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Construction of spiropyrans *via* [4+2] photocycloaddition reactions and its computational investigation

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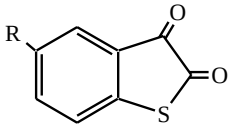
[4+2]-Photochemical cycloaddition provides one of the most efficient and versatile route for the exploring of carbocyclic and heterocyclic frameworks of different sizes with high atom economy. [4+2] photocycloaddition of the chalcones **(2a-h)** obtained by Knoevenagel condensation of thiosatin and different heteroaryl ketones *viz.* 2-acetyl, 3-acetyl, 4-acetylpyridines and 2-acetylthiophene olefinic 2-chloropropene with as dienophiles led to the construction of six membered novel spiropyran heterocycles (**3a-h**) with 60% yield. The mechanism of the [4+2] photocycloaddition reaction has been investigated in detail by DFT-B3LYP/6-31-G+ (2d, 2p) computational method.

Keywords: Chalones, 2-Chloropropene, DFT-B3LYP/6-31-G+ (2d,2p), Heteroary ketones, Thioisatin

Almost 90% of the medicines we use are made up of heterocyclic compounds such as analgesic (fever reducing), antibiotics (penicillin the most widely used), antimalarial, local anaesthetic, antianxiety, antidepressant, antihistaminic, antioxidant, antitubercular, antiparkinson's, antidiabetic, antiobesity and agrochemical immunomodulatory agents, etc[1-4]. The main reason for this interest have been their biological activities and unique structure that leads to several applications in different areas of pharmaceuticals and research, in material sciences for example cytostatic drugs such as alkylating agents, antimetabolites, alkaloids and antitumor antibiotics[5-7]. Among the numerous heterocycles, sulphur, oxygen and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis[8, 9].

The construction of aryl- and heteroaryl fused derivatives constitutes important scaffolds in medicinal chemistry with significant pharmacological properties[10, 11]. In recent years, the benzo[b]thiophene-2, 3-diones have attracted considerable attention due to their ability to act as intermediates in the preparation of a series of fused spiroheterocycles. Among this the thiophenic and benzothiophenic frameworks are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in a wide number of natural and synthetic agents[12-18]. In the present we have utilized benzo[b]thiophene-2, 3-dione, commonly known as *thioisatin* (**1a**), and its 5-methyl derivative (**1b**) as synthons for construction of novel spiropyrans[19, 20].



1

1a : R = H
1b : R = CH_3

Synthetically numerous reactions of benzo[b]thiophene-2,3-dione have been described which were reviewed by Hartough and Meisel[21] in 1959 and F.D. Popp and M. Rajopadhye[22] in 1988. Subsequently the present study deals with the synthesis of a variety of spiropyrans for which we have evolved strategies *viz.* [4+2] photocycloaddition (spiropyrans **3a-h**). A detailed computational study of synthesized spiropyrans has been carried out on Gaussian 03 suite[23] of program to address the regio- and stereoselectivity as well as to find out their mechanism and stability order under different types of substitutions.

Results and Discussion

The Knoevenagel condensation between the substituted thioisatin (**1a, b**) and heteroaryl ketones or their derivatives in the presence of diethylamine to produced the aldol products, which underwent facile dehydration with conc. HCl-AcOH mixture to yield the α, β-unsaturated carbonyl compounds *3-(o-pyridineacylidine-2)benzo[b]thiophene-2-ones* (**2a**), commonly known as *chalcones*, in about 60-65% yield (Scheme I)

The conformation of structures of the synthesized chalcones was confirmed by physical (Table I) and spectral data.

Photocycloaddition reaction of chalcones (2a-h) with 2-chloropropene

The [4+2]-photocycloaddition reaction of chalcones with 2-chloropropene was carried out under nitrogen atmosphere in dry toluene with constant stirring in Heber Photoreactor with medium pressure mercury arc lamp at 312 nm. The photochemical reaction was continued until no further thioisatin was consumed (Scheme II). Subsequently, the reaction mixture was evaporated and the crude products were purified by column chromatography over silica gel to afford photo-adducts (**3a-h**) in 52-58% yield (Table II).

