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Metal-free, visible-light photoredox catalysis: transformation of arylmethyl bromides to alcohols and aldehydes†

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A mild, simple, and controllable metal-free photocatalytic system for the transformation of arylmethyl bromides to corresponding alcohols and aldehydes in high yields with visible-light irradiation has been achieved. Eosin Y was found to be an efficient promoter for this oxidative dehalogenation reaction under photo irradiation conditions.

Benzyl halides are versatile intermediates in organic synthesis¹ and they can be utilized as starting materials in the preparation of alcohols and aldehydes.² Although there are many methods that have been developed for the transformation of arylmethyl halides to the corresponding alcohols and the oxidation of arylmethyl alcohols to the corresponding aldehydes, some fatal problems such as drastic conditions or environmentally detrimental heavy metals still remain.³ As a result, considerable effort has been directed towards the development of mild and efficient methods for preparation of benzyl alcohols and corresponding aldehydes from benzyl halides.

Sunlight is an important, abundant, clean, and renewable energy source. Visible light accounts for 43% of the incoming solar radiation, and therefore many chemical transformations have been developed with visible light to meet the challenge of environmental sustainability.⁴ Many visible-light photoredox catalysts such as ruthenium or iridium polypyridyl complexes have been used to solve the problem of visible light absorption efficiency.⁵ The groups of Yoon,⁶ MacMillan,⁷ Stephenson⁸ and others⁹ have demonstrated the ability of photoredox catalysts such as Ru(bpy)₃Cl₂, and [Ir(bpy)₂(dtbbpy)]PF₆. Notably, such photocatalysts were utilized to functionalize C–H bonds and reduce activated C–Br bonds to afford intra- and intermolecular

radical reactions. Recently, Jiao described a Ru(bpy)₃Cl₂ and pyridine-cocatalyzed utilization of sunlight and air in the aerobic oxidation of benzyl halides to corresponding carbonyl compounds¹⁰ (Scheme 1). However, photoredox metal-catalysts are toxic and expensive. In 2001, Itoh's group developed an oxidative transformation of arylmethyl bromides to corresponding alcohols and aldehydes with a combination of alkali iodides under photoirradiation conditions¹¹ (Scheme 1).

On the other hand, because of their inexpensive and environmentally friendly nature, organic dyes, such as Eosin Y, would be an appropriate alternative to metal photocatalysts.¹² To explore the application of photocatalysts and to overcome the drawbacks of the above-mentioned transformation methods, herein we report the controllable transformation of benzylic bromides to the corresponding alcohols and benzaldehydes using Eosin Y as a photocatalyst with visible-light irradiation under mild conditions (Scheme 1).

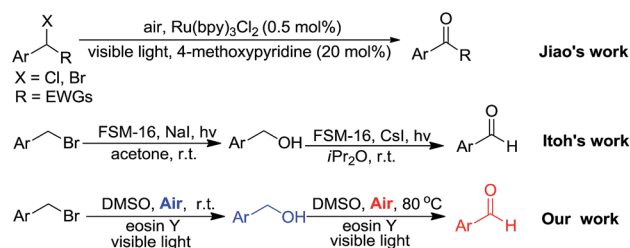
We initiated our investigations using 3-nitrobenzyl bromide (**1a**) as the model substrate. We tested various reaction conditions for the transformation of 3-nitrobenzyl bromide to the corresponding alcohol and aldehyde (Table 1). First, 3-nitrobenzyl bromide was dissolved in DMSO without catalyst at room temperature for 12 hours under fluorescent bulb irradiation and no products **2a** or **3a** were obtained (entry 1, Table 1). Then 5 mol% of Eosin Y was employed; the reaction occurred to afford **2a** in 92% yield in 12 hours (entry 2, Table 1). The

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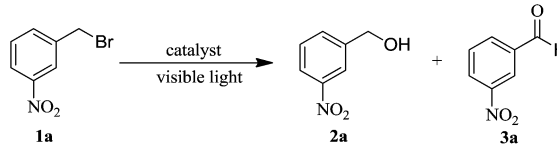
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Scheme 1 Transformation of arylmethyl bromides to alcohols and aldehydes.

