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Intramolecular 1,3-dipolar Cycloreversion - a Key Step in Novel Thermal Isomerisations of Cyclobutane Di-(carbomethoxy) Triazolines

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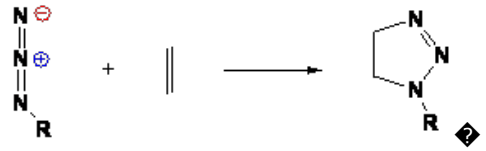
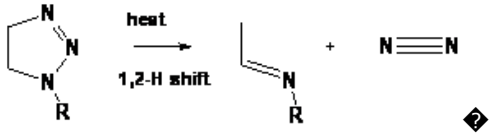
Abstract. Thermal isomerisation of the strained cyclobutane diester triazoline led to the formation of the product possessing a novel 1,2,7-triaza-[3.3.0]octa-2-ene ring system incorporated in a norbornane framework. Experimental evidence and quantum chemical calculations (DFT) have been used to support a postulated reaction mechanism involving as the first step, a rare example of intramolecular 1,3-dipolar cycloreversion. Subsequently, several steps involving 1,3-dipolar ring closure, [1,3]hydrogen-shifts and an intramolecular addition are postulated leading to the observed product of this deep-seated isomerization. The influence of changing substituents on the product outcome of this novel reaction cascade was also studied.

Introduction. Standard 1,2,3-triazoline chemistry involves formation of 1,2,3-triazolines by 1,3-dipolar addition of azides to alkenes. This reaction works best with electron-rich olefins (**Scheme 1**).**[1]**



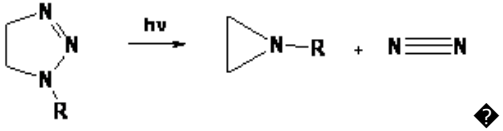
Scheme 1.

Thermolysis of 1,2,3-triazolines and imine formation is the standard chemical behaviour of this class of compounds (**Scheme 2**).**[2]** However, unusual reaction products were formed in some cases, especially with substituted substrates.**[3]**



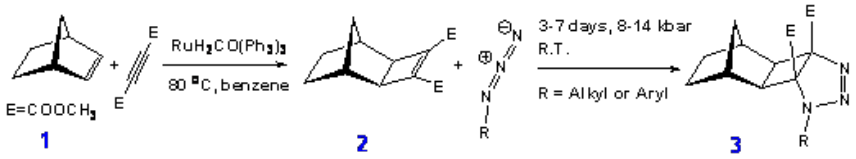
Scheme 2.

Furthermore, photolysis of 1,2,3-triazolines is a standard way to aziridine preparation (**Scheme 3**).**[4]**



Scheme 3.

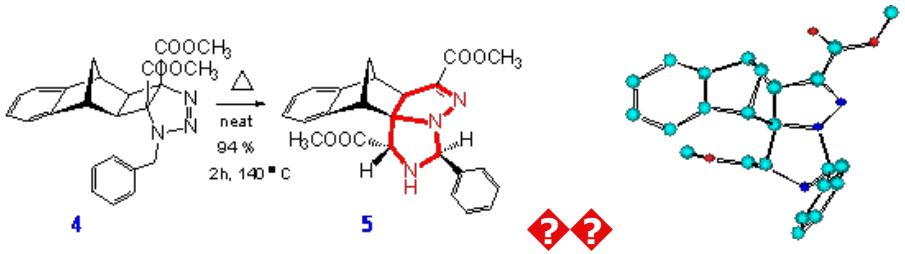
Results and discussion. Preparation of 2,3,4-triazabicyclo[3.2.0]hept-3-enes, substrates required for our research was achieved employing the standard synthetic procedures developed in our laboratories. The first step was ruthenium catalyzed [2+2] cycloaddition reaction of norbornenes **1** and dimethylacetylene decarboxylate (Mitsudo reaction) to form corresponding cyclobutene diesters **2** in high yields**[5]** (**Scheme 4**). These cyclobutene diesters, were further subjected to high pressure azide additions in dichloromethane to form cyclobutene diester triazolines **3**[6].



Scheme 4.

