Intramolecular Thia-anti-Michael Addition of a Sulfur Anion to Enones: A Regiospecific Approach to Multisubstituted Thiophene Derivatives

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The intramolecular thia-anti-Michael addition starting from readily available α-alkenoyl-α’-carbamoyl ketene-(3,S)-acetics 1 containing a 1,3-dithiolane moiety was developed. In particular, in the presence of aliphatic primary amines, a series of tetrasubstituted thiophene derivatives, 2-(alkylamino)-5-alkyl-4-hydroxythiophene-3-carboxamides 2, were synthesized via tandem fragmentation, substitution, and intramolecular thia-anti-Michael addition reactions of 1, where amine played the dual roles of a base and a nucleophile. The intramolecular thia-anti-Michael addition, as the key step, proceeded in a regiospecific manner and showed a general scope to the β-substituents of enones 1. A possible mechanism for the formation of the multisubstituted thiophenes was proposed. By this research, a new and efficient route to various tetrasubstituted thiophene derivatives was created.

Introduction

The Michael reaction is one of the most fundamental approaches for the formation of new carbon–carbon and carbon–heteroatom bonds.1 Among the manifold carbon–carbon and carbon–heteroatom bond-forming reactions, the Michael addition is especially valuable for creating a new bond selectively at the β-position of α,β-unsaturated carbonyl compounds or the electrophilic alkenes and alkyens in which the electron-withdrawing groups (EWG) act in concert for main-


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intelligent method for redirecting the regioselectivity of the addition of a nucleophile from the classical β-addition mode to an α-addition by simply changing the base is quite remarkable.11

Over the past decades, the utility of α-oxo ketene-(S,S)-acetals as versatile intermediates in organic synthesis has been recognized.12 In our research on the chemistry of functionalized ketene-(S,S)-acetals,13 we found that the easily available and structurally flexible α-alkenyl ketene-(S,S)-acetals showed fascinating structural features as novel organic intermediates.14

On one hand, as a useful five-carbon 1,5-bielectrophilic double Michael acceptor, six-membered carbo/heterocycles including highly substituted phenols (Scheme 1, path A), functionalized 2,3-dihydro-4-pyridones (Scheme 1, path B), and 2,3-dihydrothiopyran-4-ones (Scheme 1, path C) were synthesized on the basis of [5C+1C],14a [5C+1N],14b,c and [5C+1S]14d annulation strategies, respectively. Asokan and co-workers reported the synthesis of substituted 2,3-dihydro-4H-thiopyran-4-ones via dimlysion mediated tandem fragmentation cyclization reactions of α-alkenyl ketene-(S,S)-acetals containing a 1,3-dithiolane moiety (Scheme 1, path D).15 Except for the above examples based on Michael addition reactions, on the other hand, starting from the corresponding α-alkenyl cyclic

![Scheme 1](image)

*For Paths A–C, *R*₂ = CH₂CH₃. For Paths D–F, *R*₁,R*₂ = (CH₂CH₃).*
moiety. As the key step, the thia-anti-Michael addition proceeded in a regiospecific manner and showed the general scope to the $\beta$-substitutes of enones 1. By this research, not only a new and efficient route to various tetrasubstituted thiophene derivatives has been created but also the subtle situation—the efficiency on redirecting the regioselectivity of the addition of a nucleophile from the classical $\beta$-addition mode to an $\alpha$-addition—may be understood as an important concept.\textsuperscript{11,15,16,22}

In this paper, the experimental results were presented in detail and the possible reaction mechanism was proposed.

### Results and Discussion

#### Synthesis of the Substrates 1

The substrates, $\alpha$-alkenoyl-$\alpha$-carbamoyl ketene-(S,S)-acetals 1 (Scheme 2), were prepared in excellent yields either by the condensation reactions of the corresponding 2-(1,3-dithiolan-2-ylidene)-3-oxobutanamides with aldehydes or by amination of the corresponding 2-(1,3-dithiolan-2-ylidene)-3-oxopent-4-enoic acids (for details see Supporting Information).

