

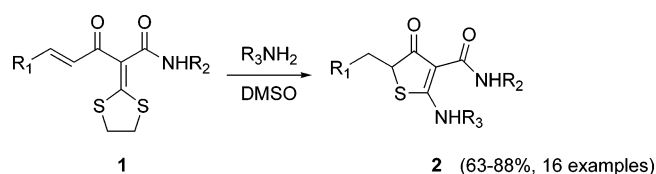
Intramolecular Thia-anti-Michael Addition of a Sulfur Anion to Enones: A Regiospecific Approach to Multisubstituted Thiophene Derivatives

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R₁ = alkyl, aryl and heteroaryl; R₂ = H, alkyl and aryl; R₃ = alkyl

The intramolecular thia-anti-Michael addition starting from readily available α -alkenyl- α' -carbamoyl ketene-(*S,S*)-acetals **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 alkynes in which the electron-withdrawing groups (EWG) act in concert for maintenance of the regioselectivity.^{1a} In recent years, however, some reactions, known as anti-Michael additions,²⁻⁶ contra-Michael

additions,⁷ 1,3-additions,⁸ nucleophilic α -additions,⁹ or reverse additions,¹⁰ have been reported and, among these reports, the

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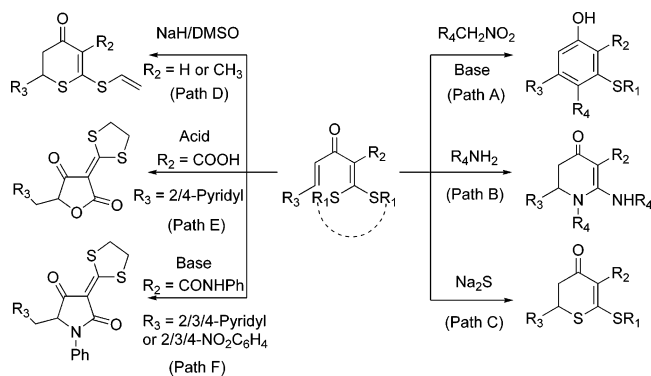
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SCHEME 1^a

^a For Paths A–C, R₁ = CH₂CH₃. For Paths D–F, R₁, R₁' = (CH₂CH₂).

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,14c} and [5C + 1S]^{14d} annulation strategies, respectively. Asokan and co-workers reported the synthesis of substituted 2,3-dihydro-4*H*-thiopyran-4-ones via dimsyl anion 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

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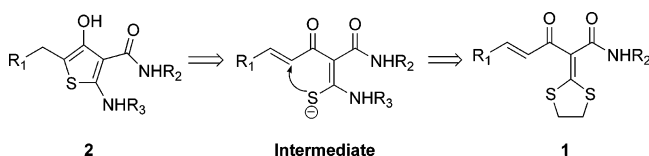
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SCHEME 2



ketene-(*S,S*)-acetals (R₂ = COOH), we obtained tetronic acid derivatives (Scheme 1, path E)^{16a} under acidic conditions via the pyridinium-induced intramolecular oxa-anti-Michael addition, and more recently, a series of tetramic acid derivatives (Scheme 1, path F) were prepared from α -alkenyl- α' -carbamoyl cyclic ketene-(*S,S*)-acetals with NaOEt as the base via aza-anti-Michael addition.^{16b} However, these anti-Michael addition reactions were limited to the α,β -enones bearing a strong electron-withdrawing aryl group at the β -position (Scheme 1, paths E and F).¹⁶

