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# Substituent-Controlled Selective Synthesis of *N*-Acyl 2-Aminothiazoles by Intramolecular Zwitterion-Mediated C–N Bond Cleavage

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The cleavage of C–N bonds is an interesting and challenging subject in modern organic synthesis. We have achieved the first zwitterion controlled C–N bond cleavage in the MCR reaction among lithium alkynethiolates, bulky carbodiimides, and acid chlorides to construct *N*-acyl 2-aminothiazoles. This is a simple, highly efficient and general method for the preparation of *N*-acyl 2-aminothiazoles with a broad range of substituents. The selective synthesis of *N*-acyl 2-aminothiazoles significantly depends on the steric hindrance of carbodiimides. The result is in striking contrast with our previous convergent reaction giving 5-acyl-2-iminothiazolines via 1,5-acyl migration. It is indeed interesting that the slight change of the substituents on the carbodiimides can completely switch the product structure. Experimental and theoretical results demonstrate the reason why the C–N bond cleavage in the present system is prior to the acyl migration. The intramolecular hydrogen relay via unprecedented Hofmann-type elimination is essential for this totally new zwitterion controlled C–N bond cleavage.

# INTRODUCTION

The cleavage of C–N bonds is an interesting and challenging subject in modern organic synthesis.<sup>1</sup> The C–N bonds are usually activated by oxidative addition of a low-valent transition-metal complex<sup>2</sup> or conversion to diazonium salts,<sup>1b</sup> ammonium salts,<sup>3</sup> triazenes,<sup>4</sup> imidazoles,<sup>5</sup> and so on.<sup>6</sup> However, as far as we are aware, the zwitterion controlled C–N bond activation has not yet been achieved (Scheme 1). On the other hand, the Hofmann elimination reaction, which is the thermal decomposition of a quaternary ammonium salt in the presence of base, is considered generally as a classical method to construct useful olefins by the expulsion of the tertiary amine. In the whole process, the cleavage of both C–N bond and C–H bond is observed by the E2 elimination or the *cis*-ylide mechanism.<sup>7</sup> To date, no example of Hofmann elimination has been reported via six-membered-ring transition state by the intramolecular zwitterion hydrogen relay.





We reported a procedure-controlled selective synthesis of 5-acyl-2-iminothiazolines by a convergent multicomponent reaction (MCR) from lithium alkynethiolates, carbodiimides ( $R^1N=C=NR^2$ ,  $R^2=Ph$ , <sup>*i*</sup>Pr, and Cy ), and acid chlorides,<sup>8-10</sup> in which 1,5-acyl migration was considered to be important for the transformation (Scheme 1*a*). Herein we wish to report the substituent-controlled selective synthesis of *N*-acyl 2-aminothiazoles by reaction of lithium

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alkynethiolate, bulky carbodiimides ( $R^2 = {}^tBu$ ,  ${}^tOct$ , and 1-adamantyl(Ad)), and acid chlorides via the first zwitterion controlled C–N bond cleavage (Scheme 1*b*). It is indeed interesting that the slight change of the substituents on the carbodiimides can completely switch the product structure. The new approach permits a concise and straightforward route to a wide range of *N*-acyl 2-aminothiazoles. Experimental and theoretical results demonstrate the reason why the C–N bond cleavage in the present system is prior to the acyl migration. The intramolecular hydrogen relay via unprecedented Hofmann-type elimination is essential for this totally new zwitterion controlled C–N bond cleavage.

## **RESULTS AND DISCUSSION**

**Synthesis of** *N*-Acyl 2-aminothiazoles. When *N*-tert-butyl-*N*'-ethylcarbodiimide (EtN=C=N<sup>t</sup>Bu) was allowed to react with 4-trifluoromethyl benzoyl chloride at room temperature for 48 h, and then the mixture was treated with lithium phenylalkynethiolate at 80 °C for 12 h in THF, the new compound **1a** could be obtained in 81% yield upon isolation. X-ray crystallographic analysis of **1a** revealed unambiguously it *N*-acyl 2-aminothiazole. The acyl group is still attached on the nitrogen atom and no <sup>t</sup>Bu is observed in the skeleton of **1a** (See Supporting Information for X-ray structure of **1a**).

This result clearly shows C–N bond cleavage occurs in carbodiimide. The selective synthesis of *N*-acyl 2aminothiazole significantly depends on the steric hindrance of the R<sup>2</sup> substituent (R<sup>2</sup> = <sup>*i*</sup>Bu). The result is in striking contrast with our previous convergent reaction giving 5-acyl-2-iminothiazolines from lithium alkynethiolates, carbodiimides (R<sup>1</sup>, R<sup>2</sup> = <sup>*i*</sup>Pr, Cy, Ph), and acid chlorides.<sup>8</sup> Although carbodiimides can act as versatile reagents for organic synthesis and organometallic chemistry,<sup>11-13</sup> the cleavage of chemical bonds in carbodiimide is relatively less explored in chemical transformations.<sup>14-16</sup>

As summarized in Table 1, this substituent-controlled reaction displayed a broad scope for terminal alkynes. Aromatic terminal alkynes with either electron-donating or electron-withdrawing substituents all performed well, giving the corresponding 2-aminothiazoles **1a-f**. Comparatively, when the substituent was on the *ortho*-position of phenyl ring, the reaction proceeded sluggishly and the yield was relatively lower than that of *meta-* or *para-*positions. Besides, heteroaromatic terminal alkyne such as 2-ethynylthiophene, enyne such as cyclohexenylacetylene, and aliphatic terminal alkynes such as 1-hexyne and cyclohexylacetylene, were also well tolerated, furnishing the corresponding products **1g-j**. Then, a series of acid chlorides were suitable acyl source for this reaction. Both the

electron-donating benzoyl chlorides and electron-withdrawing benzoyl chlorides reacted well, and the desired products **1k-r** were formed. It was noteworthy that 3-phenylacryloyl chloride could afford **1s**. Additionally, aliphatic acid chlorides gave the corresponding product **1t** with slightly lower yield as compared to the aromatic acid chlorides. When  $R^1N=C=NR^2$  ( $R^1$  = Me, hexenyl, and Bn;  $R^2 = {}^tBu$ ,  ${}^tOct$ , and Ad) were utilized, the corresponding compounds **1u-y** could be obtained in good yields. Meanwhile, when  $R^2 = {}^tOct$  and Ad, similar C–N bond cleavage occurred.

