Synthetic Methods

$ZnCl_2$-Catalyzed [4+1] Annulation of Alkylthio-Substituted Enaminones and Enaminothiones with Sulfur Ylides

Yuan He,[a, b] Jiang Lou,[a, b] Zhengkun Yu,*[a, c] and Yong-Gui Zhou*[a]

Abstract: Concise construction of furan and thiophene units has played an important role in the synthesis of potentially bioactive compounds and functional materials. Herein, an efficient Lewis acid $ZnCl_2$ catalyzed [4+1] annulation of alkylthio-substituted enaminones is reported, that is, α-oxo ketene N,S-acetals with sulfur ylides to afford 2-acyl-3-aminofuran derivatives. In a similar fashion, [4+1] annulation of the corresponding enaminothiones, that is, α-thioxo ketene N,S-acetals, with sulfur ylides efficiently proceeded to give multisubstituted 3-aminothiophenes. This method features wide substrate scopes as well as broad functional group tolerance, offering a concise route to highly functionalized furans and thiophenes.

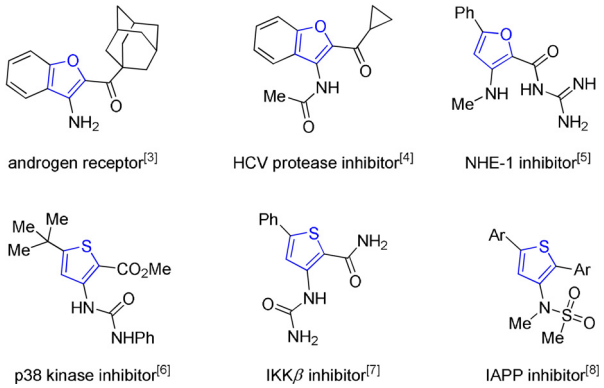

Figure 1. Furan and thiophene motifs in selected biologically active molecules.

The furan and thiophene motifs are important structural units abundant in many biologically active natural products, pharmaceuticals, and agrochemicals.[1] Furan and thiophene derivatives can also function as versatile building blocks for the synthesis of organic functional polymers due to their interesting electrochemical and optical properties.[2] For example, the 3-aminobenzofuran motif has been widely used as the key structural unit for the construction of pharmaceutical agents such as androgen receptors[3] and HCV protease inhibitors,[4] and 2-carboxamidefuran derivatives can act as NHE-1 inhibitors.[5] 3-Aminothiophene derivatives have also been medically considered as the potent inhibitors of p38 kinase,[6] IKKβ,[7] and islet amyloid polypeptide (IAPP)[8] (Figure 1). Continuous efforts have been devoted to the synthesis of substituted furans by means of cyclization of the suitable precursor compounds.[9] In this regard, transition-metal-catalyzed dehydrogenative heterocylization has been used to construct furan-fused carbocycles or multisubstituted furans.[10,11] Intramolecular cyclizations[12] involving alkynyl epoxides,[13] allenyl ketones,[14a] allenyl or homopropargylic alcohols,[14b] vinyl diazoesters,[14c] and allene-1,3-dicarboxylic esters[14d] were employed for the same purpose. Copper-catalyzed intermolecular heterocyclization of alkynyl ketones and imines,[14e] iron-catalyzed cyclization of 1,6-enynes,[14f] phosphine-mediated reductive condensation of γ-acyloxybutynoates,[14g] Brønsted acid promoted cyclization of 1,4-diketones,[15] and palladium-catalyzed condensation of N-arylimines and alkynylbenziodoxolones[16] all afforded the corresponding furan derivatives. A two-step reaction procedure of aldehydes with propargylic alcohols was also developed for the preparation of highly substituted furans.[17] In general, the synthesis of thiophene derivatives involves either an indirect way by functionalization of the thiophene ring[18] or a direct way via ring closure of suitable precursors.[19] The latter approach is clearly more versatile and attractive, but it has less been developed. In this area, Fiesselmann,[20] Gewald,[21] Paal,[22] and Hinsberg[23] reactions were developed for the direct construction of a thiophene ring in specific thiophene derivatives. Internal alkenes α-oxo ketene S,S-acetals[24a] were applied as the building blocks to establish a thiophene ring.[24b] 3-Aminothiophenes are considered as the important small molecules for drug development,[7] but only a few methods were documented for their synthesis.[25,26] Enaminothiones of type α-thioxo ketene N,S-acetals[27] have been reported to react with activated methylene compounds in the presence of stoichiometric $Hg(OAc)_2$[28] or with diazo compounds under Rh^{II} catalysis,[29] giving 3-aminothiophenes. Considerable advances have recently been achieved in the synthesis of thiophenes, but direct and concise methods are still strongly desired to access highly functionalized thiophene derivatives.

