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Photoinduced [4 + 2] cycloaddition reactions of benzo[b]thiophene-2,3-dione with alkenes

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Abstract [4 + 2]-Photocycloadditions of benzo[b]thiophene-2,3-dione with electron-rich and electron-deficient alkenes have been described. Olefins preferentially add at both carbonyl groups to give the head-to-head [4 + 2] cycloadducts, i.e., dioxanes only. Comprehensive molecular orbital calculations at DFT-B3LYP level have been carried out to address the mechanism as well as regiochemical course of the reaction.

Keywords Photocycloaddition · Thioisatin · Dioxanes · Regioselectivity · DFT calculations · Intermediate biradicals

Introduction

Over the last three decades, the photochemistry of organic molecules has grown into an important and pervasive branch of organic chemistry [1, 2]. Photochemical cycloaddition provides one of the most efficient and versatile methods for the construction of carbo- and hetero-cycles of different sizes with high atom economy [3]. Carbonyl compounds constitute a major type of substrates in photocycloadditions. Most commonly, photochemical reactions of carbonyl compounds are classified to cleavage reactions, hydrogen abstractions, and cycloaddition [4, 5]. The [4 + 2] cycloaddition reactions constitutes one of the most frequently employed synthetic method for the construction of highly regio- and enatio-selective six-membered and polycyclic ring systems [6–8]. Over the past three decades, numerous photocycloaddition reactions have been carried out on α-diketones [9] but most of these studies are limited to understanding the electronic structure of the species rather than understanding the mechanism as well as theoretical studies of the

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reactions [10]. Chow and coworkers [11] have described the photoadditions of α-diketones yet the fascinating photochemistry of benzo[b]thiophenes has remained largely unexplored. Synthetically numerous reactions of thioisatin have been described [12] but to our knowledge, photochemically no reaction has been explored. Motivated by our recent works on stereoselectivity in [3 + 2] cycloadditions of azomethine ylides [13, 14] and photochemistry of quinones and their [2 + 2/[3 + 2] photocycloadditions [15–18], we have examined photocycloaddition reactions of benzo[b]thiophene-2,3-diones with various electron-rich and electron-deficient alkenes. The synthetic results complemented by computational study are presented herein.

Experimental

General

Melting points were determined in an open-glass capillary and are uncorrected. The solvents were purified by standard procedures [19, 20]. The IR spectra were recorded on Nicolet Magna IR TM model 550 in KBr pellets. The ^{1}H and ^{13}C NMR spectra were obtained on a JEOL AL-300 instrument at 300 and 75 MHz using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ ppm. Elemental analyses were performed by Perkin-Elmer series C, H, N, and S analyser-2400. Photochemical irradiation was conducted in a Heber multilamp photoreactor (Model: HML-COMPACT-SW-MW-LW888) consisting of a quartz/borosilicate reactor surrounded by 8 + 8 + 8 numbers of UV lamps (eight lamps can be operated at a time: either at 254/312/365 nm with 8 + 8 + 8 separate controls) permanently fixed inside the reaction chamber with a built-in highly polished anodized aluminium reflector (85% reflection) so that UV rays are focused at the center where the sample is kept. The reaction chamber is covered by a reactor house that does not allow leakage of any UV irradiation. Thin-layer chromatography (TLC) was performed on alumina foil on Merck's Kiesel gel 60 F_{254} sheets, visualization was achieved at ultra fluorescence on an Indian Equipment Corporation equipment, IEC-312 at 354 nm. Column chromatography was carried over silica gel 60–120 mesh as absorbent, using solvents of rising polarity.

Computational details

All computations were performed via different theoretical methods by using the Gaussian 03 suite of programs [21]. The optimization of the geometries and population analysis were carried out using generalized gradient approximation Becke3-Lee-Yang-Parr (B3LYP) level of theory with 6–31G basis set. Harmonic vibration frequencies of all stationary points have been computed to characterize them as energy minima (all frequencies are real) or transition states (one and only one imaginary frequency). An imaginary frequency has been obtained for each transition state, which substantiates the actual formation of the transition state.

