

Primary and secondary H/D isotope effects in the addition of triazolinedione to 2,5-dimethyl-2,4-hexadiene. Mechanistic insights into the reaction pathways

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Dedicated with appreciation to Professor Gerasimos J. Karabatsos
on the occasion of his 70th birthdate

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Abstract

Primary and secondary isotope effects were determined for the reaction of 4-methyl[1,2,4]-triazoline-3,5-dione with 2,5-dimethyl-2,4-hexadiene-1,1,1,2',2',2'-*d*₆. The results are consistent with the formation of an aziridinium imide intermediate in equilibrium with an open zwitterion. At higher temperatures, the aziridinium imide prevails and can be either transformed to the ene adduct in a slow step, or trapped by the solvent if the reaction is carried out in methanol. At lower temperatures, the entropically favored open zwitterion is formed preferentially, that either polymerizes in chloroform or can be trapped by methanol.

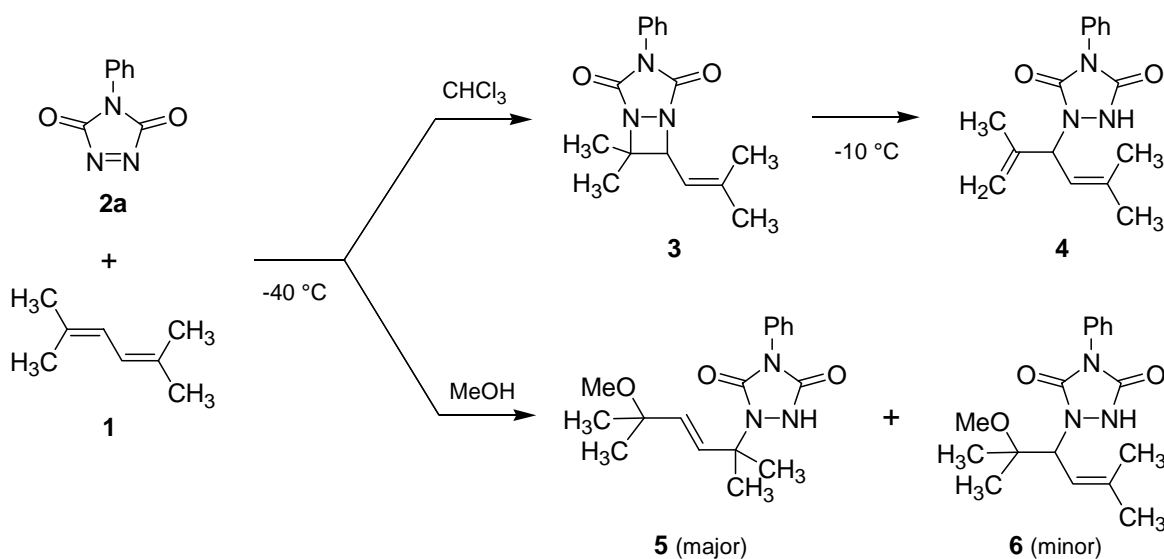
Keywords: Triazolinedione, ene reaction, isotope effects, reaction mechanism

Introduction

4-Methyl- and 4-phenyl[1,2,4]triazoline-3,5-dione (MTAD and PTAD, respectively) readily react with conjugated dienes to form [4+2] adducts.¹ The stereochemistry of the Diels-Alder adducts from the reaction of PTAD with 2,4-hexadienes² and alkoxy-substituted 1,3-butadienes³ is consistent with both concerted and stepwise mechanisms; e.g. (*E,E*)-2,4-hexadiene affords stereospecifically the *cis* Diels-Alder adduct following the Woodward-Hoffmann rules. However, (*Z,Z*)-2,4-hexadiene affords the adduct with the “wrong” *trans* stereochemistry as major product. Furthermore, when the reaction is carried out in methanol, solvent trapping adducts are formed in a non-stereospecific manner.² DFT theoretical calculations reported by Houk and Foote⁴ on dienes that easily adopt the *s-cis* conformation reveal that the concerted pathway is favored over a non-symmetrical transition state. For dienes that cannot easily adopt the *s-cis* conformation, a stepwise pathway operating via formation of an aziridinium imide (**AI**)

intermediate is most probable. The **AI** can either afford an ene adduct, or transform into an open zwitterion. In the light of this theoretical work, we present a study on the isotope effect in the reaction of MTAD with the bulky 2,5-dimethyl-2,4-hexadiene (DMHD). The present results corroborate the calculations, and reveal new mechanistic details of this interesting reaction.

