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Facile synthesis of 5-arylidene rhodanine derivatives using Na_2SO_3 as an eco-friendly catalyst. Access to 2-mercaptop-3-aryl-acrylic acids and a benzoxaborole derivative

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ABSTRACT

A simple, efficient and environment-friendly procedure for the synthesis of 5-arylidene rhodanines derivatives *via* a Knoevenagel type reaction was developed using rhodamine, a variety of differently substituted aldehydes and Na_2SO_3 as benign catalyst in ethanol. Selected 5-arylidene rhodanines were subjected to basic hydrolysis to afford 2-mercaptop-3-substituted-acrylic acids. The presence of a boronic acid group is well tolerated in such transformations. In the case of 2-formylphenylboronic acid, this sequence opens access to a new benzoxaborole derivative.

Keywords: Knoevenagel reaction 5-Arylidene rhodanine 2-Mercaptoacrylic acids Sodium sulfite Benzoxaborole

1. Introduction

Heterocycles display an impressively high biological potential and were also used as important intermediates in the area of organic synthesis. Derivatives containing the 2-thioxothiazolidin-4-one (rhodanine) substructure are an interesting and important part of this wide library of bioactive compounds and exhibit a wide variety of biological activities,^{1,2} as anti-fungal,³ anti-bacterial,⁴⁻⁷ anti-inflammatory,⁸⁻¹⁰ anti-cancer,¹¹⁻¹³ anti-Alzheimer,^{14,15} anti-viral¹⁶⁻¹⁸ and anti-diabetic (Figure 1).¹⁹⁻²² More precisely, they act, for example, as inhibitors of aldose reductase, protein tyrosine phosphatase PTP, aggregation of Tau proteins, HIV-1 integrase, hepatitis C virus, protease and β -lactamase.^{1,2}

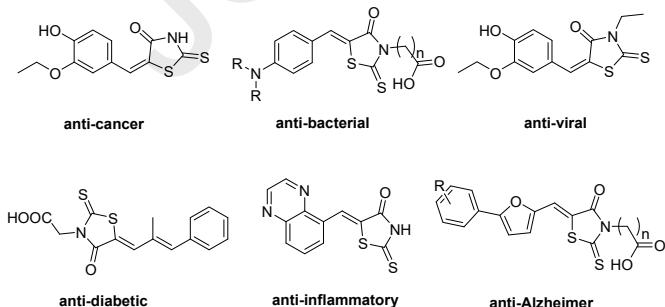
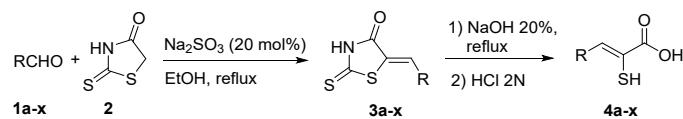


Fig. 1: Structures of some bioactive arylidene rhodanines.

In addition, they are versatile synthetic intermediates since they can undergo many chemical transformations, such as hydrolysis in basic medium to lead to mercaptoacrylic acids,²³

Michael-type addition,²⁴ Diels Alder reactions to access dihydropyrans²⁵ and 2-thioxopyrano[2,3-*d*][1,3]thiazoles.²⁶

For these reasons, 5-arylidene rhodamines have been the subject of numerous investigations and a number of procedures have been reported for their preparation. The main method of synthesis is the Knoevenagel reaction between rhodamine and aldehydes in the presence of various catalysts, such as, for example, ammonium acetate,²⁷ 2-hydroxyethylammonium acetate,²⁸ NaOAc/HOAc ,²⁹ 2,2,6,6-tetramethyl piperidine,³⁰ glycine,³¹ 1-butyl-3-methyl imidazolium hydroxide,³² $\text{NH}_4\text{Cl}/\text{NH}_4\text{OH}$,³³ piperidine,³⁴ supported K_2CO_3 on Al_2O_3 under microwave irradiation³⁵ or in the presence of an ionic liquid.³⁶ As a continuation of our research for an new environment-friendly approaches,³⁷⁻³⁹ we herein propose a new simple and eco-compatible procedure for the preparation of 5-arylidene rhodanines using Na_2SO_3 as catalyst in EtOH at reflux under conventional heating (Scheme 1). The hydrolysis of some of them was carried out in a second step to provide the corresponding 2-mercaptop-3-substituted-acrylic acids 4.

