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Stereoselective Preparation of Spiro[4.4] Cyclic Compounds by the Photochemical Activation of Oxazoles

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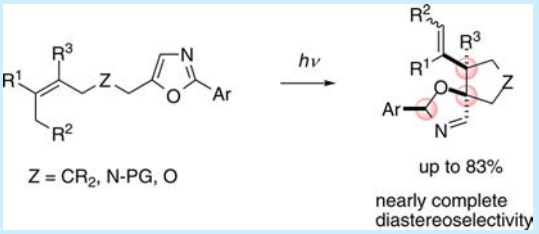
Supporting Information

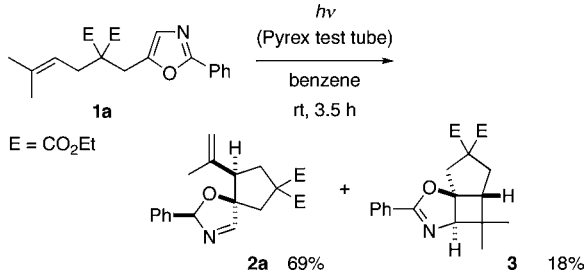
ABSTRACT: A novel photocyclization of 2-aryloxazole derivatives linked with an alkene moiety through a three-atom spacer at the 5-position gave a range of functionalized spiro[4.4] cyclic compounds that included cyclopentane, tetrahydrofuran, and pyrrolidine moieties in moderate to high yields with excellent diastereoselectivity.



Photochemical reactions have long been utilized in organic synthesis as a powerful tool for realizing molecular complexity.[1,2] Photochemical transformation can be performed by simply irradiating a solution containing a starting material to provide a metal-free access to complex molecules from readily available compounds. The [2 + 2] cycloaddition reaction,[3] the meta-photocycloaddition onto arenes,[4] and the di-π-methane rearrangement[5] are the typical examples employed in total syntheses of natural products. In contrast to these widely employed reactions, the photochemical reaction of five-membered heteroaromatic compounds was less explored,[6−11] though they are a common motif in organic chemistry. We focused our attention on the unique photochemical behavior of five-membered heteroaromatics to develop new and efficient chemical transformations, and identified several interesting photocyclizations of furans and thiophenes.[12,13] In the course of our investigation, we found that oxazoles show quite interesting behavior under photochemical conditions to give rise to an unprecedented intramolecular cyclization. Bond formation at the 4- or 5-position of oxazoles accompanied by dearomatization provides an efficient approach to the construction of a protected 1,2-aminoalcohol moiety.[9,14] We report herein the novel photocyclization of 2-aryloxazoles giving functionalized spiro[4.4] cyclic compounds including cyclopentane, pyrrolidine, and tetrahydrofuran skeletons in a highly stereoselective manner.

We synthesized 2-phenyloxazole derivative **1a**, which had an alkene moiety, through a three-carbon spacer at the 5-position for the substrate of the photoreaction. External irradiation of a solution of **1a** in benzene by a high-pressure mercury lamp through Pyrex glass afforded an unexpected cyclized product **2a** in moderate yield (estimated from ^{1}H NMR integrals) with concomitant formation of the [2 + 2] addition product **3** (Scheme 1). It was quite surprising that the unusual spirocyclic compound **2a** was preferably produced over the conventional [2 + 2] adduct **3**.[9a−d,15] More importantly, the reaction proceeded in a highly stereoselective manner to give **2a** as a single diastereomer with a cis-configuration of the alkenyl group and the alkoxy moiety. The structure of **2a** was deduced by careful spectroscopic analyses, including NMR (^{1}H, ^{13}C, 2Ds, and NOE), HRMS, and IR (see the Supporting Information). We were interested in this new photochemical transformation of oxazole derivatives and decided to investigate the reaction in detail.

Scheme 1. Stereoselective Functionalized Cyclopentane Formation from an Oxazole Derivative 1a



At the beginning of our study, we tried the reaction in a series of solvents. The results are summarized in Table 1. The reaction proceeded in moderately polar solvents such as 1,4-dioxane, MTBE,[16] and ethyl acetate as well as in benzene (entries 1−4), while the reaction in hexane, acetonitrile, and methanol gave a lower yield of **2a** with 8−20% recovery of the starting material **1a** (entries 5−7). The production of **2a** was completely inhibited in acetone (entry 8). In benzotrifluoride,[17] although **1a** was consumed completely, **2a** was obtained in only 38% yield with formation of an uncharacterizable mixture (entry 9).