This reaction sequence was used in our previous work to synthesise corresponding aziridines and finally fused 7-azanorbornanes.**[7,8]** It was found during the work-up and handling that 2,3,4-triazabicyclo[3.2.0]hept-3-enes are thermally unstable systems where substituents weaken central cyclobutane C-C bond. These strained bicyclic systems possess several functionalities which enhance their reactivity. Our first observed thermal isomerisation of **4** led to the formation of novel 1,2,7-triaza-bicyclo[3.3.0]octa-2-ene ring system, which is highlighted in red (**Scheme 5**), **product type 1**. We have published a short research paper on this synthesis earlier**[9]**, and here we give more detailed mechanistic study in the lights

of new experimental evidence supporting the novel reaction cascade. [10]

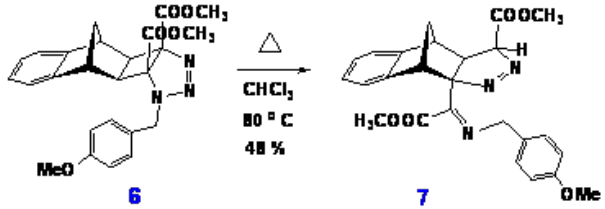


Scheme 5.

Figure 1

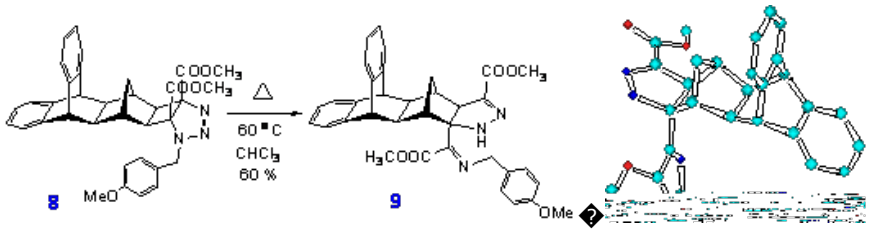
Structure of this novel compound **5** was unambiguously confirmed by X-ray structural analysis (**Figure 1**, hydrogens are omitted for clarity).

Mixture of products formed by thermal reaction of cyclobutene triazolines are highly under influence of reaction temperature and substituents. Therefore, heating of triazoline **6** at 80 ^{o}C in chloroform, gave as a main product dihydropyrazole benzylimine **7**, **product type 2** (**Scheme 6**).



Scheme 6.

Furthermore, thermal rearrangement of triazoline **8** at 60 ^{o}C in chloroform yielded rearranged dihydropyrazole benzylimine **9**, **product type 3** (**Scheme 7**). X-ray structure of this compound is given in **Figure 2** (again, hydrogens are omitted for clarity). Elucidation of structures of key-intermediates, products of type 2 and 3 was critical for completion of overall reaction mechanism picture.



Scheme 7. **Figure 2.**

In addition to X-ray structural analysis, NMR spectroscopy was employed for structural study of all new products. Results obtained from ^{1}H spectra, 2D COSY and NOESY correlations were combined. Especially ^{1}H-NMR spectra were the most informative and show some interesting features. For instance, ^{1}H-NMR spectra of two isomeric products

5R and **5S** were depicted in **Figure 3**. In both isomers, one of the unsymmetrical ester signals is shielded by aromatic ring and shifted towards higher magnetic field by cca. 1 ppm. Furthermore, there is an obvious difference in a chemical shifts of bridgehead protons He, due to the orientation of phenyl substituent. In this case, He is de-shielded in a case of **5S**- product. Finally, there is a large difference in the positions of the benzylic protons Hb.

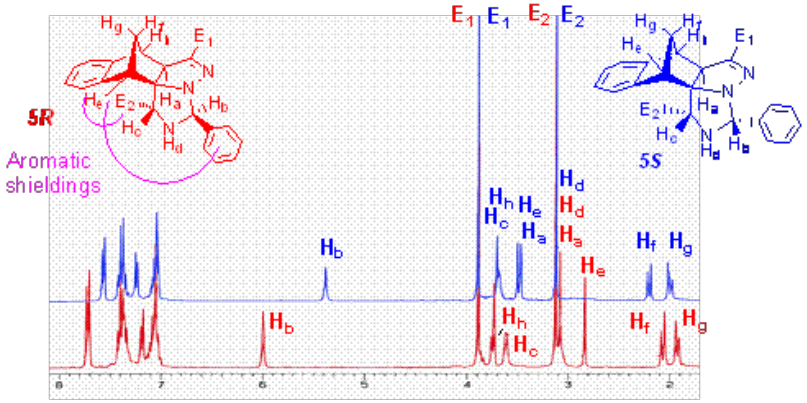


Figure 3. ^{1}H-NMR spectra of two isomeric products 5**R** and 5**S**

Structures of products type 2 (**7**) and type 3 (**10**) could be easily distinguished on the basis of analysis of characteristic ^{1}H-NMR chemical shifts and their coupling patterns (**Figure 4**). Therefore, protons Ha and Hd are coupled in the case of product type 2, while this coupling is absent in product type 3. Furthermore, proton Hd appears at d 2.95 in the case of molecule **7**, while it is shifted to the lower field in the molecule **10** (d 6.69). Accordingly, *endo* protons Ha appear at d 3.20 and 4.34, respectively.

