ORGANIC
LETTERS

2012
Vol. 14, No. 9
2414–2417

Direct and Selective Benzylic Oxidation of Alkylarenes via C−H Abstraction Using Alkali Metal Bromides

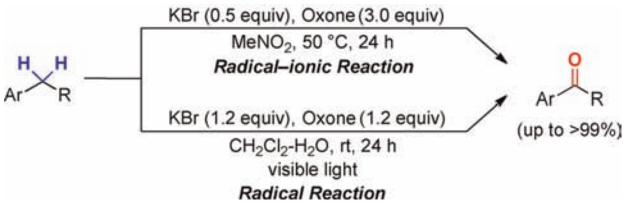
Katsuhiko Moriyama,* Misato Takemura, and Hideo Togo*

Graduate School of Science, Chiba University, Yayoi-cho 1-33, Inage-ku,
Chiba 263-8522, Japan

moriyama@faculty.chiba-u.jp; togo@faculty.chiba-u.jp

Received April 4, 2012

ABSTRACT



A direct benzylic oxidation of alkylarenes via C−H bond abstraction was developed using alkali metal bromides and oxidants under mild conditions. This reaction proceeded with excellent selectivity by thermal oxidation or photooxidation to provide a broad range of carbonyl compounds containing electron-deficient aryl carbonyl compounds in high yields.

The direct C−H bond functionalization of hydrocarbons via C−H bond activation for organic synthesis has attracted much interest in recent years.[1] In particular, chemoselective functionalization under metal-free conditions, which is one of the requirements for the realization of green chemical processes, remains a tremendous challenge in organic chemistry. As a representative C−H bond functionalization process, the direct benzylic oxidation of alkylarenes is an important protocol to provide the corresponding carbonyl compounds for use as versatile building blocks in the production of functional chemicals and pharmaceuticals.[2]

Numerous methods have been developed for the direct benzylic oxidation of alkylarenes using heavy metals. A stoichiometric amount of metal reagents, such as Cr(VI)[3] and $KMnO_4$,[4] had been required as oxidative reagents in conventional methods. The heavy metal catalyzed benzylic oxidation was also accomplished using Mn,[5] Fe,[6] Co,[7] Ru,[8] Rh,[9] Bi,[10] and Au[11] catalysts with an excess amount of oxidant. Metal-free reactions using an organocatalyst[12] and a stoichiometric amount of hypervalent iodine[13] have been developed as sustainable oxidation methods. However, in most cases, alkylarenes bearing an electron-withdrawing group on the aryl or alkyl moiety, whose C−H bond at the benzylic position is more inert, could not be used for the direct

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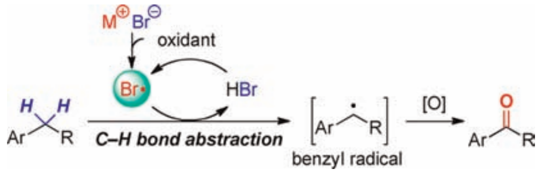
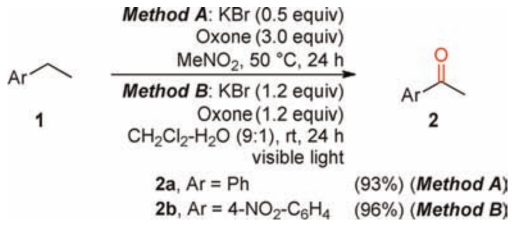
oxidation with a combination of HBr and H_2O_2 has also been reported,[14] it is impractical to use only a limited number of substrates because this leads to the noticeably low yield and low selectivity of the desired products. We recently found that the activated bromonium-like species obtained by the oxidative umpolung of alkali metal bromides with Oxone could efficiently promote the bromoamination of *N*-alkenyl sulfonamides without producing the corresponding organic waste.[15] We report here a heavy metal-free direct and selective benzylic oxidation of alkylarenes via C−H abstraction using an alkali metal bromide/oxidant system, focused toward meeting the goals of green chemistry (Scheme 1). This oxidation efficiently proceeded through different reaction pathways under thermal conditions in polar solvent and photochemical conditions in halogenated solvents.

