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Direct Synthesis of Polyfunctionalized Unsaturated δ-Lactones and δ-Lactams from α-Alkenoyl α-Carboxyl/Carbamoyl Ketene *S*,*S*-Acetals under Vilsmeier Conditions

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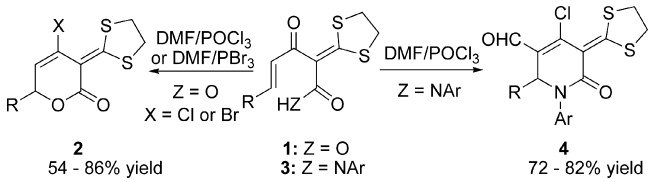

An efficient method for direct synthesis of polyfunctionalized unsaturated δ-lactones **2** and δ-lactams **4** has been developed from the reaction of the easily available α-alkenoyl α-carboxyl/carbamoyl ketene *S*,*S*-acetals **1**/**3** and Vilsmeier reagents ($DMF/POCl_3$ or DMF/PBr_3) via a cyclization followed by a halovinylation or haloformylation sequence.

The core structures of δ-lactones and δ-lactams exist in a large number of natural and unnatural pharmaceutically and biologically important compounds.[1] General methods for their synthesis involve cyclization of appropriately substituted open chain precursors.[2] However, many of these methods are limited in their use by a relatively narrow scope of substrates, harsh reaction conditions, multiple steps, or the use of not easily available starting materials. Therefore, the development of an efficient synthetic approach for the construction of these heterocyclic scaffolds, especially those with polyfunctional groups, is an important task for further studies.

Functionalized ketene *S*,*S*-acetals are versatile intermediates in organic synthesis.[3,4] During the course of our studies in this context,[5−9] we found that the readily available α-alkenoyl ketene *S*,*S*-acetals showed fascinating structural features as novel intermediates for their dense substitution patterns and flexible alkylthio functionality able to play multiple roles. A number of annulation strategies based on them have been developed in our group for the synthesis of various carbo- and heterocyclic compounds, such as the [5 + 1] annulations for phenols[6a] and pyrrolizidines,[6e] the domino reaction for fused tetraheterocyclic compounds,[7] and the three-component [4 + 2] cycloaddition for cyclohexanones.[8] In addition, tetronic acid,[9a] tetramic acid,[9b] and thiophene derivatives[9c] were synthesized with α-alkenoyl α-carboxyl/carbamoyl ketene *S*,*S*-acetals as starting materials through intramolecular oxa/aza/thia-anti-Michael addition reactions, respectively. However, in comparison, the direct intramolecular oxa/aza-Michael addition of either α-alkenoyl α-carboxyl or α-alkenoyl α-carbamoyl ketene *S*,*S*-acetals leading to the corresponding six-membered heterocycles has not been established[9,10] due to decarboxylation of the former under both basic and acidic conditions[9a,10a] and competition of the aza/thia-anti-Michael additions of the latter under basic conditions.[9b,c] Very recently, as an alternative route, a one-pot synthesis of functionalized unsaturated δ-lactones via reduction−lactonizations of α-alkenoyl α-carboxyl ketene *S*,*S*-acetals has been reported by us.[11] As part of a continuing interest in solving the problems in the synthesis of the corresponding six-membered heterocycles starting directly from the easily available α-alkenoyl α-carboxyl

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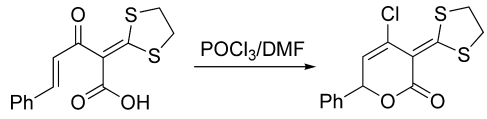
TABLE 1. Optimization of Reaction Conditions of 1a under Vilsmeier Conditions[a]



entry	**1a**: $POCl_3$	T (°C)	time (h)	yield of **2a** (%)[b]
1	1:1	60	9.0	50
2	1:2	60	7.0	79
3	1:2	70	5.0	82
4	1:2	90	4.5	80
5	1:2	100	4.0	81
6	1:3	70	4.5	83
7	1:4	70	4.0	81

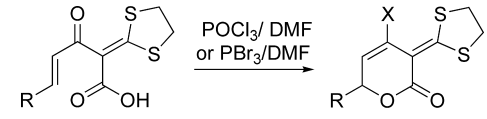
[a] **1a** (1.0 mmol), DMF (5.0 mL). [b] Isolated yields.

and α-alkenoyl α-carbamoyl ketene *S*,*S*-acetals, the Vilsmeier reagent (VR) mediated cyclization reactions of α-alkenoyl α-carboxyl/carbamoyl ketene *S*,*S*-acetals were studied.[12] In this paper, we wish to report the results.