For the aza-anti-Michael addition (Scheme 1, path F),^{16b} a slightly wider scope to β -substitutes of α -alkenyl ketene-(*S,S*)-acetals than the oxo-anti-Michael addition (Scheme 1, path E)^{16a} was observed, and the mechanism of carbamoyl anion redirected intramolecular aza-anti-Michael addition was proposed.^{16b} As part of our continuing research on the synthetic applications of α -alkenyl ketene-(*S,S*)-acetals,^{14,16} we became interested in the exploration of the corresponding intramolecular thia-anti-Michael addition. On the basis of the findings just mentioned,¹⁶ together with the observations made by Trost and Dake (phosphine redirected α -addition of amides to alkynoates)¹¹ and Yokozawa and co-workers (strong +*I* effect of the aminyl anion to the carbonyl of the enone by a conjugated chain),¹⁷ the research plan of intramolecular thia-anti-Michael addition from a nucleophilic sulfur anion to the α,β -enones was designed (Scheme 2). We anticipated that under basic conditions, similar to the work by Asokan and co-workers,¹⁵ a sulfur anion intermediate could be generated by the fragmentation of the 1,3-dithiolane moiety of α -alkenyl- α' -carbamoyl ketene-(*S,S*)-acetals **1**.^{15,18} Indeed, in the presence of aliphatic primary amines and upon heating, a series of tetrasubstituted thiophene derivatives,^{19,20} 2-(alkylamino)-5-alkyl-4-hydroxythiophene-3-carboxamides **2**, were synthesized from open-chain precursors²¹ via amine-mediated tandem fragmentation, substitution, and intramolecular thia-anti-Michael addition reactions of α -alkenyl- α' -carbamoyl ketene-(*S,S*)-acetals **1** containing the 1,3-dithiolane

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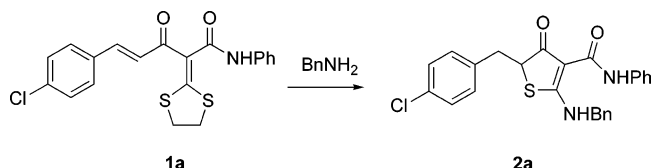
moiety. As the key step, the thia-anti-Michael addition proceeded in a regiospecific manner and showed the general scope to the β -substitutes of enones **1**. By this research, not only a new and efficient route to various tetrasubstituted thiophene derivatives has been created but also the subtle situation—the efficiency on redirecting the regioselectivity of the addition of a nucleophile from the classical β -addition mode to an α -addition—may be understood as an important concept.^{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, α -alkenoyl- α -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-(1,3-dithiolan-2-ylidene)-3-oxo-*N*-phenylpent-4-enamide (**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-*N*-phenyl-4,5-dihydrothiophene-3-carboxamide **2a** on the basis of its spectra and analytical data, although the yield was low (entry 2). The reaction conditions, including reaction temperature, solvents, and the feed ratio of **1a** and benzylamine, were then optimized. In the case of DMF as the solvent and stirring at 120 °C for 6 h, the reaction of **1a** (1.0 mmol) with benzylamine (1.2 mmol) afforded the desired product **2a** in 72% yield (entry 3). When DMSO was used as the solvent, the reaction gave **2a** in 52% yield at 90 °C for 3 h (entry 4), whereas **2a** was given in 88% yield when the reaction temperature was raised to 120 °C with the reaction time of only 0.7 h (entry 5). The molar ratio of

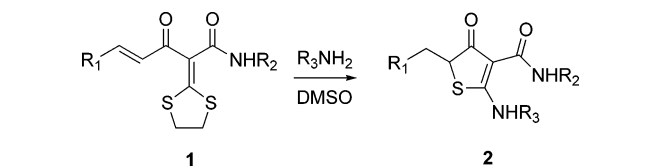
TABLE 1. Reaction of **1a** with Benzylamine under Different Conditions



entry	1a (mmol)	BnNH ₂ (mmol)	<i>T</i> (°C)	solvent	time (h)	2a yield ^a (%)
1	1.0	1.2	rt	CH ₃ CN	30	no reaction
2	1.0	1.2	reflux	CH ₃ CN	15	19
3	1.0	1.2	120	DMF	6	72
4	1.0	1.2	90	DMSO	3	52
5	1.0	1.2	120	DMSO	0.7	88
6	1.0	2.0	120	DMSO	0.7	88
7	1.0	0	120	DMSO	24	no reaction

^a Isolated yields after column chromatography.