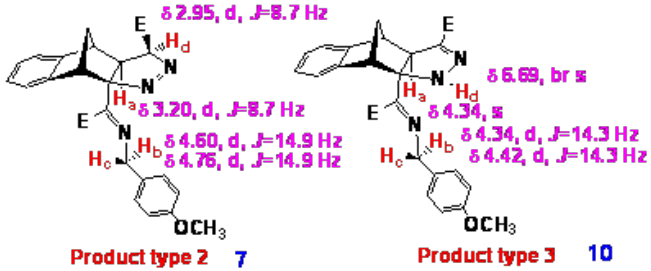
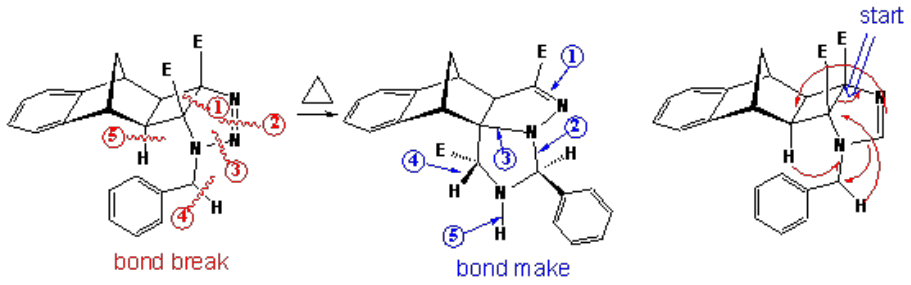


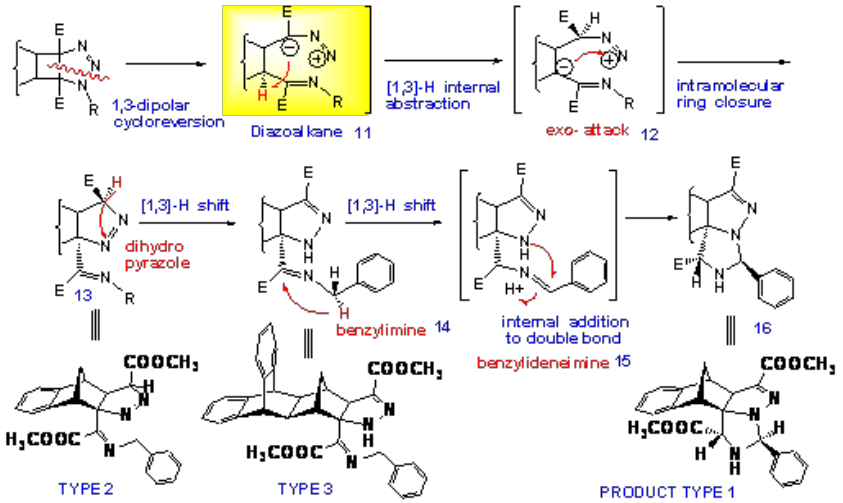
Figure 4. Characteristic ^{1}H-NMR chemical shifts of products type 2 and type 3

Mechanistic considerations. An overall mechanistic picture of deep-seated rearrangement involving three [1,3]H-shifts is depicted in **Scheme 8**. It involves five bonds to break, and also five new bonds to be formed in the process. We assume that rearrangement starts with breaking of weakened central cyclobutane bond.



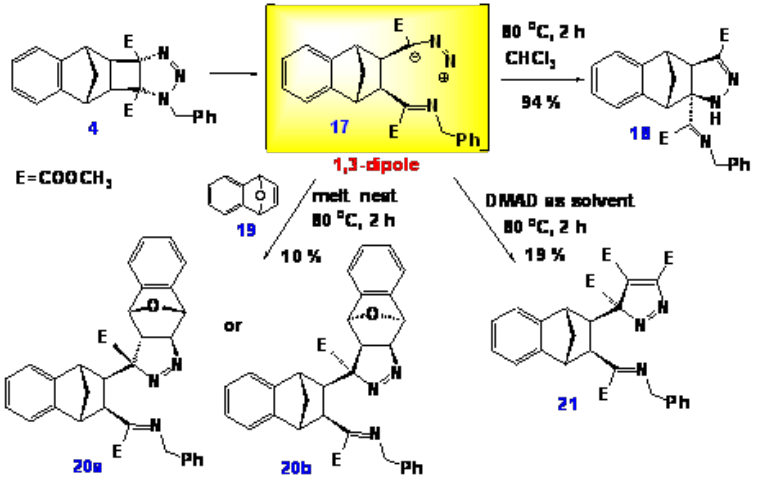
Scheme 8. An overall mechanistic picture of deep-seated rearrangement involving three [1,3]H-shifts

