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An easy and fast one-pot preparation of 2-thiomethyl and 2-thioacyl benzothiazoles, benzoxazoles, and benzimidazoles

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A one-pot preparation of 2-thiomethyl and 2-thioacyl benzazolium derivatives using *o*-aminothiophenol, *o*-aminophenol or 1,2-phenilenediamine as starting material is reported in the present paper. This novel method involves a combination of microwave heating and ultrasound irradiation, affording the title compounds with good to excellent yields, without isolating the intermediate products.

Keywords: 2-thiomethylbenzothiazoles, 2-thiomethylbenzoxazoles, 2-thiomethylbenzimidazoles, 2-thioacylbenzothiazoles, 2-thioacylbenzoxazoles, 2-thioacylbenzimidazoles.

INTRODUCTION

Quaternary 2-thiomethylbenzazoles are important class of intermediates involved in the synthesis of symmetric and asymmetric monomethine cyanine dyes. In addition to, 2-methylmercaptobenzothiazole, and 2-methylmercaptobenzoxazole derivatives represent an essential group of compounds for the synthesis of cyanine dyes [1–3]. S-Alkylated heterocyclic derivatives are known as key compounds, finding application in copper and copper alloys protection against corrosion [4–6].

Thiocarboxylic acid esters (2-thioacyl derivatives) can be used in various chemical transformations, such as asymmetric aldol reactions [7], and as cephalosporin derivatives [8]. Thioethers play an important role in the development of thiol drugs, especially in masking the unpleasant odor and taste of the native thiol [9]. Recently we have published two methods as an environmentally benign ways the former of which involves the synthesis of substituted 2-thiobenzothiazoles, 2-thiobenzoxazoles, 2-thiobenzimidazoles, and 1,3-oxazolopyridine-2-thiols [10], as well as an easy and fast ultrasonic selective S-alkylation of hetaryl thiols proceeding at room temperature as presented in the latter publication [11].

Herein we report that those two methods mentioned above can be joined together in a novel synthetic procedure, for an easy and fast one-pot preparation of 2-thiomethylbenzothiazoles, 2-thiomethylbenz- oxazoles, 2-thiomethylbenzimidazoles or 2-thioacylbenzothiazoles, 2-thioacylbenzoxazoles and 2-thioacylbenzimidazoles.

EXPERIMENTAL

All reagents and solvents were purchased from Sigma-Aldrich, Organica Feinchemie GmbH Wolfen, Fluka, Alfa-Aesar, and were used without further purification. The deuterated solvents were purchased from Deutero GmbH. The target 2-thioalkyl and 2-thioacyl benzazolium derivatives were compared to previously reported ones. Melting point temperatures were determined on a Kofler bench and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker Avance III HD, 500 MHz in DMSO-d_6 at room temperature. The chemical shifts were reported in ppm in δ-values with respect to tetramethylsilane (TMS) as an internal standard.

Synthesis of potassium salts of substituted or unsubstituted 2-mercaptobenzazoles 7a-7k

3.7 g. potassium hydroxide **1** (0.066 mol) was dissolved in 20 ml of 2-methoxyethanol **2** upon heating in a microwave oven at 450 W for 45 sec. The experiment was held in a well-ventilated hood. At this stage, the solution turned yellowish, indicating the formation of intermediate **3**. After allowing it to cool down to room temperature, 3.9 ml of carbon disulfide **4** (0.066 mol) was added to the solution. Normally, the formation of a white precipitate of 2-methoxyethyl xanthate **5** can be observed. The reaction mixture is self-warmed. The content of the flask was allowed to cool down again, and substituted or unsubstituted 2-aminothiophenol, 2-aminophenol or 1,2-diaminobenzene **6a**-**6k** (0.066 mol) were added to it with stirring. The resulting mixture was heated up

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in a microwave oven at 450 W for 2 min (note, the heating was stopped for about 15 sec on every 30 seconds, in order to avoid overheating of the sample). The potassium salt 7a-7k of the corresponding hetaryl thiol crystallizes and the solvent is almost evaporated (Scheme 1).

Preparation of 2-thioalkyl and 2-thioacyl benzazolium derivatives 8a-8k

Procedure A: The resulting potassium salt **7a-7k**, was dissolved in 50 ml water (in case of undissolved particles, the solution was filtered), followed by addition of ice and 6.25 ml dimethylsulfate (0.066 mol) to the filtrate. The solution was stirred for 15-30 min and the precipitate was filtered off. The pH of the final reaction mixture was maintained between 8–9. The resulting precipitate was dried. In the case of product **8f,** the reaction mixture was extracted with dichloromethane, and dried over anhydrous sodium sulfate. The product was filtered off, and the solvent was evaporated, yielding an oily product. The corresponding yields and melting point temperatures of the products are given in Table 1.

Procedure B: similar to the procedure reported above, except that the alkylation step was carried out with methyl iodide instead of dimethylsulfate. In addition, ultrasound irradiation was performed for 5 min in the presence of 50 ml acetone which was added to the aqueous solution of the potassium salt **7a-7k**. The resulting precipitate was filtered off. Again, the pH of the final reaction mixture should be in between 8-9. The precipitate was dried.

