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Novel Intramolecular Photocyclization of α-Arylthiophene Derivatives

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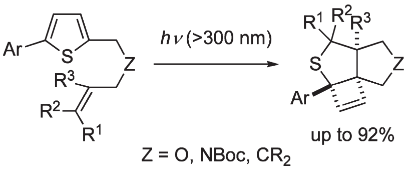
ABSTRACT



Photoirradiation of α-arylthiophene derivatives linked with an alkene moiety through a three-atom spacer gave unprecedented cyclobutene-fused perhydrothiapentalene-type compounds in high yields, but neither [2 + 2] nor [4 + 2] cycloaddition products. The reaction afforded a single diastereomer in many cases. The chemical structure and relative configuration of a typical product were unambiguously determined by X-ray crystallographic analysis.

Considerable attention has been paid to the photochemical behavior of thiophene derivatives in a wide range of scientific fields, for example, light emitting materials,[1] photochromic compounds,[2] organic photovoltaic devices,[3] and physical organic chemistry.[4] However, synthetic use of the photoreaction of thiophenes is quite limited, and has mostly consisted of the simple rearrangement between regioisomers, electrocyclization, and [2 + 2] addition.[5−10] In addition, a few examples of [4 + 2] addition have also been reported.[11] In the course of our study on the photoreaction of 5-membered heteroaromatic compounds,[12] we found that α-arylthiophenes linked with an alkene moiety through a three-atom spacer cyclized to give cyclobutene-fused perhydrothiapentalene-type compounds under UV (> 300 nm) irradiation. We report here the preliminary results of an unprecedented type of photoreaction of thiophene derivatives.

When a solution of thiophene derivative **1a** in degassed benzene was irradiated by a high-pressure mercury lamp[13] through a Pyrex glass vessel for 2 h at ambient temperature

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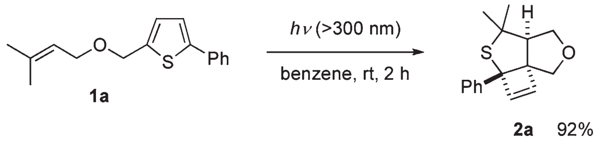
(13) Riko UVL-100HA photoreactor.

10.1021/ol3002305

(around 25 °C), an unexpected compound **2a** was obtained in high yield (Scheme 1). The product **2a** was obtained as a single diastereomer. The structure of **2a** was determined by careful NMR experiments (^{1}H, ^{13}C, DEPT, H–H COSY, HMQC, HMBC, and DPFGSE-NOE). The product **2a** was a stable colorless crystalline compound. We succeeded in obtaining a single crystal suitable for X-ray crystallographic analysis to confirm its structure unambiguously as shown in Figure 1 (CIF in the Supporting Information).

Scheme 1. Photocyclization of **1a**



The novel cyclization forming a perhydro-oxathiapentalene framework fused with a cyclobutene ring is significantly different from the well-known [2 + 2] photocyclization of thiophenes affording cyclobutane-fused thiacycle compounds.[10,14−16] We were interested in this extraordinary photoreaction of thiophene derivatives, and decided to investigate the reaction in detail.

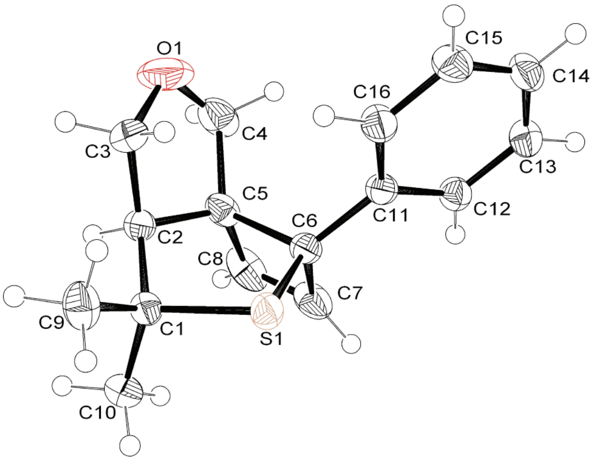
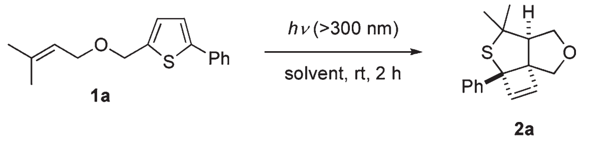


Figure 1. ORTEP drawing of compound **2a**.

