Reversible shifting of a chemical equilibrium by light: the case of keto-enol tautomerism of a β-ketoester
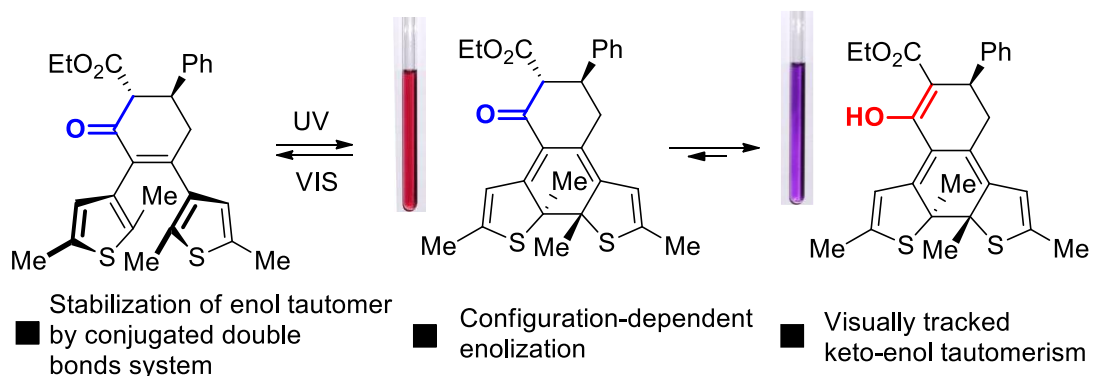
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- Stabilization of enol tautomer by conjugated double bonds system
- Configuration-dependent enolization
- Visually tracked keto-enol tautomerism

ABSTRACT

Manipulating the equilibrium between a ketone and an enol by exposure to light opens up ample opportunities in material chemistry and photopharmacology since it allows one to reversibly control the content of the enol tautomer, which acts as a hydrogen atom donor, with high spatio-temporal and energy resolution. Although tautomerization of β-ketoesters or their analogs was studied in numerous papers, their light-induced reversible tautomerization to give thermally stable enols (photoenolization) is an unexplored area. To shed light on this "blind spot", we report an unprecedented property of diarylethene **2A** assembled from fragments of photoactive dithienylethene and a β-ketoester as part of the cyclohexenone bridge. In a pristine state, the tautomeric equilibrium of **2** is almost completely shifted towards the ketone. Photocyclization of the hexatriene system results in a new equilibrium system containing a significant fraction of the enol tautomer, both in polar and non-polar solvents. Due to the considerable spectral separation (35 nm), the keto-enol tautomerization process could be observed visually. The tendency of **2A** to undergo light-induced enolization was proved by isolating a related byproduct of photochemical 1,2-dyotropic rearrangement stabilized in the enolic
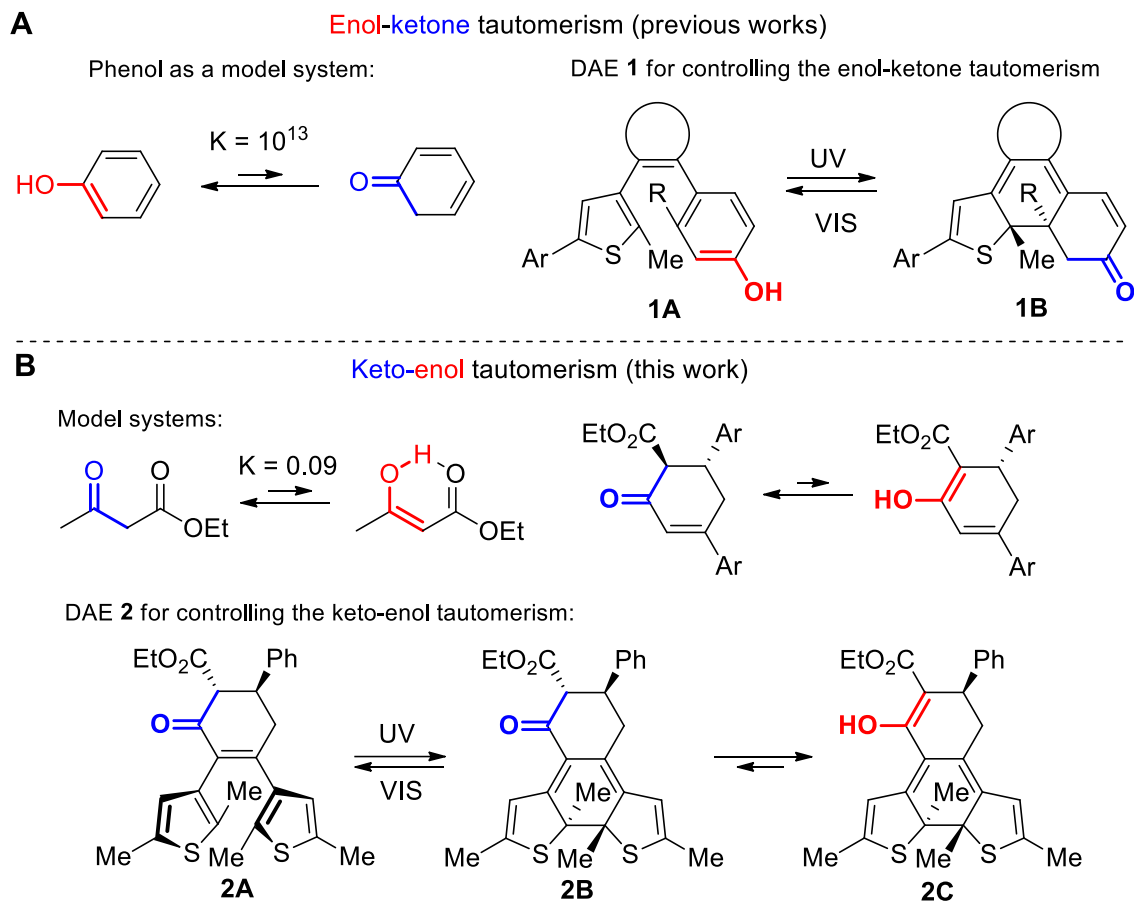
form. Our results provide a novel tool for controlling the keto-enol tautomerism that might find use in the development of novel photocontrollable processes.

