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Regiospecific 6-*Endo*-Annulation of *in Situ* Generated 3,4-Dienamides/Acids: Synthesis of δ-Lactams and δ-Lactones

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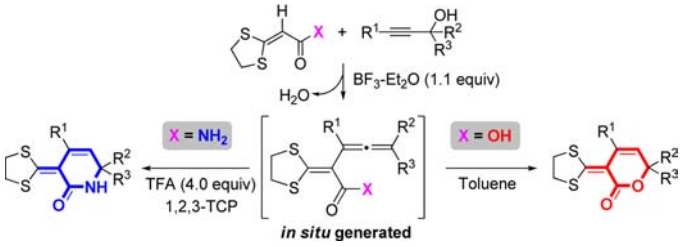
ABSTRACT



A novel and efficient method for the construction of α-(1,3-dithiolan-2-ylidene) δ-lactam and δ-lactone rings has been developed. It involves the regiospecific 6-*endo*-annulation of *in situ* generated 2-(1,3-dithiolan-2-ylidene)-3,4-dienamides/acids from the dehydrative coupling of α-oxo ketene dithioacetals with tertiary propargyl alcohols promoted by $BF_3 \cdot Et_2O$. A range of α-(1,3-dithiolan-2-ylidene) δ-lactams and δ-lactones are obtained in good to high yields. In addition, indenes are prepared by using α-acetyl ketene dithioacetal as the precursor.

δ-Lactone and δ-lactam rings are often found as the core structural motif in naturally occurring bioactive compounds and synthetic drugs.[1] α-Alkylidene δ-lactones and δ-lactams are special subclasses of δ-lactone/δ-lactam derivatives with a characteristic exoalkylidene moiety conjugated with a carbonyl group, the distinct feature believed to be crucial for their biological activities.[2] α-Alkylidene δ-lactones have been identified in a variety of natural products (Crassin,[3] Artemisitene,[4] Teucrium Lactone,[5]Pentalenolactone E,[6] etc.) (Figure 1). These compounds show significant biological activities such as cytotoxicity against human pharyngeal carcinoma (KB) cells as well antibiotic and antimalarial properties. Natural α-alkylidene δ-lactams, on the other hand, were almost unknown until the very recent isolation of a new humantenine-type alkaloid, Gelegamine B, from *Gelsemium elegan*.[7]

In recent years, the growing interest in the biological activities of α-alkylidene δ-lactams/δ-lactones has

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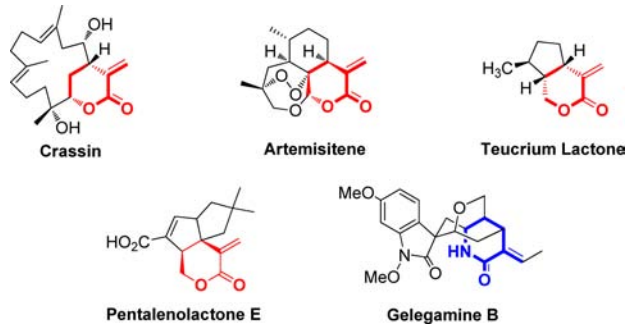
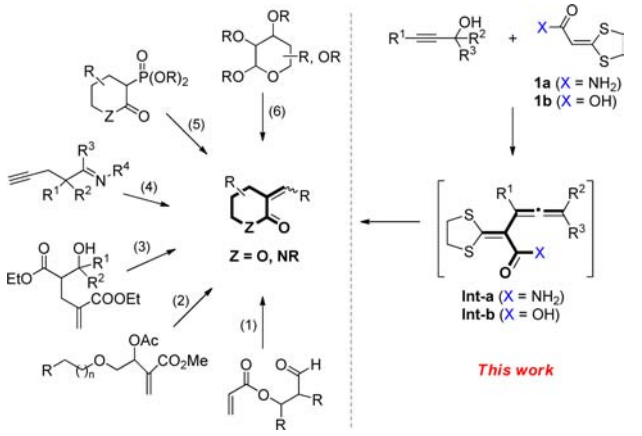


Figure 1. Natural compounds containing a α-alkylidene δ-lactone or δ-lactam unit.

