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Synthesis of novel selenium and tellurium-containing tetrazoles: a class of chalcogen compounds with antifungal activity

Francieli M. Libero [a], Maurício C. D. Xavier [a], Francine N. Victoria [b], Patrícia S. Nascente [c], Lucielli Savegnago [d], Gelson Perin [a,*], Diego Alves [a,*]

[a] LASOL, CCQFA, Universidade Federal de Pelotas, UFPel, PO Box 354, 96010-900 Pelotas, RS, Brazil
[b] Faculdade de Agronomia Eliseu Maciel, DCTA, Universidade Federal de Pelotas, UFPel, Pelotas, RS, Brazil
[c] Instituto de Biologia, Universidade Federal de Pelotas, UFPel, Pelotas, RS, Brazil
[d] CDTec, Unidade Biotecnologia, Universidade Federal de Pelotas, UFPel, Pelotas, RS, Brazil

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ABSTRACT

We describe herein the synthesis and antifungal activity of new 5-arylchalcogenoalkyl-1*H*-tetrazoles **4**. Arylchalcogenoalkyl-1*H*-tetrazoles **4** have been synthesized in high yields by reaction of arylchalcogenolate anions with chloronitriles **2**, and subsequent [2+3] cycloaddition of resulting arylchalcogenoalkylnitriles **3** with sodium azide by zinc catalysis in aqueous solution. The obtained compound **4a** was screened for antifungal activity and presented inhibitory property against seven fungal strains. This protocol is an efficient method to produce new selenium–nitrogen compounds with antifungal activity.

Tetrazoles, classic nitrogen heterocyclic compounds,[1] have shown valuable properties in a wide range of applications, such as in material sciences,[2] catalysis,[3] propellants,[4] information recording systems,[5] explosives,[6] and possible application in high-energy chemistry.[7] Tetrazole derivatives are well known compounds with a high level of biological activity,[8] such as antiviral, antibacterial, antiallergic, anticonvulsant, anti-inflammatory properties, and use in pharmaceuticals as carboxylic acids isosteres.[9] An advantage of tetrazole derivatives over carboxylic acids is that they are resistant to various biological metabolic degradation pathways, conferring on the corresponding drug longer bioavailability.[9] Usually, the most attractive way for the synthesis of 5-substituted 1*H*-tetrazoles is [2+3] cycloaddition involves nitriles and azides (NaN_3 and $TMSN_3$).[10] A variety of synthetic methods have been reported in the literature using these reaction partners and the methodologies were performed in the presence of catalysts such as $AlCl_3$,[10a] $BF_3{\cdot}OEt_2$,[10b] TBAF,[10c] $Pd(PPh_3)_4$,[10d] Zn/Al hydrotalcite,[10e] mesoporous ZnS nanospheres,[10f] Cu–Zn alloy nanopowder,[10g] ZnO,[10h] Cu_2O[10i] and $FeCl_3$–SiO_2.[10j] However, some methods have little drawbacks such as the use of toxic metals and strong Lewis acids and harsh reaction conditions. To overcome these drawbacks, Sharpless and co-workers described the synthesis of 1*H*-tetrazoles by the addition of sodium azide to nitriles using zinc bromide in water and this discovery facilitates the preparation of functionalized tetrazoles.[11] Additionally, tetrazole rings were incorporated in a large number of famous antihypertensive (Losartan, Valsartan, and Irbesartan) and antifungal (TAK-456) agents (Fig. 1).[12] Therefore, remains the necessity for a deep study on the combinations of substrates for the synthesis of more functionalized and complex 1*H*-tetrazoles.

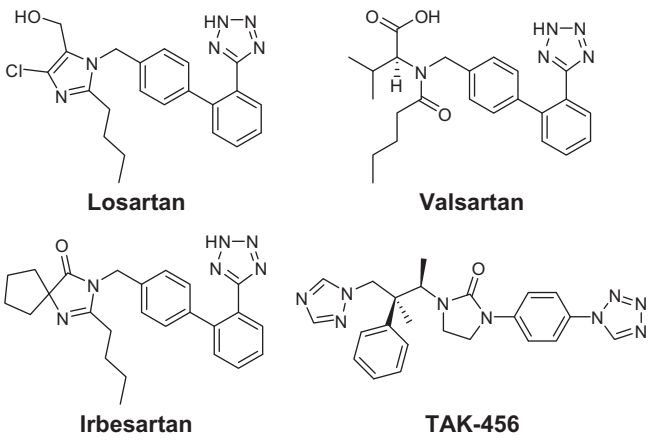

Figure 1. Drugs containing tetrazolyl moiety in their structure.

