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One-pot syntheses of α,α -dibromoacetophenones from aromatic alkenes with 1,3-dibromo-5,5-dimethylhydantoin

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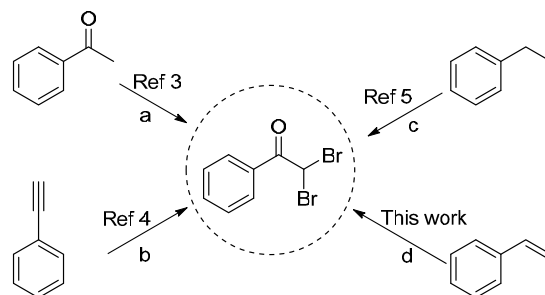
Keywords: α,α -Dibromoacetophenone; 1,3-Dibromo-5,5-dimethylhydantoin; One-pot synthesis; Oxidative bromination; Alkene

Abstract: A novel method for the preparation of α,α -dibromoacetophenones from aromatic alkenes was reported. This procedure was mediated by 1,3-dibromo-5,5-dimethylhydantoin, which served as bifunctional reagent, proceeding oxidation and bromination in one-pot.

α,α -Dibromoacetophenones are versatile intermediates used for the preparations of natural products and pharmaceuticals.¹ These compounds are regarded as superior alternatives to α -bromoacetophenones in heterocycles synthesis because of their high reactivity, non-lachrymatory nature, and convenient preparation from diverse starting materials.² Pioneered by Parkinson's work a century ago, the most known methods for preparing α,α -dibromoacetophenones are based on bromination of acetophenones with molecular bromine,^{3a} or other bromine source such as thionyl bromide,^{3b} hexabromocyclopentadiene,^{3c} benzyltrimethylammonium tribromide,^{3d} dioxane-dibromide,^{3e} and $\text{H}_2\text{O}_2\text{-HBr}$ ^{3f} (Scheme 1a). In the past decades, oxidative bromination of alkynes has attracted attention because it installs two versatile handles simultaneously for further structural elaboration (Scheme 1b).⁴ Recently, Itoh and co-workers⁵ developed a tandem oxidation/bromination of ethyl aromatics to α,α -dibromoacetophenones with molecular oxygen under visible light irradiation (Scheme 1c). Although significant progresses have been made in this field, many of the known strategies suffer from one or more limitations, such as expensive reagents, poor yields, toxic chemicals, or the use of heavy metals. Therefore, the development of new, mild, and economic approaches to α,α -dibromoacetophenones is still highly desired.

1,3-Dibromo-5,5-dimethylhydantoin (DBH) is a cheap bulk chemical widely used as disinfection agents and bleaching agents in industrial and domestic water treatment.⁶ This environmental benign reagent is usually utilized as bromine source in the bromination of alkenes, alkynes, and aromatic C-H bonds.⁷ DBH is also known as a good oxidant in the preparation of ketones from secondary alcohols and disulfides from thiols.⁸ Very recently, we reported that DBH could be served as a bifunctional reagent (oxidative bromination) in one-pot syntheses of α -bromo/amino ketones from alkenes.⁹ In the course of further study of these reactions, we also found that DBH

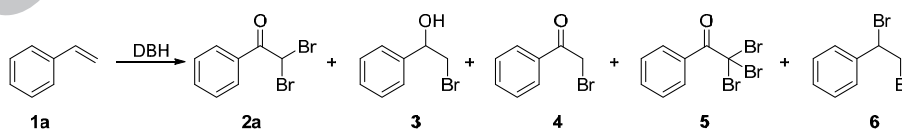
was efficient for converting aromatic alkenes to corresponding α,α -bromoketones by tuning reaction conditions. To the best of our knowledge, such conversions have not been reported so far (Scheme 1d).



Scheme 1. Strategies for synthesis of α,α -dibromoacetophenones.

Initially, we conducted the reaction by using styrene as a test substrate (Table 1). Low reaction temperature was invalid to the desired transformation, leaving mainly the unconsumed intermediates **3** and **4** (Table 1, entries 1-4). Heating the reaction mixture to 80 °C and stirred for 9 h gave dibromoketone **2a** in good yield, along with some over-brominated tribromoketone **5** (Table 1, entries 5-6). However, lots of the intermediate monobromoketone **4** remained and was isolated when the reaction was quenched after stirring at this temperature for 2 h (Table 1, entries 7-8). On the other hand, it also indicated that the desired oxidative bromination is more effective when performed in DME-H₂O than in dioxane-H₂O (Table 1, entry 7 vs 8). Similar results were also observed at low temperature (Table 1, entry 3 vs 4). The former gave 83% yield of monobromoketone **4**, while the later gave only 36% of this intermediate along with 40% unoxidated alcohol **3**. Thus the mixed solvent of DME-H₂O was adopted, in which the desired product **2a** was afforded in 69% yield after 4 h (Table 1, entry 9). Reducing the loading of DBH from 3.0 to 2.0 equiv. gave very low yield of **2a**; while when 4.0 equiv. of DBH was loaded, the yield increased slightly only (Table 1, entries 10-11). Interestingly, appropriate amount of water was beneficial to improving the yield of **2a** (Table 1, entry 12 vs 11), but too much water retarded the further brominating of monobromoketone **4** to dibromoketone **2a** (Table 1, entries 13-14).