The frame of the photocycloadducts (**3a-h**) has been ascertained from their spectral data. Disappearance of one >C=O group in IR/^{13}C NMR as well as appearance of spirocarbon at ~ δ 81.0 ppm in ^{13}C NMR confirmed the formation of products. ^{1}H NMR data showed following signals; CH_2 protons as a double doublet in the range 2.72 to 2.76 and multiplets in the range of 6.60-7.82 for aromatic and heteroaromatic protons, decisively confirmed the formation of *spiro {2' (heteroaryl)-6'-chloro, 6'-methyl-2H-pyran-4',3}-benzo[b]thiophene-2-one* (**3a-h**) products.

Regio- and stereoselectivity of photocycloaddition

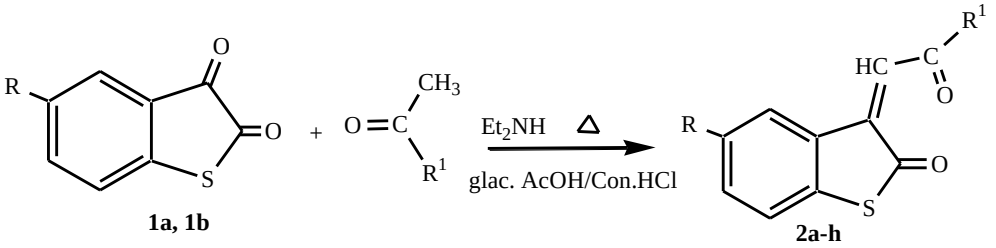
The regio- and stereoselectivity of [4+2] photocycloaddition reaction has been investigated by DFT calculation. *2-Chloropropene* attack as a dienophile on chalcone (**2a)** may result in the formation of four isomers (**3a-1)** to (**3a-4)** (Scheme III).

Optimized geometries of all four possible stereoisomers are shown in Figure 1 at B3LYP/6-31+G (2d, 2p) level and the relative energies of the stereoisomers are presented in Table III**.**

The Table III proves that the total energy of stereoisomer (**3a-1**) is thermodynamically more stable than other stereoisomers. The bulkiness of the chlorine atom feels minima interaction in its spatial arrangement than the remaining three (**3a-2** to **3a-4**) stereoisomers.

Energy content and relative stabilities

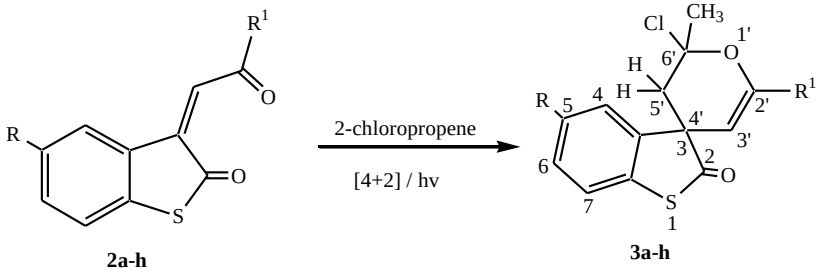
For comparing the values of energy, single point energy (SPE) of the spiropyrans were also estimated at various levels of theory like semiempirical



Scheme I

Table I — Physical data of chalcone derivatives (2a-h)

Entry	Product	R	R^1	Time (hr)	M.p (^{0}C)	Yield (%)
1	**2a**	H		17	180-182	64
2	**2b**	CH_3		15	186-188	59
3	**2c**	H		17	178-180	62
4	**2d**	CH_3		10	201-203	58
5	**2e**	H		15	196-200	59
6	**2f**	CH_3		18	156-157	58
7	**2g**	H		21	186-184	63
8	**2h**	CH_3		20	201-204	60



