Ene reactions between two alkynes? Doors open to thermally induced cycloisomerization of macrocyclic triynes and enediynes†

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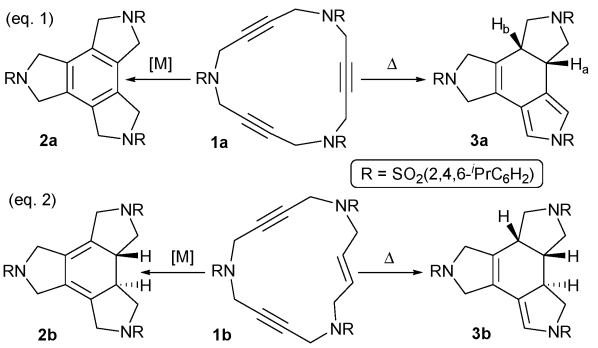
A domino process is described combining an ene reaction between two alkynes and a Diels–Alder cycloaddition of the vinylallene formed. The process accounts for the thermally induced cycloisomerization of macrocyclic triynes and enediynes to give fused tetracycles in a stereoselective manner.

A highly efficient way of constructing complex organic molecules consists in the use of domino reactions.[1] When pericyclic transformations, endowed with complete atom economy and regio- and stereochemical control, are linked in a domino process, this as a whole will share these characteristics, achieving highly efficient chemical processes. In this communication we present a domino process consisting of two pericyclic steps: an unprecedented ene reaction between alkynes and a Diels–Alder cycloaddition.

Triaza macrocyclic scaffolds of type **1** have previously been transformed by a rhodium catalyzed [2 + 2 + 2] cycloaddition into tetrafused structures of type **2** (Scheme 1).[2] A moderate yield of a new product, **3a**, was obtained when the catalytic system tested was unable to promote the [2 + 2 + 2] cycloisomerization of **1a**. The new isomer featured a pyrrole ring fused to a central cyclohexene ring with its double bond conjugated to those of the pyrrole. The process was stereoselective since the saturated azacyclopentyl ring had a *cis* ring fusion (H_a, H_b in Scheme 1). Macrocycle **1a** was then treated without any catalyst and product **3a** was isolated from decomposition products and some starting material with a 32% yield (Entry 1, Table 1). Remarkably, the formation of compound **2a** was not detected in any case so excluding the possibility of both a thermal [2 + 2 + 2] cycloaddition process and an isomerization of **3a** to **2a**.

To check the generality of this reaction, macrocyclic enediyne **1b** was submitted to the same conditions (Entry 2, Table 1). Again the cyclohexadiene tetrafused product **2b** obtained in the metal-catalyzed process was not isolated but rather a 45% yield of a much more asymmetrical isomer **3b** was obtained in a stereoselective manner (Scheme 1). Almost half of the starting material decomposed during the prolonged heating time, but no isomer **2b** was detected in the NMR spectra of the crude reaction mixture.



Scheme 1 Metal-catalyzed *vs.* thermally-induced cycloisomerizations.

Table 1 Thermal cycloadditions of **1a** and **1b**[a]

Entry	Substrate	Additive[b]	Reaction time	Product/Yield (%)
1	**1a**	—	30 h	**3a**/32
2	**1b**	—	6 days	**3b**/45
3	**1a**	1,4-CHD	60 h	**3a**/77
4	**1b**	1,4-CHD	6 days	**3b**/78

[a] Reactions were run in toluene at 110 °C. [b] 20 equiv.

On excluding metal catalysis, the possibility of there being a radical mechanism proposed for thermally induced intramolecular cycloisomerization of open-chain triynes[3] was examined. Since radical species were engaged as intermediates for the formation of the isomerized products, the effect of an excess of 1,4-cyclohexadiene (1,4-CHD) added to the reaction mixture was evaluated. An increase in the yield of the cycloisomerized products **3a** and **3b** was obtained (entries 3–4, Table 1) although no formal addition of H occurred in the overall reaction.

To further understand the scope of the reaction, cycloaddition of macrocycle **1c**, bearing a phenyl substituent on the double bond, was studied. Two isomeric products with an overall 81% yield were obtained, which after isolation were assigned to structures **3c** and **3c′** (Scheme 2). The reaction was again stereoselective.