The reaction of DMHD **1** with PTAD **2a** was originally reported by Gillis and Hagarty⁵ and was found to afford an acyclic addition product containing an acetoxy group. The authors suggest that the adduct is formed by trapping the possible dipolar intermediate with $\text{Pb}(\text{OAc})_4$ used to oxidize 4-phenylurazole to PTAD **2a**. Later, Foote and Jensen² have found when this reaction was carried out at low temperature ($-40\text{ }^\circ\text{C}$) in chloroform, a labile adduct with the possible structure of 1,2-diazetidene **3** was formed, which at higher temperature ($-10\text{ }^\circ\text{C}$) rearranged to the ene adduct **4** (Scheme 1). In addition, variable amounts of unidentified polymeric material were formed. In methanol this reaction was performed furnished a mixture of 1,4- and 1,2-methoxy adducts **5** and **6**, respectively (ratio 80:20).



Scheme 1. Reaction of 2,5-dimethyl-2,4-hexadiene (**1**) with PTAD **2a** in CHCl_3 and MeOH.

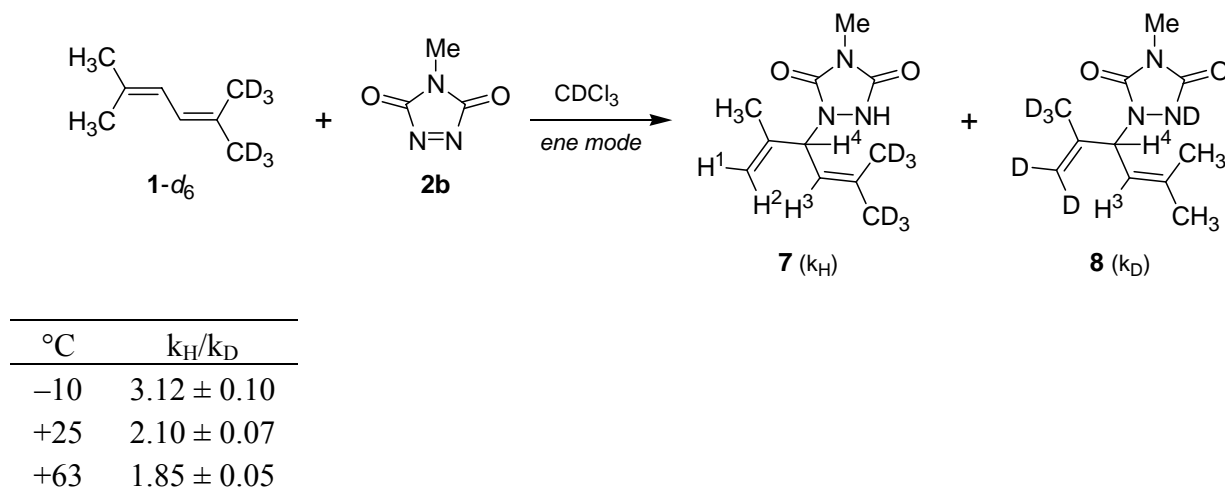
Results

To elucidate the energy profile, and to shed light on mechanistic details of this intriguing reaction, we determined the primary and secondary isotope effects for the two possible pathways (ene in CHCl_3 and solvent trapping in methanol). For this purpose, 2,5-dimethyl-2,4-hexadiene-1,1,1,2',2',2'- d_6 (**1- d_6**) with *gem* CD_3 groups was prepared according to a published procedure.⁶

Reaction in chloroform

For the addition of MTAD **2b** to **1** in CHCl_3 , the main product was the ene adduct **4** ($\text{R} = \text{Me}$), while significant amounts of unidentified by-products (polymeric material) were formed depending on the reaction temperature. When the reaction was carried out at low temperature (below $-30\text{ }^\circ\text{C}$), the crude reaction mixture contained a substantial amount (major component) of unidentified by-products. However, when the reaction was carried out at higher temperature ($20\text{ }^\circ\text{C}$) the amount of by-products was surprisingly minimized. Moreover, in boiling chloroform, the ene adduct is the only reaction product.