TABLE 2. Scope of the Intramolecular Thia-anti-Michael Addition Reaction of **1**



entry	substrates 1	R ₁	R ₂	R ₃	products 2	time (h)	2 yield (%) ^a
1	1a	4-ClPh	Ph	Bn	2a	0.7	88
2	1b	4-FPh	Ph	Bn	2b	1.0	85
3	1c	2-ClPh	Ph	Bn	2c	1.0	87
4	1d	3-NO ₂ Ph	Ph	Bn	2d	1.2	86
5	1e	Ph	Ph	Bn	2e	1.5	80
6	1f	PhCH=CH	Ph	Bn	2f	1.5	81
7	1g	<i>t</i> -Bu	Ph	Bn	2g	3.0	63
8	1h	4-MePh	Ph	Bn	2h	3.5	70
9	1i	4-MeOPh	Ph	Bn	2i	4.5	66
10	1j	3,4-OCH ₂ CH ₂ OPh	Ph	Bn	2j	3.0	75
11	1k	2-furyl	Ph	Bn	2k	2.5	79
12	1l	2-thienyl	Ph	Bn	2l	2.5	80
13	1a	4-ClPh	Ph	Et	2m	0.7	86
14	1a	4-ClPh	Ph	<i>n</i> -Bu	2n	0.7	87
15	1m	4-ClPh	<i>n</i> -Bu	Bn	2o	0.7	87
16	1n	4-ClPh	H	Bn	2p	1.0	81

^a Isolated yields after column chromatography.

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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 α -alkenoyl ketene-(*S,S*)-acetals **1** (1.0 mmol) and amines (1.2 mmol) were carried out at 120 °C in DMSO (Table 2). First of all, the influence of the nature of the substitutes R₁ on the efficiency of the anti-Michael addition reaction was examined in detail. Thus, the substitutes R₁ were selected to have either electron-withdrawing or electron-donating properties and varied from alkyl to aryl and heteroaryl groups. As a result, in both cases of the electron-withdrawing and electron-donating substitutes R₁, the intramolecular thia-anti-Michael addition reactions of **1** were proved to be successful and yielded the desired thiophene derivatives **2** in good to high

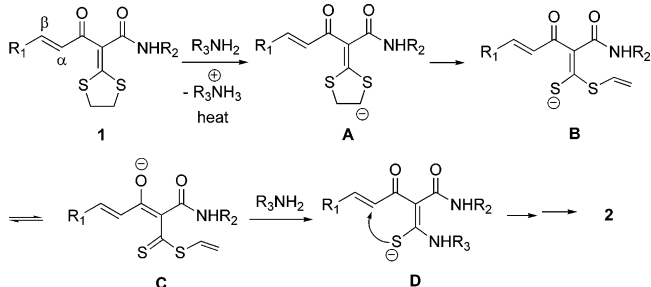
yields (Table 2, entries 1–12). To further confirm the structures of **2**, the single crystals of **2a** with an electron-deficient 4-chlorophenyl group and **2i** with an electron-rich 4-methoxyphenyl group were grown. Fortunately, the structures of both **2a** and **2i** were established by X-ray diffraction analysis (see Supporting Information, Figure S1).²³ The single-crystal X-ray diffraction of **2** indicates that the thiophenes **2** only exist in the ketone form, which is consistent with the results of the corresponding ¹H NMR and ¹³C NMR spectra (for copies of the NMR spectra, see Supporting Information).

All the above results indicated the efficiency of the anti-Michael reaction. The scope of the reaction system was extended to the substrates containing various alkyl, aryl, and heteroaryl groups at the β -position of the α,β -unsaturated carbonyl compounds **1**. It was found from Table 2 that the substrates containing an electron-deficient group at the β -position of enone exhibited higher reactivity than the substrates containing an electron-rich group at the β -position. In particular, the reactions of **1a–d** ($R_1 = 4\text{-ClPh}$, 4-FPh , 2-ClPh , and $3\text{-NO}_2\text{Ph}$, respectively, entries 1–4) gave higher yields (85–88%) and a shorter reaction time (0.7–1.2 h) than those of **1g–i** (entries 7–12, reaction time of 2.5–4.5 h and yields of 63–80%). Nevertheless, the molecular versatility of the products with variable R_1 , R_2 , and R_3 groups meets the need for the library synthesis.

