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Introduction

Mechanistic understanding of domino cyclization between gem-dialkylthio vinylallenes and benzylamine towards economic synthesis: a computational study⁺

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DFT investigations are carried out to improve the domino cyclization between gem-dialkylthio vinylallenes and benzylamine. Economic reaction approaches were explored, namely, this reaction can occur under organic solvent-free conditions either catalyzed by trace water or self-catalyzed by BnNH₂. Three types of reactions (DMSO-assisted, trace water-catalyzed, and self-catalyzed by BnNH₂) shared the same reaction mechanism with the nucleophilic attack of BnNH₂ on the allenic carbon of thioamide intermediate **Re**. For trace water-catalyzed reaction another mechanism was also found that is the BnNH₂ attacks the carbonyl carbon of the conformational isomer of **Re**. Among the investigated mechanisms, the trace watercatalyzed one is suggested to be the most efficient and convenient synthetic method for pyrroles. Our calculated results were further confirmed by the experimental observation, which opens a new strategy for the synthesis of pyrroles.

Green chemistry is an important topic in academic and industrial research,¹ because it efficiently utilizes raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.² In recent years, great efforts have been directed towards the development of new organic transformations under environmentally friendly conditions for generation of the desired target molecules. The use of "safer solvents" and "design for energy efficiency" of the green chemistry 12 principles can be considered as the two key principles of relevance to synthetic chemistry.3 Water, as the sole medium for organic reactions, has advantages of being low cost, safe, and environmentally friendly that make it an ideal reaction medium in synthetic chemistry.⁴ The classical role of water has been regarded as a dielectric solvent, which enhances the rates and affects the selectivity of a wide variety of organic reactions.⁵ Recently studies indicate that water not only acts as a nonspecific, passive dielectric medium in many biological and chemical processes, but also as an active participant in

reactions.⁶ Moreover, the catalytic action of water is implied in many fundamental reactions, such as acid-base reaction,⁷ keto-enol tautomerization,^{6b} prototropic tautomerization as well as proton transfer in basic biological function,^{6,8} and the hydration of carbonyl compounds⁹ as well as the [1,2]-proton shift.¹⁰ Thus, the importance of water catalysis offered by mechanism insights through computational studied is necessary.

Our coworkers¹¹ recently discovered an efficient method to synthesize pyrroles through gem-dialkylthio vinylallenes and their alkylthio-regulated reactivity (Scheme 1), featuring a metal-free, step-economic domino cyclization process. Moreover, we found that gem-dialkylthio vinylallene was the real precursor of the product and obtained 95% yield with BnNH₂ (2.5 equiv.) in DMSO at 100 °C within 1 min. Meanwhile, the 1,3-dithiolane moiety of gem-dialkylthio vinylallenes undergoes ring-opening by BnNH₂ to form the thioamide intermediate.¹² Although a plausible mechanism was proposed in our previous work,¹¹ the detailed ones for the formation of pyrroles are still unknown. To develop a greener process, in comparison to the above experiment, we consider more environmentally friendly processes and even without any additional organic reagent other than the reacting substrates. Herein, we present our theoretical investigation using density functional theory (DFT) calculations as well as the experimental study of the domino cyclization of pyrroles aiming at green synthesis. We took thioamide intermediate (Re) and benzylamine as a model system to explore the detailed

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Scheme 1 The reaction of gem-dialkylthio vinylallenes and benzylamine.

mechanism under three different conditions: DMSO-assisted, trace water-catalyzed, and dehydrated solvent-free.

Computational method

All calculations were carried out with the Gaussian 09 suite of quantum chemical programs.¹³ The density functional theory B3LYP¹⁴ and well-established PBE1PBE^{6b,15} were used for the computations. Pople's 6-31G** basis set was employed for all calculations in the gas phase. The stationary points were confirmed by frequency calculations in order to verify that TSs have one and only one imaginary frequency. Intrinsic reaction coordinate (IRC) calculations were performed to ensure that the transition states led to the expected reactants and products.¹⁶ Energies and Gibbs free energies were obtained by adding scaled zero-point vibrational energy corrections, and thermal contributions to the gas-phase energies. The single point energies were subsequently computed at the B3LYP and PBE1PBE level using the 6-311+G** basis set in both the gas phase and the solvent phase. Solvent effect (solvent = DMSO) was calculated using a polarizable continuum model (PCM).¹⁷ The energies employed for discussions in the text are the energies and Gibbs free energies obtained at the PBE1PBE/ 6-311+G** level of theory (see details in the ESI Tables S1 and S2†).