#### Synthesis of Thiophene Derivative 2a

The initial experiments were carried out between 5-(4-chlorophenyl)-2,1-(1,3-dithiolan-2-ylidene)-3-oxo-4-n-pent-4-enoamide (1a) and benzylamine under different conditions (Table 1). No product was observed (monitored by TLC) when the reaction of 1a (1.0 mmol) and benzylamine (1.2 mmol) proceeded for 30 h in acetonitrile at room temperature (entry 1). Under reflux conditions, the reaction of 1a and benzylamine took place but was sluggish. After 15 h, to our delight, a white solid was obtained upon workup and the only product was characterized as 5-(4-chlorobenzyl)-2-(benzylamino)-4-oxo-4-pentyldiene)-3-oxobutanamide 2a (for details see Supporting Information).

In the case of DMF as the solvent and stirring at 120 °C, 2a was obtained in 43% yield at 90 °C and 55% yield when the reaction temperature was raised to 120 °C (entry 4). The molar ratio of benzylamine to the substrate 1a in the above experiments is 1.2:1.0. A further increase of the amount of benzylamine did not improve the yield of the product 2a (entry 6). Comparatively, in the absence of benzylamine, the reaction could not proceed efficiently (entry 7).

#### Synthesis of Thiophene Derivatives 2a–p

Under the optimized conditions described above (Table 1, entry 5), a range of reactions between $\alpha$-alkenoyl ketene-(S,S)-acetals 1 (1.0 mmol) and amines (1.2 mmol) were carried out at 120 °C in DMFS (Table 2). First of all, the influence of the nature of the substituents R 1 on the efficiency of the anti-Michael addition was examined in detail. Thus, the substitutes R 1 , the intramolecular thia-anti-Michael addition reactions of 1a were proved to be successful and yielded the desired thiophene derivatives 2 in good to high yields. The theoretical results were presented in detail and the possible reaction mechanism was proposed.
Thia-anti-Michael Addition of a Sulfur Anion to Enones

reaction time of 2.5 h and yields of 63–80%. Nevertheless, the molecular versatility of the products with variable R1, R2, and R3 groups meets the need for the library synthesis.

Next, under conditions identical to those above, we examined the thia-anti-Michael reaction by changing the carbamoyl unit of 1 or using other amines instead of benzylamine. The experiments gave the following results: (1) reactions of 1a with ethylamine and butylamine for 0.7 h gave the desired products 2m and 2n in 86% and 87% isolated yield (entries 13 and 14), respectively; (2) only 1a was recovered for the reaction of 1a with aniline or triethylamine for 8 h; (3) the reaction of 1m (carbamoyl unit = butylcarbamoyl; \( R_1 = p\text{-CIC}_{6}H_4 \)) with benzylamine for 0.7 h led to the desired intramolecular thia-anti-Michael adduct 2o in 87% yield (entry 15); (4) the reaction of 1n (carbamoyl unit = carbamoyl; \( R_1 = p\text{-CIC}_{6}H_4 \)) with benzylamine for 1.0 h led to the desired product 2p in 81% yield (entry 16); (5) reaction of 1a with diethylamine or dibutylamine for 6 h (repeated 5 times for each) led to a complicated mixture with a large amount of 1a intact; (6) the reaction of 1o (carbamoyl unit = dimethylcarbamoyl; \( R_1 = p\text{-CIC}_{6}H_4 \)) with benzylamine for 1.5 h led to the formation of N-benzyl-3-(4-chlorophenyl)acrylamide in 90% isolated yield (the reason for this is currently not clear); and (7) the reaction of the same substrate as that described by Asokan et al. (carbamoyl unit = H; \( R_1 = p\text{-CIC}_{6}H_4 \), Scheme 1, path D) with benzylamine gave no product, and the substrate was recovered in 95% yield.