To further study yield enhancement by 1,4-CHD, we conducted an EPR study (Table 2). The use of a spin trap,

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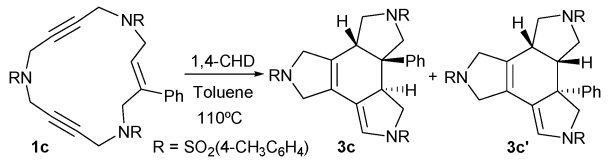


Scheme 2 Thermally-induced cycloaddition of macrocycle **1c**.

either 2-methylnitrosopropane (MNP) or α-phenyl-*N*-*tert*-butyl nitrone (PBN), was necessary as no radical was detected when the EPR experiment was recorded for the macrocycle alone (Entry 1). The addition of an excess of MNP allowed two radical adducts to be detected which were centred at the same position. These were ascribed to species **A** and **B** (Entry 2, Fig. S36†). The former is an adduct of the spin trap MNP and a *tert*-butyl radical resulting from its own decomposition. The blank experiment excluding macrocycle **1** (Entry 3) showed the formation of **A** to be independent of the presence of the substrate. However, species **B** originates from the reaction of MNP and a benzyl radical formed during the process. The formation of benzyl radicals was confirmed by the use of the more thermally stable PBN allowing the detection of spin adduct **C** (Entry 4), which was not formed in a blank experiment without macrocycle **1a** (Entry 5, Fig. S37†). Hence, the EPR experiments did not detect any radical species in **1a** but showed that benzyl radicals were formed in the reaction media, presumably due to H abstraction from toluene *via* homolytic cleavage. At this point, a deuteration experiment was undertaken. Macrocycle **1a** was heated at 110 °C in toluene-d^8 but no incorporation of deuterium was observed either by NMR or ESI-MS.

Once a radical mechanism was discarded, the role of the radicals needed to be understood (Table 3). First, the reaction medium was switched to chlorobenzene, which is less prone to radical homolytic cleavage, and the yield for both **3a** and **3b** was substantially increased (compare Entries 1–2, Table 3 with Entries 1–2, Table 1). Then, benzoyl peroxide was added to the reaction mixture and complete decomposition of the starting material was observed by TLC and NMR after 24 h of reaction (Entries 3–4). The experiments confirm the detrimental behavior of radicals, which decompose the starting material. This hypothesis was reinforced by DFT calculations,[4] which showed that the reaction of toluene with **1a** to yield the benzyl

Table 2 Radicals detected in the spin-trapping experiments

Entry	Mixture	*g* factor	LW (Gauss)	hfcc (Gauss)	Detected radical adduct structure
1	**1a**	—	—	—	—
2	**1a** + MNP	2.0062	1.1	a_N 15.2	$^tBu-\overset{O^\bullet}{N}-{}^tBu$ **(A)**
		2.0062	0.9	a_N 15.2 a_H 7.4	$^tBu-\overset{O^\bullet}{N}-CH_2-Ph$ **(B)**
3	MNP	2.0061	1.0	a_N 15.3	$^tBu-\overset{O^\bullet}{N}-{}^tBu$ **(A)**
4	**1a** + PBN	2.0061	1.2	a_N 14.5 a_H 2.7	$Ph-CH_2-\overset{Ph}{CH}-\overset{O^\bullet}{N}-{}^tBu$ **(C)**
5	PBN	—	—	—	—

Table 3 Effect of the radicals on the cycloisomerization reaction[a]