[a] Y. He, J. Lou, Prof. Dr. Z. K. Yu, Prof. Dr. Y.-G. Zhou
Dalian Institute of Chemical Physics, Chinese Academy of Sciences
457 Zhongshan Road, Dalian 116023 (P. R. China)
E-mail: zkyu@dicp.ac.cn
ygzhou@dicp.ac.cn
[b] Y. He, J. Lou
University of Chinese Academy of Sciences, Beijing 100049 (P. R. China)
[c] Prof. Dr. Z. K. Yu
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032 (P. R. China)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
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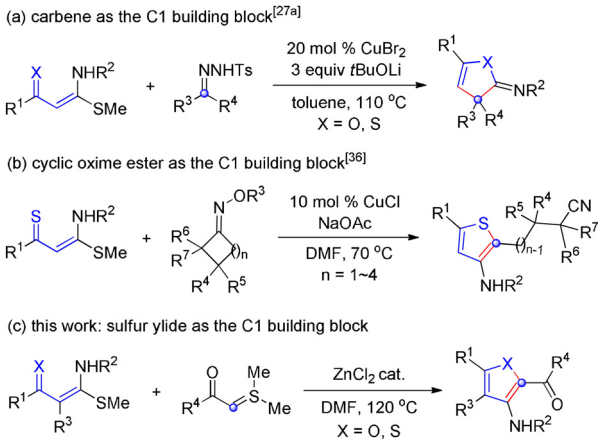
Sulfur ylides are among the most important and widely applied reagents in organic synthesis,[30] which are usually perceived as the 1,1′-dipole reagents for the synthesis of three-membered carbo- and heterocycles through [2+1] annulation.[31] Sulfur ylide [3+3] and [4+2] cycloaddition reactions were also realized.[32] However, [4+1] annulation of sulfur ylides has been paid less attention in recent years although it can be used as a powerful method to access diverse five-membered rings.[33] In this regard, Xiao et al. reported a formal [4+1] annulation of stabilized sulfur ylides with α,β-unsaturated imines to prepare polysubstituted pyrroles by a one-pot, two-step process.[34] Chandrasekhar et al. developed a highly efficient [2+2]/[4+1] cycloaddition cascade of arynes and stable sulfur ylides to synthesize 2-aroyl benzofurans.[35]

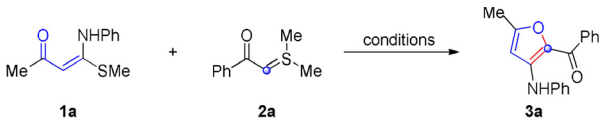
We recently found that alkylthio-substituted enaminones and enaminothiones, that is, α-oxo (thioxo) ketene N,S-acetals, could undergo carbene insertion reactions to establish O- and S-heterocycles under copper(II) catalysis[27a] or metal-free conditions[27b] (Scheme 1 a), and cycloketone oxime esters were also used as the C1 building blocks to react with enaminothiones in the presence of a copper(I) catalyst to give thiophene derivatives (Scheme 1 b).[36] Thus, we envisioned that sulfur ylides might also act as the suitable C1 building blocks to react with alkylthio-substituted enaminones and enaminothiones to execute [4+1] annulation to afford multisubstituted furan and thiophene derivatives (Scheme 1 c).



Scheme 1. [4+1] Annulations of α-oxo (thioxo) ketene N,S-acetals.

