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# Electron transfer promoted photochemical reductive radical cyclization reactions of allyl 2-bromoaryl ethers

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## ABSTRACT

Tin-free, photoinduced electron transfer promoted reductive radical cyclization reactions of allyl 2bromoaryl ethers in the presence of NaOH in 2-PrOH were found to take place efficiently to give 3methyl-2,3-dihydrobenzofurans. In contrast to conventional radical cyclization reactions that employ AIBN/Bu<sub>3</sub>SnH in benzene, the new method utilizes NaOH and 2-PrOH that are both readily available and benign. Consequently, the newly developed photochemical process serves as a versatile and environmentally friendly method for carrying out aryl radical cyclization reactions.

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Radical cyclization reactions have become powerful methods for the preparation of cyclic organic compounds.<sup>1</sup> An example of this process is found in the radical cyclization reaction of allyl 2bromophenyl ether that produces 3-methyl-2,3-dihydrobenzofuran in high yield (Scheme 1).<sup>2</sup> Transformations of this type are typically performed using AIBN as a radical initiator agent and Bu<sub>3</sub>SnH as a halogen/hydrogen transfer reagent. However, the overall utility of radical cyclization reactions is limited by the toxicity of these reagents and difficulties associated with the removal of tin containing byproducts. As a result, several recent efforts have focused on developing tin-free radical cyclization processes. These efforts have uncovered conditions that involve the use of LiAlH4,<sup>3</sup> NaBH<sub>4</sub>/methyldihydroacridine and visible light irradiation,<sup>4</sup> N-heterocyclic carbene boranes with thiols,<sup>5</sup> and electrochemical reduction in the presence of phenanthrene.<sup>6</sup> In addition, photoinduced reductive methodologies, employing either the enolate anion of acetone or the anion of ethyl benzoate with 2-propoxide ion (2-PrO<sup>-</sup>),<sup>7</sup> represent highly environmentally-friendly procedures for promoting radical cyclization reaction of allyl 2-bromophenyl ether. However, these processes require the use of both an excess of t-BuOK or sodium metal for anion generation and liquid ammonia as solvent. As a consequence of their synthetic power, simple methods for promoting reductive radical cyclization reactions that do not require toxic or expensive reagents and that can be conducted under a mild condition are desired.

Recently, we reported that Birch-type reductions of arenes and reductive dehalogenations of aryl halides take place under photoinduced electron transfer (PET) conditions in the presence of NaOH and 2-PrOH.<sup>8</sup> In these processes, the excited triplet states of aromatic chromophores participate as acceptors in single electron transfer (SET) processes in which hydroxide or 2-propoxide ions serve as donors. This process generates arene radical anions, which are either protonated to form cyclohexadienyl radicals in the reduction pathway or undergo loss of halide to form aryl radicals in the dehalogenation route. These earlier observations encouraged us to carry out a study to determine whether this mechanistic scenario would operate to promote photoinduced reductive aryl radical cvclization reactions of allyl 2-bromoaryl ethers. The results of an investigation, described below, targeted at evaluating this possibility show that the photochemical method can be used to generate aryl radicals as part of cyclization reactions that take place under mild conditions and employ less toxic and readily available reagents.

In order to probe the feasibility of the photoinduced radical cyclization methodology, 3 mM solutions of various allyl 2-bromoaryl ethers **1** (Table 1) in 2-PrOH containing NaOH (20 mM) under an argon atmosphere at room temperature were irradiated using a 100 W high-pressure mercury lamp and a Pyrex filter ( $\lambda > 280$  nm). In each case, the photolysate was concentrated in vacuo to give a residue that was subjected to column chromatography on silica gel. These reactions generated the respective 3-methyl-2,3-dihy-





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Scheme 1. Conventional radical cyclization reaction of allyl 2-bromophenyl ether using AIBN/Bu<sub>3</sub>SnH in benzene.

#### Table 1

Photocyclization reactions of allyl 2-bromoaryl ethers 1a-e<sup>a</sup>



Entry	1	Irrad. time (h)	Yield of $2^{b}$ (%)
1	<b>1a</b> (3 mM)	5	8 (80) <sup>c</sup>
2	<b>1b</b> (3 mM)	3	71
3	1c (3 mM)	3	60
4	1d (3 mM)	1	5 (85) <sup>c</sup>
5	1e (3 mM)	1	82
6	1e (3 mM)	3	68
7 <sup>d</sup>	1e (3 mM)	1	10
8	<b>1e</b> (5 mM)	1	81
9	<b>1e</b> (10 mM)	1.5	78

<sup>a</sup> Photoreactions of **1** were carried out in 2-PrOH solutions containing 20 mM NaOH under an Ar atmosphere.