Natural bond orbital (NBO) analysis was performed at the PBE1PBE/6-311+G** level to study the charge distribution and donor–acceptor interactions.¹⁸ Topological analysis of the electron densities at the critical points, with Bader's Atom-in-Molecule (AIM) framework, was carried out using Multiwfn program to confirm the weak interactions.¹⁹

Results and discussion

Two types of mechanisms were proposed for the domino cyclization of pyrroles, as shown in Scheme 2. One is the originally proposed mechanism for the cycloaddition of pyrroles by us.¹¹ In this mechanism, the reaction starts from selective attack of BnNH₂ on the allenic carbon of Re, followed by a cyclization and the elimination of water, denoted as M1. Considering the different reaction conditions, mechanism M1 contains M1-1, M1-2, and M1-3, corresponding to DMSO-assisted, trace watercatalyzed, and self-catalyzed ones. The newly proposed mechanism, denoted as M2, begins with the BnNH₂ attacking the carbonyl carbon of Re' (the conformational isomer of Re), followed by an intramolecular cyclization and elimination of water. Herein, we will first investigate DMSO-assisted mechanism (M1-1) of the domino cyclization of pyrroles. Secondly, a detailed study of the trace water-catalyzed mechanism (M1-2 and M2) by using water instead of DMSO. Finally, we will discuss the possibility of the reaction being under dehydrated solvent-free condition (M1-3).

DMSO-assisted mechanism of the domino cyclization of pyrroles

It is noteworthy that in our previous work we did not consider the solvent effect for DMSO-assisted mechanism calculation, *i.e.*, only gas phase results were provided, besides, both DMSO and BnNH₂ were not included in the processes of keto–enol tautomerization and cycloaddition.¹¹ Therefore, we present here a detail investigation for the domino cycloaddition. The DFT computed the most favorable energy profile (pathway 1) in the solvent for the domino cyclization of pyrroles as depicted in Fig. 1–3, the relative energies and free energies of the starting material (BnNH₂ + **Re**) are set as the reference zero of the energy in this study. The competing pathways 1' and 1" are provided in Fig. S1 in the ESI.[†]

There are two possible attacking sites (either allenic or carbonyl carbon of **Re**) for the nucleophilic reaction process between **Re** and BnNH₂ corresponding to two types of reaction mechanisms (Scheme 2). Our calculations show that only the mechanism M1 is reasonable in the presence of solvent DMSO as a catalyst (M1-1). M1-1 consists of five processes: (I) the nucleophilic addition process (**Com1D** \rightarrow **Int1D**), (II) the intermolecular deprotonation and protonation process (**Int2D** \rightarrow **Int5D**), (III) keto–enol tautomerization (**Int5D** \rightarrow **Int6D** (**Int6'D**)), (IV) intramolecular cyclization (**Int6'D** \rightarrow **Int7'D** and **Int6D** \rightarrow **Int7D**), (V) the elimination of water (**Int8'D** (**Int8D**) \rightarrow **Pr**). In the DMSO-assisted domino reactions, DMSO acts as a solvent and a catalyst; BnNH₂ plays a ternary role in the domino cyclization by acting as a reactant, a base, and a catalyst.

Process I is the nucleophilic addition of BnNH₂ to the allenic carbon of **Re**, which takes place *via* C–N bond formation transition state **TS1D** assisted by single DMSO, with the energy barrier ($\Delta\Delta E^{\ddagger}$) of 17.1 kcal mol⁻¹. Intermolecular hydrogen-bonding interactions between the O atom of DMSO and the H atom of BnNH₂ as well as the S atom of **Re** and the H atom of BnNH₂ facilitate this process. Process II is a DMSO-assisted two-step proton-transfer process *via* transition states **TS2D** and **TS3D**, including the deprotonation of the hydrogen H1 from N1 and protonation of the carbon atom C1. It is