Intrinsic reaction coordinates (IRC) calculation was carried out to confirm the reaction pathway and the transition state.

General procedure for synthesis

3-Phenyl-2,3-dihydro-1,4-dioxo-9-benzo[b]thiophene ***3a*** A solution of benzo[b]-thiophene-2,3-dione **1** (0.36 g, 2.0 mmol) and styrene **2a** (0.2 g, 2.0 mmol) in dry benzene (35 ml) was placed in a quartz tube and irradiated at 312 nm under nitrogen atmosphere using Heber Multilamp photoreactor for 16 h with magnetic stirring. After completion of the reaction as monitored by TLC, the concentration of the reaction mixture under reduced pressure furnished the product **3a** as a brown mass, which was purified by column chromatography over silica gel. The petroleum ether-choroform (2:8) fraction afforded a brown solid.

Brown solid, mp. 138–140 °C. IR (KBr) ν_{max}: 3020 (Ar-H), 1650 (C=C), 1050 (C–O–C), 670 (C–S) cm^{-1}.^{1}H-NMR ($CDCl_3$) δ 7.45–7.86 (m, 4H, Ar-H), 7.14 (m, 5H, Ar-H), 5.21(s, 1H, H-3), 3.54 (dd, 2H, H-2, $J = 3.51$ Hz, $J = 1.4$ Hz). ^{13}C-NMR ($CDCl_3$) δ 135.14–128.32 (Ar-C), 121.25–122.48 (C=C), 54.55 (C-2), 61.43 (C-3).

Anal. calcd for C_{16} $H_{12}O_2S$: C, 72.31; H, 5.01; S, 11.36; O, 11.33. Found: C, 71.45; H, 4.78; S, 10.46; O, 10.21.

2,3-Diphenyl-2,3-dihydro-1,4-dioxo-9-benzo[b]thiophene ***3b*** Brown solid, mp. 152–154 °C. IR (KBr) ν_{max}: 3025 (Ar-H), 1615 (C=C), 1030 (C–O–C), 665 (C–S).^{1}H-NMR ($CDCl_3$) δ: 7.32–7.89 (m, 4H, Ar-H), 7.18 (s, 10H, Ar-H), 4.54 (dd, 2H, H-2,H-3 $J = 4.72$ Hz, $J = 1.8$ Hz). ^{13}C-NMR ($CDCl_3$) δ 138.14–131.32 (Ar-C), 122.41–121.48 (C=C), 61.82 (C-2, C-3).

Anal. calcd for C_{22} $H_{16}O_2S$: C, 77.07; H, 5.06; S, 8.95; O, 8.93. Found: C, 67.78; H, 4.12; S, 8.06; O, 8.01.

3-Bromo-3-methyl-2,3-dihydro-1,4-dioxo-9-benzo[b]thiophene ***3c*** Shiny brown solid, mp. 105–103 °C. IR (KBr) ν_{max}: 3025 (Ar-H), 1665 (C=C), 1100 (C–O–C), 670 (C–S) 550 (C–Br).^{1}H- NMR ($CDCl_3$) δ 7.48–7.97 (m, 4H, Ar-H), 4.45 (s, 2H, H-2), 2.25 (s, 3H, H-3).^{13}C NMR ($CDCl_3$) δ 134.36–129.32 (Ar-C), 123.25–122.58 (C=C), 59.91 (C-2), 63.03 (C-3), 18.91 (CH_3).

Anal. calcd. (%) for C_{11} H_9BrO_2S: C, 48.17; H, 3.71; S, 10.72; O, 10.70. Found : C, 48.03; H, 3.71; S, 9.98; O, 9.85.