The proposed reaction mechanism starts with an intramolecular 1,3-dipolar cycloreversion and formation of corresponding diazoalkane (**Scheme 9**). This is one rare example of intramolecular 1,3-dipolar cycloreversion reaction**[11-13]**. Diazoalkane formed in such manner undergoes facile [1,3]hydrogen migration and formation of 1,5-dipole **11**. Intramolecular ring closure leads to benzylimine dihydro pyrazole **13** (product type 2). After [1,3]hydrogen shift on dihydro pyrazole ring, a conjugated benzylimine dihydro pyrazole **14** (product type 3) is formed. Consecutive [1,3]hydrogen shift within a benzylimine moiety gave an intermediate benzylideneimine **15**. Internal addition to double bond and ring closure gave a final ring structure **16**, product type 1.



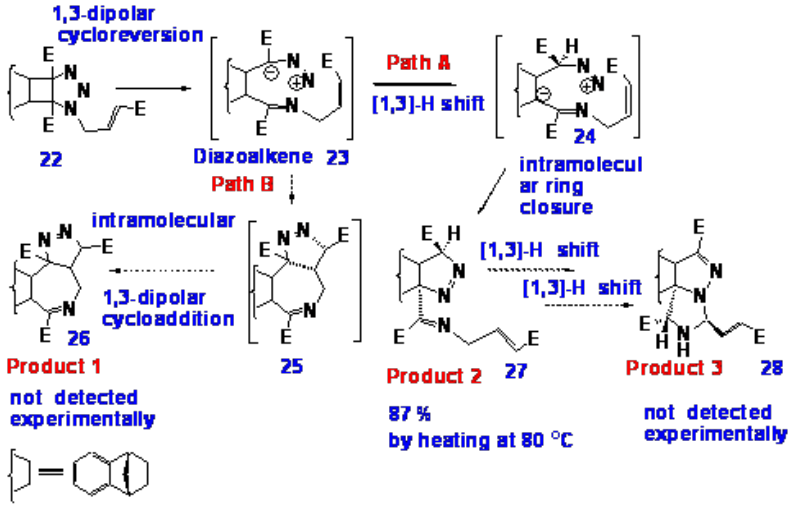
Scheme 9. Proposed reaction mechanism

There is some experimental evidence in support of proposed reaction mechanism. Firstly, spectroscopic data for stable and isolated products type 1-3. Secondly, several 1,3-dipole trapping experiments were conducted in order to prove existence of initially formed diazoalkane **17**. High reactivity of this species leads to formation of product **18**, when trapping experiments were conducted using diluted samples of triazoline and trapping reagent (in chloroform). However, when trapping experiments were done in more concentrated solutions, in neat dipolarophile as solvent (7-oxabenzonorbornadiene and dimethylacetylene decarboxylate), at 80 ^{o}C trapping products **20** and **21** were formed in 10 and 19% yield, respectively. Even in these reaction conditions, major product was **18**, indicating very low energy barrier of initial intramolecular hydrogen migration. Adduct **20** is actually consisted of two isomeric products **20a** and **20b** which were not separated and are not distinguishable by NMR spectroscopy.



