COMMUNICATION

gem-Dialkylthio vinylallenes: alkylthio-regulated reactivity and application in the divergent synthesis of pyrroles and thiophenes[†]

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gem-Dialkylthio vinylallenes were obtained for the first time and applied to the divergent synthesis of fully-substituted pyrroles and thiophenes by domino cyclizations. These two cyclization pathways were regulated by alkylthio groups. Plausible reaction mechanisms were presented and supported by DFT calculations. An unprecedented metal-free carbothiolation was discovered in the formation of thiophenes.

Design and utilization of novel multi-functionalized synthons constitutes a powerful strategy to build useful molecules, particularly through step-economic domino reactions.1 Vinylallenes are a unique class of allene derivatives² that have been recognized as a versatile synthon in organic synthesis.³ Significant substituent effects have been observed on the reactivity of vinylallenes, however, it is limited to previously known reactions such as 1,4-electrocyclization, [1,5]-sigmatropic rearrangement and other annulation process for silyl-,4a boryl-,4b phosphinoyl,4c sulfinyland sulfonyl-substituted^{4d} and titanated vinylallenes.^{4e} Most of these substituents were not involved in the reactions. Hence, combining the regulation effect and the intrinsic reactivity of substituents would be a useful strategy to develop novel reactions for vinylallenes. Of particular relevance to this is a recent example reported by Sherburn et al., who showed that 1,1-divinylallene reacted with three maleimides to produce a complex hexacycle.⁵

In the synthetic utility of ketene dithioacetals,⁶ the reactions tuned by dialkylthio groups are especially important for the synthesis of useful and complex compounds.⁷ Therefore, we envisaged that the introduction of dialkylthio groups onto the skeleton of vinylallene could elicit novel reactivity and synthetic use.⁸ Herein, we report our preliminary results in this direction and describe the first preparation of *gem*-dialkylthio vinylallenes and their alkylthio-dependent reactivity. As a new class of multifunctional groups-integrated synthon (MFGIS), the *gem*-dialkylthio vinylallenes possess several useful features, including: (1) ready *in situ* generation through the isomerization

of *gem*-dialkylthiopenten-4-ynes;⁹ (2) unique structural feature integrating ketene dithioacetal (blue) and allene (green) units into a vinylallene system (yellow) (Fig. 1); (3) alkylthio group-dependent reactivity in which the alkylthio group not only acts as a regulator but also as a reactive group in the cyclizations as verified by the divergent synthesis of pyrroles¹⁰ and thiophenes;¹¹ and (4) unprecedented metal-free carbothiolation of *gem*-dialkylthio vinylallenes bearing acyclic alkylthio groups.¹²

Initially, the reaction of *gem*-dialkylthiopenten-4-yne **1a1** containing a 1,3-dithiolane moiety with benzylamine was performed. To our delight, this reaction was complete within 5 h under the optimal conditions (DMSO as solvent at 100 °C; for details see Table S2†) and gave pyrrole **3a1** in 85% yield (Scheme 1). In a stepwise experiment, *gem*-dialkylthio vinylallene **2a1** was exclusively produced in 95% yield by quenching the reaction within 1–2 min, and further reaction with benzylamine gave **3a1** in 87% yield, thus indicating that **2a1** was the real precursor of **3a1**. Benzylamine appears to play a dual role in the domino cyclization by acting both as a base and a reactant. Notably, **2a1** can be prepared on a multigram-scale in a one-pot operation and is stable under ambient conditions (Fig. S1†).

Encouraged by this preliminary result, we began to investigate the reaction scope (Table 1). Under optimal conditions,





Scheme 1 Cyclization between *gem*-dialkylthiopenten-4-yne 1a1 and benzylamine.

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Table 1 Synthesis of fully-substituted pyrroles 3a



the reactions of substrates **1a2–1a11** bearing a carbonyl group (EWG = R'CO) with various amines produced the corresponding pyrroles 3a2-3a18 in good to high yields. A series of functional groups including aryl, heteroaryl, fused aryl, alkyl, hydroxyl, alkenyl and cyclopropyl can be easily incorporated into the pyrrole scaffold. In addition, gem-dialkylthio vinylallenes 2a2-2a11 bearing a 1,3-dithiolane functionality can be quickly prepared in nearly quantitative yields from 1a2-1a11 through base-promoted isomerization (Table S1⁺). Furthermore, 2-aminopyrroles 3a19-3a28 were synthesized in good to high yields from the reactions of gemdialkylthiopenten-4-ynes 1 that has a cyano group (EWG = CN) with amines (Table 1). The structures of 3a8 and 3a26 were unambiguously confirmed by X-ray diffraction. In spite of the fact that numerous methods for pyrrole syntheses are well established,¹⁰ few examples are known for the preparation of 2-aminopyrroles.¹³ which have great potential to make pharmaceutical compounds.14

Interestingly, when substrate **1b1** containing 1,3-dithiane functionality was subjected to the same reaction conditions as above, *gem*-dialkylthio vinylallene **2b1** was obtained in 91% yield within 10 min (eqn (1)). However, no pyrrole product (for example, **3a1**) could be detected even after a prolonged reaction time. This result gave further support to our previous observations that the 1,3-dithiolane ring of α -oxo ketene dithioacetals was broken under basic conditions, whereas 1,3-dithiane appeared to be stable.^{7a,15} Similarly, such a regulation effect existed in *gem*-dialkylthio vinylallenes. Therefore, the ring-opening of 1,3-dithiolane is likely to be the initial step in the domino cyclization of **2a1** with benzylamine.

