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Mohamed Elagawany, Lamees Hegazy, Bahaa Elgendy

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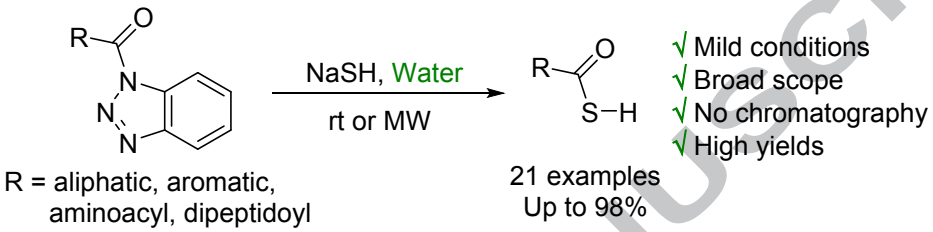

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Catalyst- and Organic Solvent-Free Synthesis of Thioacids in Water

Mohamed Elagawany [a,b,c], Lamees Hegazy [a,b], and Bahaa Elgendy [a,b,d,*]

[a]Department of Pharmaceutical and Administrative Sciences St. Louis College of Pharmacy, St. Louis, MO 63110, USA
[b]Center for Clinical Pharmacology, Washington University School of Medicine and St. Louis College of Pharmacy, St. Louis, MO 63110, USA
[c]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Damanhour University, Damanhour, Egypt
[d]Chemistry Department, Faculty of Science, Benha University, Benha 13518, Egypt

* Corresponding author. Tel.: +1-314-446-8336; fax: +1-314-446-8136; e-mail: belgendy@wustl.edu

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ABSTRACT

Thioacids and thioamino acids were synthesized in excellent yields from readily available acyl benzotriazoles and sodium hydrosulfide in water at room temperature. The new methodology features mild reaction conditions, high yields, short reaction times, and does not involve the use of organic solvents or bases. The reaction is eco-friendly, and the workup procedure is simple and does not require chromatographic separation.

1. Introduction

Thioacids are carboxylic acid analogues and they represent an important class of organic compounds. They possess higher solubility, acidity and nucleophilicity than their corresponding carboxylic acids. Thioacids are of considerable interest in medicinal chemistry and have been used widely in the synthesis of interesting chemical scaffolds. Thioacids react with azides,[1-4] isonitriles,[5-6] amines,[7] and aziridines,[8-9] to facilitate the synthesis of some of the most challenging amides and peptides. Upon trace level of oxidative activation, thioacids can serve as excellent acyl donors and form amide bonds quiet easily with N-terminal peptides.[10] In peptide chemistry, C-terminal thioacids are important precursors in thio-formimidate carboxylate mixed anhydride (thio-FCMA) ligation that enables the construction of peptides that are difficult to synthesize. Recently, activation of C-terminal thioacids using isonitriles was used in combination with native chemical ligation in the total synthesis of all-*L*- and all-*D*-amino acid biotinylated variants of oncogenic mutant KRas G12V.[11]

Thioamino acids are invaluable building blocks for constructing complex biologics such as glycopeptides and glycoproteins. Moreover, they hold great potential for the treatment of cardiovascular diseases. For example, thioglycine and *L*-thiovaline releases H_2S, which is a known gasotransmitter that enhance the formation of cGMP, and consequently promote vasorelaxation in mouse aortic rings.[12]

In nature, proteins containing thiocarboxylate functional group are biosynthetic sulfide donors.[13] These proteins are involved in the biosynthesis of vitamin B1, biotin, molybdopterin, cysteine, thioquinolobactin and *S*-adenosylmethionine.