Scheme 10. 1,3-dipole trapping experiments

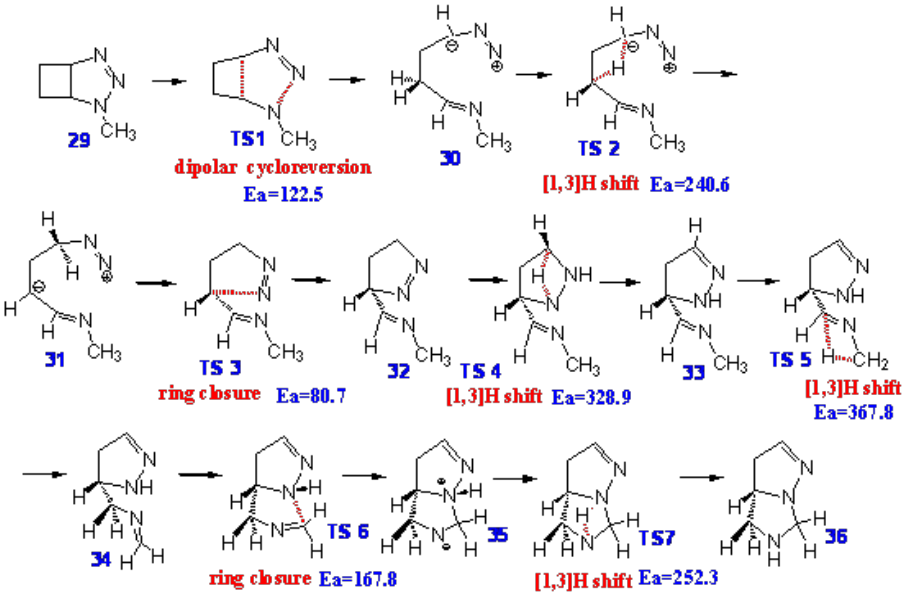
Furthermore, intramolecular 1,3-dipole trapping**[14]** experiments were also attempted (**Scheme 11**). In this reaction, conducted in chloroform at 80 ^{o}C, diazoalkene **23** went through **path A** and formed dihydro pyrazole **27** in 87% yield. Formation of expected product **26** was not detected spectroscopically. There is a literature precedent of rearrangement of triazolines to bicyclic system via intramolecular trapping of diazoalkene.**[15]** However, while literature example is conformationally more flexible, our molecular system, possessing larger molecular strain might prevent reaction **pathway B**.



Scheme 11. Intramolecular 1,3-dipole trapping experiments

Quantum chemical calculations.**[16]** In order to further study reaction mechanism, DFT quantum chemical calculations (B3LYP/6-31G* level) were employed. All reactants, products, intermediates and transition states were calculated and corresponding activation energies estimated (**Scheme 12**). For the sake of computational efforts, benzonorbornene

moiety was removed, as well as methyl ester substituents.



Scheme 12. RB3LYP/6-31G* optimized structures and activation energies in kJ/mol

An inspection of results obtained by the RB3LYP/6-31G* method reveals several conclusions which are in good agreement with experimental results: 1) activation barriers indicate that concerted [1,3]dipolar cycloreversion (**TS1**) is favoured over stepwise, diradical mechanism by 7.5 kJ/mol; 2) ring closure process (**TS3**) which follows [1,3]hydrogen shift (**TS2**) has significantly lower activation barrier, suggesting facile formation of dihydropyrazole **32**. This conclusion is in good agreement with our experimental evidence of high reactivity of dipole **30**; 3) activation energy for [1,3]hydrogen shift of dihydropyrazole **32** (**TS2**) to dihydropyrazole **33** is significantly higher. Indeed, we have found experimentally that this rearrangement requires somehow higher reaction temperatures; 4) transition state (**TS5**) has the highest activation barrier in the whole reaction scheme. We have found experimentally that formation of the final product **36** requires more drastic reaction conditions; 5) calculated activation energies for an intramolecular cyclization (**TS6**) and consecutive [1,3]hydrogen migration (**TS7**) are lower than $E_{a(TS5)}$, indicating that in reaction conditions, required for formation of product **36**, these TSs are easily obtained. All our attempts to locate TS, where intramolecular ring closure and [1,3]hydrogen migration are taking place in a single step failed.

Transition state structures for [1,3]hydrogen migrations involved in the reaction mechanism are depicted in **Figure 5**. These structures represent pseudopericyclic TSs for 1,3-sigmatropic hydrogen migration**[17]** nd show some interesting geometrical features. Due to the asymmetry of molecules, all of them are found to be unsymmetrical. Bond lengths for new forming/breaking bonds between migrating hydrogen atom and the rest of molecule are within a range of 1.300 and 1.579 **□**.