Procedure C: performed as procedure B. Herein S-acylation occured using benzoyl chloride. The reaction conditions and sonication time remained unaltered. Product **8h** is reported as novel.

2-(methylthio)-5-phenylbenzo[d]oxazole (**8h**):

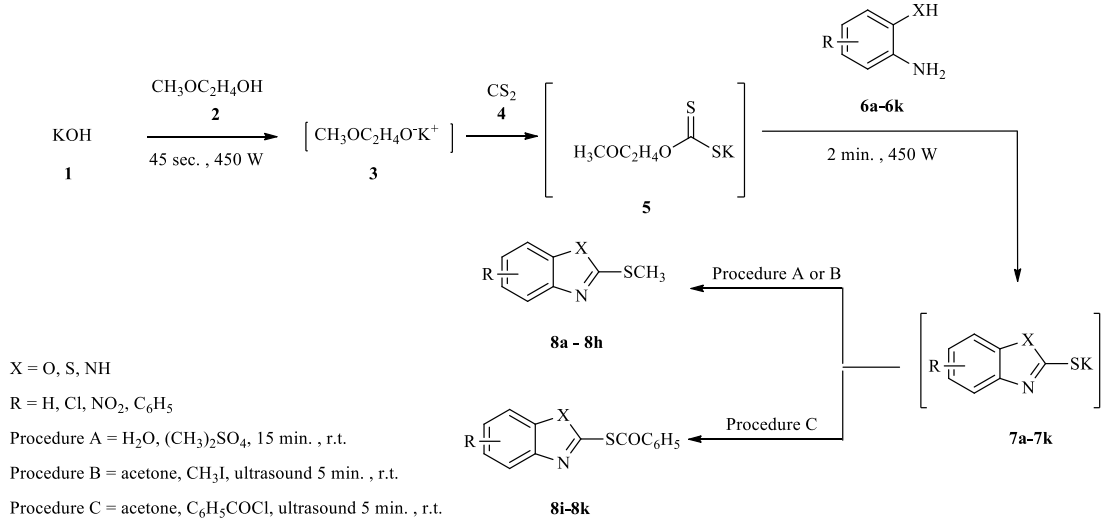
^{1}H NMR (500 MHz, DMSO-d_6, δ/ppm):2.79 (s, 3H, $\underline{CH_3}$-S), 7.37-7.40 (m, 1H, ArH), 7.47-7.50 (m, 2H, 2 x ArH), 7.60 (dd, 1H, J 1.7, 8.4, ArH), 7.70-7.73 (m, 2H, 3 x ArH), 7.89-7.90 (*m*, 1H, ArH);

^{13}C NMR (125 MHz, DMSO-d6, δ/ppm): 14.7; 110.8; 116.7; 123.6; 127.6; 127.6; 127.8; 129.4; 129.4; 137.8; 140.4; 142.6; 151.5; 166.4;

RESULTS AND DISCUSSION

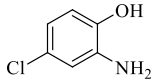
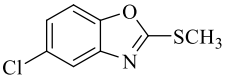
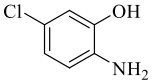
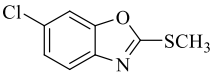
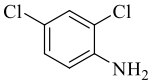
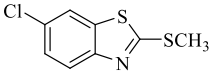
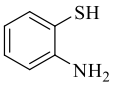
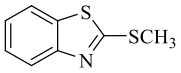
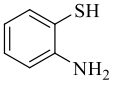
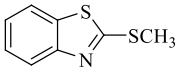
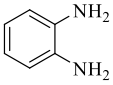
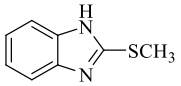
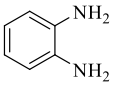
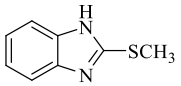
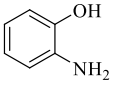
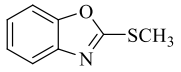
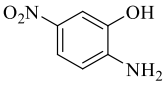
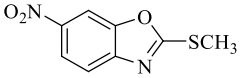
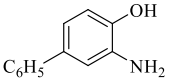
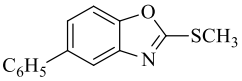
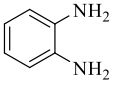
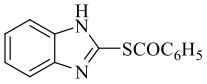
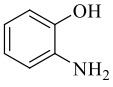
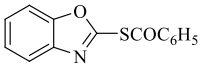
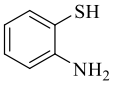
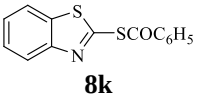
Based on the experimental part of the present work, we achieved the preparation of potassium salts of different benzothiazoles, benzoxazoles and benzimidazoles, which can subsequently be selectively S-alkylated or S-acylated. The reaction (four steps) can be run in one reaction vessel without isolating the intermediates. The first step involves the preparation of 2-methoxyethyl xanthate in 2-methoxyethanol, followed by the formation of potassium salts of substituted or unsubstituted benzothiazoles, benzoxazoles and benzimidazoles under microwave irradiation for a relatively short time. Due to the fact that the potassium salts of substituted or unsubstituted 2-mercaptobenzothiazoles, 2-mercaptobenzoxazoles and 2-mercaptobenzimidazoles are readily water soluble compounds, the final step (S-alkylation or S-acylation), is carried out using suitable alkylating or acylating agents in an aqueous solution at room temperature. The alkylation step using methyl iodide (**Procedure B**) or acylation (**Procedure C**), can be performed under ultrasound irradiation, in order to accelerate the experimental outcome.

