Photosensitized intramolecular cyclization of furan and non-activated alkene: pathway switching by the substituent on the furan ring

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ABSTRACT

A photosensitized reaction of furan with a non-activated simple alkene was investigated. Intramolecular Diels–Alder-type cycloaddition reactions between furan and a trisubstituted alkene were found to proceed in high yield in the presence of 9,10-dicyanoanthracene under UV irradiation to afford oxabicyclo[2.2.1]heptane derivatives in high stereoselectivity when the furan was alkyl substituted. On the other hand, the aryl-substituted furan cyclized via a completely different pathway to give spirocyclic and tricyclic products.

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Diels–Alder reaction of furans is known as a powerful synthetic tool to construct a six-membered ring system equipped with oxygen functionality.[1] The intramolecular Diels–Alder reaction of furans is a particularly attractive method, since two or more ring systems can be constructed in a single step with high regio- and stereoselectivity.[2] In these reactions, based on the well-known frontier orbital theory, the dienophiles coupled with furans should have an electron-withdrawing group in order for the reaction to proceed smoothly.[3] A wide range of cyclo-adducts can be obtained in reactions with such combinations of furans and electron-deficient dienophiles; however, a readily proceeding reverse reaction sometimes lowers the yields of the products.[4,5] Development of Diels–Alder reactions between furans and electron-rich dienophiles under mild conditions would enhance the synthetic versatility of the reaction. In general, Diels–Alder reactions between electron-rich dienes and dienophiles are known to proceed with difficulty and to require harsh reaction conditions.[6] Even when the reaction was performed in an intramolecular manner, only 40% conversion was reported in the reaction of allyl(2-furylmethyl)malonate.[7] Sternbach et al. reported that intramolecular Diels–Alder reaction of furan and simple alkenes gave adducts in high yields when the substrates had appropriate substituents on the linker moiety.[8,9] Quite recently, Hsung and Lohse reported intra-

molecular [4+2] cycloaddition of furans through tandem propargyl amide isomerization-cyclization.[10]

The use of cycloaddition reactions through radical ions or excited states can be an effective method for making the Diels–Alder reaction between electron-rich dienes and alkenes proceed more easily. Bauld and co-workers reported that Diels–Alder-type dimerization of 1,3-cyclohexadiene and other electron-rich dienes proceeded well via single electron transfer with triarylamminium salts.[11–13] A radical cation chain process was proposed for these reactions.[12]

Several research groups described that the [4+2] cycloaddition reactions of 1,3-cyclohexadiene and related compounds with electron-rich dienophiles were catalyzed by cyanoarenes under UV irradiation.[14,15] Schuster and co-workers proposed that these reactions proceed through intermediate excited-state ternary complexes.[15] To our knowledge, however, this reaction strategy has never been applied to furan and its derivatives.[16] We therefore investigated the intramolecular Diels–Alder reaction of furans under photosensitized conditions and found that the reactions with appropriately designed furyl alkenes proceeded in high yield with excellent stereoselectivity.[17] In the course of this study, we also found that the substituent on the furan ring had a dramatic effect on the reaction pathway.
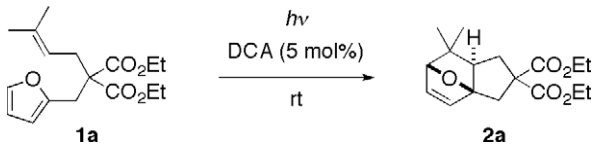
We chose diethyl malonate derivative **1a** as a substrate, and examined the photocycloaddition reaction in various solvents in the presence of 9,10-dicyanoanthracene (DCA). The results are summarized in Table 1.

All reactions were carried out in a Pyrex® tube under irradiation by a high-pressure mercury lamp.[18] Irradiation of 8 h gave the cor-

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Table 1
Solvent effect on the photocycloaddition of **1a**[a]

Entry	Solvent	Irr. time (h)	Yield of **2a**[b] (%)	Recov. of **1a**[b] (%)
1	Toluene	8	21	78
2	Benzene	8	36	61
3	THF	8	25	71
4	DME	8	31	63
5	1,4-Dioxane	8	31	65
6	AcOEt	8	40	58
7	CH$_3$CN	9	2	87
8	CH$_3$OH	9	0	94
9	Benzene	84	89 (79)[c]	2
10[d]	Benzene	85	85	10

[a] The reaction was conducted under the following conditions: initial concentration of **1a**, 0.04 M; DCA, 5 mol %; temperature, 20 °C; carried out in a Pyrex® tube under irradiation by high-pressure mercury lamp.
[b] Estimated by ^{1}H NMR integration by using pyrazine as an internal standard.
[c] Isolated yield.
[d] **1a**, 0.016 M; DCA, 25 mol %.

