Monatshefte für Chemie - Chemical Monthly
https://doi.org/10.1007/s00706-020-02565-x

ORIGINAL PAPER

Green synthesis and antibacterial activity of chalcogenoesters

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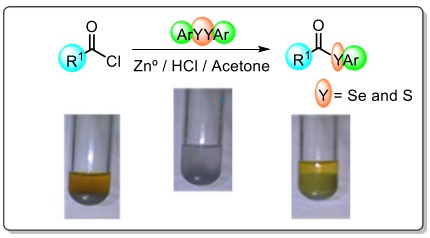
Received: 2 December 2019 / Accepted: 17 February 2020

Abstract

Herein, we present a new variation for an eco-friendly methodology for the synthesis of chalcogenoester in good-to-excellent yields in a short time, with an easy work-up/purification step, and in a greenest methodology, affording the minimum generation of solid and liquid waste, in comparison to that described in the literature. Additionally, some selected compounds were evaluated as antimicrobial agents, showing moderate activity against a variety of microorganisms including the *K. pneumoniae*, *P. aeruginosa* and also some selected fish pathogenic bacteria.

Graphic abstract



Keywords Thermal diastereomerization · Photochemistry · Acidity · Fluorescence · Absorption

Introduction

Organochalcogen chemistry has been gaining considerable attention due to a high number of publications involving this class of compounds in different scientific fields, including those of biochemistry [1, 2], chemistry [3] and materials [4]. Since chalcogen atoms have an important hole in oxidation processes due to their chemical properties, as well as they are present in the structure of some enzymes [5, 6], they are often reported as a glutathione peroxidase mimic [7–9] even as antitumor agents [10–14]. Regarding organochalcogen compounds, chalcogenoesters offer a wide variety of applications. In organic synthesis, they have been used as a precursor of the acyl radical [15] and acyl anions [16] as well as in the synthesis of new materials, such as molecular conductors and superconductors [17], molecular machines [18, 19], V-shaped materials [20], and liquid crystals [21, 22]. Considering the wide applications of chalcogenoesters, recently, there was an

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00706-020-02565-x) contains supplementary material, which is available to authorized users.

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Published online: 27 March 2020

increase in the development of new and effective methodologies providing the desired products. Thereby, there is a large number of protocols for synthesis of chalcogenoesters based on metals including palladium complexes [23], samarium [24], indium [25], mercury [26], bimetallic systems [27], and zinc [28]. However, despite some protocols proved to be highly efficient, they require a conventional purification step, which generally employs a large volume of solvents and silica gel which are normally discarded.

Therefore, research on the development of methodologies that enhance the environment-friendly nature of chemical processes is currently a subject of great interest, mainly in synthetic organic chemistry [29, 30]. In this intend, the preparation of chalcogenoesters using a greener approach, as using ionic liquids (ILs) or solid-phase reactions has been described in the literature [31, 32]. However, for a real account, all synthetical steps must be considered, including the purification process and the toxicity of chemicals involved. In this context, the *E* factor, which is defined as the real amount of waste produced during a transformation and measured by the total mass of waste according to the mass ratio of the desired product, represents a valuable tool for the evaluation of the laboratory chemical synthesis processes, considering the total amount of residue generated, as shown in Fig. 1 [33, 34].

In what concerns the importance of antimicrobial activity, there were 52.8 Mio. deaths globally in 2010 and infectious diseases were among the main causes. These illnesses are represented primarily by lower respiratory infections (2.8 Mio.), neonatal disorders (2.2 Mio.), diarrheal disease (1.4 Mio.), tuberculosis (1.2 Mio.), measles (0.13 Mio.), and tetanus (0.06 Mio.) [35]. In the beginning of this decade, *Enterobacteriaceae*, which produces *Klebsiella pneumoniae carbapenemase* (KPC), was reported in the USA and subsequently worldwide. These KPC-producing bacteria are predominantly involved in systemic and nosocomial infections [36]. The emergence of these multi-drug-resistant bacteria is, therefore, of concern, since antimicrobial treatment options are very restricted, because this enzyme leads to decreased susceptibility or even resistance to virtually all β-lactam drugs [37]. The few therapeutic options available are limited to the polymyxins, which are drugs with high nephro and neurotoxic potential [38]. Another microorganism of high clinical importance is *Pseudomonas aeruginosa*, which is one of the leading nosocomial pathogens. The increasing frequency of multi-drug-resistant *P. aeruginosa* strains severely limits the number of effective antimicrobials against infections caused by this pathogen [39]. These are the only two examples of the current critical situation that most hospitals around the world have been facing.

