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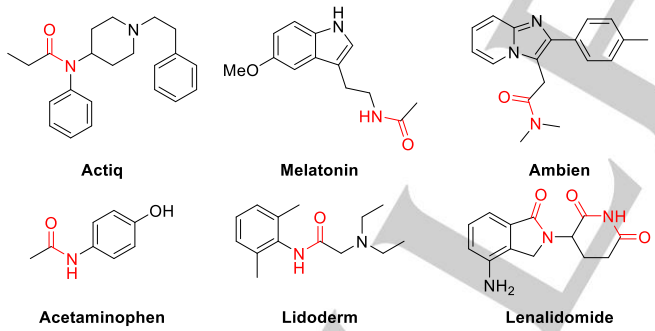
Amide Synthesis from Thiocarboxylic Acids and Amines by Spontaneous Reaction and Electrosynthesis

Li Tang, [a] Jack H. Matuska,[b] Yu-Han Huang, [a] Yan-Hong He,* [a] and Zhi Guan*[a]

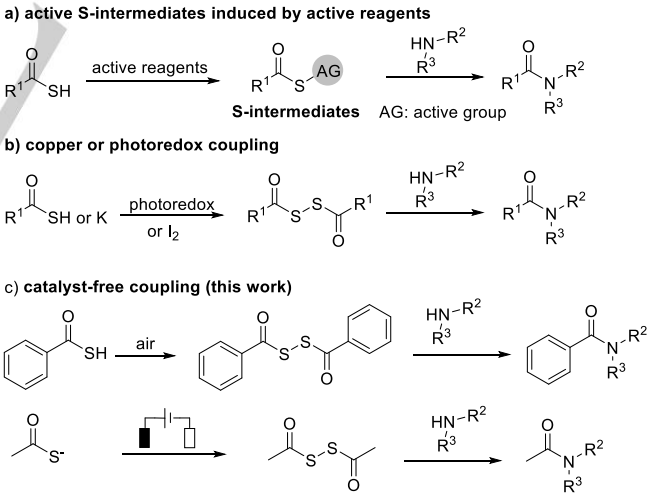
Abstract: Amide bond formation is one of the most important basic reactions in chemistry. A catalyst free approach for constructing amide bonds from thiocarboxylic acids and amines has been developed. The mechanistic studies showed that the disulfide is the key intermediate for this amide synthesis. Thiobenzoic acids can be automatically oxidized to disulfides in air, while thioaliphatic acids can be electrooxidized to disulfides, and the resulting disulfides react with amines to give the corresponding amides. By this method, various amides can be easily synthesized in excellent yields without using any catalyst and activator. The successful synthesis of bioactive compounds also highlights the synthetic utility of this strategy in medicinal chemistry.

The amide bond is not only the essential backbone of certain natural products (e.g., peptides, proteins, and chitins), but also one of the most important functional groups in organic compounds (e.g., catalysts, pharmaceuticals, agrochemicals, and materials).[1] A 2006 survey showed that the amide bond was present in 2/3 of drug candidates,[2] and in the newly approved drugs of 2017, 60% of the drugs were found to contain amide bonds.[3] The amide bond is a vital motif of some top selling drugs such as Actiq, Melatonin, Ambien, Acetaminophen, Lidoderm, and Lenalidomide (**Scheme 1**). Therefore, the development of versatile strategies for the formation of amide bonds is one of the main objectives of organic chemistry.



Scheme 1. Top selling amide bond-containing drugs.

Thioacids as acyl sources to form amide bonds under mild conditions have drawn increased attention from organic chemists in the last decade.[4] So far, there are two main strategies for the formation of amide bonds from thioacids. One is that thioacids react with some chemical reagents such as Sanger reagents & Mukaiyama reagents,[5] oganoisonitriles,[6] Cu(II)-reagents,[7] Carbon disulphide,[8] organonitrite,[9] and nanocatalyst[10] to form more reactive thio-intermediates, which can react with amines to give the amides (**Scheme 2, a**). The other one is that thioacids can be converted to disulfides, which can be nucleophilically substituted by amines to form corresponding amides.[11-13] Methods for converting thioacids to disulfides have been reported by several research groups. Gopi's group used I_2 as a mediator to form disulfides.[11] Tan's group developed a photo-oxidation process using $Ru(bpy)_3Cl_2$ as a photocatalyst to obtain disulfides from potassium thioacids .[12] Biswas's group reported that CdS nanoparticles can act as a heterogeneous photocatalyst to catalyze the formation of disulfides form thioacids [13] (**Scheme 2, b**). While these reported strategies are effective, they have some drawbacks, such as the use of toxic reagents, metals or expensive catalysts. Therefore, it is necessary to develop more sustainable and greener approaches for amide bond formation from thioacids to avoid extra reagents such as catalysts, activating reagents or toxic solvents.[14]



Scheme 2. The approaches for activing thioacids to form amides.