2a-h **3a-h**

Scheme II — Synthesis of spiropyrans

Table II — Substitution pattern in photocycloadducts (**3a-h**)

Entry	Product	R	R^1	Time (hr)	M.p (^{0}C)	Yield (%)
1	**3a**	H		21	201-203	54
2	**3b**	CH_3		23	172-174	57
3	**3c**	H		20	192-194	52
4	**3d**	CH_3		21	206-210	58
5	**3e**	H		27	221-224	56
6	**3f**	CH_3		24	200-203	58
7	**3g**	H		20	192-194	56
8	**3h**	CH_3		21	212-214	57

AM1 and B3LYP/6-311+G (2d, 2p). The energies computed for various species involved in the formation of spiropyrans at different levels are presented in Table IV

The value of energies improved as the computational technique was improved. All the energy values are in negative (–), which indicates that the species are thermodynamically stable by itself. The stability of the spiropyrans depends on the energy change of the reaction of its formation from corresponding chalcones. Thermodynamically spiropyran (**3h)** is more stable and the stability order of synthesized products are: **3h** >**3g** > **3d** > **3f** > **3b** >**3a** > **3e** >**3c.** This result also interpretation by *Frontier molecular orbital analysis* of these synthesized compounds.

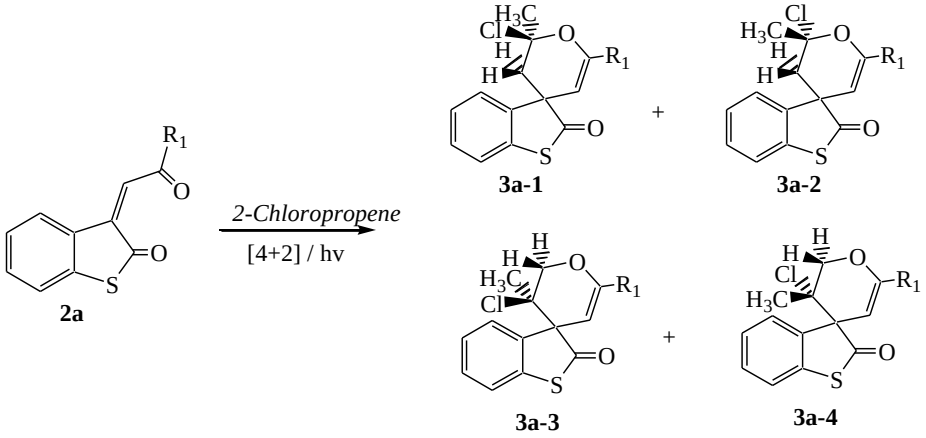
Frontier molecular orbital analysis

The Eigen values of LUMO and HOMO and its energies gap reflect the molecular activity. LUMO as an electron acceptor represents the ability to obtain electrons, and HOMO as an electron donor represents the ability to donate electrons. The lesser the energy gap between the LUMO and HOMO, the easier it is for electrons of HOMO to be excited. In simple molecular orbital theory approaches, the HOMO energy (E_{HOMO}) is related to the ionization potential (IP) and the LUMO energy (E_{LUMO}) is used to estimate the electron affinity.

If $E_{HOMO} \approx$ IP and $E_{LUMO} \approx$ EA, then the average values of the HOMO and LUMO energies are related to the electro negativity defined by Mulliken as χ = (IP+EA)/2. In addition, the HOMO-LUMO gap is related to the hardness (η) and also is an approximation to the first electron excitation energy. The electronegativity and hardness are used extensively to make predictions about chemical behavior.

Our objective was to analyze the HOMO-LUMO energies of spiropyrans (**3a-h)**. The Eigen values of the HOMO and the LUMO and the energy gap between these two frontier orbitals in spiropyrans (**3a-h)** are given below in Table V

From the **Table I.5** it is clear that the energy gap for all the photocycloadducts (**3a-h)** is all most similar; though cycloadducts **(3g)** and (**3h)** relatively appear to be more stable. Consequently, the excitation of the spiropyran from singlet ground state to triplet excited state may occur easily in these spiropyrans.