Communication

Tautomerism, i.e., the existence of compound as a mixture of two or more structurally distinct tautomers that are in rapid equilibrium, is an important phenomenon for biochemistry,[1] materials,[2] and synthetic chemistry.[3] The interconversion between a ketone and an enol is the most known and thoroughly studied example of tautomerism.[4] The remote manipulation of this equilibrium to achieve a control over the content of a proton-donor enol tautomer is an intriguing task. A number of approaches were used to this end, including encapsulation,[5] modulation of chemical environment[6] and solvent polarity.[7] However, an application of non-invasive external stimuli to shift a tautomeric equilibrium is a challenging task, and light is an appealing tool that provides high spatial, temporal, and energy resolution.[8,9]

Photoswitchable tautomeric systems featuring relatively stable at room temperature ketone and enol forms could be designed using photochromic molecules as basis for switchability. The diarylethenes (DAEs) is a well-established class of bistable compounds featuring thermally stable photoinduced form,[10] which renders those photochromes highly prospective candidates for manipulating the keto-enol equilibrium. For the first time, this approach was used by Uchida et al., who reported light-induced switching of keto-enol equllibrium using diarylethenes **1** (Scheme 1A).[11] Thus, whereas the keto-enol equilibrium is fully shifted towards the thermodynamically stable enol (phenol) form, the photocyclization of the hexatriene motif shifted the equilibrium to the corresponding ketone form. Very recently, using derivatives of **1**, Hecht et al. developed a photoswitchable catalytic system for *in situ* remote-controlled polymerization[12] and also achieved the bidirectional manipulation of a dynamic covalent system by light.[13]

Scheme 1. Photochromic diarylethene-based approaches to control keto-enol equilibrium.