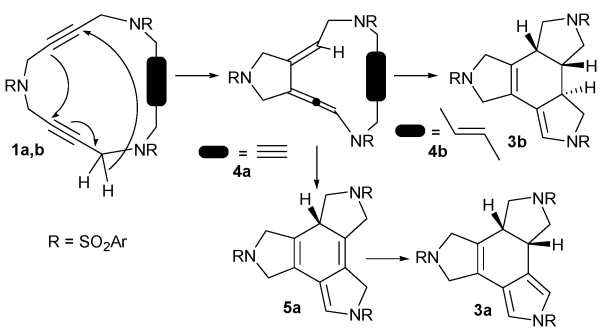
Entry	Substrate	Solvent/Additive	React. time	Prod./Yield
1	**1a**	Chlorobenzene/none	30 h	**3a**/62%
2	**1b**	Chlorobenzene/none	60 h	**3b**/60%
3	**1a**	Toluene/benzoyl peroxide[b]	24 h	Decomposes
4	**1b**	Toluene/benzoyl peroxide[b]	24 h	Decomposes

[a] Reactions were run at 110 °C. [b] A steady supply of radicals was generated by adding benzoyl peroxide at fixed time intervals.

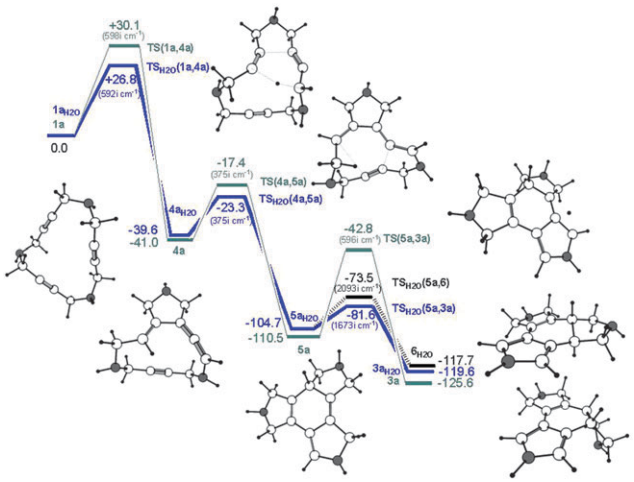
radical plus **[1a-H]** (formed by reaction of one of the N atoms in the macrocycle **1a** with a H) is endergonic by 38.4 kcal mol^{-1} suggesting that such a transformation is feasible at the reaction temperature. Therefore, the addition of 1,4-CHD increases the yield by neutralizing the radicals generated in the reaction media and so it effectively acts as a radical scavenger.

Given the lack of radical involvement, a mechanistic proposal was made for the reaction based on a domino process composed of an unprecedented intramolecular ene reaction between two alkynes[5] followed by a Diels–Alder reaction (Scheme 3). To the best of our knowledge, such an ene reaction has not been previously described, although acetylenic enophiles as well as acetylenic "enes" have been shown to participate in intramolecular ene-reactions,[6] and more recently an ene reaction of arynes with alkynes has been published.[7] This ene reaction affords a vinylallene intermediate **4** which may undergo a Diels–Alder reaction with the third unsaturation. If this is a triple bond (**4a**), the Diels–Alder reaction gives a 1,4-cyclohexadiene (**5a**) which undergoes a hydrogen rearrangement to yield **3a**. If the third unsaturation is a double bond (**4b**), the Diels–Alder reaction directly yields **3b**. In the case of macrocycle **1c**, the same mechanism accounts for both **3c** and **3c′**, each arising from one of the two non-equivalent alkynes participating as the ene or enophile in the reaction.

We then performed DFT calculations[4] to evaluate the feasibility of the mechanism. The energy profile is presented in Scheme 4. We analyzed whether the reaction occurs both with and without a water molecule (blue/green profile, respectively). As a single water molecule was found to be needed to assist the final hydrogen transfer, only data related to this profile will be discussed. The overall reaction is exergonic by *ca.* 120 kcal mol^{-1}. Initially, two triple bonds approach each other so that the distance between the propargylic hydrogen and the enophilic alkyne is suitable (bond lengths of C_6–C_9 and C_{10}–H are 2.077 and 1.682 Å,



Scheme 3 Mechanistic proposal for the thermally induced process.



Scheme 4 Reaction Gibbs free energy profile (green: without water molecule/blue: with one water molecule) for the domino ene/Diels–Alder reaction. All energies in kcal mol^{-1} are referred to **1a** or **1a** + H_2O.