$$E\text{-factor} = \frac{(m_{\text{reactants}} - m_{\text{products}})}{m_{\text{products}}}$$

Fig. 1 E-factor calculation, *m* (mass)

Additionally, bacterial multi-resistance is also a problem in aquaculture. Intensification in fish production led to an increase in density, generating stress and infectious diseases and consequently, increasing the use of antimicrobial agents [40]. These diseases are mainly caused by Gram-negative bacteria, such as *Aeromonas hydrophila*, *A. veronii* [41], and *Citrobacter freundii* [42]. As well as *Raoltella ornithinolytica* is a Gram-negative bacillus that produces histamines, which leads to poisoning by ingestion of contaminated fish [43]. Overuse of antimicrobials led to an increase of bacterial resistance, residues in the aquatic environment and in the fish meat, generating a public health problem [44]. With increasingly resistant microorganisms coupled with limited therapeutic options, it is essential that research studies aim at the development of new classes of antimicrobial drugs, especially to combat resistant microorganisms.

Therefore, we report a new variant of a low-cost and highly eco-friendly methodology for the synthesis of chalcogenoesters. The desired esters were obtained in good-to-excellent yields in a short reaction time, with an easy work-up/purification step and a lower *E* factor, compared with similar protocols (Fig. 2).

The antimicrobial activity of the compounds obtained against Gram-positive and Gram-negative bacteria, including *K. pneumoniae*, *P. aeruginosa* and fish pathogenic bacteria was investigated. It should be noted that the present protocol represents a 'greener' variant aimed at improving a traditional methodology for the preparation of chalcogenoesters and consists of a simple molecular building blocks for new antimicrobial compounds.

Results and discussion

Synthesis of the chalcogenoesters

To synthesize the chalcogenoesters, diphenyl diselenide was diluted in acetone followed by the addition of four

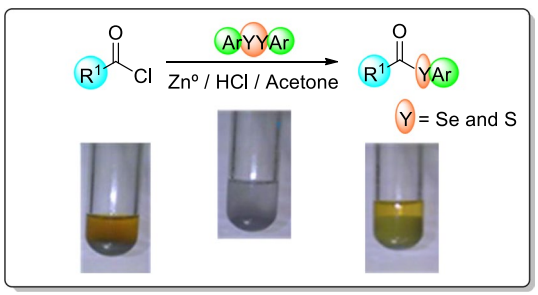


Fig. 2 General synthesis scheme

equivalents of zinc dust (Zn^0) as the reducing agent and 1 cm^3 of hydrochloric acid (HCl) 1 M. After 5 min, a complete disappearance of the yellow coloration was observed, indicating total reduction of diselenide. *p*-toluoyl acyl chloride was then added and the reaction was monitored by thin-layer chromatography (TLC). After 30 min, a precipitate was visible and the consumption of the starting material was confirmed by TLC. Aiming at the development of a 'green' work-up, 5 cm^3 of 0.1 M HCl was added to the reaction vessel, forcing the precipitation of the desired product. A filtration under vacuum was then carried out, leading to a mixture of the desired product and metallic zinc. Subsequently, the residual selenol was removed by the HCl solution, avoiding the oxidation of selenol in the presence of the product. The mixture with the chalcogenoester and zinc was finally diluted in acetone and filtered. The solvent was removed under vacuum, affording the pure product. To evaluate the scope of the methodology, a variety of dichalcogenides containing electron-withdrawing and donating groups as well as different acyl chlorides were employed. The results are summarized in Table 2.

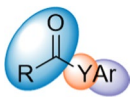
The synthesized chalcogenoesters were obtained in good-to-excellent yields, with selenium species providing the respective compounds in better yields comparing to those bearing the sulfur moiety. This result is probably due to the higher nucleophilicity of the selenium atom (Se) compared with sulfur (S).