* Corresponding authors.
E-mail address: diego.alves@ufpel.edu.br (D. Alves).

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In this way, organochalcogen compounds, specially containing selenium and tellurium, are attractive synthetic targets because of their interesting biological activities[13] and applicability in organic reactions, well described in a great number of books and reviews.[14] Between these organochalcogen compounds, those containing nitrogen atoms in their structure are a special class of molecules and they have been employed in various organic transformations, for instance, in asymmetric synthesis.[15] Consequently, the search for new and efficient methods for the synthesis of novel nitrogen-functionalized organochalcogen compounds remains still widely explored.

In this regard, selenium-containing tetrazoles were synthesized by reaction of arylselanylcyanates with sodium azide affording the corresponding products in good yields.[16] This class of compounds have a great importance since they combine the well known applicability of the tetrazole group[2–9] with that of the selenium containing group.[13–15] However, to the best of our knowledge, the synthesis of organoselenium and tellurium-tetrazoles is scarce and has not been well explored. In this sense, and due to our interest correlated to preparation of nitrogen-functionalized organochalcogen compounds,[17] we describe herein the synthesis of arylchalcogenoalkyl-1*H* tetrazoles **4** by [2+3] cycloaddition of arylchalcogenoalkyl nitriles **3** with sodium azide by zinc catalysis in aqueous solution (Scheme 1).

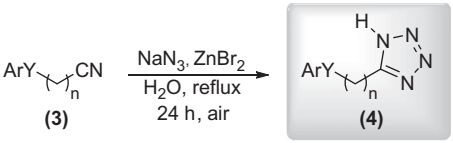
Initially, our studies were focused on the synthesis of 2-(phenylselanyl)acetonitrile **3a**,[18] the starting material for the synthesis of the desired 5-(phenylselanylmethyl)-1*H*-tetrazole **4a**. Thus, phenylselenolate anion, generated in situ by the reaction of diphenyl diselenide **1a** with $NaBH_4$/EtOH, reacted with chloroacetonitrile at room temperature, affording compound **3a** in excellent yield (Scheme 2).[18a]

After that, we turned our attention to the application of obtained 2-(phenylselanyl)acetonitrile **3a** in the synthesis of 5-(phenylselanyl-methyl)-1*H*-tetrazole **4a**. The synthesis of compound **4a** is significant since their carboxylic acid analogues and derivatives were synthesized and shown interesting biological activities.[19] Thus, some experiments were performed to synthesize compound **4a** in satisfactory yield (Scheme 2).

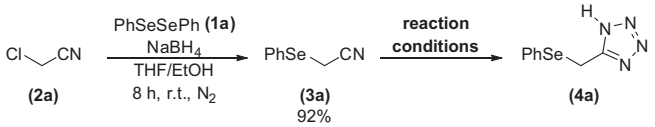
Recently, Das et al. developed the synthesis of 5-substituted 1*H*-tetrazoles by treatment of organic nitriles with NaN_3 in the presence of catalytic amount of iodine in DMF at 120 °C.[20] Applying these reaction conditions to nitrile **3a**, arylselanyl-tetrazole **4a** was obtained in 60% yield (Condition A, Scheme 2). In other experiment, $TMSN_3$ was reacted with nitrile **3a** using Cu_2O (5 mol %) as catalyst in a mixture of DMF/MeOH (9:1) at 100 °C, according to the methodology described by Yamamoto.[10i] Under these conditions, the desired product **4a** was formed in 52% yield (Condition B, Scheme 2). To our satisfaction, when the reaction of nitrile **3a** was performed with NaN_3 using 1 equiv of $ZnBr_2$ in H_2O at 100 °C for 24 h,[11a] product **4a** was achieved in 82% (Condition C, Scheme 2). Unfortunately, when the $ZnBr_2$ ratio was reduced from 1.0 to 0.5 equiv, a decrease in the yield of product **4a** was observed (Condition D, Scheme 2). After these experiments, we choose to continue the synthesis of different 5-arylchalcogenoalkyl-1*H*-tetrazoles **4**, by the method developed by Sharpless and co-workers, due to the fact that this protocol is safer and uses water as the solvent (Condition C, Scheme 2).