The reaction of **1-d₆** with MTAD **2b** in CDCl_3 reveals a temperature dependence of the primary isotope effect for the ene pathway (Scheme 2). At $-10\text{ }^\circ\text{C}$ an intramolecular isotope effect of $k_{\text{H}}/k_{\text{D}} = 3.12 \pm 0.10$ was determined, whereas at $63\text{ }^\circ\text{C}$ $k_{\text{H}}/k_{\text{D}} = 1.85 \pm 0.05$. The isotope effect was obtained from signal integration of the terminal olefinic H^1 at δ 5.04 and H^2 at δ 5.00, corresponding to $2 k_{\text{H}}$, and that of the allylic proton signal H^4 at the carbon attached to the urazol ring at δ 5.31 or the olefinic hydrogen H^3 at δ 5.22, both corresponding to $k_{\text{H}} + k_{\text{D}}$.

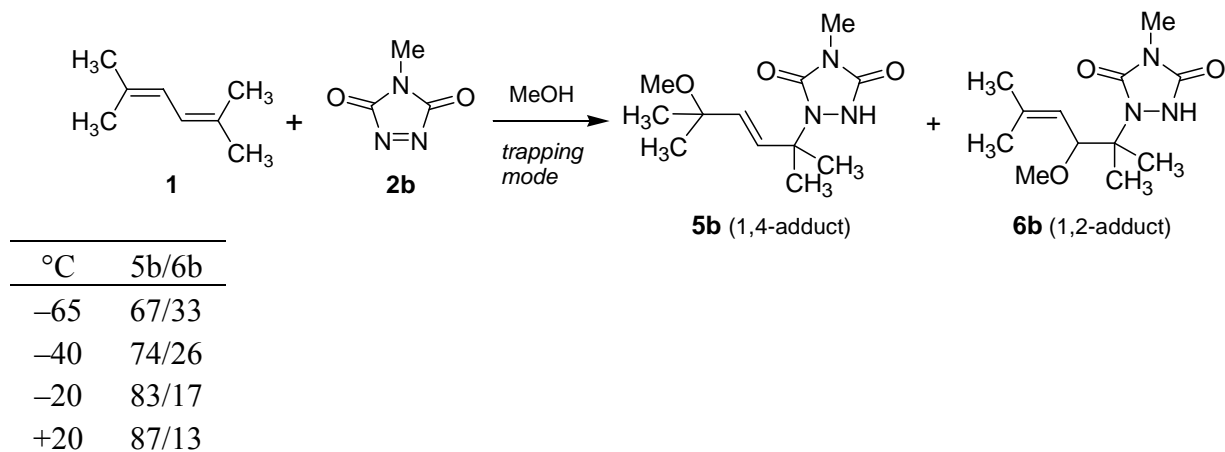


Scheme 2. Ene reaction of **1-d₆** with MTAD **2b**; temperature dependent primary isotope effect.

Reaction in methanol

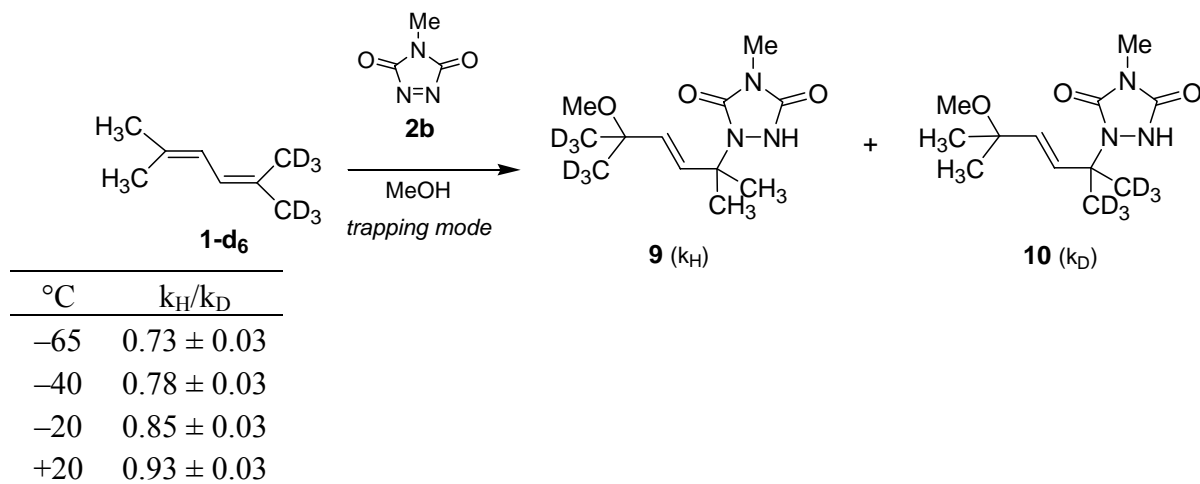
The addition of MTAD **2b** to **1** in methanol or in chloroform containing 10% methanol afforded a mixture of 1,4- and 1,2-methoxy addition products **5b** and **6b**, respectively (Scheme 3). These adducts arise from methanol intercepting the presumed intermediate(s). The trapping reaction is highly favored, even trace amounts of ethanol admixed to chloroform (in commercial solvent) intercept the intermediate(s) forming mainly ethoxy adducts, while the ene product is the minor reaction product. The ratio of adducts **5b/6b** in methanol as determined by integration of significant ^1H NMR signals and by gas chromatography (GC) is temperature dependent. At higher temperatures the amount of the 1,2-adduct **6b** formed is very small, but lowering the reaction temperature increases the relative yield of **6b** substantially (Scheme 3).