Initially, the reaction of enaminone α-oxo ketene N,S-acetal (**1a**) with S,S-dimethyl sulfur ylide (**2a**) was conducted to screen the reaction conditions (Table 1). Various Lewis acids were first tested as the catalysts, and $ZnCl_2$ was found to be the most efficient one to facilitate the desired reaction among the screened metal chlorides $AlCl_3$, LiCl, $Zn(OTf)_2$, $ZnBr_2$, and $ZnCl_2$ (Table 1, entries 1–5). In the presence of 10 mol% $ZnCl_2$ as the catalyst, DMF was the superior choice compared to other solvents (Table 1, entries 5–7). 120 °C seemed to be the best reaction temperature (Table 1, entries 7–9). Under the optimized conditions, the reaction of **1a** and **2a** in a 1:2 molar ratio afforded the target annulation product, that is, (5-methyl-

Table 1. Screening of reaction conditions.[a]



1a **2a** **3a**

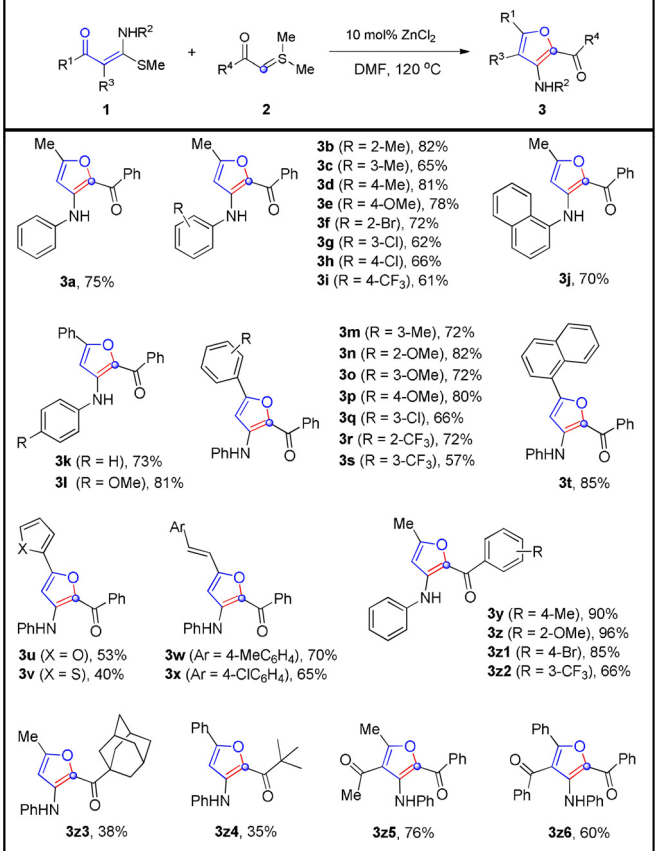
Entry	Lewis Acid	Solvent	*T* [°C]	Yield[b] [%]
1	$AlCl_3$	toluene	110	29
2	LiCl	toluene	110	39
3	$Zn(OTf)_2$	toluene	110	24
4	$ZnBr_2$	toluene	110	25
5	$ZnCl_2$	toluene	110	63
6	$ZnCl_2$	DMSO	110	70
7	$ZnCl_2$	DMF	110	72
8	$ZnCl_2$	DMF	100	60
9	$ZnCl_2$	DMF	120	74 (72)[c]
10[d]	$ZnCl_2$	DMF	120	61
11[e]	$ZnCl_2$	DMF	120	45
12[f]	$ZnCl_2$	DMF	120	79 (75)[c]
13[g]	$ZnCl_2$	DMF	120	34
14		DMF	120	0

[a] Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), Lewis acid (10 mol%), solvent (3.0 mL), 0.1 MPa N_2, 24 h. [b] Determined by ^{1}H NMR analysis by using 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yield given in parentheses. [d] Solvent (2.0 mL). [e] Solvent (4.0 mL). [f] **1a** (0.5 mmol), **2a** (1.0 mmol). [g] Lewis acid (5 mol%).