Setting benzene as a suitable solvent for this reaction, we carried out the reaction using a range of oxazole derivatives. The results are shown in Table 2. The reactions shown in Table

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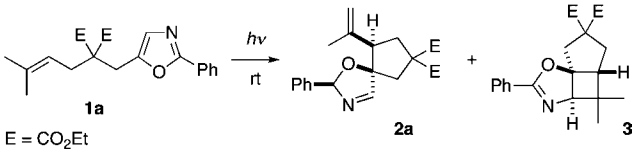
Table 1. Solvent Screen[a]



entry	solvent	time (h)	yield (%)[b] 2a	3	recovery of 1a[b]
1	benzene	3.5	69	18	0
2	1,4-dioxane	3	53	26	7
3	MTBE[c]	3	53	21	1
4	AcOEt	3	61	7	3
5	hexane	3.5	40	17	8
6	CH_3CN	3.5	50	30	20
7	CH_3OH	3.5	42	24	10
8	acetone	3.5	0	<1	47
9	$C_6H_5CF_3$	3	38	0	0

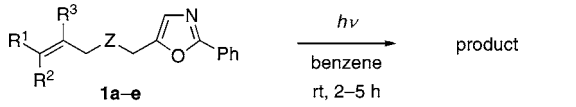
[a]All reactions were carried out in a Pyrex test tube by external irradiation at a concentration of 2.7−2.9 mM. [b]Determined by ^{1}H NMR integral ratio using 1,1,2,2-tetrachloroethane as an internal standard. [c]Methyl *tert*-butyl ether.

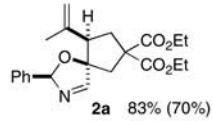
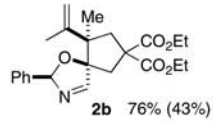
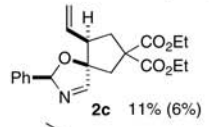
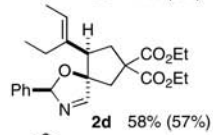
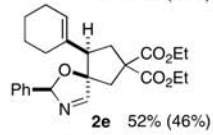
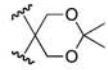
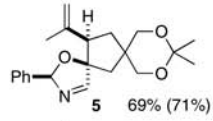
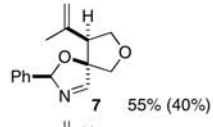
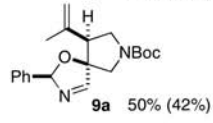
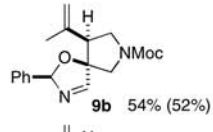
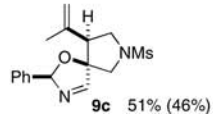
2 were conducted in a photochemical reaction vessel for the internal irradiation. A yield of **2a** even higher than that by external irradiation was achieved (Table 2, entry 1 vs Table 1, entry 1). Although **2a** was somewhat susceptible to hydrolytic decomposition during the conventional chromatographic purification, we could isolate the compound in pure form with only a slight loss of yield. The substituents at the alkene moiety had a notable impact on the reaction. The reaction of **1b** with a tetrasubstituted alkenyl group revealed that the bulkiness of the alkene did not affect the reaction (entry 2). It should be noted that neighboring quaternary carbon centers were created stereoselectively, suggesting the high potential of this reaction for the synthesis of organic molecules with a congested structure. Irradiation of the substrate **1c**, which has an (*E*)-crotyl side chain instead of prenyl, gave vinyl-substituted cyclopentane, but the yield was much decreased (entry 3). This detrimental effect on the yield is discussed in the following section. We could employ linker moieties other than diethyl malonate derivatives (entries 4−8). Thus, compounds linked with oxygen or protected nitrogen (**6** and **8a**−**c**) gave the corresponding products, substituted tetrahydrofuran and pyrrolidine, in more than 50% yields (entries 5 and 6−8).