Scheme III — Possible stereoisomers for the cycloadduct **3a**

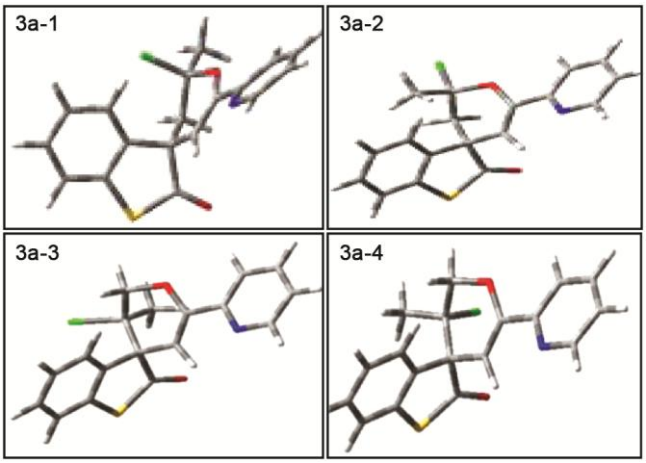


Figure 1 — Optimized geometries of possible stereoisomers of 3a

Table III — Total energy of possible stereoisomers

Energy (kcal/mol)	**3a-1**	**3a-2**	**3a-3**	**3a-4**
	-1103167.93	-1103163.07	-1103159.23	-1103157.22

Table IV — Absolute energies of spiropyrans, computed at B3LYP/6-31G (2d, 2p) level. Energies are given in Kcal/mol

Basic Sets	**Species**			
	3a	**3b**	**3c**	**3d**
AM1	-14.9850	-7.2587	-12.47153	-4.73085
B3LYP/6-31+G (2d, 2P)	-1103232.661	-1127842.200	-1103165.428	-1127840.141
	3e	**3f**	**3g**	**3h**
AM1	-13.22716	-5.47491	-7.985704	-0.253788
B3LYP/6-31+G (2d, 2P)	-1103165.447	-1127840.135	-1294378.292	-1313267.966

Mechanism

A plausible mechanism for the formation of spiropyrans (**3a-1**) is depicted in Scheme IV

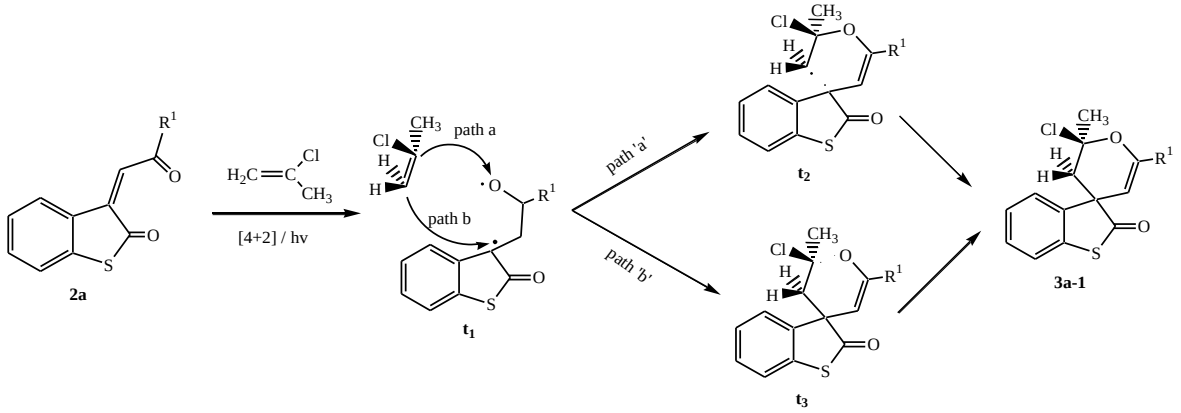
Like photocycloadditions of other α, β-unsaturated ketones occur *via* triplet excited state, this photocycloaddition reaction also proceeds through a triplet biradical intermediate, $\mathbf{t_1}$. There are two pathways for the attack of 2-chloropropene on triplet biradical ($\mathbf{t_1}$). In path '**a**' the attack of 2-chloropropene may takes place on the oxygen radical generating $\mathbf{t_2}$ and in path '**b**' 2-chloropropene first attacks on the carbon radical producing $\mathbf{t_3}$. Then both $\mathbf{t_2}$ and $\mathbf{t_3}$ may cyclise to give the photocycloadduct (**3a-1**). All the reactants, products and intermediate triplet biradicals