3-(phenylamino)furan-2-yl)-(phenyl)methanone (**3a**), in 75% isolated yield (Table 1, entry 12). Use of 5 mol% $ZnCl_2$ as the catalyst dramatically diminished the yield of **3a** to 34%, and the reaction did not occur in the absence of $ZnCl_2$ catalyst (Table 1, entry 14).

Under the optimized reaction conditions, the protocol generality for the synthesis of furans **3** was explored (Table 2). With α-acetyl ketene N,S-acetals **1b**–**1i** as the substrates, compounds **3b**–**3i** were obtained in 61–82% yields from their reactions with sulfur ylide **2a**. Functional groups methyl, methoxy, chloro, bromo, and trifluoromethyl were tolerated on the anilino groups (NHAr) in which 2- and 4-positioned electron-donating methyl and methoxy groups facilitated the reaction, while 3-Me, 3-Cl, 4-Cl, and 4-CF_3 diminished the product yields to 61–66%, and 2-Br led to 72% yield for **3f**. The bulky 1-naphthylamine-derived enaminone **1j** reacted smoothly to give **3j** (70%). α-Aroyl ketene N,S-acetals **1k**–**1s** also efficiently reacted with **2a** to form **3k**–**3s** (57–82%), and a clear negative electronic effect was observed for 3-positioned Me, OMe, Cl, and CF_3 groups on the α-aroyl moieties of enaminones **1**. α-(1-Naphthoyl) ketene N,S-acetal **1t** reacted well with **2a** to afford the target product **3t** (85%), exhibiting no steric effect. However, α-(2-furoyl) and -(2-thienoyl)-based substrates only achieved a moderate reaction efficiency to form **3u** (53%) and **3v** (40%), respectively. α-Cinnamoyl-functionalized ketene N,S-acetals **1w** and **1x** also effectively reacted with **2a**, yielding **3w** and **3x** in 65–70% yields. It should be noted that alkylamine and benzylamine-derived α-oxo ketene N,S-acetals could not execute the same type of annulation reaction under the stated conditions, and secondary amine-based enaminones did not react either. These results have suggested that an NH functionality in the enaminone substrates is crucial for the [4+1] annu-

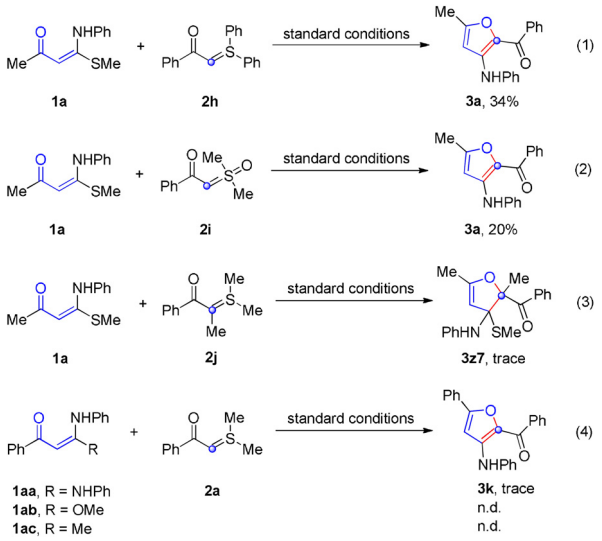
Table 2. Substrate Scopes for the Synthesis of Furans (3).[a]



[a] Conditions: **1** (0.5 mmol), **2** (1.0 mmol), $ZnCl_2$ (0.05 mmol), DMF (3 mL), 0.1 MPa N_2, 120 °C, 24 h.