responding product **2a** in moderate yields in non-polar solvents (entries 1 and 2), as well as medium polar ones (entries 3–6). We confirmed that **2a** was stable under the conditions employed because irradiation of **2a** resulted in quantitative recovery of **2a** without isomerization. The cyclized product **2a** was obtained in diastereomerically pure form, judging from the ^{1}H NMR spectrum. The relative configuration was determined by a NOE experiment (Fig. 1). When H$_a$ was irradiated, clear NOE enhancements were observed for the signals of H$_b$, H$_c$, and H$_d$. This observation indicates that compound **2a** has the relative configuration depicted in the figure (*exo*-adduct). In the *endo*-adduct, H$_a$ and H$_d$ are located too far apart to show the NOE correlation. The relative configurations of the following compounds were determined in the same way.

It should be noted that cyclization between a trisubstituted alkene and a furan affording the multi-substituted oxabicyclo[2.2.1]heptane moiety in high selectivity has never been reported. The cyclizations of furan with only a terminal non-substituted alkene (vinyl type) have been investigated,[8,9] with the exception that the cyclization with methylenecyclopropane derivatives gave the corresponding adducts under high-pressure conditions.[19]

In contrast to the results in entries 1–6, the reactions in highly polar solvents hardly proceeded and resulted in almost complete recovery of **1a** (entries 7 and 8). This result strongly suggests that the cycloaddition of **1** proceeds not through the electron transfer producing **1a**$^{+•}$ and DCA$^{-•}$, but through the formation of an exciplex between **1a** and DCA, as proposed by Schuster and co-workers.[15] We also observed the following results which support the above consideration: (1) Irradiation of **1a** in benzene for 15 h without

DCA resulted in quantitative recovery of **1a** and (2) Treatment of **1a** with (4-BrC$_6$H$_4$)$_3$N$^{+•}$(SbCl$_6^-$) in CH$_2$Cl$_2$ resulted in the recovery of **1a** without the production of **2a**.

With regard to the choice of photosensitizer, 1,4-dicyanobenzene (DCB) and 1,4-dicyanonaphtharene (DCN) gave much poorer results (<10% yield of **2a**).

In the above investigation, benzene seemed to be the solvent of choice, since the yield of **2a** was relatively high and the sensitizer was less decomposed in that solvent (entry 2). We next tried the reaction in benzene for a prolonged period of time and found that the yield of **2a** increased to a synthetically useful level (89%, entry 9). We also carried out the reaction under the condition of high DCA loading, with the hope of increasing the reaction rate, and found that the cyclized product **2a** was obtained with a yield as high as that in entry 9, though the expected acceleration was not observed (entry 10).

We next examined the effect of substituents around the alkene and the tether moiety. The results are summarized in Table 2. The structure around the olefinic moiety had a pronounced effect on the yield of the cyclized products. In contrast to **1a** (entry 1), neither the simple allyl substrate **1b**, methallyl type **1c**, or trisubstituted substrate **1d** underwent the cyclization under the standard reaction conditions, resulting in the recovery of the starting materials (entries 2–4). Only tetrasubstituted alkene **1e** afforded the sterically congested product in **2e** 35% yield after 64 h irradiation (entry 5). It is quite interesting that only the most bulky substrate could afford the product, and although the reason for this finding is unclear at this stage, both electronic and steric factors might be involved.

On the other hand, the tether moiety was found to be less critical for the cyclization. That is, alkenyl furan tethered by amine linkage (**1f**) cyclized under the standard reaction conditions described above to afford the product **2f** in moderate yield with complete stereoselectivity (entries 6 and 7). In regard to **1f**, dioxane gave a better yield than benzene.

The diester moiety can be replaced with other functionalities. For instance, diether **1g** also gave the corresponding cyclized product **2g** in good yield (entry 8).

Substitution on the furan ring did not have an inhibitory effect on the reaction. Thus, when the 5-methyl derivative **1h** was employed as a substrate, the corresponding cyclized product **2h** was obtained in high yield and exclusive stereoselectivity (entry 9). It should be noted that the trimethyl-substituted oxabicyclo[2.2.1]heptane moiety with high steric hindrance was constructed by a simple operation, as well as **2e**.