Thus, before the synthesis of the corresponding 5-arylchalcogenoalkyl-1*H*-tetrazoles **4**, a variety of arylchalcogenoalkyl nitriles **3b–m** were synthesized by reactions with arylchalcogenolate anions with a range of chloronitriles **2** and the results are shown in Table 1. In general, arylchalcogenoalkyl nitriles **3b–j** derived from different diaryl diselenides and chloronitriles **2** were obtained in good yields (Table 1, entries 1–9). Extending this protocol to the synthesis of tellurium analogues, satisfactory yields of desired aryltellanyl nitriles **3k–m** were achieved (Table 1, entries 10–12).

Next, the synthesized arylchalcogenoalkyl nitriles **3b–m** (0.5 mmol) were reacted with NaN_3 (0.5 mmol) and $ZnBr_2$ (0.5 mmol) in H_2O at 100 °C for 24 h to produce arylchalcogenoalkyl-1*H*-tetra-



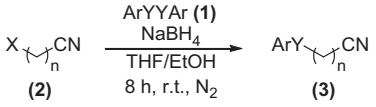
Scheme 1. General scheme of the reaction.

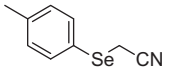
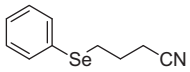
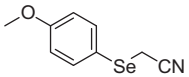
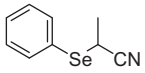
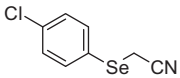
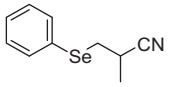
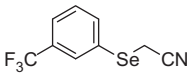
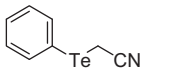
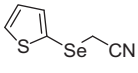
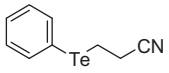
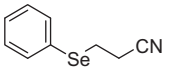
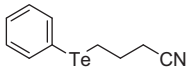


Condition A: NaN_3, I_2 (1 mol%), DMF at 120 °C (60%)
Condition B: $TMSN_3$, Cu_2O (5 mol%), DMF/MeOH at 100 °C (52%)
Condition C: NaN_3, $ZnBr_2$ (1 eq.), H_2O at 100 °C (82%)
Condition D: NaN_3, $ZnBr_2$ (0.5 eq.), H_2O at 100 °C (35%)

Scheme 2. Optimization of synthesis of 5-(phenylselanyl-methyl)-1*H*-tetrazole **4a**.

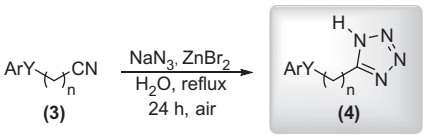
Table 1
Arylchalcogenoalkyl nitriles **3b–m** synthesized[a]



Entry	Product (**3**) (yield)	Entry	Product (**3**) (yield)
1	 **3b** (98%)	7	 **3h** (77%)
2	 **3c** (99%)	8	 **3i** (75%)
3	 **3d** (91%)	9	 **3j** (73%)
4	 **3e** (89%)	10	 **3k** (85%)
5	 **3f** (88%)	11	 **3l** (81%)
6	 **3g** (73%)	12	 **3m** (82%)

[a] Reactions are performed in the presence of diaryl dichalcogenides **1** (1.0 mmol), chloronitriles **2** (2.0 mmol), and $NaBH_4$ (3.0 mmol) in EtOH (15 mL) and THF (5 mL) at room temperature for 8 h in nitrogen atmosphere.