Our investigation began with carrying out the reaction in a series of solvents using **1a** as a standard substrate. The results are summarized in Table 1. The reaction proceeded in hexane, dioxane, THF, ethyl acetate, and acetonitrile, as well as in benzene to give the product **2a** in high yields (entries 1–6). These results show the polarity of the solvents has little effect on this reaction. Methanol, a protic solvent, was also suitable for this reaction (entry 7). On the other hand, the reaction in benzotrifluoride gave a somewhat inferior result with recovery of only a small amount of **1a** (entry 8). The reaction rate in acetone was relatively slow, resulting in the product in 62% yield with the recovery of **1a** in 28% yield (entry 9). Taking the results shown in Table 2 into account, this retardation seemed to be caused mainly by absorption by acetone rather than quenching of the excited species with acetone, though the detailed reaction mechanism is not clear at this stage.

Table 1. Solvent Screening[a]



entry	solvent	yield of **2a** (%)[b]	recovery of **1a** (%)[b]
1	benzene	92	0
2	hexane	89	0
3	1,4-dioxane	90	0
4	THF	91	0
5	AcOEt	85	1
6	CH_3CN	84	0
7[c]	CH_3OH	84	0
8	$C_6H_5CF_3$	76	4
9	acetone	62	28

[a] All reactions were carried out in a Pyrex test tube by external irradiation at a concentration of 5–6 mM. [b] Determined by ^{1}H NMR integral ratio using 1,1,2,2-tetrachloroethane as an internal standard. [c] Small amount of unidentified compound was detected.

When the irradiation was stopped in 20 min, a small amount of another compound was detected. Careful NMR study revealed that this compound was the [2 + 2] addition product **3a** (Scheme 2). This result shows the possibility that **2a** is produced through **3a** as an intermediate.[17] To check this possibility, we irradiated isolated **3a** under the same reaction conditions leading to the formation of **1a** as a major product with the concomitant formation of **2a** in low yield (Scheme 3). In contrast, irradiation of **2a** under the identical conditions resulted in quantitative recovery of **2a**. These results suggest that the [2 + 2] cycloaddtion of **1a** forming **3a** is reversible and the adduct **3a** is not an intermediate of the transformation to **2a**.

To obtain additional information about this reaction, we carried out several reactions that were stopped at low conversion as above. The results are summarized in Table 2. The [2 + 2] adducts **3a**–**c** were the only detectable byproducts in all cases. The reaction rate was little influenced by solvent polarity and the protic characteristics, though slightly lower conversion was observed in dioxane (entries 1–5). These data suggest that polar intermediates are less productive in this reaction. However, the electronic

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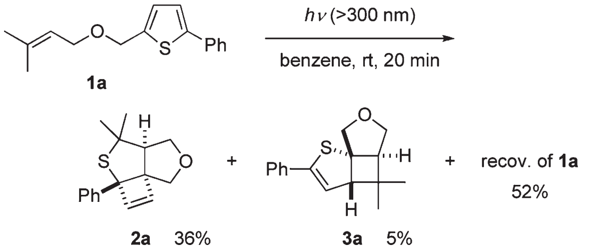
Scheme 2. Products at an Early Stage of the Reaction



properties of the substrates turned out to show some effect on the reaction. In fact, replacement of the phenyl group on the thiophene 2-position with the 4-methoxyphenyl group notably retarded the reaction (entry 6), while the introduction of a 4-chlorophenyl ring showed little influence (entry 7). The yield of **2a** was somewhat decreased in the presence of triplet quenchers,[18] but the reaction was not completely inhibited (entries 8 and 9). 9,10-Dicyanoanthracene (DCA), a singlet sensitizer that is known to promote the photoinduced pericyclic reactions,[12,19] did not affect the reaction features (entry 10).