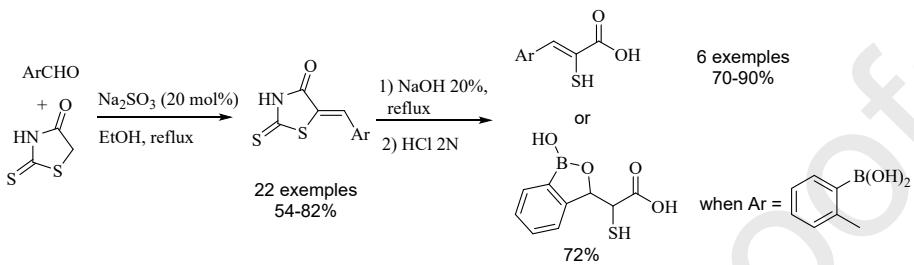


Scheme 1: Synthesis of 5-arylidene rhodanines 3 under Na_2SO_3 catalysis. Conversion to 2-mercaptop-3-substituted-acrylic acids 4.

Graphical Abstract

Facile synthesis of 5-arylidene rhodanine derivatives using Na_2SO_3 as an eco-friendly catalyst. Access to 2-mercaptop-3-arylacrylic acids and a benzoxaborole derivative

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2. Results and discussion

The optimal conditions to access 5-arylidene rhodanines **3** were first determined with rhodanine and 4-nitrobenzaldehyde as model compounds using different experimental conditions of temperature, solvent and amount of Na_2SO_3 as catalyst (Table 1). The modification of the initial procedure (r.t., 20% Na_2SO_3 , EtOH, Entry 1) by heating the reaction mixture at reflux 2 h

significantly improved the formation of the 5-arylidene rhodanines (Entry 2). This beneficial effect slightly diminished with a smaller quantity of catalyst (Entries 3 and 4), while an increase is also unfavorable (Entries 5-7). No improvement was found by using H_2O , $\text{EtOH}/\text{H}_2\text{O}$ (1/1) or $\text{THF}/\text{H}_2\text{O}$ (1/1) as solvents (Entries 8-10).

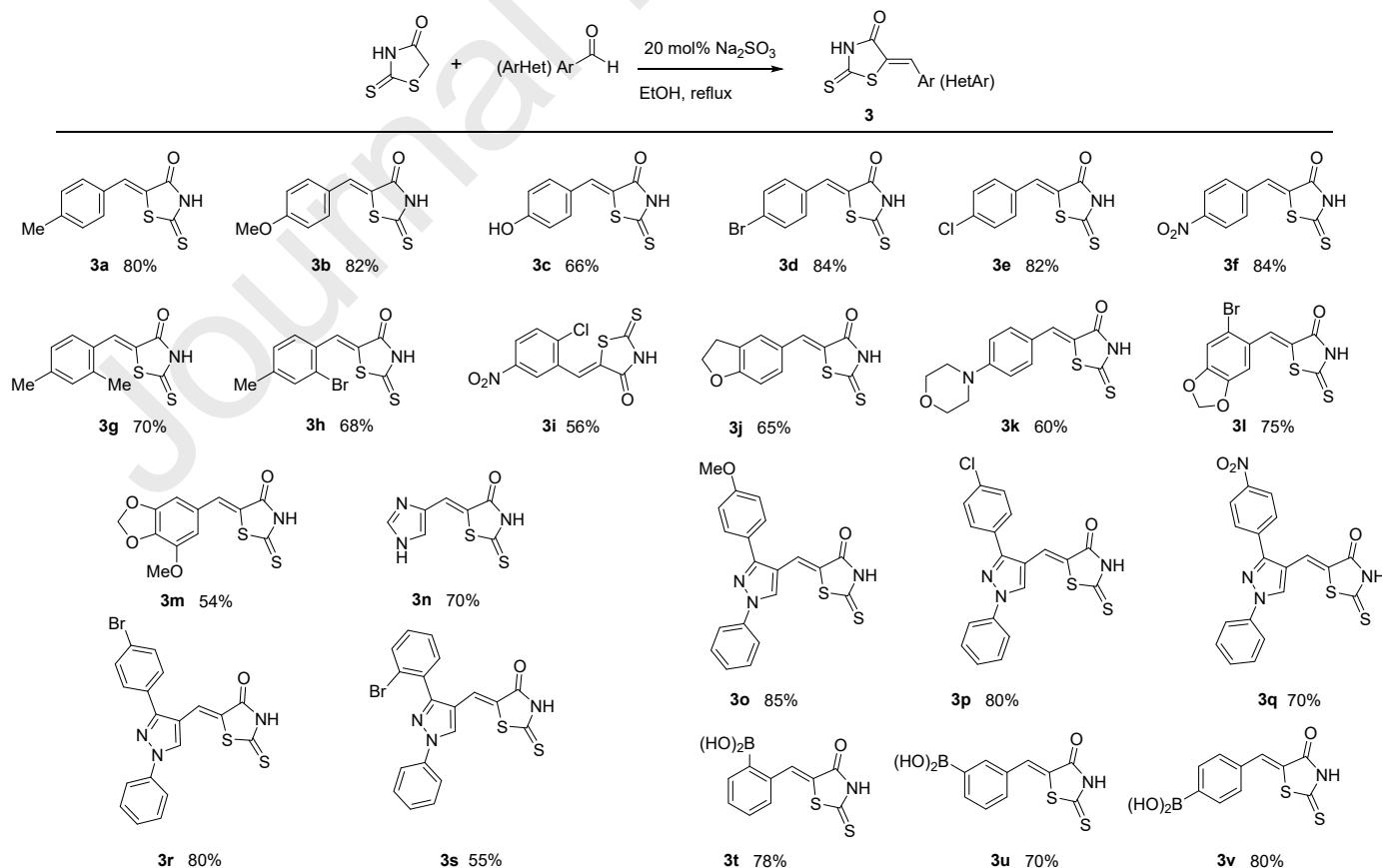
Table 1. Synthesis of 5-arylidene rhodanines **3**. Optimization of the reaction conditions