Table 1. Formation of Various N-Acyl 2-aminothiazoles<sup>a,b</sup>



<sup>a</sup> Conditions: terminal alkynes, 1 mmol; sulfur, 1 mmol; carbodiimides, 1 mmol; acid chlorides, 1 mmol; THF, 10 mL, unless otherwise noted. <sup>b</sup> Isolated yield.

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*N*-Acyl 2-aminothiazole is considered as an important class of small molecule in medicinal and pharmaceutical chemistry because of their good bioactivities.<sup>17</sup> Especially, when *N*-substituent is methyl group, *N*-acyl-*N*-methyl-2-aminothiazoles has been reported to be the cancer cell inhibitors, antiprion molecules, and ligand for the positron emission tomography (PET) imaging. For example, compound **1u**, which could be conveniently synthesized by present method, was reported to be the inhibitor of cancer cell migration. The low toxicity to healthy cells might lead this compound **1u** to be a therapeutic agent to block tumor metastasis.<sup>17a</sup> The syntheses of *N*-acyl 2-aminothiazoles are usually obtained by the reaction of 2-aminothiazoles with carboxylic acid derivatives,<sup>18</sup> or the reaction of 2-thioureidoacetic acids and thioacetic acids.<sup>19</sup> However, the scope of the reported *N*-acyl 2-aminothiazoles is limited because of the unavailability of the starting materials. The present route with a wide range of substrate scope is a valuable complement to the existing arsenal of *N*-acyl 2-aminothiazole synthesis.

#### Mechanistic Study.

1) The Proposed Mechanisms. Three main pathways were proposed in Scheme 2. In pathway *I*--Nucleophilic addition/LiCl elimination/cyclization/isobutylene elimination, the elimination of LiCl took place before cyclization. The reaction of  $R^1N=C=NR^2$  with acid chloride at room temperature for 48 h yielded efficiently *N*-acyl chloroformamidine.<sup>20</sup> The nucleophilic attack of the lithium alkynethiolate (**A**) on *N*-acyl chloroformamidine should yield the intermediate **B** with the elimination of LiCl. The five-membered-ring zwitterion intermediate **C** would then be produced by intramolecular cyclization. An intramolecular hydrogen atom relay, the over-all result similar to that of intramolecular Hofmann-type elimination,<sup>7</sup> occurred synergistically in the zwitterion intermediate **D** giving **1** with the elimination of isobutylene. Alternatively, the stepwise process was also possible. The *tert*-butyl group in intermediate **C** would abstract one proton from the *tert*-butyl cation, delivering **1** with the elimination of isobutylene.

In pathway *II*--Nucleophilic addition/cyclization/LiCl elimination/isobutylene elimination, elimination of LiCl took place after cyclization. The nucleophilic attack of **A** on *N*-acyl chloroformamidine resulted in the formation of anion intermediate **B'**. The five-membered anion intermediate **C'** was then produced by intramolecular nucleophilic cyclization. Then, the elimination of LiCl took place to yield **D** or **D'**. Similar to the trapping of proton atom in pathway *I*, **1** was finally obtained by concerted or stepwise processes.

In pathway *III--*<sup>*t*</sup>BuCl Elimination/nucleophilic addition/cyclization/isobutylene elimination, the elimination of <sup>*t*</sup>BuCl in the *N*-acyl chloroformamidine occurred in the first step to give *N*-acyl cyanamide. Then, *N*-acyl cyanamide reacted with **A**, giving the intermediate **B''**. The following intramolecular nucleophilic cyclization in **B''** gave **D'**. Finally, **D'** would extract one proton from the eliminated *tert*-butyl group, delivering the final product **1**.

Scheme 2. Proposed Mechanisms.



In the proposed mechanistic processes, there are four core aspects to be dealt with: (i) The origin of the hydrogen attached to the C5 atom in 2-aminothiazole ring. No external proton was added in the present system, so the hydrogen atom should be from the reaction substrates; (ii) The fate or existence form of the cleaved *tert*-butyl or *tert*-octyl group via C–N bond cleavage; (iii) The key steps of C–N and C–Cl bond cleavage in *N*-acyl chloroformamidine. The C–Cl bond cleavage takes place before or after C–N bond cleavage or both occur simultaneously. In other words, the elimination sequence of LiCl in the reaction process is the key; (iv) The reason why C–N bond cleavage in the present **ACS Paragon Plus Environment** 

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system is prior to the acyl migration. Thus, we expected to explore the reaction mechanism by the combined experimental and theoretical studies.

2) Experimental Studies. To gain mechanistic insight into the origin of the hydrogen at the C5-position of *N*-acyl 2-aminothiazole ring, the isotopic labeling experiment was performed. When <sup>*n*</sup>HexN=C=NC(CD<sub>3</sub>)<sub>3</sub> was used under above conditions, the deuterium was incorporated exclusively to the C5-position of the product 1w-D (Scheme 3).<sup>21</sup> Deuterium-labeling study unambiguously indicated that the hydrogen atom at the C5-position of 2-aminothiazole ring was from the *tert*-butyl group of carbodiimide.