inspired the development of several synthetic approaches (Scheme 1), including the intramolecular cyclizations based on Baylis–Hillman acetates (pathways 1, 2, and 3),[8] tandem carbonylation/radical cyclization of pent-4-yn-1-imine derivatives (pathway 4),[9] and Horner–Wadsworth–Emmons reaction of α-(dialkoxyphosphoryl)-δ-lactams/-lactones (pathways 5)[10] and synthetic transformations of sugar derivatives (pathway 6).[11] However, the broad applications of these methods have been impeded by several drawbacks such as nonreadily available substrates, multistep reactions, longer reaction times, and/or lower yields.[9−11] As a result, the development of efficient and practical methods to access these important heterocyclic frameworks remains imperative. Allenes[12] and ketene dithioacetals[13] are two classes of synthons with respectively unique structural characters and reactivities. Reports on the synthesis of δ-lactams and δ-lactones from allenoic amides/acids are relatively rare,[14] while the formation of α-alkylidene δ-lactams and δ-lactones from functionalized allenes remains elusive.[12] As part of our continuing efforts to explore the synthetic potency of *gem*-dialkylthio vinylallenes[15] and develop novel cyclization reactions,[16] we report herein a straightforward method for the divergent synthesis of α-alkylidene δ-lactams and δ-lactones by the tandem dehydrative coupling/intramolecular cyclization of ketene dithioacetals and tertiary propargyl alcohols (Scheme 1).

Scheme 1. Strategies for the Construction of α-Alkylene δ-Lactams/δ-Lactones



In our initial search for optimal conditions, the reaction of 2-(1,3-dithiolan-2-ylidene)acetamide (**1a**) and propargyl alcohol (**2a**) was evaluated in the presence of $BF_3 \cdot Et_2O$ (1.1 equiv) in 1,2,3-trichloropropane (1,2,3-TCP),[17] and as envisioned, 2-(1,3-dithiolan-2-ylidene)-3,5-diphenylhexa-3,4-dienamide (**Int-1a**) was exclusively obtained in 93% yield within 20 min. Treatment of this intermediate with 4 equiv of trifluoroacetic acid (TFA) for another 20 min afforded 88% of α-(1,3-dithiolan-2-ylidene) δ-lactams (**3a**). Notably, TFA was crucial for the cyclization step, as formation of **3a** was never achieved even by increasing the amount of $BF_3 \cdot Et_2O$ (4 equiv). Next solvent screening showed 1,2,3-TCP to be absolute, as other solvents such as DMSO, 1,4-dioxane, and CH_3CN were unfit for the transformation. Intrigued by this successful synthesis of α-alkylidene-δ-lactams in 1,2,3-TCP solvent, we imagined that 2-(1,3-dithiolan-2-ylidene)acetic acid (**1b**) will similarly react with **2a** to afford α-(1,3-dithiolan-2-ylidene) δ-lactone (**4a**) under the same reaction conditions. To our dismay, the reaction did not proceed and **1b** was almost recovered completely in 1,2,3-TCP. In our persistent exploration for possibilities we discovered that **1b** and **2a** could efficiently interact at room temperature in the presence of 1.1 equiv of $BF_3 \cdot Et_2O$ in toluene to afford **4a** in 91% isolated yield within 20 min. It is worth mentioning that, unlike **Int-1a**, the intermediate **Int-1b** cannot be isolated under the reaction conditions.

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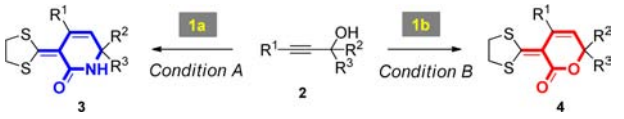
Table 1. Synthesis of α-(1,3-Dithiolan-2-ylidene) δ-Lactams **3**/δ-Lactones **4**

