

Study on the synthesis of thioamides from aldehyde N-tert-butylsulfinyl amide and sulfur in aqueous media

Pham Xuan Thao^{1*}, Pham Minh Tuan¹, Cao Hai Thuong²

¹Institute of Chemistry - Materials, Academy of Military Science and Technology;

²Department of Physics and Chemical Engineering, Military Technical Academy.

*Email: thaovn1987@gmail.com.

Received 25 October 2021; Revised 15 November 2021; Accepted 12 December 2021.

DOI: <https://doi.org/10.54939/1859-1043.j.mst.76.2021.54-60>

ABSTRACT

Thioamides have been widely used in the fields of medicine and organic chemistry, some of which are essential bioactive compounds, plant protection agents, and drugs. It could also be used as a vulcanizing agent, an additive to lubricants and greases, and a ligand in organic synthesis. Usually, thioamide is synthesized at high temperatures or in the microwave using an expensive noble metal complex as catalysts. This paper presented a straightforward method for synthesizing thioamides by using N-tert-butylsulfinyl amide, aldehyde, and sulfur. The reaction was carried out in water, which is an environmentally friendly solvent. The reaction selectivity and yield were up to 89%.

Keywords: Thioamide; Amine; Aldehyde; Aqueous solvent.

1. INTRODUCTION

Thioamides are well known in the fields of biochemistry and organic chemistry. The development in the preparation procedures and applications of thioamides has diversified in many fields due to the great benefits of these compounds [1]. Thioamide is an essential intermediate in organic synthesis and the synthesis of biologically active natural compounds. Some thioamides are known as plant protection agents, or active medicinal ingredients [2], used as vulcanizers [3], lubricant additives [3], and as ligands in synthetic chemistry [4],... With its importance and wide applications, scientists worldwide have been interested in studying and preparing thioamide by various methods [5]. One of these protocols is the Willgerodt-Kindler (WK) reaction [6], a commonly used method to obtain various thioamides under extreme reaction conditions, such as a high temperature or microwaves. Other N-thioamide derivatives have also been prepared using sulfur transition agents such as P₂S₅ and Lawesson's agent [7]. However, the main disadvantages of the above thioamide synthesis reactions is the use of expensive catalysts, organic solvents, complicated processes, and low efficiency.

This paper presents a simple, efficient and uses environmentally friendly methods to prepare the thioamides by the reaction of N-tert-butylsulfinyl amide, aldehyde and sulfur with high efficiency and selectivity in aqueous solution.

2. EXPERIMENTAL

All reagents were obtained commercially and used without further purification. All reactions have been carried out under a nitrogen atmosphere and dry conditions. The reaction mixtures were magnetically stirred with Teflon stirring bars, and the temperatures were measured externally. The reactions were monitored by thin-layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254). The eluents used were mixtures of n-pentane and ethyl acetate (EtOAc), with detection by UV light or a KMnO₄ staining solution. Across silica gel (60, particle size 0.040–0.063 mm) was used for column chromatography. Infrared spectrum has been recorded with Spectrum Two, Perkin Elmer at Le Quy Don Technical University. The nuclear magnetic resonance (NMR) spectra have been recorded with Bruker Avance 500 MHz

spectrometers at Vietnam National University. ^1H NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS), using δ (CDCl_3) = 7.26 ppm as internal reference. ^{13}C NMR spectra: δ (C) are given in ppm relative to TMS, using δ (CDCl_3) = 77.0 ppm as internal reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quadruplet (q), quintuplet (qt), multiplet (m) or br (broad).