A   Enol-ketone tautomerism (previous works)

Phenol as a model system: DAE **1** for controlling the enol-ketone tautomerism

B   Keto-enol tautomerism (this work)

Model systems:

DAE **2** for controlling the keto-enol tautomerism:

Importantly, the enol form was a thermodynamic ground state in this case and light-induced *enol-to-ketone* transformation was realized. However, to the best of our knowledge, no examples of *reverse* light-induced *ketone-to-enol* transformation using thermally stable diarylethenes have been demonstrated thus far. Previous examples of so-called photoenolization[14] of various types of compounds feature a number of drawbacks, including low thermal stability of photoenol (few minutes),[15] air-sensitivity,[16] and activity only in the solid state.[17] On-demand generation of thermally stable H-donor enol form at ambient conditions in solution is highly attractive, for instance, for remote-controlled polymerization[18] and switching acidity in many biological applications.[19]

Herein we report an unprecedented reversible shifting of keto-enol equilibrium towards a thermally stable enol form upon photocyclization of diarylethene **2A** (Scheme 1B), which has been achieved in polar and non-polar solvents. Implementation of this approach allowed us to control a well-known keto-enol equilibrium of *β*-ketoesters (e.g., ethyl acetoacetate, Scheme 1B)[20] by light irradiation only.

Diarylethene **2A** was synthesized by Robinson-type annulation of ketoester **3** and chalkone **4** (Scheme 2A).[21] The molecular structure of **2A** has been confirmed by X-ray crystallography. Single crystal analysis reveals the presence of two conformers **2A'** and **2A''** (Scheme 2). Both conformers adopt a distorted half-chair (sofa) geometry of the cyclohexenone bridge with *anti*-position of the pseudo-equatorial CO_2Et and phenyl groups (for simplicity, we considered only 1*S*,2*R*- enantiomer). The thienyl moieties reveal antiparallel orientation, with the respective *α*-methyl groups pointing in different directions. The difference between the major conformer **2A'** and the minor conformer **2A''** is due to differing helicity imposed by thienyl rings (*M* and *P* helicity, respectively).

Scheme 2. Synthesis, molecular structure, and solid-state photochromism of diarylethene 2A.

M-Conformer **2A'** (87.6%)   *P*-Conformer **2A''** (12.4%)
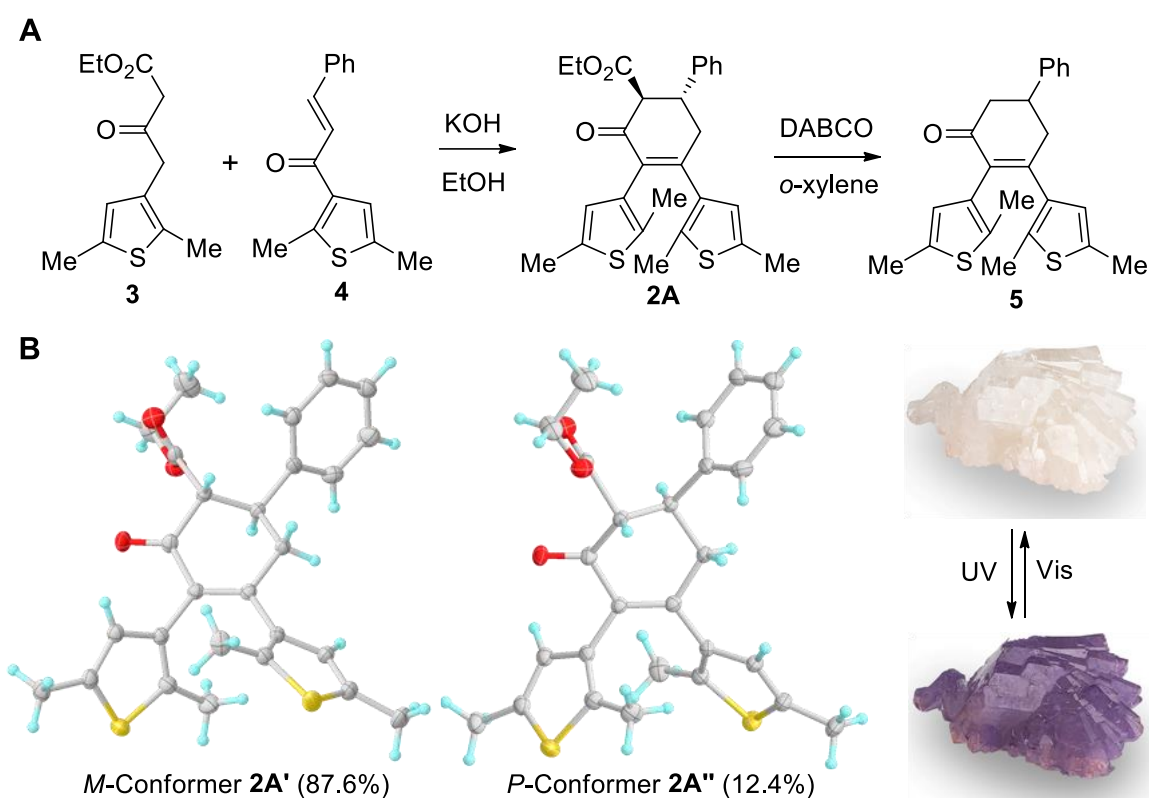
X-ray crystallography reveals the presence of a carbonyl group in the bridge, which is supported by NMR spectroscopy. ^{1}H NMR spectrum of **2A** reveals the multiplets of four cyclohexenone aliphatic protons in 2.88-4.05 ppm range (for details, see SI). The ^{13}C NMR spectrum shows a peak of a carbonyl group at 193.2 ppm. Thus, we conclude that **2A** exists exclusively in a ketone form. However, previous studies on tautomerism of 4,6-diarylsubstituted analogs of **2A** (see model system on Scheme 1B) demonstrated their tendency to enolization.[22] For this reason, we carried out additional