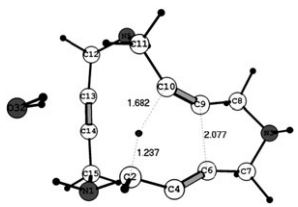


Fig. 1 Optimized structure (B3LYP/cc-pVDZ) for **TS$_{H_2O}$(1a,4a)**.

respectively, Fig. 1) to permit the six-electron pericyclic process, with suprafacial orbital interaction. The Gibbs free activation barrier of this process is 26.8 kcal mol^{-1}, which is the rate-determining step. The process from **1a** through the **TS(1a,4a)** gives the vinylallene species **4a**, from which the second pericyclic process takes place.

The transformation from **4a$_{H_2O}$** into **5a$_{H_2O}$** has a barrier of 16.3 kcal mol^{-1} and is exergonic by 65.1 kcal mol^{-1}. Finally, a hydrogen rearrangement is required. A thermal [1,3]-H sigmatropic rearrangement through **TS(5a,3a)** with a suprafacial orbital interaction with a high barrier (67.7 kcal mol^{-1}) due to the extremely strained four-membered ring formed in the TS was rejected. However, when a water molecule was added to the theoretical model to assist the H rearrangement *via* **TS$_{H_2O}$(5a,3a)** (Fig. 2), the barrier was much lower (23.1 kcal mol^{-1}). We also studied the possibility of forming product **6** with a *trans* ring fusion. In this case the energy barrier **TS$_{H_2O}$(5a,6)** (Fig. 2) is 31.2 kcal mol^{-1}, 8.1 kcal mol^{-1} higher compared to **TS$_{H_2O}$(5a,3a)**, thus explaining the formation of only **3a**, which is thermodynamically and kinetically favoured with respect to **6**.[8]

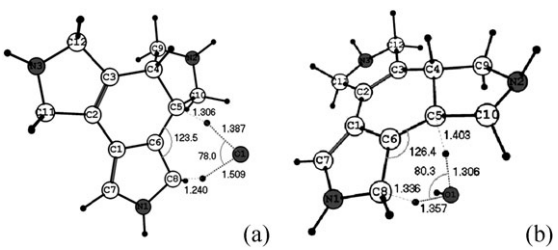


Fig. 2 Optimized structure (B3LYP/cc-pVDZ) for (a) **TS$_{H_2O}$(5a,3a)** and (b) **TS$_{H_2O}$(5a,6)**.

The assistance of a water molecule was experimentally supported by conducting the reaction of **1a** in anhydrous chlorobenzene with added D_2O. The product showed quantitative deuterium incorporation in H_a (Scheme 1) as observed both in NMR and ESI-MS spectroscopies (see SI†).

Experimental support for the proposed mechanism was also obtained from DSC measurements. As expected for thermally activated processes, the peak temperature T_P of the first process increases with the heating rate (Fig. S39†). For **1a** the Kissinger plot[9] of T_P exhibits the characteristic linear dependence related to processes governed by an Arrhenius-type rate constant $k(T)$, ($k(T) = A\exp(-E_A/RT)$) where E_A is the activation energy and A the preexponential term. An activation energy of 30.4 kcal mol^{-1} was obtained from the fit to the Kissinger plot, which is in reasonable agreement with DFT calculations that yield 25.0 kcal mol^{-1} for this activation energy obtained from the calculated enthalpy barrier $\Delta H^{\ddagger}$ plus the RT term calculated at 298 K. A reaction enthalpy of 120.8 kcal mol^{-1} for the complete transformation was determined by integrating the heat released, which agrees quite well with the DFT enthalpy of 118.3 kcal mol^{-1}.

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8 The **5a$_{H_2O}$** → **2a$_{H_2O}$** transformation assisted by a water molecule was also examined. It presents a large barrier (**TS$_{H_2O}$(5a,2a)**, Fig. S38†) of 46.9 kcal mol^{-1}, 23.8 kcal mol^{-1} higher in comparison with **TS$_{H_2O}$(5a,3a)**. So, **2a$_{H_2O}$** is the most stable product (is more stable than **3a$_{H_2O}$** by 3.3 kcal mol^{-1}) but it is not kinetically accessible.
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