General procedure for the synthesis of thioamide: In a round-bottomed flask 100 ml was added *N*-tert-butylsulfinyl amide (1 mmol, 1 eq.), aldehyde (1.5 mmol, 1.5 eq), 0.096 g sulfur powder (3 mmol, 2 eq), 0.276 g K_2CO_3 (2 mmol) and H_2O (3 mL). The reaction mixture was stirred with a magnetic stirrer and refluxed at 100 °C for 24 h. After the reaction was completed, the mixture was cooled to room temperature and extracted with ethyl acetate. The organic phase was dried with Na_2SO_4 , and the solvent was removed by vacuum rotary distillation. The product was purified by silica gel column chromatography (n-hexane/EtOAc: 4/1), and the reaction yield is calculated on the weight of **3a-f** product.

***N*-tert-butylsulfinyl benzothioamide (3a):** Prepared according to the general method: 0.121 g *N*-tert-butylsulfinyl amide (1 mmol, 1 eq.), 0.159 g benzaldehyde (1.5 mmol, 1.5 eq.). The product **3a** was isolated as white solid (0.197g, 85% yield). R_f = 0.56. IR (cm^{-1}): 3490 (ν_{NH}); 3062 ($\nu_{\text{C-H arene}}$); 2959, 2925 ($\nu_{\text{CH(sp}^3\text{)}}$); 1605, 1501 ($\nu_{\text{C-C (arene)}}$). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.59 (s, 1H, NH); 7.87–7.84 (m, 2H, arene); 7.53–7.45 (m, 3H, arene); 1.26 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 162.9 (C(C=S)); 134.2 (C, arene); 132.5 (C, para); 129.5 (C, meta); 129 (C, ortho); 57.9 (C, C(CH₃)₃); 22.7 (C, CH₃).

***N*-(tert-butylsulfinyl)-4-methylbenzothioamide (3b):** Prepared according to the general method: 0.121 g *N*-tert-butylsulfinyl amide (1 mmol, 1 eq.), 0.180 g 4-methyl-benzaldehyde (1.5 mmol, 1.5 eq.). The product **3b** was isolated as white solid (0.215g, 89% yield). R_f = 0.58. IR (cm^{-1}): 3486 (ν_{NH}); 3050 ($\nu_{\text{C-H arene}}$); 2925, 2906 ($\nu_{\text{CH(sp}^3\text{)}}$); 1606, 1505 ($\nu_{\text{C-C (arene)}}$). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.57 (s, 1H, NH); 7.787–7.75 (m, 2H, arene); 7.30–7.28 (m, 2H, arene); 2.43 (s, 3H, CH₃); 1.28 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 162.5 (C(C=S)); 143.1 (C arene, para); 131.67 (C, C-C=S); 129.6 (C, meta); 129.4 (C, ortho); 57.6 (C, C(CH₃)₃); 21.7 (C, CH₃).

***N*-(tert-butylsulfinyl)-4-methoxybenzothioamide (3c):** Prepared according to the general method: 0.121 g *N*-tert-butylsulfinyl amide (1 mmol, 1 eq.), 0.204 g 4-methoxy-benzaldehyde (1.5 mmol, 1.5 eq.). The product **3c** was isolated as white solid (0.214g, 79% yield). R_f = 0.56. IR (cm^{-1}): 3493 (ν_{NH}); 3055 ($\nu_{\text{C-H arene}}$); 2945, 2918 ($\nu_{\text{CH(sp}^3\text{)}}$); 1608, 1512 ($\nu_{\text{C-C (arene)}}$). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.51 (s, 1H, NH); 7.80–7.79 (m, 2H, arene); 6.98–6.95 (m, 2H, arene); 3.74 (s, 3H, CH₃); 1.33 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 161.7 (C(C=S)); 131.3 (C arene, para); 131.6 (C, C-C=S); 116.0 (C, meta); 114.3 (C, ortho); 55.5 (C, OCH₃); 55.5 (C, C(CH₃)₃); 22.5 (C, CH₃).