Table V — HOMO and LUMO energies and HOMO-LUMO energy gap in spiropyrans derivatives, computed at B3LYP/6-31+G (2d, 2p) level

Species	HOMO (eV)	LUMO (eV)	HOMO-LUMO (eV)
3a	-6.3675	-1.8231	4.5444
3b	-6.2813	-1.7959	4.5854
3c	-6.5035	-1.8231	4.6804
3d	-6.3943	-1.7687	4.6253
3e	-6.6124	-2.0136	4.5988
3f	-6.4491	-1.9864	4.4627
3g	-6.0953	-1.7687	4.3265
3h	-6.0409	-1.7415	4.2994

Table VI — Energy of reactants, biradical intermediates and transition states

Species	**2a**	*2-chloropropene*	t_2	t_3	**3a-1**
Energy (kcal/mol)	-740750.523	-362402.082	-1103134.822	-1103132.39	-1103167.586



Scheme IV — Mechanism of photocycloaddition reaction

as well as transition states have been optimized at B3LYP/6-31+ G (2d, 2p) level to predict their mechanistic pathway. The results are summarized in Table V-VII. The transition state geometry of (**3a-1**) is given in Figure 2.

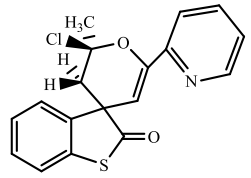
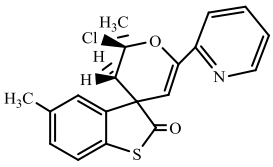
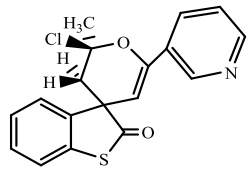
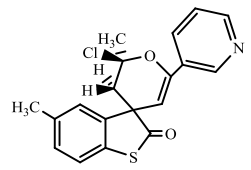
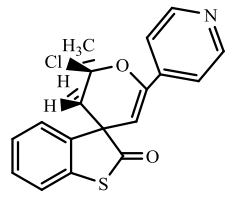
The higher stability of triplet radical $\mathbf{t_2}$ than $\mathbf{t_3}$ may be due to extended conjugation of carbon radical with the labile π-electron pair as well as heteroaryl group.

For $\mathbf{t_2 \rightarrow 3a\text{-}1}$ conversion the energy required is 27.566 kcal/mol while that of $\mathbf{t_3 \rightarrow 3a\text{-}1}$ conversion is 29.998 kcal/mol (Figure 3). Hence it may be concluded that this photocycloaddition proceeds through the primary biradical $\mathbf{t_2}$.