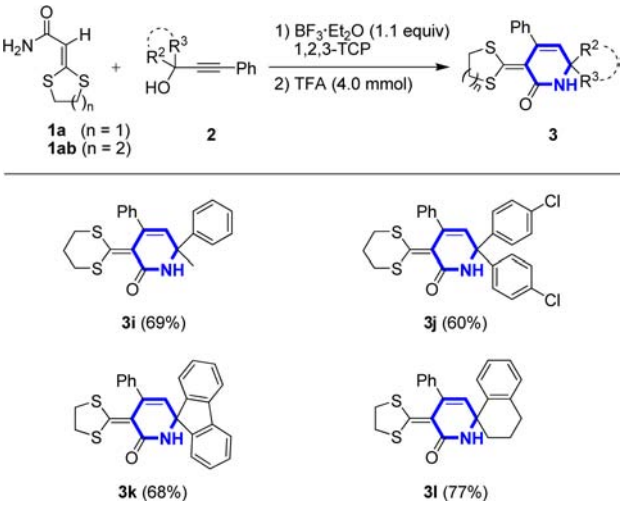


entry		2	C[a]	product	time (min)	yield[b] (%)
1	**2a**	R^1 = Ph R^2 = Ph	A	**3a**	20	88
2		R^3 = Me	B	**4a**	20	91
3	**2b**	R^1 = Ph R^2 = 2-ClC_6H_4	A	**3b**	20	88
4		R^3 = Me	B	**4b**	45	95
5	**2c**	R^1 = Ph R^2 = 3-ClC_6H_4	A	**3c**	20	83
6		R^3 = Me	B	**4c**	40	96
7	**2d**	R^1 = Ph R^2 = 4-ClC_6H_4	A	**3d**	20	79
8		R^3 = 4-ClC_6H_4	B	**4d**	60	88
9	**2e**	R^1 = Ph R^2 = Ph	A	**3e**	20	86
10		R^3 = Ph	B	**4e**	50	80
11	**2f**	R^1 = Ph R^2 = Ph	A	**3f**	20	61
12		R^3 = Ethyl	B	**4f**	30	45
13	**2g**	R^1 = 4-FC_6H_4 R^2 = Ph	A	**3g**	20	67
14		R^3 = Me	B	**4g**	120	61
15	**2h**	R^1 = 4-$MeOC_6H_4$ R^2 = Ph	A	**3h**	20	75
16		R^3 = Me	B	**4h**	70	65

[a] *Conditions A*: **1a** (1.0 mmol), **2** (1.2 mmol), $BF_3 \cdot Et_2O$ (1.1 mmol), 1,2,3-TCP (2.0 mL), and TFA (4.0 mmol) at room temperature. *Conditions B*: **1b** (1.0 mL), **2** (1.2 mmol), $BF_3 \cdot Et_2O$ (1.1 mmol), and toluene (2.0 mL) at room temperature. [b] Isolated yields.

Next, the reaction scope of the ketene dithioacetal **1a** or **1b** was explored with respect to the propargylic alcohols **2a**–**h** under the optimal reaction conditions (*Conditions A* for α-alkylidene δ-lactams **3**; *Conditions B* for α-alkylidene δ-lactones **4**). The results as summerized in Table 1 showed that **1a**/**1b** reacted efficiently with **2a**–**e** to afford the corresponding α-(1,3-dithiolan-2-ylidene) δ-lactams **3a**–**e**/δ-lactones **4a**–**e** in good yields (entries 1–10). However, when ethyl was introduced to the C3-position of **2** (e.g., **2f**), only a moderate yield of **3f**/**4f** could be obtained, which might be due to the steric effect of the ethyl group (entries 11, 12). It is worth noting that the yields of **3g**–**h**/**4g**–**h** were significantly lower than those of **3a**–**c**/**4a**–**c** (entries 13–16). This is indicative of the remarkable influence of substituent groups linking the phenyl at the C1 position of **2** on the synthesis of α-(1,3-dithiolan-2-ylidene) δ-lactams/δ-lactones. Notably, the six-membered structures of products **3** and **4** were further established by the HSQC and HMBC studies of **3h** and **4a**. As shown in Scheme 2, δ-lactam derivatives **3i** and **3j**, bearing a 1,3-dithian-2-ylidene unit, were obtained in 69 and 60% yields, respectively, by using substrates **1ab**. Delightfully, 6-spiro-δ-lactams **3k** and **3l** could be also produced in good yields by varying the propargyl alcohols **2**.

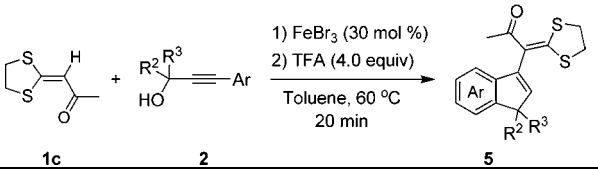
Scheme 2. Synthesis of δ-Lactam Derivatives **3i**–**3j**[a]



[a] Isolated yields.

Further studies disclosed that when the carboxyl group of **1b** was changed to an acetyl group (**1c**), the α-acetyl ketene dithioacetals **1c** reacted with phenyl-substituted tertiary propargyl alcohols **2** to rapidly produce functionalized *gem*-dialkylthio vinylallenes (**Int-c**) under $FeBr_3$ catalysis.[15a] Interestingly, when TFA was added to this reaction mixture, which was allowed to sit for an additional 30 min, a series of indene derivatives were generated in moderate to good yields (Table 2).[18] The structure of **5a** was resolved from ^1H NMR, ^{13}C NMR, HMBC, and HRMS spectral data, and that for **5e** was unambiguously confirmed from X-ray diffraction analysis (Figure 2).