The reaction of **1-d₆** with MTAD **2b** in methanol furnished mainly the 1,4-methanol addition products, and the β -secondary isotope effects were determined (Scheme 4). The 1,4-adduct **9** (with the new C–N bond extended from the carbon atom bearing the geminal CH₃ groups) is defined as k_H , and adduct **12** as k_D (C–N bond on the carbon atom bearing the geminal CD₃ groups).



Scheme 3. Temperature dependent formation of 1,4- and 1,2-methoxy trapping adducts **5b** and **6b**.

At ambient temperature, the 1,4-adducts **9** and **10** were formed with a slightly inverse β -secondary isotope effect of $k_H/k_D = 0.93 \pm 0.03$. The isotope effect was determined by measuring the integration of singlet signals at δ 1.29 corresponding to k_D , and at δ 1.57 corresponding to k_H . By lowering the temperature increases the isotope effect in favor of k_D , and at -65 °C it becomes $k_H/k_D = 0.73 \pm 0.03$, or $k_D/k_H = 1.37$. This value corresponds to $k_D/k_H = 1.06 \pm 0.01$ per D atom.

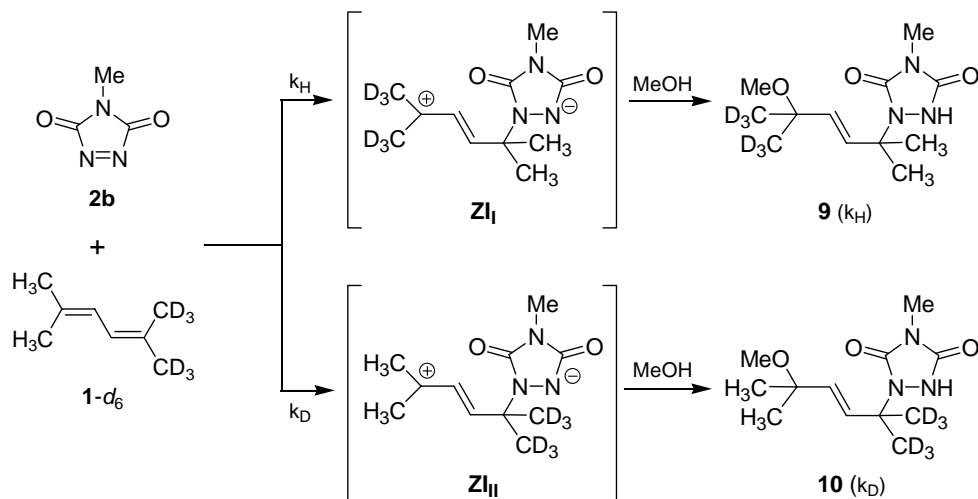


Scheme 4. β -Secondary isotope effect for the 1,4-trapping mode in the reaction of **1-d₆** with MTAD **2b** in methanol.

Discussion

The significant feature of this reaction⁷ are the temperature dependent changes according to the following observations: (i) the ratio of the ene versus the polymeric byproduct in chloroform; (ii) the primary isotope effect for the ene pathway in chloroform; (iii) the ratio of the 1,2-/1,4-methoxy trapping adducts **5b/6b** in methanol; and (iv) the β -secondary isotope effect for the 1,4-trapping mode in methanol.

In order to explain these changes, we consider the formation of two intermediates, bicyclic aziridinium imides **AI** and open zwitterions **ZI**. The nature of these intermediates affects significantly the outcome of the reaction. The open zwitterion **ZI** is entropically more favorable compared to **AI**. At low temperatures, formation of the entropy-favored zwitterion **ZI** occurs preferentially. For steric reason, the zwitterionic intermediate **ZI** cannot lead to a [4+2] cycloadduct; instead, it polymerizes. At higher temperatures, formation of the aziridinium imide **AI** prevails giving rise to a very clean reaction (only the ene product is formed).