The reaction with 4-bromobenzenesulfonamide derivative **8d** gave spiro product **9d** and [2 + 2] cycloadduct **10** (Scheme 2). Prolonged irradiation severely decreased the yields of both **9d** and **10** without improving the relative amount of **9d**. Fortunately, the products **9d** and **10** were crystalline compounds and we could obtain single crystals of each that were suitable for X-ray crystallographic analysis. The structures of **9d** and **10** with relative stereochemistry were thus unambiguously confirmed (Figure S1, Supporting Information). 2-Methyl- and 2-unsubstituted oxazole derivatives gave no cyclized product with nearly quantitative recovery of the starting materials.

Next, we checked the electronic effect of the aryl group at the 2-position of the oxazoles (Table 3). Replacement of the phenyl group with a 4-fluorophenyl group afforded **2f** in 69% yield (entry 2), whereas the substrate with a 4-methoxyphenyl group **1g** gave the product in somewhat lower yield with

Table 2. Substrate Screen[a]



entry	subst.	Z	R1	R2	R3	product[b]
1	1a	$C(CO_2Et)_2$	Me	Me	H	 2a 83% (70%)
2	1b	$C(CO_2Et)_2$	Me	Me	Me	 2b 76% (43%)
3	1c	$C(CO_2Et)_2$	Me, H (*E*:*Z* = 83:17)		H	 2c 11% (6%)
4	1d	$C(CO_2Et)_2$	Et	Et	H	 2d 58% (57%)
5	1e	$C(CO_2Et)_2$	-$(CH_2)_5$-		H	 2e 52% (46%)
6	4		Me	Me	H	 5 69% (71%)
7	6	O	Me	Me	H	 7 55% (40%)
8	8a	NBoc	Me	Me	H	 9a 50% (42%)
9	8b	NMoc[c]	Me	Me	H	 9b 54% (52%)
10	8c	NMs	Me	Me	H	 9c 51% (46%)

[a]All reactions were carried out in a Pyrex reaction vessel for photochemical reaction by internal irradiation at a concentration of 2.6−5.0 mM. [b]Determined by the ^{1}H NMR integral ratio using 1,1,2,2-tetrachloroethane or pyrazine as an internal standard. The numbers in parentheses are the isolated yields. [c]Moc = Methoxycarbonyl.

complex byproducts (entry 3). Thus, the electronic property of the substituent on the benzene ring has little effect on the yield or the stereoselectivity of the products.

The spirocyclic compound **2a** was stable under the photochemical reaction, as irradiation of isolated **2a** caused no decomposition. In contrast, when isolated **3** (containing

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Scheme 2. Photoirradiation of 4-Bromobenzenesulfonamide Derivative 8d

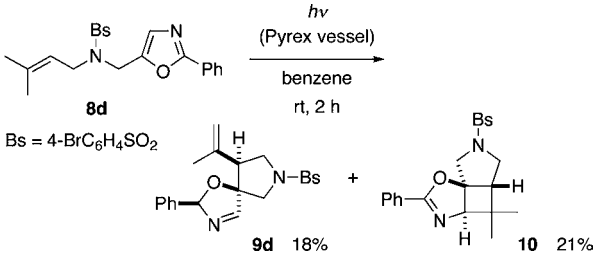
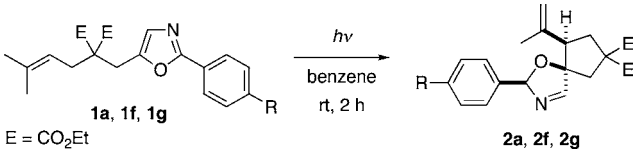


Table 3. Electronic Effect of the Substituent at the 2-Position of the Oxazole Ring[a]

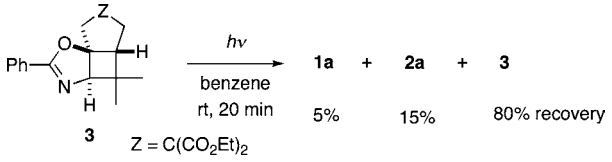


entry	subst.	R	yield (%)[b]
1	**1a**	H	83 (70)
2	**1f**	F	69 (69)
3	**1g**	OMe	54 (52)

[a]All reactions were carried out in a Pyrex reaction vessel for photochemical reaction by internal irradiation at a concentration of 2.5–2.7 mM. [b]Determined by the ^{1}H NMR integral ratio using 1,1,2,2-tetrachloroethane or pyrazine as an internal standard. The numbers in parentheses are the isolated yields.

small amounts (<5%) of unidentified impurities) was irradiated under the same reaction conditions, **2a** and **1a** were slowly produced to give a mixture consisting of **1a**:**2a**:**3** = 5:15:80 (Scheme 3). These results suggest that the [2 + 2] cycloaddition of **1a** forming **3** is reversible and the adduct **3** is not likely an intermediate of the production of **2a**.