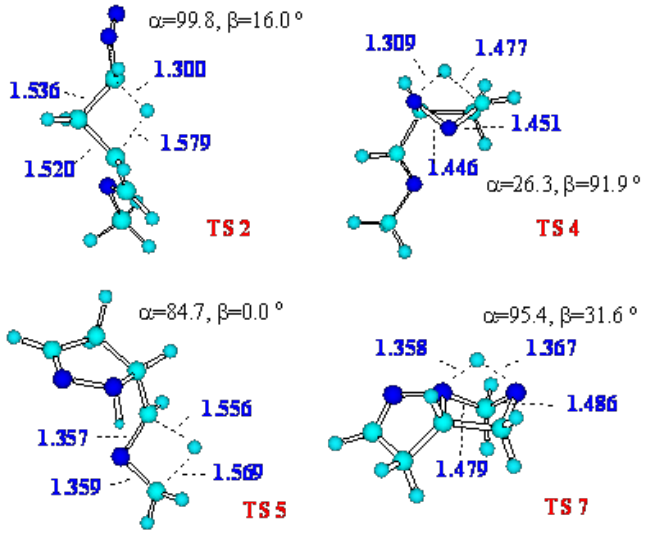


Figure 5. Pseudopericyclic TSs for 1,3-sigmatropic hydrogen migration (angles a and out of plane angles b in ^{o})

Stereochemical considerations of the final ring closure step. It was found that in the case of triazolines **1**-**3**, two stereoisomers were isolated by thermal rearrangement. Carbon atom 6 of the 1,2,7-triaza-[3.3.0]octa-2-ene moiety is an chiral centre of interest. These isomers were carefully separated and experimentally obtained isolated ratios are collected in **Table 1**. In all reactions investigated, *S*- isomer is favored over *R*- isomer and *p*-methoxybenzyl substitution gave the highest S:R ratio.

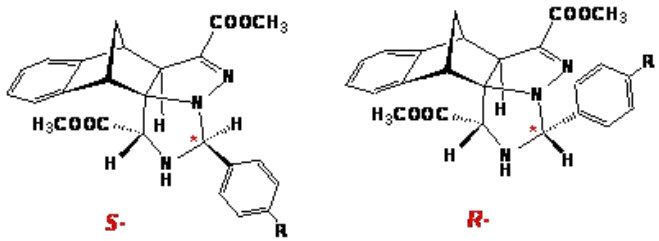
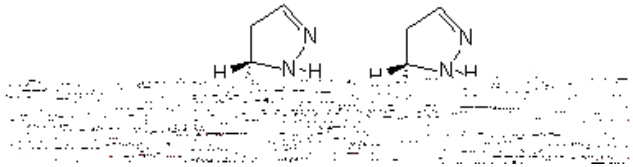


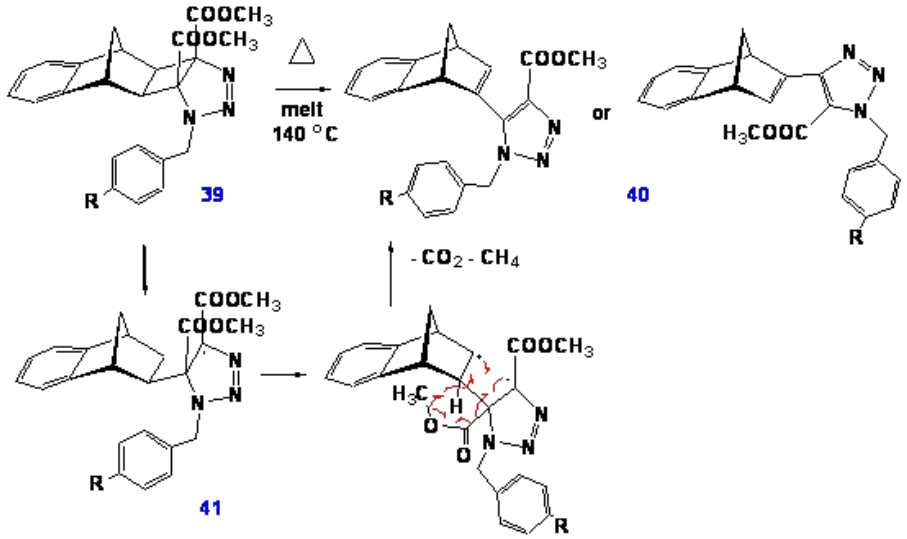
Table 1

5	R=H	*S*- : *R*- 5:1
37	R=OCH_3	*S*- : *R*- 10:1
38	R=NO_2	*S*- : *R*- 6:1

Conducted model DFT calculations of the ring closure (TS6, **Scheme 12**) are in a good agreement with available experimental results. For these calculations, aryl substituents were replaced by methyl group. Theoretically predicted relative stabilities (differences in activation energies for two modes of approach) and relative stabilities of products obtained at different levels of theory are collected in **Table 2**. The inspection of these results shows that all calculations levels employed correctly predict *S*- product to be favoured. Preference for this stereoisomer mainly arises from the steric hindrance of norbornane *endo* protons and aryl substituents under the dihydropyrazole ring in transition states.