Next, the *tert*-octyl substituted carbodiimide (<sup>*n*</sup>BuN=C=N<sup>*t*</sup>Oct) was chosen to detect the by-product alkene by gas chromatography mass spectrometry (GC-MS) spectroscopic analysis (Scheme 3). The GC retention time and molecular-weight mass fragment ion (m/z = 112) of the alkene was consistent with the standard sample 2,4,4-trimethylpent-1-ene (See supporting information (SI)). These results of GC-MS analysis demonstrated that the eliminated *tert*-octyl group was converted into the corresponding alkenes.

In principle, the reaction between *N*-acyl cyanamide and lithium alkynethiolate might also yield *N*-acyl 2aminothiazole (pathway *III*). Therefore, we synthesized the pure *N*-acyl cyanamide compound **2** by the thermal decomposition of *N*-acyl chloroformamidine (Scheme 3).<sup>20</sup> No expected reaction between **2** and lithium alkynethiolate was observed. This result illustrated that <sup>*t*</sup>Bu and chloride atom in *N*-acyl chloroformamidine was not released before the reaction, and the C–N bond cleavage should take place after nucleophilic attack of lithium alkynethiolate on *N*-acyl chloroformamidine. So the result ruled out the possibility of pathway *III*.

These experimental results have clearly demonstrated: (i) The hydrogen attached to the C5 atom in 2-aminothiazole ring was from the eliminated *tert*-butyl or *tert*-octyl group of carbodiimide. (ii) The cleaved *tert*-butyl or *tert*-octyl group was converted into the corresponding alkenes; (iii) The elimination of 'BuCl from *N*-acyl chloroformamidine giving *N*-acyl cyanamide does not occur in this process.

Although we could exclude the possibility of the proposed pathway III in Scheme 2, it was still difficult to distinguish I from II by experiments. In other words, based on the experimental results, we could not know in which step the elimination of LiCl would occur and whether the proton shift was concerted or stepwise. In addition, the reason why C–N bond cleavage pathway in the present system was more favored than the acyl migration process was still unclear. Thus, computational studies were performed to probe this process.



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**3)** Computational Studies. DFT calculations were carried out with the GAUSSIAN 03 program package using the B3LYP method and 6-31G(d) basis set.<sup>22</sup> The computational results of two possible pathways are shown in Figure 2 and discussed as follows. Both pathways start with the same cyclization procedure to give a zwitterion thiazoline intermediate IM4. IM4 then undergoes either a C–N bond cleavage process to generate the *N*-acyl 2-aminothiazole product IM5, or an acyl migration to generate the 5-acyl-2-iminothiazoline product IM8.

The Reaction Pathway to Generate the *N*-Acyl 2-aminothiazole IM5. The computational results of C–N bond cleavage are shown in Figure 1. The reaction between lithium alkynethiolate IM1 and *N*-acyl chloroformamidine IM2 gives IM3. The large decrease of thermal energy in this step is attributed to the elimination of LiCl, so this calculation result excludes the possibility of pathway *II*. However, the released LiCl is still coordinated to the molecule and behaves as the linker in the dimerization and following steps. IM3 undergoes further transformation via a single

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intramolecular cyclization transition state **TS1** with an energy barrier of 29.3 kcal/mol, giving the zwitterion intermediate **IM4**, which is 21.1 kcal/mol more unstable than **IM3**. Due to the **IM4**'s zwitterionic nature, the Gibbs free energy of the dimer **2IM4** is favored by 6.2 kcal/mol. Affected by this, the C–N bond cleavage based on **2IM4** is more favored than that based on monomeric intermediate **IM4** (see SI for details).

The transformation of **2IM4** to **IM5** and isobutylene, in which C–N bond cleavage and the C–H bond formation occurred, is a single step with only one transition state **TS2** involved. The Gibbs free energy of **IM5** and isobutylene is 52.4 kcal/mol lower than **2IM4** and 37.5 kcal/mol lower than **IM3**. The energy barrier for the C–N bond cleavage step is 27.9 kcal/mol, lower than that of the cyclization step (29.3 kcal/mol). These results clearly revealed that pathway *I* in which concerted proton shift occurs in **C** is reasonable, and the mechanism of C–N bond cleavage involves nucleophilic addition/LiCl elimination/intramolecular cyclization/intramolecular Hofmann-type elimination as key steps.



Figure 1. Calculated potential energy surfaces. Coordinated LiCl is omitted for clarity.

**The Reaction Pathway to Generate the 5-Acyl-2-iminothiazoline IM8.** The transformation of **2IM4** to 5-acyl-2-iminothiazoline product by acyl migration mechanism is also explored (Figure 1). The acyl migration undergoes through an intermolecular nucleophilic addition-elimination mechanism. For the whole acyl migration pathway, although the Gibbs free energy decreases by 32.3 kcal/mol, the highest energy barrier is 45.2 kcal/mol (**TS4**), much higher than that of the C–N bond cleavage pathway. Thus, when one of the substituents on the carbodiimide is *tert*-butyl group, the C–N bond cleavage is more preferred than the acyl migration. The calculation results above are in well agreement with the experiments that only C–N bond cleavage product *N*-acyl 2-aminothiazole could be obtained in the present reaction.

The DFT calculations of C–N bond cleavage pathway and acyl migration pathway clearly displayed the selectivity of this unique C–N bond cleavage reaction and explained why different class of *N*-containing heterocyclic compounds could be obtained from the same starting materials by simply switching one of the substituents on the carbodiimide to the *tert*-butyl group.