Scheme 2 Proposed mechanisms (M1 and M2) for domino cyclization of pyrroles under three different conditions, DMSO-catalyzed (red), trace water-catalyzed (green), and self-catalyzed (olive).

achieved by single hydrogen bond (O---H-N, 1.89 Å) and double hydrogen bonds (O···H-N, 1.90 Å and 1.84 Å) assisting. Thus, DMSO acts as a hydrogen-bonding acceptor in processes I and II. BnNH₂ acts as a hydrogen-bonding donor in process I and a donor and an acceptor in process II, respectively. Three possible pathways (1', 1", and 1) were investigated for the ketoenol tautomerization process III (Fig. S1[†] and Fig. 2). Pathway 1' is a direct intramolecular [1,3]-H shift from the C4 atom to the O1 atom *via* transition state **TS4'D**, with a high $\Delta \Delta E^{\ddagger}$ value of 52.4 kcal mol⁻¹ (Fig. S1,[†] gray line). Thus, this direct intramolecular [1,3]-H shift pathway is kinetically unfeasible. Pathway 1" is a [1,3]-H shift involving two molecules of water that act as a relay in the shift of the proton from the C4 atom to the O1 atom via transition state TS4WD (Fig. S1,† dark gray line). Pathway 1 is a stepwise keto-enol tautomerization process via transition states TS4aD (11.1 kcal mol^{-1}) and TS4bD (2.8 kcal mol⁻¹) assisted by two molecules of DMSO (Fig. 2, black line), the $\Delta \Delta E^{\ddagger}$ value of **TS4bD** is 49.6 kcal mol⁻¹ and 9.6 kcal mol⁻¹ lower than that of TS4'D and TS4WD, respectively. Thus, the DMSO-assisted keto-enol tautomerization pathway 1 is the most favored one. In the intramolecular cyclization process IV, the C-N bond forming step shows that DMSO-assisted transition state TS5D (pathway 1, in black) is more stable than TS5'D (pathway 1", in dark gray) by 19.3 kcal mol⁻¹ (Fig. 3 and S1[†]). This result indicates that DMSO can

efficiently stabilize the intramolecular cyclization transition state TS5D via triple hydrogen bonds. Both DMSO and BnNH2 act as a hydrogen-bonding donor and an acceptor in processes III and IV, respectively. In the subsequent water eliminating process V, the location of the transition state of the deprotonated step shows a similar observation as intramolecular cyclization that TS6D is favorable compared with TS6'D by 3.5 kcal mol^{-1} (Fig. S1[†]). Subsequently, the protonated BnNH₂ delivers the H2 to the -OH group assisted by two molecules of DMSO, leading to H₂O *via* transition state **TS7D** with the $\Delta\Delta E^{\ddagger}$ value of 2.1 kcal mol⁻¹. Finally, the product **Pr** is formed. Thus, DMSO acts as a hydrogen-bonding acceptor, BnNH₂ acts as a hydrogen-bonding donor and an acceptor in process V. As shown in Fig. 2, 3, and S1,[†] the rate-determining step of DMSO-assisted the domino reaction of pyrroles is the nucleophilic addition of BnNH₂ to the allenic carbon of Re, with the activation barrier of 17.1 ($\Delta \Delta E^{\ddagger}$) or 20.6 (free energy barrier, $\Delta\Delta G^{\ddagger}$) kcal mol⁻¹.

Trace water-catalyzed mechanism without organic solvent

The Lewis-basic nature of water allows it to modify the reactivity of Lewis acid species, leading in some cases to accelerated reactions.²⁰ Thus, we use water instead of organic solvent DMSO to investigate the mechanism of the domino reaction following green chemistry principles. Both M1 and M2 are



Fig. 1 The geometry structures of intermediates for DMSO-assisted pathway 1, distances are in Å.

reasonable in the presence of trace water for domino cyclization of pyrroles. Four possible reaction pathways were proposed and examined (Fig. 4 and S3†). Pathways 1W (in light gray) and 2W (in gray) correspond to one- and two water-catalyzed M1-2, pathways 1W' (in black) and 2W' (in dark gray) are the two water-catalyzed M2. The difference between pathways 1W' and 2W' lies in the sequence of intramolecular cyclization and the water elimination. The corresponding energy profile of the most favorable pathway 1W' is depicted in Fig. 4, the other competing pathways 1W, 2W, and 2W' are provided in Fig. S3 in the ESI.† In pathway 1W (2W), a single (double) water molecule instead of solvent DMSO was introduced into the model to evaluate its effect on the M1. The calculation results indicate that water can act as a catalyst and a proton shuttle to accelerate the formation of pyrroles. The energy barrier for a water-catalyzed cyclization step *via* **TS4W** is 23.5 kcal mol⁻¹, which is less favored than **TS1D** by 6.4 kcal mol⁻¹ (see computational details in Fig. S3 and S4 in the ESI[†]).