3-Chloro-3-methyl-2,3-dihydro-1,4-dioxo-9-benzo[b]thiophene ***3d*** Chocolate-brown solid, mp. 112–110 °C. IR (KBr) ν_{max}: 3045 (Ar-H), 1670 (C=C), 1055 (C–O–C), 760 (C–Cl) 665 (C–S). ^{1}H-NMR ($CDCl_3$ δ 7.54–7.88 (m, 4H, Ar-H), 4.36 (s, 2H, H-2), 2.32 (s, 3H, H-3).^{13}C-NMR ($CDCl_3$) δ 134.32–129.41 (Ar-C), 124.46–123.58 (C=C), 55.01 (C-2), 65.03 (C-3) 20.01 (CH_3).

Anal. calcd. for C_{11} H_9ClO_2S: C, 56.50; H, 4.35; S, 12.59; O, 12.56. Found: C, 55.58; H, 4.03; S, 11.98; O, 11.76.

1,4-Dioxo-9-benzo[b]thiophene-2,2,-3,3,tetracarbonitrile ***3e*** Buff solid, mp. 120–115 °C. IR (KBr) $v_{\max}$: 3025 (Ar-H), 2265 (C≡N) 1675 (C=C), 1105 (C–O–C), 675 (C–S).

^{1}H-NMR ($CDCl_3$) δ 7.45–7.89 (m, 4H, Ar-H). ^{13}C-NMR ($CDCl_3$) δ 134.94–129.32 (Ar-C), 123.58–122.43 (C=C), 118.43–117.21 (C≡N), 59.38 (C-2, C-3).

Anal. calcd. for $C_{14}H_4N_4O_2S$: C, 58.82; H, 1.97; S, 10.47; O, 10.45. Found: C, 57.78; H, 1.09; S, 9.48; O, 9.56.

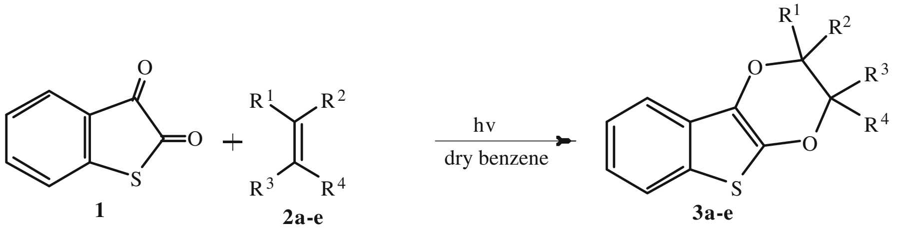
Results and discussion

The photocycloaddition reaction of thioisatin **1** with different alkenes **2** (styrene, *trans*-stilbene, 2-bromopropene, 2-chloropropene and tetracyanoethylene) was carried out under a nitrogen atmosphere in dry benzene with constant magnetic stirring in Heber photoreactor with medium pressure mercury arc lamp at 312 nm (Fig. 1). The photochemical reaction was continued for 22 h until no further thioisatin was consumed. Subsequently, the reaction mixture was evaporated and the crude products purified by column chromatography over silica gel to afford photoadducts in 46–68% yield.

The structure of the cycloadducts **3a–e** has been ascertained from their spectral data. All the spectral data are in harmony with the assigned structures. On the basis of detailed NMR analysis, it has been unambiguously concluded that in all cases head-to-head 1,4-dioxane adducts are formed discarding the possibility of formation of [2 + 2] Paternò–Büchi adducts.