Table 1 Study of reaction conditions utilizing styrene as a model substrate^a



Entry	DBH (eq.)	Solvent	Temp (°C)	Time (h)	Yield ^b (%)				
					2a	3	4	5	6
1	3.0	DME/H ₂ O=10/1	25	16	3	38	30	/ ^c	8
2	3.0	Dioxane/H ₂ O=10/1	25	16	/	40	29	/	10
3	3.0	DME/H ₂ O=10/1	40	12	4	/	83	/	6
4	3.0	Dioxane/H ₂ O=10/1	40	12	3	40	36	/	10
5	3.0	DME/H ₂ O=10/1	80	9	65	/	17	5	5

6	3.0	Dioxane/H ₂ O=10/1	80	9	63	/	22	5	5
7	3.0	DME/H ₂ O=10/1	80	2	54	/	24	/	7
8	3.0	Dioxane/H ₂ O=10/1	80	2	11	/	73	/	6
9	3.0	DME/H ₂ O=10/1	80	4	69	/	20	/	7
10	2.0	DME/H ₂ O=10/1	80	8	21	/	51	/	7
11	4.0	DME/H ₂ O=10/1	80	4	71	/	7	13	6
12	3.0	DME/H ₂ O=4.5/1	80	4	87	/	3	/	/
13	3.0	DME/H ₂ O=2.5/1	80	4	37	/	59	/	/
14	3.0	H ₂ O (with 1% tween-80)	80	4	45	/	40	/	/


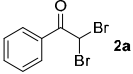

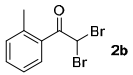
^a Performed with 0.5 mmol of styrene (**1a**) in 1.5 mL of solvent.


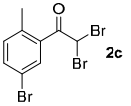
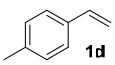
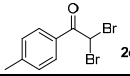
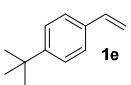
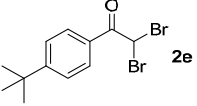
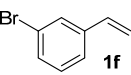
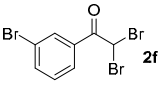
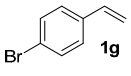
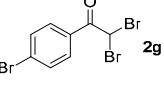
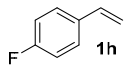
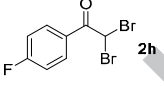
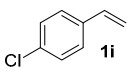
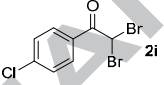

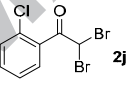
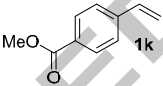
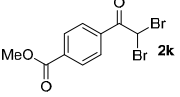
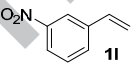
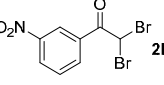
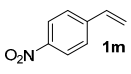
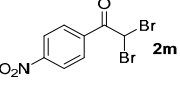

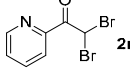
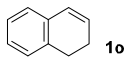
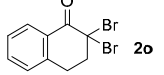
^b Isolated yield by PTLC.

^c “/” means not observed or only trace by TLC but could not be isolated by PTLC.

Having established the optimal reaction conditions, we then examined the generality of this DBH mediated one-pot oxidative bromination. As shown in Table 2, most α,α -dibromoacetophenones are obtained in good yields regardless of an electron-withdrawing or donating group on the benzene ring. Note that *o*-methyl styrene (**1b**) was sensitive to temperature. Standard protocol gave α,α -dibromoacetophenone with additional bromination of the benzene ring (**2c**, Table 2, entry 3). When performed at lower temperature, desired α,α -dibromoacetophenone **2b** was obtained in the yield of 57%, leaving the benzene ring intact (Table 2, entry 2). Br, F, and Cl substituents on the phenyl ring were well tolerated, which enable potential applications in further coupling (Table 2, entries 6-10). Ester and nitro groups were also compatible, albeit with moderate yields (Table 2, entries 11-13). Furthermore, 2-vinylpyridine (**1n**) and internal styrene derivative 1,2-dihydronaphthalene (**1o**) were transformed to corresponding α,α -dibromoketones smoothly in satisfactory yields (Table 2, entries 14-15).