The most conventional way of synthesizing thioacids is to activate the corresponding carboxylic acids using mixed anhydride method or active esters such as *p*-nitrophenyl esters,[14] or *N*-hydroxysuccinimidyl esters,[15] followed by nucleophilic substitution with hydrosulfide anion ($^-$SH). The common sources of hydrosulfide anion are hydrogen sulfide gas (H_2S), sodium sulfide (Na_2S), lithium sulfide (Li_2S), or sodium hydrosulfide (NaSH). Solid-phase peptide synthesis (SPPS) over Kaiser's oxime ester resin is the most used method for large peptide thioacids, which can be obtained after cleavage from the resin with hexamethyldisilathiane and tetrabutylammonium fluoride. An important one-step method to synthesize thioacids was developed by Danishefsky and involves the treatment of carboxylic acids with Lawesson's reagent in dichloromethane under microwave irradiation (Method A, Figure 1).[16] Recently, Katritzky et al.[17] have developed a method to synthesize protected amino/peptide thioacids from the corresponding acyl benzotriazoles using H_2S and *N*-methylmorpholine (NMM) in THF (Method B, Figure 1).

N-Protected α-amino/peptide thioacids were also synthesized from their corresponding oxoacids via reaction with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and Na_2S in DMF (Method C, Figure 1).[18] Although the reaction conditions are mild and yields are good, the intermediates that is formed from the reaction of the carboxylic acids with EDC is unstable and prone to rapid hydrolysis in aqueous solution. *N*-Protected α-amino thioacids can be synthesized using thioacetic acid and NaSH in THF (Method D, Figure 1).[19] However, separation of the thioacid was problematic and requires further oxidative dimerization to be separated from the corresponding amino acid. Recently, Kanai and his co-workers reported a catalytic one-step method for peptide thioacids (Method E, Figure 1).[20] They were

able to convert the carboxy group at the C-terminus into a thiocarboxy group using potassium thioacetate (AcSK) and diacetylsulfide (Ac_2S) in DMF. This method was used successfully in the synthesis of peptide drug leuprorelin but requires protection of the peptides side chains and suffers from poor atom economy.

All reported methods are not green in nature and involve the use of hazardous chemicals and organic solvents. For example, Lawesson's reagent is very toxic and liberates toxic and flammable gases upon contact with water. Dichloromethane (DCM) is often used in the synthesis of thioacids. This solvent is well known to cause many health problems and is not suitable for large scale production in an industrial setting because of its high volatility. High concentrations of H_2S cause convulsions and inability to breathe and can lead to coma or even death. Moreover, these methods suffer from poor atom economy and in most cases produce large amounts of side products and requires purification with column chromatography. In case of amino- and peptide thioacids, longer reaction times and purification processes lead to oxidation which in turn decreases the overall yield of these reactions.

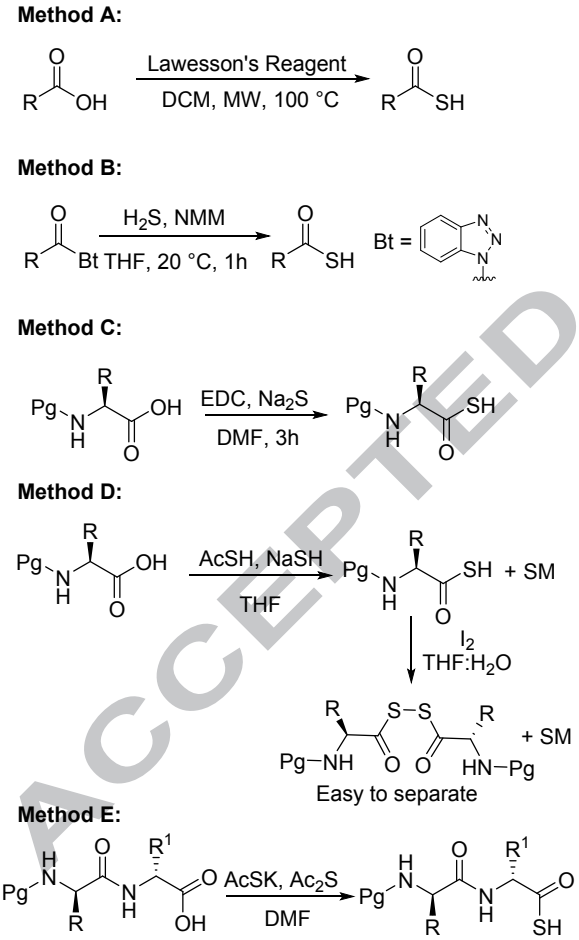


Figure 1. Examples of previously reported synthetic strategies toward thioacids.

