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Graphical Abstract





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An Approach to the Synthesis of Naphtho[*b*]furans from Allyl Bromonaphthyl Ethers Employing Sequential Photoinduced Radical Cyclization and Dehydrohalogenation Reactions

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A simple method has been developed for the efficient synthesis of naphtho[*b*]furans from allyl bromonaphthyl ethers. The approach utilizes a novel photochemical process involving sequential radical cyclization and dehydrohalogenation. Because light is a readily available, environmentally friendly reagent that produces no by-products, the new process serves as a green synthetic method.

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Naphtho[*b*]furans are structural components of a large number of interesting natural and synthetic compounds (Figure 1).¹ Some naturally occurring substances in this family exhibit a variety of interesting pharmacological properties.² Common methods developed for the synthesis of naphtho[b]furans usually involve cyclization reactions of allyl naphthols or allyl iodonaphthyl ethers promoted using metal catalysts such as Cu and Pd.³ In an exploratory study aimed at uncovering synthetic approaches that rely on the use of less toxic and more readily available reagents, we observed that photochemical reductive radical cyclization reactions of allyl 2-bromoaryl ethers in *i*-PrOH containing NaOH produce dihydrobenzofurans.⁴ In this study, we also found that photoreactions of allyl bromonaphthyl ethers in the absence of NaOH generate naphtho[b]furans. Below, we present the results of an effort in which we have developed a simple, environmentally friendly photochemical method to prepare naphtho[b]furans from allyl bromonaphthyl ethers.



Figure 1. Structures of naphtho[2,1-*b*] and [1,2-*b*]furans.

Initial exploratory studies were carried out using allyl 1bromo-2-naphthyl ether 1a (Table 1). Irradiation of an acetonitrile solution of 1a (3 mM), using a 100 W high-pressure

Corresponding author. Tel.: +81-776-27-8633; fax: +81-776-27-8747; e-mail: yyoshimi@u-fukui.ac.jp. (Y. Yoshimi) mercury lamp and Pyrex glass filter (>280 nm) and an argon atmosphere, at room temperature for 3 h leads to formation of 2methylnaphtho[2,1-*b*]furan **2a** in 72% yield (Entry 1).⁵ The efficiency of this process is significantly lowered when irradiation is carried out on a solution of **1a** under an air atmosphere (Entry 2). This observation suggests that a molecular oxygen quenchable triplet state of **1a** is participates in this process.⁶ In addition, the yield of **2a** decreases when higher concentrations of **1a** (5 or 10 mM) in acetonitrile are employed in the photoreaction (Entries 3 and 4). While a variety of solvents including hexane, benzene, diethyl ether, and acetone can be



$ \begin{array}{c} Br \\ \hline \\ $				
	1a		2a	
Entry	Solvent	Concentration of 1a/mM	Yield of 2a /% ^b	
1	CH₃CN	3	72	
2 ^c			11	
3		5	57	
4 ^d		10	51	
5	hexane	3	70	
6	benzene		64	
7	diethyl ether		61	
8	acetone		58	

^aPhotoreactions were carried out for 3 h under Ar atmosphere. ^bIsolated yield. ^cUnder air atmosphere. ^dIrradiation time is 6 h.

Tetrahedron



utilized for this process (Entries 5–8), irradiation of 1a in THF and alcohols such as methanol, ethanol and *i*-PrOH gives rise to complex product mixtures. Interestingly, when *t*-BuOH is employed as solvent, photoreaction of 1a generates 2a (32%) along with the 2-bromomethyl substituted naphthodihydrofuran 3a (27%) (Scheme 1). Similarly, the respective 2-halomethyl substituted naphthodihydrofurans 3a-c are generated along with 2a when acetonitrile solutions of the ethers 1a-c are irradiated for 1 or 3 h (Scheme 2). Moreover, iodo-ether 1b is entirely transformed to 3b (79%) along with 2a (8%) after a 1 h irradiation time whereas only 62% of chloro-ether 1c is converted to 2a (22%) and 3c (17%) using a longer 3 h irradiation period.