Table 2. One-pot oxidative bromination of aromatic alkenes mediated by DBH.

Entry	Substrate	Product	Isolated yield (%)
1			87
2 ^a			57

3 ^b			73
4			80
5			91
6			81
7			76
8			83
9			78
10 ^c			38
11			52
12			33
13			49
14			63
15			74

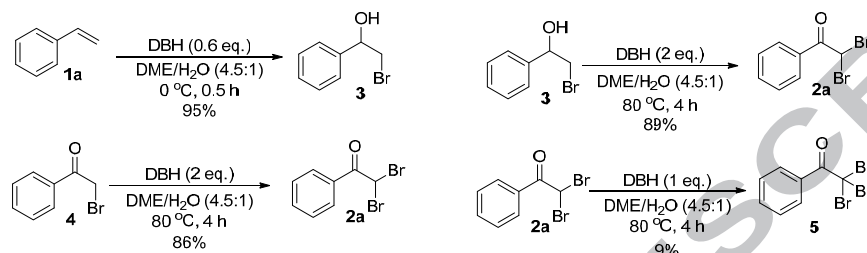
^a Carried out at 70 °C for 4 h.

^b Carried out at 80 °C for 5 h.

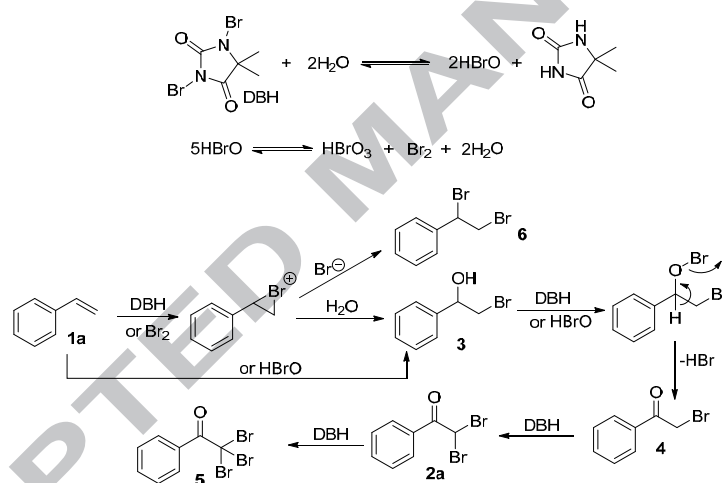
^c Carried out at 75 °C for 2.5 h.

To probe the mechanism of the reactions, some information has been gathered. As presented in Table 1, all the TLC detectable products were isolated and subjected to

NMR analysis. Furthermore, we also performed some control experiments, as shown in Scheme 2. Based on these results mentioned above and related reports,¹⁰ a plausible mechanism is proposed in Scheme 3. The reaction was initiated by the release of active specie HBrO when DBH was dissolved in water.¹¹ Both alcohol **3** and dibromide **6** were generated via three-membered cyclic bromonium ion intermediate. The former bromohydrin then converted to hypobromite intermediate, which cleaves one molecular of HBr to give α -bromoketone **4**. Further bromination of **4** gave desired α,α -dibromoketone **2a** and over-brominated product **5**, respectively.



Scheme 2. Control experiments.



Scheme 3. Plausible reaction mechanism.

In summary, we have developed a convenient procedure for the synthesis of α,α -dibromoacetophenones mediated by DBH. This easy-to-handle and metal-free one-pot protocol has established a new bridge between aromatic alkenes and α,α -dibromoacetophenones. More explorations of DBH promoted reactions are ongoing in our laboratory and will be reported in due course.

Acknowledgments

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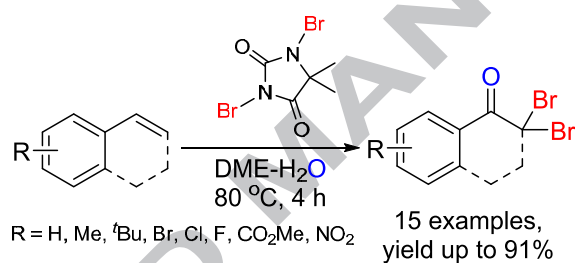
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High lights:

- First report for the preparation of α,α -dibromoacetophenones from aromatic alkenes.
- Readily available starting materials, metal-free and easy to handle procedures.
- One-pot oxidative bromination mediated by bifunctional reagent 1,3-dibromo-5,5-dimethylhydantoin.