Scheme 3. Irradiation of **3a**

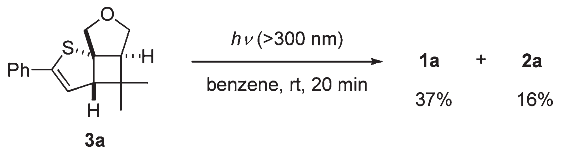
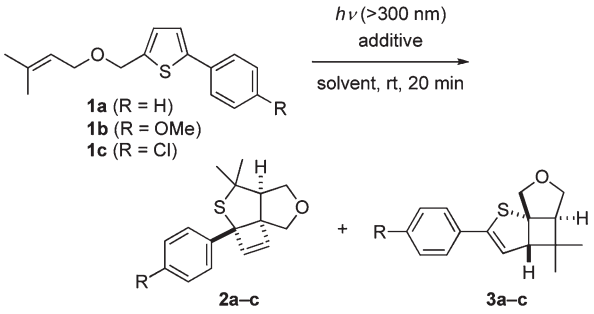


Table 2. Product Distribution at an Early Stage of the Reaction[a]



entry	R	solvent	additive	**1** (%)[b]	**2** (%)[b]	**3** (%)[b]
1	H	benzene	none	52	36	5
2	H	hexane	none	46	42	4
3	H	dioxane	none	76	18	6
4	H	CH_3OH	none	57	31	6
5	H	CH_3CN	none	49	40	8
6	MeO	benzene	none	81	16	3
7	Cl	benzene	none	57	43	<1
8	H	benzene	*p*-terphenyl[c]	63	34	3
9	H	benzene	O_2[d]	54	22	0
10	H	benzene	DCA[e]	64	27	9

[a] All reactions were carried out in a Pyrex test tube by external irradiation at a concentration of 5–6 mM. [b] Determined by ^1H NMR integral ratio using 1,1,2,2-tetrachloroethane as an internal standard. [c] An amount of *p*-terphenyl equimolar to **1a** was added. [d] Benzene saturated by O_2 bubbling was used. [e] An amount of DCA equivalent to half a mole of **1a** was added.

Considering these experimental results and previous reports in the literature,[5,6,20] the reaction seems to proceed mainly via the singlet excited state of **1a** followed by the formation of noncharge-separated reactive species. A plausible reaction pathway is proposed in Scheme 4. Photoexcitation of **1a** could cause a 4π electrocyclic reaction to give a "Dewar thiophene" (5-thiabicyclo[2.1.0]pent-2-ene) type intermediate **A**. Then the thiirane moiety in **A** reacts with the pendant alkene to afford the product **2a**. A part of **1a** undergoes reversible formation of **3a**. The formation of the Dewar thiophene type intermediate is postulated in the photoisomerization of 2-substituted thiophene to 3-substituted thiophene.[5,6,20−25] Some of these intermediates were trapped and characterized.[26−28] The thiirane ring-opening and successive cyclization are known under thermal conditions.[29] The details of the mechanism should be disclosed in a further investigation.