It is well-known that water is a polar molecule that can act as a hydrogen-bond acceptor and/or donor.²¹ Meanwhile, water is an amphoteric substance, it can serve as an acid and a base^{20b} and act as a general acid–base catalyst.²² Our calculation results indicate that the two-water cluster as a catalyst is more favorable in reducing the energy barrier of the [1,3]-H shift process than the one water or three water-cluster (see ESI S1, Tables S3 and S4† for details). Therefore, we investigated the M2 by introducing two water molecules to the domino reaction of pyrroles, as shown in Fig. 4 and S3† (in black and

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Fig. 2 DFT computed energy surface of pathway 1 for the DMSO-catalyzed domino reaction of pyrroles (from **Com1D** to **Int6D**) in the solvent phase and the corresponding key optimized structures of transition states, distances are in angstrom and relative energies and free energies are given in kcal mol^{-1} . S: yellow, N: blue, C: gray, O: red, H: white.

dark gray). M2 can be described as four processes including nucleophilic addition, intramolecular cyclization/water elimination, (deprotonation and protonation)/intramolecular cyclization, water elimination/(deprotonation and protonation) (pathway 1W'/2W'). The formation of complex **Com1W**' is favorable with a binding energy of -13.5 kcal mol⁻¹. The intermediate **Int1W**' is formed *via* a concerted proton transfer and C-N bond formation transition state **TS1W**' with the $\Delta\Delta E^{\ddagger}$ value of 8.6 kcal mol⁻¹. In the conversion of **Com1W**' to **Int1W**', the carbonyl group serves as a proton acceptor, and the water molecules act as a bifunctional catalyst, extracting the H1 atom from N1 and donating one of its H atoms to the carbonyl oxygen. Thus, hydrogen bonding interaction is the intrinsic driving force to promote the nucleophilic attack of nitrogen of BnNH₂ on the carbonyl carbon of **Re'**. From the intermediate **Int1W'**, the reaction follows two alternative pathways (pathways 1W' and 2W') differing in the sequence of intramolecular cyclization and water elimination. In pathway 1W', water assisted the five-membered ring closure affords the intramolecular cycloadduct **Int2W'** via a cyclic transition state



Fig. 3 DFT computed energy surface of pathway 1 for the DMSO-catalyzed domino reaction of pyrroles (from **Int6D** to **Pr**) in the solvent phase and the corresponding key optimized structures of transition states, distances are in angstrom and relative energies and free energies are given in kcal mol⁻¹. S: yellow, N: blue, C: gray, O: red, H: white.

TS2W', with the $\Delta \Delta E^{\ddagger}$ value of 19.0 kcal mol⁻¹. The following step is a water-catalyzed concerted proton transfer process, including the deprotonation of hydrogen H2 from N1 and protonation of carbon atom C1. The intermediate Int3W' is formed via transition state TS3W'. It is a barrier-free proton transfer process with the $\Delta \Delta E^{\ddagger}$ value of -2.3 kcal mol⁻¹. Intermediate Int3W' is then converted to the Int4W' by water eliminating via a six-membered ring transition state TS4W', with the $\Delta \Delta E^{\ddagger}$ value of 15.2 kcal mol⁻¹. In pathway 2W', a transition state TS2-1W' is located, wherein the two water molecules serve as a proton bridge in the elimination of the water process. The $\Delta \Delta E^{\ddagger}$ value of **TS2-1W**' is 29.5 kcal mol⁻¹, which is 14.3 kcal mol⁻¹ higher than that of **TS4W**' of pathway 1W' (15.2 kcal mol^{-1}). Thus, later dehydration is better than the early one, mainly due to the much more relief of the ring strain of six-membered ring TS4W' as compared to eight-membered ring TS2-1W'.23 Next, the intermediate Int3-1W' is formed via an intramolecular five-membered ring transition state **TS3-1W**' with the $\Delta \Delta E^{\ddagger}$ value of 14.5 kcal mol⁻¹. The following deprotonation and protonation step from Int3-1W' to Int4-1W' via a proton relay ten-membered ring transition state **TS4-1W'** with the low $\Delta \Delta E^{\ddagger}$ value of 1.7 kcal mol⁻¹. Finally, three-water clusters are released to generate the product Pr.