Regio- and stereoselectivity of the photocycloaddition reaction

The regio- and stereoselectivity of the [4 + 2] photocycloaddition reactions has been investigated in detail by DFT molecular orbital calculations. In this study,



2a: $R^1=R^3=R^4=H$; $R^2 = C_6H_5$
2b: $R^1=R^3=C_6H_5$; $R^4=R^2=H$
2c: $R^1=CH_3$; $R^2=Br$; $R^3=R^4=H$
2d: $R^1=CH_3$; $R^2=Cl$; $R^3=R^4=H$
2e: $R^1=R^2=R^3=R^4=CN$

Fig. 1 Reaction of thioisatin with different alkenes

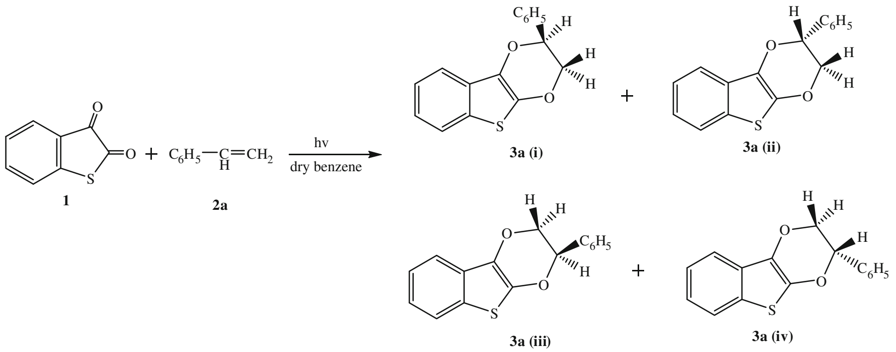


Fig. 2 Possible head-to-head and head-to-tail photocycloadducts **3a(i)–3a(iv)**

photocycloaddition of thioisatin with styrene was chosen as the model reaction. The attack of styrene on thioisatin results in the formation of four isomers **3a(i)–(iv)** (Fig. 2). Among them **3a(i)** and **3a(ii)** are head-to-head regioisomers while **3a(iii)** and **3a(iv)** are head-to-tail photoadducts.

The geometry and energy of all four regioisomers have been optimized at DFT-B3LYP level. The optimized geometries of all the isomers are shown in Fig. 3 and the relative energies are presented in Table 1.

It is evident from Table 1 that the head-to-head regioisomers **3a(i)** and **3a(ii)** are thermodynamically more stable than the head-to-tail regioisomers. The proximity of the bulky phenyl group to sulfur atom may be attributed to the relative destabilization of head-to-tail adducts. Again, among the stereoisomers **3a(i)** and **3a(ii)**, the latter is slightly more favored due to its higher stabilization energy. The minimization of steric repulsion of phenyl group in **3a(ii)** may lead to its enhanced stability. The transition state geometries of **3a(i)** and **3a(ii)** given in Fig. 4.

Mechanism of the photocycloaddition reaction

The next task was to illustrate a feasible mechanism for the formation of **3a(ii)**. A plausible mechanism has been proposed for the [4 + 2] photocycloaddition reaction and is depicted in Fig. 5.

Generally, the photocycloadditions of α-diketones occur via triplet excited states [9]. In this mechanistic pathway, the photocycloaddition reaction is proposed to proceed through triplet biradical intermediates. Thioisatin **1** is excited to its triplet state leading to the formation of a triplet biradical **t1**. The attack of dienophile styrene **2a** on triplet biradical **t1** can take place via two different pathways. In path ‘**a**’ the attack of styrene takes place on the oxygen far from sulfur (**O1**) generating intermediate triplet biradical **t2** and in path ‘**b**’ styrene first attacks on the oxygen near to sulfur (**O2**) yielding another intermediate triplet biradical **t3**. Further, both **t2** and **t3** may cyclize to give the photocycloadduct **3a(ii)**. All the ground state reactants and products as well as intermediate triplet biradicals and transition states have been optimized at DFT-B3LYP level to estimate their energy and to predict the feasible mechanistic pathway. The results are summarized in Table 2.