We found that in the absence of any catalyst or activating reagent, the reaction of thiobenzoic acid with amines in air atmosphere can produce corresponding benzamides in excellent yields. However, the performance of thioaliphatic acids is not as good as thiobenzoic acid under the same conditions. Our mechanistic studies showed that disulfide is the key intermediate in this process. It has been reported that potassium thioacid can be oxidized to disulfide by photo-oxidation.[12] Thus, we

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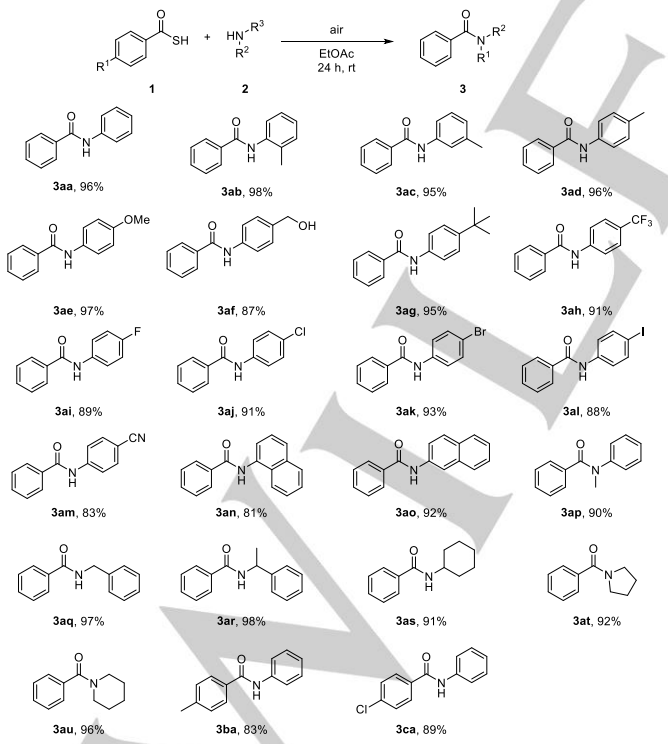
hypothesized that potassium thioacids may also be electro-oxidized to thio-radicals, which can form disulfides by self-coupling. Organic electrosynthesis has several advantages, such as the use of electrical current as an inexpensive, renewable, and inherently safe reagent. Therefore, this method has attracted more and more attention from organic chemists.[15] Kärkäs provided an overview on the C-N bond formation by anodic electrochemical methods.[16] Lei's group reported the electro-oxidative S-H/S-H crossing-coupling to construct the disulfides without oxidants or catalysts.[17] Bunge obtained the disulfides by electrolyzing thiocarboxylic acid.[18] Although the above results showed the possibility of our hypothesis, there are some challenges of electrosynthesis of amides. Waldvogel group reported that amides could be transformed to amidyl radicals by electro-oxidation which were able to process various reactions.[19] This indicates that the electrolysis of products must be avoided during the amide electrosynthesis. To verify our idea, potassium thioacetate and amines were subjected to constant-current electrolysis in an undivided cell, and after optimization of the reaction conditions, the corresponding amides were obtained in excellent yields. Therefore, a catalyst-free synthetic methodology for constructing amide bonds from thioacids was developed. The key step in this process is the formation of disulfides. Thiobenzoic acids can be automatically oxidized to disulfides in air, while thioaliphatic acids can be electrooxidized to disulfides, and the resulting disulfides react with amines to give the corresponding amides (**Scheme 2, c**). Herein, we report this environmentally friendly, high-yield, easy-to-implement amide bond synthesis method.