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Scheme 2 A plausible reaction mechanism for pyrroles.

Based on the above results and our previous reports, 7a, 15 a plausible reaction mechanism for the formation of pyrroles was proposed and supported by DFT calculations (Scheme 2, with **1a1** as an example; key geometry structures of the pathway are presented, for more details, see Fig. S2⁺). First, isomerization of the propargyl moiety of 1a1, which is promoted by benzylamine, takes place yielding gem-dialkylthio vinylallene 2a1. Then, the 1,3-dithiolane moiety of 2a1 undergoes ring-opening by benzylamine (Re2) to furnish thioamide intermediate Re1. Following the selective attack of benzvlamine on the allenic carbon, an enamine intermediate Int7 is produced along with significant reduction of relative energy (ΔE) to -35.43 kcal mol⁻¹. Subsequently, enol intermediate Int8 is formed through keto-enol tautomerization, in which H₂O presumably assisted this transformation by forming an eight-membered ring transition state TS4b,16 as suggested by theoretical calculations. Following the intramolecular 1,4-conjuation addition, an intermediate Int9 is formed through **TS5** that required an activation energy $(\Delta \Delta E^{\ddagger})$ as high as 29.58 kcal mol⁻¹. Finally, pyrrole **3a1** is produced with the elimination of H₂O. Obviously, the ring-closing reaction from Int8 to Int9 would make a major contribution to the ratelimiting step because of the highest activation barrier, which appears reasonable in view of the fact that the reaction needed to be performed at 100 °C for 5 h (Scheme 1).

Next, we were interested in evaluating *gem*-dialkylthio vinylallenes containing acyclic alkylthio groups (Scheme 3). Unexpectedly, thiophene **3c1** was isolated from the reaction mixture of **1c1** with benzylamine. Further optimization of the reaction conditions increased the yield of **3c1** to 88% in the presence of DBU (30 mol%) in DMSO at room temperature (see Table S3[†]).



Scheme 3 Intramolecular cyclization of acyclic *gem*-dialkylthio vinylallene 1c1.





Interestingly, vinylallene 2c1 was not isolatable probably due to its quick conversion into thiophene 3c1. A DFT calculation also supported this conclusion (Scheme 3; for details, see Fig. S3[†]). The formation of thiophenium intermediate Int-a seemed to be involved in the ring-closing step of gem-dialkylthio vinylallene 2c1 through an unprecedented carbothiolation of allene under metal-free conditions. Following a 1.3-alkyl migration of the ethyl group from sulfur atom to benzylic carbon, thiophene 3c1 was produced. Carbothiolation of π -bond systems including alkynes, allenes and alkenes through C-S σ-bond addition affords an opportunity to install C-C and C-S bonds in a single reaction.¹² Although remarkable progress has been made since the first report of carbothiolation by Choi et al.,¹⁷ the presence of a transition-metal catalyst such as Pd, Pt, Rh, Au is generally required.¹⁸ Moreover, little has been known about the carbothiolation of allenes (only two isolated examples available in 25 and 76% yields, respectively).¹⁹ To the best of our knowledge, the carbothiolation of π -bond systems under metal-free conditions has not been reported.^{19,20} Therefore, the ring-closing of 2c1 represents the first example of metal-free carbothiolation, which constitutes an atomeconomic and cost-effective approach to thiophenes.

The reaction scope of this cyclization reaction is broad. Variation of the substituents (EWG, R^1 , R^2 and R) has no influence on the rearrangement, leading to thiophenes **3c2-3c9** in good to high yields (Table 2), among which the structure of **3c2** was unambiguously confirmed by X-ray crystallography. Of note is the presence of diversified functional groups such as the alkylthio, cinnamoyl, acetyl, amide and aryl on thiophenes **3c1-3c9**, thereby allowing for further synthetic modifications. For example, the alkylthio group has the potential to be converted into hydrogen, sulfoxide or (hetero)aryl groups through reduction,²¹ oxidation,^{7c} and Liebeskind–Srogl coupling reactions.

In conclusion, we have described the first *gem*-dialkylthio vinylallenes and their alkylthio-regulated reactivity. A wide range of pyrroles and thiophenes were separately prepared from *gem*-dialkylthio vinylallenes simply by choosing an appropriate alkylthio group, thus constituting a novel and powerful route to these two important heterocycles. DFT calculations provided mechanistic insights, and disclosed an unprecedented metal-free carbothiolation.

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