Table 1 Optimization of the model reaction^a


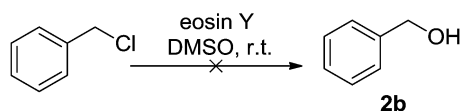
Entry	Catalyst	T (°C)	Solvent	Yield ^b (%) 2a/3a
1	—	25	DMSO	—
2	Eosin Y	25	DMSO	92/6
3 ^c	Eosin Y	25	DMSO	—
4 ^d	Eosin Y	25	DMSO	5/0
5	Eosin Y	25	H ₂ O	2/0
6	Eosin Y	25	DMF	—
7	Eosin Y	25	DMA	—
8	Eosin Y	25	NMP	Trace/—
9	Eosin Y	25	CH ₃ CN	4/0
10	Eosin Y	25	DME	—
11 ^e	Eosin Y	25	DMSO	81/15
12 ^f	Eosin Y	25	DMSO	78/20
13	Eosin Y	40	DMSO	12/56
14	Eosin Y	80	DMSO	11/85

^a 3-Nitrobenzyl bromide **1a** (0.5 mmol) in solvent (1 mL) was mixed with 5 mol% of catalyst at r.t. for 12 hours. ^b GC yields. ^c Proceeded without visible light. ^d Proceeded under Ar atmosphere. ^e Stirred for 24 hours. ^f Stirred for 48 hours.

reaction did not proceed at all without the radiation of visible light (entry 3, Table 1). Next we carried out the reaction under Ar atmosphere and only 5% yield of **2a** was found, meaning that O₂ is essential for the reaction process. Further studies were thus carried out regarding the influence of different solvents, such as H₂O, DMF, DMA, NMP, and CH₃CN. It is interesting that 4% to 0% yields were detected with GC-MS (entries 5–10, Table 1). Moreover, when prolonging the reaction time, the yield of 3-nitrobenzyl alcohol was promoted. Gratifyingly, the yield of the corresponding aldehyde increased to 85% after 12 hours when the temperature was increased from 25 °C to 80 °C (entry 14, Table 1).

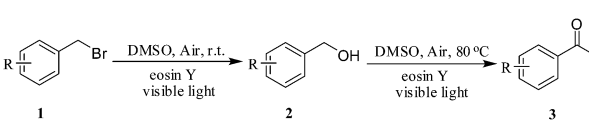
It is noteworthy that (chloromethyl)benzene could not transform into the desired product. When (chloromethyl)benzene was utilized under standard conditions, no desired product **2b** was observed (Scheme 2).

After screening of various catalysts, reaction temperatures and solvents, it can be concluded that the optimized reaction conditions are as follows: benzylic bromides in DMSO is reacted under fluorescent bulb irradiation with 5 mol% Eosin Y at 25 °C for preparation of benzylalcohols and higher temperature for benzaldehydes.



Scheme 2 Transformation of (chloromethyl)benzene to alcohols.