# CONCLUSION

We have achieved the first zwitterion controlled C–N bond cleavage in the MCR reaction among lithium alkynethiolates, bulky carbodiimides, and acid chlorides to construct *N*-acyl 2-aminothiazoles. This is a simple, highly efficient and general method for the preparation of 2-aminothiazoles with the broad range of the substituents. The reaction for the selective synthesis of 2-aminothiazoles is significantly dependent on the steric hindrance of 'Bu, 'Oct or Ad. In this process, the formation of  $C(sp^2)$ –N,  $C(sp^2)$ –S, and  $C(sp^2)$ –H bonds as well as the cleavage of  $C(sp^3)$ –N and  $C(sp^2)$ –Cl bonds are observed. The combined experimental and theoretical studies strongly support the idea that the reaction proceeds through nucleophilic addition/LiCl elimination/intramolecular cyclization/intramolecular Hofmann-type elimination as key steps. These results show that: (i) The reaction rate-determining step is intramolecular cyclization, and the eliminated 'Bu, 'Oct or Ad which are finally converted into alkenes; (iii) The proton shift is concerted by an unprecedented Hofmann-type elimination via the zwitterion-mediated six-membered-ring transition **ACS Paragon Plus Environment** 

state; and (iv) When one of the substituents on the carbodiimide was changed to the bulky group, C–N bond cleavage is more favored than the acyl migration.

# **EXPERIMENTAL SECTION**

**General Method:** Unless otherwise noted, all starting materials were commercially available and were used without further purification. Solvents were purified by a solvent purification system and dried over fresh Na chips in the glovebox.  $C_6D_6$  (all 99+ atom% D) was dried over fresh Na chips in the glovebox for NMR analysis. All reactions were carried out under a dry and oxygen-free nitrogen atmosphere in slightly positive pressure by using Schlenk techniques or under a nitrogen atmosphere in the glovebox. The nitrogen in the glovebox was constantly circulated through a copper/molecular sieve catalyst unit. The oxygen and moisture concentrations in the glovebox atmosphere were monitored by an  $O_2/H_2O$  Combi-Analyzer to ensure both were always below 1 ppm. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at room temperature in  $C_6D_6$  solutions, or in CDCl<sub>3</sub> solutions and with tetramethylsilane (0.00 ppm) as internal standard, unless otherwise noted. Infrared spectra (IR) were recorded on a FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a FTMS mass spectrometer using ESI (electrospray ionization), and the mass analyzer of the HRMS was ICR (ion cyclotron resonance).

Synthesis of *N*-Acyl 2-aminothiazoles 1a-z: In a 25 mL of flask, an acid chloride (1 mmol) was added to a carbodiimide (1 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 48 h. In another 25 mL of flask, *n*-BuLi (1 mmol, 1.6 M in hexane) was added dropwise at -78 °C to a stirred solution of terminal alkynes (1 mmol) in THF (5 mL). After stirring at -78 °C for 0.5 h, sulfur (1 mmol, 32 mg) was added and the reaction mixture was allowed to warm to room temperature for 2 h. The above two reaction solutions were mixed into one flask, which was allowed to heat up to 80 °C for 12 h in THF. The solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give products **1a-z**.

**1a:** Yellow solid, isolated yield 81% (305 mg); mp: 52.7-53.3 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.39 (t, *J* = 6.9 Hz, 3H), 4.23 (q, *J* = 6.9 Hz, 2H), 7.27 (s, 1H), 7.31-7.35 (m, 1H), 7.40-7.46 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H) 7.91 (d, *J* = 7.6 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 45.2, 109.4, 123.6 (q, *J* = 272.5 Hz), 125.8 (q, *J* = 3.7 Hz), 126.0, 127.1, 128.0, 128.7, 128.8, 132.3 (q, *J* = 33.0 Hz), 134.6, 138.7, 149.7, 169.1. IR (film): *v* 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>19</sub>H<sub>16</sub>F<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 377.0935, found 377.0933.

**1b:** Yellow solid, isolated yield 57% (223 mg); mp: 145.4-145.8 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.35 (t, J = 6.9 Hz, 3H), 2.46 (s, 3H), 4.19 (q, J = 6.9 Hz, 2H), 7.06 (s, 1H), 7.25-7.27 (m, 3H), 7.58-7.60 (m, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 21.3, 45.1, 112.8, 123.6 (q, J = 272.4 Hz), 125.8 (q, J = 3.7 Hz), 125.9, 127.1, 128.0, 129.0, 129.6, 130.9, 132.3 (q, J = 32.9 Hz), 134.7, 136.1, 138.8, 150.3, 169.0. IR (film): v 1649 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>20</sub>H<sub>18</sub>F<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 391.1092, found 391.1086.

1c: Yellow solid, isolated yield 70% (273 mg); mp: 96.9-97.8 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.38 (t, *J* = 6.9 Hz, 3H), 2.39 (s, 3H), 4.23 (q, *J* = 6.9 Hz, 2H), 7.21-7.24 (m, 3H), 7.63-7.65 (m, 2H), 7.75-7.80 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 21.2, 45.2, 108.7, 123.6 (q, *J* = 272.5 Hz), 125.8 (q, *J* = 3.7 Hz), 125.9, 127.1, 129.3, 131.9, 132.2 (q, *J* = 32.8 Hz), 137.8, 138.7, 149.8, 158.4, 169.0. IR (film): *v* 1639 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>20</sub>H<sub>18</sub>F<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 391.1092, found 391.1094.

1d: Yellow solid, isolated yield 80% (335 mg); mp: 193.5-194.5 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.38 (t, J = 6.9 Hz, 3H), 3.00 (s, 6H), 4.22 (q, J = 6.8 Hz, 2H), 6.77 (d, J = 7.3 Hz, 2H), 7.05 (s, 1H), 7.63-7.65 (m, 2H), 7.74-7.89 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 45.5, 45.2, 106.2, 122.4 (2C), 123.3, 123.6 (q, J = 280.8 Hz), 125.8 (q, J = 3.4 Hz), 127.0 (2C), 127.2, 132.2 (q, J = 32.9 Hz), 139.0, 150.4, 168.9. IR (film): v 1649 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>N<sub>3</sub>OS [M+H]<sup>+</sup>: 420.1357, found 420.1361.