Scheme 4. Plausible Reaction Pathway

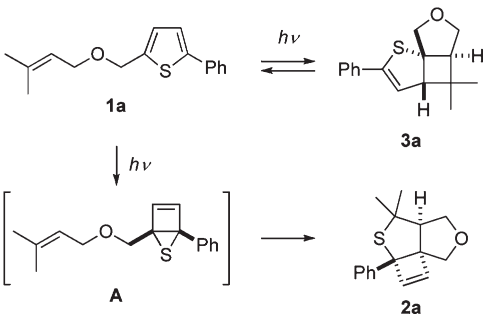


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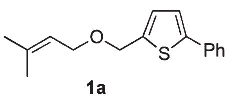
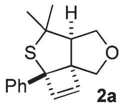
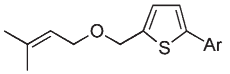
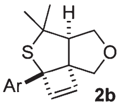
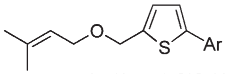
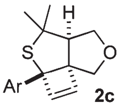
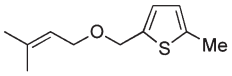
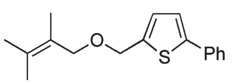
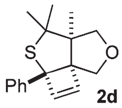
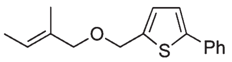
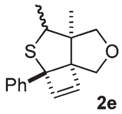
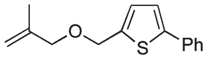
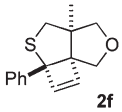
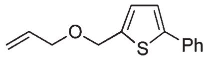
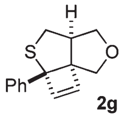
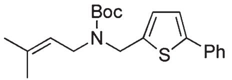
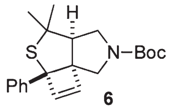
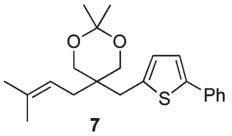
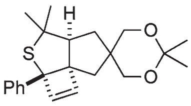
Table 3. Substrate Screening[a]

entry	substrate	product	yield (%)[b]
1[c] 2[e]	 **1a**	 **2a**	92[d] 86
3	 **1b** (Ar = 4-MeOC$_6$H$_4$)	 **2b**	63
4	 **1c** (Ar = 4-ClC$_6$H$_4$)	 **2c**	88
5	 **4**	f	f
6	 **1d**	 **2d**	48
7	 **1e**	 **2e**	76[g]
8	 **1f**	 **2f**	50
9	 **1g**	 **2g**	20
10	 **5**	 **6**	68
11	 **7**	 **8**	75[h]

[a] All reactions were carried out by internal irradiation through a Pyrex glass jacket at a concentration of 5–6 mM, until the starting material (0.2 mmol) was completely consumed (typically 2–5 h) (for details, see the Supporting Information). [b] Isolated yield. [c] The reaction was carried out in a Pyrex test tube by external irradiation at a concentration of 5–6 mM. [d] Determined by ^{1}H NMR integral ratio using 1,1,2,2-tetrachloroethane as an internal standard. [e] The reaction was carried out using 2 mmol of **1a** at a concentration of 0.1 M. [f] No cyclized product was obtained, and unreacted **4** was recovered (91%). [g] Obtained as a diastereomeric mixture (7:3). [h] The sample contained small amounts of inseparable impurities.

Next, we performed the reaction using a variety of substrates with the different alkenyl groups and linker moieties. The results are listed in Table 3.

We confirmed that this reaction could be conducted under the preparative conditions to give the product **2a** in high isolated yield by using the typical substrate **1a** (entry 2), though the following examples were carried out on a small scale for convenience. Replacement of the phenyl group with a 4-methoxyphenyl group afforded **2b** in 63% yield accompanied by the formation of unidentified byproduct (entry 3). A substrate with a 4-chlorophenyl group **1c** gave the product in quite good yield (entry 4). The reaction with a methyl-substituted compound **4** resulted in the recovery of most of **4** (entry 5). No cyclized product was observed. These results indicate that the aromatic ring at the α position plausibly plays an important role in the stabilization of intermediates that leads to the formation of the tricyclic compound.

The substituents at the alkene moiety showed notable effects on the reaction. The reaction of **1d** with a tetrasubstituted alkenyl group revealed that the bulkiness of the alkene did not strongly inhibit the reaction, though the yield of the product decreased (entry 6). Both compound **1e** (the regioisomer of **1a**) and the terminal alkene **1f** gave the cyclized compounds in moderate yields, while the reaction with the simple allylic compound **1g** resulted in a low yield of the product (entries 7–9). Linker moieties other than ether bonds were also usable. Thus, compounds linked with NBoc or sp^3-carbon (**5** and **7**) gave the corresponding products in high yields (entries 10 and 11).

All the tricyclic products except **2e** were obtained as almost pure single diastereomers. This notably high stereoselectivity plausibly arises from the fact that the formation of other possible stereoisomers can hardly cyclize due to their severe steric strains.

In conclusion, we have developed a new photochemical transformation of thiophene derivatives with an alkene moiety that provides a variety of unique tricyclic frameworks. With appropriate substrates, the reaction proceeds cleanly in a short time to afford the products in high yields.

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Supporting Information Available. Experimental procedures, characterization data for all new compounds, X-ray crystal information file (CIF) for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.