α-Alkenoyl α-carboxyl ketene *S*,*S*-acetals **1** were prepared in excellent yields by the aldol condensation of α-acetyl ketene *S*,*S*-acetals with aldehydes (including aliphatic and aromatic aldehydes) under basic conditions according to the reported procedure.[11] In the present research, the reaction of (*E*)-2-(1,3-dithiolan-2-ylidene)-3-oxo-5-phenylpent-4-enoic acid **1a** with Vilsmeier reagent was initially performed. As described in Table 1, entry 1, treatment of **1a** (1.0 mmol) with $POCl_3$ (1.0 mmol) in DMF (5.0 mL) at 60 °C for 9.0 h, a colorless semisolid was isolated after workup and column chromatography of the resulting mixture. The product was characterized as an unsaturated δ-lactone, 4-chloro-3-(1,3-dithiolan-2-ylidene)-6-phenyl-3,6-dihydro-2*H*-pyran-2-one **2a** (50% isolated yield), on the basis of the spectral and analytical data. Then the optimization of the reaction conditions with respect to the molar ratio of **1a** to $POCl_3$ and the reaction temperatures was investigated. It was found that a higher temperature and excess of $POCl_3$ resulted in a high yield of **2a** in shorter reaction times (Table 1, entries 2−7). In comparison, the reaction performed at 70 °C with a 1:3 molar ratio of **1a** to $POCl_3$ was chosen as the optimal condition in terms of yields and reaction time (Table 1, entry 6).

Under the optimal conditions, a range of reactions of α-alkenoyl α-carboxyl ketene *S*,*S*-acetals **1b**−**i** was carried out and the results are summarized in Table 2. It is clear that, according to the experimental results (Table 2), this protocol provides an efficient approach for the synthesis of polyfunctionalized unsaturated δ-lactones **2** starting directly from α-alkenoyl α-carboxyl ketene *S*,*S*-acetals **1**. The substrates **1** bearing an aromatic substituent (Table 2, electroneutral, entry 1; electron-deficient, entries 2−4; or electron-rich, entries 5−7),

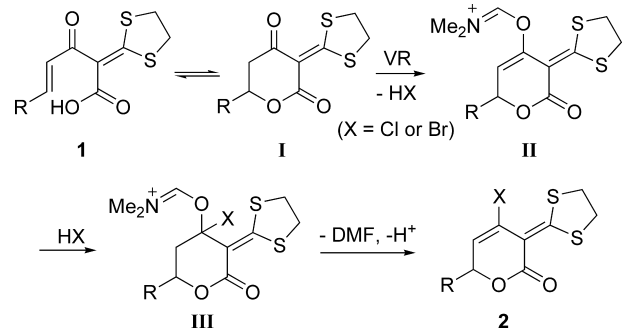
TABLE 2. Cyclizations of α-Alkenoyl α-Carboxyl Ketene *S*,*S*-Acetals 1 under Vilsmeier Conditions[a]



entry	**1**	R	**2**	X	time (h)	yield (%)[b]
1	**1a**	C_6H_5	**2a**	Cl	5.0	83
2	**1b**	2-ClC_6H_4	**2b**	Cl	5.5	76
3	**1c**	4-ClC_6H_4	**2c**	Cl	5.5	80
4	**1d**	4-$NO_2C_6H_4$	**2d**	Cl	10	54
5	**1e**	4-MeC_6H_4	**2e**	Cl	4.0	84
6	**1f**	4-$MeOC_6H_4$	**2f**	Cl	3.5	86
7	**1g**	3,4-$CH_2O_2C_6H_3$	**2g**	Cl	3.5	83
8	**1h**	2-thienyl	**2h**	Cl	4.0	80
9	**1i**	*t*-Bu	**2i**	Cl	5.0	78
10	**1a**	C_6H_5	**2j**	Br	6.0	82

[a] **1** (1.0 mmol), $POCl_3$ or PBr_3 (3.0 mmol), DMF (5.0 mL), 70 °C. [b] Isolated yields.