Experimental Protocols

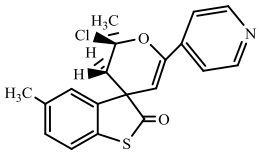
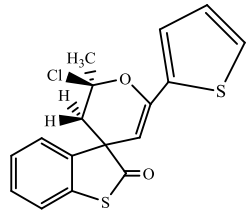
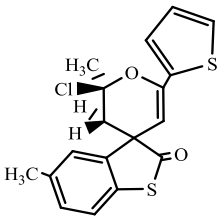
Melting points were determined in open glass capillary and are uncorrected. The solvents were purified by standard procedures[24]. The IR spectra were recorded on Nicolet Magna IR TM model 550 in KBr pellets. The ^{1}H and ^{13}C NMR spectra were obtained on a JEOL AL-300 instrument at 300 and 75 MHz using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ ppm. 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 (8 lamps can be operated at a time: either at 254nm/312nm/ 365nm with 8+8+8 separate controls) permanently fixed inside the reaction chamber with built-in highly polished anodized aluminium reflector (85% reflection) so that UV rays are focused at the centre where the sample being kept. The reaction chamber is covered by reactor house which 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 adsorbent, using solvents of rising polarity.

Table VII — Tabulation of spectral data's of synthesized compounds

Structures & Nomenclatures	IR	^{1}H NMR	^{13}C NMR
 *Spiro {2' (o-pyridine)-6'-chloro, 6'-methyl-2H-pyran-4',3}-benzo[b]thiophene-2-one* ***(3a)***	3010-3040 (Ar-H), 1722 (C=O), 1605 (C=C), 1590 (C=N),610 (C S)cm^{-1}	δ 1.78 (s, 3H, CH_3), 2.72 (d, 1H, *J* = 3.7, CH_2), 2.76 (d,1H, *J* = 4.2, H2, CH_2) 5.64 (s, 1H, CH), 6.76-7.82 (m, 8H, Ar-H) ppm	δ 192.10 (C=O), 126.00-153.10 (Ar-C), 80.57 (spiro C), 55.65 (CH), 53.12 (CH), 23.12 (CH_3) ppm
 *Spiro{2' (o-pyridine)-6'-chloro, 6'-methyl-2H-pyran-4', 3}-5-methylbenzo[b]thiophene-2-one* ***(3b)***	3010-3040 (Ar-H), 1722 (2-C=O), 1605 (C=C), 1590 (C=N) 610 (C-S) cm^{-1}	δ 1.72 (S, 3H, CH_3), 2.70 (d, 1H, *J* = 2.7 Hz, CH_2), 2.77 (d,1H, *J* = 4.1 Hz, CH_2), 5.62 (s, 1H, CH), 6.62-8.21 (m, 7H, Ar-H) ppm	δ 190.01 (C=O), 127.00-154.10 (Ar-C), 82.21 (spiro C), 72.85 (CH), 54.65 (CH), 52.23 (CH), 24.09 (CH_3), 21.03 (CH_3) ppm
 *Spiro{2' (m-pyridine)-6'-chloro,6'-methyl-2H-pyran-4',3}-benzo[b]thiophene-2-one* ***(3c)***	3030-3010 (Ar-H), 1732 (C=O), 1608 (C=C),1591 (C=N), 608 (C-S) cm^{-1}	δ 1.72 (S, 3H, CH_3), 2.62 (d, 1H, *J* = 3.4 Hz, CH_2), 2.71 (d, 1H, *J* = 1.7 Hz, CH_2) 5.54 (s, 1H, CH), 6.63-8.12 (m, 8H, Ar-H) ppm	δ 191.13 (C=O), 128.02-152.11 (Ar-C), 83.20 (spiro-C), 69.89 (CH), 51.85 (CH), 53.10 (CH_2), 23.02 (CH_3) ppm
 *Spiro{2' (m-pyridine)-6'-chloro,6'-methyl-2H-pyran-4',3}-5-methylbenzo[b]thiophene-2-one* ***(3d)***	3040-3030 (Ar-H), 1721 (C=O), 1601 (C=C), 1598 (C=N) 615 (C-S) cm^{-1}	δ 1.70 (S, 3H,-CH_3), 2.28 (s, 3H, *J* = 5.3 Hz, CH_3), 2.60 (d, 1H, *J* = 4.3 Hz, CH_2), 2.68 (d, 1H, CH_2) 5.16 (s, 1H, CH), 8.26-6.62 (m, 7H, Ar-H) ppm	δ 190.53 (C=O), 127.02-153.31 (Ar-C), 81.20 (spiro-C), 71.19 (CH), 52.65 (CH), 54.10 (CH), 23.21 (CH_3), 21.03 (CH_3) ppm
 *Spiro{2' (p-pyridine)-6'-chloro-6'-methyl-2H-pyran-4',3} benzo[b] thiophene-2-one* **(3e)**	3040-3010 (Ar-H), 1722 (C=O), 1605 (C=C), 1590 (C=N) 610 (C-S) cm^{-1}	δ 1.72 (S, 3H, CH_3), 2.58 (d, 1H, *J* = 2.9, CH_2), 2.61 (d, 1H, *J* = 1.7, CH_2) 5.14 (s, 1H, CH), 6.69-8.19 (m, 8H, Ar-H) ppm	δ 192.10 (C=O), 126.00-153.10 (Ar-C), 85.20 (spiro C), 61.95 (CH), 55.65 (CH), 53.15 (CH) ppm