Table 2. Synthesis of Indenes **5**



entry	R^2	R^3	Ar	5	yield (%)[a]
1	Ph	CH_3	Ph	**5a**	78
2	4-ClC_6H_4	CH_3	Ph	**5b**	75
3	4-MeC_6H_4	CH_3	Ph	**5c**	70
4	Ph	CH_3	4-$MeOC_6H_4$	**5d**	61
5	4-ClC_6H_4	4-ClC_6H_4	Ph	**5e**	67

[a] Isolated yields.

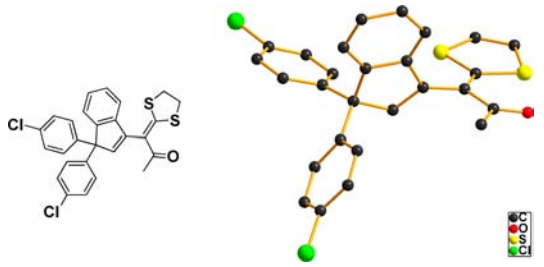
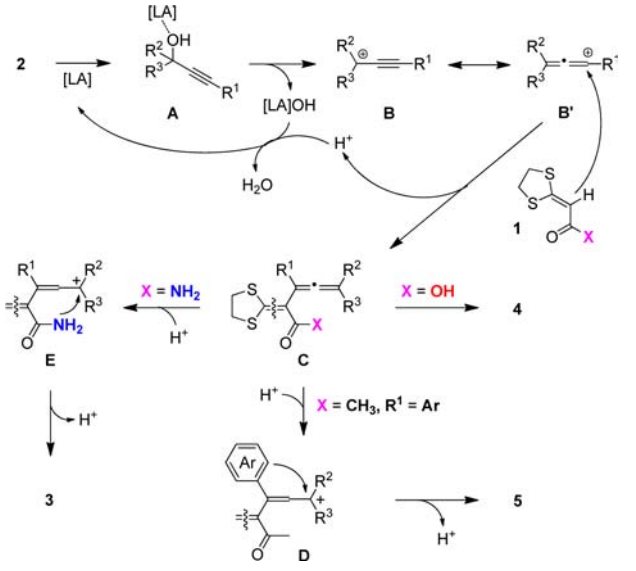


Figure 2. Crystal structure of compound **5e**.

Scheme 3. A Plausible Reaction Mechanism



On the basis of these experimental findings and our previous work,[14,15] plausible reaction mechanisms for the formation of δ-lactams (**3**), δ-lactones (**4**), and indenes (**5**) are proposed (Scheme 3). First, the −OH of **2** is polarized by the interaction with a Lewis acid [LA], so that the incipient propargylic carbocation **B** is formed by the loss of [LA]OH which would subsequently accept a H^+ to regenerate the [LA]. A resonance balance between propargylic carbocation **B** and allenic carbocation **B′** exists,[19] and here the latter is preferably attacked by the electron-rich α-carbon of ketene dithioacetals (**1**), leading to the allenic amides, acids, and ketones **C** (**Int-a**, **-b**, **-c**), with the consequent loss of H^+ at this stage. For the allenic amides, protonation takes place on the central carbon of the allenic system, and the nitrogen atom of the amino group attacks the tertiary carbocation in an intramolecular nucleophilic addition fashion to produce the δ-lactams **3**. For the allenic acids, the allene is activated by coordination to a Lewis acid prior to the subsequent intramolecular nucleophilic attack by the carbonyl oxygen of the acid group to form the δ-lactones **4**. Analogous to the δ-lactams, the formation of indene **5** also involves the initial protolactonization of the central carbon of the allenic system to give intermediate **D** which then undergoes cyclization through electrophilic aromatic substitution to yield the target **5**.

In summary, we have developed a novel route to generate δ-lactams and δ-lactones from *in situ* generated 3,4-dienamides and acids under mild acid-mediated reaction conditions. Further studies disclosed that indenes can be prepared by choosing α-acetyl ketene dithioacetal. Efforts are ongoing in extending the scope of this methodology.

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Supporting Information Available. Experimental procedures; ^{1}H NMR, ^{13}C NMR, HSQC, and HMBC spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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