SCHEME 1. Proposed Mechanism for the Formation of 2



a heteroaromatic substituent (Table 2, entry 8), and an aliphatic substituent (Table 2, entry 9) at the β-position of the alkenoyl moiety of **1** can give the desired δ-lactones **2** in high yield in general. In the case of **1d**, with a strong electron-withdrawing group (4-nitrophenyl), longer reaction time was required and the yield of **2d** was moderate (Table 2, entry 4). In addition, PBr_3/DMF was proven to be effective for this procedure as well. The corresponding δ-lactone **2j** was afforded in 82% yield (Table 2, entry 10).

On the basis of the above results and related studies,[10−14] a plausible mechanism for the formation of unsaturated δ-lactones **2** is presented in Scheme 1. The first step of the reaction may involve the formation of an unstable intramolecular Michael adduct, δ-lactone **I**.[10a] Formation of δ-lactone **I** results in the release of acyl structure, which leads to halogenated δ-lactones **2** by halovinylation of **I** under Vilsmeier conditions (**I** → **II** → **III** → **2**).[13,14] In the above mechanism, the Vilsmeier reagent plays a significant role, probably at the stage of the halovinylation (**I** → **II** → **III** → **2**), which is the driving force to move the equilibrium (**1** → **I**) toward more stable δ-lactones **2**.

Encouraged by the successful synthesis of unsaturated δ-lactones **2** and with an aim to provide more information about the scope and mechanism of this protocol, the reactions of α-alkenoyl α-carbamoyl ketene *S*,*S*-acetals **3** under Vilsmeier condi-

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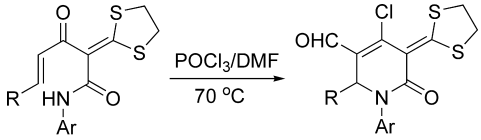
TABLE 3. Reactions of α-Alkenoyl α-Carbamoyl Ketene *S*,*S*-Acetals 3 under Vilsmeier Conditions[a]



3 **4**

entry	3	R	Ar	4	time (h)	yield (%)[b]
1	**3a**	C_6H_5	C_6H_5	**4a**	4.5	82
2	**3b**	C_6H_5	4-ClC_6H_4	**4b**	5.0	76
3	**3c**	C_6H_5	4-$MeOC_6H_4$	**4c**	4.0	72
4	**3d**	4-ClC_6H_4	4-$MeOC_6H_4$	**4d**	5.0	70
5	**3e**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**4e**	3.5	80

[a] **3** (1.0 mmol), $POCl_3$ (3.0 mmol), DMF (5.0 mL), 70 °C. [b] Isolated yields.

tions were examined. At first, the substrates α-alkenoyl α-carbamoyl ketene dithioacetals **3** were prepared in excellent yields either by condensation of the corresponding 2-(1,3-dithiolan-2-ylidene)-3-oxobutanamides with aldehydes or by amination of the corresponding α-alkenoyl α-carboxyl ketene *S*,*S*-acetals **1**.[9b] Then, the reaction of (*E*)-2-(1,3-dithiolan-2-ylidene)-3-oxo-*N*,5-diphenylpent-4-enamide **3a** with $POCl_3$ (3.0 equiv) in DMF at 70 °C was performed. To our delight, the reaction proceeded smoothly and afforded unsaturated δ-lactam **4a** in 82% yield within 4.5 h (Table 3, entry 1). Interestingly, in contrast with the reaction of **1** with Vilsmeier reagents, the reaction of **3a** under identical conditions gave 4-chloro-5-formyl unsaturated δ-lactam. The tolerance of the selected substrates **3** to this reaction was subsequently explored. The experimental results are presented in Table 3. Clearly, all the reactions of **3b**−**e** with $POCl_3$ (3.0 equiv) in 5.0 mL of DMF at 70 °C could afford the corresponding 4-chloro-5-formyl unsaturated δ-lactams **4b**−**e** in high yields (Table 3, entries 2−5). It is worth noting that, similar to the mechanism for the formation of 4-chloro-unsaturated δ-lactones **2**, a tandem cyclization−chloroformylation process would be involved for the formation of 4-chloro-5-formyl-unsaturated δ-lactams **4**. In comparison, the extra step, the formylation of the corresponding 4-chloro-unsaturated δ-lactam intermediate, may be due to the 4-chloro unsaturated δ-lactam being more reactive toward Vilsmeier reagents than the corresponding 4-chloro-unsaturated δ-lactones **2**.[13,15]