Table 2
Arylchalcogenoalkyl-1*H*-tetrazoles **4b–m** synthesized[a]



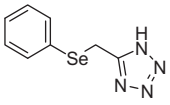
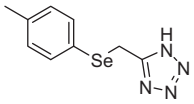
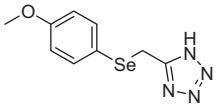
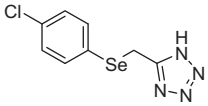
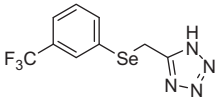
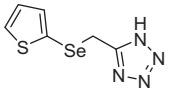
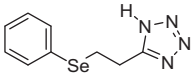
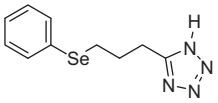
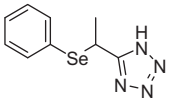
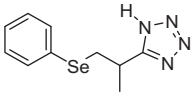
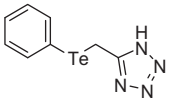
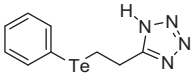
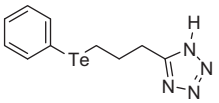
Entry	Product (**4**)	Isolated yield[b] (%)
1	 **4a**	82
2	 **4b**	71
3	 **4c**	72
4	 **4d**	83
5	 **4e**	86
6	 **4f**	84
7	 **4g**	71
8	 **4h**	61
9	 **4i**	73
10	 **4j**	74
11	 **4k**	75
12	 **4l**	74

Table 2 (*continued*)

Entry	Product (**4**)	Isolated yield[b] (%)
13	 **4m**	65

[a] Reactions are performed in the presence of arylchalcogenoalkyl nitriles **3** (0.5 mmol), NaN_3 (0.5 mmol), and $ZnBr_2$ (0.5 mmol) in H_2O at 100 °C for 24 h in open atmosphere.
[b] Yields are given for isolated products.

Table 3
Evaluation of the antifungal activity of compound **4a** against the fungal strains[a]

Fungal strain	Minimum inhibitory concentration (μM)	
	Compound **4a**	Fluconazole
C. albicans	104.2 ± 36.2	62.5 ± 0
C. lipolytica	156.25 ± 62.5*	31.25 ± 0
C. parapsilosis	166.72 ± 72.2	52.1 ± 18.0
C. laurentii	250 ± 0*	62.5 ± 0
T. asahii	125 ± 0	83.3 ± 36.1
C. guilhermondi	125.0 ± 0*	62.5 ± 0
C. globosa	187.5 ± 72.2	166.6 ± 72.0

[a] The values were analyzed by one-way ANOVA followed by the Newman–Keuls multiple comparison test, each value is expressed as the mean ± standard deviation. The tests were performed three times in duplicate. Asterisks represent significant effects (*p <0.05) compared with fluconazole, for each strain.

zoles **4b–m**.[21] The results disclosed in Table 2 reveal that our protocol worked well for a variety of substituted compounds **3**, affording good yields of the desired selenium and tellurium-tetrazoles. In a general way, the reactions are a little sensitive to the electronic effect of the aromatic ring in the arylselenium moiety. For example, arylselenium nitriles containing electron-withdrawing group (EWG) gave a slightly higher yield than those bearing electron-donating group (EDG) (Table 2, entries 4,5 vs. 2,3). When the reaction was performed with 2-thienylselanyl acetonitrile **3f**, the respective selenium tetrazole **4f** was obtained in 84% yield (Table 2, entry 6). Extending the scope of obtained selenium-tetrazoles, different phenylselanylalkyl nitriles **3g–j** furnished the corresponding tetrazoles **4g–j** in satisfactory yields (Table 2, entries 7–10).

Additionally, the possibility of synthesis of tellurium-tetrazoles was investigated and phenyltellanylalkyl nitriles **3k–m** were efficiently cyclized with NaN_3 to phenyltellanylalkyl-1*H*-tetrazoles **4k**, **4l,** and **4m** in 75%, 74%, and 65% yield, respectively (Table 2, entries 11–13).

Finally, according to the literature, tetrazole derivatives are well known compounds with an antifungal activity.[8] Research and development of potent and effective antimicrobial agents represent one of the most important advances in therapeutics, not only in the control of serious infections, but also in the prevention and treatment of some infectious complications. Over the past decade, fungal infections have become an important complication and a major cause of morbidity and mortality in immunocompromised individuals.[22] Thus, the antifungal activity[23] of synthesized 5-(phenylselanylmethyl)-1*H*-tetrazole **4a** was evaluated using seven fungal strains, and the results are shown in Table 3.