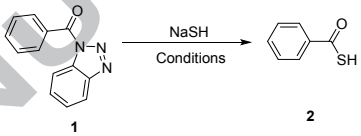
The use of water as a medium for organic reactions is environmentally friendly and sustainable practice. The use of organic solvents by fine chemicals and pharmaceutical industries has become a real burden on the environment.[21] It has been estimated that solvents are 85% of the mass of the raw materials used to prepare active pharmaceutical ingredients (APIs).[22] Replacement of organic solvents with water in any chemical process is economically feasible, make the process more sustainable, and will definitely reduce the use of toxic organic solvents.

As part of our ongoing research program to develop bioactive compounds, we use thioacids as synthetic intermediates. One of our objectives is to develop pharmaceutical reagents in a green way. Herein, we report a simple and green method for the synthesis of thioacids and thioamino acids in water.

2. Results and discussion

N-Acylbenzotriazoles are versatile synthetic auxiliaries and have been used as N-, C-, O- and S-acylating agents.[23] Similar to acid chlorides, *N*-acylbenzotriazoles activate carboxylic acids for nucleophilic substitutions but they are more stable and can be stored for months. Moreover, they are neutral acylating reagents and can be used in presence of substituents sensitive to acidic or basic conditions.[24] *N*-Acylbenzotriazoles are commercially available and can be purchased or conveniently prepared from 1-(methanesulfonyl)-1*H*-benzotriazole following previously published procedure.[25]

Table 1. Optimization of the reaction conditions.



1 2

Entry	Conditions	Yield (%)
1	THF/H_2O (3:1), rt, overnight	80
2	CH_3CN/H_2O (3:1), rt, overnight	79
3	DMF, rt, overnight	79
4	CH_3CN, microwave, 80 °C, 1 h	83
5	H_2O, microwave, 80 °C, 15 min	88
6	H_2O, rt, 3h	92

Our goal was to synthesize thioacids from *N*-acylbenzotriazoles in water and without the use of any catalyst or base. Water is the most benign solvent and it is an excellent solvent for salts and acids. Furthermore, the use of water will reduce the E-factor as solvents are the major mass of waste in any given synthetic procedure.