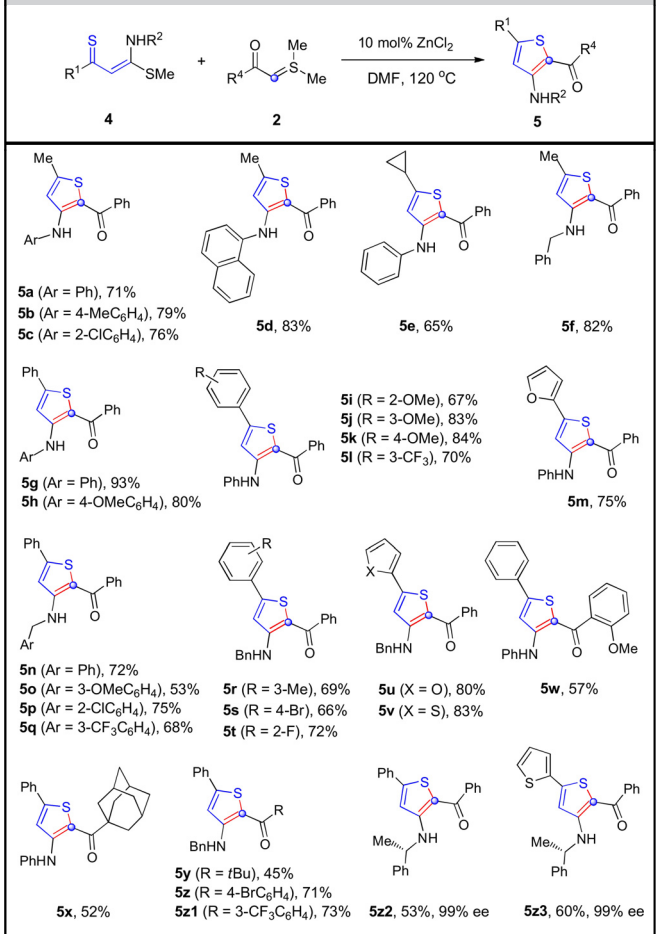
lation reaction in which the sulfur ylides acted as the C1 building blocks. Electron-donating methyl and methoxy, and bromo-substituted sulfur ylides **2b**–**2d** efficiently reacted with **1a** to give the target products **3y**–**3z1** in excellent yields (85–96%), while 3-CF_3-bearing sulfur ylide **2e** only reached 66% yield for the target product **3z2** in the reaction with **1a**. The bulky adamantyl and *tert*-butyl-functionalized sulfur ylides **2f** and **2g** reacted much less efficiently than their aryl-based analogues with **1a** and **1k** to form **3z3** (38%) and **3z4** (35%), respectively. Unexpectedly, the fully substituted enaminones **1y** (R^3 = MeCO) and **1z** (R^3 = PhCO) also effectively reacted with sulfur ylide **2a**, giving the corresponding tetrasubstituted furan **3z5** (76%) and **3z6** (60%), respectively.

S,S-Diphenyl sulfur ylide **2h** was also applied in the reaction with **2a**, giving the target product **3a** in 34% yield [Eq. (1)]. By means of the corresponding oxide of sulfur ylide **2a**, that is, benzoyl sulfoxonium ylide (**2i**), as the coupling partner, **3a** was obtained in a low yield (20%) [Eq. (2)]. The fully substituted sulfur ylide **2j** exhibited a poor reactivity to **2a**, and it could not execute the reaction to form the desired product **3z7** [Eq. (3)]. In the cases of using PhNH-, MeO-, or methyl-functionalized α-oxo ketene N,N-acetal **1aa**, N,O-acetal **1ab**, and enaminone **1ac**, the reaction with **2a** could hardly occur [Eq. (4)]. These results have revealed the crucial role of the alkylthio functionality at the N-functionalized terminus of the internal C=C backbone in the enaminone substrates.