<sup>b</sup> Isolated yields.

<sup>c</sup> Yields determined by using GC-MS analysis of the crude photolysates are in parentheses.

<sup>d</sup> Photoreaction was carried out under an air atmosphere.

drobenzofuran derivatives **2** in modestly high isolated yields (entries 1–5), except in the cases of benzofurans **2a** and **2d**, which were produced in low isolated yields. GC–MS analysis of the crude photolysates revealed that **2a** and **2d** are indeed formed in high yields prior to isolation (entries 1 and 4), indicating that their high volatility is responsible for losses incurred in workup and purification steps.

Further studies provided mechanistically and synthetically important information about the new cyclization strategy. Even though the efficiencies of the excitation of the allyl 2-bromoaryl ethers 1 are low in this light source (see Supplementary data for absorption spectra of 1a-e), irradiation is required to promote these reactions. In addition, the irradiation times needed to drive these reactions to completion were found to be dependent on the aryl ring substituent R. Moreover, high yields of 2 were obtained in photoreactions of substrates possessing both electrondonating and withdrawing substituents. For example, irradiation of a 3 mM solution of 1e (R = CN) for 1 h led to formation of 2e in a high isolated yield (entry 5). However, the use of a longer irradiation time (3 h) caused the yield of **2e** to decrease owing to the existence of secondary photoreactions of 2e (entry 6). In fact, irradiation of 2e (3 mM) for 3 h in a NaOH (20 mM) containing 2-PrOH solution followed by workup led to only a 47% yield of recovered **2e** due to the photochemical Birch-type reduction of the aromatic ring of **2e** reported by us.<sup>8</sup>

The results of further investigations showed that the efficiency of the photoreaction of **1e** was significantly suppressed when an air atmosphere was utilized (entry 7), suggesting that

#### Table 2

Base effect on the photocyclization reactions of allyl 2-bromoaryl ether 1e<sup>a</sup>

Entry	Base	Yield of $2e^{b}$ (%)
1	NaOH (1 mM)	14
2	NaOH (3 mM)	61
3	NaOH (10 mM)	78
4	NaOH (20 mM)	82
5	NaOH (50 mM)	73
6	NaOH (100 mM)	70
7	KOH (10 mM)	57
8	LiOH (10 mM)	85
9	<i>n</i> -BuLi (20 mM)	80

 $^{\rm a}\,$  Photoreactions of 2-PrOH solutions of  $1e\,(3\text{ mM})$  containing bases under an Ar atmosphere were carried out for 1 h.

Isolated yields.



Scheme 2. Photoreactions of 3 and 5 with NaOH in 2-PrOH.

the molecular oxygen quenchable triplet state of **1e** is involved in the process. Furthermore, the yields of **2e** were observed to slightly decrease when higher concentrations of **1e** (5 or 10 mM) were employed in the photoreaction (entries 8 and 9).

The effects of base and solvent on the photoreaction of **1e** were examined. The results show that the use of higher concentrations of NaOH caused an increase in the yield of 2e (Table 2, entries 1-4) but that when the concentration of NaOH was greater than 20 mM the yield of 2e decreases, presumably a consequence of the occurrence of secondary photoreaction(s) (entries 5 and 6). In addition, KOH and LiOH<sup>9</sup> can be utilized in place of NaOH in the photoreactions of 1e and the yields of 2e were found to increase in the order KOH < NaOH < LiOH (entries 3, 7, and 8). Moreover, when n-BuLi is employed instead of NaOH to generate the 2-propoxide ion (2-PrO<sup>-</sup>) the photocyclization reaction of **1e** takes place in a high yield (entry 9). This observation demonstrates that 2propoxide ion can serve as electron donors in these SET promoted photoreactions. Primary alcohols (e.g., CH<sub>3</sub>OH and CH<sub>3</sub>CH<sub>2</sub>OH) are not effective solvents for the photoreaction of **1e** (1 h) in the presence of NaOH (20 mM), as indicated by the low yields of 2e (13% and 45%, respectively) produced and the significant amounts of starting 1e recovered (65% and 15%, respectively). Also, 2e was not generated in the photoreaction of 1e carried out in the tertiary alcohol (CH<sub>3</sub>)<sub>3</sub>COH<sup>10</sup> or aq CH<sub>3</sub>CN. These findings show that the photocyclization reaction requires the use of an alcohol that has a readily donatable hydrogen atom at the  $\alpha$ -position to the hydroxy group. Finally, when NaOH was not present in the reaction mix-

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Scheme 3. Deuterium labeling experiment of 1e in 2-propanol-2d<sub>1</sub>.

tures, photoreactions of **1** (3 mM) in 2-PrOH (1 h) resulted in significantly lower yields of **2** (**2a**; 1%, **2b**; 7%, **2c**; 17%, **2d**; 9%, **2e**; 7%)<sup>11</sup> and in each case by-products, such as 2-bromophenol derivatives produced via photo-Claisen type rearrangements, were generated.<sup>12</sup>

In a brief effort aimed at elucidating the substrate scope of the process, PET promoted photocyclization reactions of allyl 2-bromoaryl ethers **3** and **5**, which contain methyl substituted alkene moieties, were carried out using the optimal conditions (NaOH (20 mM) in 2-PrOH for 1 h) (Scheme 2). Each of these processes was found to generate the corresponding 2,3-dihydrobenzofuran derivatives **4** and **6** in modestly high yields.