(Contd.)

Table VII — Tabulation of spectral data's of synthesized compounds

Structures & Nomenclatures	IR	^{1}H NMR	^{13}C NMR
 *Spiro{2' (p-pyridine)-6'-chloro,6'-methyl (diphenyl)-2H-pyran-4',3}-5-methylbenzo[b]thiophene-2-one* **(3f)**	3038-3000 (Ar-H), 1725 (C=O), 1600 (C=C), 1595 (C=N), 608 (C-S) cm^{-1}	δ 1.68 (S, 3H, CH_3), 2.21 (s, 1H, CH_3), 2.60 (d, 1H, *J* = 3.1 Hz, CH_2), 2.62 (d, 1H, *J* = 2.8 Hz, CH_2) 5.24 (s, 1H, CH), 6.79-8.19 (m, 7H, Ar-H) ppm	δ 190.19 (C=O), 152.09-127.00 (Ar-C), 83.01 (C_{spiro}), 61.52 (CH), 55.15 (CH), 53.65 (CH) ppm
 *Spiro{2' (o-thiophene)-6'-chloro,6'-methyl-2H-pyran-4',3}-benzo[b]thiophene-2-one* ***(3g)***	3040-3010 (Ar-H), 1722 (C=O), 1605 (C=C), 1590 (C=N), 610 (C-S) cm-1	δ 1.72 (S, 3H, CH_3), 2.52 (d, 1H, *J* = 3.1 Hz, CH_2), 2.56 (d, 1H, *J* = 2.8 Hz, CH_2) 5.34 (s, 1H, CH), 6.60-7.29 (m, 7H, Ar-H), ppm	δ 187.39 (C=O), 126.90-148.12 (Ar-C), 78.31 (spiroC), 60.12 (CH), 55.15 (CH), 54.25 (CH) ppm
 *Spiro{2' (o-thiophene)-6'-chloro,6'-methyl-2H-pyran-4',3}-5-methylbenzo[b]thiophene-2-one* ***(6h)***	3034-3022 (Ar-H), 1725 (S-C=O), 1727, 1592 (C=Caro), 802 (C-Haro), 640 (C-S) cm^{-1}	δ 1.69 (S, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.53 (d, 1H, CH_2), 2.58 (d, 1H, CH_2) 5.44 (s, 1H, CH), 6.72-7.62 (6H, 1H, Ar-H) ppm	δ 188.26 (C=O), 127.90-138.23 (Ar-C), 121.22 (=CH) 80.23 (spiro C), 61.23 (CH), 52.85 (CH), 51.15 (CH), 23.12 (CH_3), 21.02 (CH_3) ppm