As shown in Fig. 4 and S3,[†] the rate-determining steps are predicted to be the intramolecular cyclization for pathways 1W' and 2W as well as the elimination of H₂O for pathway 2W', respectively. The $\Delta\Delta E^{\ddagger}$ value of **TS2W'** is 4.5 kcal mol⁻¹ and 10.5 kcal mol⁻¹ lower than that of **TS4W** and **TS2-1W'**,

respectively. Obviously, pathway 1W' is the most favored one among the three pathways, and the trace water-catalyzed mechanism M2 is preferred over the M1-2. In addition, the trace water-catalyzed M2 is relatively preferred over the DMSOassisted M1-1 by the $\Delta\Delta G^{\ddagger}$ value of 1.2 kcal mol⁻¹, although the $\Delta\Delta E^{\ddagger}$ value of **TS2W**' is 1.9 kcal mol⁻¹ higher than that of **TS1D**. Therefore, our calculated results imply that organic solvent DMSO is not necessary in this reaction. Moreover, the new trace water-catalyzed mechanism provides an efficient and convenient green synthetic method for pyrroles, which meets the promising view point of green chemistry in modern chemical research.

The reaction possibility of the domino cyclization of pyrroles under dehydrated solvent-free conditions

We also investigated the mechanism of the domino cyclization of pyrroles under solvent-free and dehydrated conditions. The corresponding energy profile is given in Fig. 5. The calculation result shows that only the mechanism M1 is reasonable for the reaction self-catalyzed by BnNH₂ (M1-3). The **Re** binds with two molecules of BnNH₂ and forms complex **Com1F**. Formation of **Com1F** is exothermic by -10.2 kcal mol⁻¹. The next step is the nucleophilic attack of the nitrogen of BnNH₂ on the allenic carbon of **Re** *via* transition state **TS1F** to form **Int1F**. The corresponding activation energy barrier is 20.4 kcal mol⁻¹. This result indicates that BnNH₂ plays two roles in the nucleophilic addition process, that is, BnNH₂ acts as both a nucleophile and a catalyst to facilitate this process. The catalyst



Fig. 4 DFT computed energy surface for the water-catalyzed domino reaction of pyrroles and the corresponding geometry structures of reactants, intermediates, and transition states for pathway 1W'. Distances are in Å and relative energies and free energies are given in kcal mol⁻¹. S: yellow, N: blue, C: gray, O: red, H: white.

BnNH₂ plays an anchoring role by binding to the S atom of **Re** and the H atom of nucleophile BnNH₂. Thus, double hydrogen bonds (S···H3–N2, N2···H1–N1) stabilize the transition state **TS1F** (see Fig. 5). Subsequently, the hydrogen H1 migrates to the N2 of BnNH₂ *via* a low energy barrier transition state **TS2F** of 1.2 kcal mol⁻¹. The ΔE value of **Int2F**' is 5.3 kcal mol⁻¹, which is 1.4 kcal mol⁻¹ higher than the transition state **TS2F**. Thus intermediate **Int2F**' is not stable, which rapidly releases a proton and transfers to a stable intermediate **Int2F** *via* a barrier-free deprotonation process. Another BnNH₂ molecule binds with intermediate **Int2F**, resulting in intermediate **Int3F**. From intermediate **Int3F** to intermediate **Int5F**, it is the BnNH₂-catalyzed two-step deprotonation and protonation processes. In the deprotonation transition state **TS3F** with BnNH₂ assisting, the H4 is transferred from the C4 to the N2 of BnNH₂, the corresponding $\Delta\Delta E^{\ddagger}$ value is 8.9 kcal mol⁻¹. The following protonation step from **Int4F** to **Int5F** is a barrier-free process (see details in the ESI Fig. S5[†]), the H4 transfer to O1 of carbonyl. The formation of **Int5F** is exothermic by -41.1 kcal mol⁻¹. The intermediate **Int6F** is formed *via* an intramolecular five-membered ring transition state **TS5F** with the $\Delta\Delta E^{\ddagger}$ value of 33.0 kcal mol⁻¹. The last step is the release of the water molecule *via* transition state **TS6F** to form intermediate **Int7F**, with the $\Delta\Delta E^{\ddagger}$ value of 18.6 kcal mol⁻¹. Then a single water molecule and two molecules of BnNH₂ are released to form the product **Pr**.