Scheme 1. Direct Benzylic Oxidation by Generation of Bromoradical from Metal Bromides

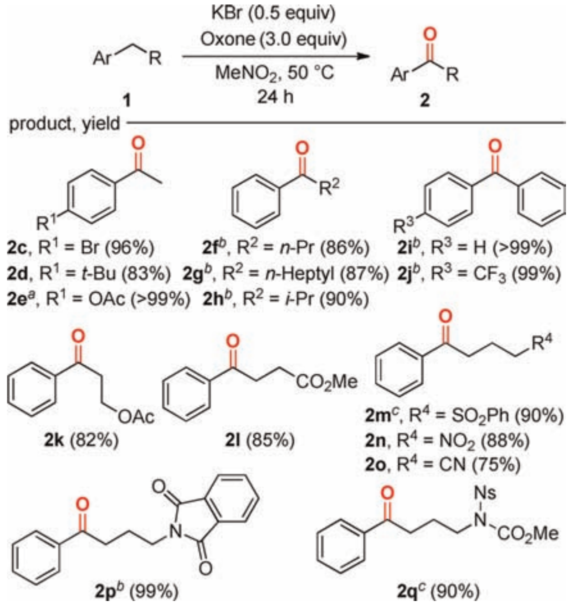


First, we screened a series of bromo reagents, oxidants, and solvent for direct benzilic oxidation of alkylarenes (**1a** and **1b**) (Table S1 in the Supporting Information). The optimum reactions were found to involve **1a**, KBr (0.5 equiv), and Oxone (3.0 equiv) in $MeNO_2$ at 50 °C (Method A), and **1b**, KBr (1.2 equiv), and Oxone (3.0 equiv) in a mixture of CH_2Cl_2 and H_2O at room temperature under visible light irradiation (Method B) (Scheme 2).

Scheme 2. Direct Benzylic Oxidation of Alkylarenes **1a** and **1b**



Scheme 3. Thermal Direct Benzylic Oxidation of Alkylarenes **1** (Method A)



[a] Reaction was carried out with KBr (1.2 equiv). [b] Reaction was carried out at room temperature. [c] Reaction was carried out at 40 °C.

To explore the scope of the direct benzylic oxidation, various alkylarenes **1** were examined using alkali metal bromides under optimized Method A conditions (Scheme 3). When *p*-substituted alkylarenes bearing Br (**1c**), *t*-Bu (**1d**), and AcO (**1e**) were used, oxidative products **2c**, **2d**, and **2e** were obtained in good yields (83−>99%). The reaction of *n*-butylbenzene (**1f**), *n*-octylbenzene (**1g**), and isobutylbenzene (**1h**) gave corresponding ketones **2f**, **2g**, and **2h** in 86%, 87%, and 90% yields, respectively. Diarylmethanes (**1i** and **1j**) were also efficiently converted into diarylketones (**2i** and **2j**) in quantitative yields, respectively. Furthermore, various alkylarenes bearing functional groups, such as ester (**1k** and **1l**), sulfonyl (**1m**), nitro (**1n**), nitrile (**1o**), and imide (**1p** and **1q**), provided desired products **2k**−**2q** in high yields (75−99%), respectively.

To our surprise, photooxidation (Method B) was much more effective than thermal oxidation (Method A) for the direct benzylic oxidation of alkylarenes **1** bearing an electron-withdrawing group (Table S1 in the Supporting Information). Next, we investigated the photochemical direct benzylic oxidation of alkylarenes using alkali metal bromides under the optimized Method B conditions

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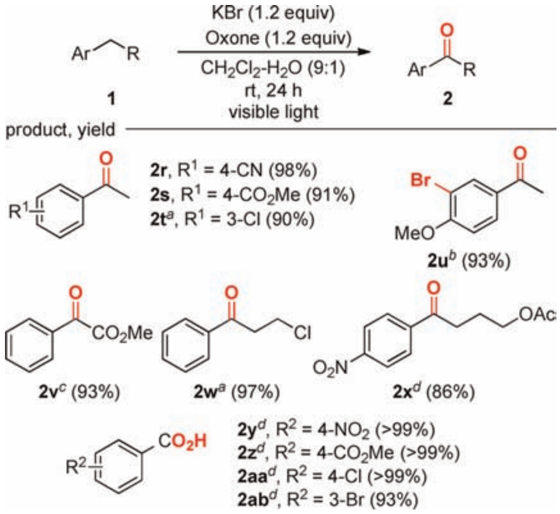
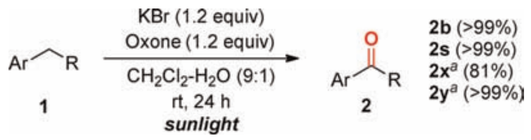
(Scheme 4). Treatment of ethylarenes bearing 4-CN (**1r**), 4-CO_2Me (**1s**), and 3-Cl (**1t**) at the aryl group gave corresponding products (**2r**−**2t**) in excellent yields (90−98%), respectively. When 4-methoxyethylbenzene (**1u**) was used, the concurrently brominated product **2u** was obtained in 93% yield. Alkylarenes containing a functional group, such as methyl ester (**1v**) and Cl (**1w**), were efficiently oxidized to the desired products (**2v** and **2w**) in high yields, respectively. 4-(4′-Nitrophenyl)butyl acetate (**1x**) also provided the oxidative product (**2x**) in 86% yield. Moreover, the reaction of methylarenes (**1y**−**1ab**) with twice the amounts of KBr and Oxone provided carboxylic acids (**2y**−**2ab**) in excellent yields (93−>99%). Importantly, when the photooxidation of **1b**, **1s**, **1x**, and **1y** was carried out under natural sunlight at ambient temperature, the desired products **2b**, **2s**, **2x**, and **2y** were obtained in excellect yields (Scheme 5). The use of natural sunlight for organic synthesis is an energy-saving methodology.