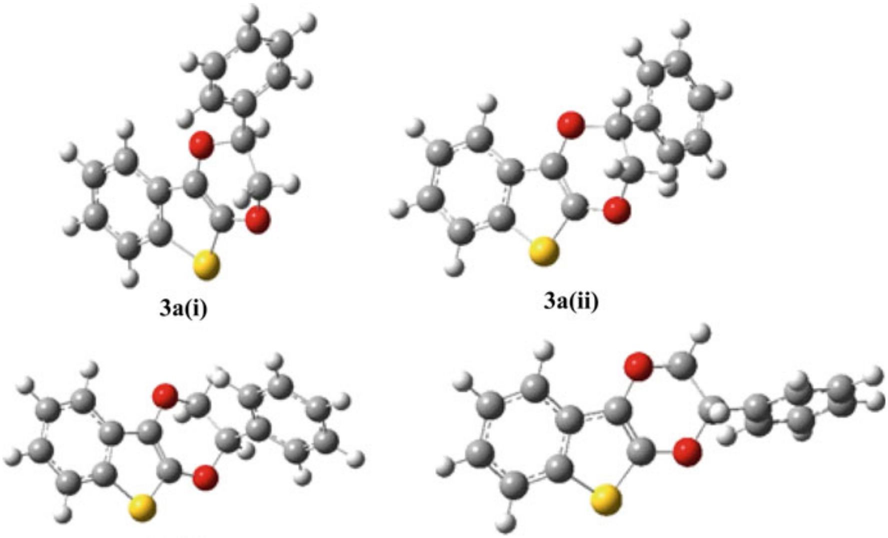

3a(i) 3a(ii) 3a(iii) 3a(iv)

Fig. 3 Optimized geometries of the possible regioisomers **3a(i)–3a(iv)**

Table 1 Relative energies of the regioisomers **3a(i)**–**3a(iv)**

Regioisomer	Relative energy* (Kcal/mol)
3a(i)	−11.86
3a(ii)	−13.80
3a(iii)	−00.50
3a(iv)	−04.02

*Relative to reactants (**1** + **2a**)

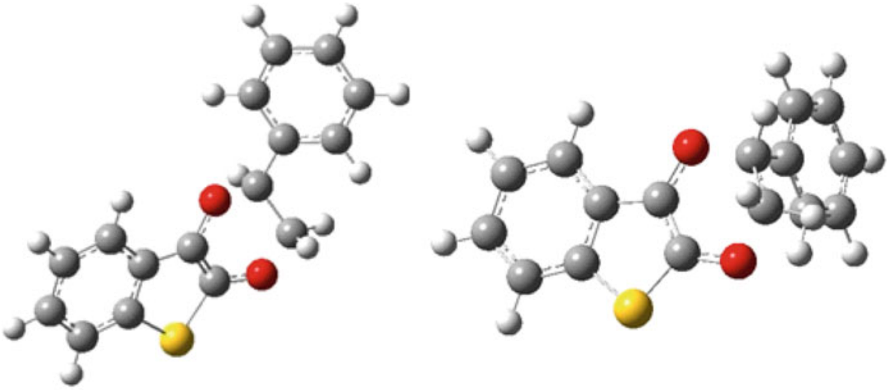

3a(i) 3a(ii)

Fig. 4 Transition-state geometries of the head-to-head photocycloadducts **3a(i)** and **3a(ii)**

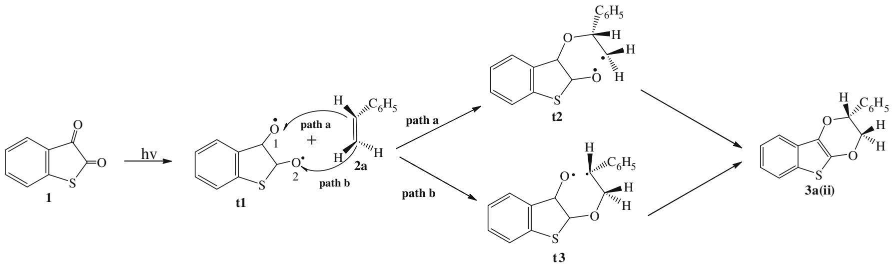


Fig. 5 Proposed mechanism for [4 + 2] photocycloaddition reaction

Table 2 Energy of reactants, biradical intermediate, and transition states computed at B3LYP level of calculation corresponding to attack of styrene