To evaluate the potential of compound **4a** as an antifungal agent we compared the results obtained with fluconazole, a known antifungal drug, using statistical analysis (one-way ANOVA). The results show that the minimum inhibitory concentration of

fluconazole was not different when compared with compound **4a** for *Candida albicans, Candida globosa, Thrichosporum asahii,* and *Candida parapsilosis.* Based on this, it is possible to conclude that the effect of compound **4a** is comparable with an active antifungal drug largely used for the treatment of fungal infections. On the other hand, the minimum inhibitory concentration of fluconazole was different when compared with compound **4a** for *Candida lipolytica*, *Cryptococcus laurntii,* and *Candida guilhermondi.* Thus, our results are a contribution to the research about the development of new antifungal drugs, and compound **4a** evaluated shows good results when compared to fluconazole.

In summary, we have demonstrated the efficient synthesis of novel selenium and tellurium containing tetrazoles. The corresponding 5-arylchalcogenoalkyl-1*H*-tetrazoles were synthesized in high yields by 1,3-dipolar cycloaddition of arylchalcogenoalkylnitriles with sodium azide by zinc catalysis in aqueous solution. The obtained compound **4a** was screened for antifungal activity and presented good results on inhibition of *T. asahii* and *C. lipolytica*. This protocol is an efficient method to produce new selenium-nitrogen compounds with antifungal activity. Studies regarding evaluation of antifungal activity of the 5-arylchalcogenoalkyl-1*H*-tetrazoles synthesized are ongoing in our lab.

Acknowledgments

We are grateful to CAPES, CNPq, FINEP, and FAPERGS for the financial support.

References and notes

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21. *General procedure for the synthesis of arylchalcogenoalkyl-1H-tetrazoles* ***4a–m****:* To a 5 mL round-bottomed flask was added the corresponding arylchalcogenoalkyl nitrile **3a–m** (0.5 mmol), sodium azide (0.5 mmol), zinc bromide (0.5 mmol), and 2 mL of H_2O. The reaction mixture was refluxed for 24 h under vigorous stirring. After this time, HCl (2 M, 3 mL) and ethyl acetate (15 mL) were added, and vigorous stirring was continued until no solid was present and the aqueous layer had a pH of 1. The organic layer was isolated and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. The resultant products **4a–m** were isolated in chromatography column with hexane/ethyl acetate as eluent and recrystallized if necessary.
*Selected spectral and analytical data for 5-(phenylselanylmethyl)-1H-tetrazole (****4a****):* Yield: 0.097 g (82%); white solid; mp: 78–79 °C. MS: *m*/*z* (rel. int.) 242 (M+2, 10), 240 (M, 57), 172 (10), 157 (57), 118 (38), 91 (48), 77 (100), 55 (86). IR (KBr): ν = 3356, 2997, 2852, 2713, 2609, 1653, 1558, 1473, 1433, 1369, 1255, 1209, 1051, 1020, 839, 742, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.44 (m, 2H), 7.29–7.24 (m, 3H), 4.3 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.09, 134.12, 129.54, 128.59, 127.77, 16.74. HRMS: *m*/*z* calculated mass to $C_8H_8N_4Se+H^+$: 239.9914; found: 239.9915.
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23. *Minimum inhibitory concentration (MIC)—Microdilution assay:* Recommendations of National Committee for Clinical Laboratory Standards (NCCLS) (2002, M27-A2) were mostly used to measure the minimum inhibitory concentration (MIC) values. Compound **4a** was diluted on dimethyl sulfoxide (DMSO) tested in concentrations ranging from 500 to 0.85 μM, in triplicate in each assay, and the assays were repeated three times in their entirety to confirm the results. Compound **4a** (100 μL) was serially diluted by 50% with the medium RPMI 1640 (with glutamine and phenol red without bicarbonate) buffered in MOPS (3-(*N*-morfolin)propanosulfonic acid) in 96 well microtiter plates, and 100 μL of fungal culture was added to each well. The MIC was recorded as the lowest concentration of the tested drug that inhibited the fungal growth.