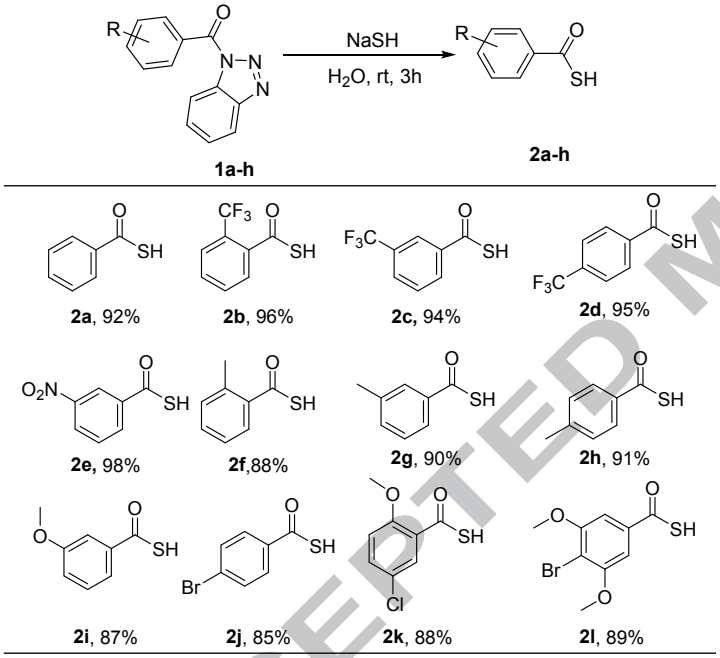
In order to determine the best reaction conditions, we used 1-benzoyl-1*H*-benzotriazole (**1a**) as the model substrate and sodium hydrosulfide (NaSH) as the hydrosulfide anion (^-SH) source. Initially, the desired product **2a** was obtained in 80% yield when the reaction was performed in THF/H_2O at room temperature. The yield was not improved when we replaced THF/H_2O with CH_3CN/H_2O or with DMF. These reactions were performed overnight (Table 1, entries 1-3). The reaction time was shortened to 1 h and the yield of **2a** was enhanced slightly to 83% when we performed the reaction in CH_3CN at 80 °C under microwave (MW) irradiation (Table 1, entry 4). We then ran the reaction under the same conditions using H_2O as a solvent. To our delight, the reaction was completed in only 15 min and **2a** was obtained in 88% yield (Table 1, entry 5)

Running reactions at room temperature is advantageous as it is energy efficient and attenuate decomposition, racemization, and side reactions. When we ran the reaction in H_2O at room temperature, we obtained compound **2a** in an excellent yield (92%) in 3 h (Table 1, entry 6). In a typical reaction, NaSH was dissolved in water and compound **1** was added slowly to the reaction mixture. The reaction was stirred vigorously at room

temperature and monitored by LC-MS. After 1 hours, the suspension turned into clear solution and we started to observe the appearance of mass peak corresponding to the product. The starting *N*-acylbenzotriazole (**1**) was consumed completely after 3 h. The product crashed out of solution upon acidification with HCl (2N) and obtained in a pure form with no need to further purification. It is noteworthy to point out that 3 equivalents of NaSH was needed to accelerate the reaction. The reaction works well with 1 equivalent of NaSH but the reaction time of compound **1** increased to 5 hours.

We have tested the acid chloride and imidazole derivatives of compound **1**. In case of benzoyl chloride, the reactant underwent hydrolysis and gave the corresponding benzoic acid. Stability of *N*-acyl benzotriazoles in aqueous media is a known advantage over their acid chloride analogous. Interestingly, when *N*-benzoyl imidazole was subjected to our optimized reaction conditions, the corresponding thiobenzoic acid was obtained in 82% yield. This observation suggests that *N*-acylimidazoles are good substrates for our novel method.

Table 2. Reaction scope of *N*-acyl benzotriazoles and NaSH.



The scope and generality of the reaction was explored by using substituted benzoyl benzotriazoles (**1a-l**). Generally, electron-withdrawing substituents gave better yields (94-98%) and their reactions were completed in shorter times. The trifluoromethyl group (-CF_3) worked well in *o*-, *m*-, and *p*-positions of the phenyl ring of the benzoyl benzotriazoles (**1b-d**). Nitro group (-NO_2) worked as well as CF_3 and gave the desired thioacid (**2e**) in 98% yield (Table 2). Electron-donating substituents gave slightly lower yields (88-91%) and took longer reaction times. The phenyl ring bearing methyl group in all three positions worked smoothly and gave the corresponding thioacids (**2f-h**) in very good yields (Table 2). Several other substituents (e.g. OMe, Br, Cl) at different positions of the phenyl ring were well tolerated. For example, methoxy group (-OMe) at *m*-position and bromo group (-Br) in *p*-position gave compounds **2i** and **2j** in 87 and 85% yield, respectively.