In the course of the study of substituents on the furan ring, we also observed a unique behavior of phenyl-substituted furan **3**. Irradiation of **3** under the conditions described above did not gave [4+2]-type products, but two new compounds. Detailed investigation of the NMR spectra revealed that these products have the structures of spirocyclic **4** and tricyclic **5** depicted in Scheme 1. The yields estimated by ^{1}H NMR integration are shown because the quantity of these compounds was somewhat decreased after purification, probably due to decomposition. They were diastereomerically pure, though the relative configurations have not been determined yet. In contrast to the reaction of **1**, this cyclization proceeded in polar solvents such as methanol and acetonitrile as well as benzene and ethyl acetate. The ratio of produced **4**–**5** depended on the solvents to some extent. To our knowledge, this type of cyclization of furan is unprecedented. Though the details of the reaction mechanism are not clear at this stage, it is conceivable that the process may involve radical ions instead of short-lived biradicals, especially in a polar solvent.

In conclusion, we investigated the photosensitized Diels–Alder reaction between furan and non-activated alkenes and found that appropriately substituted substrates (**1a**, **1e**, **1f**, **1g**, and **1h**) gave
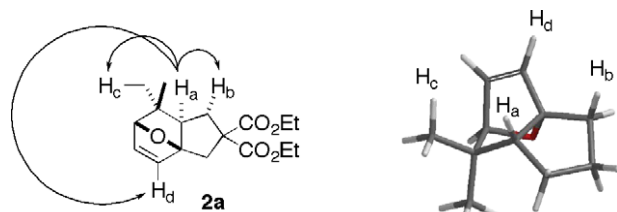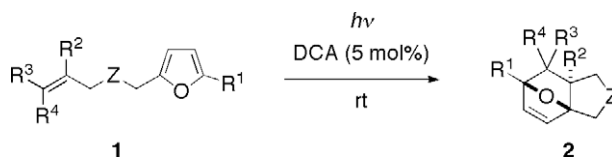

Figure 1. NOE enhancements for **2a**. Ethoxycarbonyl groups are omitted in the stereographic for clarity.

Table 2
Substituent effect on the photocycloaddition

Entry	Compound	R^1	R^2	R^3	R^4	Z	Solvent	Time (h)	Yield[a] (%)
1	**1a**	H	H	Me	Me	$C(CO_2Et)_2$	Benzene	84	**2a**, 79
2	**1b**	H	H	H	H	$C(CO_2Et)_2$	Benzene	72	0
3	**1c**	H	Me	H	H	$C(CO_2Et)_2$	Benzene	72	0
4	**1d**	H	Me	Me	H	$C(CO_2Et)_2$	Benzene	84	Trace
5	**1e**	H	Me	Me	Me	$C(CO_2Et)_2$	Benzene	64	**2e**, 35[b]
6	**1f**	H	H	Me	Me	NBoc	Benzene	93	**2f**, 38[b]
7	**1f**	H	H	Me	Me	NBoc	Dioxane	93	**2f**, 55[b]
8	**1g**	H	H	Me	Me	$C(CH_2OMe)_2$	Benzene	72	**2g**, 82
9	**1h**	Me	H	Me	Me	$C(CO_2Et)_2$	Benzene	68	**2h**, 82

[a] Isolated yield.
[b] Contains small amounts (approx. 2–3%) of inseparable DCA.

	4	5
benzene	26%	35%
AcOEt	26%	38%
CH_3CN	28%	24%
CH_3OH	28%	32%
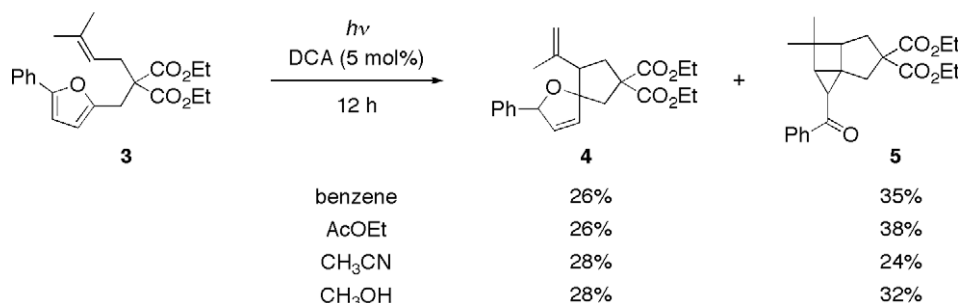
Scheme 1. Photosensitized cyclization of **3**.

the cyclized products in good to moderate yields with excellent stereoselectivity. When a phenyl group was introduced to the furan ring, the reaction proceeded along a completely different pathway to afford the spirocompound **4** and tricyclic compound **5**.

Acknowledgment

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.123.

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