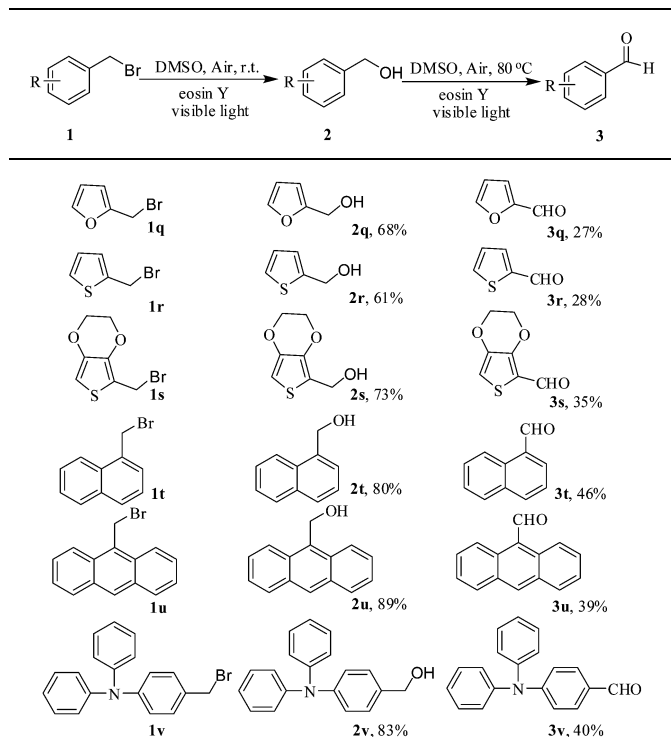
With the optimized reaction conditions in hand, we probed the scope of benzylic bromides. The results are summarized in Table 2. The reaction scope was subsequently explored by using various benzylic bromides; the substrates bearing an electron-withdrawing group on benzene ring **1e–1f** resulted in better yields than those bearing an electron-donating group **1h–1i**. Likewise, *meta*-substituted substrates posed no problem in this reaction, as exemplified by *m*-fluorine product **2l** and *m*-nitro product **2a**. Steric bulk in the *ortho*-position was very well tolerated, as demonstrated by the substrates **1m–1p** to yield highly congested products **2m–2p**. Furthermore, all of the above reactions smoothly proceeded to give benzaldehydes **3** in moderate yields at 80 °C in 12 hours.

Table 2 Transformation of arylmethyl bromides to alcohols and aldehydes^{a,b,c}


2b , 85%	3b , 51%	2j , 59%	3j , 32%
2c , 88%	3c , 37%	2k , 81%	3k , 31%
2d , 81%	3d , 53%	2l , 89%	3l , 35%
2e , 78%	3e , 54%	2m , 87%	3m , 53%
2f , 91%	3f , 67%	2n , 90%	3n , 47%
2g , 76%	3g , 37%	2o , 85%	3o , 67%
2h , 76%	3h , 40%	2p , 80%	3p , 36%
2i , 69%	3i , 32%		

^a Standard conditions: arylmethyl bromides (**1**) (0.5 mmol) in DMSO (1 mL) were mixed with 5 mol% of Eosin Y at r.t. for 12 hours to give alcohols (**2**); the mixture was stirred at 80 °C overnight to give aldehydes (**3**). ^b Isolated yields. ^c Representative procedure: under air atmosphere, arylmethyl bromides (**1**) (0.5 mmol) in DMSO (1 mL) were mixed with 5 mol% of Eosin Y under 24 W fluorescent bulb irradiation at r.t./80 °C for 12/24 hours, H₂O (2 mL) and CH₂Cl₂ (5 mL) were added to the reaction mixture separately, the water phase was extracted with CH₂Cl₂ (5 mL × 3), the organic layer was combined and concentrated, and the residue was purified by column chromatography (SiO₂, petroleum ether–ethyl acetate = 10 : 1–4 : 1) to give the corresponding alcohols or aldehydes.

Table 3 Transformation of arylmethyl bromides to alcohols and aldehydes^{a,b}



^a Standard conditions. ^b Isolated yields.

Encouraged by the results above, we then extended the substrate to heterocyclic and fused rings using the Eosin Y-catalyzed system shown in Table 3.

It can be seen that the heterocyclic substituted benzylic bromides proved to be viable starting materials; some afforded lower yields, such as 2-furan bromide **1q**, whilst 2-thiophenyl

bromide **1r** and **1s** afforded the desired products in moderate yields (**2q–2s** and **3q–3s**, Table 3). The fused ring substrates also worked well and afforded products **2t** and **2u** in 80% and 89% yields, respectively.