A combination of -OMe in *o*-position and chlorine (-Cl) in *m*-position on the same ring, and two -OMe in *m*-position and -Br in *p*-position gave compounds **2k** and **2l** in 88% and 89% yield, respectively (Table 2). Having electron-withdrawing or electron-donating substituents at ortho position did not affect the reactivity of substrates negatively (Table 2). Similarly, a mixture of electron donating and electron withdrawing substituents at various positions did not hamper down the reactivity (e.g. **2k** and **2l**). Most of the products precipitated out of the reaction mixture upon acidification. When we used cinnamoyl benzotriazole, we were not able to isolate the corresponding thioacid. Instead, we obtained intractable mixture that contains significant amount of the dimeric product, cinnamic dithioperoxyanhydride.

To further explore the generality of this reaction, aliphatic thioacids (**3a-c**) were prepared from their corresponding *N*-acylbenzotriazoles (Figure 2). Thioacetic acid and thiopropanoic acids were separated as sodium salts **3a** and **3b** in nearly quantitative yields. Both compounds were isolated in a pure form as white microcrystals. Obtaining the free acid was extremely difficult because the products dissolve in water upon acidification and cannot be recovered easily. Benzeneethanethioic acid (**3c**) was prepared from the corresponding *N*-phenylacetylbenzotriazole using our optimized conditions (Figure 2). Based on these results, we were encouraged to apply our method to synthesize thioamino acids. We synthesized a diverse group of *N*-protected amino and dipeptide thioacids. For example, we synthesized aliphatic thioamino acids (i.e. *Cbz*-Gly-SH (**4a**) and *Cbz*-*L*-Ala-SH (**4b**)), and sterically hindered isoleucine derivative (**4c**). Moreover, we have synthesized an aromatic thioamino acid (i.e. *Boc*-*L*-Phe-SH (**4d**)) and simple dipeptide thioacids (i.e. *Cbz*-*L*-Ala-*L*-Phe-SH (**5a**) and *Cbz*-Gly-*L*-Phe-SH (**5b**)) (Figure 2). Compounds **4a-d** and **5,b** were prepared in very good yields (83-95%) and were stable at 0 °C for weeks. Specific rotations, ^{1}H and ^{13}C-NMR of **4b-d** and **5a,b** show no epimerization occurred under our reaction conditions.

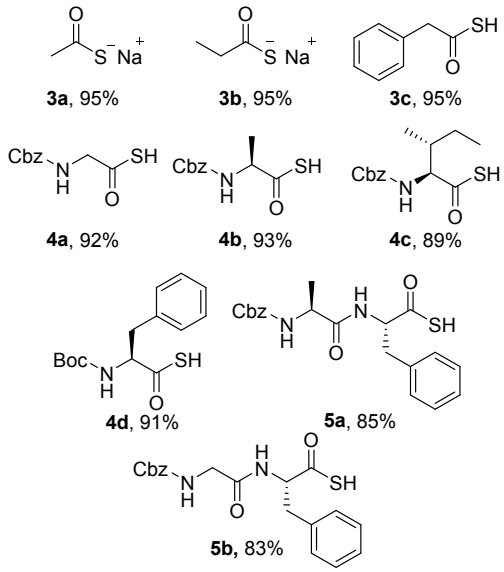


Figure 2. Aliphatic-, amino-, and dipeptide thioacids (**3-5**).

Conclusions

In summary, we have developed a versatile and green method for the synthesis of thioacids. The synthesis is conducted in water at room temperature without the need of any catalyst or base. The synthesis is amenable to be conducted under microwave irradiation in shorter time. A diverse set of aromatic, aliphatic, thioamino acids, and simple dipeptide thioacids were synthesized in high yields using the new method. The reaction conditions are convenient, straightforward, general, and the workup procedure is very simple and does not involve chromatographic separation.

Acknowledgments

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Supplementary Material

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Highlights

- Synthesis of thioacids and thioaminoacids in water.
- Catalyst- and organic solvent-free method.
- Mild reaction conditions, high yields, and simple workup.
- No chromatography purification.