As a consequence, the results suggest that $BnNH_2$ not only serves as a reactant, but also acts as a base. It abstracts the



Fig. 5 DFT computed energies and free energies for the dehydrated solvent-free domino reaction of pyrroles and the corresponding geometry structures of reactants, intermediates, and transition states. Distances are in Å and relative energies and free energies are given in kcal mol⁻¹.

hydrogen and accelerates the dehydrated solvent-free reaction as a catalyst. Furthermore, the weak interaction between the S atom of the C=S group and the hydrogen atom of BnNH₂ facilitates the initial nucleophilic addition and deprotonation/ protonation processes. In addition, judging from the relative energies listed in Fig. 5, it is clear that the five-membered ring closure process is the rate-determining step. The $\Delta\Delta E^{\ddagger}$ ($\Delta\Delta G^{\ddagger}$) value of **TS5F** is 15.9 (12.9) kcal mol⁻¹ and 14.0 (14.1) kcal mol⁻¹ higher than those for **TS1D** of DMSO-assisted and **TS2W**' of trace water-catalyzed pathways. Therefore, the DMSOassisted and trace water-catalyzed processes for the formation of pyrroles are preferred than that of the BnNH₂-assisted one. More interestingly, DMSO-assisted pathway 1 (Fig. 1–3) is competitive with the trace water-catalyzed pathway 1W' (Fig. 4). In addition, we also consider the effect of water–DMSO on the energy barrier of the rate-determining step in pathway 1. The calculated results suggest that the $\Delta\Delta G^{\ddagger}$ value of water–DMSO catalyzed transition state **TS1WD** is less favored than trace water-catalyzed **TS2W**' by 6.2 kcal mol⁻¹ (see Fig. S6 in the ESI[†]).

Orbital analysis

Analysis of the frontier molecular orbitals (FMO) of the transition states species of TS1D, TS2W', and TS5F, leads to a



Fig. 6 Secondary orbital interactions in HOMOs of the TSs for the C-N bond (pink ellipse) formation.

rationalization of the calculation results mentioned above. As depicted in Fig. 6, the secondary orbital interaction between C2 and N1 in the HOMO-15 of TS1D is larger than that between C5 and N1 in HOMO-9 of TS5F. Thus, the nucleophilic attack of the N1 atom on C2 of TS1D is more favorable. In TS2W', HOMO-11 shows a much stronger orbital interaction between N1 and the vinylallene as well as the two benzene rings, because the electron extensively delocalizes over the N1, the vinylallene, and the benzene ring part. Therefore, trace water molecules effectively stabilize the structure of TS2W' and reduce the energy barrier of the nucleophilic attacking process. Additionally, the electron delocalization of the reaction site in the case of TS2W' is higher than in TS1D. Consequently, the orbital interaction order of the TSs follows TS2W' > TS1D > TS5F, indicating that the trace water-catalyzed domino cyclization of pyrroles is the most favored one.