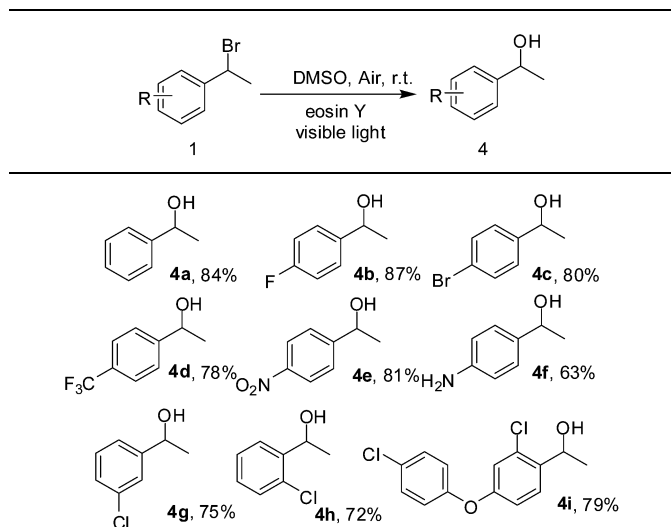
Subsequently, we explored the scope of benzylic bromides under optimized reaction conditions, with substituted (1-bromoethyl)benzene employed as substrates. As shown in Table 4, both electron-rich and electron-deficient groups at different position (*para*-, *meta*-, and *ortho*-position) of (1-bromoethyl)benzenes could be smoothly transformed into the desired products with good yields. A wide range of different groups at the aromatic moiety of (1-bromoethyl)benzenes, such as halogen, trifluoromethyl, nitro and amine, generated the corresponding 1-phenylethanol products **4** in 63–87% yields (Table 4), even for the slightly more complex substrate **4i**.

It was interesting that when (1-bromoethyl)benzene was used, the corresponding product 1-phenylethanol (**4a**) was obtained in 84% yield at room temperature after 12 hours, but if the mixture continued to stir for another 12 hours at 80 °C, 2,2-dihydroxy-1-phenylethanone **5** was collected in 80% yield (Scheme 3).

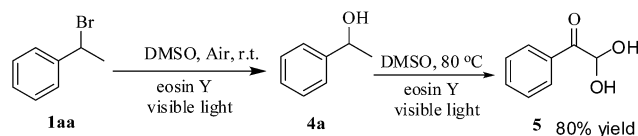
This photocatalyst transformation could serve as a new method for the synthesis of important intermediates for pharmaceutical as well as natural products. Rosuvastatin, a synthetic inhibitor of HMG-CoA reductase which plays a major role in second generation drugs,¹³ was chosen as the target compound.¹⁴ The benzyl bromide intermediate (**6**)¹⁵ was treated under standard conditions, and 82% yield of benzyl alcohol **7** and 31% yield of benzyl aldehyde (**8**) were obtained accordingly (Scheme 4).

In conclusion, a simple and efficient transformation of arylmethyl bromides to the corresponding alcohols and the oxidation of arylmethyl alcohols to the corresponding

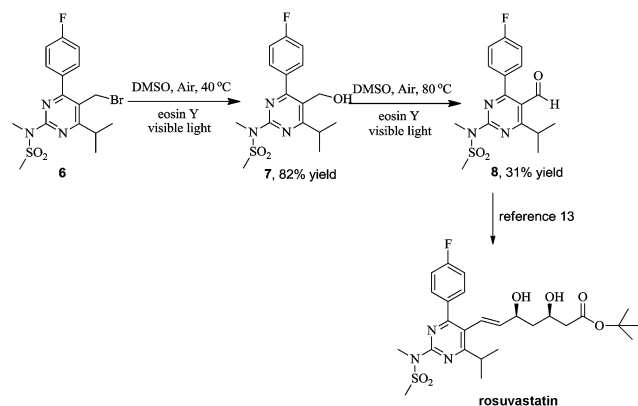
Table 4 Transformation of (1-bromoethyl)benzene aryls to alcohols^{a,b}



^a Standard conditions. ^b Isolated yields.



Scheme 3 Photoredox catalysis of (1-bromoethyl)benzene.



Scheme 4 Synthesis of rosuvastatin using the photocatalyst strategy.

aldehydes has been developed with Eosin Y as the photocatalyst in DMSO. Various benzylic bromides and (1-bromoethyl)benzene (**1**) could perform the reaction under mild reaction conditions, producing alcohols and aldehydes in up to 91% yields. This method could be used in the syntheses of intermediates for pharmaceutical and natural products. Further investigations on the mechanism are currently underway in our lab.

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