Species	Energy (Eh)
1	−855.7840
2a	−309.5790
t2	−1165.2643
t3	−1165.2921
3a(ii)	−1165.3854
TS [t2/3a(ii)]	−1165.3025
TS [t3/3a(ii)]	−1165.3058

The triplet radical **t2** is a primary biradical while **t3** is a secondary biradical. Also, the energy of **t3** is found to be lower than that of **t2** (Table 2). Subsequently, the formation of intermediate biradical **t3** via path '**b**' is expected to be more feasible. This is further substantiated by transition state studies. The transition states for the final step **t2** → **3a(ii)** or **t3** → **3a(ii)** conversion have been located. The calculations showed that the transition state energy is lower for **t3** → **3a(ii)** conversion. The potential energy diagrams for these conversions and transition state geometries are given below in Figs. 6 and 7.

The potential energy barrier for **t3** → **3a(ii)** conversion is 58.55 kcal/mol while that of **t2** → **3a(ii)** conversion is 76.0 kcal/mol. This clearly indicates that the photocycloaddition proceeds via the secondary biradical **t3** to yield the final cycloadduct **3a(ii)**.

Conclusions

A series of novel 1,4-dioxane derivatives were synthesized by [4 + 2]-photocycloadditions of thioisatin with different dienophiles. DFT-B3LYP studies have been employed to understand the regioselectivity of [4 + 2] photocycloaddition reaction that leads to the formation of six-membered head-to-head dioxane derivatives

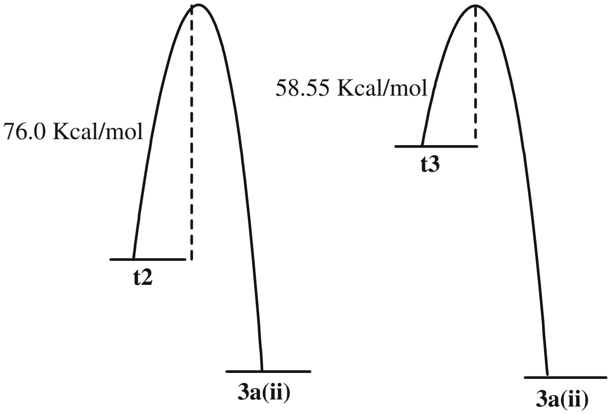


Fig. 6 Potential energy barrier diagram for intermediate biradicals **t2** and **t3**

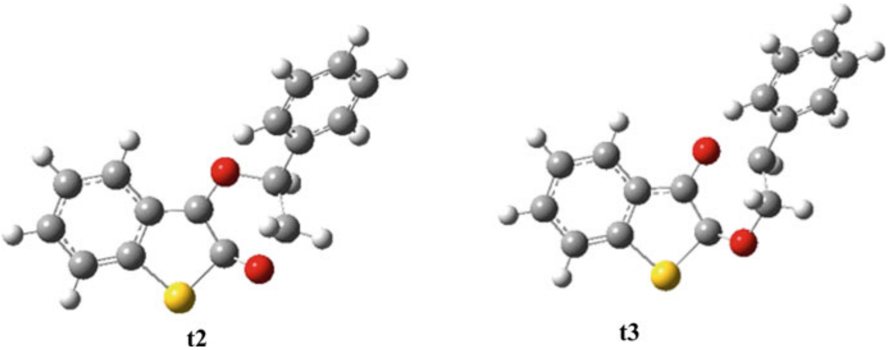


Fig. 7 Transition-state geometries of the intermediate biradicals **t2** and **t3**

predominantly. The mechanism of the reaction pathway is also illustrated by transition state studies.

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