoacetophenones with zerovalent transition metals produces ketocarbenoid to afford cyclopropanes by self-condensation or trapping olefins.<sup>2</sup> In addition, lithium alkynolates, generated by the reaction of  $\alpha,\alpha$ -dibromoketones with lithium hexamethyldisilazane, react with aldehydes or acid chlorides to give the corresponding unsaturated acids and ynol esters, respectively.<sup>3</sup>

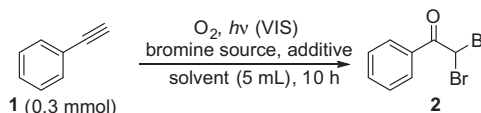
Generally,  $\alpha,\alpha$ -dibromoacetophenones are synthesized from acetophenones using an excess of molecular bromine,<sup>4</sup> bromine source,<sup>5</sup> or its complex compounds.<sup>6–8</sup> Furthermore, oxidations of aromatic alkynes for the synthesis of  $\alpha,\alpha$ -dibromoacetophenones have also been known; however, these methods involve the use of heavy metals<sup>9</sup> and complex organic compounds<sup>10</sup> or a complicated operation.<sup>11</sup> Due to an increasing demand for more environmentally benign synthesis, molecular oxygen has received much attention as an ultimate oxidant, since it theoretically produces only water as the endo product and has large atom efficiency than that of the other oxidants. With this perspective, we have studied the oxidation with molecular oxygen, and have already reported the aerobic photo-oxidation of methyl aromatics or alcohols to the corresponding carboxylic acids in good yield in the presence of a catalytic amount of bromine sources.<sup>12</sup> In the course of our further study of this photo-oxidation protocol, we found that aromatic alkynes are oxidized under the similar conditions to successfully provide the corresponding  $\alpha,\alpha$ -dibromoacetophenones (Scheme 1). Our method is of interest from a viewpoint of green chemistry because of the use of visible light from a general purpose fluorescent lamp, molecular oxygen, and easily handled and inexpensive bromine sources such as 48% aq HBr. In this Letter, we report the detailed study of aerobic photo-oxidative syntheses of  $\alpha,\alpha$ -dibromoacetophenones from aromatic alkynes.



Scheme 1.

Table 1

Study of reaction conditions for aerobic photo-oxidation



Entry	Bromine source (equiv)	Additive ( $\mu$ L)	Solvent	Yield <sup>a</sup> (%)
1	48% aq HBr (2.2)	—	EtOAc	13
2	48% aq HBr (2.2)	—	CH <sub>2</sub> Cl <sub>2</sub>	17
3	48% aq HBr (2.2)	—	Hexane	17
4	48% aq HBr (2.2)	—	<i>i</i> -Pr <sub>2</sub> O	17
5	48% aq HBr (2.2)	—	Benzene	37
6	48% aq HBr (2.2)	—	Acetone	37
7	48% aq HBr (2.2)	—	MeOH	54
8	48% aq HBr (2.2)	—	MeCN	76
9	48% aq HBr (2.2)	H <sub>2</sub> O (50)	MeCN	83 (81)
10	48% aq HBr (2.2)	H <sub>2</sub> O (100)	MeCN	79
11	48% aq HBr (2.1)	H <sub>2</sub> O (50)	MeCN	81 (84)
12	48% aq HBr (2.0)	H <sub>2</sub> O (50)	MeCN	81 (78)
13	48% aq HBr (2.1)	H <sub>2</sub> O (50)	MeCN	0 <sup>b</sup>
14	48% aq HBr (2.1)	H <sub>2</sub> O (50)	MeCN	Trace <sup>c</sup>
15	Br <sub>2</sub> (2.2)	—	MeCN	55 <sup>d</sup>
16	MgBr <sub>2</sub> ·OEt <sub>2</sub> (2.2)	—	MeCN	50
17	CBr <sub>4</sub> (2.2)	—	MeCN	30
18	NBS (2.2)	—	MeCN	22
19	LiBr (2.2)	—	MeCN	8
20	NaBr (2.2)	—	MeCN	0
21	KBr (2.2)	—	MeCN	0

<sup>a</sup> <sup>1</sup>H NMR analysis. Numbers in parentheses are isolated yields.

<sup>b</sup> The reaction was carried out in the dark.