Yang *et al.* reported an invaluable approach to detect noncovalent interactions in real space, based on analyzing the electron densities and their reduced density gradient RDG isosurface.²⁴ The analysis of the RDG for the rate-determining step transition states structures under these different catalyzed conditions of domino cyclization of pyrroles was conducted by using the Multiwfn^{19b} and VMD.²⁵ The results are shown in Fig. 7. It is clear that strong (in blue color) quadruple stabilizing C1^{-...}H1–O1', O1'...H1'–O2', O1'...H2–N1, and O2'...H3'– O1 hydrogen bonds and weak (in green color) O2'...H2–N1, and π ...H2'–O1' interactions are present in trace water-catalyzed transition state **TS2W'**. For **TS1D**, there are strong single O2...H1–N1 hydrogen bond interactions and several weak S…H–N, S…H–C as well as π …H–C interactions. Similarly, strong single N2…H4–O1 and weak double O1…H5–N3 and



Fig. 7 Noncovalent interactions analysis (blue, strong interaction; green, weak interaction; and red, strong repulsion) for C–N bond formation transition states under DMSO-assisted, trace water-catalyzed, and solvent-free conditions.

N3…H3–N2 interactions are in self-catalyzed transition state **TS5F**, as shown in different colors. For a further quantitative description of the interaction energy of these hydrogen bonds in these transition states and interpret the origin of the reaction activity of the three different reaction conditions, we carried out NBO analysis as follows.

NBO analysis

To further explore the origin of the difference of the domino cyclization of the pyrroles under DMSO-assisted, trace watercatalyzed, and solvent-free conditions, we carried out a second-order perturbation analysis¹⁹ on the three rate-determining step transition states **TS1D**, **TS2W**', and **TS5F**.

As shown in Table 1, for **TS1D**, the E(2) value of $\sigma \rightarrow \pi^*$ interaction between N1-H2 and C2-C3 is 2.06 kcal mol⁻¹, which is lower and larger than those of $\sigma \rightarrow \pi^*$ between N1–H2 and C2– C1 in **TS2W**' (2.17 kcal mol⁻¹), and $\sigma \rightarrow \sigma^*$ between N1–H2 and C5–O1 in **TS5F** (0.54 kcal mol^{-1}). The results suggest that the ring closure assisted by trace water is more favored than those of DMSO-assisted and self-catalyzed, which is consistent with the free energy barrier order of $\Delta \Delta G_{\mathbf{TS2W}'}^{\ddagger} < \Delta \Delta G_{\mathbf{TS1D}}^{\ddagger} < \Delta \Delta G_{\mathbf{TS5F}}^{\ddagger}$. There is a weak interaction between the benzene ring and C6-N1 of BnNH₂ (N marked with 1) in these three transition states, which makes the N1 much more negatively charged. In addition, the large E(2)value of $n \rightarrow \sigma^*$ interaction between O2 and N1-H1 of TS1D as well as the S atom and N1-H2 are 28.83 kcal mol⁻¹ and 12.66 kcal mol⁻¹, respectively, which indicates DMSO and the hydrogen bond (S···H2-N1) can stabilize the rate-determining step transition state TS1D to some extent. The developing carboanion C1 in transition state TS2W' is efficiently stabilized by the water molecules via strong quadruple (C1^{-...}H1-O1', O1' ···H1'-O2', O1'···H2-N1, and O2'···H3'-O1) and weak double $(\pi \cdots H2'-O1'$ and $O2'\cdots H2-N1$) interactions, with the total stabilization energy amount to 48.74 kcal mol⁻¹. Three kinds of hydrogen bonding interactions (O1…H5-N3, N3…H3-N2,

Table 1 Selected donor-acceptor bond orbital interaction and second-order perturbation stabilization energies (E(2), kcal mol⁻¹) for transition states

Species	Donor	Acceptor	Interaction	E(2)
TS1D	BD N1-H2	BD* C2-C3	$\sigma \rightarrow \pi^*$	2.06
	BD Ph	BD* C6-N1	$\pi \rightarrow \sigma^{\star}$	3.39
	LP O2	BD* N1-H1	n→σ*	28.83
	LP S	BD* N1-H2	n→σ*	12.66
TS2W'	BD N1-H2	BD* C2-C1	$\sigma \rightarrow \pi^{\star}$	2.17
	BD Ph	BD* C6-N1	$\pi \rightarrow \sigma^{\star}$	3.68
	BD Ph	BD* O1'-H2'	$\pi \rightarrow \sigma^{\star}$	0.48
	BD C2-C1	BD* O1'-H1	$\pi \rightarrow \sigma^{\star}$	12.87
	LP O1'	BD* O2'-H1'	n→σ*	14.49
	LP O1'	BD* N1-H2	n→σ*	5.23
	LP O2'	BD* O1-H3'	n→σ*	14.70
	LP O2'	BD* N1-H2	n→σ*	0.97
TS5F	BD N1-H2	BD* C5-O1	$\sigma \rightarrow \sigma^*$	0.54
	BD Ph	BD* C6-N1	$\pi \rightarrow \sigma^{\star}$	5.14
	LP O1	BD* N3-H5	n→σ*	1.29
	LP N3	BD* N2-H3	n→σ*	5.77
	LP N2	BD* 01-H4	$n \rightarrow \sigma^{\star}$	35.08