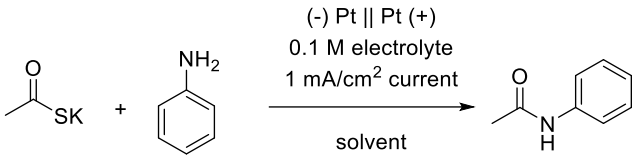
Scheme 3. Substrate scope for spontaneous reaction to form benzamides. Reaction conditions: **1** (1.0 mmol) and **2** (0.5 mmol) in 5 mL of EtOAc stirred under air at rt for 24 h. Isolated yields.[a]

Encouraged by our discovery that in the absence of any catalyst or activating reagent, the reaction of thiobenzoic acid **1a** with aniline **2a** can get the product **3aa** in an excellent yield of 96% under air atmosphere in ethyl acetate (EtOAc) with molar ratio of **1a**:**2a** = 2:1 (for the optimization of molar ratio of **1a** to **2a**, see the Supporting Information (SI), **Table S1**, entries 1-3), we further optimized this reaction. Firstly, several common solvents were screened (SI, **Table S1**, entries 4-7) and it was found that solvent strongly influences yield of **3aa**. The reaction in tetrahydrofuran (THF) gave almost the same yield (95%) as in EtOAc. Considering that EtOAc is cheaper and safer than THF (THF can form peroxides in air), EtOAc was chosen as the optimal solvent for the reaction. To our surprise, the reaction in MeCN, CH_2Cl_2 and EtOH gave very low yields. In order to understand the effect of the solvent on the reaction, we investigated the effects of the different solvents on the disulfide formation step and the step of forming the amide from the disulfide and aniline, respectively. It was found that solvents have a great influence on the formation of disulfide by air oxidation of **1a**. The yields of disulfide (after 24 h) in EtOAc and THF were much better than in CH_3CN, CH_2Cl_2 and EtOH (SI, **Table S2**). THF was slightly more efficient than EtOAc, probably because a portion of THF forms peroxides in air which promote the oxidation of **1a**. For the step of forming amide **3aa** from the disulfide and aniline **2a**, the reaction can be carried out with high yields in almost all of the tested solvents in a relatively short time (5 h) (SI, **Table S3**). Therefore, we speculate that the spontaneous reaction in EtOAc and THF gave good yields, probably because they facilitate the formation of the disulfide under air. Next, we investigated the effect of reaction time on the spontaneous reaction (SI, **Table S4**). It was found that as the reaction time increased from 6 h to 24 h, the yield of **3aa** increased from 55% to 96%. We tried to speed up the reaction by improving the contact between air and solution. The reaction was carried out under continuous air bubbling and 1 mL EtOAc was added every 2 h at rt, which gave **3aa** in 79% yield after 6 h. Although the bubbling method can increase the reaction rate, we did not choose it due to the rapid evaporation of the solvent and the odor of the reactants.

We then tested the generality of the spontaneous reaction in EtOAc (**Scheme 3**). Firstly, an array of amines were examined. There was no significant difference between the performance of *ortho*-Me-, *meta*-Me- and *para*-Me-substituted anilines, and they all gave the amides in excellent yields (**3ab** – **3ad**). The anilines with electron-rich groups (**3ae** and **3ag**) and electron-deficient groups (**3ah**, **3ai**, **3aj** and **3am**) could all be converted into the corresponding amides in good to excellent yields. In general, the former could achieve better yields than the latter, which is consistent with the electronic effect of nucleophiles. It is important to mention that the reaction is chemoselective between alcohol and amine (**3af**). The naphthylamines (**3an** and **3ao**) also worked well in this reaction scheme. The slightly lower yield offered by 1-aminonaphthalene compared to 2-aminonaphthalene may be due to steric hindrance effects. The secondary aromatic amine (**3ap**) also participated well in the reaction, but the yield was slightly lower compared to the primary aromatic amine, probably due to steric hindrance. Benzylamine (**3aq** and **3ar**), alkyl primary amine (**3as**) and alkyl secondary amines such as pyrrolidine (**3at**) and piperidine (**3au**) could also effectively participate in the reaction to

give the corresponding amides in excellent yields. This spontaneous reaction could also occur with the electron-donating group and the electron-withdrawing group substituted thiobenzoic acids, leading to the corresponding amides **3ba** and **3ca** in good yields.