experiments. Solutions of **2A** in various solvents were kept in the dark for a long time and were monitored by NMR spectroscopy. Only negligible enolization of **2A** was detected in acetonitrile (4% of enol in the equilibrium mixture), while the spectrum of **2A** remained unchanged in toluene (see Section IV.1 in SI).

Diarylethene **2A** demonstrates typical for this family of photochomes[10] photophysical properties in MeCN solution and in the crystalline state (Figure 1, Scheme 2). The open-ring form **2A** reveals an absorption maximum at 326 nm. Irradiation with UV light (λ = 365 nm) resulted in the emergence of a new band in the visible at 550 nm due to the photocyclization to the closed-ring form **2B** (Scheme 1). The photostationary state (PSS) conversion at λ = 365 nm is estimated at 65% (for **2B** $\varepsilon(550)$ = 5×10^3 L·mol^{-1}cm^{-1}). Irradiation with visible light (green LED, λ = 520 nm) resulted in the disappearance of the new band and the restoration of the spectrum of open-ring form **2A** (Figure S18). Reversible photocyclization can be repeated several times (Figure 1b).

Unexpectedly, we found that the photoinduced form **2B** has been slowly converted to an unknown compound upon storage in the dark in solution at room temperature. After one day, the 550 nm band of **2B** shifted hypsochromically to 515 nm. The new compound remains photochromic and its long-wave band disappears upon irradiation with visible light (Figure S19).
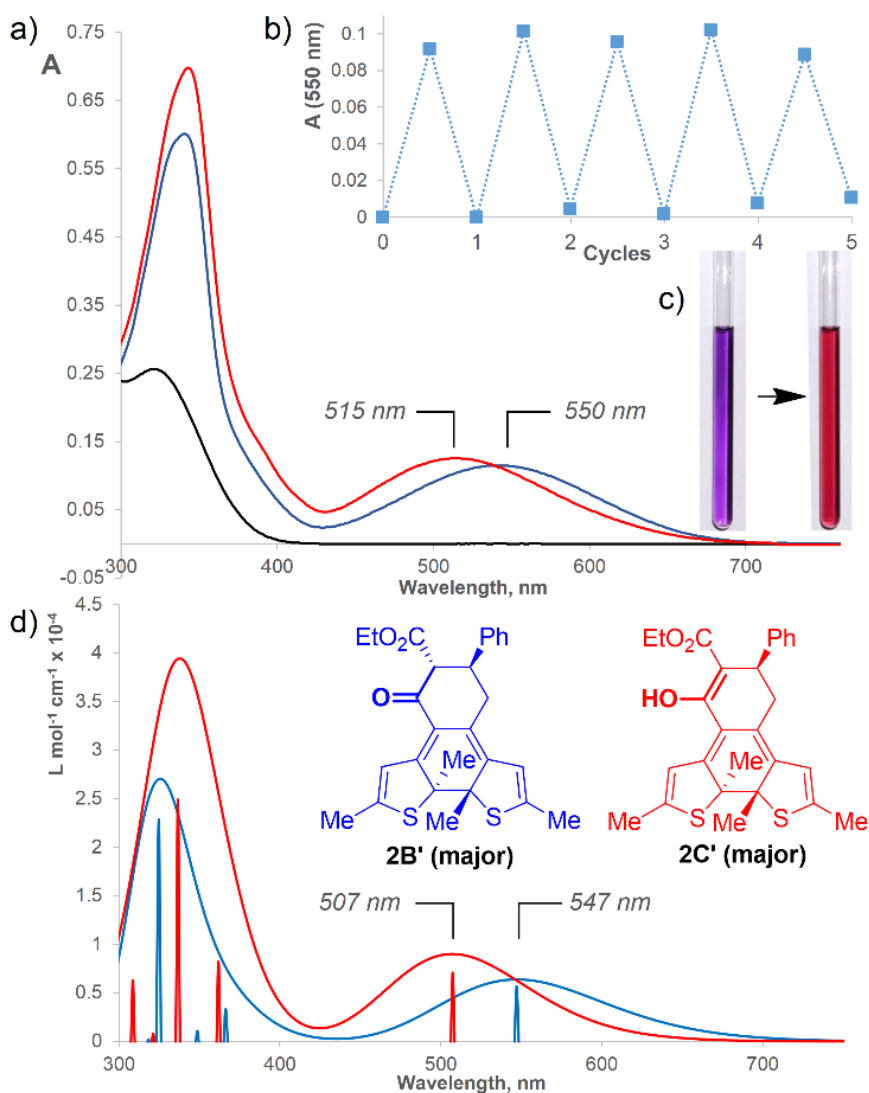
Figure 1. a) UV/Vis spectra **2A** in CH$_3$CN (c = 4.3×10^{-5} M): pristine (black), after irradiation with UV (λ = 365 nm) for 40 s (blue), and after subsequent storing in the dark at rt for 1 day (red). b) reversible switching by alternating irradiation with UV and green LED. c) Solution of **2A** in CH$_3$CN (c = 3.0×10^{-3} M) after irradiation with UV (left, PSS was not reached) and after subsequent storing for 3 days (right). d) Calculated spectra of **2B'** and **2C'** (see text for details).

On contrary, the model compound **5** without a CO$_2$Et group in the bridge did not show any thermal shift of the corresponding long-wavelength band of the photoinduced form. A plausible explanation of the notable phenomenon observed for **2B** is that keto-enol tautomerization of the β-ketoester motif occurs after successful photocyclization (reaction **2B'** → **2C'** in Scheme 3). To support this hypothesis, we calculated the electronic absorption spectra of **2B'** and **2C'**. We used the approach

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recommended[23] by Patel and Masunov for diarylethenes: M05-2X/6-31G(d)//TD-M05/6-31G(d) level of theory, including Polarizable Continuum Model. The calculated spectra (Figure 1d) are in good agreement with the experimental ones for the ketone tautomer (λ_{exp} = 550, λ_{calc} = 547 nm) and the enol tautomer (λ_{exp} = 515 nm, λ_{calc} = 507 nm). The considerable difference in the absorption maxima (35 nm) of **2B'** and **2C'** allowed us to track the keto-enol tautomerization process visually (Figure 1c). In principle, such band separation is a key for selective addressing the electrocyclic ring-opening in either one or the other compound in an equilibrium mixture.[13,24]