**1e:** Yellow solid, isolated yield 83% (337 mg); mp: 67.8-68.4 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.38 (t, *J* = 6.9 Hz, 3H), 3.85 (s, 3H), 4.22 (q, *J* = 6.9 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.13 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.7 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 45.2, 55.3, 107.7, 114.0, 123.6 (q, *J* = 272.6 Hz), 125.8 (q, *J* = 3.7 Hz), 127.1, 127.3, 127.6, 130.9, 132.4 (q, *J* = 32.6 Hz), 138.8, 149.5, 159.5, 169.0. IR (film): *v* 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>20</sub>H<sub>18</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S [M+H]<sup>+</sup>: 407.1041, found 407.1039.

**1f:** Yellow solid, isolated yield 75% (340 mg); mp: 129.7-130.3 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 1.39 (t, J = 6.9 Hz, 3H), 4.23 (q, J = 6.9 Hz, 2H), 7.29 (s, 1H), 7.33-7.37 (m, 1H), 7.43-7.47 (m, 2H), 7.62-7.66 (m, 6H), 7.75 (d, J = 8.1 Hz, 2H), 7.97 (d, J = 8.2 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 14.1, 45.2, 109.5, 123.6 (q, J = 272.4 Hz), 125.8 (q, J = 3.6 Hz), 126.4, 126.9, 127.1, 127.3, 127.4, 128.8 (2CH), 132.3 (q, J = 33.0 Hz), 133.5, 138.7, 140.6, 149.3, 158.5, 169.1. IR (film): v 1632 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>25</sub>H<sub>20</sub>F<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 453.1248, found 453.1250.

**1g:** Red solid, isolated yield 60% (229 mg); mp: 128.5-129.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 1.37 (t, J

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= 6.9 Hz, 3H), 4.21 (q, J = 6.9 Hz, 2H), 7.10 (s, 1H), 7.35-7.37 (m, 1H), 7.47-7.48 (m, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.62-7.78 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 45.2, 109.0, 121.7, 123.6 (q, J = 272.5 Hz), 125.8, 125.8 (q, J = 3.7 Hz), 126.2, 127.1, 128.8, 132.3 (q, J = 33.0 Hz), 136.9, 138.7, 145.9, 169.1. IR (film): v 1648 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>17</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>OS<sub>2</sub> [M+H]<sup>+</sup>: 383.0500, found 383.0498.

**1h:** Red solid, isolated yield 68% (258 mg); mp: 74.4-75.2 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.33 (t, J = 6.9 Hz, 3H), 1.68-1.69 (m, 2H), 1.78-1.79 (m, 2H), 2.24 (brs, 2H), 2.40 (brs, 2H), 4.16 (q, J = 6.9 Hz, 2H), 6.72-6.76 (m, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.0, 22.3, 22.6, 25.5, 25.8, 45.1, 107.5, 123.6 (q, J = 272.5 Hz), 125.7 (q, J = 3.7 Hz), 126.3, 127.1, 128.8, 131.1, 132.2 (q, J = 32.8 Hz), 138.9, 151.5, 169.0. IR (film): v 3056 (C-H), 1670 (C=C), 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>19</sub>H<sub>20</sub>F<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 381.1248, found 381.1253.

**1i:** Yellow oil, isolated yield 65% (232 mg); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  0.93 (t, J = 7.3 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.34-1.42 (m, 2H), 1.63-1.65 (m, 2H), 2.69 (t, J = 7.3 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 6.64 (s, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  13.8, 13.9, 22.2, 31.1, 31.4, 45.0, 109.6, 123.6 (q, J = 272.5 Hz), 125.6 (q, J = 3.3 Hz), 127.1, 129.9, 132.1 (q, J = 33.0 Hz), 139.0, 152.5, 168.7. IR (film): v 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>17</sub>H<sub>20</sub>F<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 357.1248, found 357.1242.

**1**j: Yellow solid, isolated yield 54% (206 mg); mp: 60.7-61.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.30 (t, *J* = 6.9 Hz, 3H), 1.36-1.41 (m, 4H), 1.71-1.80 (m, 4H), 2.01-2.03 (m, 2H), 2.63-2.67 (m, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 6.61 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.0, 26.2, 26.3, 32.6, 40.4, 45.0, 107.9, 123.6 (q, *J* = 272.6 Hz), 125.6 (q, *J* = 3.6 Hz), 127.1, 128.8, 132.0 (q, *J* = 32.8 Hz), 139.1, 157.6, 168.8. IR (film): *v* 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>19</sub>H<sub>22</sub>F<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 383.1405, found 383.1399.

**1k:**<sup>23</sup> Yellow solid, isolated yield 68% (210 mg); mp: 163.5-164.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.38 (t, J = 6.9 Hz, 3H), 4.27 (q, J = 6.9 Hz, 2H), 7.24 (s, 1H), 7.30-7.34 (m, 1H), 7.40-7.44 (m, 2H), 7.46-7.57 (m, 5H), 7.91-7.93 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 45.2, 109.1, 126.0, 126.6, 127.8, 128.60, 128.63, 130.3, 134.7, 135.2, 149.4, 158.8, 170.6. IR (film): v 1654 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 309.1062, found 309.1056.

**11:** Yellow solid, isolated yield 55% (178 mg); mp: 113.6-114.5 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.29 (t, J = 6.9 Hz, 3H), 2.33 (s, 3H), 4.13 (brs, 2H), 7.25 (m, 1H), 7.28-7.43 (m, 7H), 7.92 (d, J = 7.7 Hz, 2H); <sup>13</sup>C NMR (100

MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  13.8, 19.1, 44.5, 109.0, 125.7, 125.9, 126.0, 127.8, 128.6, 129.7, 130.6, 134.3, 134.7, 135.1, 149.4, 158.3, 170.5. IR (film): *v* 1654 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 323.1218, found 323.1217.