In summary, a convenient and efficient method for the synthesis of polyfunctionalized unsaturated δ-lactones **2** and δ-lactams **4** has been developed. This strategy allows the direct application of α-alkenoyl α-carboxyl/carbamoyl ketene dithioacetals **1** and **3** under Vilsmeier conditions. A mechanism involving the Vilsmeier reagent-induced cyclization followed by a halovinylation or haloformylation is proposed. This synthetic protocol is associated with readily available starting materials, a wide range of products, and easy control of the reaction conditions. The potential utilization and extension of the scope of the methodology are currently under investigation.

(15) In our research, the corresponding 4-chloro-unsaturated δ-lactams were not obtained under the reaction conditions used.

Experimental Section

Typical Procedure for the Synthesis of Unsaturated δ-Lactones 2 (2a as an example). To a solution of α-alkenoyl α-carboxyl ketene dithioacetal **1a** (292 mg, 1.0 mmol) in DMF (5.0 mL) was added $POCl_3$ (0.27 mL, 3.0 mmol) in one portion at room temperature. The reaction mixture was then heated to 70 °C with stirring for about 5 h. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash silica gel chromatography with petroleum ether/ether (8/1, v/v) as eluent to give **2a** (257 mg, 83%) as a colorless semisolid.

4-Chloro-3-(1,3-dithiolan-2-ylidene)-6-phenyl-3,6-dihydro-2*H*-pyran-2-one (2a): colorless semisolid; ^1H NMR (500 MHz, $CDCl_3$) δ 3.37−3.39 (m, 2H), 3.47−3.49 (m, 2H), 5.83 (d, J = 4.0 Hz, 1H), 6.06 (d, J = 4.0 Hz, 1H), 7.35−7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 164.4, 137.8, 129.0, 128.9 (2C), 128.8, 126.9 (2C), 122.8, 109.0, 78.1, 38.7, 37.7; IR (KBr) 3060, 2924, 2854, 1693, 1464, 1213, 1154, 890 cm^{-1}; MS (ESI) *m*/*z* 311 $[(M + 1)]^+$. Anal. Calcd for $C_{14}H_{11}ClO_2S_2$: C, 54.10; H, 3.57. Found: C, 53.96; H, 3.50.

4-Chloro-5-(1,3-dithiolan-2-ylidene)-6-oxo-1,2-diphenyl-1,2,5,6-tetrahydropyridine-3-carbaldehyde (4a): yellow crystal, mp 72−74 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 3.31−3.36 (m, 1H), 3.44−3.54 (m, 3H), 5.83 (s, 1H), 7.07 (d, J = 8.5 Hz, 2H), 7.20−7.31 (m, 8H), 10.13 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.6, 172.5, 163.3, 142.9, 140.9, 139.3, 129.5, 128.7 (2C), 128.6 (2C), 127.8, 126.8, 126.0 (2C), 125.9 (2C), 114.0, 61.0, 38.0, 37.4; IR (KBr) 3050, 2856, 2411, 1694, 1539, 1465, 1387, 1239, 1003 cm^{-1}; MS (ESI) *m*/*z* 414 $[(M + 1)]^+$. Anal. Calcd for $C_{21}H_{16}ClNO_2S_2$: C, 60.93; H, 3.90, N, 3.38. Found: C, 60.78; H, 3.86; N, 3.34.

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Supporting Information Available: Experimental details, spectral and analytical data for compounds **2** and **4**, and copies of ^1H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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