Next, the protocol was employed to synthesize thiophene derivatives (Table 3). Under the optimal conditions, (*E*)-4-(methylthio)-4-(phenylamino)but-3-ene-2-thione, that is, enaminothione (α-thioxo ketene N,S-acetal) **4a**, reacted with sulfur ylide **2a** to give the target thiophene product **5a** in 71% yield. With α-acetyl ketene N,S-acetals **4b** and **4c** as the substrates, thiophene derivatives **5b** and **5c** were obtained in 76–79% yields. 1-Naphthylamine-derived enaminothione **4d** efficiently reacted to form product **5d** (83%), while (*E*)-1-cyclopropyl-3-(methylthio)-3-(phenylamino)prop-2-ene-1-thione (**4e**) exhibited a lower reactivity to **2a**, yielding the target thiophene product **5e** in 65% yield. Benzylamine-derived α-thioxo ketene N,S-acetal **4f** also reacted well with **2a** to afford the product **5f** (82%). In comparison to the synthesis of furans **3k** (73%) and **3l** (81%) (Table 2), the corresponding thiophene compounds **5g** (93%) and **5h** (80%) were readily accessed. Steric and electronic effects were observed from the 2-OMe and 3-CF_3 substituents on the aryl groups of the α-arylthioxo moieties, leading to thiophenes **5i** and **5l** in yields (67–70%) lower than those (83–84%) for **5j** and **5k**. 2-Furyl-substituted thiophene **5m** was obtained in a much higher yield (75%) than its furan analogue **3u** (53%) (Table 2). It should be noted that the benzylamine-derived enaminothiones **4n**–**4v** reacted with **2a** to give the corresponding thiophene products **5n**–**5v** in high yields (53–83%), among which 2-furyl and 2-thienyl-substituted thiophenes **5u** and **5v** were generated in much higher yields (80–83%) than **3u** and **3v** (40–53%), whereas the corresponding benzylamine-derived enaminones of type **1** could not react with **2a** to form furan products under the same conditions due to the ready decomposition of the substrates during the reaction. Diverse aryl and alkyl sulfur ylides could also act as the effective partners to couple with various enaminothiones, producing functionalized thiophenes **5w**–**5z1** (45–73%). Interestingly, chiral benzylamino-based enaminothiones reacted with **2a** to yield the corresponding chiral thiophene derivatives

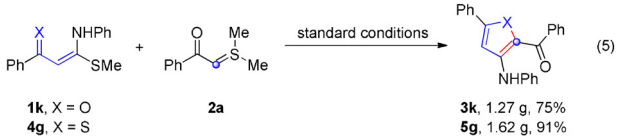
Table 3. Substrate Scopes for the Synthesis of Thiophenes (5).[a]



[a] Conditions: **4** (0.5 mmol), **2** (1.0 mmol), $ZnCl_2$ (0.05 mmol), DMF (3 mL), 0.1 MPa N_2, 120 °C, 24 h.

5z2 (53%) and **5z3** (60%) with unchanged enantiopurity (99% *ee*). Secondary amine-derived enaminothiones of type **4** could not react with the sulfur ylides, further demonstrating the crucial role of an NH functionality at the S-functionalized terminus of the internal C=C backbone in **1** and **4**. The molecular structures of compounds **3** and **5** were further confirmed by the X-ray single crystal structural determinations of furan **3a** and thiophene **5h** (Figure 2, see the Supporting Information for details).

To demonstrate the applicability of the present synthetic protocol, gram-scale preparation was carried out under the standard conditions by means of the reactions of **1k** and **4g** with **2a** [Eq. (5)]. The target products **3k** and **5g** were obtained in 75% and 91% yields, respectively, demonstrating a reaction efficiency comparable to those on a smaller reaction scale.



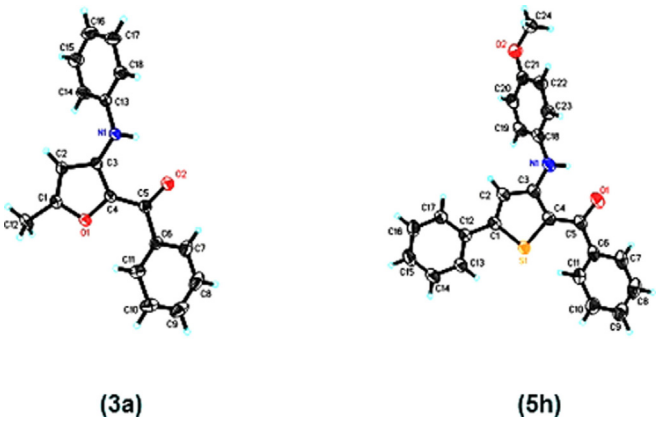
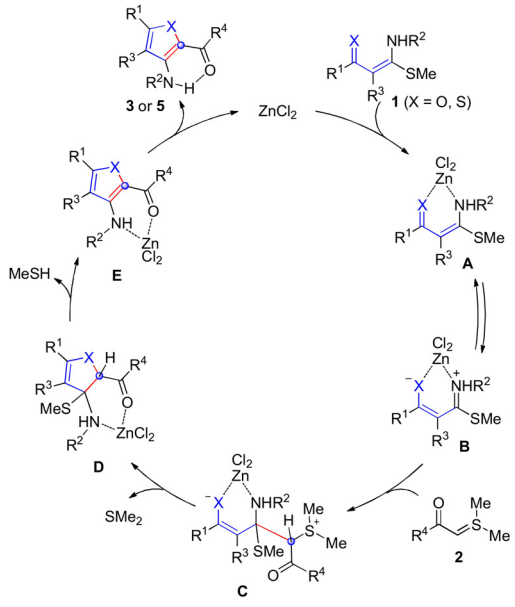