***N*-(tert-butylsulfinyl)-4-nitrobenzothioamide (3d):** Prepared according to the general method: 0.121 g *N*-tert-butylsulfinyl amide (1 mmol, 1 eq.), 0.227 g 4-nitrobenzaldehyde (1.5 mmol, 1.5 eq.). The product **3d** was isolated as white-yellow solid (0.218g, 76% yield). R_f = 0.52. IR (cm^{-1}): 3502 (ν_{NH}); 3051 ($\nu_{\text{C-H arene}}$); 2945, 2916 ($\nu_{\text{CH(sp}^3\text{)}}$); 1601, 1502 ($\nu_{\text{C-C (arene)}}$). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 10.1 (s, 1H, NH); 8.07–8.03 (m, 4H, arene); 1.30 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 191.4 (C(C=S)); 161.8 (C arene, para); 133.3 (C arene, C-C=S); 130.7 (C, meta); 130.3 (C, meta); 123.7 (C, ortho); 123.3 (C, ortho); 22.7 (C, CH₃).

***N*-(tert-butylsulfinyl)-4-(methylthio)benzothioamide (3e):** Prepared according to the general method: 0.121 g *N*-tert-butylsulfinyl amide (1 mmol, 1 eq.), 0.228 g 4-(methylthio)benzaldehyde (1.5 mmol, 1.5 eq.). The product **3e** was isolated as white solid (0.233g, 81% yield). R_f = 0.55. IR (cm^{-1}): 3494 (ν_{NH}); 3056 ($\nu_{\text{C-H arene}}$); 2950, 2915 ($\nu_{\text{CH(sp}^3\text{)}}$); 1608, 1510 ($\nu_{\text{C-C (arene)}}$). ^1H NMR

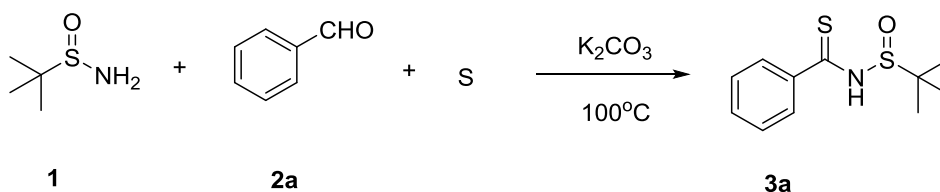
(500 MHz, CDCl_3) δ (ppm): 8.54 (s, 1H, NH); 7.78–7.76 (m, 2H, *arene*); 7.32–7.30 (m, 2H, *arene*); 2.54 (s, 3H, CH_3); 1.27 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 161.9 (C, C=S); 145.1 (C, *arene*), 131.0 (C *arene*, *para*); 129.6 (C *arene*, *meta*); 125.6 (C *arene*, *ortho*); 22.6 (C, CH_3), 14.9 (C, SCH_3).

***N*-(*tert*-butylsulfinyl)-4-(methylsulfonyl)-benzothioamide (3f):** Prepared according to the general method: 0,121 g *N*-*tert*-butylsulfinyl amide (1 mmol, 1 eq.), 0,276 g 4-(methylsulfonyl)benzaldehyde (1,5 mmol, 1,5 eq.). The product **3f** was isolated as white solid (0.246g, 77% yield). IR (cm^{-1}): 3491 (ν_{NH}); 3055 ($\nu_{\text{C-H arene}}$); 2924, 2906 ($\nu_{\text{CH(sp}^3\text{)}}$); 1615, 1510 ($\nu_{\text{C=O}}$). $R_f = 0.5$. ^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.46 (s, 1H, NH); 7.71–7.69 (m, 2H, *arene*); 7.60–7.57 (m, 2H, *arene*); 1.63 (s, 3H, CH_3); 1.16 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 161.89 (C, C=S); 144.8 (C, *arene*), 132.5 (C *arene*, *para*); 129.79 (C *arene*, *meta*); 126.15 (C *arene*, *ortho*); 58.4 (C, $\text{C}(\text{CH}_3)_3$); 29.8 (C, $\text{CH}_3(\text{SO}_2)$), 22.63 (C, SCH_3).