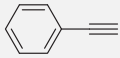
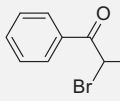
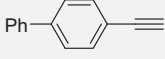
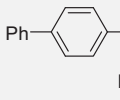
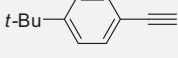
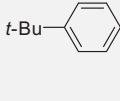
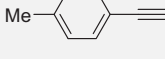
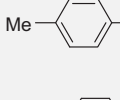
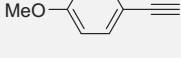
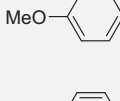
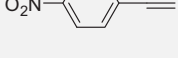
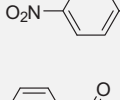
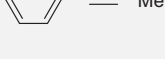
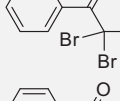
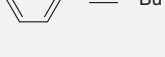
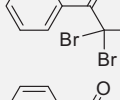
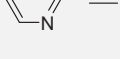
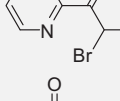

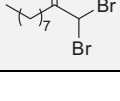
<sup>c</sup> The reaction was carried out under N<sub>2</sub> atmosphere.

<sup>d</sup>  $\alpha,\beta$ -Dibromostyrene (14%) was obtained as by-product.

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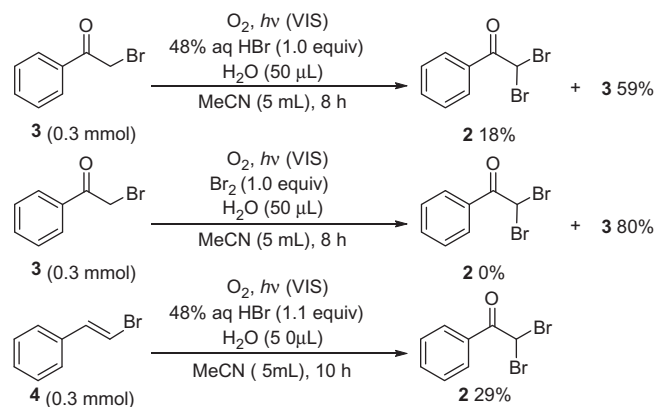
**Table 2**Aerobic photo-oxidative syntheses of  $\alpha,\alpha$ -dibromoacetophenones from aromatic alkynes

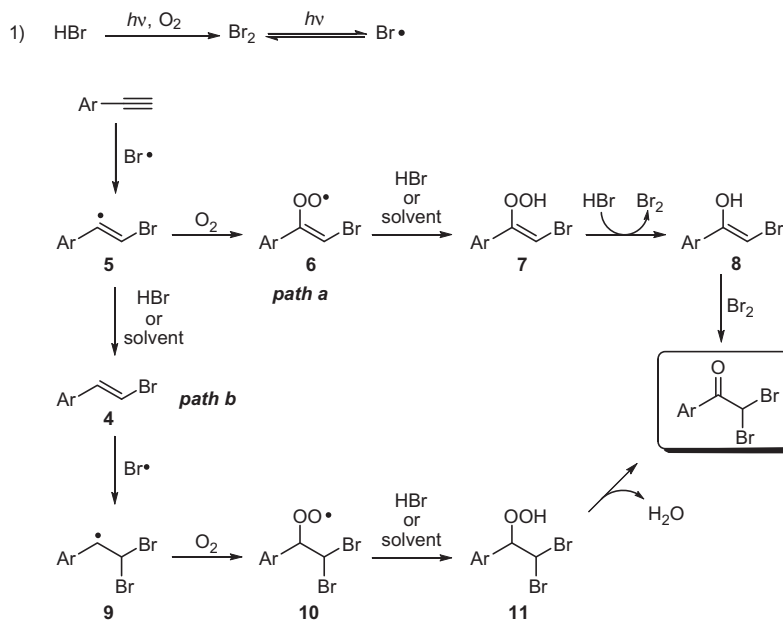
Entry	Substrate	Time (h)	Reaction Conditions		Product	Yield <sup>a</sup> (%)
			substrate (0.3 mmol)	$O_2, h\nu$ (VIS) 48% aq HBr (2.1 equiv) $H_2O$ (50 $\mu$ L) MeCN (5 mL)		
1		10				84
2		10				71
3		7				77 <sup>b</sup>
4		10				73 <sup>c</sup>
5		24				66
6		15				75
7		10				75
8		10				69
9		10				55
10		10				17 <sup>d</sup>

<sup>a</sup> Isolated yields.<sup>b</sup> With 48% aq HBr (2.3 equiv).<sup>c</sup> With  $H_2O$  (100  $\mu$ L).<sup>d</sup> With EtOAc (5 mL) as solvent.

Table 1 shows the reaction conditions for the aerobic photo-oxidative synthesis of  $\alpha,\alpha$ -dibromoacetophenone (**2**) from phenylacetylene (**1**) as a test substrate. Among the solvents and bromine sources examined, MeCN and 48% aq HBr were found to afford the desired product **2** most efficiently (entries 1–8 and 15–21), and addition of  $H_2O$  increased the yield of **2** (entry 9). Among our detailed examinations, addition of  $H_2O$  (50  $\mu$ L) and 48% aq HBr (2.1 equiv) was the most suitable reaction condition (entries 9–12). The fact that **2** was not obtained without irradiation and molecular oxygen indicates their essentiality for this reaction (entries 13 and 14).