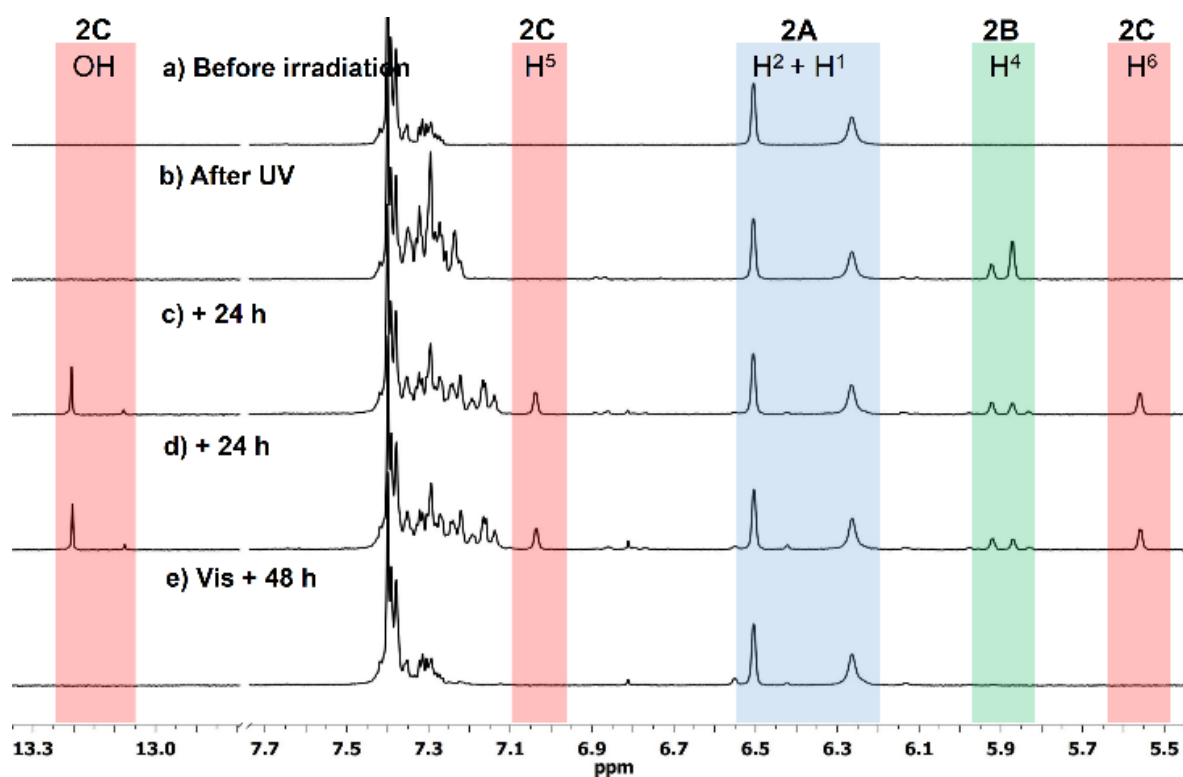**Scheme 3. Light-induced keto-enol transformations of diarylethene 2.**
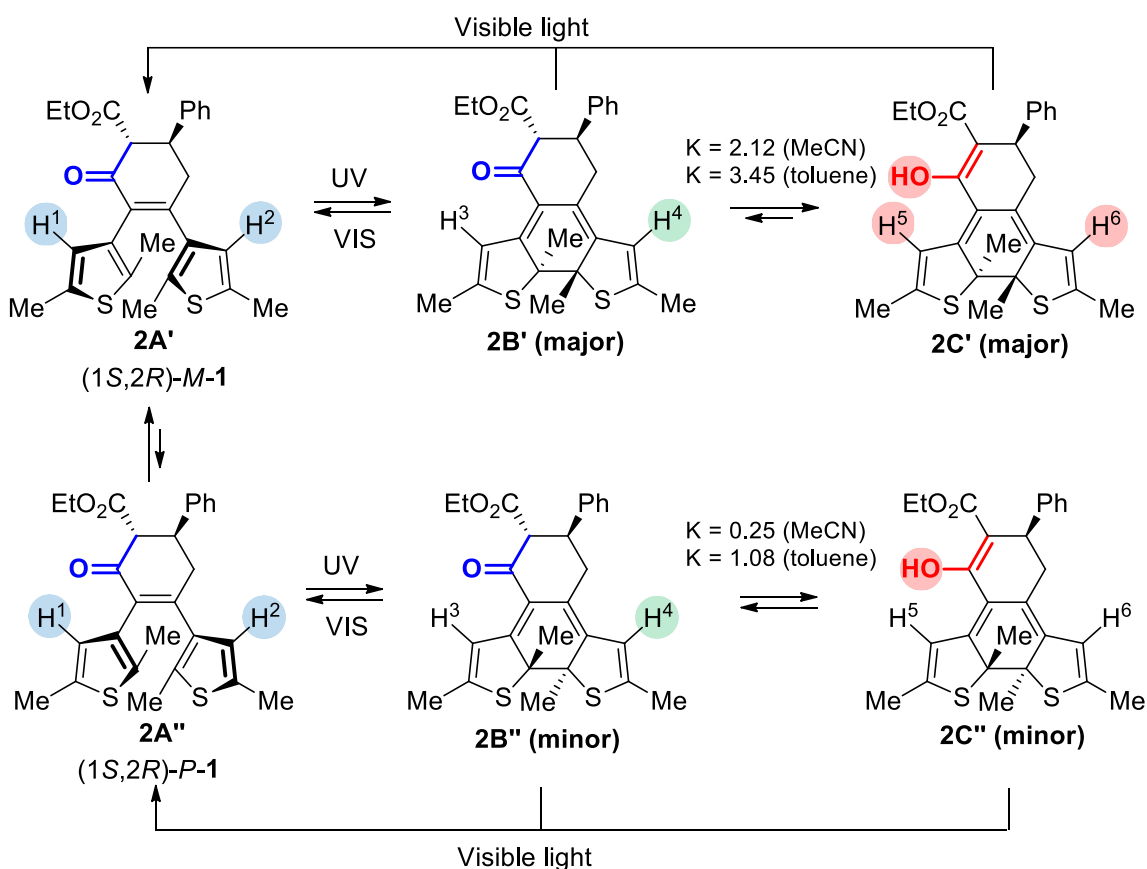
Figure 2. ^{1}H NMR spectra of **2A** (300 MHz, CD$_3$CN, 298 °C, c = 0.013 M): a) pristine sample, b) after UV irradiation (313 nm, 6W, 40 min), c)-d) after keeping in the dark, and e) after irradiation with green LED and keeping for 2 days in the dark.