3. RESULTS AND DISCUSSION

3.1. Effect of potassium carbonate concentration on reaction yield

Firstly, thioamide synthesizing was studied by reacting *N*-*tert*-butylsulfinyl amide with benzaldehyde and sulfur at 100 °C, for 24 h without using alkaline agent, resulting thioamide product is not formed. Next, the synthesis of thioamide from *N*-*tert*-butylsulfinyl amide reacted with benzaldehyde and sulfur at 100 °C, for 24 h in an aqueous medium in addition of several Lewis acid agents: Na_2CO_3 , NaHCO_3 , K_2CO_3 , KH_2PO_4 , and K_3PO_4 with an equivalent molar ratio of 1:1 (scheme 1).



Scheme 1. Synthesis of *N*-*tert*-butyl-sulfinyl benzothioamide.

The results showed that the K_2CO_3 used agent gained the highest yield of 51%. In contrast, when using other types of alkaline agents such as Na_2CO_3 , NaHCO_3 , KH_2PO_4 , and K_3PO_4 the yields were only in rang of 32 ÷ 37% and with the obtained with CuFe_2O_4 agent was about 23% (table 1).

Table 1. Effect of Lewis acid on the reaction yield.

Reagent	Na_2CO_3	NaHCO_3	K_2CO_3	CuFe_2O_4	KH_2PO_4	K_3PO_4
Yield of 3a	42%	37%	51%	23%	32%	35%

To optimize the reaction yield, the K_2CO_3 proportion with different ratios of 1 eq., 2 eq., 3 eq., were investigated at reaction temperature of 100 °C, for 24 hours in aqueous media. The results shown in table 2 indicate that the K_2CO_3 content significantly affects to the reaction yield. When increasing the ratio from 1 eq. to 2 eq. mol compared to amide, the yield increased significantly, but when increasing to 3 eq., the change in the yield was negligible. Thus, with a K_2CO_3 /amide ratio of 2:1, the highest reaction yield was obtained ot be 85%.

Table 2. Effect of K_2CO_3 ratio on the reaction yield.

Molar ratio of K_2CO_3	1 eq.	2 eq.	3 eq.
Yield of 3a	51 %	85 %	82 %

3.2. Effect of temperature on the reaction yield

The reaction temperature is of great effect on the yields of thioamide. Continuously, the

synthesis of thioamide between *N*-*tert*-butylsulfinyl amide with benzaldehyde and sulfur was carried out with 2 eq. mol of K_2CO_3 in aqueous media, 24 hours with various temperature conditions of room temperature, 60 °C, 80 °C, and 100 °C. The results show that at room temperature, the thioamide product was not formed, when gradually increasing the temperature to 60 °C, 80 °C and 100 °C, the reaction efficiency increases from 27% to the best 85% at 100 °C. The reason is that the process of opening the S_8 ring of sulfur in a slightly alkaline environment requires a large amount of energy (table 3).

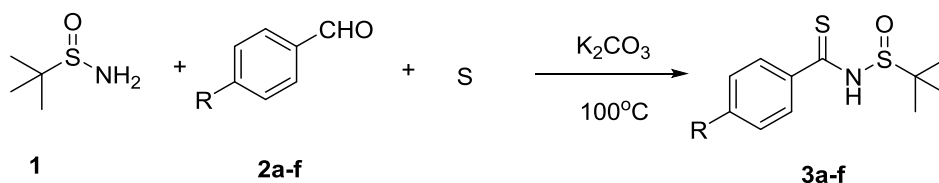
Table 3. Effect of temperature on the reaction yield.

Temperature	Room temperature	60 °C	80 °C	100 °C
Yield of 3a	0%	27%	68%	85%

3.3. Effect of aldehyde nature on the reaction yield

Finally, the synthesis of thioamide from *N*-*tert*-butylsulfinyl amide with sulfur was investigated with some benzaldehyde derivatives using the K_2CO_3 agent with a molar ratio of 02 eq., at temperature of 100 °C, for 24 hours in aqueous media. The results show that when aldehyde with electron-sucking substituents (OCH_3 , NO_2 , SCH_3 , $(SO_2)CH_3$), the reaction efficiency is reduced comparing to benzaldehyde. In contrast, with aldehyde containing the electron repulsive group (CH_3), the reaction yield reaches to 89% (table 4).