**1m:** Yellow solid, isolated yield 65% (200 mg); mp: 92.8-93.5 °C; <sup>1</sup>H NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.38 (t, *J* = 6.9 Hz, 3H), 2.42 (s, 3H), 4.25 (q, *J* = 6.9 Hz, 2H), 7.24 (s, 1H), 7.30-7.36 (m, 5H), 7.40-7.44 (m, 2H), 7.93 (d, *J* = 8.1 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 21.4, 45.2, 109.1, 123.5, 126.0, 127.2, 127.8, 128.5, 128.6, 131.0, 134.8, 135.1, 138.6, 149.4, 158.9, 170.8. IR (film): *v* 1652 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 323.1218, found 323.1218.

**1n:** Yellow solid, isolated yield 84% (274 mg); mp: 90.9-91.5 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.39 (t, *J* = 6.9 Hz, 3H), 4.29 (q, *J* = 6.9 Hz, 2H), 7.15-7.20 (m, 2H), 7.25 (s, 1H), 7.31-7.34 (m, 1H), 7.40-7.44 (m, 2H), 7.53-7.57 (m, 2H), 7.91 (d, *J* = 7.4 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 45.2, 109.5, 123.6 (d, *J* = 272.4 Hz), 125.8 (d, *J* = 3.6 Hz), 126.4, 127.0, 127.1, 127.4, 132.3 (d, *J* = 33.0 Hz), 133.6, 138.7, 140.7, 149.3, 158.6, 169.1. IR (film): v 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>18</sub>H<sub>16</sub>FN<sub>2</sub>OS [M+H]<sup>+</sup>: 327.0967, found 327.0964.

**10:** Yellow solid, isolated yield 72% (247 mg); mp: 125.8-126.8 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.38 (t, J = 7.0 Hz, 3H), 4.26 (q, J = 7.0 Hz, 2H), 7.25 (s, 1H), 7.31-7.34 (m, 1H), 7.40-7.48 (m, 6H), 7.91 (d, J = 7.3 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.1, 45.3, 109.3, 126.1, 127.9, 128.3, 128.7, 129.0, 133.6, 134.6, 136.7, 149.7, 158.9, 169.5. IR (film): v 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>18</sub>H<sub>16</sub>ClN<sub>2</sub>OS [M+H]<sup>+</sup>: 343.0666, found 343.0669.

**1p:** Yellow solid, isolated yield 72% (279 mg); mp: 128.0-128.6 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.33 (t, J = 6.9 Hz, 3H), 3.85-3.90 (m, 1H), 4.41-4.45 (m, 1H), 7.25-7.44 (m, 7H), 7.66 (d, J = 7.9 Hz, 1H), 7.93 (d, J = 7.5 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  13.8, 45.6, 99.9, 109.2, 119.2, 126.0, 127.65, 127.8, 128.6, 131.0, 133.0, 134.7, 137.0, 149.5, 158.0, 168.1. IR (film): v 1647 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>18</sub>H<sub>16</sub>BrN<sub>2</sub>OS [M+H]<sup>+</sup>: 387.0163, found 387.0167.

**1q:** Yellow solid, isolated yield 64% (217 mg); mp: 77.8-78.2 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 1.39 (t, J = 6.7 Hz, 3H), 3.84 (s, 3H), 4.27 (q, J = 6.9 Hz, 2H), 7.03-7.10 (m, 3H), 7.24 (s, 1H), 7.30-7.34 (m, 1H), 7.37-7.44 (m, 3H), 7.92 (d, J = 7.5 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 14.2, 45.2, 55.4, 109.2, 112.0, 116.3, 118.7, 1256.0, 127.8, 128.6, 129.8, 134.7, 136.4, 149.5, 158.8, 159.7, 170.3. IR (film): v 1648 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>S [M+H]<sup>+</sup>: 339.1167, found 339.1160.

**1r:** Yellow solid, isolated yield 70% (269 mg); mp: 109.4-110.2 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 1.42 (t,

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J = 6.9 Hz, 3H), 4.33 (q, J = 6.9 Hz, 2H), 7.25 (s, 1H), 7.30-7.34 (m, 1H), 7.38-7.49 (m, 5H), 7.60-7.64 (m, 4H), 7.69-7.71 (m, 2H), 7.93 (d, J = 7.3 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.2, 45.3, 109.1, 126.0, 127.1, 127.3 (2CH), 127.8, 128.0, 128.6, 128.9, 133.8, 134.7, 139.9, 143.2, 149.5, 158.9, 170.4. IR (film): v 1654 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>24</sub>H<sub>21</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 385.1375, found 385.1361

**1s:** Yellow solid, isolated yield 65% (217 mg); mp: 119.8-120.4 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  1.50 (t, J = 7.0 Hz, 3H), 4.52 (q, J = 6.7 Hz, 2H), 7.04 (d, J = 15.3 Hz, 1H), 7.20 (s, 1H), 7.28-7.32 (m, 2H), 7.39-7.42 (m, 4H), 7.58-7.60 (m, 2H), 7.91-7.98 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  14.4, 42.9, 109.3, 116.0, 125.9, 127.7, 128.2, 128.5, 128.9, 130.4, 134.6, 134.7, 145.9, 149.2, 159.0, 165.1. IR (film): v 3127 (C-H), 1649 (C=C), 1616 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>20</sub>H<sub>19</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 335.1218, found 335.1213.

1t: Yellow solid, isolated yield 52% (142 mg); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 0.99-1.03 (m, 2H), 1.22-1.26 (m, 2H), 1.51 (t, J = 7.0 Hz, 3H), 2.01-2.07 (m, 1H), 4.56 (q, J = 6.9 Hz, 2H), 7.15 (s, 1H), 7.29-7.32 (m, 1H), 7.39-7.43 (m, 2H), 7.91 (d, J = 7.4 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 9.3, 12.4, 14.1, 43.0, 108.7, 126.0, 127.7, 128.6, 129.3, 134.9, 149.3, 172.9. IR (film): v 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 273.1062, found 273.1051.