The influence of the substituent attached to the aromatic ring of the acyl chloride was also studied. In a general view, the protocol was not sensible to electronic effects (Table 1, compounds **1**–**4**) with a slight decrease in the yield observed in compound **4** when *t*-Bu group in para position was employed (Table 1, compound **4**). Furthermore, the influence by groups attached to the aromatic ring of selenium moiety was investigated. It was possible to observe that strong electron-donating groups affect the dichalcogenide cleavage step. For instance, compound **5** required the longest time to allow the cleavage of dichalcogenium bond comparing to other substituted diselenides, probably due to Se–Se

Table 2 Values of minimal inhibitory concentration of compounds **1**, **2**, **6**, **9**, and **10** in mg/cm^3

Compound	Gram-positive bacterial strains		Gram-negative bacterial strains	
	S. aureus	*L. monocytogenes*	*K. pneumoniae*	*P. aeruginosa*
1	1.17	0.58	0.58	0.58
2	0.58	0.58	–	0.29
6	–	–	0.58	–
9	–	0.58	–	0.58
10	–	1.17	–	1.17

Table 1 Results obtained for the chalcogenoester-synthesized **1**–**12**



Entry	Comp	R	Ar	Y	Reagents	Waste	Product	*E* factor	Yield/%[a]	References
1	**1**	4-Me-C_6H_4	C_6H_5	Se	3.65	3.38	0.264	12.82	96	[47]
2	**2**	4-NO_2-C_6H_4	C_6H_5	Se	3.68	3.39	0.290	11,68	95	[25]
3	**3**	2-Cl-C_6H_4	C_6H_5	Se	3.67	3.37	0,292	11.56	99	[48]
4	**4**	4-*t*-Bu-C_6H_4	C_6H_5	Se	3.69	3.44	0.250	13.76	79	[48]
5	**5**[b]	4-Me-C_6H_4	2-OMe-C_6H_4	Se	3.68	3.41	0.271	12.58	89	–
6	**6**	4-Me-C_6H_4	4-Me-C_6H_4	Se	3.66	3.38	0.280	12.07	97	[49]
7	**7**	4-Me-C_6H_4	4-Cl-C_6H_4	Se	3.68	3.38	0.294	11.51	95	[47]
8	**8**	4-NO_2-C_6H_4	C_6H_5	S	3.63	3.39	0.233	14.55	90	[50]
9	**9**	4-Me-C_6H_4	4-Cl-C_6H_4	S	3.63	3.41	0.218	15.65	83	[51]
10	**10**	4-NO_2-C_6H_4	4-Cl-C_6H_4	S	3.67	3.40	0.270	12.60	92	[52]
11	**11**	4-NO_2-C_6H_4	4-OMe-C_6H_4	S	3.66	3.41	0.245	13.94	85	–
12	**12**	2-Cl-C_6H_4	4-Cl-C_6H_4	S	3.65	3.43	0.223	15.38	79	–
13[c]	**12**	2-Cl-C_6H_4	4-Cl-C_6H_4	S	182.56	182.34	0.223	817.67	79	

[a]Product isolated direct from the reaction and characterized by ^{1}H NMR, ^{13}C NMR, and CG/MS

[b]Required 20 min to cleave the diselenide

[c]Comparative result of entry 12 using conventional column purification/extraction step. Extraction with 50 cm^3 CH_2Cl_2 (66.5 g); column using 10 g of silica flash and 150 cm^3 of solution 10% ethyl acetate (13.45 g) in *n*-hexane (88.96 g)

bond strengthening by the presence of the electron-donating group.

To verify the scope of the methodology concerning the chalcogenium source, experiments were carried out using different species of disulfides and the results are summarized in Table 1 (compounds **8**–**12**). In general, disulfides showed comparable behavior as diselenides in terms of reactivity with different acyl chlorides and without a deep variation comparing the electronic effects of the substituents attached to aromatic ring in the disulfide moiety.

The *E*-factor calculations for laboratorial reactions could afford an interesting panorama about the greenest way developed in the synthetical protocols. Based on the experimental procedure, it was possible to calculate the *E* factor of the described methodology. In this context, an arithmetic average was calculated to the methodology using Fig. 1. As a result, it was obtained a medium *E*-factor total corresponding to the synthesis, extraction and purification. For a comparative analysis, an extraction and purification steps were introduced in the methodology (Table 1, entry 13) for the highest *E* factor obtained, related to entry 12. Using a conventional extraction with 50 cm^3 of CH_2Cl_2 and a traditional purification employing 10 g of silica flash and 150 cm^3 of a mixture of ethyl acetate and *n*-hexane (10%), the *E* factor of this example increased from 15.38 to 817.67, showing how greenest this methodology is in the synthesis of chalcogenoesters (see supplementary data).