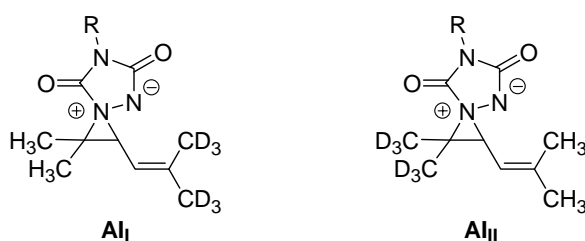


Scheme 5. Zwitterionic intermediates **ZI** in the reaction of **1-d₆** with MTAD **2b** in methanol.

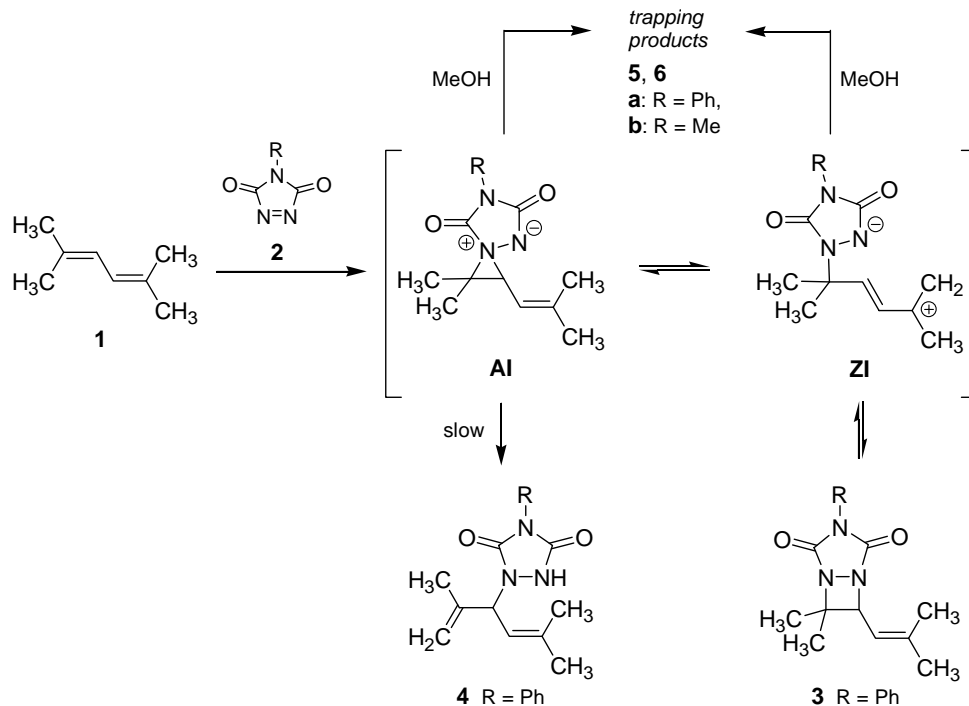
The significant primary isotope effect of the ene reaction of **1-d₆** with MTAD **2b** indicates that hydrogen atom abstraction occurs in the rate-determining step. The temperature dependence of the isotope effect indicates the existence of a tunneling effect. Probably, this effect results from the severe steric hindrance in the transition state of the second rate-determining step (intramolecular hydrogen transfer) of the ene reaction. A similar tunneling effect has been already recognized in the ene reaction of PTAD **2a** with *gem* tetramethylethylene-*d*₆.⁸

The temperature dependence of the β -secondary isotope effect for the 1,4-trapping mode of the reaction in methanol (Scheme 4) can be explained as follows. At low temperature (-65 °C), the entropically favored open zwitterion **ZI** is formed preferentially relative to **AI**. Among the two possible zwitterionic intermediates **ZI_I** and **ZI_{II}** (Scheme 5), the latter prevails due the better

hyperconjugative stabilization of the carbocation by the CH₃ groups relative to the CD₃ groups. Reaction of methanol with **ZI_I** and **ZI_{II}** forms a mixture of adducts **9** and **10** (ratio 1.37:1). Similar values of an inverse isotope effect were measured for the [2+2] cycloaddition reaction of TCNE with **1-d₆**.⁹ At higher temperatures, formation of the aziridinium imide intermediate **AI** predominates. The two possible intermediates **AI_I** and **AI_{II}**, shown below, are expected to be formed in almost equal amounts. Reaction of methanol with **AI_I** and **AI_{II}**, in a Michael type addition, will eventually form the 1,4-adducts **9** and **10** with a negligible isotope effect. We assume that the slightly inverse k_H/k_D values found if the methoxy-trapping reaction occurs at ambient temperature may be mostly due to steric reasons (the approach of MTAD to form **AI_{II}** is expected to be slightly more favorable from the steric point of view, since the CH₃ is slightly more bulkier than the CD₃ group).