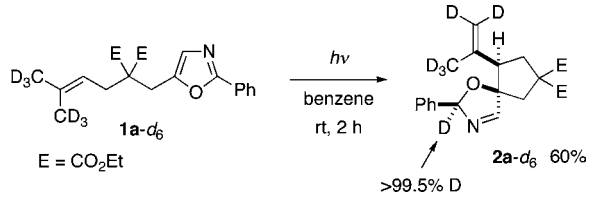
Scheme 3. Photoirradiation of the [2 + 2] Cycloadduct 3



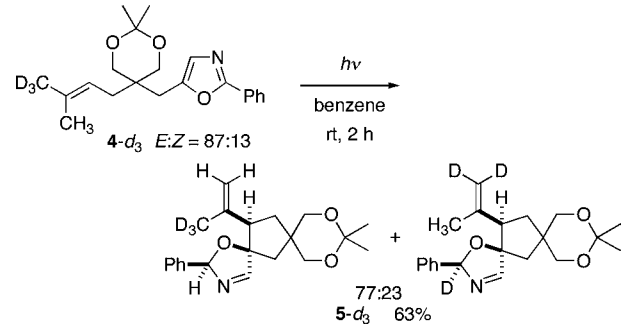
To obtain insights into the reaction mechanism, we carried out the reaction using a deuterium-labeled compound. When **1a**-d_6 was irradiated under the reaction conditions shown in Table 2, **2a**-d_6 was exclusively produced (Scheme 4). This result clearly shows that the hydrogen at the benzylic position comes from the methyl of the prenyl moiety.

When we conducted the reaction using **4**-d_3 (E/Z = 87:13), we obtained **5**-d_3 with an H/D ratio of 23:77 (Scheme 5). As

Scheme 4. Reaction with a Hexadeuterated Substrate



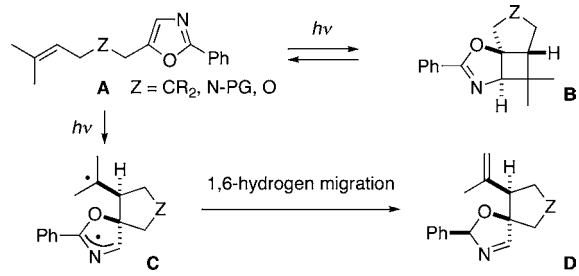
Scheme 5. Reaction with a Trideuterated Substrate



shown in Scheme 4, it is clear that the benzylic hydrogen comes only from either of the prenyl methyls. The result shown in Scheme 5 indicates that the benzylic hydrogen mainly comes from the Z-oriented methyl. This observation is consistent with the low yield in the reaction of **1c** with an (E)-enriched crotyl side chain (Table 2, entry 3).

Though the detailed mechanism is not clear at this stage, we surmise that the pathway is as shown in Scheme 6 based on the

Scheme 6. Plausible Reaction Pathway



results of Schemes 3, 4, and 5. Photoexcited **A** would form a biradical intermediate **C** via the formation of a carbon–carbon bond between the 5-position of oxazole and the alkene moiety, followed by 1,6-hydrogen migration,[18] to give the cyclized product **D**. As described before, the starting material **A** reversibly formed the [2 + 2] adduct **B**. Direct formation of **D** from **B** should be unlikely, as this process would require an intramolecularly impossible hydrogen transfer, taking into account the site selectivity shown in Scheme 5. The overall process can be called a photoene reaction.[19,20]

In conclusion, we have developed a new method for the photochemical construction of unique spirocyclic frameworks by the irradiation of oxazole derivatives with an alkene moiety. With appropriate substrates, the reaction proceeds cleanly in a couple of hours to afford the products in synthetically acceptable yields. More importantly, the products are obtained in a highly stereoselective manner in all cases.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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