Entry	Solvent	Temperature	Cat (mol%)	Time (h)	Yield %
1	EtOH	r.t.	20	16	44
2	EtOH	reflux	20	2	84
3	EtOH	reflux	5	2	82
4	EtOH	reflux	10	2	75
5	EtOH	reflux	30	2	67
6	EtOH	reflux	40	2	68
7	EtOH	reflux	50	2	68
8	H_2O	reflux	20	2	70
9	$\text{EtOH}/\text{H}_2\text{O}$ (1/1)	reflux	20	2	73
10	$\text{THF}/\text{H}_2\text{O}$ (1/1)	reflux	20	2	67

Having optimized conditions in hands, we then changed the nature of the aldehyde to evaluate the scope and eventual limitations of this method (Table 2). This procedure is tolerant with a large range of functional groups (halogen, alcohol, nitro, ether, acetal, amino, imidazole). Good yields were also observed in the case of heterocycles as imidazole or *1H*-pyrazole-4-

carbaldehydes, an important class of pharmacophores.⁴⁰⁻⁴⁴ The excellent chemoselectivity of this method was illustrated by its compatibility, whatever the position on the aromatic nucleus, with a boronic acid moiety, a substituent which is becoming common into drug discovery processes⁴⁵ and is also a source of diversity given the versatility of this function.

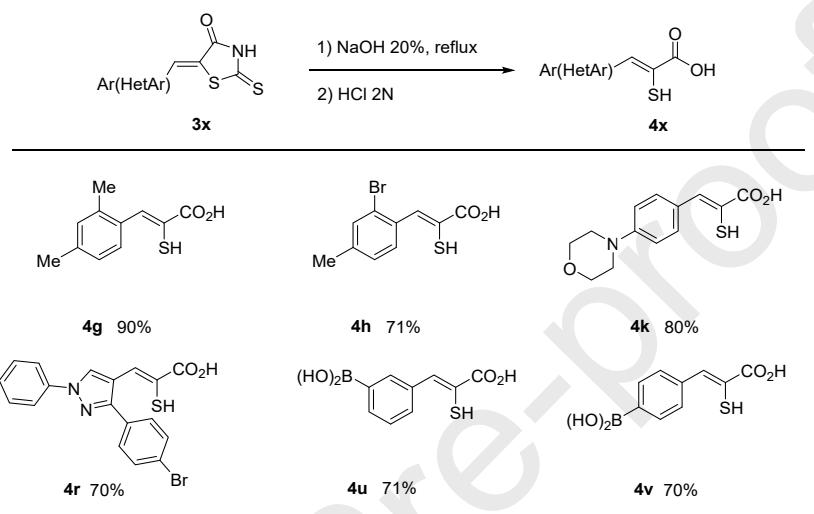
Table 2. Synthesis of 5-arylidene rhodanines **3**. Scope and limitations ^a



^a Aryl (Hetaryl)aldehyde (1 mmol), rhodanine (1 mmol) and 20 mol% Na_2SO_3 in 5 mL of EtOH at reflux, 2 h for **3a-3n** and **3t-3v** and 7 h for **3o-3s**.