Table 4. Synthesis of some thioamides from *N*-*tert*-butylsulfinyl amide.



Entry	Name	R	Product	Yield
1	3a	H		85 %
2	3b	CH_3		89 %
3	3c	OCH_3		79 %
4	3d	NO_2		76%
5	3e	SCH_3		81 %
6	3f	$(SO_2)CH_3$		77%

The synthesis of thioamide occurs by the general mechanism of the Willgerodt-Kindler reaction (figure 1). First, the reaction between aldehyde and amine to form the intermediate product (imine), with assistance of K_2CO_3 agent at appropriate temperature, the sulfur ring S_8 is opened and connected to the imine's double bond by the Nucleophile addition mechanism and finally form thioamide molecules.

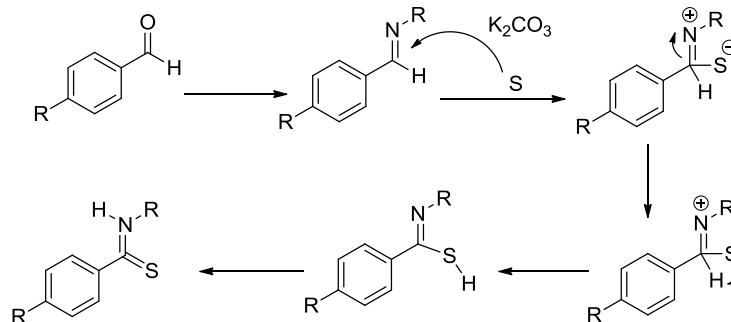


Figure 1. Mechanism of thioamide synthesis.

On the 1H NMR spectrum, singlet peaks appear at 8.59 ppm, corresponding to the H of the -NH-group, 7.87–7.84 ppm and 7.53–7.45 ppm corresponding to the 5H of the benzene ring, and the 1.26 ppm peak corresponds to the 9H of the *tert*-butyl group (figure 2).