The results of UV-vis spectroscopy were supported by ^{1}H NMR spectroscopy (Figure 2). Photocyclization of **2** upon UV irradiation (λ = 313 nm) in MeCN-d$_3$ resulted in two diastereomeric products **2B'** and **2B''** that slightly differed in the chemical shift of the characteristic proton H^4 in the dihydrothiophene moieties (5.92 and 5.87 ppm, respectively, Scheme 3). The peaks of H^3 atoms are shifted in downfield due to the magnetic anisotropy of the carbonyl group.[25] In accordance with the Woodward–Hoffmann rule,[26] photocyclization of **2A** occurs in a conrotatory fashion and thus originates from the major M- and minor P-helical antiparallel conformations (**2A'** and **2A''**, respectively). It is a result of a free rotation of thienyl moieties with low barrier. The ratio between diastereomers **2B'** and **2B''** (67.7% and 32.3%, respectively) is generally consistent with the results of X-ray crystallography of **2A** (Scheme 2). In addition, photocyclization of model diarylethene **5** without an ester group resulted in two photoproducts with a similar ratio (section III in SI).

Keeping the NMR sample in the dark at rt resulted in the appearance of a new compounds with specific downfield peaks at 13.21 (major) and 13.08 ppm (minor). Evidently, these signals correspond to enols **2C'** and **2C''**, respectively. For major enol **2C'** the characteristic protons in the dihydrothiophene moieties H^5 and H^6 were assigned. We found that thermodynamic ketone-enol equilibrium in acetonitrile was reached after two days. Interestingly, the enol tautomer was formed primarily from the major photoproduct **2B'** as confirmed by a gradual decrease of the corresponding signal at 5.92 ppm. Thus we conclude that the major enol has structure **2C'**.

At the same time, a minor peak at 13.08 ppm is likely due to the minor **2C''** enol. The analysis of NMR spectra revealed that equilibrium conversion from ketone to enol is 68% (K = 2.12) and 20% (K = 0.25) for the major and minor diastereomer, respectively. The equilibrium in **2** is strongly affected by solvent polarity as observed for related systems.[7,20c]. In non-polar toluene solution, the equilibrium was reached after 3 weeks (Figure S9). The enolization of both diastereomers **2B'** and **2B''** in toluene was more effective than in polar acetonitrile (78% (K = 3.45) and 52% (K = 1.08), respectively, see section IV.3 in SI). Different equilibrium parameters of the diastereomers **2B'** and **2B''** could be explained by discriminate strain energies of the cyclohexenone ring. Related effects were described earlier by Prelog et al[27] and Kresge et al.[28] Irradiation of equilibrium mixtures of **2B** and **2C** with visible light (green LED) resulted in the restoration of the **2A** spectrum (Figure 2e, Figure S10).