Table 1. Optimization of reaction conditions for synthesis of amide by electrooxidation.[a]



4a **2a** **5aa**

entry	electrolyte	solvent	yield (%)[b]
1	nBu$_4$NBF$_4$	MeCN	63
2	nBu$_4$NPF$_6$	MeCN	57
3	nBu$_4$NTs	MeCN	29
4	nBu$_4$NAc	MeCN	84
5	LiClO$_4$	MeCN	20
6	NaBF$_4$	MeCN	57
7	KCl	MeCN	57
8	nBu$_4$NBF$_4$	DCM	46
9	nBu$_4$NBF$_4$	acetone	48
10	nBu$_4$NBF$_4$	THF	63
11	nBu$_4$NBF$_4$	EtOAc	97
12	--	EtOAc	N.R.
13[c]	nBu$_4$NBF$_4$	EtOAc	83
14[d]	nBu$_4$NBF$_4$	EtOAc	trace

[a] Unless otherwise noted, reaction conditions: **4a** (1.0 mmol), **2a** (0.5 mmol), electrolyte (0.1 M) in solvent (5.0 mL), Pt (1.0 × 1.0 cm^2) anode and cathode, undivided cell, J = 1.0 mA/cm^2, total charge: 1.8 F/mol (24 h), rt; [b] isolated yield; [c] J = 2.0 mA/cm^2, total charge: 1.8 F/mol (12 h); [d] J = 0 mA/cm^2, 24 h.

When aliphatic thiocarboxylic acids were used in this spontaneous reaction, the reaction efficiency was not satisfactory, and the amides were obtained only in low yields (As an example, see SI, **Table S6**, entry 1). Therefore, we attempted to use electrooxidation to promote the synthesis of amides from aliphatic thiocarboxylic acids. We first investigated the reaction between potassium thioacetate **4a** and aniline **2a**. In our initial investigation, we used MeCN as a solvent to set the reaction at a high current density of 10 mA/cm^2 for total charge 1.8 F/mol, but only trace of the desired amide was detected by TLC, and many side reactions occurred. Thus, we set the reaction at a low current density to optimize the reaction conditions. Utilizing nBu$_4$NBF$_4$ as the electrolyte and MeCN as the solvent, acetanilide **5aa** could be obtained in a 63% yield under 1 mA/cm^2 constant current density in an undivided cell for 24 h (1.8 F/mol of charge) (**Table 1**, entry 1). Encouraged by this result, several other electrolytes were examined (**Table 1**, entries 2-7). A good yield was obtained using nBu$_4$NAc (**Table 1**, entry 4), but it also can give a good yield when no acyl source was involved. None of the other electrolytes achieved the yield observed with nBu$_4$NBF$_4$. The electrosynthesis with aqueous electrolyte (KCl) in MeCN was also tested, which gave 57% yield (**Table 1**, entry 7). Next, other commonly used solvents were also screened (**Table 1**, entries 8-11), and the yield was significantly increased to 97% when EtOAc was used as the solvent (**Table 1**, entry 11). There was no reaction without the electrolyte because the conductivity of the solution was not high enough for our equipment (**Table 1**, entry 12). When the current density was increased to 2 mA/cm^2, the yield was reduced to 83% (**Table 1**, entry 13), indicating that increasing the current density was detrimental to the reaction. When the reaction was carried out under the same conditions except that there was no electricity, only a trace amount of product was detected by TLC (**Table 1**, entry 14). In addition, the effect of the molar ratio of **4a** to **2a** on the reaction was also investigated, and **4a**:**2a** = 2:1 was found to be the optimum ratio (**SI**, **Table S5**). After determining the optimal reaction conditions (**Table 1**, entry 11), we examined the generality of the amine component in the reaction with potassium thioacetate as an acyl source (**Scheme 4)**. Firstly, the *ortho*-Me-, *meta*-Me-, and *para*-Me-substituted anilines were tested, and the corresponding *N*-phenylacetamides **5ab** – **5ad** were obtained in good to excellent yields. Notably, the yield of the *ortho*-Me-substituted product **5ab** was relatively low possibly due to steric hindrance. The reaction using 4-methoxyaniline as the amine reagent produced the product **5ae** in an excellent yield. Next, the different halogenated anilines were examined, and the corresponding products **5af** – **5ai** were obtained in good yields. To verify the influence of electronic effect on the reaction, the electron-withdrawing group -CF$_3$ and electron-donating group *tert*-butyl substituted anilines were tested. It was found that electron-rich aniline gave better yield than electron-deficient aniline (**5aj** and **5ak**), and this phenomenon can also be seen from **5ad**-**5af**. This may be due to the stronger nucleophilicity of the electron-rich anilines, which makes them easier to nucleophilically attack the intermediate disulfides to form the corresponding amides. Secondary amines were also suitable for this reaction, but with low yields (**5al** and **5am**), probably due to steric hindrance and the oxidation of a portion of the secondary amine to the imine,[20] which was observed when we prepared **5am**. Besides, the benzylamine was also compatible with the reaction to give a satisfactory yield (**5an**).