Scheme 4. Photochemical Direct Benzylic Oxidation of Alkylarenes **1** (Method B)



[a] Reaction was carried out in a mixture of CH_2Cl_2 and H_2O (19:1) (3 mL). [b] Reaction was carried out with KBr (2.5 equiv) and Oxone (2.5 equiv) in a mixture of CH_2Cl_2 and H_2O (1:1). [c] Reaction was carried out with KBr (2.0 equiv) and Oxone (2.0 equiv) in a mixture of CH_2Cl_2 and H_2O (19:1) (3 mL) under O_2. [d] Reaction was carried out with KBr (2.0 equiv) and Oxone (2.0 equiv).

Scheme 5. Direct Benzylic Oxidation under Natural Sunlight



[a] Reaction was carried out with KBr (2.0 equiv) and Oxone (2.0 equiv).

We carried out comparative experiments using alkylarenes (**1a**−**1ab**) under thermal oxidation conditions and photooxidation conditions (Table S2 in the Supporting Information). Whereas the direct oxidation of diarylmethanes (**1i** and **1j**) proceeded under both sets of conditions, the photooxidation of *p*-substituted ethylbenzenes (**1c**−**1e**) and alkylbenzenes bearing functional groups (**1k**−**1q**) was much less selective than the thermal oxidation to provide α-bromoketones (**3**) as the byproduct. In particular, the reaction of **1** bearing a large alkyl group (**1f**−**1h**) furnished **3** and α-bromoalkylarenes (**4**) as the major products together with **2** in low yields (8−13%). In contrast, when alkylarenes bearing an electron-withdrawing group (**1r**−**1t** and **1v**−**1ab**) were treated with KBr and Oxone under Method A conditions, the corresponding carbonyl compounds were not obtained and compound **4** was formed in approximately 50% yields (36−49%), respectively.

In order to elucidate the mechanism of the present direct benzylic oxidation, various supporting experiments were conducted and the results indicated the following: (i) the use of a galvinoxyl free radical for the direct oxidation of alkylarenes completely disrupted both reactions (Method A and Method B); (ii) inadequate thermal oxidation (Method A) induced the formation of **4** and α-hydroxyalkylarene, whereas inadequate photooxidation (Method B) induced the formation of **4** and α,α′-dibromoalkylarene (**5**);[16] (iii) thermal oxidation of **4a** with Oxone alone gave ketones (**2a** and **3a**) in high yield. The same reaction under dark conditions also proceeded to provide **2a** and **3a** with complete consumption of **4a** (Scheme 6, eq 1). (iv) The photooxidation of **4b** with a catalytic amount of KBr (0.2 equiv) and Oxone provided desired ketone **2b** in high yield, whereas the photooxidation of **4b** with Oxone alone did not proceed (Scheme 6, eq 2). The KBr-catalyzed reaction of **4b** with Oxone under dark conditions generated a trace amount of ketone together with the recovery of **4b** in 98% yield. (v) Treatment of α,α′-dibromo-4-nitroethylbenzene (**5b**) in a mixture of CH_2Cl_2 and H_2O under visible light irradiation conditions smoothly promoted the hydrolysis to generate **2b** in 98% yield (Scheme 6, eq 3).

Based on these results, we suggest that direct benzylic oxidation using alkali metal bromides undergoes an ionic reaction with Method A and a radical reaction with Method B after generation of the benzylic radical by oxidative C−H abstraction.