Biological activity

Minimal inhibitory concentration (MIC) of compounds 1, 2, 6, 9, and 10 against Gram-positive (*Staphylococcus aureus* and *Listeria monocytogenes*) and Gram-negative (*K. pneumoniae* and *P. aeruginosa*) bacterial strains

The evaluation of the antibacterial activity of compounds **1**, **2**, **6**, **9**, and **10** was performed through the technique of micro-dilution, in which the MIC of the tested compounds can be observed against Gram-positive (*S. aureus* and *L. monocytogenes*) and Gram-negative (*K. pneumoniae* and *P. aeruginosa*) bacterial strains (Table 2).

Interestingly, the respective chalcogenoesters showed a modulation in the antimicrobial activity according to the groups present in the molecules. For instance, a broad activity against all strains was observed for compound **1,** while a very selective activity was observed for compound **6** which was proved active only against *K. pneumoniae*. This result increases the interest for clinical application of these chalcogenoesters, because either a broad spectrum of action or a selective activity is highly desirable depending on the type of infection observed. When some antimicrobial treatment is performed based on the results of antimicrobial susceptibility testing, the treatment with narrow-spectrum drugs is advantageous for preventing the activity of the drug against beneficial microorganisms of the normal microbiota. However, in most cases, depending on the severity of the infection, it is not possible to establish the causal agent. In these cases, the use of narrow-spectrum drugs is not appropriate, and the availability of broad-spectrum drugs is fundamental.

Minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of compounds 1 and 2 against fish pathogenic bacteria

Based on the results shown above, compounds **1** and **2** were tested against fish pathogenic bacteria (Table 3). The bacteria tested and their ascension numbers in GenBank were: *A. hydrophila* (MF372509), *A. hydrophila* (MF372510), *A. veronii* (MF372508), *C. freundii* (MF565839) and *R. ornithinolytica* (MF372511).

Compound **1** showed good bacteriostatic and bactericidal activity against strains of the genus *Aeromonas* and moderate activity against the other strains. Compound **2** showed moderate bacteriostatic activity and weak bactericidal activity against bacteria isolated from fish.

Florfenicol and oxytetracycline are approved by the Food and Drug Administration (FDA) for use in aquaculture [45]. These two conventional antimicrobials were tested against the strains *A. hydrophila* (MF372510), *C. freundii* (MF565839), and *R. ornithinolytica* (MF372511) in a previous study under the same experimental conditions. In this study, the florfenicol MIC values were 1.01 μg/cm^3 for *A. hydrophila* strain and 8.13 μg/cm^3 for *C. freundii* and *R. ornithinolytica* strains. In addition, the oxytetracycline MIC values were 0.51 μg/cm^3 for *A. hydrophila* strain and 4.06 μg/cm^3 for *C. freundii* and *R. ornithinolytica* strains [46].

Table 3 MIC and MBC values of compounds **1** and **2**, against fish-isolated bacterial strains in mg/cm^3

Comp	*A. hydrophila* MF372509		*A. hydrophila* MF372510		*A. veronii* MF372508		*C. freundii* MF565839		*R. ornithinolytica* MF372511	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
1	0.65	0.65	0.65	0.65	1.3	1.3	2.6	2.6	2.6	2.6
2	2.3	2.3	2.3	2.3	2.3	4.6	2.3	>4.6	4.6	>4.6

Conclusions

In summary, a new methodology for the 'greener' synthesis of chalcogenoesters was developed. Following an easy, clean and not expensive synthetical protocol, 12 chalcogenoesters were obtained in good-to-excellent yields, in short reaction times and employing a low toxicity metal as the reducing agent. Among them, chromatographic purification methods are not required, eliminating the use of a large amount of solvents affording low waste generation and leading to an appreciably low *E*-factor value. In addition, the synthesized compounds showed an antimicrobial activity, notably on clinically important microorganisms and also against fish pathogenic bacterial strains. Consequently, these chalcogenoesters open up possibilities for the development of new small molecular architectures for antimicrobial drugs, with both narrow and broad spectra of antimicrobial activity.

Experimental

General procedure for the synthesis of chalcogenoesters 1–12

In a Schlenck tube under argon atmosphere was added 2 mmol of zinc dust, $(ArY)_2$ (0.5 mmol), 1 cm^3 acetone, and 0.75 cm^3 of HCl (1 M) in this sequence. The mixture was stirred until complete disappearance of coloration and then acyl chloride (1.0 mmol) was added. The reaction was stirred during 30 min at room temperature. Then, 5 cm^3 HCl (0.1 M) was added and the reaction mixture was quickly filtrated under vacuum. The mixture between Zn^0 and chalcogenoester was transferred to an Erlenmeyer flask and 3 cm^3 acetone was added. After solubilizing the entire product, a new filtration was performed to separate the product and zinc dust. The solution was evaporated under reduced pressure and the desired product dried in vacuum pump. The NMR data and spectra of all compounds are available in the Supplementary Material.