Figure 2. Molecular structures of compound **3a** and **5h**.

Control experiments were conducted to probe into the reaction mechanism. Thus, the reaction of **1a** with **2a** was performed in the presence of 4.0 equivalents of 2,2,6,6-tetramethyl-1-piperi-dinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenyl (BHT) (see the Supporting Information for details). Under the standard conditions, these radical-trapping reagents could not inhibit the annulation reaction, leading to **3a** in 63–70% yields. Furthermore, no EPR signal was observed from the reaction mixture, which excludes a radical pathway in the catalytic cycle. The adduct of **1a** with stoichiometric $ZnCl_2$ was considered as the reaction intermediate, but it was not successfully prepared from the 1:1 molar ratio reaction of **1a** and $ZnCl_2$ at ambient temperature or under heating conditions. Based on the possible Lewis acid catalysis pathway, a plausible reaction mechanism is proposed in Scheme 2. Initially, Lewis acid $ZnCl_2$ interacts with enaminone **1** or enaminothione **4** through coordination to the metal center by the oxygen or sulfur atom of the C=X functionality and the amino nitrogen atom. Reactant



Scheme 2. Proposed mechanism.

1 or **4** is thus activated to form adduct **1**(**4**)·$ZnCl_2$ (**A**)/zwitterion species **B**. Nucleophilic attack of sulfur ylide **2** at the iminium carbon of species **B** yields species **C**. Subsequent release of dimethyl sulfide results in intermediate **D** from which methanethiol is further eliminated to generate adduct intermediate **E**. Regeneration of the Lewis catalyst gives the target product **3** or **5**, finishing a catalytic cycle.

N-Dearylation of 3-aminofurans (**3**) and 3-aminothiophenes (**5**) was tried to cleave the aryl on the nitrogen functionality by means of ceric ammonium nitrate (CAN)[37] or silver(II) persulfate $[Ag(Py)_4]S_2O_8$[38] according to the literature methods, but failed. The oxidative N-dearylation reaction of **3e** only led to complicated mixtures from which the desired N-dearylation product was not isolated.

In summary, an efficient Lewis acid catalyzed protocol has been developed for the synthesis of 2-acyl-3-amino-substituted furan and thiophene derivatives from enaminones and enaminothiones, that is, α-oxo (thioxo) ketene N,S-acetals, and sulfur ylides. The [4+1] annulation featured allows for broad substrate scopes, high efficiency, and good functional-group tolerance. This work has demonstrated the potential applicability of the present method for the synthesis of highly functionalized furan and thiophene derivatives.

Experimental Section

General procedure for the synthesis of 3

Synthesis of 3a: Under a nitrogen atmosphere, a mixture of (*E*)-4-(methylthio)-4-(phenylamino)but-3-en-2-one (**1a**) (104 mg, 0.5 mmol), *S,S*-dimethyl sulfur ylide (**2a**) (180 mg, 1.0 mmol), and $ZnCl_2$ (7 mg, 0.05 mmol) in DMF (3 mL) was stirred at 120 °C for 24 h. After cooled to ambient temperature, 5 mL CH_2Cl_2 was added and the resultant mixture was filtered through a short pad of Celite, followed by rinsing with 10 mL CH_2Cl_2. The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/EtOAc = 50:1, v/v) to afford **3a** as a yellow solid (104 mg, 75%).

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: annulation · enaminones · enaminothiones · sulfur ylides · zinc

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