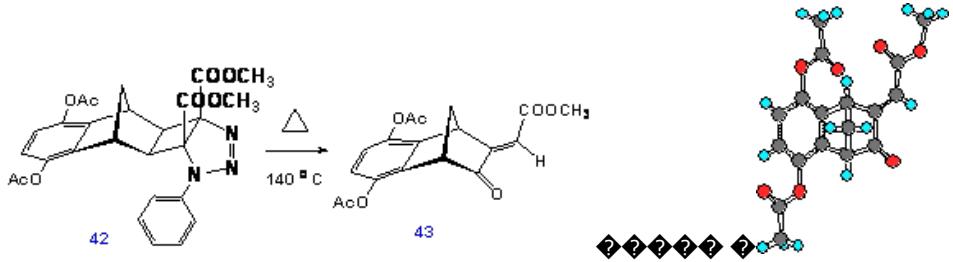


Other thermolysis products. While the products described above are the major products isolated, thermal decomposition of certain cyclobutane diester triazolines led to the formation of new and unprecedented products. For instance, thermolysis of triazolines **39** at 140 ^{o}C yields triazoles **40** as a product (**Scheme 13**). It was not possible to determine by NMR spectroscopy which of these two products has formed. The influence of substitution seems to be the critical for this reaction, when R=H triazole is formed as a minor product (14 %), while triazoline with R=OCH_3 gave corresponding triazole as a major product (43 %). The tentative reaction mechanism is also proposed, involving cyclobutane carbon-carbon bond breaking, and formation of diradical **41**, followed by 8 electron reorganization and concomitant loss of CO_2.



Scheme 13.

Another unprecedented thermolysis product **43** was formed by heating of triazoline **42** in standard manner (**Scheme 14**). Structure of this novel product was unequivocally determined by X-ray analysis (**Figure 3**). Reaction mechanism leading to this product is still under investigation.



Scheme 14.

Figure 3.

Substituent effects. Influence of various substituents on reaction outcome was also studied. Here, various substituents on triazoline and cyclobutane ring were investigated (**Figure 4**).

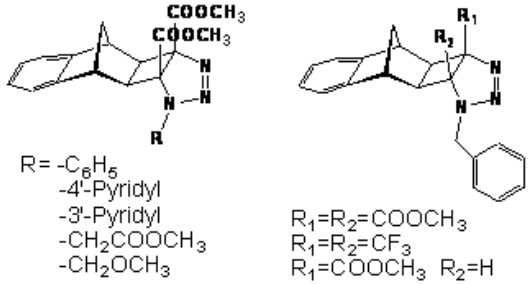
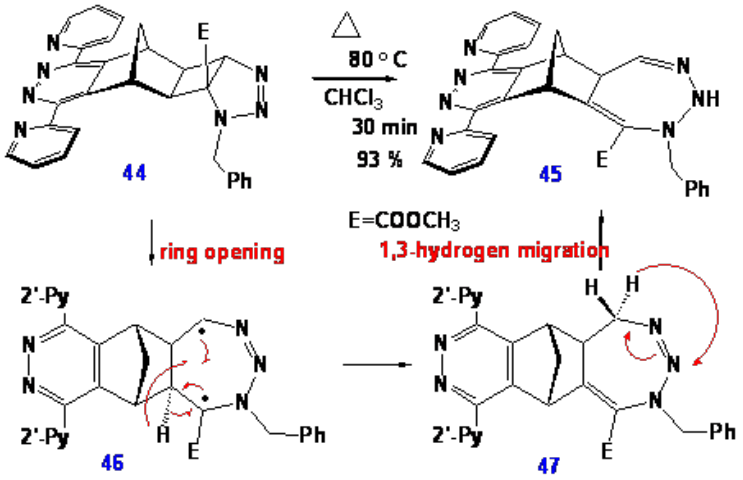


Figure 4.

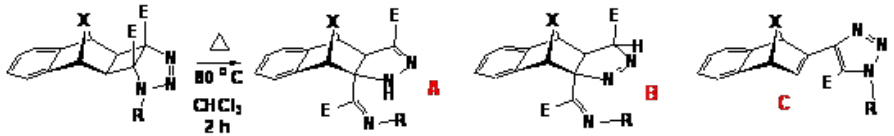
It was found that variation of substituents has profound effect on reaction outcome. For instance, thermolysis of triazoline **44** possessing single methyl ester substituent gave novel product **45** (**Scheme 15**). Proposed reaction mechanism consists initially of central cyclobutane bond cleavage, formation of diradical **46**, followed by [1,3]hydrogen migrations.