A general mechanistic overview, as described in the discussion above, is presented in Scheme 6.



Scheme 6. Proposed mechanism for the reaction of 2,5-dimethyl-2,4-hexadiene **1** with triazolinediones **2**.

In conclusion, based on primary and secondary isotope effects, we elucidated the energy profile for the reaction of triazolinediones **2** with 2,5-dimethyl-2,4-hexadiene **1**. In addition, the present results corroborate the previous assumption for the intermediacy of an aziridinium imide **AI** and an open zwitterionic intermediate **ZI**.

Acknowledgements

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Experimental Section

General Procedures. Nuclear magnetic resonance spectra were recorded on a 500 MHz spectrometer, in CDCl₃. Isomeric purities were determined by ¹H NMR spectroscopy and by analytical gas chromatography on an SP-5 capillary column. 4-Methyl[1,2,4]triazoline-3,5-dione (MTAD, **2b**) is commercially available, 2,5-dimethyl-2,4-hexadiene-1,1,1,2',2',2'-d₆ (**1-d₆**) was prepared as described earlier.⁶

The reaction of **1-d₆** with MTAD **2b** using equimolar amounts of the starting materials in CDCl₃ and in MeOH were performed at different temperatures. The reaction products were purified by flash column chromatography using a mixture of hexane/EtOAc = 1:1 as eluent. The spectral data of the MTAD addition products are similar to the PTAD analogues.²

Mixture of 1-(1-isopropenyl-3-methylbut-2-enyl)-4-methyl[1,2,4]triazolidine-3,5-diones d₆ (7) and (8). ¹H NMR (500 MHz, CDCl₃): δ 1.71 (d, *J* = 1.0 Hz, 3H, **8**), 1.78 (d, *J* = 0.9 Hz, 3H, **8**), 1.79 (s, 3H, **7**), 3.03 (s, 3H, **7**, and 3H, **8**), 5.00 (s, 1H, **7**), 5.04 (br s, 1H, **7**), 5.22 (d, *J* = 8.9 Hz, 1H, **7**, and 1H, **8**), 5.31 (d, *J* = 8.9 Hz, 1H, **7**, and 1H, **8**).

1-[(2E)-4-Methoxy-1,1,4-trimethylpent-2-enyl]-4-methyl[1,2,4]triazolidine-3,5-dione (5b). ¹H NMR (500 MHz, CDCl₃): δ 1.29 (s, 6H), 1.57 (s, 6H), 3.02 (s, 3H), 3.15 (s, 3H), 5.70 (AB, Δδ = 0.17 ppm, *J* = 16.2 Hz, 2H), 8.90 (br s, NH).

1-(2-Methoxy-1,1,4-trimethylpent-3-enyl)-4-methyl[1,2,4]triazolidine-3,5-dione (6b). ¹H NMR (500 MHz, CDCl₃): δ 1.42 (s, 3H), 1.51 (s, 3H), 1.73 (d, *J* = 1.2 Hz, 3H), 1.82 (d, *J* = 1.1 Hz, 3H), 3.03 (s, 3H), 3.22 (s, 3H), 4.10 (d, *J* = 9.8 Hz, 1H), 5.04 (br d, *J* = 9.8 Hz, 1H), 8.65 (br s, NH).

Mixture of 1-[(2E)-4-methoxy-1,1,4-trimethylpent-2-enyl]-4-methyl[1,2,4]triazolidine-3,5-diones d₆ (9) and (10). ¹H NMR (500 MHz, CDCl₃): δ 1.29 (s, 6H, **10**), 1.57 (s, 6H, **9**), 3.02 (s, 3H **9**, and 3H, **10**), 3.15 (s, 3H, **9**, and 3H, **10**), 5.70 (AB, Δδ = 0.17 ppm, *J* = 16.2 Hz, 2H, **9** and 2H, **10**), 8.90 (br s, NH).

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