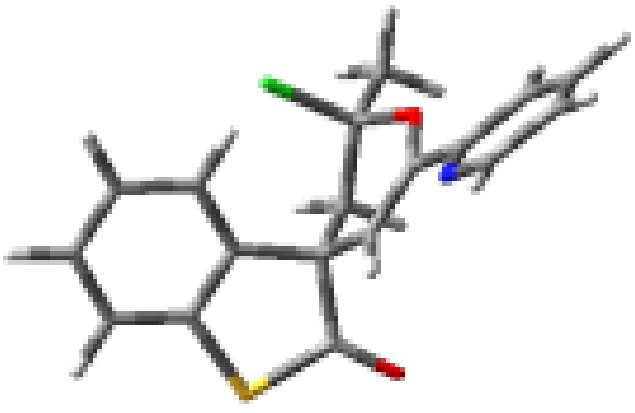


Figure 2 — ts-3a-1

Computational details

All computations were performed *via* different theoretical methods by using the Gaussian 03 suite of programs. The optimization of the geometries and population analysis were carried out in detail by DFT molecular orbital calculations. Harmonic vibration

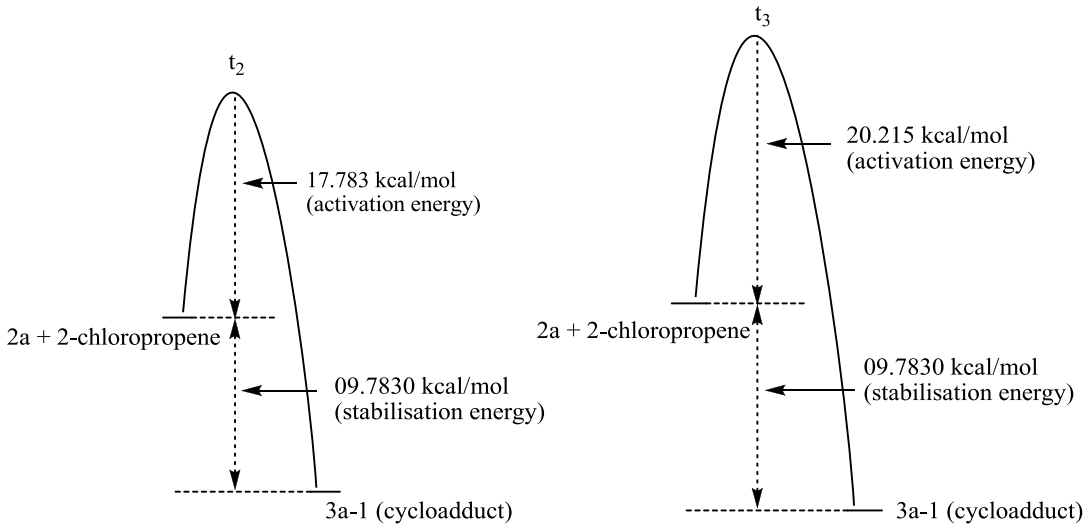


Figure 3 — Energy profile diagram for the formation of cycloadduct 3a-1

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.

General procedure

A mixture of substituted thioisatin (0.820 g, 0.005mol) and heteroaryl ketone (0.005 mol) in equimolar ratio was refluxed for 17-21 hr in the dry ethanol (50 ml). For good yield this mixture was converted into basic medium by adding a few drops of diethylamine. After completion of the reaction as monitored by TLC, the reaction mixture was concentrated and then allowed to stand overnight. It was filtered and then dehydrated using con. HCl-AcOH (20 ml) to afford α, β-unsaturated carbonyl compound (chalcone **2a-h**), as crude solid product. It was purified by column chromatography over silica gel by elution with solvents of rising polarity. The compounds were obtained from chloroform: petroleum ether (1:4) fraction. A reaction mixture of chalcone (0.003mol) and 2-chloropropene (0.006mol) and dry toluene (30 ml) was irradiated in Heber Photoreactor for 22-24hr with constant stirring under nitrogen atmosphere. The photochemical reaction was continued until no further chalcone **(2a-h)** was consumed. The reaction mixture was evaporated and the crude products were purified by column chromatography over silica gel to afford photo-adducts in 52-60% yield.

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