Possible Reaction Mechanism. On the basis of the above experimental results, we proposed a possible mechanism for the formation of thiopeptide derivatives 2, as depicted in Scheme 3. Mediated by the amine and upon heating, deprotonation at one of the methylene groups of the dithiolen moiety should have triggered the ring-opening reaction to generate the intermediate thiolate anion \( B \). This was stabilized via delocalization of the negative charge to give intermediate C. The displacement of the vinlylthio group of C by an amine (SMe),\(^n\) gave rise to the formation of D. Finally, the intramolecular regiospecific addition of a sulfur anion to the \( \alpha \)-position of the \( \alpha,\beta \)-enones led to the production of multisubstituted thiophenes 2. Certainly, further experiments and calculations are needed to clarify the reasons for the \( \alpha \)-addition, rather than the \( \beta \)-addition to such kind of an \( \alpha,\beta \)-enone system.\(^{14,15,16b,22,24,25}\)

Conclusion

In summary, the first example of intramolecular thia-anti-Michael addition starting from alkenoyl compounds, the corresponding \( \alpha \)-alkenoyl ketene-\((S,S)\)-acetals, has been developed. Various \( \beta \)-substituents, including alkyl, aryl, and heteroaryl, with an electron-deficient or electron-rich nature could furnish the regiospecific anti-Michael addition. The preliminary application of this anti-Michael addition provides a facial and efficient approach for the preparation of multisubstituted thiophene derivatives. The molecular versatility of the products meets the need for the library synthesis. Further work on the extension of the scope of the anti-Michael addition reaction, its mechanism, and its synthetic applications is in progress.

Experimental Section

Synthesis of 2a–p. General procedure for the preparation of 2a–p (with 2a as an example): To a solution of \( \alpha \)-alkenoyl-\( \alpha',\beta' \)-carbamoyl ketene-\((S,S)\)-acetal 1a (448 mg, 1.0 mmol) in DMSO (4 mL) was added benzylamine (0.13 mL, 1.2 mmol) at room temperature. The reaction mixture was heated to 120 °C under stirring for 0.7 h. After cooling to room temperature, the mixture was poured into brine (10 mL) and extracted with CHCl\(_3\) (3 × 5 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/diethyl ether \( \alpha = 6:1 \)) to give 2a as a white solid (394 mg, 88%): \( \delta \) 144–146 °C; \( ^1H \) NMR (CDCl\(_3\), 500 MHz) \( \delta \) 3.00 (dd, \( J = 10.0, 14.0 \) Hz, 1H), 3.56 (dd, \( J = 4.0, 14.0 \) Hz, 1H), 4.18 (dd, \( J = 4.0, 14.0 \) Hz, 1H), 4.19–4.57 (m, 2H), 7.08 (t, \( J = 7.5 \) Hz, 1H), 7.18 (d, \( J = 8.5 \) Hz, 2H).


(25) To gain insight into the reaction mechanism of this thia-anti-Michael reaction, the deuterium labeling experiment was carried out. D\(_2\)O (1.0 equiv) was added slowly to the reaction mixture of 1a and benzylamine in DMSO at 120 °C. As a result, deuterated thiopeptide derivative 2a-D was formed. It was observed from the \( ^1H \) NMR spectra of 2a and 2a-D that there are obvious changes in the range of \( \delta = 2.9–4.3 \) ppm (see Supporting Information, Figure S2). The disappearance of the \( \gamma \)-coupling in the \( ^1H \) NMR spectrum of 2a-D indicates that the methylene group is deuterated during the intramolecular thia-anti-Michael addition process.
7.24–7.39 (m, 9H), 7.59 (d, J = 7.5 Hz, 2H), 10.87 (s, 1H), 10.94 (s, 1H); 13C NMR (125 MHz, CDCl₃) δ 193.3, 181.2, 163.1, 137.0, 134.7, 134.0, 132.1, 129.5 (2C), 128.1 (2C), 127.9 (2C), 127.8 (2C), 127.4, 126.5 (2C), 122.8, 119.3 (2C), 97.3, 55.4, 48.9, 36.9; IR (KBr, cm⁻¹) 3731, 3649, 3063, 1649, 1546, 1091, 750; MS calcd m/z 448.1, found 449.4 [(M + 1)]⁺. Anal. Calcd for C₂₅H₂₁ClN₂O₂S: C, 66.88; H, 4.71; N, 6.24. Found: C, 66.79; H, 4.65; N, 6.18.

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**Supporting Information Available:** Experimental details, spectral data for compounds 1–3, ¹H NMR spectrum of deuterated thiophene derivative 2a-D (Figure S2), and CIF data for 2a and 2i. This material is available free of charge via the Internet at http://pubs.acs.org.

Li et al.