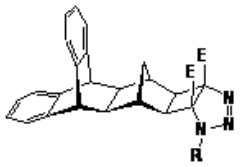
Scheme 15.

Tables 3 and **4** summarize effects of substitution changes on reaction outcomes, at low temperature (80 ^{o}C) and at elevated temperature (140 ^{o}C).

Table 3

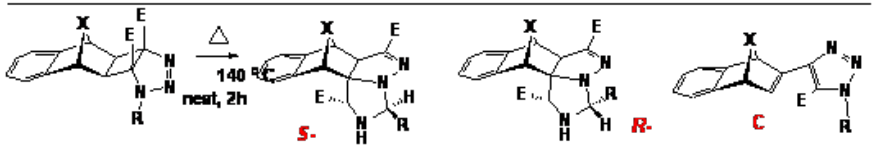


X	R	A	B	C
		yield %		
CH_2	CH_2-Ph	94	-	-
CH_2	CH_2-Ph-OCH_3	30	48	12
CH_2	CH_2-$COOCH_3$	-	95	-
▽	CH_2-Ph	95	-	-
CH_2	Ph	-	46	-



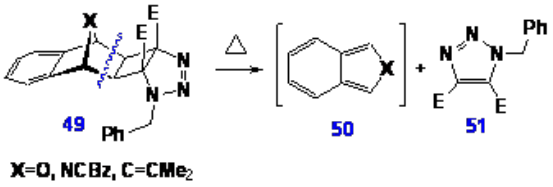
CH_2-Ph-OCH_3	A	B
CH_2-Ph-SCH_3	A	B

Table 4



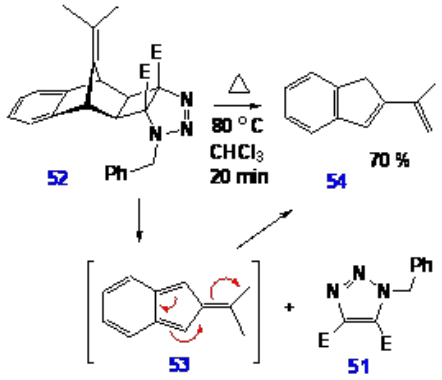
X	R	S-	R-	C
CH_2	CH_2-Ph	24	18	14
CH_2	CH_2-Ph-OCH_3	18	4	12
CH_2	CH_2-Ph-NO_2	21	7	

In the case of 7-oxa, 7-aza- and 7-isopropylidene benzonorbornene cyclobutane di-(carbomethoxy) triazolines **49**, thermal fragmentation takes different route and the formation of reactive isobenzo species **50** and 1-benzyl-4,5-di(carbomethoxy)-triazole **51** was found (**Scheme 16**). This fragmentation pattern has been observed by us earlier in cyclobutane di-(carbomethoxy) triazoline photochemistry**[18]** and cyclobutane di-(carbomethoxy) aziridine cycloaddition chemistry**[19]**.



Scheme 16.

Furthermore, it was found that thermal fragmentation of 7-isopropylidene benzonorbornene cyclobutane di-(carbomethoxy) triazoline **52**, after (isopropylidene)isoindene **53** has been formed, leads to its rearrangement and formation of novel alkene **54** in 70% yield (**Scheme 17**).



Scheme 17.

Conclusion. In this study, novel cascade thermal rearrangement of a series of cyclobutane di-(carbomethoxy) triazolines has been described. It was found that intramolecular 1,3-dipolar cycloreversion is a key step in isomerisation, followed by series of hydrogen migrations and intramolecular cyclizations. Postulated reaction mechanism is in full accord with experimental quantum chemical calculations. Although this reaction pattern is general in the series of cyclobutane triazolines, variations of reaction conditions and substituents of triazoline and cyclobutane rings lead in some cases to formation of unexpected products and various composition of reaction mixtures.

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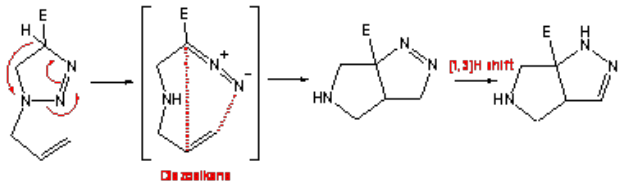

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