Next, under conditions identical to those above, we examined the thia-anti-Michael reactions 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; $R_1 = p\text{-ClC}_6\text{H}_4$) 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; $R_1 = p\text{-ClC}_6\text{H}_4$) 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; $R_1 = p\text{-ClC}_6\text{H}_4$) 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; $R_1 = p\text{-ClC}_6\text{H}_4$, 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 thiophene derivatives **2**, as depicted in Scheme 3. Mediated by the amine and upon heating, deprotonation at one of the methylene groups of the dithiolane moiety^{15,18} should have triggered the ring-opening reaction to generate the intermediate thiolate anion **B**,¹⁵ which was stabilized via delocalization of the negative charge to give intermediate **C**. The displacement of the vinylthio group of **C** by an amine (S_NV) gave rise to the formation of **D**.^{14b,c} Finally, the intramolecular

SCHEME 3. Proposed Mechanism for the Intramolecular anti-Michael Addition Reactions of **1**



regiospecific addition of a sulfur anion to the α -position of the α,β -enones led to the production of multisubstituted thiophenes **2**. Certainly, further experiments and calculations are needed to clarify the reasons for the α -addition, rather than the β -addition to such kind of an α,β -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 α -alkenoyl ketene-(*S,S*)-acetals, has been developed. Various β -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 α -alkenoyl- α' -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 CH_2Cl_2 (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 = 6:1) to give **2a** as a white solid (394 mg, 88%): mp 144–146 °C; ¹H NMR (CDCl_3 , 500 MHz) δ 3.00 (dd, $J = 10.0, 14.0$ Hz, 1H), 3.56 (dd, $J = 4.0, 14.0$ Hz, 1H), 4.18 (dd, $J = 4.0, 10.0$ Hz, 1H), 4.19–4.57 (m, 2H), 7.08 (t, $J = 7.5$ Hz, 1H), 7.18 (d, $J = 8.5$ Hz, 2H),

(24) (a) Rudorf, W.-D.; Schwarz, R. *Synlett* **1993**, 369–374. (b) Rudorf, W.-D.; Schwarz, R. *Tetrahedron Lett.* **1987**, 37, 4267–4270. In these two reports, reaction of 4-phenyl-3-butyn-2-one and 1-phenyl-1-pentyn-3-one with carbon disulfide in the presence of sodium hydride in DMF followed by alkylation afforded a mixture of isomeric 2-alkylthio-6-phenyl-4*H*-thiopyrans and 5-alkylthio-2-benzylidene-3(2*H*)-thiophenones in a ratio of about 4:1.

(25) To gain insight into the reaction mechanism of this thia-anti-Michael reaction, the deuterium labeling experiment was carried out. D_2O (1.0 equiv) was added slowly to the reaction mixture of **1a** and benzylamine in DMSO at 120 °C. As a result, deuterated thiophene 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 $\delta = 2.9\text{--}4.3$ ppm (see Supporting Information, Figure S2). The disappearance of the ²*J* coupling in the ¹H NMR spectrum of **2a-D** indicates that the methylene group is deuterated during the intramolecular thia-anti-Michael addition process.

(23) X-ray diffraction data for **2a** and **2i** have been deposited in the Cambridge Crystallographic Data Centre with supplementary publication numbers of CCDC 299096 (**2a**) and 603091 (**2i**). The CIF files are also available in the Supporting Information.

7.24–7.39 (m, 9H), 7.59 (d, $J = 7.5$ Hz, 2H), 10.87 (s, 1H), 10.94 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) 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 $[(\text{M} + 1)]^+$. Anal. Calcd for $\text{C}_{25}\text{H}_{21}\text{ClN}_2\text{O}_2\text{S}$: 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>.

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