Next, we investigated this electro-oxidization reaction using aliphatic thiocarboxylic acids as the acyl source. Although the yiled is not good for direct andoic oxidation of acetic thioacid (**Table S6**, entry 2),[18] it was found that, based on the electrooxidation conditions used for potassium thioacetate, the addition of triethylamine allows the direct use of thioacetic acids as the acyl source to give amides in excellent yields (for the optimization of the reaction using thioacetic acid as the acyl source, see **SI, Table S6**). We then tested the suitability of the reaction for different alkyl thiocarboxylic acids and we were pleased to find that the corresponding amides (**Scheme 4, 5ba** - **5fa**) were obtained in excellent yields.

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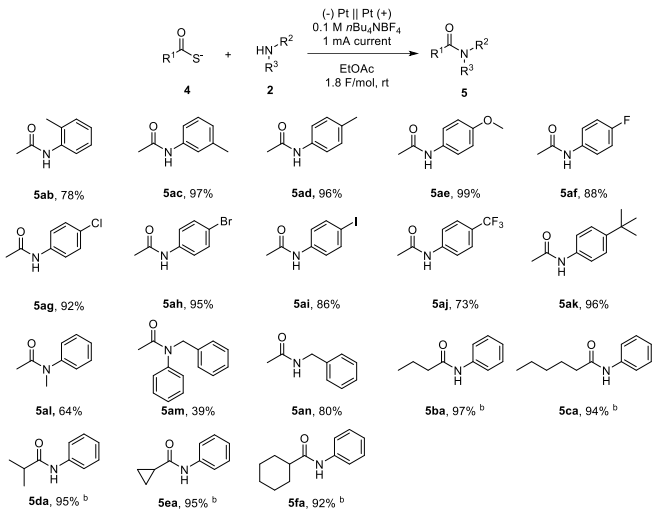
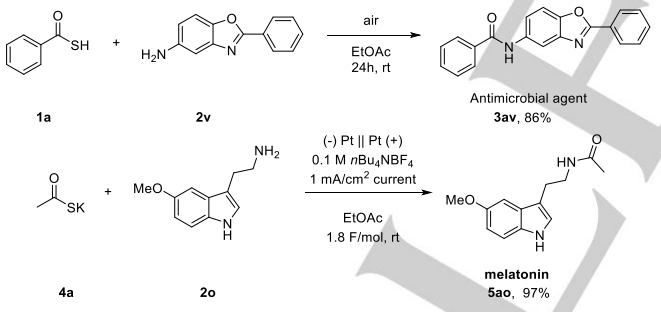
Overall, both spontaneous reactions and electrosynthesis were relatively clean and there were no significant organic by-products. Most amines are completely converted to amides due to the use of 2 equivalents of thioacids. Excess thioacids remained as unconverted and disulfides.



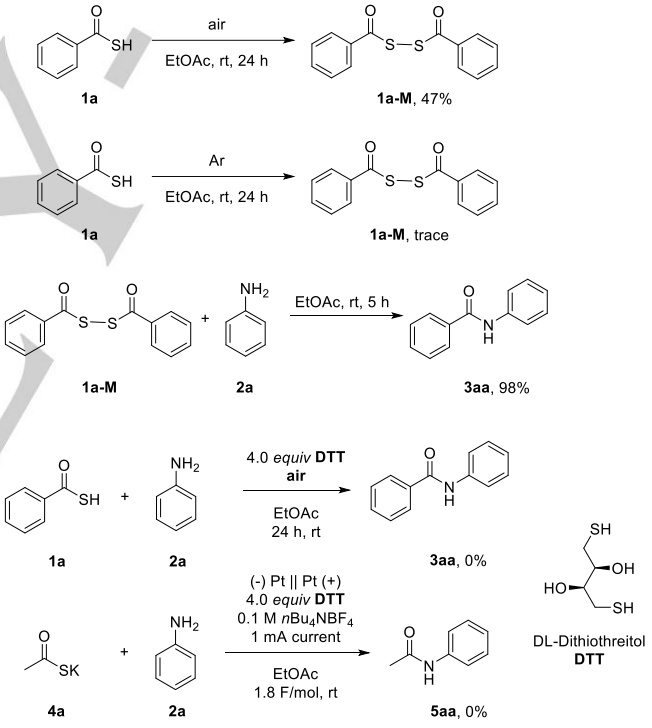
Scheme 4. Substrate scope for the synthesis of amides by electrooxidation**.** Reaction conditions: [a] Unless otherwise noted, reaction conditions: **4** (1.0 mmol), **2** (0.5 mmol), nBu$_4$NBF$_4$ (0.1 M) in EtOAc (5.0 mL), Pt (1.0 × 1.0 cm^2) anode and cathode, undivided cell, J = 1.0 mA/cm^2, total charge: 1.8 F/mol (24 h), rt. Isolated yields; [b] **4-SH** (1.0 mmol), **2a** (0.5 mmol), triethylamine (1.0 mmol), nBu$_4$NBF$_4$ (0.1 M) in EtOAc (5.0 mL), Pt (1.0 × 1.0 cm^2) anode and cathode, undivided cell, J = 1.0 mA/cm^2, total charge: 1.8 F/mol (24 h), rt.