Se-(2-Methoxyphenyl) 4-methylbenzoselenoate (5, $C_{15}H_{14}O_2Se$) Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$ (d, $J = 8.07$ Hz, 2H), 7.60 (m, 1H), 7.42 (td, $J = 7.58$, 1.51 Hz, 1H), 7.25 (d, $J = 8.07$ Hz, 2H), 7.00 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.9$, 159.2, 144.6, 138.3, 136.0, 131.2, 129.4, 127.4, 121.4, 114.8, 111.2, 56.0, 21.7 ppm.

S-(4-Methoxyphenyl) 4-nitrobenzothioate (11, $C_{14}H_{11}NO_4S$) Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.33$ (d, $J = 8.8$ Hz, 2H), 8.16 (d, $J = 8.80$ Hz, 2H), 7.42 (d, $J = 8.80$ Hz, 2H), 7.02 (d, $J = 8.80$ Hz, 2H), 3.85 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.9$, 161.6, 151.0, 141.8, 136.7, 128.7, 124.2, 117.1, 115.5, 55.7 ppm.

S-(4-Chlorophenyl) 2-chlorobenzothioate (12, $C_{13}H_8Cl_2OS$) Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (dd, $J = 7.58$, 1.22 Hz, 1H), 7.50–7.41 (m, 6H), 7,36 (td, $J = 7.58$, 1.71 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.5$, 136.7, 136.2, 135.9, 132.6, 130.9, 129.6, 129.1, 126.8, 126.6, 125.9 ppm.

Microorganisms

For the evaluation of the biological activity of the chalcogenoesters prepared, compounds **1**, **2**, **6**, **9**, and **10** were tested for their efficacy as antibacterial agents against Gram-positive (*Staphylococcus aureus* and *Listeria monocytogenes*) and Gram-negative (*K. pneumoniae* and *P. aeruginosa*) bacterial strains, expressed through MIC (minimal inhibitory concentration). Also, MIC and MBC (minimal bactericidal concentration) assays were performed against fish pathogenic bacteria, their ascension numbers in GenBank were *A. hydrophila* (MF372509), *A. hydrophila* (MF372510), *A. veronii* (MF372508), *C. freundii* (MF565839), and *R. ornithinolytica* (MF372511).

Antibacterial activity

The antibacterial activity of chalcogenoesters **1**, **2**, **6**, **9**, and **10** was determined by the minimal inhibitory concentration (MIC) according to the Clinical and Laboratory Standards Institute (CLSI) (Wayne, 2009). The MIC was determined by micro-dilution technique in Mueller–Hinton broth (Difco). The assay was carried out in 96-well microtitre plates. In each well with Müller–Hinton broth was placed an inoculum prepared in the same medium at a density adjusted per tube to 0.5 of the McFarland scale (1.5×10^8 CFU/cm^3) with sterile saline and lastly placed different concentrations of chalcogenoesters performed in triplicate. Microtiter trays were incubated at 37 °C and the MICs were recorded after 24 h of incubation. There was bacterial growth in the wells selected as positive growth and no bacterial growth was observed in the wells that did not receive the inoculums (negative controls—DMSO). The MIC was defined as the lowest concentration of compound that inhibits microbial growth. The tests to evaluate the antibacterial activity (MIC) and minimal bactericidal concentration (MBC) of compounds **1** and **2** against fish pathogenic bacteria were performed according to CLSI specific for these microorganisms (Wayne 2014) and at 28 °C. Values of MBC were confirmed by re-inoculation of 10 mm^3 of each bacterial culture on Mueller–Hinton Agar (28 °C/24 h), and the lowest concentration of the substances showing no growth was defined as the MBC.

Acknowledgements The authors gratefully acknowledge CAPES-Finance Code 001, CAPES PRINT-NANOMATERIAIS, CAPES-PROEX, CAPES-PRINT, CNPq (Ed. Universal 400791/2016-1, Produtividade em Pesquisa 303387/2015-7, 306240/2018-1 Pesquisador Visitante-401397/2014-9) for financial support.

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