A plausible mechanism for the direct benzylic oxidation of alkylarenes with alkali metal bromides is depicted in Scheme 7. In the first step of this reaction, both reactions involve the oxidation of KBr with Oxone to generate a

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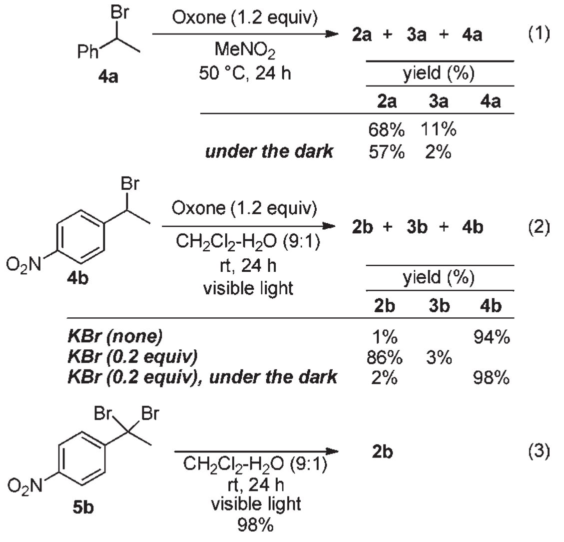
(16) Treatment of **1c** with KBr (0.5 equiv) and Oxone (3.0 equiv) in $MeNO_2$ at 50 °C for 3 h gave **2c** (16%), **4c** (16%), and 4-bromo-α-methylbenzylalcohol (11%), together with the recovery of **1c** (32%). Reaction of **4c** in a mixture of $MeNO_2$ and H_2O (9:1) at 50 °C for 24 h provided 4-bromo-α-methylbenzylalcohol (5%) and 4-bromostyrene (6%), together with the recovery of **4c** in 89% yield. On the other hand, when **1b** was treated with KBr (1.2 equiv) and Oxone (1.2 equiv) in a mixture of CH_2Cl_2 and H_2O (9:1) at room temperature under visible light irradiation for 3 h, **2b**, **4b**, and **5b** were produced in 26%, 58%, and 10% yield, respectively.

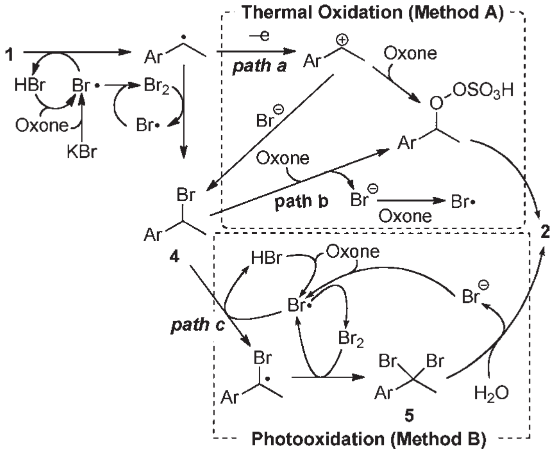
Scheme 6. Mechanistic Study of Direct Benzylic Oxidation



bromo radical in situ. This is followed by C–H hydrogen-atom abstraction at the benzyl position by the bromo radical. The benzyl radical generates a benzyl cation via the one-electron oxidation with Oxone (path a) or an α-bromoalkylarene (**4**) through carbon–bromine bond formation with bromine. A benzylic peroxysulfate intermediate is formed not only by the combination of the benzyl cation with Oxone but also by the nucleophilic substitution of **4** with Oxone (path b) in polar solvent. Subsequently, oxidative β-cleavage of the benzylic peroxysulfate intermediate occurs to provide ketones **2** (Method A). In contrast, the photooxidation of **4** by a bromo radical induces the second benzylic hydrogen-atom abstraction to generate an α-bromobenzylic radical (path c), followed by the construction of an α,α′-dibromoalkylarene (**5**) via bromination with bromine. The hydrolysis of formed **5** smoothly occurs to produce ketone **2** (Method B).

In conclusion, we have developed a direct benzylic oxidation of alkylarenes via benzylic C–H abstraction using the oxidation of alkali metal bromides without heavy metals. This selective oxidation crucially shows that it proceeds through thermal oxidation or photooxidation depending on the substituents of the alkylarenes to give corresponding carbonyl compounds. This method is an environmental sustainability strategy for organic synthesis as it does not require heavy metals or organic reagents under mild conditions. We have high hopes that oxidative C–H abstraction using alkali metal bromides would be applicable to fine organic synthesis.

Scheme 7. Plausible Reaction Mechanism



Acknowledgment. Financial support in the form of a Grant-in-Aid for Scientific Research (No. 24750033) from the Ministry of Education, Culture, Sports, Science and Technology in Japan (K.M.), the Iodine Research Project in Chiba University, and the Eisai Award in Synthetic Organic Chemistry, Japan (K.M.) is gratefully acknowledged.

Supporting Information Available. Experimental procedures, spectral data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.