**1u:**<sup>17a</sup> Yellow solid, isolated yield 62% (182 mg); mp: 82.3-83.0 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  3.76 (s, 3H), 7.26 (d, J = 2.8 Hz, 1H), 7.31-7.34 (m, 1H), 7.41-7.44 (m, 2H), 7.50-7.53 (m, 3H), 7.57-7.59 (m, 2H), 7.93 (d, J = 7.4 Hz, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  38.4, 109.2, 126.1, 127.6, 127.9, 128.6, 128.7, 130.9, 134.7, 134.8, 149.5, 160.1, 170.4. IR (film):  $\nu$  1652 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 295.0905, found 295.0900.

**1v:**<sup>24</sup> Yellow solid, isolated yield 73% (225 mg); mp: 73.1-73.9 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  3.76 (s, 3H), 7.16-7.20 (m, 2H), 7.25 (s, 1H), 7.30-7.34 (m, 1H), 7.40-7.44 (m, 2H), 7.59-7.62 (m, 2H), 7.92 (d, *J* = 7.4 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  38.5, 109.2, 115.8 (d, *J* = 22.0 Hz), 126.0, 127.9, 128.7, 130.1 (d, *J* = 8.8 Hz), 130.7, 134.6, 149.5, 160.0, 164.1 (d, *J* = 252.0 Hz), 169.3. IR (film): *v* 1658 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>17</sub>H<sub>14</sub>FN<sub>2</sub>OS [M+H]<sup>+</sup>: 313.0811, found 313.0806.

1w: Yellow solid, isolated yield 64% from R = <sup>t</sup>Bu (276 mg), 54% from R = <sup>t</sup>Oct (233 mg); mp: 48.5-49.4 °C; <sup>1</sup>H
NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 0.83 (t, J = 6.5 Hz, 3H), 1.21-1.26 (m, 6H), 1.78-1.81 (m, 2H), 4.16 (t, J = 7.2 Hz, 2H), 7.26 (s, 1H), 7.31-7.35 (m, 1H), 7.41-7.44 (m, 2H), 7.65 (d, J = 7.9 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 7.9 Hz), 7.9

 7.6 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  13.9, 22.4, 26.2, 28.3, 30.2, 50.0, 109.4, 123.6 (q, *J* = 272.7 Hz), 125.7 (q, *J* = 3.3 Hz), 126.0, 127.3, 127.9, 128.7, 132.7 (q, *J* = 33.0 Hz), 134.5, 138.7, 149.6, 158.8, 169.2. IR (film): *v* 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>23</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 433.1561, found 433.1550.

**1x:** Yellow solid, isolated yield 61% (286 mg); mp: 105.4-106.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  3.82 (s, 3H), 5.47 (s, 2H), 6.89-6.97 (m, 2H), 7.09-7.13 (m, 3H), 7.23-7.26 (m, 3H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.7 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  52.9, 55.3, 108.0, 114.0, 123.5 (q, *J* = 273.6 Hz), 125.5 (q, *J* = 3.8 Hz), 126.8, 127.3, 127.4, 127.5, 127.6, 128.6 (2CH), 132.4 (q, *J* = 32.7 Hz), 136.8, 138.3, 149.5, 159.5, 169.5. IR (film): *v* 1653 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>25</sub>H<sub>20</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S [M+H]<sup>+</sup>: 469.1198, found 469.1194.

**1y:** Yellow solid, isolated yield 73% (320 mg); mp: 117.7-118.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  5.48 (s, 2H), 7.08-7.10 (m, 2H), 7.23-7.31 (m, 5H), 7.35-7.39 (m, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 7.4 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si):  $\delta$  53.0, 109.7, 123.5 (q, J = 272.5 Hz), 125.6 (q, J = 3.6 Hz), 126.0, 126.8, 127.5, 127.6, 128.0, 128.6 (2CH), 129.1, 132.4 (q, J = 32.1 Hz), 134.3, 136.7, 138.2, 149.7, 169.5. IR (film):  $\nu$  1666 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>24</sub>H<sub>18</sub>F<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 439.1092, found 439.1087.

**1z:** Red oil, isolated yield 61% (216 mg); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 0.83-0.88 (m, 3H), 1.24-1.31 (m, 2H), 1.76-1.81 (m, 2H), 4.21-4.26 (m, 2H), 7.15-7.21 (m, 1H), 7.25-7.27 (m, 1H), 7.32-7.36 (m, 1H), 7.41-7.46 (m, 2H), 7.53-7.58 (m, 2H), 7.70-7.75 (m, 1H), 7.90-7.93 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 13.6, 19.9, 30.5, 49.9, 109.2, 115.8 (d, J = 22.0 Hz), 126.0, 127.9, 128.5 (d, J = 12.5 Hz), 128.7, 129.4 (d, J = 8.6 Hz), , 131.4 (d, J = 27.4 Hz), 132.3 (d, J = 10.7Hz), 134.6, 1149.6, 159.3, 163.8 (d, J = 255.1 Hz), 169.8. IR (film): v 1654 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>20</sub>H<sub>20</sub>FN<sub>2</sub>OS [M+H]<sup>+</sup>: 355.1275, found 355.1284.

**Deuterium Labeling Study:** In a 25 mL of flask, 4-(trifluoromethyl)benzoyl chloride (1 mmol, 208 mg) was added to deuterated *N-tert*-butyl-*N'-non*-hexyl carbodiimide (1 mmol, 191 mg) in THF (10 mL), and the mixture was stirred at room temperature for 48 h. In another 25 mL of flask, *n*-BuLi (1 mmol, 1.6 M in hexane) was added dropwise at -78 °C to a stirred solution of phenylacetylene (1 mmol, 102 mg) in THF (5 mL). After stirring at -78 °C for 0.5 h, sulfur (1 mmol, 32 mg) was added and the reaction mixture was allowed to warm to room temperature for 2 h. The above two reaction solutions were mixed into one flask, which was allowed to heat up to 80 °C for 12 h in THF. The solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give the deuterated 2-aminothiazole **1w-D**.