To the best of our knowledge, the S-alkylation and S-acylation of hetaryl thiols at room temperature, promoted by the combination of microwave heating and ultrasound irradiation for the preparation of hetaryl thiols in a one-pot synthesis has not been reported. Herein, we present a highly reproducible one-pot synthesis of 2-thiomethylbenzazoles and 2-thioacylbenzazoles.



Scheme 1. One-pot preparation of 2-thioalkyl and 2-thioacyl benzazolium derivatives

Table 1. 2-Thiomethyl- and 2-thioacylbenzothiazoles, benzoxazoles and benzimidazoles

Entry	Starting compound (6)	Product (8)	Yield[a] (%) Procedure	Mp. / lit. Mp. (°C)
1	 **6a**	 **8a**	70 **A**	87-88 / 89 [12]
2	 **6b**	 **8b**	78 **A**	90-91 / 88-90 [11]
3	 **6c**	 **8c**	85 **A**	93-95 / 95 [13]
4	 **6d**	 **8d**	84 **A**	45-46 / 46 [14]
5	 **6d**	 **8d**	85 **B**	45-46 / 46 [14]
6	 **6e**	 **8e**	70 **A**	200-201 / 201-203 [15]
7	 **6e**	 **8e**	75 **B**	200-201 / 201-3 [15]
8	 **6f**	 **8f**	75 **A**	Oil [11]
9	 **6g**	 **8g**	75 **A**	191-192 / 193 [16]
10	 **6h**	 **8h**	89 **A**	75-77 [b]
11	 **6i**	 **8i**	95 **C**	264 / 265 [17]
12	 **6j**	 **8j**	85 **C**	84-85 / 83-85 [18]
13	 **6k**	 **8k**	87 **C**	130 / 129-131 [17]

[a] Isolated yield of crude product
[b] Novel compound

The final step to the synthesis of the title compounds involves an effectively accelerated selective S-alkylation or S-acylation reaction using ultrasonic irradiation with methyl iodide and benzoyl chlorides under mild conditions at room temperature. Such a unique combination of microwave heating and ultrasound irradiation is notably applied in the organic synthesis [19]. As an example, such a synthetic approach is applied for the preparation of biodiesel. The transesterification reaction in the study mentioned above was promoted by ultrasonic mixing and microwave irradiation of soybean oil. In the present work, the total reaction time was found to be significantly reduced compared to former studies [20].

Last but not least, such a combination is used in analytical processes [21], or applied in municipal and industrial wastewater treatment plants, in order to stabilize organic matter [22]. This process comprises four major microbiological degradation steps, such as hydrolysis, acidogenesis, acetogenesis and methanogenesis. Various patented constructions of microwave and ultrasonic apparatuses can also be found in the literature. This equipment is capable of performing numerous functions, which include ways of emitting microwave energy for heating, ultrasound energy to a given workload, whereas an overall control of both the microwave and the ultrasonic sources can be achieved [23].

For product **8h**, there are insufficient data in the literature. The only report [24] of this compound mentions its usage for the preparation of monomethine cyanine dyes, without providing any further information about it. This product was evaluated by ^{1}H –NMR, and ^{13}C -NMR spectra, as well as melting point temperature.

CONCLUSION

The newly developed synthetic approach has the following advantages: i) the reaction overall takes not more than 30 min; ii) the procedure is energy efficient, because of the application of MW heating and ultrasonic irradiation; iii) it combines selective S-alkylation and S-acylation reactions, therefore it can be applied to a wide range of hetaryl thiol derivatives; iv) it is carried out under mild conditions; v) the final products can readily be isolated; vi) the target products are obtained with high purity in good to excellent yields; vii) a small reaction volume is used.

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ЛЕСЕН И БЪРЗ МЕТОД ЗА ПОЛУЧАВАНЕ В ЕДИН СЪД НА 2-ТИОМЕТИЛОВИ И 2-ТИОАЦИЛОВИ БЕНЗОТИАЗОЛИ, БЕНЗОКСАЗОЛИ И БЕНЗИМИДАЗОЛИ

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(Резюме)

В настоящата статия е представен нов метод за получаване на 2-тиометил и 2-тиоацил бензазолиеви производни в един реакционнен съд. За целта са използвани о-аминотиофенол, о-аминофенол, и 1,2-фенилендиамин като изходни вещества. Новопредставения метод включва комбинация от микровълново нагряване и облъчване с микровълни, което води до изолиране на целевите продукти с високи до отлични добиви, без да е необходимо изолирането на междинни съединения.