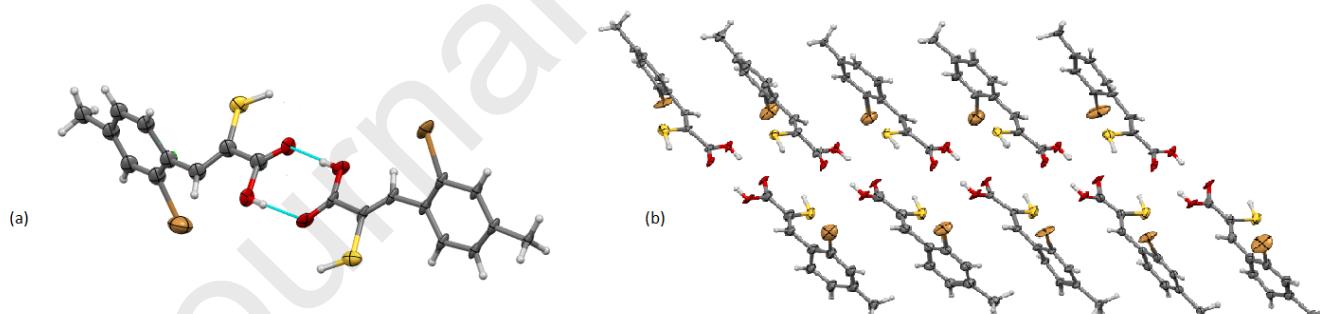
Amongst the most important transformations achieved on the thiazolidinone cycle are the alkaline hydrolysis to 2-mercaptop-3-aryl-acrylic acids,⁴⁶ which have interesting biological activities as, for example, *in vitro* chelation capacity of cadmium,⁴⁷ inhibition of metallo- β -lactamase⁴⁸ or calpains 1 and 2.⁴⁹ They have been also employed as precursors of amino acids,⁵⁰ benzo[b]thiophenes⁵¹ and naphtho[1,2-*b*]thiophenes.⁵² Selected previously synthesized 5-arylidene rhodanine derivatives are subjected to basic hydrolysis to afford new 2-mercaptop-3-aryl-acrylic acids in good to excellent yields, the boronic acid function being compatible with these experimental conditions (Table 3).

Table 3. Synthesis of 2-mercaptop-3-substituted-acrylic acids **4**^a



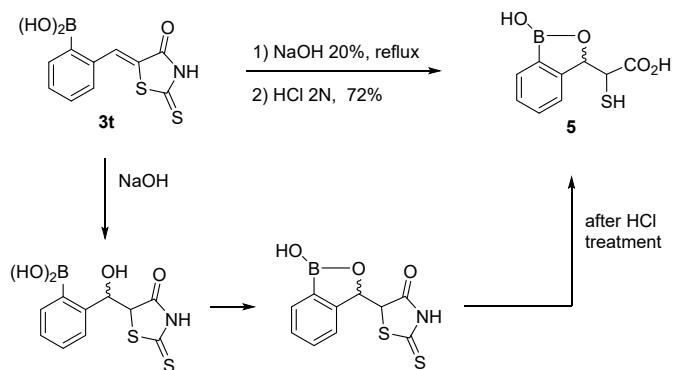
^a 1) Aryl rhodanine (0.5 mmol), 20 mol% NaOH (4 mL), reflux. 2) HCl 2N (13 mL), r.t.

Fig. 2: Structures of (a) a dimer of **4h** showing the intramolecular hydrogen bond (b) the asymmetric unit



The particular case of 5-arylidene rhodanine **3t** which has a boronic substituent at the *ortho* position deserves special comment. Contrary to what is expected, the 2-mercaptop-3-aryl-acrylic acid **4t** was not obtained. The new product was characterized by ¹H, ¹³C, and ¹¹B NMR and mass spectroscopy. Based on these data, a benzoxaborole structure, whose interest in medicinal chemistry is now widely recognized^{54,55} has been proposed. The formation of **5** can be rationalized by an oxime-Michael addition to the double bond of **3t**, followed by an intramolecular cyclization to create the boroheterocycle and finally cleavage of the 2-thioxothiazolidin-4-one ring by acid treatment (Scheme 2).

X-ray crystallographic analysis of **4h**. Furthermore, it is worthy to note that the asymmetric unit effectively contains ten crystallographically independent molecules (Figure 2). Dimers are observed with a pseudo-inversion center due to the presence of intermolecular hydrogen bonds between two COOH groups, the dihedral angle between the planes of the aryl ring and the alkenyl double bond varying from 20 to 57°. Moreover, these dimers are stacked along the [10-1] direction of the unit cell with an average pseudo-translation of 5.39 Å.



Scheme 2: Synthesis of benzoxaborole **5** and proposed mechanism for its formation.

Conclusion

In this work we propose a general procedure for the synthesis of 5-arylidene rhodanines with very good yields from a wide variety of functionalized aldehydes. Na_2SO_3 was used as benign catalyst due to its use as a food additive, its low cost and its availability. Basic hydrolysis easily afforded the corresponding 2-mercaptopropanoic acids. Of special interest is the obtention of benzoxaborole when the boronic acid group is located at the *ortho* position of the aromatic substituent.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/>

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