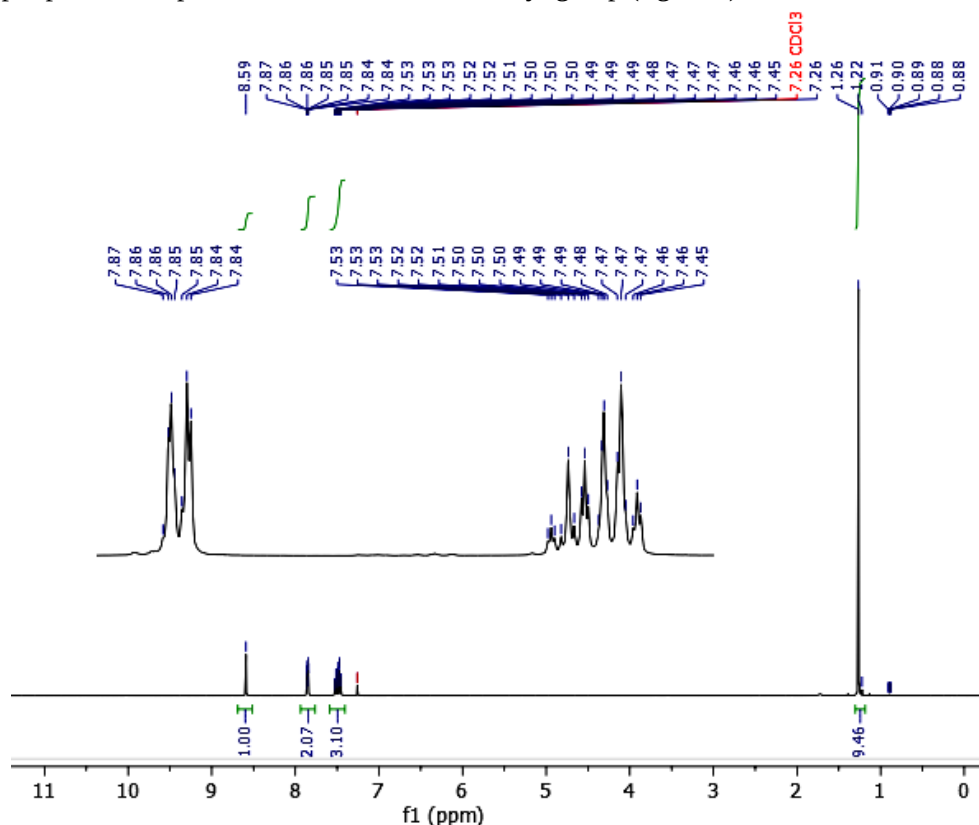


Figure 2. 1H NMR of thioamide 3a.

On the ^{13}C NMR spectrum, the 162.9 ppm peaks correspond to the carbon of the C=S group, the 134.2 ppm peak corresponds to the C of the benzene ring at the C=S binding site, the 132.5 ppm peak corresponds to the C=S binding site. C at position para; pic 129.5 ppm corresponds to C at meta position, 129 ppm corresponds to C at ortho position, pic 57.9 ppm corresponds to C

quaternary of *tert*-butyl group, peak 22.7 ppm corresponds to C primary of the *tert*-butyl group (figure 3).

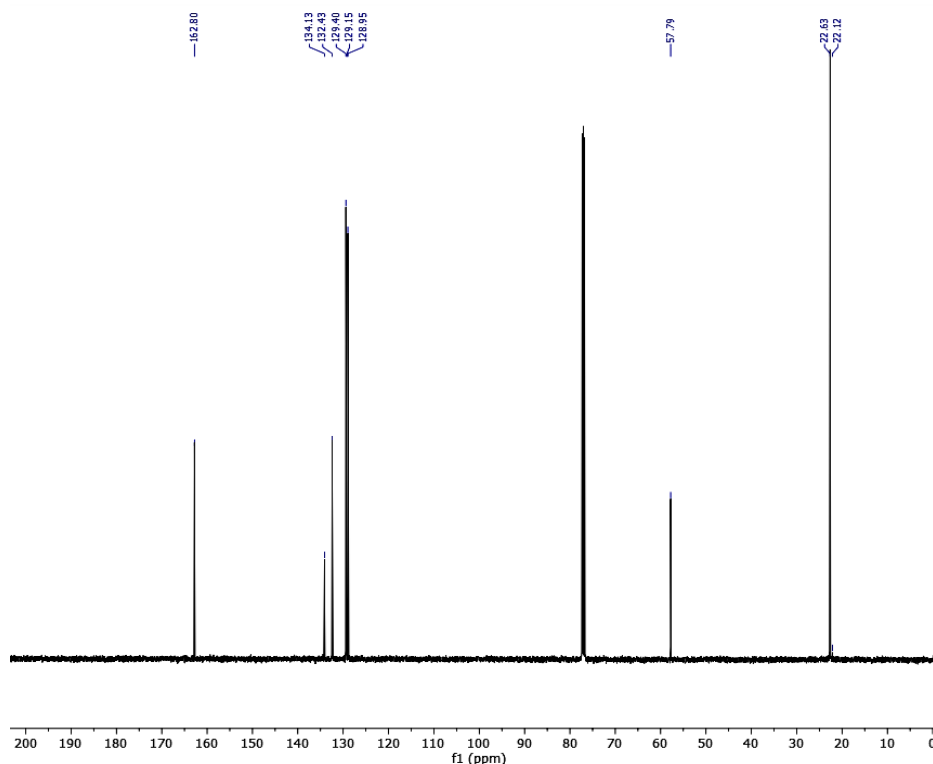


Figure 3. ^{13}C NMR of thioamide 3a.