Significantly, irradiation of acetonitrile solutions of the 2bromomethyl, 2-iodomethyl, 2-chloromethyl substituted naphthodihydrofurans (**3a–c**) for 1 h results in the production of 2-methylnaphtho[2,1-*b*]furan **2a** in respective 76%, 16%, and 5% (67% **3b** and 90% **3c** recovery) yields (Scheme 3). Moreover, the efficiency (reflected in irradiation time) of the initial photocyclization step in reaction of **1b** to generate **3b** is greater than that of the first step in reaction of **1a**, even the similar

3a (3 mM)
$$\xrightarrow{hv, 1 h}$$
 2a
 CH_3CN 76%
3b (3 mM) $\xrightarrow{hv, 1 h}$ 2a
 CH_3CN 16%
Recovery of 3b; 67%
3c (3 mM) $\xrightarrow{hv, 1 h}$ 2a
 CH_3CN 5%
Recovery of 3c; 90%

Scheme 3. Photoreactions of 3a-c for 1 h in CH₃CN.

absorption spectra of 1a and 1b are observed (Supplementary Material, Fig. S1). In addition, the efficiency of the second photochemical step involving dehydrohalogenation of 3b is lower than that of 3a. Finally, the low efficiencies of both steps in the reaction of 1c leads to a low yield of both 2a and 3c and high recovery of 1c even when a 3 h irradiation period is employed. These observations suggest that 2-halomethyl substituted naphthodihydrofurans 3 are the primary products formed from the triplet excited states of the allyl 1-halo-2naphthyl ethers 1 and that these substances undergo secondary photoinduced dehydrohalogenation generate to 2methylnaphtho[2,1-b]furan 2a. In addition, the efficiency of the first photocyclization is governed in the expected manner by the nature of the halogen substituent on the naphthalene ring of the substrate $(I > Br > Cl)^6$; however, the efficiency of the second photochemical dehydrohalogenation is not reasonable (Br > I >Cl). The investigation of the detailed mechanism of the second photoinduced dehydrohalogenation is underway in our laboratory.

Table 2. Photoreactions of **1d–g** in CH₃CN^a



^aIrradiation of solutions for 3 h under Ar atmosphere. ^bIsolated yields.

In order to gain information about the substrate scope of the 2-methylnaphtho[2,1-*b*]furan forming new process, photoreactions of allyl bromonaphthyl ethers 1d-g, 5 and 7 in acetonitrile were investigated. The results show that irradiation of solutions of ethers 1d-g (3 mM) for 3 h periods leads to the production of the respective naphtho[2,1-b]furans 2d-g in moderate yields (Table 2). Actually, irradiation of an acetonitrile solution of 1e for the short time period of 0.5 h leads mainly to formation of the dihydrofuran 4, which is then converted to 2e upon prolonged irradiation (Scheme 4). Moreover, a prolonged irradiation period of 12 h is required to transform the regioisomeric allyl 2-bromo-1-naphthyl ether 5 to the 2methylnaphtho[1,2-b]furan 6 (62%) (Scheme 5). In contrast, irradiation of a solution of allyl 3-bromo-2-naphthyl ether 7 for 12 h does not promote formation of the corresponding naphthofuran and leads to quantitative recovery of the starting material.









Scheme 5. Photoreactions of 5 and 7 in CH₃CN.

The results described above show that 2-methylnaphtho[2,1b]furans and 2-methylnaphtho[1,2-b]furans can be efficiently prepared by using photochemical reactions of the corresponding 1-bromo-2-naphthyl and 2-bromo-1-naphthyl allyl ethers. In addition, observations made in this effort suggest that a plausible mechanism for these photoreactions (Scheme 6) begins with homolytic C-halogen bond cleavage in the triplet states of the substrates to generate radical pairs,⁶ which undergo 5-exo type cyclization and halogen atom capture to produce the initially formed 2-halomethyl substituted naphthodihydrofurans 3 similar atom-transfer radical cyclizations⁷. Subsequently, to photoinduced dehydrohalogenation of 3 takes place to generate alkylidene dihydrofuran intermediates 8 that undergo tautomerization to generate the naphthofuran products 2. In the $R_2 = CH_3),$ case of 1e $(R_1 = CH_3,$ the photochemical dehydrohalogenation leads to the respective formation of 8 and the regioisomeric product 4, which is photochemically tautomerized to 2a. Compared to the conventional methods used to induce cyclization reactions of substrates similar to 1, which require the use of Pd and Cu catalysts, the new photochemical method utilizes light as a less toxic, more readily available, and non by-product forming reagent. Applications of this methodology to the synthesis of benzofurans are in progress.



Scheme 6. Plausible mechanism for photoreactions of 1.

Supplementary Material

Supplementary material (UV absorption spectra of **1a–c**, **5** and **7**, experimental procedures, and characterization of the compounds) associated with this article can be found, in the online version, at doi:###.

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- 5. General procedure for photoreactions of 1; An acetonitrile solutions containing allyl 1-bromo-2-naphthyl ethers 1 (3 mM) in Pyrex vessels (18 mm x 180 mm) were purged with argon for 10 min. The solutions were irradiated with 100 W high-pressure mercury lamp for 3 h, and the resulting mixture was evaporated. The product was purified by silica gel column chromatography using hexane and EtOAc as eluents to give 2.
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