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**1w-D:** Yellow solid, isolated yield 61% (264 mg); mp: 80.5-81.2 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 0.83 (t, J = 6.4 Hz, 3H), 1.21-1.26 (m, 6H), 1.77-1.81 (m, 2H), 4.16 (t, J = 7.2 Hz, 2H), 7.31-7.34 (m, 1H), 7.40-7.44 (m, 2H), 7.64 (d, J = 7.7 Hz, 2H), 7.75 (d, J = 7.7 Hz, 2H), 7.89-7.91 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si): δ 13.9, 22.4, 26.2, 28.3, 31.1, 50.0, 109.4, 123.6 (q, J = 270.9 Hz), 125.7 (q, J = 3.6 Hz), 126.0, 127.4, 128.0, 128.7, 132.4 (q, J = 32.7 Hz), 134.6, 138.7, 149.7, 158.9, 169.2. IR (film): v 1655 (C=O) cm<sup>-1</sup>; HRMS calcd. for C<sub>23</sub>H<sub>23</sub>DF<sub>3</sub>N<sub>2</sub>OS [M+H]<sup>+</sup>: 434.1624, found 434.1621.

2,4,4-Trimethylpent-1-ene Detected by GC-MS Analyses: In a 25 mL of flask, 4-fluorobenzoyl chloride (1 mmol, 158 mg) was added to *N-tert*-octyl-*N'-non*-butyl carbodiimide (1 mmol, 210 mg) in THF (10 mL), and the mixture was stirred at room temperature for 48 h. In another 25 mL of flask, *n*-BuLi (1 mmol, 1.6 M in hexane) was added dropwise at -78 °C to a stirred solution of phenylacetylene (1 mmol, 102 mg) in THF (5 mL). After stirring at -78 °C for 0.5 h, sulfur (1 mmol, 32 mg) was added and the reaction mixture was allowed to warm to room temperature for 2 h. The above two reaction solutions were mixed into one flask, which was allowed to heat up to 80 °C for 12 h in THF. Then, 200 µL of the reaction mixture was taken using a syringe and GC-MS analyse was carried out. GC-MS analyses were performed on a gas chromatograph coupled to MS detector (EI, quadrupole mass spectrometer, diffusion pump; 1100 ChemStation). GC-MS conditions were as follows: 30 m × 0.25 mm i.d. fused silica capillary column with 0.25 µm film thickness and a carrier gas of helium (8.8 psi) with total flow rate of 23.9 mL/min were used; initial temperature was 40 °C; temperature increased at 30 °C/min up to 300 °C; injector and detector temperatures were 250 °C.

**Isolation and Reaction of** *N***-Acyl Cyanamide:** In a 25 mL of flask, cyclohexanecarbonyl chloride (1 mmol, 146 mg) was added with stirring to *N*-*tert*-butyl-*N*'-ethyl carbodiimide (1 mmol, 126 mg) in THF (10 mL) at room temperature. After 72 h, the reaction mixture was concentrated in vacuum to give *N*-acyl cyanamide **2**. No reaction between **2** and lithium alkynethiolate was observed. This result illustrated that <sup>*t*</sup>Bu and chloride atom in *N*-acyl chloroformamidine were not be released before the reaction, and the C–N bond cleavage takes place after nucleophilic attack of lithium alkynethiolate on *N*-acyl chloroformamidine. So it ruled out the possibility of pathways *III*.

**2:** Yellow oil, isolated yield 44% (79 mg); <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  0.22-0.28 (m, 3H), 0.40-0.48 (m, 2H), 0.73-0.82 (m, 4H), 0.90-0.95 (m, 2H), 1.13-1.17 (m, 2H), 2.05-2.14 (m, 1H), 2.49-2.57 (m, 2H); <sup>13</sup>C NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  12.7, 25.2, 25.7, 29.1, 41.1, 42.9, 110.5, 174.5. HRMS calcd. for C<sub>10</sub>H<sub>17</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 181.1341, found **ACS Paragon Plus Environment** 

# 181.1333.

**Computational Methods:** All calculations were carried out with the GAUSSIAN 03 program package.<sup>25</sup> All the minima and transition states were fully optimized at the B3LYP level<sup>26</sup> using the 6-31G(d) basis set. Harmonic frequency calculations were performed at the same level for every structure to confirm it as a local minimum or transition state and to derive the thermochemical corrections for enthalpies and free energies. The intrinsic reaction coordinate (IRC) analysis<sup>27</sup> was carried out throughout the pathways to confirm that all stationary points are smoothly connected to each other. Solvent effects in THF ( $\varepsilon = 7.58$ ) were evalulated by single point calculations using the PCM model<sup>28</sup> for all the stationary points. All enthalpies and the Gibbs free energies in the text were given in kcal/mol and calculated for standard conditions (298 K, 1 atm). All distances were given in Å.

X-ray Crystallographic Studies: Single crystals of 1a suitable for X-ray analysis were grown in CH<sub>2</sub>Cl<sub>2</sub>/hexane at room temperature for 3 days. Data collections for 1a were performed at 20 °C on an IP diffractometer, using graphitemonochromated Mo K $\alpha$  radiation ( $\lambda = 0.71073$  Å). The determination of crystal class and unit cell parameters was carried out by Rapid-AUTO program package for 1a. The raw frame data was processed using Crystal Structure for 1a to yield the reflection data file. The structure of 1a was solved by use of SHELXTL program. Refinement was performed on  $F^2$  anisotropically for all the non-hydrogen atoms by the full-matrix least-squares method. The hydrogen atoms were placed at the calculated positions and were included in the structure calculation without further refinement of the parameters. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-929572(1a). Copies of these data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

# ASSOCIATED CONTENT

# **Supporting Information**

X-ray data for **1a**, scanned NMR spectra of all new products, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org

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# Notes

The authors declare no competing financial interest.

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