4. CONCLUSION

In summary, the thioamide has been successfully synthesized from the aldehyde, sulfur and *N-tert*-butylsulfinyl amide in the presence of K_2CO_3 agent with optimal ratio of 2:1 at temperature of 100 °C for 24 hours in aqueous media. With optimized synthesizing conditions, the highest yield of thioamide was estimated to be 89%. The study contributes to the prospect of applying *N-tert*-butylsulfinyl amide to synthesize natural bioactive compounds. The synthetic method using water solvent has great significance in the field of green chemistry, cost-effective and minimizing the effect of the synthesizing process on the environment.

REFERENCES

- [1]. Mahanta, N., Szantai-Kis, D. M., Petersson, E. J. Mitchell, D. A., "Biosynthesis and Chemical Applications of Thioamides", ACS Chem Biol., **14**(2) (2019), pp. 142 - 163.
- [2]. Jagodziński, T. S., "Thioamides as Useful Synthons in the Synthesis of Heterocycles", Chemical Reviews, **103**(1) (2003), pp. 197 - 228.
- [3]. Downer, N. K. Jackson, Y. A., "Synthesis of benzothiazoles via ipso substitution of ortho-methoxythiobenzamides", Org Biomol Chem., **2**(20) (2004), pp. 3039 - 3043.
- [4]. Jain, P., Verma, P., Xia, G., & Yu, J.-Q. "Enantioselective amine α -functionalization via palladium-catalysed C-H arylation of thioamides". Nature Chemistry, **9**(2) (2016), pp.140–144
- [5]. Pathare, Sagar P., Chaudhari, Pramod S. Akamanchi, Krishnacharya G., "Sulfated tungstate: An efficient catalyst for synthesis of thioamides via Kindler reaction", Applied Catalysis A: General, **425-426** (2012), pp. 125-129.
- [6]. Pribbenow, D. L. Bolm, C., "Recent advances in the Willgerodt-Kindler reaction", Chem Soc Rev., **42**(19) (2013), pp. 7870-80.

- [7]. Larik, F. A., Saeed, A., Muqadar, U., & Channar, P. A. “Application of Lawesson’s reagent in the synthesis of sulfur-containing medicinally significant natural alkaloids”, Journal of Sulfur Chemistry, **38**(2) (2016), pp. 206–227

TÓM TẮT

NGHIÊN CỨU TỔNG HỢP THIOAMIDE TỪ ALDEHYDE N-TERT-BUTYLSULFINYL AMIDE VÀ LƯU HUỖNH TRONG MÔI TRƯỜNG NƯỚC

Thioamide được sử dụng rộng rãi trong lĩnh vực hóa hữu cơ và y học như là các hợp chất hoạt tính sinh học ứng dụng làm thuốc, chất bảo vệ thực vật, hoặc được sử dụng làm chất lưu hóa, làm phụ gia cho dầu, mỡ bôi trơn, và là phối tử trong tổng hợp hữu cơ cũng như tổng hợp bất đối các hợp chất tự nhiên, chất có hoạt tính sinh học. Thông thường, thioamide được tổng hợp ở điều kiện nhiệt độ cao hoặc trong lò vi sóng sử dụng dung môi hữu cơ, các chất xúc tác đắt tiền là phức của kim loại chuyển tiếp. Trong bài báo này, chúng tôi trình bày phương pháp tổng hợp thioamide bằng phương pháp sử dụng N-tert-butylsulfinyl amide, aldehyde cộng hợp với lưu huỳnh trong môi trường nước. Kết quả thu được cho thấy phương pháp tổng hợp đơn giản, sử dụng dung môi thân thiện môi trường, hiệu suất phản ứng có thể đạt đến 89%.

Từ khóa: Thioamide; Amine; Aldehyde; Dung môi nước.