Table 2 presents the scope and limitation of the aerobic photo-oxidative synthesis of  $\alpha,\alpha$ -dibromoacetophenones from aromatic alkynes under the optimized reaction condition.<sup>13</sup> Generally, the corresponding  $\alpha,\alpha$ -dibromoacetophenones are obtained in good

**Scheme 2.** Study of reaction mechanism.



**Scheme 3.** Plausible path of aerobic photo-oxidative synthesis of  $\alpha,\alpha$ -dibromoacetophenones.

yields regardless of an electron-donating or electron-withdrawing group on the benzene ring (entries 1–6). Interestingly, methyl groups on benzene ring are inert under the oxidation condition (entry 4).<sup>12b,c</sup> Disubstituted aromatic alkynes, such as 1-phenyl-1-propyne and 1-phenyl-1-hexyne produce the corresponding  $\alpha,\alpha$ -dibromoketones in good yields (entries 7 and 8). Moreover, 2-ethynylpyridine, a heterocyclic compound, is also converted to the corresponding  $\alpha,\alpha$ -dibromoketones in modest yield (entry 9). Aliphatic alkyne, such as 1-decyne, affords the corresponding  $\alpha,\alpha$ -dibromoketone with a low yield when EtOAc is used as a solvent (entry 10).

To clarify the reaction mechanism, aerobic photo-oxidations of phenacyl bromide (**3**) in the presence of 1 equiv of 48% aq HBr or Br<sub>2</sub> were examined, and the desired  $\alpha,\alpha$ -dibromoacetophenone (**2**) was obtained in low yield or not detected, respectively, (Scheme 2). These results suggest that phenacyl bromide (**3**) is not a direct intermediate in this reaction. Furthermore, the reaction of  $\beta$ -bromostyrene (**4**) under the same conditions afforded **2** in 29% yield (Scheme 2). In addition, we infer that the yellow color of the reaction mixture indicates the formation of bromine in the reaction.

Scheme 3 shows a plausible path of this oxidation, which is postulated by considering all the results mentioned above and the necessity of molecular oxygen and continuous irradiation in this reaction. We assume that the vinyl radical species **5** is generated by the addition of bromine radical to aromatic alkynes. The bromine radical is formed under the irradiation of visible light from bromine generated by aerobic photo-oxidation of the HBr. Positive evidence remains elusive; however, we think there are two paths (path a and b) which involve the formation of both peroxy radical species **6** and  $\beta$ -bromostyrene (**4**). Peroxy radical species **6** abstracts the hydrogen from HBr or solvent, and hydroperoxide **7** is reduced by HBr to provide bromoenol **8**. Finally, molecular bromine traps **8** to afford  $\alpha,\alpha$ -dibromoacetophenone (**2**) (path a). On the other hand, benzyl radical species **9** is generated by the addition of bromine radical to  $\beta$ -bromostyrene (**4**). The radical species **9** traps molecular oxygen to afford hydroperoxide **11** via peroxy radical species **10**. Finally, dehydration of **11** affords  $\alpha,\alpha$ -dibromo-

acetophenone (path b). We think that this reaction mainly proceeds through path a, since  $\alpha,\alpha$ -dibromoacetophenone (**2**) was produced only in 29% yield when using  $\beta$ -bromostyrene (**4**) as the substrate (Scheme 2).

In conclusion, we have developed the aerobic photo-oxidative syntheses of  $\alpha,\alpha$ -dibromoacetophenones in the presence of 48% aq HBr. This method is advantageous from the viewpoint of green chemistry and organic synthesis due to using inexpensive bromine sources, harmless visible light irradiated from a general purpose fluorescent lamp, and molecular oxygen. Further application of this photo-oxidation to other reactions is now in progress in our laboratory.

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- Typical procedure*: A solution of phenylacetylene (**1**, 0.3 mmol), 48% aq HBr (0.63 mmol), and H<sub>2</sub>O (50  $\mu$ L) in dry MeCN (5 mL) in a pyrex test tube, purged with an O<sub>2</sub>-balloon, was stirred and irradiated externally with four 22 W fluorescent lamps for 10 h. The reaction mixture was washed with aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and brine, and concentrated in vacuo. Purification of the crude product by PTLC (toluene) provided  $\alpha,\alpha$ -dibromoacetophenone (*R*<sub>f</sub> = 0.70, 70.1 mg, 84%).