Scheme 5. Applications in medicinal chemistry.

In order to demonstrate the utility of these amide synthesis methods in medicinal chemistry, we readily constructed the amide bond of the antimicrobial agent **3av**[21] in 86% yield by spontaneous reaction using thiobenzoic acid as the acyl source (**Scheme 5**). We also used potassium thioacetate as the acyl source to successfully construct the amide bond of melatonin **5ao** in 97% yield by electrooxidation (**Scheme 5**). Melatonin is a hormone produced by the pineal gland in humans and animals to regulate sleep and wakefulness.[22] It can also be used as a medicine to treat insomnia.

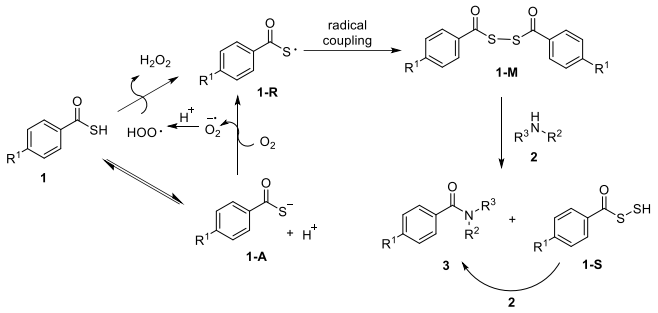
In order to gain insight into the mechanism for the preparation of amides from thiocarboxylic acids and amines by spontaneous and electrosynthetic methods, a series of control experiments were conducted (**Scheme 6**). Firstly, thiobenzoic acid **1a** was stirred in EtOAc under an air atmosphere for 24 h to give the disulfide **1a-M** in 47% yield, but only a trace amount of **1a-M** was detected by TLC when the reaction was carried out under argon. Then, the **1a-M** was used to mix with aniline **2a** in EtOAc and stirred for 5 h to afford N-phenylbenzamide **3aa** in an excellent yield of 98%. These results indicated that thiobenzoic acid **1a** can be automatically oxidized to disulfide in air, and the disulfide can spontaneously react with amine to form amide. To verify whether the disulfide is an essential intermediate for this spontaneous reaction, 4.0 equivalent of disulfide reducing agent, DL-dithiothreitol (DTT) was added to the reaction system of **1a** and **2a** under standard conditions, and no product was detected. Similarly, for the electrosynthesis reaction of **4a** and **2a**, no product was obtained in the presence of DTT (**Scheme 6**). The results of these control experiments indicated that the formation of disulfide intermediates is critical for both spontaneous and electrosynthetic reactions.



Scheme 6. Mechanism study experiments.