To gain further insight into the mechanism of this photocyclization reaction, we carried out a deuterium labeling experiment employing **1e** and the mono-deuterated solvent 2-propanol- $2d_1$ (Scheme 3). The results of a 1 h irradiation induced reaction showed that the efficiency of the photoreaction is significantly diminished (**2e** 31% and recovered of **1e** 31%), presumably a result of the operation of a deuterium kinetic isotope effect. In addition, the methyl group of **2e** was found to be mono-deuterated to the extent of 70%. These findings indicate that hydrogen atom transfer from the  $\alpha$ -position of 2-PrOH to a key radical intermediate in the reaction pathway is involved in the mechanistic route and that this step determines the quantum efficiency of the overall process.

A plausible mechanism for the PET-promoted reductive radical cyclization reactions of allyl 2-bromoaryl ethers 1, which is consistent with the observations described above, is displayed in Scheme 4. From the quenching for the formation of 2e by molecular oxygen and the heavy atom effect of 1, the excited triplet state of 1 could be the reactive species in this photoreaction. As described earlier by us,<sup>8</sup> PET from hydroxide or 2-propoxide ions, generated by the acid base reaction of NaOH with 2-PrOH, to the excited triplet state of 1 leads to the formation of the radical anion of 1 and hydroxyl or 2-propoxyl radicals. Loss of halide ion from the radical anion of **1** produces the aryl radical **7**, which then undergoes cyclization to generate the primary radical 8 that is transformed to the 3-methyl-2,3-dihydrobenzofuran 2 mainly through hydrogen atom abstraction (H-atom abstraction) from 2-PrOH or 2-propoxide ion (Scheme 4). Another possible pathway for termination of the cyclization process involves SET to radical 8 from the acetone anion radical 9, formed by H-atom abstraction of radicals (hydroxyl or 2-propoxyl or primary radicals 8) from the 2-propoxide ion or by hydroxide ion promoted deprotonation of the 2-hyroxypropyl radical.<sup>13</sup> This process generates anion **10**, which then is protonated by 2-PrOH to give **2**. However, the results of the deuterium labeling study suggest that the pathway involving product formation through H-atom abstraction from 2-PrOH predominates.

An alternative mechanistic route for the PET promoted radical cyclization reaction, differing in the method for generation of the allyl 2-bromoaryl ether radical anion, involves SET from the radical anion of acetone **9** (Scheme 4, bottom), which is a very strong electron donor implicated earlier in radical forming dehalogenation reactions of aryl halides.<sup>14</sup> Independent of the pathway followed, the PET promoted reductive radical cyclization reaction utilizes 2-PrOH as the reducing agent and produces acetone as the oxida-



**Scheme 4.** Plausible mechanism for PET-promoted reductive radical cyclization reactions of **1**.

tion product. Unfortunately, attempts to detect acetone in the product mixture were unsuccessful.<sup>15</sup>

In the study described above, we uncovered a novel and efficient photoinduced reductive radical cyclization reaction of allyl 2-bromoaryl ethers **1** that generates 3-methyl-2,3-dihydrobenzofurans **2**. The process is promoted by irradiation of the substrates in 2-PrOH solutions containing NaOH. In contrast to conventional radical cyclization methods that employ AIBN/Bu<sub>3</sub>SnH in benzene, the newly developed photocyclization process is more economical and environmentally friendly. Although a similar procedure for generating aryl radicals that uses *t*-butoxide ion without irradiation has been developed for inducing cross-coupling reactions of aryl halides with arenes,<sup>16</sup> it requires the use of high temperatures and diamines such as 1,10-phenanthroline. We envisage that the new photochemical method will be generally applicable to the formation of aryl radicals from corresponding bromoarenes under mild conditions, a proposal that is being addressed in our current studies of intramolecular and intermolecular cross coupling processes.

## Supplementary data

Supplementary data (experimental details, <sup>1</sup>H and <sup>13</sup>C NMR spectra, UV absorption of **1a–e**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/ j.tetlet.2013.02.103.

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