and N2…H4–O1) are found in BnNH₂-assisted **TS5F** and the sum of the E(2) value is 42.14 kcal mol⁻¹. Thereby, the NBO calculation results further confirm the trace water-catalyzed domino cyclization of pyrroles to be the most favored pathway relative to the DMSO-assisted and dehydrated solvent-free pathways.

Following the computational results, the effect of water on the domino reaction of pyrroles (Pr) formation was examined by experimental investigations. As shown in Table 2, 87% yield of pyrroles Pr was obtained when performing the reaction in DMSO (entry 1). A significant decrease of product yield to 74% was observed under the strict solvent-free conditions by carrying out the reaction in glove box (entry 2). However, the yield was increased to 90% when the solvent-free reaction was performed in air-open conditions, in which the presence of extremely trace amount of water is reasonable (entry 3). This outcome is consistent with the computational results that the trace amount of water may assist the transformation. Further, it was found that the amount of water played a crucial role in the reaction because the increase of water amount, for example, one drop (ca. 0.036 mL), dramatically led to the reduction of the yield to 30% (entry 4). Only a trace amount of product Pr was detected by TLC when using water as the reaction medium (entry 5). This is due to the following reasons: (i) the poor solubility of the starting material in water; (ii) the interaction between base (BnNH₂) and acid (water) weakens the nucleophilic attack of BnNH2 on the gem-dialkylthio vinylallenes and thereby reduces the reaction rate and yield; (iii) the calculated results of solvent effect indicate that the energy values of the reaction intermediates and transition states increased in the range of 6.2–9.0 kcal mol⁻¹ and 6.4–7.6 kcal mol⁻¹, compared with the case in the gas phase (see Table S5 in the ESI⁺). Consequently, these experimental observations support the computational results and confirm trace water-catalyzed domino cyclization for pyrroles **Pr** formation to be the best one.

Conclusions

In summary, the mechanism of domino cyclization of pyrroles has been explored both theoretically and experimentally under

three different conditions. Two types of mechanisms, *i.e.*, M1 and M2 were explored by DFT calculations. The difference between M1 and M2 lies in the nucleophilic attacking sites, either allenic carbon of Re or carbonyl carbon of conformational isomer of Re. Our calculations suggest that the trace water-catalyzed mechanism M2 is favorable than DMSOassisted M1. It is ascribed to the following reasons: (1) the synthetic routes of pyrroles catalyzed by trace water avoid the long multistep sequence as compared with the DMSO-catalyzed and self-catalyzed ones; (2) trace water molecules effectively stabilize the structure of the transition state in the rate-determining step and thus reduce the energy barrier of the nucleophilic attacking process via intermolecular hydrogen bonding interactions; (3) the delocalized carboanion in transition state TS2W' is efficiently stabilized by the trace water molecules via strong quadruple (C1⁻···H1-O1', O1'···H1'-O2', O1'···H2-N1, and O2'···H3'-O1) and weak double $(\pi \cdots H2'-O1')$ and O2'···H2-N1) interactions, which are absent in the DMSO catalyzed TS1D and self-catalyzed TS1F; (4) water acts as a proton shuttle and an anchoring role to facilitate the proton transfer and nucleophilic addition processes, and the carbonyl group is very critical to support the hydrogen network in these processes by acting as a proton acceptor or a proton-relay stabilizer. The frontier molecular orbitals, noncovalent interaction, and NBO analyses further confirm our results. Therefore, organic solvent DMSO is not necessary for this reaction, which is further verified by the experimental outcome. Our finding suggests more green chemistry reaction processes by either a trace water catalyst or BnNH₂ self-catalyst and provides a new synthetic strategy for pyrroles.

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