Prolonged irradiation of the open-ring **2** leads to the loss of photochromic properties due to the well known side process - formal 1,2-dyotropic rearrangement (Scheme 4).[29] Although it seems to be a highly undesirable side reaction, we used it to prove the tendency of **2B** towards enolization. Indeed, it was previously shown that the photoinduced closed-ring form and a by-product possess similar optical properties due to their similar electronic structures.[29b] Bulk photolysis of **1** allowed us to isolate annulated product **6** as a mixture of two diastereomers, similarly to **2C'** and **2C''** (Scheme 4). The structure of **6** was confirmed by 2D NMR spectroscopic techniques and mass-spectrometry. In particular, two pairs of characteristic tertiary carbons C4 and C5 were detected at 53.5/53.6 and 65.2/65.7 ppm (Scheme 4, for details see section IX.2 in SI). Similarly to the closed-ring forms **2B**, this compound shows an absorption maximum in the visible region at 482 nm in acetonitrile (Figure S17).

Scheme 4. Dyotropic rearrangement of 2A and fragment of ^{1}H NMR spectrum of 6'/6" in toluene-d$_8$.
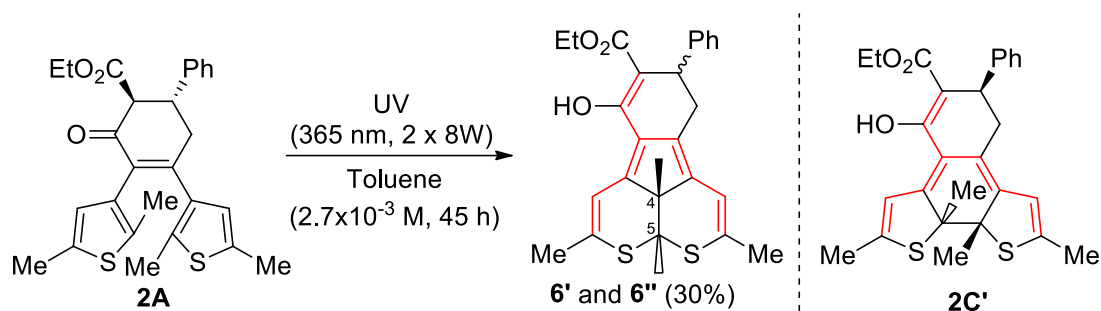
Species **6** exist exclusively as an enol tautomers in toluene, as confirmed by ^{1}H NMR spectroscopy showing a prominent signal at 13.10 ppm of OH-group (Figure S11). However, keto-enol tautomerization was observed in acetonitrile, which yielded a new equilibrium mixture containing 64% of enols (Figure S12). Apparently, the stabilization of enol tautomers (**6** and **2C**) results from the conjugation of the electron-withdrawing CO$_2$Et group with the electron-donating 2,3-dihydrothiophene motif. In principle, conjugation of the ketone group with a system of double bonds frequently contributes to the stabilization of an enol tautomer.[30]

NMR monitoring of prolonged irradiation (Figures S13-S15) revealed, that the formal 1,2-dyotropic rearrangement is a prime fatigue process for DAE **2A**. Note, that according to Herder et al.,[29b] this undesirable process could be suppressed by incorporation of 3,5-bis(trifluoromethyl)phenyl or 3,5-bis(pentafluorosulfanyl)-phenyl groups at the α-position of thiophenes in **2A**.

In conclusion, we present a new tool for the photocontrollable manipulation (photoenolization) of the keto-enol equilibrium. A simple combination of a β-ketoester and a diarylethene framework allowed us to control the tautomeric equilibrium in reversible manner in polar and non-polar solvents with light at ambient conditions. Variation of heterocyclic moieties (e.g., application of azoles[21] instead of thiophene or incorporation of electron-withdrawing groups at the α-position of thiophenes[29b]) and ethene bridges (e.g. cyclopentenone[31] instead of cyclohexenone) should provide deeper insight into the nature of this phenomenon and improve the performance of reported here photoinduced tautomerism. Ultimately, these future efforts should afford new efficient photochromic molecules for manipulating various processes in materials chemistry and biology that utilize reversible switching between ketone and enol tautomers.

ACKNOWLEDGMENT

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