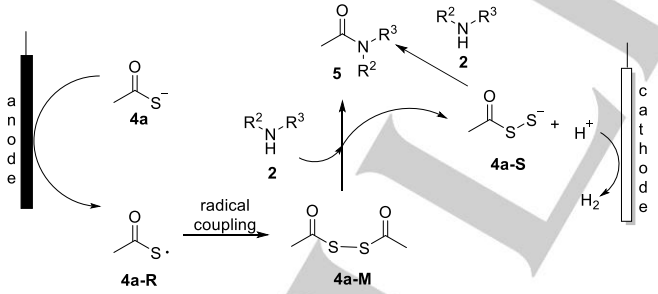
Finally, on the basis of the above control experiments and previous reports,[12,13] plausible mechanisms are proposed for the formation of amide bonds by spontaneous and electrosynthetic reactions. In the process of spontaneous reaction (**Scheme 7**), the ionization equilibrium of thiobenzoic acid **1** in EtOAc results in the presence of thiobenzoate anion **1-A** and proton. **1-A** can be single electron oxidized by oxygen leading to the benzoylthio radical **1-R** and superoxide anion radical $O_2^{\bullet-}$. $O_2^{\bullet-}$ combines with a proton to form a peroxy radical HOO•, and then the hydrogen atom transfer (HAT) between HOO• and thiobenzoic acid **1**

produces another benzoylthio radical **1-R**. Next, the self-coupling of **1-R** forms the disulfide **1-M.** The nucleophilic addition/elimination of amine **2** with **1-M** to give the desired product amide **3** and the intermediate **1-S**. **1-S** can be further subjected to aminolysis to give **3**, which can be supported by the experimental results, since the reaction of equal equivalent of **1a** and **2a** gave amide **3aa** in a yield of 63% (SI, **Table S1**, entry 1).



Scheme 7. A possible mechanism for the spontaneous reaction.

For the process of forming amides by electrosynthesis (**Scheme 8**), potassium thioacetate **4a** (E_{ox} = +0.33 V vs SCE in MeCN) (SI, **Figure S1**) is electron-oxidized to the acetylthio radical **4a-R** by anode. The radical coupling of **4a-R** forms the disulfide **4a-M**, which reacts with amine **2** (E_{ox} = +1.15 V vs SCE in MeCN) (SI, **Figure S1**) to afford acetyl amide **5** and intermediate **4a-S**. The experimental fact that the reaction of equal equivalent of **4a** and **2a** gave amide **5aa** in a yield of 66% (SI, **Table S5**) indicted that the desired product **5** can also be produced by the aminolysis of **4a-S**[12]. The proton from aminolysis can be reduced by cathode to form H_2.



Scheme 8. A possible mechanism for the electrosynthesis.

In the mechanisms proposed above, the formation of acylthio radicals is a critical step. Structurally, the benzoylthio radical **1-R** (**Scheme 7**) is more stable than acetylthio radical **4a-R** (**Scheme 8**), which means that **1-R** is easier to form than **4a-R**. Thus, we speculate that under our reaction conditions, **1-R** can be easily produced by auto-oxidation of thiobenzoic acids **1**, while the formation of **4a-R** in high yields requires electrooxidation of thioacetate **4a**. This speculation can explain the experimental results of synthesizing amide from thiobenzoic acids and thioaliphatic acids by spontaneous reaction and electrosynthesis, respectively.

In summary, we have developed a mild catalyst-free amide bond forming strategy by using various thiocarboxylic acids as the acyl source. The reaction is proposed to proceed through a disulfide intermediate that reacts with an amine to provide an amide. It is noteworthy that in the presence of air, the reaction of thiobenzoic acids with various amines can occur spontaneously, while the reaction of thioaliphatic acids with amines can be easily carried out by electrosynthesis. By this method, various amides can be readily synthesized in excellent yields without using any catalyst and activator. The successful synthesis of bioactive compounds also highlights the synthetic utility of this strategy in medicinal chemistry.

Acknowledgements

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Keywords: catalyst free • electrosynthesis • amide bond • thiocarboxylic acids • disulfide

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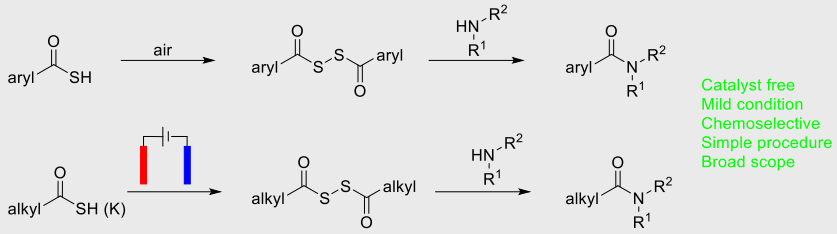

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Amide Synthesis from Thiocarboxylic Acids and Amines by Spontaneous Reaction and Electrosynthesis

A catalyst-free approach for constructing amide bonds from thiocarboxylic acids and amines has been developed.